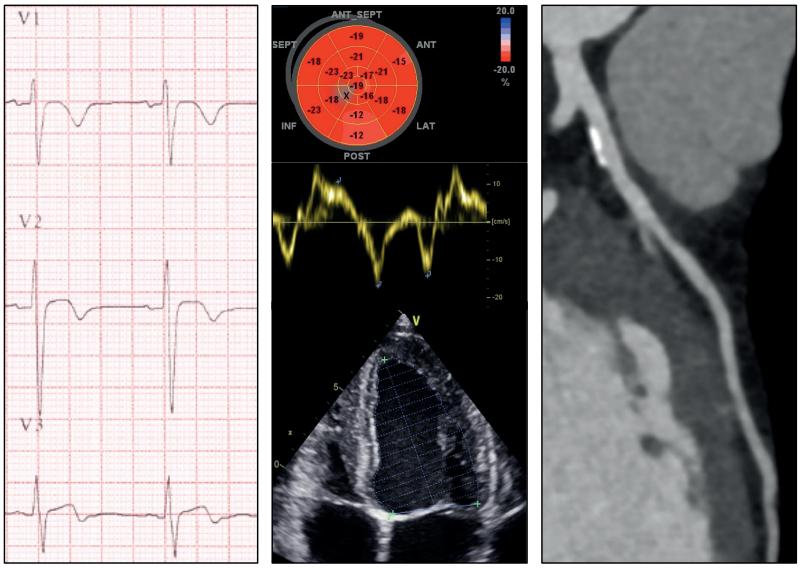
CARDIOVASCULAR RISK ASSESSMENT IN ATHLETES:

THE ROLE OF ELECTROCARDIOGRAPHY AND IMAGING



HÉLDER ALEXANDRE CORREIA DORES

Tese para obtenção do grau de Doutor em Medicina

na Especialidade em Investigação Clínica

na Faculdade de Ciências Médicas | NOVA Medical School da Universidade NOVA de Lisboa

Dezembro, 2018

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Thesis for the PhD degree in Medicine,

in the speciality of Clinical Investigation

December, 2018

To my lovely family

"Thus, the task is not so much to see what no one yet has seen,
but to think what nobody yet has thought about that which everybody sees."

Arthur Schopenhauer (1788-1860)

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

CAD	Coronary Artery Disease
Cardiac CT	Cardiac Computed Tomography
CAC	Coronary Artery Calcium
CCTA	Coronary Computed Tomography Angiography
CV	Cardiovascular
ESC	European Society of Cardiology
ECG	Electrocardiogram
ECHO	Echocardiogram
FCM	Faculdade de Ciências Médicas
GLS	Global Longitudinal Strain
IF	Impact Factor
LV	Left Ventricle
LVH	Left Ventricular Hypertrophy
LVEF	Left Ventricular Ejection Fraction
NMS	NOVA Medical School
SCD	Sudden Cardiac Death
SCORE	Systematic Coronary Risk Estimation
TTE	Transthoracic Echocardiography

ACKNOWLEDGEMENTS

First of all, I would like to thanks Professor Pedro de Araújo Gonçalves for his assistance and support throughout all the projects and studies included in this document. I am very grateful for his insightful, simplicity, pragmatism and especially his friendship.

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Thanks to Professor Nuno Neuparth for his assistance in the preparation of this document and my integration in the Pathophysiology Department of NMS | FCM.

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Thanks to all my colleagues and friends who collaborated in the several projects, for their simultaneous passion in clinical practice and research.

Thanks to all the professionals of the institutions where these projects were developed, especially to Doctor Miguel Mendes, Head of the Cardiology Department of Santa Cruz Hospital, Doctor Francisco Pereira Machado, Head of the Cardiology Department of Luz Hospital and Doctor José Monge, Head of the Cardiology Department of Armed Forces Hospital in Lisbon.

Finally, the most important, my family.

Filipa, thanks for the precious patience and understanding. Matilde and Madalena, thanks for your unconditional love. Thanks to my parents, who have guided me in all the moments and supported my decisions. Without all of you, I would not have the energy to see this project through to completion.

GENERAL CONSIDERATIONS

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The present document reflects the research performed during the last years in the field of sports cardiology, especially regarding the preparticipation evaluation and the CV risk stratification of athletes.

My interest in research began early, during the Medicine course, while in the internship of cardiology it became deeper and more systematized. After joining the Pathophysiology Department of the NMS | FCM this interest was solidified, being natural the enrolment in the Doctoral Programme in Medicine in the area of Clinical Investigation.

As a military doctor, the evaluation of candidates and military of the Portuguese Armed Forces is frequent, in which exercise training is a central component. In this setting, sports cardiology has been progressively established as the main area of my clinical practice and research.

Under the supervision of the Professor Sanjay Sharma I had the opportunity to train and to acquire experience in the *Sports Cardiology and Inherited Cardiac Diseases Centre* of the St. George's Hospital, London, United Kingdom. Beyond the clinical activity, I had the privilege to perform research and participate in several projects developed in this centre.

This background gave me the opportunity to participate in the implementation of dedicated sports cardiology clinics in Armed Forces Hospital and Luz Hospital - Lisbon, and to collaborate in the regular evaluations of athletes.

In addition to this specific interest in sports cardiology, the role of cardiac CT in the improvement of CV risk stratification and early detection of CAD was an important area of investigation. I had the opportunity to participate in the projects of the PhD thesis of Professor Pedro de Araújo Gonçalves[*] about the usefulness of cardiac CT in evaluation

[*] *De Araújo Gonçalves, P. (2013). Utilidade da tomografia computorizada cardíaca na avaliação da doença coronária. Lisboa: NMS | FCM. Available in https://run.unl.pt*

of CAD. The characterization of total coronary atherosclerotic burden with cardiac CT and the development of angiographic scores that may improve CV primary prevention gave us the hypothesis that the application of this exam in evaluation of specific populations such as veteran athletes could be useful. The last manuscripts published (and included in this document) constitute a continuation of these lines of investigation.

The curricular units and the seminars of the NMS | FCM Doctoral program were fulfilled, outlining as Doctoral Intention to study the CV risk stratification of veteran athletes, more specifically the relationship between physical exercise and CAD.

However, consequently to the systematic publication related with the CV evaluation of athletes, namely the role of exams such as ECG, TTE and cardiac CT, it was decided to present this proposal based on scientific articles alternative to the thesis. This modality was chosen due to the coherence and framing of the manuscripts, as stipulated in the Regulations.[†]

I believe that this organization is an added value for the dissemination of the work performed over the last years and published in peer-reviewed journals.

[†] *Artigo 20º do Regulamento aplicado ao ciclo de estudos conducente ao grau de Doutor em Medicina - Diário da República, 2ª série — Nº 153 — 7 de agosto de 2015*.

LIST OF PUBLICATIONS

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MANUSCRIPT 1

- ***Dores H***, *Freitas A, Malhotra A, Mendes M, Sharma S.* ***The heart of competitive athletes: an up-to-date overview of exercise-induced cardiac adaptations****. Rev Port Cardiol 2015;34(1):51-64.* **(IF: 0.873; NMS PhD 1.746)**

MANUSCRIPT 2

- *Malhotra A, Dhutia H, Gati S, Yeo TJ,* ***Dores H****, Bastiaenen R, Narain R, Merghani A, Finocchiaro G, Sheikh N, Steriotis A, Zaidi A, Millar L, Behr E, Tome M, Papadakis M, Sharma S.* ***Anterior T-wave inversion in young white athletes and nonathletes: prevalence and significance.*** *J Am Coll Cardiol 2017;69(1):1-9.* **(IF: 19.896; NMS PhD 9.948)**

MANUSCRIPT 3

- ***Dores H****, Freitas A.* ***ECG in athlete: "normal or pathologic variant?"*** *Ann Noninvasive Electrocardiol 2018;(23):3e12438.* **(IF: 1.852; NMS PhD 3.704)**

MANUSCRIPT 4

- ***Dores H****, Malhotra A, Sheikh N, Millar L, Dhutia H, Narain R, Merghani A, Papadakis M, Sharma S.* ***Abnormal electrocardiographic findings in athletes: correlation with intensity of sport and level of competition.*** *Rev Port Cardiol 2016;35(11):593-600.* **(IF: 1.195; NMS PhD 2.390)**

MANUSCRIPT 5

- ***Dores H****, Ferreira Santos J, Dinis P, Costa FM, Mendes L, Monge JC, Freitas A, Gonçalves PA, Cardim N, Mendes M.* ***Variability in interpretation of the electrocardiogram in athletes: another limitation in pre-competitive screening.*** *Rev Por Cardiol 2017;36(6):443-9.* **(IF: 0.827; NMS PhD 1.654)**

MANUSCRIPT 6

- *Dhutia H, Malhotra A, Yeo TJ, Ster IC, Gabus V, Steriotis A,* ***Dores H****, Mellor G, García-Corrales C, Ensam B, Jayalapan V, Ezzat VA, Finocchiaro G, Gati S, Papadakis M, Tome-Esteban M, Sharma S.* ***Inter-rater reliability and downstream financial implications of electrocardiography screening in young athletes.*** *Circ Cardiovasc Qual Outcomes 2017;10(8):e003306.* **(IF: 4.524; NMS PhD 2.262)**

MANUSCRIPT 7

- ***Dores H****, Dinis P, Fernandes R, Barra S, Ferreira S, Silveira MC, Rocha E, Cardoso J, Monge J.* ***Comparison of three criteria for interpretation of electrocardiogram in athletes.*** *Military Medicine 2017*;182(11):e2041-e2045. **(IF: 0.782; NMS PhD 1.564)**

MANUSCRIPT 8

- *Dinis P, Teixeira R,* ***Dores H****, Correia P, Lekedal H, Bergman M, Cachulo MC, Cardoso J, Gonçalves L.* ***Exercise-induced cardiac remodeling in athletes and in special forces soldiers.*** *Rev Por Cardiol 2018;37(3):249-56.* **(IF: 0.827; NMS PhD 0.827)**

MANUSCRIPT 9

- ***Dores H,*** *Mendes L, Dinis P, Cardim N, Monge J, Ferreira Santos J.* ***Myocardial deformation and volume of exercise: a new overlap between pathology and athlete's heart?*** *Int J Cardiovasc Imaging 2018;34(12):1869-75.* **(IF: 2.036; NMS PhD 4.072)**

MANUSCRIPT 10

- ***Dores H,*** *Mendes L, Ferreira A, Ferreira Santos J.* ***Symptomatic exercise-induced intraventricular gradient in competitive athlete.*** *Arq Bras Cardiol 2017;109(1):87-8.* **(IF: 1.186; NMS PhD 2.372)**

MANUSCRIPT 11

- *Araújo Gonçalves P, Garcia-Garcia H, Carvalho M,* ***Dores H****, Sousa PJ, Marques H, Ferreira A, Cardim N, Teles RC, Raposo L, Gabriel HM, Almeida MS, Aleixo A, Carmo MM, Machado FP, Mendes M.* ***Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited.*** *Int J Cardiovasc Imaging 2013;29(5):1105-14.* **(IF: 2.322; NMS PhD 1.161)**

MANUSCRIPT 12

- ***Dores H****, de Araújo Gonçalves P, Carvalho MS, Sousa PJ, Ferreira A, Cardim N, Carmo MM, Aleixo A, Mendes M, Machado FP, Roquette J, Marques H.* ***Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac-CT****. Eur J Prev Cardiol 2014; 21(11):1387-93.* **(IF: 3.319; NMS PhD 6.638)**

MANUSCRIPT 13

- ***Dores H****, de Araújo Gonçalves P, Ferreira AM, Carvalho MS, Sousa PJ, Cardim N, Marques H, Pereira Machado F.* ***Performance of traditional risk factors in identifying a higher than expected coronary atherosclerotic burden.*** *Rev Port Cardiol 2015;34(4):247-53.* **(IF: 0.873; NMS PhD 1.746)**

MANUSCRIPT 14

- *Rodrigues G, de Araújo Gonçalves P, Moscoso Costa F, Campante Teles R,* ***Dores H****, Mariano L, Brito J, Mesquita Gabriel H, Almeida M, Mendes M.* ***Low previous cardiovascular risk of patients with ST-elevation myocardial infarction.*** *Coron Artery Dis 2017;28(5):413-16.* **(IF: 1.823; NMS PhD 1.823)**

MANUSCRIPT 15

- *de Araújo Gonçalves P, Sousa PJ, Calé R, Marques H, Santos MB, Dias A,* ***Dores H****, Carvalho MS, Ventosa A, Martins T, Teles RC, Almeida M, Mendes M.* ***Effective radiation dose of three diagnostic tests in cardiology: single photon emission computed tomography, invasive coronary angiography and cardiac computed tomography angiography.*** *Rev Port Cardiol 2013; 32(12):981-6.* **(IF: 0.525; NMS PhD 0.263)**

MANUSCRIPT 16

- *De Araújo Gonçalves P, Garcia-Garcia H,* ***Dores H****, Carvalho MS, Sousa PJ, Marques H, Ferreira A, Cardim N, Teles RC, Raposo L, Gabriel HM, Almeida MS, Aleixo A, Carmo MM, Machado FP, Mendes M.* ***Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden.*** *Int J Cardiovasc Imaging 2013;29(7):1575-84.* **(IF: 2.322; NMS PhD 1,161)**

MANUSCRIPT 17

- *Carvalho MS, de Araújo Gonçalves P, Garcia-Garcia H, Sousa PJ,* ***Dores H****, Ferreira A, Cardim N, Carmo MM, Aleixo A, Mendes M, Machado FP, Roquette J, Marques H.* ***Prevalence and predictors of coronary artery disease in patients with a calcium score of zero.*** *Int J Cardiovasc Imaging 2013;29(8):1839-46.* **(IF: 2.322; NMS PhD 1,161)**

MANUSCRIPT 18

- ***Dores H****, de Araújo Gonçalves P, Carvalho MS, Sousa PJ, Marques H, Cardim N, Aleixo A, Carmo MM, Machado FP, Roquette J.* ***Non-obstructive coronary artery disease documented by cardiac computed tomography: discrepancy between atherosclerotic burden and cardiovascular risk.*** *Rev Port Cardiol 2013;32(7-8):613-8.* **(IF: 0.525; NMS PhD 1.050)**

MANUSCRIPT 19

- ***Dores H,*** *Araújo Gonçalves P, Cardim N, Neuparth N.* ***Coronary artery disease in athletes: an adverse effect of intense exercise?*** *Rev Por Cardiol 2018;37(1):77-85.* **(IF: 0.827; NMS PhD 1.654)**

MANUSCRIPT 20

- ***Dores H,*** *de Araújo Gonçalves, Monge J, Costa R, Tátá L, Cardim N, Neuparth N, Sharma S.* ***Coronary atherosclerotic burden in recreational male veteran athletes with low to intermediate cardiovascular risk.*** *(under review - The International Journal of Cardiovascular Imaging – CAIM-D-18-00527).*

MANUSCRIPT 21

- ***Dores H****, de Araújo Gonçalves, Monge J, Costa R, Tátá L, Malhotra A, Sharma S, Cardim N, Neuparth N.* ***Subclinical coronary artery disease in veteran athletes: is a new pre-participation methodology required?*** *Br J Sports Med 2018.* pii: bjsports-2018-099840. doi: 10.1136/bjsports-2018-099840. [Epub ahead of print] **(IF: 7.867; NMS PhD 15.734)**

AUTHOR'S CONTRIBUTIONS

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Table 1. Contributions of the author in all the manuscripts, including the quantification of IF according to the journal and the NMS | FCM regulations.

No.	TYPE	TOPICS	1ST AUTHOR	CO-AUTHOR				IMPACT FACTOR	
				Design	Data acquisition	Statistics	Writing	Journal	NMS PhD*
1	Review	Multiple	X					0.873	1.746
2	**Original**	ECG		X	X	X		19.896	9.948
3	Letter	ECG	X					1.852	3.704
4	**Original**	ECG	X					1.195	2.390
5	**Original**	ECG	X					0.827	1.654
6	**Original**	ECG		X	X	X		4.524	2.262
7	**Original**	ECG	X					0.782	1.564
8	**Original**	Echo				X	X	0.827	0.827
9	**Original**	Echo	X					2.036	4.072
10	Case report	Echo	X					1.186	2.372
11	**Original**	Cardiac CT CV risk			X	X		2.322	1.161
12	**Original**	Cardiac CT CV risk	X					3.319	6.638
13	**Original**	Cardiac CT	X					0.873	1.746
14	**Original**	CV risk		X	X	X	X	1.823	1.823
15	**Original**	Cardiac CT			X	X		0.525	0.263
16	**Original**	Cardiac CT		X	X	X	X	2.322	1.161
17	**Original**	Cardiac CT		X	X	X	X	2.322	1.161
18	Case report	Cardiac CT	X					0.525	1.050
19	Review	Cardiac CT CV risk	X					0.827	1.654
20	**Original**	Cardiac CT	X					*Submitted*	
21	**Original**	Cardiac CT CV risk	X					7.867	15.734
IF OF THE ORIGINAL INVESTIGATIONS								**51.460**	**52.410**
TOTAL IF								**56.723**	**62.930**

*IF according to the regulations of the PhD program in NMS | FCM.

COHERENCE OF RESEARCH

COHERENCE OF RESEARCH

"Good order is the foundation of all things."

Edmund Burke (1729-1797)

INTRODUCTION

The benefits of physical activity and exercise training are well known, being recommended for primary and secondary CV prevention.[1-3] In addition to merely changing the traditional CV risk factors, regular exercise can also improve CV health through non-traditional mechanisms.[4] However, in individuals with some cardiac conditions, even in a pre-clinical stage, exercise can precipitate adverse clinical events including SCD. Exercise, per se, is not a cause of increased mortality, rather, it acts as a trigger for cardiac arrest in the presence of underlying CV diseases predisposing to life-threatening ventricular arrhythmias during or after physical exercise. In this context, the preparticipation evaluation of athletes is advocated, aiming the identification of those with higher risk or even with 'occult' diseases associated with increased risk for SCD.[5]

The epidemiology of SCD varies comparing young and veteran athletes (>35 years old), mainly caused by hereditary cardiac diseases and CAD, respectively.[6] Nevertheless, some discrepancy persists about the incidence and the causes of SCD in athletes, depending on the population studied and the methods used for data collection.[7-12]

In young athletes, the leading causes of SCD are cardiomyopathies and primary arrhythmic diseases, emphasizing the relevance of a detailed clinical history and resting 12-lead ECG. This methodology remains controversial, especially regarding the inclusion of ECG. During the last years, several studies have reported that the main problem is not the inclusion of ECG in this evaluation, but how it should be interpreted. The scope of this controversy is mainly derived from the high rate of false positive cases, leading to a negative socioeconomic impact. The use of more restrictive criteria for ECG interpretation in athletes can potentially overcome this limitation.[13]

Indeed, evaluation and interpretation of the results of several diagnostic tests performed to athletes is somewhat challenging, due to the overlap between physiological adaptations ('athlete's heart') and pathological conditions.[14] This overlap occurs at electrical, structural and functional levels. The actual broad spectrum and heterogeneity of sports modalities and athletes' profiles increases the difficulty of this evaluation.

Albeit not routinely indicated in the preparticipation evaluation, the progressive development of cardiac imaging has led to a better understanding of exercise-induced cardiac adaptations and to the improvement in the diagnosis of pathology.[14] TTE, the most accessible, widespread and cost-effective cardiac imaging test, assumes a central role in athletes' evaluation. Beyond the traditional echocardiographic approach, 'new advanced' modalities can improve the differential diagnosis between 'athlete's heart' and pathology, a common concern during athletes' evaluation.

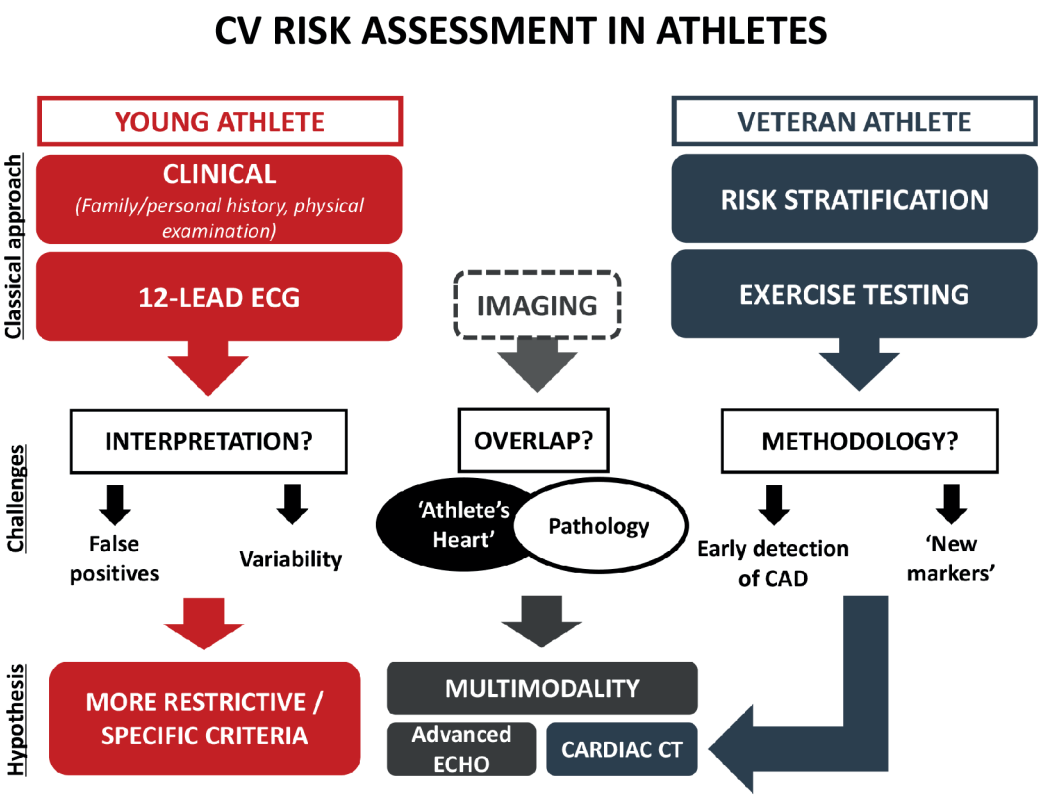
In veteran athletes, as CAD is the main cause of SCD, preparticipation evaluation should be focused on CV risk stratification and early detection of CAD.[2,15,16] With this purpose, exercise testing is traditionally the first test performed. However, the evidence has shown that this methodology has several limitations, both regarding the CV risk stratification limited to clinical characteristics and the performance of exercise testing for detection of CAD in populations with this profile. The inclusion of more objective markers, as parameters derived from imaging tests such as cardiac CT, can potentially increase the accuracy in athletes' evaluation, improving CV risk stratification and early detection of CAD.[17,18]

Otherwise, the relationship between intense lifelong exercise training and CAD has been deeply debated, being suggested a possible 'U-shaped' association between the volume or intensity of exercise and the prevalence and severity of CAD.[19,20] Although remaining speculative, this association may have several implications in the evaluation and risk stratification of veteran athletes, which constitutes a growing subset of individuals, taking in consideration not only competitive but also recreational level. A deeper analysis is needed to clarify this specific issue.

The current investigation provides an analysis of the main aspects related with CV risk assessment in athletes, highlighting several controversial points. The purpose was to study this issue throughout the broad spectrum of athletes, from young to veterans, emphasizing the role of diagnostic tests, mainly ECG, TTE and cardiac CT.

A schematic representation of the classical approach of CV risk assessment in athletes, current challenges and hypothesis that constitute the rational of the studies published are depicted in Figure 1.

Figure 1. Schematic representation of the scientific rational for the present thesis.



This document includes 21 manuscripts, 16 original investigations, 13 as first author, published in a peer-review journals with a total IF of 56.723 and an IF according to the methodology established for PhD in NMS | FCM of 62.930.

The publications are grouped in the following main topics:

1. **ECG IN ATHLETES**
   - Description of abnormal electrocardiographic findings.
   - Effect of exercise-related characteristics in electrocardiographic patterns.
   - Variability in ECG interpretation and impact of more restrictive criteria.

2. **ROLE OF ECHOCARDIOGRAPHY IN ATHLETES**
   - Characterization of cardiac remodelling induced by different exercise training programs.
   - Myocardial deformation in athletes' evaluation.

3. **CARDIAC CT IN CORONARY ATHEROSCLEROTIC BURDEN EVALUATION**
   - Detailed characterization of total coronary atherosclerotic burden.
   - Relevance of CT-derived angiographic scores in CAD evaluation.
   - Limitations of clinical CV risk factors for the detection of CAD.

4. **CAD IN VETERAN ATHLETES**
   - Prevalence of CAD detected by cardiac CT.
   - Relationship between volume of exercise and CAD.
   - Effectiveness of current preparticipation methodology to identify athletes with high coronary atherosclerotic burden.

These interrelated topics about CV risk assessment in athletes were initially discussed in a review manuscript (**MANUSCRIPT 1:** ***The heart of competitive athletes: an up-to-date overview of exercise-induced cardiac adaptations***)[21], representing a general introduction for the following investigations. This first manuscript provides an up-to-date review of exercise-induced physiological cardiac effects and an overview of the key points that should be highlighted during CV assessment of athletes. Understanding these adaptations represents a basic and essential step for an accurate evaluation of athletes.

ELECTROCARDIOGRAM IN ATHLETES

ECG constitutes an important tool in the preparticipation evaluation of athletes, being recommended by several medical and sports organizations.[12] ECG is effective in the detection of several conditions as ion channel diseases or congenital accessory pathways and may raise suspicion for the most frequent cardiomyopathies implicated in SCD.[22] The vast Italian experience showed an 89% reduction in the incidence of SCD in athletes following the inclusion of ECG in the screening programs.[23]

However, some controversy persists regarding the inclusion of ECG during athletes' evaluation, especially between the recommendations adopted in most of European countries and in United States of America, where it is still not formally recommended.

MANUSCRIPT 1[21] includes several arguments for and against the use of ECG in preparticipation evaluation of young competitive athletes. The main obstacle in the interpretation of the athlete's ECG is to distinguish abnormal patterns from physiological findings induced by exercise training, reflected by the high rate of false positive cases. Many findings that may be a cause of concern in the general population are considered normal in athletes. Misinterpretation of athlete's ECG can trigger unnecessary and expensive further investigations or lead to inappropriate disqualification from competitive sports, with a negative socioeconomic implication.[24]

One of the most common abnormal findings present in athlete's ECG is T-wave inversion, frequently challenging and difficult to interpret. There is a general consensus that T-wave inversion in lateral and inferior leads warrants additional investigations due to its association with cardiac diseases, particularly cardiomyopathies. Recently, research from reference centres have suggested that some profiles of T-wave inversion, mainly involving the anterior leads, can be considered as non-pathological in athletes. There are known characteristics responsible for more pronounced adaptations, mainly age and ethnicity, variables to take in consideration during the ECG interpretation.[25-28] For example, convex ('domed') ST-segment elevation, combined with anterior T-wave inversion in leads V1-V4, is frequently described as physiological in Black athletes, representing a specific pattern of early repolarization in this population.[27,28] Otherwise,

the significance of anterior T-wave inversion in Caucasian athletes is less well understood.

To investigate this issue, a cohort of apparently healthy white adults was studied, including a large proportion of athletes (**MANUSCRIPT 2:** ***Anterior T-wave inversion in young white athletes and nonathletes: prevalence and significance***).[29] In this study performed in United Kingdom, a sample of 14646 white adults aged between 16 and 35 years, that underwent cardiac evaluation from 2007 to 2013, was analyzed. Of these individuals, 2958 were competitive athletes involved in multiple sports. The prevalence and the extension of anterior T-wave inversion in resting 12-lead ECG were compared according to the gender and between athletes and non-athletes. All the subjects with anterior T-wave inversion underwent additional investigations to detect the broader phenotypic features of cardiomyopathies (TTE and further tests performed case by case).

As imaging phenotype may arise later than ECG changes and obscure underlying cardiomyopathy, athletes with abnormal repolarization changes and normal structurally hearts should be followed and evaluated with caution.[30,31] In fact, to consider an ECG with marked T-wave inversions as a normal variant, even in the absence of structural abnormalities in the initial imaging evaluation, as advocated and reported in some cases, can be a wrong assumption.[30] A critical analysis of one paradigmatic case report published was briefly discussed (**MANUSCRIPT 3:** ***ECG in athlete: "normal or pathologic variant?"***).[32]

Beyond the influence of demographics, several exercise-related characteristics may induce more pronounced ECG changes. Due to the wide spectrum of sports disciplines, the knowledge of these characteristics is very important during the interpretation of ECG. Integration of this data is frequently difficult, while the conventional dichotomy between endurance or dynamic and static or strength exercise seems simplistic. In fact, many sports combine elements of both types of exercise, and other variables as the level of competition and the intensity of exercise training should be considered. Different types of exercise training induce different hemodynamic changes and different cardiac adaptations, namely at electrical level.

The association between exercise-related characteristics and abnormal ECG findings

were studied in a large sample of competitive athletes (**MANUSCRIPT 4:** ***Abnormal electrocardiographic findings in athletes: correlation with intensity of sport and level of competition***).[33] In this original study, 3423 competitive young athletes (aged between 14 and 35 years) evaluated in a preparticipation screening program were included. Abnormal electrocardiographic findings were categorized according to the Seattle criteria and the 'refined criteria' and compared among four categories of variables: intensity of sport (low or moderate *versus* at least one high static or dynamic component); competitive level (regional *versus* national or international level); training volume (20 or less *versus* more than 20 hours per week); and type of sport (high static *versus* high dynamic component of exercise).

As illustrated in the previous manuscripts, several characteristics can influence the findings present in the athlete's ECG, being frequently challenging to provide a differential diagnosis between physiological adaptations and pathology. In consequence, even when experienced physicians interpret the ECG according to the current standards, there is a significant inter-observer variability that results in false-positive and false-negative results.[34-36]

The degree of variation and the accuracy in interpretation of the ECG in athletes in Portugal was unknown, leading to an original study included in this document (**MANUSCRIPT 5:** ***Variability in interpretation of the electrocardiogram in athletes: another limitation in pre-competitive screening***).[37] In this study, 20 ECGs of competitive athletes (9 confirmed as pathological) were interpreted by 58 physicians (42 cardiologists) and classified as non-pathological or pathological. Information related with demographics and the respective sports was provided, while the experience of physicians in the evaluation of athletes and the criteria used for ECG interpretation were registered. The variability in the interpretation of ECGs and the reproducibility of the study were assessed.

On the same line, aiming to investigate the degree of variation in ECG interpretation among cardiologists with different experience and the financial implications of interpretation using different criteria, other original study was performed (**MANUSCRIPT 6:** ***Inter-rater reliability and downstream financial implications of electrocardiography screening in young athletes***).[38] Eight cardiologists, four with experience in screening athletes,

reported 400 ECGs of consecutively screened young athletes, according to the 2010 ESC recommendations, Seattle criteria and 'refined criteria'.[39-41] Additionally, the physicians proposed secondary investigations after traces interpretation, which the costs were calculated based on the United Kingdom National Health Service tariff payment system, allowing a financial analysis.

To overcome some of the limitations discussed in the previously manuscripts, it is of utmost importance to improve the accuracy in ECG interpretation in athletes. A measure that may have a positive impact in the reduction of false positive cases is the application of more restrictive criteria. In this setting, as already cited, various specific criteria, progressively more restrictive, have been published in the last years.[39-42]

A comparison of the main criteria - 2010 ESC recommendations, Seattle criteria and 'refined criteria',[39-41] was performed in a young military cohort (**MANUSCRIPT 7:** ***Comparison of three criteria for interpretation of electrocardiogram in athletes***).[43] In this study, 1380 consecutive healthy young military of the Portuguese Armed Forces (Army, Navy and Air Force), with a training of at least 4 hours per week, 18% concomitantly involved in competitive sport, were prospectively included. Individuals with CV symptoms and established diagnosis of cardiac disease were excluded from this analysis. ECGs were interpreted and classified as normal, with physiological or abnormal changes using the three criteria and the rate of false positives cases was compared. The individuals with the ECGs classified as abnormal by any of the criteria used were referred for evaluation in a sports cardiology clinic and further investigations were performed accordingly.

ROLE OF ECHOCARDIOGRAPHY IN ATHLETES

Although not routinely recommended in preparticipation evaluation, TTE is frequently performed in some sports and before specific competitions, mainly in high level athletes or in military of the special forces. Otherwise, in athletes with symptoms, abnormalities in physical examination, pathological findings in ECG and findings in the 'grey zone' between physiological adaptations and abnormal changes, TTE constitutes the first-line imaging test.

Regular exercise training prompts complex cardiac remodelling to accommodate a state of enhanced CV performance.[44] The advent of echocardiography provided a non-invasive assessment of structural and functional adaptations, a constellation of changes traditionally known as 'athlete´s heart'. Globally, physiological adaptations are characterized by an homogeneous chamber enlargement and an increased mass and wall thickness, mainly involving the LV.[45] As for electrical adaptations, several demographic and exercise-related factors are associated with more pronounced structural remodelling.[46-49] The recognition of these characteristics and its integration with the data derived from additional investigations is essential for a better clarification of the cardiac morphology and function in athletes.

Although the Morganroth hypothesis postulates that strength exercise induces concentric LVH due to pressure overload and endurance exercise induces eccentric LVH due to volume overload, it is currently known that most sports share both types of exercise, leading to a mixed remodeling.[50-53] Additionally, LV remodelling seems to follow a phasic response with increase of chamber size in an acute phase and wall thickness in a chronic phase of exercise training.[54] In fact, TTE assumes an important role in the evaluation and characterization of the complex relationship between these variables and subsequent structural phenotypes.

In this context, the effect of different exercise training programs in cardiac remodeling was prospectively investigated in two populations - competitive athletes and special operation forces soldiers (**MANUSCRIPT 8:** ***Exercise-induced cardiac remodeling in athletes and in special forces soldiers***).[55] In this original study, 17 soldiers who entered and finished a special operation forces course, and 17 basketball players, were evaluated at the beginning and at the end of the military course and the sport season, respectively. The structural and functional cardiac adaptations were analyzed and compared in the two periods and between both populations. Beyond the conventional TTE modalities, myocardial deformation was also evaluated.

The distinction between physiological adaptations and cardiomyopathies remain a major challenge in the evaluation of athletes, especially when they fall in the morphological 'grey zone'. Advanced and specific echocardiographic modalities, as the

analysis of LV myocardial deformation with 2D-speckle tracking and exercise echocardiography, can improve this evaluation.[56-62]

In consequence of the previous study, in which GLS seemed to have a specific pattern in subjects undergoing intense exercise training, this issue deserved further investigation. The normal values of GLS in athletes are not established, while its relationship with different characteristics of exercise training and other echocardiographic parameters is weakly understood. For this purpose, we decided to study LV GLS profile in athletes with different intensities of exercise training in an original investigation (**MANUSCRIPT 9:** ***Myocardial deformation and volume of exercise: a new overlap between pathology and athlete's heart?***).[63] Consecutive young athletes (< 35 years old) involved in endurance sports characterized by high intensity dynamic component were enrolled. According to the training regimens, namely the level and the number of exercise training hours per week, a surrogate measure of exercise volume, two groups were defined: Group 1 (N=60) - high intensity (≥20 training-hours per week); Group 2 (N=48) - low intensity (<10 training-hours per week). All athletes had previously a clinical evaluation (detailed personal and family history, physical examination and resting 12-lead ECG) and the ones considered eligible performed a comprehensive TTE, before the competitive season. Positive personal or family history for CV disease, known CV risk factors, cardiac symptoms, positive findings in physical examination, abnormal changes in ECG, use of enhancing performance substances and TTE with inadequate image quality were exclusion criteria. TTE included the evaluation of LV GLS assessed by 2D-speckle-tracking, being compared between the two groups. GLS was correlated with other echocardiographic parameters and the independent predictors of abnormal GLS, defined as a value lower than 17%, were determined.

The functional assessment at rest complemented by exercise echocardiography may be the clue for a better clarification of several conditions, mainly in the evaluation of athletes with symptoms induced or exacerbated by exercise.[14] Exercise echocardiography can be useful, allowing the detection of specific conditions as the presence of intraventricular gradient, illustrated in a case report published (**MANUSCRIPT 10:** ***Symptomatic exercise-induced intraventricular gradient in competitive athlete***).[64]

CARDIAC CT IN CORONARY ATHEROSCLEROTIC BURDEN EVALUATION

CAD is the leading cause of SCD in veteran athletes, with a percentage that can go up to 80% of the cases.[5] As the majority of sports-related deaths occurs in older athletes and many cases are unwitnessed, the magnitude of the problem is probably underestimated.[15] This epidemiology justifies different methodologies in the preparticipation evaluation according to the age range of the athletes. Additionally, the huge number of middle-aged individuals engaged in leisure sports makes their evaluation very important, aiming to rule out CAD.

However, the methodology for CV risk stratification and detection of subclinical CAD is controversial, not only in athletes but also in the general population, in particular regarding the most appropriate exam to choose. One of the most promising exams for this purpose, with potential to be applied in veteran athletes, is cardiac CT, due to its ability to provide a non-invasive evaluation of the total coronary atherosclerotic burden (both obstructive and nonobstructive).

Several preliminary studies were initially performed in the general population to evaluate the efficacy of cardiac CT for coronary atherosclerotic burden evaluation and to test some CT angiographic scores.

CV risk stratification is recommended to identify individuals with increased risk for CV events that can benefit of early implementation of preventive and therapeutic measures.[2] CV risk results from multiple, interacting factors, and from a clinical perspective it has been recommended the used of the SCORE risk charts, that integrates clinical characteristics and estimates the 10-year risk for fatal CV disease.[65] The prognostic value of this strategy based on clinical risk factors, isolated or integrated in scores, has been widely recomended.[66,67] Although this evidence, the association of clinical risk factors with the presence and extension of coronary atherosclerosis is sometimes controversial.

The development of cardiac CT and its progressive adoption in clinical practice has led to a better characterization of this relationship. Cardiac CT can be very useful in CV risk

stratification, providing a non-invasive evaluation of the coronary atherosclerotic burden in populations with low to moderate risk.

Additionally, it was recently showed that in patients referred for the assessment of stable chest pain, the use of CCTA was associated with a lower subsequent risk of death from coronary heart disease or nonfatal myocardial infarction than standard care alone.[68]

Among the classical clinical CV risk factors, diabetes has a paradigmatic association with CAD. The coronary atherosclerotic burden and severity of CAD evaluated by CCTA in diabetic patients was the scope of one original manuscript included in this investigation (**MANUSCRIPT 11**: ***Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited***).[69] A detailed characterization of the coronary atherosclerotic burden, including localization, degree of stenosis and plaque composition, was evaluated by cardiac CT in 581 consecutive stable patients and compared according to the presence of diabetes.

At the same time, regarding other clinical characteristics as obesity and overweight, the association with atherosclerotic burden and CAD is more conflicting, being even described an 'obesity paradox'.[70-75] The relationship between body mass index and the presence and severity of CAD documented by cardiac CT was evaluated in 1706 consecutive stable patients (**MANUSCRIPT 12:** ***Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac-CT***).[76]

CV risk stratification limited to clinical characteristics has a modest predictive accuracy and fails to identify a significant number of individuals with established CAD.[77-79] Consequently, the performance of traditional CV risk factors in identifying a higher than expected coronary atherosclerotic burden was investigated in a population of 2069 patients undergoing cardiac CT for suspected CAD (**MANUSCRIPT 13:** ***Performance of traditional risk factors in identifying a higher than expected coronary atherosclerotic burden***).[80] The ability of the traditional CV risk factors to predict a higher than expected atherosclerotic burden, defined as CAC score >75th percentile according to age and gender-adjusted monograms, was assessed in a customized logistic regression model and by the

calculation of SCORE. The population attributable risk of CV risk factors for CAC score >75th percentile was calculated.

In other original study, the performance of the SCORE to estimate CV risk in a population of 1628 patients presenting with ST-elevation myocardial infarction as the first manifestation of CAD was evaluated. The SCORE risk would classify as low risk more than two-thirds of the STEMI patients before the event, underlying the need for additional tools to better identify individuals at risk (**MANUSCRIPT 14:** ***Low previous cardiovascular risk of patients with ST-elevation myocardial infarction***).[81]

Since the rupture of non-obstructive coronary plaques is a common mechanism involved in acute coronary syndromes, the inclusion of more comprehensive evaluation of both obstructive and nonobstructive CAD, plaque location and composition (calcified, non-calcified and mixed) reflects more closely the true pathophysiological process in the coronary arteries beyond the simplistic clinical risk factors approach and will certainly lead to a refined coronary risk assessment.[82-84] In this line, several markers and scores mainly derived from cardiac CT have been studied to overcome the limitations of clinical characteristics in CV risk stratification and detection of CAD.

The radiation dose of cardiac CT is the main limitation associated with this exam, but can be reduced with the use of appropriate protocols and has in fact seen impressive reductions in recent years, both due to software (new protocols) and also hardware (newer generation scanners).[85] Since this is an important issue if cardiac CT is to be considered for CV risk screening in the future, we decided to study the factors associated with radiation dose and how it compares with other cardiac exams that use ionizing radiation. In this study, the mean dose of radiation was compared among 6196 patients that underwent cardiac CT, single photon emission CT or invasive coronary angiography, as their evolution over the time (**MANUSCRIPT 15:** ***Effective radiation dose of three diagnostic tests in cardiology: single photon emission computed tomography, invasive coronary angiography and cardiac computed tomography angiography***).[86]

CAC score has a superior value in discrimination and reclassification of CV risk in intermediate-risk individuals.[87-93] On the other hand, CCTA provides a more

comprehensive evaluation on both calcified and noncalcified plaques, better lesion location and also the degree of stenosis, all variables that carry prognostic value.

Our group developed and validated a coronary atherosclerotic burden score – the CT-Leaman score, that takes in consideration all this information (plaque location, degree of stenosis and plaque composition) (**MANUSCRIPT 16:** ***Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden***).[94] In this manuscript we describe the cardiac CT-adapted Leaman score as a tool to quantify total coronary atherosclerotic burden with information regarding localization, type of plaque, degree of stenosis and to identify clinical predictors of a high coronary atherosclerotic burden. For this purpose, 581 stable patients referred for suspected CAD were included. Pre-test CAD probability was determined using both the Diamond–Forrester extended CAD consortium method and the Morise score, while CV risk was assessed with the SCORE. Beyond obstructive CAD, non-obstructive plaques have significant prognostic impact reinforcing the role of cardiac CT for coronary risk assesment.[95,96]

Some patients referred for cardiac CT might have a CAC score of zero. In those patients there are some doubts if the additional information provided by contrast enhanced exam is worthy of the additional cost and radiation burden of CT angiography. To answer this question, we decided to evaluate the prevalence of CAD in individuals with a CAC score of zero (**MANUSCRIPT 17:** ***Prevalence and predictors of coronary artery disease in patients with a calcium score of zero***).[97]

The experience acquired and the results shown in these studies with cardiac CT, namely the high negative predictive value to exclude CAD, the ability to noninvasively provide information on the total coronary atherosclerotic burden, the progressive reductions achieved in radiation dose on one hand, and also the limitations of CV risk stratification based on clinical characteristics alone, on the other hand, were the basis to study the coronary atherosclerotic burden of veteran athletes using this exam.

CORONARY ARTERY DISEASE IN VETERAN ATHLETES

Due to the development and widespread of CV imaging tests, namely cardiac CT, several studies have reported a higher than expected incidence of CAD in veteran athletes. One manuscript included depicts an illustrative case report of an extreme intensity exercise (ironman) athlete with low CV risk, normal ECG and exercise testing, but with extensive non-obstructive CAD in CCTA (**MANUSCRIPT 18:** ***Non-obstructive coronary artery disease documented by cardiac computed tomography: Discrepancy between atherosclerotic burden and cardiovascular risk***).[98]

As documented in the previous manuscripts, cardiac CT provides early detection of CAD, frequently not possible with exercise testing, the most requested investigation for CV risk stratification in veteran athletes. Although some studies had described more frequent coronary plaques in athletes than controls, their stable nature could mitigate the risk of plaque rupture.[99] Additionally, it has been shown a potential 'U-shaped' relationship between the dose of exercise and the presence and severity of CAD.[100-102] This association between CAD and exercise training is controversial and was deeply discussed in a review manuscript (**MANUSCRIPT 19:** ***Coronary artery disease in athletes: an adverse effect of intense exercise?***).[103]

Although some exercise-related factors may be potentially involved, several questions remain unanswered regarding this relationship: 1) methodological inconsistences in the studies published, with different heterogeneity in baseline characteristics and inclusion criteria, samples mainly composed by high-level athletes and involved in endurance sports, not reflecting the wide spectrum of athletes and sports modalities; 2) it is not possible to establish if exercise is associated with accelerated CAD or if represents a protector factor for CAD in individuals with intrinsic high risk; 3) it is not possible to ensure the influence of unmeasurable variables as genetic characteristics, performance enhancing substances abuse or existence of other 'occult' risk factors.[15]

In this setting, we undertook an original study aiming to characterize the coronary atherosclerotic burden by cardiac CT in veteran athletes with low to intermediate CV risk, predominantly involved in recreational sports, to evaluate its relationship with

evaluation (**MANUSCRIPT 20:** ***Coronary atherosclerotic burden in recreational male veteran athletes with low to intermediate cardiovascular risk***).[104] A total of 105 male veteran athletes aged ≥40 years old, training ≥4 hours per week during at least the last 5 years, were enrolled in this analytical, observational, prospective and multicentric cohort study. Among the exclusion criteria were the presence of symptoms, diabetes mellitus and a SCORE ≥5%. All the individuals were evaluated in a dedicated sports cardiology clinic, with a deep clinical history (personal and family) and physical examination, and performed additional tests (12-lead rest ECG, blood tests, TTE and exercise testing). The volume of exercise was calculated by Metabolic Equivalent Task Score (MET-hour per week - product of intensity, frequency and duration), being analysed by absolute values and tertiles. CAD was evaluated by cardiac CT (CAC score and CCTA), being registered several characteristics, such as the presence, degree of stenosis, localization and type of coronary plaques. Several cardiac CT scores validated in other populations, as the Segment Involvement Score and CT-Leaman score, were employed. A high atherosclerotic burden was defined as the combination of: 1) CAC score >100 Agatston units; 2) CAC score ≥75th percentile; 3) obstructive CAD (stenosis ≥50%); 4) disease in left main, three vessels or two vessels involving the proximal anterior descending artery; 5) segment involvement score >5; 6) CT-adapted Leaman score ≥5. Several exercise-related characteristics were correlated with the findings of cardiac CT.

Using the same sample of veteran athletes, a second study was performed (**MANUSCRIPT 21:** ***Subclinical coronary artery disease in veteran athletes: is a new pre-participation methodology required?***)[105], with the purpose to evaluate the effectiveness of current preparticipation methodology (clinical risk factors and exercise testing) in the identification of athletes with high coronary atherosclerotic burden. The hypothesis was that conventional CV risk assessment had a low sensitivity for the detection of CAD in veteran athletes, which might be improved by the addition of data derived from cardiac CT. The presence of CV risk factors (isolated and integrated in SCORE) and significant findings in exercise testing were correlated with the presence of a high coronary atherosclerotic burden determined by cardiac CT.

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REVIEW ARTICLE

The hearts of competitive athletes: An up-to-date overview of exercise-induced cardiac adaptations

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KEYWORDS
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Abstract Intense and regular physical exercise is responsible for various cardiac changes (electrical, structural and functional) that represent physiological adaptation to exercise training. This remodeling, commonly referred to as 'athlete's heart', can overlap with several pathological entities, in which sudden cardiac death may be the first clinical presentation. Although pre-competitive screening can identify athletes with life-threatening cardiovascular abnormalities, there are no widely used standardized pre-participation programs and those currently implemented are controversial. Data from personal and family history, features of physical examination and changes in the 12-lead electrocardiogram can raise the suspicion of cardiac disease and lead to early detection of entities such as hypertrophic cardiomyopathy. However, interpreting the electrocardiogram is often challenging, because some changes are considered physiological in athletes. Thus, clinical decision-making in such cases can prove difficult: missing a condition associated with an increased risk of life-threatening events, or conversely, mislabeling an athlete with a disease that leads to unnecessary disqualification, are both situations to avoid. This paper provides an up-to-date review of the physiological cardiac effects of exercise training and highlights key points that should be taken into consideration in the assessment of young competitive athletes.

PALAVRAS-CHAVE
Coração de atleta;
Adaptação fisiológica;

O coração dos atletas – revisão e atualização das adaptações cardíacas induzidas pelo exercício

Resumo A prática intensa e regular de exercício físico é responsável por diversas alterações cardíacas, desde eléctricas, estruturais ou funcionais, que representam adaptações

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MANUSCRIPT 1

Morte súbita;
Rastreio

fisiológicas ao exercício. Esta remodelagem, frequentemente denominada por coração de atleta, pode mimetizar alterações típicas de diversas patologias, nas quais a morte súbita pode ser a primeira apresentação clínica. Apesar do rastreio pré-competição poder identificar atletas com alterações cardíacas potencialmente fatais, os programas de rastreio não estão estandardizados e aqueles já implementados permanecem controversos. Dados da história clínica pessoal e familiar, achados do exame físico e alterações no eletrocardiograma de 12 derivações, podem aumentar a suspeita de doença cardíaca e levar à deteção precoce de entidades como a miocardiopatia hipertrófica. Contudo, a interpretação do eletrocardiograma é frequentemente desafiante porque várias alterações são consideradas fisiológicas em atletas. Assim, as decisões clínicas são por vezes difíceis: não diagnóstico de condições associadas a um risco aumentado de eventos fatais, ou por outro lado, o diagnóstico errado de patologia cardíaca em atletas saudáveis pode originar a realização de exames de diagnóstico desnecessários ou a desqualificação inapropriada do atleta. Este artigo fornece uma revisão atualizada dos efeitos cardíacos fisiológicos do exercício físico e realça pontos-chave que deverão ser tidos em consideração na avaliação de atletas jovens de competição.

Introduction

A sedentary lifestyle is associated with the development of cardiovascular (CV) risk factors, progression of coronary disease and occurrence of adverse clinical events.[1,2] Health promotion efforts aimed at CV disease prevention, emphasizing physical activity, have led to increased participation in recreational and competitive sport.[3] However, cases of sudden cardiac death (SCD) among athletes continue to raise concerns regarding the safety of exercise. A higher risk of coronary events and malignant arrhythmias during vigorous exercise has been described (the so-called exercise paradox), but the incidence of exercise-related cardiac arrest in individuals aged under 35 years has recently been shown to be low.[4,5] Nonetheless, some doubts persist regarding the impact of prolonged and intense exercise training. In a study of 102 marathon runners, 12% had myocardial scarring on cardiac magnetic resonance imaging (MRI) with variable patterns (ischemic and non-ischemic), a finding three times more common than in age-matched controls.[6] The role of exercise-induced fibrosis as arrhythmogenic substrate is as yet poorly understood. Some authors argue that a high volume of endurance exercise is responsible for adverse CV effects and that there may be a upper limit beyond which the adverse effects outweigh the benefits.[7]

Exercise training induces a constellation of physiological CV adaptations. The first descriptions of heart enlargement in athletes date to the 1890s, when increased cardiac size was demonstrated with chest auscultation and percussion in Nordic skiers and university runners.[8,9] In the 1940s, a higher prevalence of resting sinus bradycardia was reported among Boston marathon runners.[10] Nearly four decades later, in 1975, with the development of M-mode echocardiography, Morganroth described different left ventricular (LV) remodeling according to the type of exercise: concentric hypertrophy for strength and eccentric for endurance exercise,[11] an observation that came to be known as the 'Morganroth hypothesis'. However, with the increasing numbers of athletes being assessed, along with the development of cardiac imaging and the growth of published data in sports cardiology, it has been ascertained that other factors influence cardiac remodeling.

Early identification of athletes at higher risk of SCD is a cornerstone of screening. A wrong diagnosis could have serious adverse consequences: under-diagnosis of pathology may lead to life-threatening events being missed, and over-diagnosis may result in unnecessary disqualification. The ideal balance has not been struck, and the cost-effectiveness of current screening programs remains controversial. While a clinical history and physical examination are consensual, the same is not true for the electrocardiogram (ECG). Electrical and structural cardiac remodeling can induce ECG changes considered normal in athletes but pathological in non-athletes. Standardization of ECG interpretation in athletes could reduce the rate of false positives and the need for further investigations.

This paper provides an up-to-date review of exercise-induced physiological cardiac effects and an overview of the key points that should be highlighted in the assessment of athletes.

Molecular mechanisms and physiology of exercise

Several complex mechanisms have been postulated to account for the beneficial effects of physical activity. Continuous exercise training decreases myocardial oxygen demand, improves myocardial perfusion, promotes an antithrombotic environment, balances the autonomic system and prevents the development of CV risk factors such as hypertension, dyslipidemia, obesity and diabetes.[3,12–15] At the molecular level, exercise enhances antioxidant capacity,

MANUSCRIPT 1

induces myocardial heat shock proteins, and increases nitric oxide production and anti-apoptotic protection.[15,16] Transient myocardial ischemia during regular bouts of exercise increases tolerance to subsequent ischemic stress, limiting ischemia-reperfusion injury and reducing the risk of lethal arrhythmias, a mechanism known as myocardial ischemic preconditioning.[16,17]

Physiological adaptations to exercise include a complex network of mechanisms (structural, neurohumoral, autonomic, metabolic and regulatory), which increase cardiac output.[15] During exertion, increased skeletal muscle blood flow and oxygen extraction can raise cardiac output up to six times above baseline levels. The autonomic nervous system is involved in this process through parasympathetic withdrawal and sympathetic activation.[17] Increased stroke volume results from increased ventricular end-diastolic volume and, to a lesser degree, from sympathetically-mediated reduction in end-systolic volume.[18] By contrast, maximum heart rate does not significantly increase with regular exercise training.[19] Post-exercise hemodynamics returns to baseline with vagal reactivation, a process that is enhanced in highly trained athletes.[17] The effects of prolonged exercise on the right ventricle (RV) and left ventricle (LV) are different. During exercise there is a marked biventricular increase in cardiac output, but the decrease in vascular resistance is less pronounced in the pulmonary circulation. This mismatch between increased flow and vasodilation may result in an abnormal increase in pulmonary artery pressure and RV afterload, with a marked increase in RV workload. La Gerche et al.[20] showed that RV volumes increase after endurance races, whereas LV volumes decrease, resulting in decreased RV but not LV ejection fraction (LVEF). Although short-term recovery appears to be complete, the long-term clinical significance of these changes is unknown.

Factors influencing cardiac adaptations to exercise training

Several factors, especially demographic and sport-related, are associated with more pronounced cardiac remodeling (Figure 1).

Age

Although most studies are on adult athletes (18–35 years old), cardiac adaptation is also evident in the younger population. A higher prevalence of ECG changes including LV hypertrophy, left atrial (LA) and right atrial (RA) enlargement, was shown in 1000 junior athletes compared with non-athletic controls.[21] Some changes reflect normal variations at specific ages, such as the juvenile ECG pattern in individuals aged under 16. In a study of 1050 athletes (9–55 years old), those under 20 had significantly more ECG changes.[22] Trained adolescents showed greater LV wall thickness (LVWT) than non-athletes.[23] The range of LVWT differed between adolescent and adult athletes, with an upper limit of 16 mm in adults and 14 mm in adolescents, and LVWT >12 mm in ≈2% and 0.5% respectively.[23,24] This suggests that LVWT limits should be lower in younger athletes. Less skeletal muscle mass, lower accumulated training, lack of testosterone before puberty and lower catecholamine

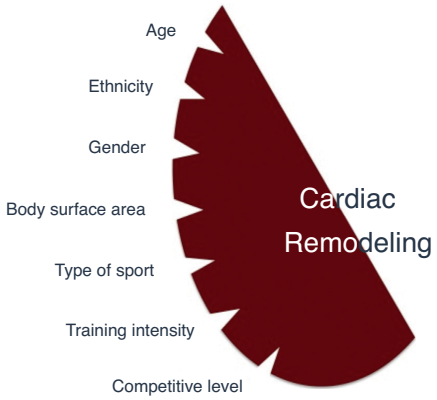

Figure 1 Factors influencing cardiac remodeling in competitive athletes.

responses to exercise in young athletes may help account for these differences. Many children are involved in intensely competitive activities early in life, but the effects of exercise training in very young athletes are unknown. Conversely, athletes are increasingly competing at older ages, and the impact of lifelong exercise training in veteran athletes is yet to be ascertained.

Gender

Cardiac remodeling is more pronounced among male athletes. Pelliccia et al. showed 23% lower LVWT and 11% smaller LV size in female compared to male athletes with similar age and training intensity.[25] In this study no female had LVWT >12 mm. Sharma et al. showed similar findings in adolescent athletes (11% lower LVWT and 6% smaller LV size in females).[25] Almost 5% of male athletes had LVWT ≥12 mm, but no females had LVWT >11 mm. Physiological ECG changes are also more frequent in male athletes.[23] It should also be noted that a greater proportion of males are involved in extreme endurance and competitive sports, and hormonal factors may explain the gender-specific differences in these studies.

Ethnicity

Black (Afro-Caribbean) athletes exhibit more pronounced cardiac remodeling than their white counterparts. Basavarajaiah et al. reported LVWT >12 mm in 18% black male athletes compared to 4% in white male athletes.[26] Additionally, 3% of the black athletes, but none of the whites, exhibited LVWT ≥15 mm. The predominance of physiological remodeling in black athletes is not restricted to male gender. Rawlins et al. showed LVWT >12 mm in 3.3% black female athletes (all 12–13 mm), but none of their white counterparts had LVWT >11 mm.[27] The prevalence of ECG abnormalities is also gender-dependent in athletes under 17 years of age.[27–29] This ethnic discrepancy can be explained by differences in blood pressure modulation,[30] endothelial function,[31] arterial stiffness,[32] angiotensin-converting

MANUSCRIPT 1

enzyme gene I/D polymorphisms[33] and insulin-like growth factor-1 expression.[34]

Sport-related factors

Hemodynamic and cardiac adaptations vary according to the type and intensity of exercise. Isotonic exercise, also referred to as endurance or dynamic exercise, increases maximum oxygen consumption and cardiac output, with normal or reduced peripheral vascular resistance. In sports such as cross-country skiing, long-distance running, tennis or soccer, volume overload is predominant. In contrast, isometric exercise, also known as strength or static exercises, substantially increases blood pressure and peripheral vascular resistance, with normal or only slightly elevated cardiac output. Sports such as climbing, gymnastics, wrestling and body-building predominantly produce pressure overload. Endurance sports generally induce more pronounced cardiac remodeling. However, sports cannot be classified simply on the basis of this dichotomy. Many disciplines combine elements of both endurance and strength exercise, and it can be difficult to identify the predominant component. Mitchell et al. proposed a classification of sports according to the intensity of exercise in static and dynamic components[35] (Figure 2). Although widely used, this classification has some limitations. Factors such as emotional stress during competition and environmental conditions were not considered. Emotional stress activates the sympathetic drive, leading to increased catecholamine concentrations, heart rate, blood pressure and myocardial contractility. These responses increase myocardial oxygen demand, potentially triggering arrhythmias and myocardial ischemia. Thus, during competition, sports associated with low myocardial oxygen demand relative to the exercise required (e.g. golf or billiards) can be associated with higher emotional stress. Environmental factors such as altitude, temperature, humidity and air pollution are responsible for different myocardial workloads, and should also be considered. Some sports have specific risks that should be borne in mind, such as those involving physical contact or projectiles (risk of commotio cordis) or those involving high velocity (risk of vertebral artery dissection due to abrupt head hyperextension).

Structural adaptations

Since the first reports by Morganroth et al.,[11] several studies have shown a direct relationship between exercise training and cardiac structural remodeling (Table 1). Compared to non-athletes, athletes have 15–20% greater LVWT and 10–15% greater LV size. In a landmark study of 1309 Italian athletes engaged in 38 sports, 45% had LV end-diastolic diameter ≥55 mm (≥60 mm in 14%).[36] A markedly dilated LV was more common in athletes with a larger body surface area and in those participating in endurance sports (cycling, cross-country skiing, and rowing/canoeing). Indexed LV mass exceeded the upper limits in 9% of male and 7% of female athletes. Another study of 286 professional cyclists revealed a dilated LV in 35%, even after adjustment for body surface area.[37] Regarding LVWT, Italian studies showed LVWT >12 mm in a small percentage of elite athletes (1.1%–1.7%),[23,36] with concomitant LV dilation. It should be emphasized that LVWT >13 mm and LV dimensions >65 mm are rare in healthy athletes. Analysis of these studies raises some concerns: they were cross-sectional in design and included mainly white male athletes; they were performed during competitive seasons, used M-mode or two-dimensional echocardiography, and controls were age- and gender-matched sedentary individuals.

Although broadly accepted, the validity of the Morganroth hypothesis is questioned by some authors.[38] Spence et al. prospectively analyzed untrained subjects randomized to supervised endurance (n=10) or resistance (n=13) exercise, with assessments at baseline, after six months of training and six weeks after detraining.[39] LV adaptation, including increased LV mass and LVWT, were only present in endurance athletes. Despite the small sample and relatively short training period, these results cast some doubt on the importance of remodeling in response to resistance exercise training.

LA dilation is also a physiological adaptation in trained athletes. Pelliccia et al. reported a 20% increase in LA dimensions (M-mode transverse dimension ≥40 mm) among 1777 athletes engaged in 38 disciplines,[40] while D'Andrea et al. showed a 28% increase in indexed LA volume in 615 endurance athletes.[41] The increased LA size can be explained by concomitant LV cavity enlargement and volume overload. Although not completely understood, LA remodeling may be one of the mechanisms associated with supraventricular arrhythmias in athletes.

Due to its unusual shape, which makes it more difficult to image, the effects of exercise on RV structure have been neglected. The RV also enlarges in response to continuous exercise training, supporting the concept of balanced biventricular enlargement.[42] Zaidi et al. confirmed greater RV dimensions in athletes compared to non-athletes, with smaller dimensions in black athletes.[43] MRI studies have confirmed RV enlargement, mainly in endurance athletes.[44]

The association of exercise and aortic root dilation is inconsistent. The largest study published (n=2317) showed that dilated aortic root is uncommon among competitive athletes: ≥40 mm in 1.3% of males and ≥34 mm in 0.9% of females (99th percentiles).[45] Dilatation of the aortic root is unlikely to represent a physiological adaptation, and is most likely an expression of pathology. The observation of a 2.5-fold increase in the aortic root over eight years of follow-up in male athletes with enlarged aortic root at initial assessment supports this fact. Other small studies report greater diameters in strength- compared to endurance-trained athletes, but also with a low prevalence of dilated aortic root.[46,47]

Functional adaptation

Functional physiological adaptations to exercise training are incompletely understood. LVEF is generally normal among athletes. Even extreme and uninterrupted endurance training over long periods of time appears not to be associated with deterioration in LVEF.[48] A meta-analysis of 59 studies showed no difference in systolic and diastolic LV function among trained athletes compared with sedentary controls.[49] However, a transient reduction in LVEF has been

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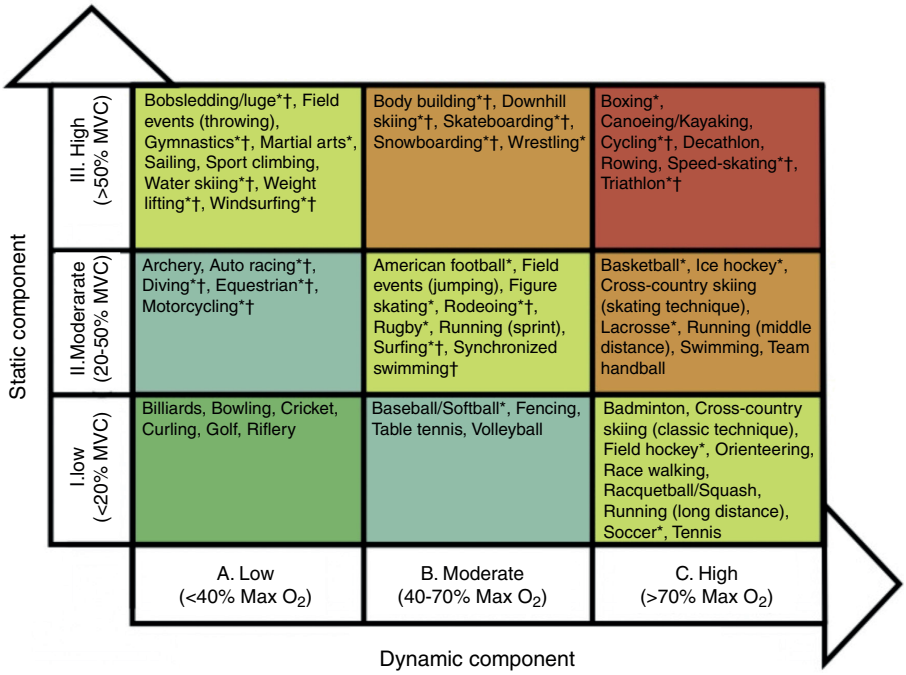

Figure 2 Sports classification based on peak static and dynamic components achieved during competition. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in green and the highest in red. Max O_2: maximal oxygen uptake; MVC: maximal voluntary contraction. *Danger of bodily collision. †Increased risk if syncope occurs (adapted from Mitchell et al. in the report of the 36th Bethesda Conference[35]).

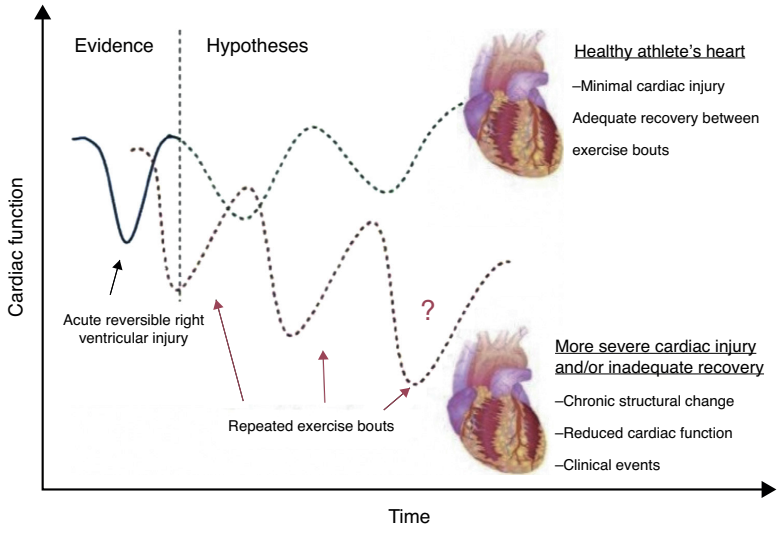

Figure 3 Potential effects of repeated exercise bouts on RV function.

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Table 1 Data of studies reporting left ventricular dimensions in athletes.

Study	n	Sport	Age (y)	Male (%)	Ethnicity	LVEDD	LVWT
Pelliccia et al.[23]	947	Multi (25)	22 ± 3	78	–	≥55 mm: 38% ≥60 mm: 4% Male: 54.2±4.0 mm (40–66) Female: 48.4±3.7 mm (40–61)	>12 mm: 1.7% Male: 10.1±1.2 mm (7–16) Female: 8.4±0.9 mm (6–11)
Pelliccia et al.[36]	1309	Multi (39)	24 ± 6	73	–	≥55 mm: 45% ≥60 mm: 14% Male: 55.5±4.3 mm (43–70) Female: 48.4±4.2 mm (38–66)	>12 mm: 1.1% Mean: 9.3±1.4 mm (5–15)
Sharma et al.[23]	720	Multi (13)	16 ± 1	75	White (98%)	Male: 51.6±3.3 mm (42–60) Female: 47.7±3.3 mm (41–55)	≥12 mm: 4% Mean: 9.5±1.7 mm (6–14)
Abergel et al.[37]	286	Cycling	28 ± 3	100	White	>60 mm: 51% Mean: 60.1±3.9 mm (49–73)	>13 mm: 8.7% Mean: 11.1±1.3 mm (7–15)
Di Paolo et al.[29]	154	Soccer	16 ± 1	100	Black	>54 mm: 16% >60 mm: 0.6% Mean: 51.0±3.6 mm (42–62)	>12 mm: 2.6% Mean: 10±1 mm (6–13)
Basavarajaiah et al.[26]	300	Multi (6)	21 ± 6	100	Black	Mean: 53±4.4 mm (44–64)	>12 mm 18% Mean: 11.3±1.6 mm (8–16)

LVEDD: left ventricular end-diastolic diameter; LVWT: left ventricular wall thickness; Multi: multiple; y: years.

demonstrated after prolonged strenuous exercise, termed 'cardiac fatigue'.[50] The interpretation of these changes as physiological is not consensual. Some authors have questioned the real effects of competitive exercise on LV dynamics, particularly after prolonged endurance training, as reported in cyclists.[37] The reduction of LVEF in endurance athletes is secondary to LV dilation, but performance-enhancing drugs could be involved. Nevertheless it should be stressed that indices of systolic function are of limited value in the assessment of ventricular performance at rest (due to the load dependence of LVEF and the fact that Doppler indices are only recorded in the systolic phase). New advances in echocardiography, including strain imaging and speckle tracking, suggest that intense exercise may lead to changes in LV systolic function that are not detected by LVEF assessment. These tools are more sensitive in assessing systolic adaptations to exercise, and hence allow early detection of systolic impairment.[42,44,51] Baggish et al. found unchanged LVEF in 20 rowers after 90 days of training, but significant changes in all the direct measures of LV systolic function[73]: peak systolic tissue velocities increased; radial strain increased similarly in all segments; longitudinal strain increased with a base-to-apex gradient; and circumferential strain increased in the LV free wall but decreased in regions adjacent to the RV. Reductions in septal circumferential strain were strongly correlated with changes in RV structure and function. This finding may reflect a novel form of ventricular interdependence. In 16 ultramarathon athletes, peak RV strain decreased in the post-race period and a slight delay in time to peak strain relative to pulmonary valve closure was identified, while in the LV, peak circumferential, radial and longitudinal strain, and torsion decreased significantly after exercise.[52] Reductions in these indices could be a consequence of intrinsic LV impairment or increased RV afterload. In fact, the RV is not a passive chamber, as previously thought, but plays a crucial role in cardiac adaptations to exercise. Intense endurance exercise causes acute RV dysfunction that recovers in the short term, but chronic structural changes and reduced RV function are evident in some athletes.[19] This hemodynamic imbalance may promote transient RV injury or incomplete recovery, with possible long-term structural consequences (Figure 3).

LV diastolic function can be enhanced by prolonged exercise training.[53,54] This improvement is essential to preserve stroke volume, mainly due to the ability of the LV to relax at high heart rates.[55] Sustained endurance training preserves ventricular compliance with age, potentially preventing heart failure in the elderly.[56] In strength sports LV relaxation appears to remain unchanged or mildly impaired, although concentric hypertrophy does occur.[44]

Electrical adaptation

More than 80% of competitive athletes have changes in resting ECG reflecting physiological adaptation to exercise training; changes potentially confounded with CV pathology are present in 10–14%.[28,57,58] Guidelines and consensus

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Table 2 The Seattle criteria for normal ECG findings in athletes (adapted from 61).

1. Sinus bradycardia (≥30 bpm)
2. Sinus arrhythmia
3. Ectopic atrial rhythm
4. Junctional escape rhythm
5. First-degree AV block (PR interval >200 ms)
6. Mobitz type I (Wenckebach) AV block
7. Incomplete RBBB
8. Isolated QRS voltage criteria for LVH
   - Except: QRS voltage criteria for LHV occurring with any non-voltage criteria for LVH such as LA enlargement, left axis deviation, ST segment depression, T-wave inversion or pathological Q waves
9. Early repolarization (ST elevation, J-point elevation, J-waves, or terminal QRS slurring)
10. Convex ('domed') ST segment elevation combined with T-wave inversion in leads V1–V4 in black athletes

AV: atrioventricular; bpm: beats per minute; LA: left atrium; LVH: left ventricular hypertrophy: RBBB: right bundle branch block.

documents on ECG interpretation in athletes have been published in recent years. The European Society of Cardiology (ESC) guidelines published in 2010[59] divide the ECG findings into two groups:

- Group 1: common and training-related changes;
- Group 2: uncommon and trained-unrelated changes.

Group 1 (normal findings) includes sinus bradycardia, first-degree atrioventricular (AV) block, incomplete right bundle branch block and isolated QRS voltage criteria for LV hypertrophy. The American guidelines, published in 2011, were in line with the ESC document,[60] while in 2013, experts in sports cardiology and sports medicine defined standards to distinguish normal from abnormal ECG findings in athletes, known as the Seattle criteria (Table 2).[61–63]

Electrical adaptations in athletes result from conditioning of the cardiac autonomic nervous system (increased vagal tone and/or sympathetic withdrawal) and structural remodeling. Increased vagal tone is responsible for findings such as bradycardia, sinus arrhythmia, early repolarization and first-degree Mobitz type I AV block, alterations that disappear with increased heart rate during exercise. Structural remodeling is responsible for criteria of increased cavity sizes.[61,64]

Electrical adaptations include the following:

- Resting bradycardia: present in 60%–80% of highly trained athletes, especially those engaged in endurance sports.[21,28,29,65] In the absence of symptoms, a heart rate ≥30 bpm and/or pauses of ≥3 s during sleep hours should be considered normal.
- Sinus arrhythmia: an exaggerated response is found in >50% of athletes, resulting from variation during the respiratory cycle.[21,65]
- Ectopic atrial rhythm: P waves with different morphologies compared to the sinus P waves (known as a 'wandering atrial pacemaker' if there are more than two different morphologies) are normal in athletes and are most easily seen when P waves are negative in the inferior leads.
- Junctional escape rhythm: resulting from a faster QRS rate than the resting P wave rate; can be found in athletes with marked bradycardia.[65]
- First-degree AV block and Mobitz type I AV block: these are considered normal findings in athletes. The former is common (3%–14%) but the second is rare (<1%).[21,28,29,64,65]
- Incomplete right bundle branch block: present in 30%–40% of athletes, particularly in endurance disciplines,[21,29,65] reflecting prolonged conduction time resulting from increased RV size secondary to regular training.[24,29,65,66]
- Isolated QRS voltage criteria for LV hypertrophy: found in approximately 45% of athletes. In black individuals >80% may be affected.[21,65,66] Association with other markers of non-voltage criteria for LV hypertrophy (LA enlargement, left axis deviation, ST-segment depression, T-wave inversions or pathological Q waves) should prompt exclusion of pathological hypertrophy.[60,61]
- Early repolarization: present in >50% of highly trained athletes, reaching 80–90% in black athletes.[29,65–68] Besides the strong association with ethnicity, early repolarization is more common in young male athletes and in those with increased QRS voltage, interventricular septal thickness and slower heart rate.[67] Tikkanen et al. showed a significant association between early repolarization in the inferior leads and increased risk of SCD in middle-aged non-athletic subjects.[68] This pattern is also common among athletes, and probably represents a dynamic process related to exercise intensity.[67] To date, there is no evidence to support a relationship between early repolarization and SCD or other cardiac events in athletes. In a recent retrospective analysis of 118 male soccer players with early repolarization, no cardiac deaths occurred during a mean follow-up of 13.3 years.[69] All the patterns of early repolarization – ST elevation at QRS end (J-point), J-wave with or without ST elevation, terminal QRS slurring with or without J-wave/new J-point – should be considered normal variants in athletes.[61]
- Repolarization in black athletes: more than two-thirds of black athletes exhibit ST-segment elevation and up to 25% show T-wave inversions.[29,66] Convex ('domed') ST-segment elevation combined with T-wave inversion in leads V1–V4 is also frequent and in the absence of symptoms, positive family history or abnormal physical examination, does not require further assessment (Figure 4).
- Juvenile pattern: T-wave inversions in the right precordial leads are a normal ECG finding in athletes aged under

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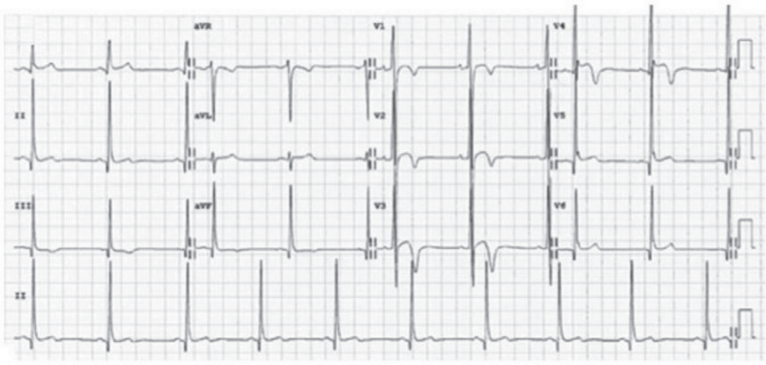

Figure 4 ECG of healthy male athlete of African origin, showing increased QRS voltage, convex ST-segment elevation and deep T-wave inversion in V1–V4 (courtesy of Cardiovascular Sciences Research Centre, St. George's, London University).

16, because of RV dominance and repolarization polarity directed posteriorly.[65]

In the interpretation of athletes' ECG, it should be stressed that some normal cut-offs differ between the sexes (e.g. prolonged QT interval according to the Seattle criteria: female >470 ms; male >480 ms).[70]

Overlap with cardiomyopathy

It can be challenging to distinguish exercise-related cardiac adaptations from cardiomyopathies (Figure 5).

Hypertrophic cardiomyopathy

The majority of dilemmas during the assessment of athletes occur when cardiac remodeling mimics phenotypical findings of hypertrophic cardiomyopathy (HCM). Almost 2% of adult male athletes show increased LVWT of 13–15 mm, falling into the gray zone between extreme expression of athlete's heart and a mild HCM phenotype.[23] In female and adolescent athletes LVWT >12 mm is extremely rare and should be investigated further.[22] As the phenotypic expression of HCM is incomplete during periods of rapid growth, younger athletes (prepubertal or pubertal) with suspected HCM should be closely monitored. The main differences between HCM and athlete's heart are depicted in Table 3. Compared to HCM patients, the hypertrophic pattern in athletes is uniform and associated with concomitant LV dilation. Reduction in LVWT (2–5 mm) after a period of detraining suggests athlete's heart, but compliance with detraining is difficult and requires the cooperation of athletes. It should be noted that in athletes with mild forms of HCM, increased LVWT could be related to both exercise and HCM and may decrease after detraining. Absence of response to detraining is suggestive of pathological LV hypertrophy, but regression with detraining does not necessarily represent only physiological hypertrophy. In contrast to physiological remodeling, in which diastolic function is preserved or even enhanced, HCM is characterized by abnormal LV relaxation indices and increased filling pressure; however, a normal diastolic filling pattern does not exclude pathological hypertrophy.

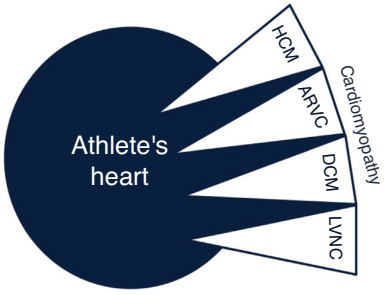

Figure 5 Overlap between cardiomyopathy and athlete's heart. ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVNC: left ventricular noncompaction.

In cases with some characteristics in the gray zone additional investigation is necessary. In cardiopulmonary exercise testing, while athletes achieve peak VO_2 that typically exceed predicted values (usually >120%), in HCM patients only 1.5% exceed these values. MRI is useful for morphological characterization, particularly of apical LV segments, but also due to the additional information it provides, such as identification of myocardial fibrosis in HCM located in thicker myocardial segments and in RV insertion points of the interventricular septum. Although there is a significant rate of false negative results, genetic tests can help in difficult cases. A positive result for one of the known mutations of HCM establishes the diagnosis. Even without structural changes suggestive of HCM, athletes exhibiting abnormal and extensive ECG repolarization changes should be followed, because these changes can precede morphological features.

Dilated cardiomyopathy

Marked LV dilatation may require a differential diagnosis between physiological adaptation and dilated

MANUSCRIPT 1

Table 3 Differences between hypertrophic cardiomyopathy and athlete's heart.

Investigation	Favors athlete's heart	Favors HCM
Family history	Absent	Known HCM diagnosis, SCD
Symptoms	Asymptomatic and good exertion tolerance	Pre-syncope, syncope, palpitations, breathlessness, chest pain, fatigue out of proportions to the degree of exertion
Physical examination	Unremarkable	Loud systolic murmur that increases with Valsalva maneuver, forceful apical impulse
ECG	Normal physiological adaptations (including isolated LVH criteria)[a]	High QRS voltage plus unusual findings Pathological Q waves ST-segment depression T-wave inversions in anterolateral leads LBBB
Echocardiogram	Symmetrical increased LVWT (usually <12 mm in female and junior athletes; rarely >13 mm in white male athletes) Normal or improved LV diastolic function Increased LV dimensions (LVEDD >55 mm) Balanced RV dilation	Asymmetric increased LVWT (>15 mm) LV diastolic dysfunction (impaired relaxation, increased deceleration time and filling pressures) Disproportionate LA dilatation Reduced LV dimension (LVEDD <45 mm) LVOT obstruction
CPET	VO_2 max >45 ml/kg/min VO_2 max >120% of predicted	VO_2 max lower than predicted
MRI[b]	Absence of late enhancement or non-specific pattern (ischemic or non-ischemic, mainly in veteran endurance athletes)	Typical late enhancement (junction of RV and interventricular septum and in the thicker segments)
Detraining	Reduction in LVWT (2–5 mm)[c]	Persistence of increased LVWT
Genetic test	Negative[d]	Positive for mutation related to HCM

CPET: cardiopulmonary exercise testing; ECG: electrocardiogram; HCM; hypertrophic cardiomyopathy; LBBB: left branch bundle block; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVH: left ventricular hypertrophy; LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; MRI: magnetic resonance imaging; RV: right ventricle; SCD: sudden cardiac death.

[a] Depicted in Table 2.

[b] Morphological findings in MRI are similar to echocardiographic findings but with greater accuracy and beret delineation of apical ventricular segments.

[c] Although suggestive, this does not exclude pathology. In athletes with mildly phenotypic HCM, LVWT can also decrease with detraining.

[d] Negative test does not exclude HCM since only about 50% of the genes responsible for HCM have been identified.

cardiomyopathy (DCM), particularly when LV ejection fraction is in the lower normal range or depressed. As previously reported, 14% of athletes have LV diastolic diameter $\geq$60 mm, and it can reach 70 mm in men.[36] In extreme endurance sports such as cycling, the prevalence and degree of LV dilation is greater, with a considerable proportion of athletes having concomitant decreased LVEF at rest, fulfilling criteria for a diagnosis of DCM.[37] In these cases of extreme LV dilation, correct assessment of LVEF and exclusion of wall motion abnormalities are fundamental. DCM patients have reduced exercise capacity, reflected in low maximum VO_2 and high VE/VCO_2 slopes on cardiopulmonary exercise testing. MRI permits accurate assessment of LVEF and detection of fibrosis, usually mid-wall.

Arrhythmogenic right ventricular cardiomyopathy

With regard to arrhythmogenic right ventricular cardiomyopathy (ARVC), a relationship has been postulated between ultra-endurance exercise and an ARVC-like phenotype. Recently 3% black and 0.3% white athletes were found to meet criteria for ARVC, but further investigation did not detect any pathological findings.[43] Extreme exercise can cause consecutive bouts of RV dilatation and dysfunction, which may alter the RV interstitial matrix. In favor of this hypothesis is the lower than expected prevalence of desmosomal gene mutations identified in endurance athletes with complex ventricular arrhythmias of RV origin.[71] This supports the concept of ARVC being acquired through intense exercise. When ARVC is suspected the combination of findings from personal and family history, ECG, Holter ECG, transthoracic echocardiogram and MRI may establish the diagnosis.

Left ventricular noncompaction

Left ventricular noncompaction (LVNC) is an unclassified cardiomyopathy for which the optimum diagnostic criteria are the subject of debate. The current criteria, based on echocardiography and MRI, reveal low specificity, leading to overdiagnosis of this entity. Furthermore, the LVNC phenotype can overlap with other cardiomyopathies such as HCM and DCM. Gati et al.[58] showed a higher prevalence of LV trabeculation in athletes compared to controls (18.3% vs. 7.0%), with 8.1% fulfilling criteria for LVNC. Only a small

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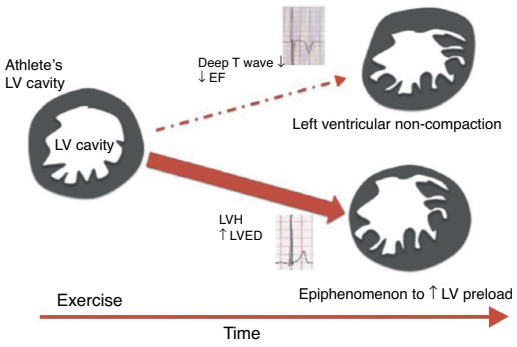

Figure 6 Scheme proposed for the significance of left ventricular trabeculation in athletes (adapted from 58). EF: ejection fraction; LV: left ventricular; LVED: left ventricular end-diastolic diameter; LVH: left ventricular hypertrophy.

proportion (0.9%) revealed reduced LVEF and marked repolarization changes in association with criteria for LVNC, raising the possibility of an underlying cardiomyopathy. LV trabeculations without other features of noncompaction or repolarization changes could be a physiological response to exercise in highly trained athletes (Figure 6). Changes in preload imposed by exercise could be the cause of these morphological changes, since LV trabeculations have been found in patients with heart failure, thalassemia and in pregnant women, conditions which are also associated with increased cardiac preload.

Pre-participation screening of competitive athletes

Pre-participation screening aims to detect silent CV abnormalities associated with risk of SCD. This issue has been the subject of intense debate, for which there is still no definite consensus. Few countries have implemented standardized screening protocols, and even among these, there is considerable heterogeneity. In 2005 the ESC published a consensus statement for CV pre-participation screening of young competitive athletes.[72] This document was mainly based on the Italian experience, and advocates the inclusion of ECG in the screening protocol for athletes (Figure 7).

Medical history

Most of the conditions associated with a higher risk of SCD in athletes are genetically determined with an autosomal dominant inheritance pattern, and so the family history is of great importance. Family history should be considered positive in the presence of SCD, coronary events, or diagnosis of cardiomyopathies or primary inherited arrhythmias in first-degree relatives (male <55 years; female <65 years). Regarding personal history, care should be taken in the presence of CV symptoms, particularly if exercise-related. Chest pain, pre-syncope, syncope, irregular beats, palpitations, breathlessness or fatigue disproportionate to exertion are the most commonly reported symptoms.

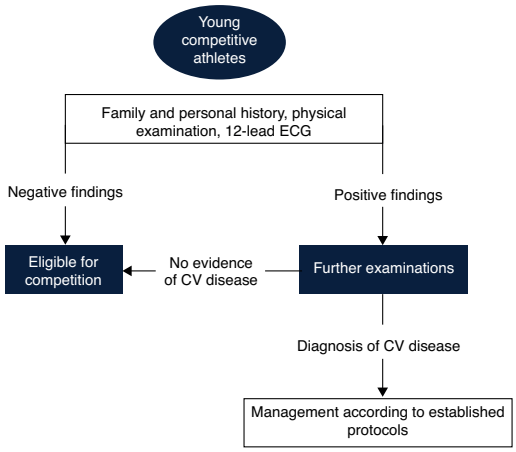

Figure 7 Proposed European Society of Cardiology screening protocol for young competitive athletes (adapted from 72). CV: cardiovascular; ECG: electrocardiogram.

Syncope is relatively common among highly trained athletes (up to 6%), most frequently of benign origin due to reflex mechanisms, and sometimes occurring in the postexertional period. Although some cases suggest that syncope could be a manifestation of exaggerated vasodilatation, episodes during exertion may have a cardiac origin and should be comprehensively investigated, initially with transthoracic echocardiogram, Holter ECG and exercise testing, which are mandatory in the diagnostic workup of these athletes.[73] Athletes with syncope or chest pain but normal echocardiogram and exercise testing should undergo coronary computed tomography angiography (CCTA) to exclude coronary artery anomalies. It is important to stress that coronary artery disease is the most frequent cause of SCD in athletes aged over 35, and it is essential to screen for CV risk factors in this population.

Physical examination

Beyond the conventional cardiac assessment, physical examination of athletes should focus on specific factors according to the suspected diagnosis (e.g. musculoskeletal features suggestive of systemic manifestations as phenotypic red flags for cardiomyopathies or Marfan syndrome). Athletes with positive findings should be referred for additional investigation, most commonly transthoracic echocardiogram, Holter ECG and exercise testing. Cardiac MRI, CCTA or invasive exams such as electrophysiological study may be required in specific situations. In the presence of extracardiac manifestations, collaboration of other specialists is important, such as neurologists in the case of abnormal neurological findings.

Electrocardiogram

The role of the ECG in athletes' screening is controversial, with arguments both for and against. Potentially lethal

MANUSCRIPT 1

conditions with ECG manifestations account for approximately two-thirds of SCD in young competitive athletes – HCM, ARVC, DCM, long QT syndrome, Brugada syndrome, short QT syndrome and pre-excitation syndromes. Some ECG changes found in cardiomyopathies precede the morphological phenotype: the condition goes through molecular, electrical and morphological stages, with risk of life-threatening arrhythmias at all these stages. However, the ECG is unable to identify other causes of SCD such as premature coronary artery disease, congenital coronary anomalies or aortic root disorders.

Evidence supporting the use of ECG in screening of athletes came from the Veneto region of north Italy, where after long-term systematic screening the rate of SCD per 100 000 person-years declined from 3.6 to 0.4 in athletes but remained unchanged in unscreened non-athletes.[74] However, some authors criticize these results, arguing that the study was not randomized, and countering with a study performed in Israel in which the mean annual SCD rate paradoxically increased after ECG screening (from 2.54 to 2.66/100 000).[75] These results also should be interpreted with caution, because the SCD rate was based on media reports and the number of athletes was estimated.

In the USA pre-participation screening is performed using personal and family history and physical examination, but without ECG. This methodology is based on the assumption that the ECG in not cost-effective for screening of large populations of athletes due to the high false positive rate. However, screening without ECG appears to have a limited ability to detect potentially fatal abnormalities. In a retrospective analysis of 115 young athletes in the USA suffering SCD and previously screened, only 3% were suspected of having CV disease based on clinical history and physical examination and <1% were correctly diagnosed.[76]

Erroneous interpretation of the ECG may trigger expensive diagnostic tests and lead to unnecessary disqualification from competitive sports. This is more important for professional athletes in whom disqualification from competition has significant financial and psychological consequences. Conversely, signs of potentially lethal CV disorders may be misinterpreted as normal variants. It is essential to recognize that false positive ECG rates are strongly influenced by the criteria used, and so it is critical to improve physicians' expertise in distinguishing normal adaptations from abnormal changes in athletes. Standardization with the Seattle criteria has led to improvement in the accuracy of ECG interpretation among several different physician specialties.[77] Nevertheless, controversy regarding which ECG changes should be analyzed in athletes continues. Gati et al.[78] recently showed that isolated axis deviation and atrial enlargement comprise a high burden of the ECG findings, but do not predict the presence of underlying structural or functional abnormalities. In this analysis, exclusion of these characteristics reduced the false positive rate from 13% to 7.5%.

Despite the intense debate concerning its efficacy and cost-effectiveness, the ECG is recommended by several organizations, including the International Olympic Committee, and is invariably performed in real-world clinical practice. Physicians responsible for assessment of athletes should therefore be able to identify exercise-induced ECG adaptations, and in the case of abnormal findings to set in motion appropriate investigation and management. Table 4 shows some arguments for and against the use of the ECG in athletes' pre-participation screening.

Unsolved problems and future directions

Several questions remain unanswered regarding the cardiac impact of exercise training and the assessment of competitive athletes.

The real prevalence of sudden cardiac death in athletes

The real prevalence of SCD in athletes remains unknown and the available data are controversial: values of 1:50 000, 1:100 000, and 1:20 000 have been proposed. Most studies are based on media reports, with obvious limitations. For example, a simple search for SCD in athletes in Portugal on www.google.com and the websites of the most widely read Portuguese newspapers (sports-related and generalist) reveals 46 cases in young or veteran athletes, 28 during competition, mainly soccer (n=13). This is unlikely to be the real number. The first death reported occurred in 1987; there were eight between 1997 and 2004, followed by the others, 12 occurring in 2004, the year of the case with the highest media profile in Portugal. This methodology is inaccurate and skewed. A systematic registry of all SCD cases is warranted and crucial for the epidemiological understanding of this tragic event.

Causes of sudden cardiac death

Without knowing the causes of death in representative samples, it will be difficult to establish appropriate preventive protocols and screening programs. Analysis of SCD victims should include all the available resources for accurate etiological identification: meticulous post-mortem analysis, molecular autopsy, genetic tests and direct family history.

Normality and adaptive variants

It is crucial to increase knowledge of normal and adaptive variant patterns of CV changes induced by exercise training at clinical, functional and morphological levels. Factors that should be taken into consideration include the impact of demographic characteristics such as ethnicity and extreme ages (from children to veterans), training-related issues, and the long-term effects of doping and intense exercise training.

Pre-participation screening programs

It is essential to define a single model for assessment of athletes that can be used in a sufficiently broad registry to draw definite conclusions on the specificity, sensitivity and overall cost-effectiveness of screening programs that would overcome the historical debate concerning the value of the ECG.

MANUSCRIPT 1

Table 4 Arguments for and against the use of the ECG in pre-participation screening of young competitive athletes.

For	Against
Availability	High false positive rate
The most common causes of SCD have characteristic findings	Lack of validated standardization criteria to define normal physiological changes
Higher sensitivity than history and physical examination	Not accurate for identifications of some causes of SCD
Italian experience showing a decline of SCD after ECG screening program implantation	Wide range of normal variants depending on demographic and sport-related characteristics
Early marker of SCD (frequently the first clinical event)	Lack of evidence from prospective studies
Improved diagnostic accuracy with modern standardized criteria	SCD is rare in young athletes and zero risk is unattainable
Lacks power and sensitivity of screening based on history and physical examination is low	Consumes healthcare resources that could be allocated to other and more common urgent needs
Identification of athletes with high risk for SCD leads to investigation of family members	Misinterpretation if physicians do not have expertise in sports cardiology
Cost-effective compared to history and physical examination	Inappropriate and expensive additional investigation
Interpretation of clinical history and physical examination are subjective and vary between physicians	Incorrect interpretation can lead to inappropriate disqualification
Low cost of mass screening (possibility of negotiating cost)	Cost-effectiveness remains to be determined
Ethical considerations: equal access should be provided to all sectors of society, not only to organizations with greater financial resources such as professional sports teams	Logistically impractical to implement for assessment of larger populations

ECG: electrocardiogram; SCD: sudden cardiac death.

Conclusions

Understanding of cardiac physiological adaptation induced by continued intense exercise training is crucial for accurate assessment of competitive athletes. The overlap between these adaptations and cardiomyopathies poses a challenge: under-diagnosis of a disease may increase the risk of life-threatening events, and over-diagnosis can result in improper disqualification from competition. A high level of suspicion and inclusion of data from clinical history, physical examination and concomitant investigations are essential. Standardization of ECG interpretation could decrease the rate of false positives and allow early detection of potentially fatal CV abnormalities.

Conflicts of interest

The authors have no conflicts of interest to declare.

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MANUSCRIPT 2

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ORIGINAL INVESTIGATIONS

Anterior T-Wave Inversion in Young White Athletes and Nonathletes

Prevalence and Significance

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ABSTRACT

BACKGROUND Anterior T-wave inversion (ATWI) on electrocardiography (ECG) in young white adults raises the possibility of cardiomyopathy, specifically arrhythmogenic right ventricular cardiomyopathy (ARVC). Whereas the 2010 European consensus recommendations for ECG interpretation in young athletes state that ATWI beyond lead V_1 warrants further investigation, the prevalence and significance of ATWI have never been reported in a large population of asymptomatic whites.

OBJECTIVES This study investigated the prevalence and significance of ATWI in a large cohort of young, white adults including athletes.

METHODS Individuals 16 to 35 years of age (n = 14,646), including 4,720 females (32%) and 2,958 athletes (20%), were evaluated by using a health questionnaire, physical examination, and 12-lead ECG. ATWI was defined as T-wave inversion in ≥2 contiguous anterior leads (V_1 to V_4).

RESULTS ATWI was detected in 338 individuals (2.3%) and was more common in women than in men (4.3% vs. 1.4%, respectively; $p < 0.0001$) and more common among athletes than in nonathletes (3.5% vs. 2.0%, respectively; $p < 0.0001$). T-wave inversion was predominantly confined to leads V_1 to V_2 (77%). Only 1.2% of women and 0.2% of men exhibited ATWI beyond V_2. No one with ATWI fulfilled diagnostic criteria for ARVC after further evaluation. During a mean follow-up of 23.1 ± 12.2 months none of the individuals with ATWI experienced an adverse event.

CONCLUSIONS ATWI confined to leads V_1 to V_2 is a normal variant or physiological phenomenon in asymptomatic white individuals without a relevant family history. ATWI beyond V_2 is rare, particularly in men, and may warrant investigation. (J Am Coll Cardiol 2017;69:1–9) © 2017 by the American College of Cardiology Foundation.

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There is general agreement that T-wave inversion (TWI) in the inferior or lateral leads in young individuals warrants further investigation for cardiac disease, particularly cardiomyopathy (1). It is also well established that adolescent athletes (2–6) and black adult athletes (7) frequently exhibit TWI in the anterior leads as part of the normal physiological or ethnic spectrum

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MANUSCRIPT 2

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

ATWI = anterior T-wave inversion

CMRI = cardiac magnetic resonance imaging

ECG = electrocardiogram

Jt = J point

SCD = sudden cardiac death

TWI = T-wave inversion

respectively. However, the general consensus for the significance of anterior TWI (ATWI), defined as T-wave inversion in ≥2 contiguous anterior leads (V_1 to V_4) in white adults varies among expert recommendations for the interpretation of the athlete's electrocardiogram (ECG). Whereas the European Society of Cardiology recommendations suggest further evaluation of athletes with TWI beyond lead V_1 (8), more recent recommendations from the Seattle criteria advocate investigation only if TWI extends beyond V_2 (9).

Both of the consensus panels have relied on data from unselected (10) or small cohorts of athletes (11); however recent studies reveal that TWI in leads V_1 to V_2/V_3 is detected in up to 6% of endurance athletes (12). Conversely, ATWI in V_1 to V_2/V_3 is a recognized repolarization abnormality in a significant proportion of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and a minority of patients with hypertrophic cardiomyopathy (7), which collectively accounts for >40% of all sudden cardiac deaths (SCDs) in young athletes (13). Differentiation of potentially pathological ATWI from a pattern that represents a normal variant or physiological remodeling in white adult athletes is essential to minimize the risk and consequences of an erroneous diagnosis (6,14).

SEE PAGE 10

Because the prevalence of ATWI has been reported in black athletes, controls of both sexes, and the adolescent population, the present study focused on the prevalence and significance of ATWI in a large cohort of apparently healthy white adults including a large proportion of athletes.

METHODS

SETTING. The United Kingdom does not support a nationally sponsored screening program for cardiac disease in young asymptomatic individuals in the absence of a family history of inherited cardiac disease or premature SCD. Several elite sporting organizations finance the evaluation of their athletes through the charitable organization CRY (Cardiac Risk in the Young). These organizations include premier league football clubs, the Lawn Tennis Association, and the English Institute of Sport. Up to 1,000 athletes are tested annually at their specific clubs or national training camps, usually using history, examination, and ECG. Financially endowed organizations such as the Football Association and the Lawn Tennis Association also incorporate echocardiography as a standard test.

CRY also offers cardiac screening to all young individuals (14 to 35 years of age) who wish to be assessed, even in the absence of symptoms, history of cardiac disease, or a family history of inherited cardiac diseases or SCD. Such screenings are conducted at community centers and high schools and are limited to history, examination, and ECG with referral for further assessment only in those with abnormal preliminary findings or if participating as controls for research studies. Screening events are advertised through the local media and on the CRY website. Individuals from the general population, including those from local high schools, self-present to screening events whereas competitive athletes attend specified screening events mandated by their relevant sporting bodies. The CRY screening program is supervised by our principal investigator (S.S.).

SUBJECTS. Between 2007 and 2013, 14,646 young, white adults between 16 and 35 years of age underwent cardiac evaluation through CRY at various testing centers in England. Ethnicity was self-reported through the questionnaire that included terms such as white British, white Irish, white European, and white other.

Athletes. The study included 2,958 athletes (20.2%) competing at regional, national, or international levels who performed ≥8 h of exercise per week. Sporting disciplines were categorized as predominantly endurance or strength. Endurance sports were defined as those typically resulting in >70% maximal oxygen uptake (Vo_{2max}) (15) and included badminton, basketball, canoeing, cycling, hockey, middle- and long-distance running, rowing, rugby, soccer, squash, swimming, tennis, and triathlon. All other sports were deemed strength disciplines, including cricket, diving, sailing, volley ball, water polo, weight lifting, and wrestling.

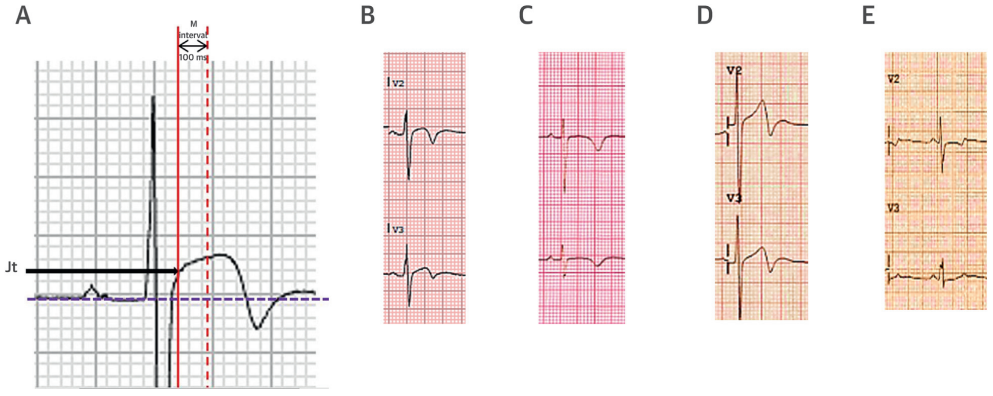
Nonathletes. The nonathlete cohort consisted of 11,688 individuals (79.8%) whose primary inclusion criterion was a sedentary lifestyle (≤2 h organized physical activity per week). Individuals with symptoms suggestive of cardiac disease, history or family history of cardiac disease or premature cardiac disease or SCD (<50 years of age) were excluded.

ELECTROCARDIOGRAPHY. A standard 12-lead ECG was performed while patient were in a supine position, using a Marquette Hellige recorder (Marquette-Hellige Medical Systems, Milwaukee, Wisconsin) at a paper speed of 25 mm/s. Wave voltages P, Q, R, S, and T and ST-segments QRS, PR, and QT intervals were measured in each lead as described elsewhere (16).

MANUSCRIPT 2

JACC VOL. 69, NO. 1, 2017
JANUARY 3/10, 2017:1-9

FIGURE 1 ST-Segment Morphology



(A) The **vertical solid line** and the **vertical dashed line** define the M interval, which has a duration of 100 ms. The **horizontal dashed line** through the onset of the QRS complex provides the reference point for the measurement of J point (Jt). Jt is elevated at 0.2 mV with a convex appearance. ST-segment morphologies with anterior T-wave inversion in chest leads V_2 and V_3 are shown as the following: **(B)** ascending convex, **(C)** isoelectric, **(D)** ascending concave, and **(E)** depressed.

Leads V_1 to V_4 were classified as anterior precordial leads. T-wave deflection ≥−0.1 mV in these leads was regarded as abnormal TWI. Deep TWI was defined as a T-wave amplitude ≥−0.2 mV. In cases of biphasic T-waves, we applied the definition to the negative component of the T-wave. In cases of ATWI, the ECG was repeated to ensure that the leads were correctly positioned according to standard recommendations. In women, the ECG electrodes were placed under the breast tissue according to American Heart Association recommendations (17). Partial right bundle branch block was defined as a QRS duration >0.1 but <0.12 s, with rSR′ morphology in lead V_1 and QRS in V_6 (18). Individuals with TWI and complete right bundle branch block (QRS: ≥0.12 s) were excluded from the ATWI group. Additional ECG markers compatible with ARVC were also sought, including terminal activation duration of the QRS complex ≥55 ms in lead V_1, V_2, or V_3 and the epsilon wave (19).

The amplitude of the J point (Jt) (20) was measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex. The Jt was considered elevated if Jt ≥0.1 mV or depressed if Jt ≤−0.1 mV. The morphology of the ST-segment in the anterior leads was ascertained in the interval, M (during the 100 ms following Jt) (20). The ST-segment at the onset of the M interval (i.e., Jt) was considered elevated if it was above Jt, depressed if it was below Jt, and isoelectric if it was in line with Jt. Ascending ST-segments were categorized as ascending convex or ascending concave (**Figure 1**).

ECHOCARDIOGRAPHY. Two-dimensional (2D) transthoracic echocardiography was performed in all subjects with ATWI by using Sonos 7500 system (model CPX50, iE33, Philips, Baltimore, Maryland) and Vivid I (GE, Tiral, Israel) machines. Standard views were obtained, and dimensions of cavities and wall thickness measurements and pulsed color and tissue Doppler measurements were made in accordance with established guidelines (21-23). Right ventricular assessment was performed as outlined previously (14). Right ventricular regional wall-motion abnormalities were defined as akinetic, dyskinetic, or aneurysmal, in accordance with diagnostic criteria for ARVC (19).

Echocardiography was also performed as standard testing in 1,079 athletes and 769 nonathletes without ATWI of similar age and sex proportion whose examinations had normal results and ECGs. The echocardiogram was part of the mandatory pre-participation cardiac evaluation in athletes, although the echocardiogram was conducted as part of research in volunteering nonathletes. These cohorts served as comparative groups for athletes and nonathletes with ATWI, respectively.

All ECG and echocardiograms were performed by nationally-accredited cardiac physiologists. Echocardiography was conducted by physiologists blinded to the ECG findings. All ECG and echocardiogram images

MANUSCRIPT 2

TABLE 1 Demographics and ECG Characteristics of Individuals With and Without ATWI

	Population With ATWI (n = 338)	Population Without ATWI (n = 14,308)	p Value
Demographics			
Age, yrs	21.1 ± 5.4	21.7 ± 5.3	0.0398
Female	60.1	31.6	<0.0001
Athlete	30.5	20.0	0.0003
BSA, m^2	1.81 ± 0.3	1.91 ± 0.2	<0.0001
Blood pressure, mm Hg	121/66 ± 12/7	123/80 ± 10/6	0.0003
ECG parameters			
Heart rate, beats/min	64 ± 14	66 ± 14	<0.0001
PR, ms	150 ± 25	151 ± 32	<0.0001
QRS, ms	93 ± 12	92 ± 13	<0.0001
QTc, ms	421 ± 28	412 ± 20	<0.0001
Incomplete RBBB	17.7	5.5	<0.0001
LBBB	0	0.02	0.77
LVH	17.9	10.1	<0.0001
RVH	1.2	1.1	0.93
ER	15.1	9.7	0.0018
Pathological Q waves	0.5	0.3	<0.0001
LA enlargement	3.3	1.4	0.002
RA enlargement	1.4	0.6	0.1
LAD	1.0	1.2	0.83
RAD	0.7	0.4	0.49
Pre-excitation	0.5	0.5	0.93

Values are mean ± SD or % overall population.

ATWI = anterior T-wave inversion; BSA = body surface area; ECG = 12-lead electrocardiogram; ER = early repolarization; LA = left atrial; LAD = left axis deviation; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; RA = right atrial; RAD = right axis deviation; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; TWI = T-wave inversion.

were reviewed by 2 independent cardiologists with the principal investigator (S.S.) adjudicating any queries.

FURTHER INVESTIGATIONS. All subjects with ATWI underwent additional investigations to detect the broader phenotypic features of a primary cardiomyopathy, particularly ARVC, hypertrophic cardiomyopathy and dilated cardiomyopathy. Predetermined diagnostic criteria for ARVC were based on the 2010 Modified Task Force criteria (19). Hypertrophic cardiomyopathy was considered in individuals with left ventricular hypertrophy where septal or wall thickness measured ≥15 mm in any myocardial segment in the absence of another condition capable of producing left ventricular hypertrophy of the same magnitude (24,25). Dilated cardiomyopathy was considered in individuals with a dilated LV (men >59 mm and women >53 mm) when accompanied by a reduced ejection fraction (<52%) (26). The vast majority of further investigations (n = 1,396; 95%) were performed at our institution.

Ambulatory ECG monitoring. Ambulatory 24-h ECG recording (Lifecard CF Holters, Spacelabs Healthcare, Snoqualmie, Washington) was used to detect ventricular arrhythmias. Subjects were encouraged to continue day-to-day activities including exercise during monitoring.

Exercise testing. Exercise testing was performed upright on a treadmill using the standard Bruce protocol (27). Subjects were exercised to volitional exhaustion and assessed for cardiac symptoms, ischemic changes, attenuated blood pressure response, or arrhythmias.

Signal-averaged ECG. Signal-averaged ECG (SAECG) was acquired according to accepted methodology using the same machines used for standard ECG, with use of a 40 Hz high-pass bidirectional filter (28). Late potentials were defined as abnormal values in 1 or more of the parameters in accordance the diagnostic criteria for ARVC (19).

Cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging (CMRI) was performed using a Philips Achiever 3.0T TX scanner (Philips, Amsterdam, the Netherlands). Delayed gadolinium enhancement images were acquired as previously described (29). Ventricular volumes and function were measured for both ventricles using standard techniques and analyzed using semi-automated software (Extended MR workspace, Philips) (30). All measures were indexed to body surface area.

ETHICAL APPROVAL. Ethics approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee in the United Kingdom. Written consent was obtained from all subjects.

STATISTICAL ANALYSIS. Data are mean ± SD or percentages, as appropriate, and were analyzed using SPSS version 20 software (SPSS, Chicago, Illinois). Comparisons between groups were performed using Student *t* test for continuous variables with adjustment for unequal variance if needed and chi-square tests or Fisher exact tests for categorical variables. Univariate analyses were performed to determine variables (sex, age, athletic status, left ventricular end diastolic diameter, and right ventricular outflow tract size [parasternal long- and short-axis measurements]) associated with ATWI. Multivariate logistic regression analyses were used to determine the independence of these associations. Significance was defined as $p < 0.05$.

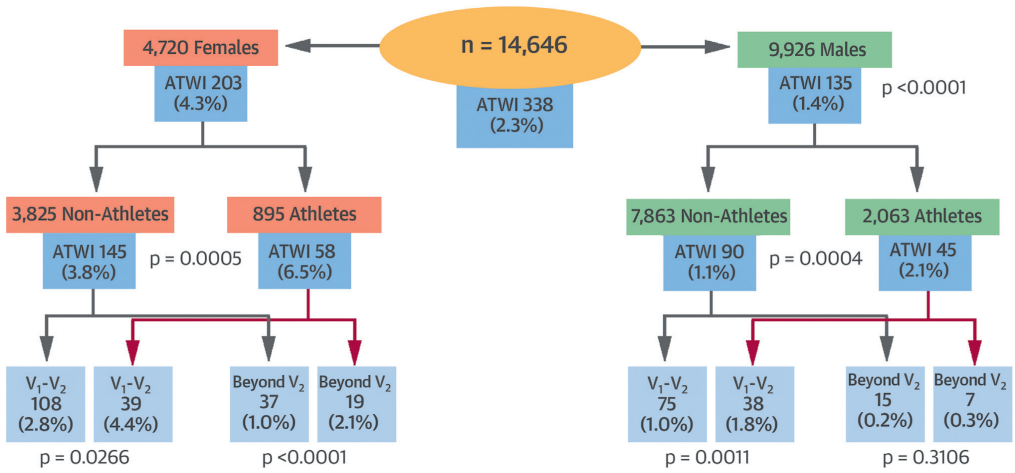
RESULTS

DEMOGRAPHICS. The mean age of the cohort was 21.7 ± 5.4 years of age. Of the 14,646 subjects, 9,926 were men (67.8%); 2,063 men (20.8%) and 895 women (19.0%) were athletes. Athletes exercised for

MANUSCRIPT 2

JACC VOL. 69, NO. 1, 2017
JANUARY 3/10, 2017:1–9

CENTRAL ILLUSTRATION **Prevalence of Anterior T-Wave Inversion in the Adult White Population**



Malhotra, A. et al. J Am Coll Cardiol. 2017;69(1):1-9.

The overall prevalence of anterior T-wave inversion (ATWI) in adult white individuals (16 to 35 years of age) was 2.3%. ATWI was more common in women and in athletes. The prevalence of ATWI beyond V_2 was rare, falling to 0.2% in male nonathletes.

an average of 15.7 ± 5.1 h/week compared with nonathletes, who exercised 1.8 ± 0.6 h/week.

PREVALENCE OF ATWI. A total of 338 individuals (2.3%) exhibited ATWI. Individuals with ATWI were of similar age and had a similar mean body surface area compared with those without ATWI (Table 1). ATWI was more common in women than in men (n = 203 [4.3%] vs. n = 135 [1.4%], respectively; p < 0.0001) and was more common in athletes than in nonathletes (n = 103 [3.5%] vs. n = 235 [2%], respectively; p < 0.0001) in both sexes (women: n = 58 [6.5%] vs. n = 145 [3.8%]; p = 0.0005, and men: n = 45 [2.1%] vs. n = 90 [1.1%]; p = 0.0004) (Central Illustration). Among athletes, ATWI was more prevalent in those engaging in endurance sports than in strength sports athletes (n = 82 [5.6%] vs. n = 41 [2.8%]; respectively; p < 0.0001). The prevalence of ATWI among those 16 to 21 years of age was similar to that in those 21 years of age and older (2.28% vs. 2.46%, respectively; p = 0.52).

DISTRIBUTION OF ATWI. A total of 260 individuals (1.8%) revealed TWI confined to leads V_1 to V_2. Those in whom TWI was confined to V_1 to V_2 constituted 77% of all ATWI cases. Only 78 individuals (0.5%) demonstrated TWI beyond V_2, which was present in 56 women (1.2%) versus 22 men (0.2%) (p < 0.0001). Among athletes, TWI in leads V_1 to V_3 was detected in 19 women (2.1%) versus 7 men (0.3%) (p < 0.0001) (Central Illustration). Four women but none of the men showed TWI extending to V_4, which equated to 2% of all ATWI in females.

Deep ATWI was more common in males than in females (55.6% vs. 33%, respectively; p = 0.0166) but did not differ between athletes and nonathletes. Fifty individuals with ATWI (14.8%) exhibited incomplete right bundle branch block that never extended beyond V_2.

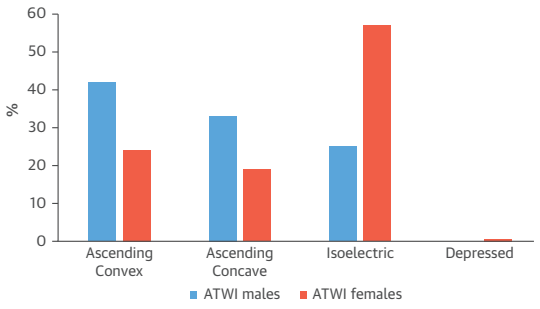
JT ELEVATION AND ST-SEGMENT MORPHOLOGY PRECEDING ATWI. Among individuals with ATWI, Jt elevation was more common in athletes than in nonathletes (49% vs. 29%, respectively; p = 0.0008) and more common in men than in women regardless of athletic status (athletes: 71.1% vs. 31.0%, respectively; p = 0.0004; nonathletes: 58.9% vs. 10.3%, respectively; p < 0.0001). None of the individuals with ATWI demonstrated a depressed Jt.

Men frequently showed an elevated ST-segment, that of ascending convex morphology (42%),

MANUSCRIPT 2

JACC VOL. 69, NO. 1, 2017
JANUARY 3/10, 2017:1–9

FIGURE 2 Bar Graph Shows ST-Segment Morphology Type Preceding ATWI in Healthy Individuals and ATWI According to Sex



An ascending convex and an ascending concave ST-segment morphology were more common in men than women. Women more commonly demonstrated an isoelectric ST-segment. ATWI = anterior T-wave inversion.

followed by an ascending concave morphology (33%) and an isoelectric pattern (25%). In women with ATWI, the ST segment was most commonly isoelectric (57%), followed by ascending convex (24%) and ascending concave (19%) morphologies. Only 1 individual with ATWI demonstrated a depressed ST-segment (Figure 2).

CARDIAC STRUCTURE AND FUNCTION IN INDIVIDUALS WITH ATWI. The echocardiographic results of all 338 individuals with ATWI (103 athletes, 235 nonathletes) were compared with the results of 1,848 individuals without ATWI (1,079 athletes, 769 nonathletes). Athletes revealed larger ventricular dimensions than nonathletes regardless of ATWI. There were no differences in left or right ventricular dimensions or function in individuals (athletes and nonathletes) with ATWI compared to those without AWTI (Table 2).

Cardiac MRI was performed in 250 subjects (74%) with ATWI. Athletes demonstrated larger left and right ventricular volumes and masses than did nonathletes (Table 2). Following gadolinium-enhanced MRI, there was no evidence of late enhancement in any subject. None of the individuals with ATWI showed unequivocal diagnostic features of ARVC, hypertrophic cardiomyopathy, or dilated cardiomyopathy.

SAECG. A total of 316 individuals (93%) with ATWI underwent SAECG, and 21 (7%) showed an abnormality in 1 of the 3 parameters. The most common abnormality was filtered QRS prolongation (60%), a phenomenon that has been reported previously in healthy individuals (31,32).

EXERCISE STRESS TESTING AND AMBULATORY ECG MONITORING. A total of 274 individuals (81%) with ATWI underwent an exercise stress test, and 293 (87%) had 24-h ECG monitoring. None of the individuals with ATWI exhibited arrhythmia during exercise, other than occasional isolated ventricular ectopic beats (n = 10; 3%) of right or left ventricular origin in the early stages of exercise. Similarly, none showed >500 ventricular ectopic beats or runs of nonsustained ventricular tachycardia during Holter monitoring (19).

DETERMINANTS OF ATWI. Univariate predictors of ATWI were female sex and athletic status. Stepwise logistic regression identified female sex (odds ratio [OR]: 3.1; 95% confidence interval [CI]: 1.96 to 4.90; $p < 0.001$) and athletic status (OR: 3.3; 95% CI: 1.91 to 5.63; $p = 0.001$) as being independently associated with ATWI in the screened adult population, regardless of age.

DETECTION OF CARDIAC PATHOLOGY. Following comprehensive clinical evaluation of 274 individuals (81%) with ATWI (including echocardiography in all 338 individuals and a mean follow-up period of 23.1 ± 12.2 months), we could not diagnose ARVC or any other cardiomyopathy. However, 16 athletes and 10 nonathletes with ATWI fell into the gray zone in which structural changes attributed to physiological adaptation needed to be differentiated from primary cardiomyopathies. These subjects included 2 athletes and 3 nonathletes with an indexed parasternal right ventricular outflow tract dimension ≥19 mm/m^2; 1 athlete with a maximal left ventricular wall thickness of 13 mm; and 6 nonathletes who initially demonstrated an absolute LVEDD (left ventricular end diastolic diameter) above the upper limit of normal (>59 mm LVEDD in male nonathletes, >53 mm in women [3], and LVEDD of >60 mm in athletes [33]).

IDENTIFICATION OF MINOR CARDIAC PATHOLOGY. Echocardiography in all 338 subjects with ATWI failed to show akinetic segments or regional wall motion abnormalities affecting the right ventricle. A small proportion revealed minor pathology in 5 subjects (1.5%) including bicuspid aortic valve (n = 2; 0.6%), mitral valve prolapse with moderate mitral regurgitation (n = 1; 0.3%), atrial septal defect (n =1; 0.3%), and patent ductus arteriosus (n = 1; 0.3%). Seven individuals (2%) had patent foramen ovale noted, and pectus excavatum was noted in 2 cases (0.6%).

MANUSCRIPT 2

JACC VOL. 69, NO. 1, 2017
JANUARY 3/10, 2017:1–9

DISCUSSION

Detection of lateral or inferolateral TWI in young black or white individuals has a relatively high yield for the diagnosis of cardiomyopathy (1). Although ATWI is a benign variant in healthy adolescents of all ethnic origins and in black adolescent and adult athletes, its significance in asymptomatic white adults is unknown. However, between 50% and 60% of probands with ARVC show ATWI in leads V_1 to V_3 (34). This study of almost 15,000 healthy, white adults, including 4,720 women and almost 3,000 athletes, showed that ATWI beyond V_1 was present in a small proportion of individuals (2.3%) and that this prevalence fell to just 0.5% beyond V_2. ATWI was more common in women than in men regardless of athletic status and validates data from much smaller studies performed 6 to 7 decades ago (35,36). Several postulations for these sex differences have been proposed, including various levels of sympathetic innervation and anatomical differences in chest wall structure, specifically breast tissue. Based on the fact that the prevalence of ATWI is almost identical in prepubertal boys and girls (3), we suspect that sex differences in adults are likely to reflect differences in lead placement as a result of increased breast tissue in women.

PREVALENCE OF ATWI IN ATHLETES. Athletes demonstrated a greater prevalence of ATWI than did nonathletes, particularly those engaging in >15 h/week of exercise. Such intense exercise regimens, particularly in endurance sports, place a greater hemodynamic load on the right ventricle that may manifest on the ECG as ATWI. Our study, however, was unable to demonstrate any structural differences between the right ventricles of individuals with ATWI and those of individuals without.

SIGNIFICANCE OF EXTRAPOLATING DATA FROM PROBANDS WITH CARDIOMYOPATHY TO LOW-RISK POPULATIONS. There are justifiable concerns about the association of ATWI with an underlying cardiomyopathy such as ARVC or hypertrophic cardiomyopathy. While isolated ATWI is rare in hypertrophic cardiomyopathy (2), ATWI beyond V_2 in probands with ARVC is common and classified as a major repolarization abnormality in the Revised Task Force Criteria for ARVC (19). In this study, none of the athletes with ATWI in leads V_2/V_3 fulfilled diagnostic criteria for ARVC based on a combination of health questionnaire, ECG, and echocardiography in 100% of cases, signal-averaged ECG in 93%, 24-h ECG in 87%, exercise testing in 81%, and cardiac magnetic resonance imaging in 74% of subjects. This observation highlights the fact that data derived from probands with ARVC for generating diagnostic criteria lack specificity in low-risk populations (29). However, TWI beyond V_2 was present in just 1 in 200 white adult athletes and could justify detailed assessment to exclude ARVC or any other cardiomyopathy. Our data support the consensus-based Seattle recommendations, which pragmatically suggest that only TWI beyond V_2 in asymptomatic white athletes requires further evaluation (9). However, these

TABLE 2 Echocardiographic and CMRI Measurements of Athletes and Nonathletes With and Without ATWI

	Athletes (n = 1,182)			Nonathletes (n = 1,004)		
	With ATWI (n = 103)	Without ATWI (n = 1,079)	p Value	With ATWI (n = 235)	Without ATWI (n = 769)	p Value
Ao, mm	28.0 ± 4.3	28.6 ± 4.5	0.2306	27.1 ± 3.6	27.4 ± 3.8	0.2839
LA, mm	33.1 ± 6.1	33.5 ± 4.9	0.4394	31.0 ± 4.3	31.3 ± 5.5	0.443
LVEDD, mm	50.8 ± 5.8	51.5 ± 5.6	0.2272	48.1 ± 4.5	48.5 ± 5.8	0.3315
LVESD, mm	34.0 ± 6.1	33.9 ± 4.8	0.844	31.1 ± 3.9	31.6 ± 5.1	0.1666
MLVWT, mm	9.2 ± 2.3	8.9 ± 2.1	0.1699	8.5 ± 2.2	8.3 ± 1.5	0.1126
LVMI, g/m^2	105 ± 15	103 ± 16	0.2233	94 ± 8	95 ± 9	0.1267
% EF	60 ± 9	59 ± 8	0.231	66 ± 8	67 ± 9	0.1267
$RVOT_{plax}$, mm	29.9 ± 5.4	29.8 ± 4.8	0.8417	26.0 ± 3.7	25.4 ± 3.6	0.1072
$RVOT_{plax}$, mm/m^2	16.7 ± 2.1	16.8 ± 3.7	0.7871	15.2 ± 2.5	14.8 ± 3.1	0.2041
$RVOT_{psax}$, mm	31.6 ± 4.9	32.3 ± 5.6	0.221	28.2 ± 5.8	29.1 ± 5.7	0.1266
$RVOT_{psax}$, mm/m^2	17.8 ± 2.5	17.5 ± 2.9	0.3106	16.0 ± 2.1	16.1 ± 2.5	0.6945
RVOT2, mm	25.8 ± 4.8	25.1 ± 4.4	0.1263	22.6 ± 3.7	23.2 ± 4.3	0.0537
RVD1, mm	41.1 ± 6.6	40.6 ± 5.8	0.4093	35.3 ± 4.9	35.6 ± 5.5	0.4534
RVD2, mm	34.1 ± 6.4	33.3 ± 5.5	0.165	28.2 ± 4.5	28.7 ± 5.7	0.2181
RVD3, mm	84.2 ± 10.5	82.0 ± 13.2	0.1008	73.5 ± 11.4	74.9 ± 11.1	0.093
RVWT, mm	4.8 ± 1.5	4.6 ± 1.3	0.1416	4.2 ± 0.8	4.1 ± 1.0	0.1613
TAPSE, mm	23.4 ± 5.3	23.5 ± 4.2	0.8219	22.8 ± 4.7	22.9 ± 4.5	0.768
PASP, mm Hg	17.6 ± 7.7	15.9 ± 6.5	0.0128	17.8 ± 3.3	18.3 ± 4.0	0.0816
TV E/A	1.9 ± 0.5	2.0 ± 0.4	0.0181	1.9 ± 0.6	2.0 ± 0.8	0.0771
TV S′, cm/s	14.8 ± 2.6	14.9 ± 2.5	0.6992	14.6 ± 2.8	14.2 ± 2.8	0.0556
TV E′, cm/s	13.9 ± 3.4	14.1 ± 3.1	0.5353	14.9 ± 2.9	15.1 ± 3.5	0.426
RAA, cm^2	19.2 ± 3.4	18.8 ± 3.7	0.2915	15.2 ± 2.8	15.1 ± 4.8	0.7613
% RV FAC	38.7 ± 4.9	39.6 ± 4.8	0.0698	36.2 ± 4.1	37.3 ± 6.2	0.0108

CMRI	ATWI Athletes (n = 76)	ATWI Nonathletes (n = 174)	
LVM-I, g/m^2	105 ± 15	94 ± 9	<0.05
LVEDVI, ml/m^2	105.8 ± 15	94.3 ± 14.0	<0.05
% RVEF	52.5 ± 5.1	55.5 ± 5.9	<0.05
RVEDVI, ml/m^2	105.3 ± 14.0	94.3 ± 14.0	<0.05
% LGE	0	0	-

Values are mean ± SD.

Ao = aorta; ATWI = anterior T-wave inversion; CMRI = cardiac magnetic resonance imaging; EF = ejection fraction according to Simpson's biplane; FAC = fractional area change; LA = left atrial; LGE = late gadolinium enhancement; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricular end-diastolic volume index; LVESD = left ventricular end-systolic diameter; LVM-I = left ventricular mass index; MLVWT = maximum left ventricular wall thickness; PASP = pulmonary artery systolic pressure; RAA = right atrial area; RV = right ventricular; RVD1 = right ventricular basal dimension; RVD2 = right ventricular midventricular dimension; RVD3 = right ventricular longitudinal dimension; RVEDV = right ventricular end-diastolic volume; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVOT1 = proximal right ventricular outflow tract dimension; RVOT2 = distal right ventricular outflow tract dimension; $RVOT_{plax}$ = right ventricular outflow tract dimension (parasternal); $RVOT_{sax}$ = right ventricular outflow tract dimension (short axis); RVWT = right ventricular free wall thickness; S′ = peak systolic velocity; TAPSE = tricuspid annular plane systolic excursion; TV = tricuspid valve; TV E′ = tricuspid valve early myocardial relaxation velocity.

MANUSCRIPT 2

recommendations are at odds with recommendations from the European Society of Cardiology and the recently published refined criteria (8,37). Given the potentially sinister ramifications of false negative tests with regard to ARVC in particular, more robust data are necessary before such criteria can be adopted with more certainly in future updates for ECG interpretation in athletes. This comprehensive study of a large population of athletes with ATWI provides support for the Seattle consensus.

POTENTIAL MARKERS OF DISEASE IN INDIVIDUALS WITH ATWI. In athletes with TWI beyond V_1, information from the preceding Jt or ST-segment may provide valuable diagnostic information when considering ARVC. Based on comparisons between 45 athletes with ATWI and 35 patients with ARVC, we have previously reported that a Jt and ST-segment in line with the onset of the QRS complex or a depressed ST-segment preceding ATWI is a powerful discriminator between the 2 entities (29). Moreover, a recent study examining ATWI as a marker of cardiomyopathy in a small cohort of athletes of black and white ethnicity showed that Jt elevation (≥0.1 mV) preceding the TWI excluded ARVC (34). Our large study of almost 15,000 white individuals provides validation for these concepts in males but reveals that Jt may be in line with the onset of the QRS complex in as many as 50% of healthy females with ATWI. Importantly, only 1 athlete demonstrated ATWI with preceding ST-segment depression and none of the individuals with ATWI showed Jt depression suggesting that the presence of such electrical markers may be pointers for cardiac pathology.

There remains the possibility that ATWI confined to V_1 to V_2 may be a manifestation of ARVC. We have examined our own cohort of 35 probands with ARVC and identified ATWI in V_1 to V_2 alone in 6%. All of these patients either expressed symptoms or other electrical features diagnostic of ARVC (29).

STUDY LIMITATIONS. This study was cross-sectional in nature, and although there were no adverse clinical events in the ATWI group during a follow-up of nearly 2 years, we cannot be certain whether ATWI may precede the development of ARVC by several years. Familial evaluation was not performed in any of the individuals with ATWI because none fulfilled overt criteria for a cardiomyopathy. However, we concede that such practice may have highlighted some individuals with incomplete expression of disease. A small proportion of ATWI individuals were lost to follow-up due to logistical difficulties that could not be overcome (e.g., emigration). CMRI is the recognized gold standard for the investigation of primary cardiomyopathies but was only performed in 250 (74%) individuals with ATWI. However, 81% of all individuals with ATWI had all of ECG, echocardiography, SAECG, Holter, and exercise stress test, which are sufficient to diagnose ARVC according to modified task force criteria (19). Voluntary cardiac screening programs of nonathletes in the community conducted through organizations such as CRY do have a potential for inherent selection bias though given the large numbers included in this study of nearly 15,000 participants, the potential of any such bias is significantly mitigated.

CONCLUSIONS

ATWI is present in 2.3% of the young white population and is more common in women and in athletes. Almost 80% of ATWI is confined to leads V_1 to V_2 and has a poor diagnostic yield for cardiac pathology, implying that this ECG pattern could be considered a normal phenomenon in asymptomatic individuals without a family history of cardiomyopathy or premature SCD. In contrast, TWI extending beyond V_2 is present in only 1% of females and 0.2% in men and may justify further evaluation in white individuals, particularly when preceded by Jt depression or ST-segment depression.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ATWI confined to leads V_1 and V_2 may be a normal variant or physiological phenomenon in asymptomatic white individuals without a family history of relevant heart disease.

TRANSLATIONAL OUTLOOK: Further research is needed to understand the clinical significance of TWI beyond lead V_2, which occurs in approximately 1 in 200 young, white athletes and in an unknown proportion of nonathletes.

MANUSCRIPT 2

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KEY WORDS anterior T-wave inversion, arrhythmogenic right ventricular cardiomyopathy, ECG screening, ethnicity

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LETTER TO THE EDITOR

WILEY

ECG in athlete: "Normal or pathologic variant?"

Dear Editor,

We read with interest the case reported by Noyes and Schulman titled "*Normal variant T-wave changes in an athlete with structurally normal cardiac anatomy and function*" (Noyes and Schulman 2016). The authors describe a challenging case, showing a common controversy—interpretation of athlete's electrocardiogram (ECG). They described a 26-year-old black competitive athlete with occasional episodes of very fast heartbeat unrelated to exertion, associated with mild dizziness, and ECG changes (deep T-wave inversions in inferior-lateral leads). Further investigations did not detect pathology and the ECG findings were classified as a "normal variant."

We have some comments regarding the management of this case. Independently of the criteria used, the ECG is clearly abnormal and although unremarkable results in imaging tests, we think that it is abusive to classify these findings as a "normal variant" (Papadakis et al., 2011; Pelliccia et al., 2008). This expression may mislead the readers, leading to wrong interpretations with potential adverse clinical impact. As cited in the discussion, abnormal ECGs may represent the initial expression of underlying cardiomyopathies, point that should have been deeply discussed. If these changes were a "normal variant" or an extreme expression of physiological adaptations, a more pronounced structural remodeling would be expected. In the brief description of echocardiogram and cardiac magnetic resonance, it seems to not occur, but the description of "minimal increase in left ventricular wall thickness with slightly greater thickness in the apical region" is intriguing (early manifestation of apical hypertrophic cardiomyopathy, commonly presented with similar ECGs?). Furthermore, the global shape and geometry of the left ventricle do not suggest adaptation to exercise. Other fundamental point is the fact that the athlete was symptomatic. Although not exercise-related and unspecific, those symptoms can be present in disorders as arrhythmias, and exercise testing and 24-hr Holter could help the investigation. In these cases it is mandatory a closer follow-up, but no data were given how the ECG and imaging tests behave in the following 3 years.

Controversial cases in sports cardiology are common and sharing experiences add value to a best approach. This ECG pattern is markedly abnormal and suggestive of pathology until proven otherwise, being important to remember that imaging phenotype may arise later and obscure underlying cardiomyopathy. On the other hand it have been referred warning symptoms and family history "that was concerning for an inherited cardiomyopathy." We must be very cautious in assessing this type of ECG changes, because its classification as "normal variant" may be a wrong message.

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MANUSCRIPT 4

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ORIGINAL ARTICLE

Abnormal electrocardiographic findings in athletes: Correlation with intensity of sport and level of competition

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KEYWORDS
Electrocardiogram;
Athletes;
Type of sport;
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Abstract
Introduction: Athletes can exhibit abnormal electrocardiogram (ECG) phenotypes that require further evaluation prior to competition. These are apparently more prevalent in high-intensity endurance sports. The purpose of this study was to assess the association between ECG findings in athletes and intensity of sport and level of competition.
Methods: A cohort of 3423 competitive athletes had their ECGs assessed according to the Seattle criteria (SC). The presence of abnormal ECGs was correlated with: (1) intensity of sport (low/moderate vs. at least one high static or dynamic component); (2) competitive level (regional vs. national/international); (3) training volume (≤20 vs. >20 hours/week); (4) type of sport (high dynamic vs. high static component). The same endpoints were studied according to the 'Refined Criteria' (RC).
Results: Abnormal ECGs according to the SC were present in 225 (6.6%) athletes, more frequently in those involved in high-intensity sports (8.0% vs. 5.4%; p=0.002), particularly in dynamic sports, and competing at national/international level (7.1% vs. 4.9%; p=0.028). Training volume was not significantly associated with abnormal ECGs. By multivariate analysis, high-intensity sport (OR 1.55, 1.18-2.03; p=0.002) and national/international level (OR 1.50, 95% CI 1.04-2.14; p=0.027) were independent predictors of abnormal ECGs, and these variables, when combined, doubled the prevalence of this finding. According to the RC, abnormal ECGs decreased to 103 (3.0%), but were also more frequent in high-intensity sports (4.2% vs. 2.0%; p<0.001).

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MANUSCRIPT 4

Conclusions: There is a positive correlation between higher intensity of sports and increased prevalence of ECG abnormalities. This relationship persists with the use of more restrictive criteria for ECG interpretation, although the number of abnormal ECGs is lower.

PALAVRAS-CHAVE
Eletrocardiograma;
Atletas;
Tipo de desporto;
Nível competitivo

Alterações eletrocardiográficas em atletas: correlação com a intensidade de desporto e o nível de competição

Resumo
Introdução: O eletrocardiograma (ECG) do atleta pode apresentar alterações que requerem avaliações adicionais, aparentemente mais frequentes nos desportos de *endurance*. O objetivo deste trabalho foi avaliar a associação entre a presença de alterações no ECG do atleta com a intensidade de desporto e nível competitivo.
Métodos: Uma coorte de 3423 atletas de nível competitivo realizaram ECG que foi interpretado pelos critérios de Seattle (CS). A presença de alterações anormais foi correlacionada com: 1) intensidade de desporto (baixo/moderado *versus* pelo menos um componente elevado, estático ou dinâmico); 2) nível competitivo (regional *versus* nacional/internacional); 3) volume de treino (≤20 *versus* >20 horas/semana); 4) tipo de desporto (elevados componentes dinâmico *versus* estático). Os mesmos *endpoints* foram estudados pelos *Refined Criteria* (RC).
Resultados: De acordo com os SC, 225 (6,6%) atletas tinham alterações patológicas, mais frequentes nos envolvidos em desportos de elevada intensidade (8,0 *versus* 5,4%; p=0,002), sobretudo dinâmica, e em nível nacional/internacional (7,1 *versus* 4,9%; p=0,028). O volume de treino não esteve significativamente associado a estas alterações. Em análise multivariada, desporto de elevada intensidade (OR 1,55, IC 95% 1,18-2,03; p=0,002) e o nível nacional/internacional (OR 1,50, IC 95% 1,04-2,14; p=0,027) foram preditores independentes de ECG anormais, variáveis que combinadas duplicaram a prevalência. Com os RC o número de ECG patológicos decresceu para 103 (3,0%), também mais frequentes nos desportos de elevada intensidade (4,2 *versus* 2,0%; p<0,001).
Conclusões: Verificou-se uma correlação positiva entre desporto de elevada intensidade e nível competitivo com alterações ECG consideradas patológicas. Apesar do menor número destas alterações, esta relação persiste com o uso de critérios mais restritivos na sua interpretação.

Introduction

Repeated exercise training induces various cardiovascular adaptations that can manifest as changes in the resting 12-lead electrocardiogram (ECG). These changes can be classified as pathological in non-athletic individuals but considered physiological and training-related in athletes.[1] However, evaluation of the athlete's ECG is challenging because various physiological adaptations can overlap with conditions associated with an increased risk of sudden cardiac death.

The prevalence, pattern and degree of ECG changes are not uniform among athletes and are dependent on various factors including age,[2,3] gender[4–6] and ethnicity.[7,8] Although a higher prevalence of marked ECG changes has been reported in athletes engaged in high-intensity endurance sports, the association between the type of sport and the occurrence of abnormal ECG findings in athletes is not well established. The majority of existing studies reporting ECG changes according to the type of sport were performed in small populations, mainly covering endurance disciplines, and did not include sports characterized by different loading conditions.[2,9,10]

The conventional dual division between endurance/dynamic and static/strength sports seems rather simplistic. Many sporting disciplines combine elements of both types of exercise, and it can therefore be difficult to establish which is predominant. Additionally, factors such as duration of training and emotional stress related to competition are not taken into consideration.[11]

The purpose of the study was to assess the association between intensity of sport and level of competition with the presence of abnormal ECG findings in athletes.

Methods

Athletes

Between September 2006 and July 2012, 15 175 young individuals (aged between 14 and 35 years) underwent cardiac evaluation in the UK, as part of a pre-participation screening

MANUSCRIPT 4

program established by the charitable organization Cardiac Risk in the Young. For the purpose of this study selected athletes were defined as individuals involved in regular competition (regional, national or international) and training more than four hours per week. The final population comprised 3423 athletes. Cardiac evaluation consisted of a self-report health questionnaire, physical examination and a 12-lead ECG. On an individual basis, when indicated for clinical reasons, ECG abnormalities or research, transthoracic echocardiography was also performed. All the athletes included in this analysis were asymptomatic and normotensive at rest (<140/90 mmHg). Ethnicity, number of hours of exercise-training/week and level of competition were self-assigned.

12-lead electrocardiogram

A 12-lead ECG was performed using GE® Marquette Hellige (Milwaukee, WI, USA) or Philips® Pagewriter Trim III (Bothell, WA, USA) electrocardiographs, with a paper speed of 25 mm/s and amplification of 0.1 mV/mm, as previously described.[12] Heart rate and QRS axis were calculated; intervals, durations, and voltages were measured in each lead. The ECGs were analyzed by the cardiologist responsible for each screening session and later read independently by two cardiologists, highly experienced in sports cardiology, cardiomyopathies and primary electrical cardiac diseases. All ECGs were interpreted and categorized as normal (without changes or with training-related changes) or abnormal (with changes that justified additional investigations for exclusion of cardiac pathology) in accordance with the Seattle criteria (SC) and the Refined Criteria (RC).[13–16]

Transthoracic echocardiogram

Transthoracic echocardiography was performed by a cardiologist or a senior cardiac physiologist, using a Philips® Sonos 7500, Philips® iE33, or Philips® CPX50 (Bothell, WA, USA) and Acuson Computed Sono-graph® 128XP/10c (San Jose, CA, USA). Standard views and chamber measurements were performed as previously suggested.[17] Left ventricular wall thickness was measured in two-dimensional (2D) parasternal short axis, at the level of the mitral valve and papillary muscles, and right ventricular dimensions were measured in apical 4-chamber view and right ventricular outflow in parasternal short-axis view at the aortic valve level. Color tissue Doppler and 2D continuous and pulsed Doppler were performed using standard parasternal and apical views. Assessment of diastolic function included pulsed Doppler across the mitral valve and tissue Doppler velocity imaging of the septal and lateral mitral valve annulus and free wall tricuspid valve annulus. An experienced cardiac physiologist independently repeated all cardiac measurements.

Classification of sports

The sporting disciplines of all the athletes included in the study were categorized according to the classification proposed by Mitchel et al. in the 36th Bethesda Conference guidelines.[11] This classification is based on the peak of static and dynamic components achieved during exercise, evaluated by maximal oxygen uptake and maximal voluntary contraction.

The volume of training was analyzed according to the number of hours performed per week and the competitive level was stratified according to the nature of the competition – regional, national or international.

The following categories were formulated, according to which the distribution of abnormal ECG changes was analyzed:

- Intensity of sport: low/moderate vs. at least one high static or dynamic component (categories III and/or C of the Mitchell et al. classification)[11]
- Competitive level: regional vs. national/international
- Training volume: $\leq$20 vs. >20 hours/week
- Type of sport: high static vs. high dynamic component.

Ethical approval and consent

Written consent was obtained from individuals aged 16 years or over and from a parent for those aged less than 16 years. The National Research Ethics Service, Essex 2 Research Ethics Committee, granted ethical approval in the UK.

Statistical analysis

Continuous variables with normal distribution were expressed as means and standard deviations. Normality was tested with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages. Statistical comparison of baseline characteristics was performed using the chi-square test or Fisher's exact test, when appropriate, and the Student's t test or the Mann-Whitney test for continuous variables. To identify independent predictors of abnormal SC, multivariate analysis using a binary logistic regression model (enter method) was performed. Two-tailed tests of significance are reported. For all comparisons, a p value of <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CI) were calculated. The statistical analysis was performed with SPSS version 21.0 (SPSS® Inc., Chicago, IL, USA).

Results

Baseline characteristics

Of the 3423 athletes included in the final analysis, mean age was 20.1±5.0 years, 2468 (72.1%) were male and the majority were Caucasian (90.1%). Athletes were engaged in 43 sporting disciplines, with rugby (35.0%), football (9.7%), swimming (6.3%) and rowing/canoeing (4.6%) being the most popular sports. Almost half of the overall population (46.3%) were engaged in sports with a high static and/or high dynamic component (category III and/or C). Regarding the competitive level, 795 (23.2%) athletes were involved in regional, 1277 (37.3%) in national and 1352 (39.5%) in international competitions. The mean number of training

MANUSCRIPT 4

Table 1 Abnormal electrocardiographic changes.

Characteristics	n (%)
Left atrial enlargement	76 (2.1)
Left axis deviation	47 (1.4)
T-wave inversion (excluding aVR, III and V1)	42 (1.2)
Wolff-Parkinson-White pattern	28 (0.01)
Right axis deviation	23 (0.01)
Long QT interval	13 (<0.01)
ST-segment depression	3 (<0.01)
Complete left bundle branch block	1 (<0.01)
Intraventricular conduction delay (QRS >140 ms)	1 (<0.01)
Pathological Q waves	1 (<0.01)
Brugada type 2 pattern	1 (<0.01)

hours/week was 16.2±7.7 (5-50 hours), with 714 (20.9%) of athletes training for >20 hours/week.

Electrocardiographic findings

Based on the SC, approximately 80% of the overall population (n=2731) had alterations in the 12-lead ECG: normal/training-related in 2482 (72.5%) and abnormal/training-unrelated in 225 (6.6%) athletes. Among the abnormal ECG changes, the most prevalent were left atrial enlargement in 76 athletes (2.1%), left axis deviation in 47 (1.4%), T-wave inversions in 42 (1.2%) and Wolff-Parkinson White pattern in 28 (0.01) (Table 1). These abnormal ECG findings were more frequent in athletes involved in high-intensity sports (8.0% vs. 5.4%; p=0.002) (Figure 1A). Athletes with abnormal SC were more likely to be of Black/Caribbean descendent (8.0% vs. 5.0%; p=0.047) and to compete at national/international level (82.7% vs. 76.3%; p=0.028) in sports with a high static or dynamic component (56.0% vs. 45.6%; p=0.002). Athletes involved in disciplines with predominantly high dynamic intensity (classes C–I/II) had a higher rate of abnormal ECG changes (9.1% vs. 5.5%; p<0.001), but there was no significant difference in sports with high static intensity (III-A/B) (4.5% vs. 6.7%; p=0.153). Comparing only athletes involved in disciplines with isolated high dynamic intensity (classes C-I/II) with those in high static intensity (classes III-A/B), the former had a higher rate of abnormal ECG changes (9.1% vs. 4.5%; p=0.014). Exercising >20 hours/week was not significantly associated with the presence of abnormal ECG changes (Table 2).

By multivariate analysis, national/international level (odds ratio [OR] 1.50, 95% confidence interval [CI] 1.04-2.14; p=0.027) and high-intensity sport (OR 1.55, 1.18-2.03; p=0.002) were independent predictors of abnormal ECG changes, with a trend for Black/Caribbean ethnicity (OR 1.58, 95% CI 0.95-2.62; p=0.078) (Table 3). The combination of the two independent variables revealed a significantly higher frequency of abnormal ECG findings in athletes competing in high-intensity sports at national/international level (8.7% vs. 5.5%; p<0.001) (Figure 2A).

Interpretation of ECGs with the RC led to a decrease of more than half in the number of abnormal/training-unrelated ECG changes, to 103 (3.0%) athletes, including among those involved in high-intensity sports (4.2% vs. 2.0%; p<0.001) (Figure 1B). These athletes with abnormal RC were

Table 2 Prevalence of baseline characteristics according to the presence or absence of abnormal Seattle criteria.[13–15]

Variables n (%)	Overall population	With abnormal SC	Without abnormal SC	p*
Demographic				
Age (mean ± D)	20.1±5.0	19.8±5.0	20.1±5.0	0.316
Male	2468 (72.1)	156 (69.3)	2312 (72.3)	0.338
Caucasian	3085 (90.1)	197 (87.6)	2888 (90.3)	0.181
Black/Caribbean	177 (5.2)	18 (8.0)	159 (5.0)	0.047
Asian	43 (1.3)	4 (1.8)	39 (1.2)	0.467
Other ethnicity	118 (3.4)	6 (2.7)	112 (3.5)	0.507
Competitive level and training volume				
National/international	2625 (76.7)	186 (82.7)	2439 (76.3)	0.028
No. hours/week (mean ± D)	16.2±7.7	16.0±7.2	17.7±7.7	0.734
>20 hours/week	714 (20.9)	48 (21.3)	666 (20.8)	0.856
Intensity of sports (Mitchell classification)[11]				
Class A	540 (15.8)	36 (16.0)	504 (15.8)	0.924
Class B	1566 (45.7)	75 (33.3)	1491 (46.6)	<0.001
Class C	1317 (38.5)	114 (50.7)	1203 (37.6)	<0.001
Class I	933 (27.3)	67 (29.2%)	866 (27.1)	0.380
Class II	1938 (56.6)	126 (56.0)	1813 (56.7)	0.840
Class III	552 (16.1)	32 (14.2)	520 (16.3)	0.422
High intensity (at least one of III/C)	1584 (46.3)	126 (56.0)	1458 (45.6)	0.002
Greater dynamic intensity (C-I/II)	1033 (30.2)	94 (41.8)	939 (29.4)	<0.001
Greater static intensity (III-A/B)	267 (7.8)	12 (5.3)	255 (8.0)	0.153

D: deviation; SC: Seattle criteria.
* p value for comparisons: athletes with abnormal SC vs. athletes without abnormal SC.

MANUSCRIPT 4

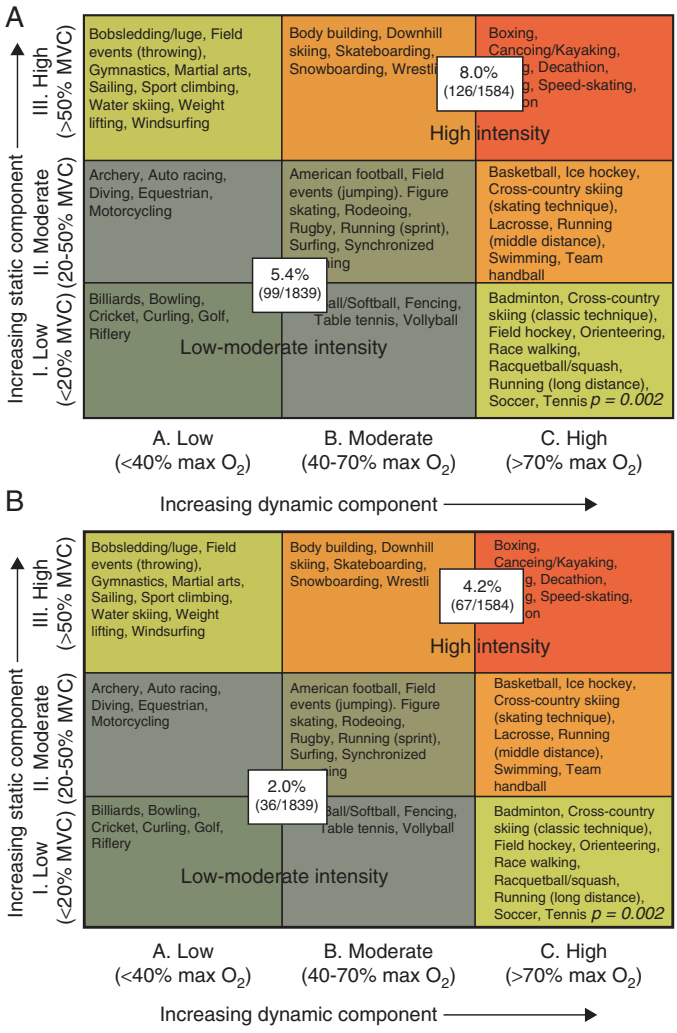

Figure 1 Distribution of abnormal (training-unrelated) ECG findings (A: Seattle criteria; B: Refined Criteria) according to intensity of sport – low-moderate vs. high (categories III and/or C). Max O_2: maximal oxygen uptake; MVC: maximal voluntary contraction. Adapted from Mitchell et al.[11]

Table 3 Independent predictors of abnormal changes according to the Seattle criteria by multivariate analysis (binary logistic regression).

Variables	OR	95% CI	p
Black/Caribbean ethnicity	1.58	0.95-2.63	0.078
National/international level	1.50	1.04-2.14	0.027
High-intensity sports	1.55	1.18-2.03	0.002

CI: confidence interval; OR: odds ratio.

more likely to be female (47.6% vs. 27.3%; <0.001) and to be involved in disciplines with predominantly high dynamic intensity (classes C-I/II) (4.7% vs. 2.3%; p<0.001), but there was no significant difference in disciplines with predominantly high static intensity (III-A/B) (2.6% vs. 3.0%; p=0.700). Comparing only athletes involved in disciplines with isolated high dynamic intensity (classes C-I/II) with those in high static intensity (classes III-A/B), there was no significant difference in prevalence of abnormal ECG changes (4.7% vs. 2.6%; p=0.127). Competing at national/international level (82.5% vs. 76.6%; p=0.161) and training >20 hours/week

MANUSCRIPT 4

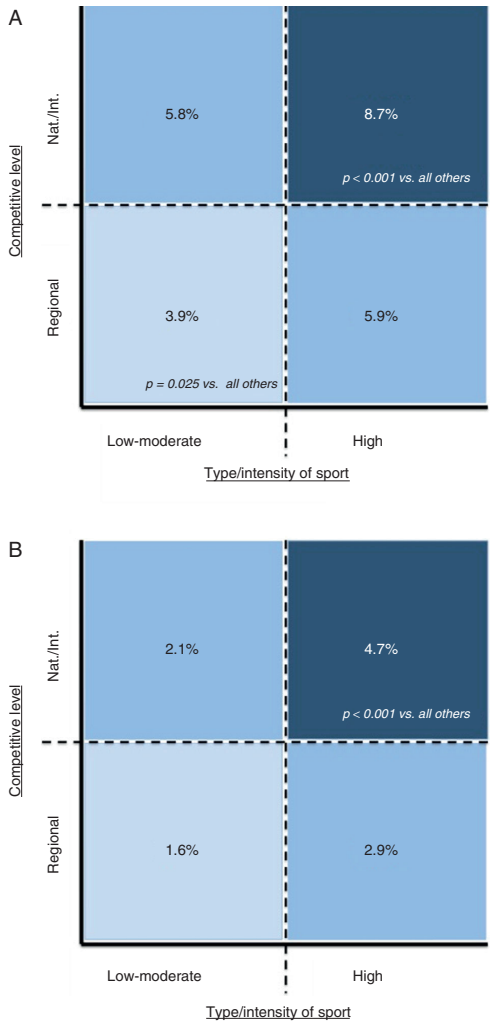

Figure 2 Distribution of abnormal ECG changes (A: Seattle criteria; B: Refined Criteria) according to the combination of type/intensity of sport and competitive level. Int.: international; Nat.: national.

(19.4% vs. 20.9%; p=0.715) were not significantly associated with abnormal RC. However, the combination of intensity of sport and competitive level revealed significant abnormal ECG changes in athletes involved in high-intensity sports at national/international level (4.7% vs. 2.1%; p<0.001) (Figure 2B).

Transthoracic echocardiography

Of the overall population, 1345 (39.3%) athletes underwent transthoracic echocardiography. Structural findings were interpreted as abnormal in 26 (0.8%) athletes. The echocardiographic findings classified as abnormal were aortic bicuspid valve (n=7), isolated right ventricular changes (e.g. hypertrabeculation) (n=5), mitral valve prolapse (n=4), anomalous coronary origin (n=2), dilated aortic root (n=2), left ventricular hypertrophy with interventricular septum ≥15 mm (n=1), large patent foramen ovale (n=1), tricuspid valve prolapse (n=1), pulmonary valve stenosis (n=1), atrial septal defect (n=1) and cor triatriatum (n=1). These structural alterations were more frequent in athletes with both abnormal SC (2.7% vs. 0.6%; p=0.010) and abnormal RC (3.9% vs. 0.7%; p<0.001). A higher frequency of echocardiographic changes classified as abnormal was also evident in athletes engaged in high-intensity sports and competing at national/international level (1.3% vs. 0.5%; p=0.012).

Discussion

In the large cohort of competitive athletes under analysis, the rate of abnormal ECG changes suggestive of cardiovascular abnormalities decreased with the use of more restrictive criteria. Independently of the criteria used (SC or RC), ECG abnormalities were more common among athletes involved in sports characterized by a high dynamic and/or static component, mainly elite athletes competing at national or international level. Otherwise, there was no significant association between the number of hours of training/week and abnormal ECG changes. Abnormal structural changes identified by transthoracic echocardiography were more common in athletes with concomitant abnormal changes on the ECG, as well as in those involved in high-intensity sports and at the national/international level.

The rate of abnormal ECGs was lower than has previously been reported (10-14%), which is related to the use of more restrictive criteria (the SC and particularly the RC).[1,8,16,18–20] In a recent study,[20] use of the SC compared to the European Society of Cardiology (ESC) recommendations[21] significantly reduced the rate of false-positive ECG screening results, while still identifying athletes with cardiac conditions. The RC[16] showed an additional improvement compared to the SC, with a significant decrease in false positives in both black and white athletes, without compromising the sensitivity of the ECG in detecting pathological conditions. In fact, some ECG findings, including isolated axis deviation and atrial enlargement, which account for a large number of changes in athletes' ECGs, do not predict structural cardiac disease when assessed by transthoracic echocardiography.[19]

Intensity and type of sport

Few studies have reported the association of type of sport with ECG findings in athletes, and these were mainly performed before the publication of guidelines for ECG interpretation in athletes, in which the sporting disciplines were analyzed individually and not according to the intensity of the dynamic and static components of exercise.[20,21] A higher prevalence of ECG changes in athletes has been mainly reported in endurance disciplines. Pelliccia et al.,[9] in 1005 athletes performing at national or international level in 38 different sporting disciplines, showed that abnormal ECG changes were more common in endurance sports

MANUSCRIPT 4

such as cycling, canoeing/rowing and cross-country skiing. Athletes engaged in endurance sports exhibit more pronounced physiological structural remodeling, which may also manifest with marked ECG alterations. The present study revealed that this relationship between intensity of sport and ECG changes is also evident for non-physiological changes. However, these results should be interpreted with caution. Despite the differences in cardiac loading conditions induced by different types of exercise, some ECG abnormalities are found in athletes engaged in predominantly dynamic as well as in those in predominantly static sports. Although the association is more evident in sports with high dynamic levels, sporting disciplines in this study are typically characterized by a combination of both types of exercise (at least one type with moderate intensity), as in rugby, swimming and basketball.

Competitive level

The impact of competitive level on electrical remodeling is also not well established and has not been considered in previous classifications of sports. The majority of previous studies were performed in athletes with similar levels of competition, mostly at national or international level. Nonetheless, given the large number of individuals involved in regular sports training at low levels of competition (club or regional) or even not competing, it is important to analyze cardiovascular adaptations in a broad spectrum of competitive levels as well as the other factors that play a part.[22] Although this idea is controversial, it has been proposed that the emotional stress of competition can induce sympathetic activation, which is a potential trigger for arrhythmias or myocardial ischemia.[10] It might be assumed that sports played at higher levels of competition (national or international), independently of the intensity of physical exercise, would be associated with greater psychological stress. Nevertheless, no relation between emotional stress induced by highly competitive sport and ECG abnormalities has been reported.

Training volume

Although there is an empirical assumption that the cause-effect relationship between the volume of training and electrical remodeling is obvious, there is little evidence of abnormal ECG findings and the idea is controversial. In a study by Papadakis et al.[23] in adolescent Caucasian athletes, the duration of training was not an independent predictor for T-wave inversion in the precordial leads, one of the most frequent abnormalities seen in the ECGs of competitive athletes. Comparing athletes training for fewer hours a week with those training more, the latter more frequently have ECG changes, as shown by Gati et al.[19] with respect to left axis deviation and left atrial enlargement.

Our results offer new insights regarding the association of intensity and level of competition with the presence of abnormal ECG findings, and highlight characteristics that should be considered together when interpreting an athlete's ECG.

Limitations

The present study has some limitations that should be highlighted. The analysis was retrospective. Some of the characteristics, such as the volume of training, were self-reported by the athletes. Although this was a large cohort compared to previous studies, larger populations should be analyzed, bearing in mind the low rate of the endpoints studied. The low representation of some groups, such as females and non-Caucasians, limits the generalization of these results. Athletes at the extreme end of the spectrum (those with the highest sporting intensity and competitive level) may be more prone to develop abnormal ECG changes. For those with intermediate levels of intensity and competition, correlation with the presence of abnormal ECG findings is difficult to establish due to the dichotomized criteria used in this study. The categorization of sports into nine groups, as in the classification of Mitchell et al.,[11] makes this less easy to implement and further subdividing sports may hinder reliable comparisons between the different categories. Although this was not the aim of the study, it is difficult to establish associations between echocardiographic abnormalities and ECG findings; transthoracic echocardiography was not systematically performed and the main purpose of the study was research.

Conclusions

The present study shows a positive correlation between greater intensity of sport and increased prevalence of ECG abnormalities. This relationship persists with the use of more restrictive criteria for ECG interpretation (the 'Refined Criteria'), although the number of abnormal ECGs is lower. The characteristics of specific sports should be taken into account when evaluating elite athletes, to help with early identification of those who may be more prone to develop ECG abnormalities and to prevent unnecessary subsequent evaluation and unwarranted disqualification from competitive sport.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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MANUSCRIPT 4

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MANUSCRIPT 5

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ORIGINAL ARTICLE

Variability in interpretation of the electrocardiogram in athletes: Another limitation in pre-competitive screening☆

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KEYWORDS
Electrocardiogram;
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Abstract
Introduction: Assessment of the electrocardiogram (ECG) in athletes remains controversial, with lack of standardization and difficulty in applying specific criteria in its interpretation. The purpose of this study was to assess variability in the interpretation of the ECG in athletes.
Methods: Twenty ECGs of competitive athletes were assessed by cardiologists and cardiology residents, 11 of them normal or with isolated physiological changes and nine pathological. Each ECG was classified as normal/physiological or pathological, with or without the use of specific interpretation criteria.
Results: The study presents responses from 58 physicians, 42 (72.4%) of them cardiologists. Sixteen (27.6%) physicians reported that they regularly assessed athletes and 32 (55.2%) did not use specific ECG interpretation criteria, of which the Seattle criteria were the most commonly used (n=13). Each physician interpreted 15±2 ECGs correctly, corresponding to 74% of the total number of ECGs (variation: 45%-100%). Interpretation of pathological ECGs was correct in 68% (variation: 22%-100%) and of normal/physiological in 79% (variation: 55%-100%). There was no significant difference in interpretation between cardiologists and residents (74±10% vs. 75±10%; p=0.724) or between those who regularly assessed athletes and those who did not

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MANUSCRIPT 5

(77±12% vs. 73±9%; p=0.286), but there was a trend for a higher rate of correct interpretation using specific criteria (77±10% vs. 72±10%; p=0.092). The reproducibility of the study was excellent (intraclass correlation coefficient=0.972; p<0.001).
Conclusions: A quarter of the ECGs were not correctly assessed and variability in interpretation was high. The use of specific criteria can improve the accuracy of interpretation of athletes' ECGs, which is an important part of pre-competitive screening, but one that is underused.

PALAVRAS-CHAVE
Eletrocardiograma;
Interpretação;
Variabilidade;
Atletas

Variabilidade na interpretação do eletrocardiograma do atleta: mais uma limitação na avaliação pré-competitiva

Resumo
Introdução: A interpretação do eletrocardiograma (ECG) do atleta permanece controversa, com ausência de estandardização e dificuldade na aplicação de critérios específicos na sua interpretação. O objetivo deste trabalho é avaliar a variabilidade na interpretação do ECG de atletas.
Metodologia: Vinte ECG de atletas foram avaliados por cardiologistas e internos de cardiologia, 11 normais ou apenas com alterações fisiológicas e nove patológicos. Cada ECG foi classificado pelos inquiridos em normal/com alterações fisiológicas ou patológico, usando ou não critérios específicos na sua interpretação.
Resultados: Foram incluídas as respostas de 58 médicos, 42 (72,4%) cardiologistas. Dezasseis (27,6%) afirmaram avaliar frequentemente atletas e 32 (55,2%) não usar critérios específicos na interpretação do ECG, sendo os mais usados os critérios de Seattle (n=13). Em média, cada médico interpretou corretamente 15±2 ECG, correspondendo a 74% dos traçados (variação: 45-100%). A interpretação dos ECG foi correta em 68% (variação: 22-100%) dos patológicos e em 79% (variação: 55-100%) dos normais/com alterações fisiológicas. Não houve diferença significativa na interpretação entre cardiologistas e internos (74±10% *versus* 75±10%; p=0,724), nem entre os que avaliam frequentemente ou não atletas (77±12% *versus* 73±9%; p=0,286), verificando-se uma tendência para interpretação mais correta com critérios específicos (77±10% *versus* 72±10%; p=0,092). A reprodutibilidade do estudo foi excelente (*intraclass correlation coefficient*=0,972; p<0,001).
Conclusão: Na amostra estudada, cerca de um quarto dos ECG foram incorretamente avaliados, havendo uma elevada variabilidade na sua interpretação. O uso de critérios específicos na interpretação do ECG do atleta pode melhorar a acuidade deste exame no *screening* de atletas, mas são ainda subutilizados.

Introduction

The main purpose of pre-competitive screening of athletes is to enable early (pre-clinical) identification of pathological conditions associated with increased risk of serious clinical events, including sudden death. Data from Italy show an 89% reduction in the incidence of sudden death in competitive athletes following the inclusion of the electrocardiogram (ECG) in pre-competitive screening.[1] In view of this, most European countries currently recommend that pre-competitive screening should include personal and family history, physical examination, and a resting 12-lead ECG.[2]

Despite this evidence and the many arguments in support of ECG assessment, the inclusion of this exam in pre-competitive screening remains controversial, basically because of disagreement between Europe and the US, where it is not formally recommended.[3,4] Of the arguments put forward against ECGs in athletes, the most frequent is the high false-positive rate, which can lead to unnecessary additional diagnostic exams and inappropriate exclusion of healthy individuals from competition. Most false positives result from incorrect interpretation of the ECG, mainly because alterations caused by exercise-induced physiological adaptations of the heart are wrongly classified as pathological.[5–7] Thus, the central issue in this controversy is not whether the ECG should be included in pre-participation screening, but rather how the exam should be interpreted.

Various increasingly restrictive criteria have been published with the aim of standardizing interpretation of the ECG in athletes, notably those of the European Society of

MANUSCRIPT 5

Table 1 Main characteristics of the athletes and electrocardiograms under analysis.

ECG	Athlete	Interpretation	Main alterations
1	Male, Caucasian, age 35 years; running	Pathological (Brugada syndrome)	Type 1 Brugada
2	Male, Caucasian, age 24 years; judo	Pathological (ARVD)	Voltage criteria for RVH; right axis deviation (>120°)
3	Female, black, age 22 years; handball	Pathological (HCM)	Negative T waves in inferior leads and V5-V6
4	Male, Caucasian, age 23 years; gymnastics	Physiological	Sinus bradycardia; incomplete right bundle branch block
5	Male, Caucasian, age 30 years; 11-a-side soccer	Pathological (anomalous coronary artery origin)	ST-segment depression in lateral leads, negative T waves in inferior leads
6	Male, Caucasian, age 23 years; running	Pathological (HCM)	Pathological Q waves in inferior and lateral leads
7	Male, Caucasian, age 31 years; running	Physiological	Sinus bradycardia; early repolarization
8	Male, Caucasian, age 35 years; running	Physiological	Sinus bradycardia; voltage criteria for LVH
9	Male, Caucasian, age 22 years; running	Physiological	Sinus bradycardia; early repolarization; voltage criteria for LVH
10	Male, black, age 24 years; boxing	Physiological	Sinus bradycardia; negative T waves in V1-V4; voltage criteria for LVH
11	Female, Caucasian, age 24 years; running	Physiological	Sinus bradycardia
12	Male, Caucasian, age 18 years; kickboxing	Physiological	Sinus arrhythmia; early repolarization; voltage criteria for LVH
13	Male, Caucasian, age 31 years; tennis	Pathological (WPW)	Short PR interval (<120 ms), delta wave
14	Male, Caucasian, age 30 years; cycling	Physiological	Sinus bradycardia
15	Male, Caucasian, age 19 years; 11-a-side soccer	Physiological	Sinus bradycardia; early repolarization; voltage criteria for LVH
16	Male, Caucasian, age 22 years; running	Physiological	Type 1 2nd-degree atrioventricular block
17	Male, black, age 25 years; 11-a-side soccer	Pathological (HCM)	Negative T waves in inferior leads and V3-V6
18	Female, Caucasian, age 30 years; cycling	Pathological (ARVD)	Isolated PVCs with LBBB pattern and negative T waves in inferior leads
19	Male, Caucasian, age 15 years; swimming	Pathological (LQTS)	Long QT interval (QTc >480 ms)
20	Male, Caucasian, age 16 years; rugby	Physiological	Sinus bradycardia; juvenile pattern (negative T waves in V1-V3)

ARVD: arrhythmogenic right ventricular dysplasia; HCM: hypertrophic cardiomyopathy; LBBB: left bundle branch block; LQTS: long QT syndrome; LVH: left ventricular hypertrophy; PVCs: premature ventricular contractions; QTc: corrected QT interval; RVH: right ventricular hypertrophy; WPW: Wolff-Parkinson-White syndrome.

Cardiology (ESC), the Seattle criteria, and the 'refined' criteria.[8–11] However, although the application of these criteria has led to a significantly lower number of false positives, they are still underused, and variability in the interpretation of the ECG in athletes remains high.[12,13]

The purpose of this study was to assess variability in the interpretation of the ECG in competitive athletes, with or without the use of specific criteria, in a sample of cardiologists and cardiology residents in Portugal.

Methods

Study population and selection of electrocardiograms

Twenty ECGs of competitive athletes from pre-competitive screening assessments were selected. Most athletes were male (n=18) and Caucasian (n=17); median age was 24 (22-31) years. They performed at least eight hours of training a week and participated in various sports, most involving high-intensity dynamic exercise: medium- or long-distance running (n=7), soccer (n=4), cycling (n=2), rugby (n=1), swimming (n=1), gymnastics (n=1), tennis (n=1), boxing (n=1), judo (n=1) and kickboxing (n=1).

Of the selected ECGs, 11 were normal or with isolated physiological changes, and nine were pathological. The traces were selected after a validation and classification process agreed unanimously by three cardiologists experienced in sports medicine, particularly in interpreting athletes' ECGs. For the pathological ECGs, the diagnosis of heart disease (cardiomyopathy or primary arrhythmia) was established on the basis of additional diagnostic exams. Table 1 presents the main characteristics of the athletes and ECGs under analysis.

Figure 1 shows two examples of the ECGs included in this study, one non-pathological (Figure 1A), with only physiological alterations irrespective of the criteria used for its

MANUSCRIPT 5

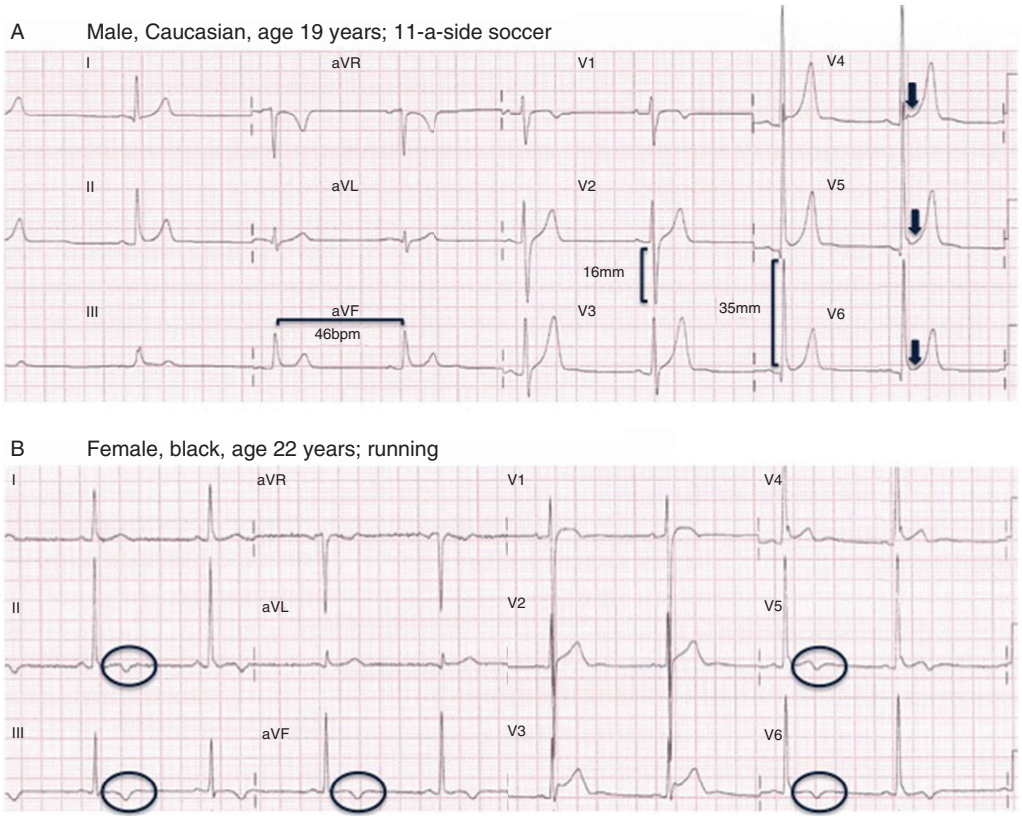

Figure 1 Two of the electrocardiograms (ECGs) in the study questionnaire. (A) ECG showing physiological alterations (sinus bradycardia, isolated voltage criteria for left ventricular hypertrophy and early repolarization); (B) ECG showing pathological alterations (negative T waves in all inferior leads and V5-V6), in an athlete diagnosed with hypertrophic cardiomyopathy.

interpretation, and the other pathological (Figure 1B), that of an athlete with hypertrophic cardiomyopathy.

Interpretation of electrocardiograms

The ECGs selected for this analysis were included in a form developed on the Google Forms platform (https://docs.google.com/forms/d/1vpVaTKSSlp2TfjiIkGtvX4qZBmkiNnnKnSKHKUYJSR4/viewform). The form was emailed to cardiologists and cardiology residents working in representative cardiology departments throughout Portugal (a total of 186 physicians). After an introductory text explaining the study's background and aims, the physicians were asked to identify themselves as a cardiologist or a cardiology resident and to state the main area of their clinical practice (specifically whether they worked within a subspecialty of cardiology), whether they regularly assessed athletes' ECGs and whether they used specific criteria to do so, and if so, which. Each ECG was accompanied by information on the athlete's demographic characteristics (age, gender and race) and sport. For each ECG, the respondent was asked whether they considered the trace pathological or non-pathological. Only questionnaires with responses to all questions were considered valid, and only one could be submitted by each physician. Data collection took place over a period of one month (November 2015). All records were kept confidential and only the lead investigator had access to the results.

Statistical analysis

The data were analyzed using SPSS for Windows, version 22.0. Categorical variables were expressed as absolute values and percentages and compared with the chi-square test, while continuous variables were expressed as means ± standard deviation and were compared with the Student's t test under conditions of normality and homoscedasticity or as medians and interquartile range (25th-75th percentile) for non-normal distributions. The reproducibility of the study was assessed by calculating the intraclass correlation coefficient. Results with $p<0.05$ were considered statistically significant.

MANUSCRIPT 5

Table 2 Interpretation of electrocardiograms according to the characteristics of the physicians surveyed and the methods used.

n (%)	Total	Mean percentage of correctly interpreted ECGs		
		Total	Non-pathological	Pathological
Main area of clinical practice				
Cardiologist	42 (72.4)	74	79	67
Cardiology resident	16 (27.6)	75	79	70
Clinical cardiology	41 (70.7)	75	80	70
Other areas of cardiology	17 (29.3)	72	78	64
Regular assessment of athletes	16 (27.6)	77	84	68
Interpretation of ECG				
Based on clinical experience	32 (55.2)	72	80	73
Based on specific criteria	26 (44.8)	77	78	75
ESC criteria	8 (13.8)	72	74	69
Seattle criteria	13 (22.4)	77	80	74
Refined criteria	4 (6.9)	86	86	86
Other criteria	1 (1.9)	70	55	89

ECG: electrocardiogram; ESC: European Society of Cardiology.

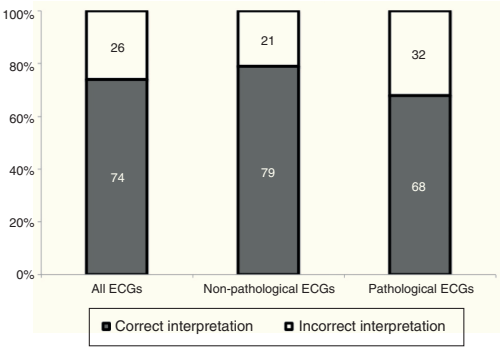

Figure 2 Proportions of correct and incorrect interpretations of electrocardiograms. ECG: electrocardiograms.

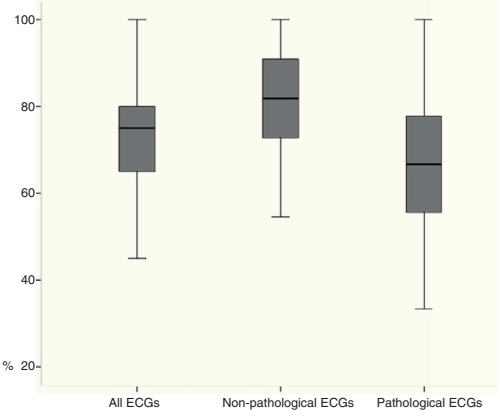

Figure 3 Variability in proportions of correctly interpreted electrocardiograms. ECG: electrocardiograms.

Results

The study included responses from 58 physicians (response rate 31%), 42 (72.4%) of them cardiologists and the remainder cardiology residents; 16 (27.6%) of the physicians stated that they regularly assessed athletes. More than half (32; 55.2%) did not use specific criteria for assessing athletes' ECGs, and of those who did, the most commonly used were the Seattle criteria (n=13), followed by the ESC criteria (n=8). Table 2 presents the characteristics of the physicians surveyed and the percentages of correctly interpreted ECGs.

Each physician correctly interpreted a mean of 15±2 traces, corresponding to 74% of the ECGs analyzed, ranging between 45% and 100%. For pathological ECGs, the interpretation was correct in 68% of cases, ranging between 22% and 100%, while for non-pathological traces it was correct in 79% of cases (55%-100%) (Figures 2 and 3).

There were no statistically significant differences between cardiologists and residents concerning correctness of interpretation (74±10% vs. 75±10%; p=0.724), or between physicians who regularly assessed athletes' ECGs and those who did not (77±12% vs. 73±9%; p=0.286). There was a trend for a higher rate of correct interpretation using specific criteria (77±10% vs. 72±10%; p=0.092). The intraclass correlation coefficient was 0.972 (95% confidence interval 0.951-0.987; p<0.001), showing that the reproducibility of the study was excellent.

Discussion

This study demonstrates that assessment of the ECG in athletes remains less than optimal, since around a quarter of the ECGs analyzed were not correctly assessed and variability in interpretation was high. Although most of the physicians surveyed (cardiologists and residents) stated that

MANUSCRIPT 5

they did not use specific criteria for ECG interpretations, there was a trend for a higher rate of correct interpretation using such criteria.

These results are consistent with previously published findings, and empirically there is a perception that variability (intra- and inter-observer) in interpretation of the ECG in athletes is high. However, there have been few recent studies on the subject. Berte et al.[12] carried out a similar study, using a larger number of ECGs (138) and a smaller number of physicians (seven cardiologists and seven sports physicians), in which the ECGs were interpreted according to established criteria; variability was high, with disagreement on 35% of the ECGs overall. In a study by Hill et al.[14] using a similar sample to the present work (18 ECGs analyzed by 53 pediatric cardiologists), the rate of incorrect interpretation was 31%. Analyzing 40 ECGs of athletes interpreted by physicians of various specialties, Drezner et al.[15] showed that accuracy improved significantly after participants were provided with and asked to adopt the Seattle criteria; among cardiologists, the proportion of ECGs interpreted incorrectly fell from 15% to 4%.[15]

Although the difference was not statistically significant, in our study the rate of correct interpretation was lower for pathological ECGs, i.e. the proportion of false negatives was higher than that of false positives. Since the main problem with interpreting athletes' ECGs is the high false-positive rate, the opposite would be expected. Irrespective of the characteristics analyzed, the proportion of pathological ECGs interpreted correctly was low except with the refined criteria,[11] which were only used by a small number of physicians. Since these are the most recent criteria, they are probably more familiar to physicians with more experience and/or more interest in the area, who are thus more likely to interpret the ECG correctly. In previous studies the false-positive rate was similar, with more accurate interpretation seen after the adoption of specific criteria.[14–16] For example, an assessment of the diagnostic accuracy of the Seattle criteria showed that the false-positive rate fell from 30% to 9% after they were applied.[15] It is thus essential to raise awareness of specific criteria for the interpretation of the ECG in athletes and ensure they are correctly applied.

Variability in interpretation means that many athletes undergo unnecessary additional diagnostic exams, which have a considerable socioeconomic impact. There is also the question of the psychological stress caused by an incorrect reading, as well as the fact that these exams do not identify all causes of sudden death or ensure that athletes have been inappropriately barred from competing. Furthermore, the low prevalence of pathological ECGs in athletes means that they are more difficult to identify, increasing the variability of interpretation (the prevalence effect).[15] Another important aspect is the influence of exercise-induced (physiological) electrical adaptations in the heart, which are affected by the athlete's demographic characteristics and the type of sport.[5]

There are many arguments in favor of including the ECG in pre-competitive screening of athletes, but it is still essential to optimize their interpretation. Possible ways to achieve this include training, standardization of methods, and centralized screening in specialized units. It is also important to raise awareness of the specific criteria for interpreting athletes' ECGs and of their advantages and disadvantages, ideally through the publication of consensus documents and protocols indicating which criteria to adopt, in order to encourage standardization. However, the current criteria are the product of expert opinion and retrospective studies, and there have been few prospective analyses that can identify the ECG alterations that correlate most closely with clinical events, especially sudden death. Despite the shortcomings of the currently available criteria, their limitations cannot be evaluated, let alone overcome, until they have been applied in clinical practice.

Limitations

This study has certain limitations that should be pointed out. The sample size was small, which limits the applicability of its results, and fewer than one third of surveyed physicians responded to the questionnaire. However, even so, the final study population was larger than in some previous studies on this subject. The characteristics of the selected athletes were very similar, with few non-Caucasians, females, or older athletes included. Although the questionnaire responses were confidential, physicians who were more interested and experienced in this area may have been more motivated to respond, and this also may have skewed the results. Some of the participants may have consulted the criteria when analyzing the ECGs, which hampers assessment of their existing knowledge; however, this does not affect the main purpose of the study and is in fact to be recommended in clinical practice, particularly for physicians who do not regularly assess athletes.

Conclusions

In the study population, a quarter of athletes' ECGs were not correctly assessed and variability in interpretation was high. Standardization of ECG interpretation in athletes with the use of specific criteria can improve the accuracy of this exam in pre-competitive screening. However, these criteria are still underused, a situation that could be changed by improvements in medical training in this area.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

MANUSCRIPT 5

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MANUSCRIPT 6

Original Article

Inter-Rater Reliability and Downstream Financial Implications of Electrocardiography Screening in Young Athletes

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Background—Preparticipation screening for cardiovascular disease in young athletes with electrocardiography is endorsed by the European Society of Cardiology and several major sporting organizations. One of the concerns of the ECG as a screening test in young athletes relates to the potential for variation in interpretation. We investigated the degree of variation in ECG interpretation in athletes and its financial impact among cardiologists of differing experience.

Methods and Results—Eight cardiologists (4 with experience in screening athletes) each reported 400 ECGs of consecutively screened young athletes according to the 2010 European Society of Cardiology recommendations, Seattle criteria, and refined criteria. Cohen κ coefficient was used to calculate interobserver reliability. Cardiologists proposed secondary investigations after ECG interpretation, the costs of which were based on the UK National Health Service tariffs. Inexperienced cardiologists were more likely to classify an ECG as abnormal compared with experienced cardiologists (odds ratio, 1.44; 95% confidence interval, 1.03–2.02). Modification of ECG interpretation criteria improved interobserver reliability for categorizing an ECG as abnormal from poor (2010 European Society of Cardiology recommendations; κ=0.15) to moderate (refined criteria; κ=0.41) among inexperienced cardiologists; however, interobserver reliability was moderate for all 3 criteria among experienced cardiologists (κ=0.40–0.53). Inexperienced cardiologists were more likely to refer athletes for further evaluation compared with experienced cardiologists (odds ratio, 4.74; 95% confidence interval, 3.50–6.43) with poorer interobserver reliability (κ=0.22 versus κ=0.47). Interobserver reliability for secondary investigations after ECG interpretation ranged from poor to fair among inexperienced cardiologists (κ=0.15–0.30) and fair to moderate among experienced cardiologists (κ=0.21–0.46). The cost of cardiovascular evaluation per athlete was $175 (95% confidence interval, $142–$228) and $101 (95% confidence interval, $83–$131) for inexperienced and experienced cardiologists, respectively.

Conclusions—Interpretation of the ECG in athletes and the resultant cascade of investigations are highly physician dependent even in experienced hands with important downstream financial implications, emphasizing the need for formal training and standardized diagnostic pathways. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003306. DOI: 10.1161/CIRCOUTCOMES.116.003306.)**

Key Words: athletes ■ cardiologists ■ death, sudden, cardiac ■ heart disease ■ sports

Preparticipation cardiovascular screening of young athletes with electrocardiography (ECG) is effective for detecting potentially serious cardiac disease and is endorsed by the European Society of Cardiology (ESC) and several international sporting bodies.[1–3] However, the accuracy of the ECG is dependent on the individual interpretation of the test, which may vary considerably among cardiologists of differing experience.[4,5]

See Editorial by Prutkin and Drezner

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MANUSCRIPT 6

WHAT IS KNOWN

- The inclusion of the ECG to a health questionnaire and physical examination screening protocol in young athletes improves sensitivity to detect serious cardiac disease; however, a concern of the ECG as a screening tool relates to the potential for variation in interpretation especially in inexperienced hands.

WHAT THE STUDY ADDS

- There is only moderate interobserver reliability for ECG interpretation even among cardiologists with experience in the cardiovascular evaluation of young athletes.
- Modification of ECG interpretation criteria improves reliability among inexperienced cardiologists.
- The decision to propose secondary investigations after ECG interpretation varies among inexperienced and experienced cardiologists, respectively, with significant downstream financial implications.
- The findings of this study highlight that formal training and development of standardized diagnostic pathways are essential to support cardiologists involved in cardiovascular screening of young athletes.

Recent modification of ECG interpretation recommendations has improved the efficacy of the ECG as a screening tool by reducing the false-positive rate and cost of screening.[3,6–8] Whether such modification has an impact on the variation of ECG interpretation in young athletes is unknown. Furthermore, whether experience of reporting ECGs in athletes affects variability of interpretation and recommended secondary testing among cardiologists is also unknown. This study evaluated the variation of interpretation of the athlete's ECG and its financial impact between experienced and inexperienced cardiologists using 3 internationally recognized ECG interpretation recommendations.[3,6,7]

Methods

Study Population

The charitable organization Cardiac Risk in the Young has an established cardiac screening program for young individuals aged 14 to 35 years, which serves many professional sporting organizations in the United Kingdom (www.c-r-y.org.uk). The Cardiac Risk in the Young screening protocol consists of a health questionnaire pertaining to symptoms suggestive of cardiac disease or a family history of cardiac disease, a physical examination, and a 12-lead ECG. The first 400 consecutively assessed athlete's ECGs from the program in 2014 were used for the primary analysis of interobserver agreement. These athletes have been presented previously as part of a nationwide ECG screening cost analysis.[8] None of the athletes were considered to have symptoms suggestive of cardiovascular disease, and none had a significant family history of cardiovascular disease. All had a normal physical examination. These athletes were evaluated by different experienced sports cardiologists. Purely as a reference, 24 (6.0%) of the athletes were referred for further evaluation, 23 (5.8%) underwent echocardiography, 6 (1.5%) exercise stress testing, 8 (2.0%) Holter, and 5 (1.3%) cardiac magnetic resonance imaging.

Participants

Eight cardiologists independently participated in the interpretation of the ECGs, of whom 4 were experienced in evaluating the ECG in athletes. For the purposes of the study, we defined cardiologists with experience as those who were working in a specialist sports cardiology unit for >2 years and had independently conducted preparticipation ECG screening with ECG in ≥1000 athletes. Conversely, inexperienced cardiologists were defined as those who did not routinely report on athlete's ECG. Both groups consisted of 3 general cardiologists and 1 electrophysiologist.

ECG Interpretation

All cardiologists were provided with the 400 anonymized ECGs in random order and in a digital printable format, which included the age, sex, and ethnicity of the athlete. The cardiologists were informed that all athletes had normal history and physical examination findings. Digital measurements of heart rate, QRS duration, PR interval, and QT interval were omitted.

The cardiologists were provided with a copy of published documents detailing the 2010 ESC recommendations, the Seattle criteria, and the refined criteria 1 month before commencement of ECG interpretation (Table 1).[3,6,7] Each cardiologist was instructed to assign the ECGs as normal or abnormal per criterion and specify the abnormities.

All cardiologists calculated the QT interval manually. Instructions were provided on measuring the QT interval using the tangent method.[9] Cardiologists were advised to report the longest QT interval value as the absolute QT and to correct the QT interval for heart rate using the Bazett formula, where the corrected QT interval (QTc)=QT/$\sqrt{}$RR interval.[10]

Secondary Investigations and Financial Analysis

The initial preparticipation screening tests (history, physical examination, and ECG) were performed at a subsidized cost of $53 per athlete screened.

In the event of an abnormal ECG, the cardiologists were instructed to propose specific secondary investigations based on their usual clinical practice. The cost of secondary investigations was calculated based on the 2014/2015 UK National Health Service tariff payment system (Table I in the Data Supplement). Genetic testing was not included in the cost analysis because it is usually reserved for individuals with disease phenotype for the purposes of cascade screening.

Statistics

The data were graphically explored and summarized accordingly, that is, means, SDs, median interquartile range, and range for continuous data and proportions for categorical or binary independent data.

Raw indices of interobserver agreement are presented as the overall and specific proportions of agreement among the groups of cardiologists. Cohen κ coefficient was used to calculate the overall interobserver reliability in ECG interpretation between groups of cardiologists (experienced and inexperienced) with κ<0.20 representing poor interobserver reliability, 0.20 to 0.40 representing fair reliability, 0.40 to 0.60 representing moderate reliability, 0.60 to 0.80 representing good agreement, and 0.80 to 1.00 representing very good reliability. To disentangle the potential heterogeneities in the κ values across age, sex, and ethnicity, 2 novel binary variables were constructed for each group of clinical experts in a similar fashion: 1 if all 4 clinicians perfectly agreed, 0 otherwise. Then, a bivariate logistic regression was applied to the joined binary outcome for a simultaneous flavor of the odds of perfect agreement within the 2 clinical groups. As this is not an indication of agreement because some information is lost, the Cohen agreement coefficient was recalculated across heterogeneous groups in the population indicated by this analysis and subsequently presented. Further referrals comprised 5 destinations (echocardiography, exercise stress test, Holter, cardiac magnetic resonance imaging, and family screening) with the possibility that a patient required >1. Given the binary nature of this

MANUSCRIPT 6

Table 1. Summary of Definition of ECG Abnormalities in Athletes According to the 2010 ESC Recommendations, Seattle Criteria, and Refined Criteria[3,6,7]

All 3 criteria	ST-segment depression
	Pathological Q waves
	Complete left bundle branch block
	Ventricular pre-excitation
	Brugada-like early repolarization pattern
	Premature ventricular contractions
	Atrial or ventricular arrhythmia
2010 ESC recommendations	T-wave inversion
	Long-QT interval >440 ms (male) or >460 ms (female)
	Short-QT interval <380 ms
	Right ventricular hypertrophy
	Right- or left-axis deviation
	Right or left atrial enlargement
	Complete right bundle branch block
	Nonspecific intraventricular delay (QRS >120 ms)
Seattle criteria	T-wave inversion beyond V2 in white athletes
	T-wave inversion beyond V4 in black athletes
	Long-QT interval ≥470 ms (male) or ≥480 ms (female)
	Short-QT interval ≤320 ms
	Right ventricular hypertrophy (in presence of right-axis deviation)
	Left-axis deviation
	Right or left atrial enlargement
	Nonspecific intraventricular delay (QRS ≥140 ms)
Refined criteria	T-wave inversion beyond V1 in white athletes
	T-wave inversion beyond V4 in black athletes
	Long-QT interval ≥470 ms (male) or ≥480 ms (female)
	Short-QT interval ≤320 ms
	Complete right bundle branch block
	Borderline variants (requiring investigation if >1 present)
	T-wave inversion up to V4 in black athletes
	Right ventricular hypertrophy
	Right- or left-axis deviation
	Right or left atrial enlargement

ESC indicates European Society of Cardiology.

multivariate response, we adopted a simpler yet easily interpretable approach. Each destination was considered a separate binary outcome, and a 2-level logistic regression applied to account for the inherent dependencies in the data arising from multiple measurements for the same athlete.

P values <0.05 were considered statistically significant, and the uncertainty of the estimates is expressed as their 95% confidence intervals (CI). Marginal predictions, that is, predicted proportions summarized according to the clinical relevance, are also presented. The analyses were performed in Stata (StataCorp 2015, Stata Statistical Software).

Ethics

Ethical approval was granted by the Essex 2 Research Ethics Committee. Written consent was obtained from individuals ≥16 years of age and from a parent/guardian for those <16 years of age.

Results

Demographics

Athletes were aged 20.5±4.8 years. Two hundred and eighty-five (71%) were male. Three hundred and eighteen (79%) athletes were white and 43 (11%) were of African/Afro-Caribbean origin (black). Thirty-nine (10%) athletes consisted of other ethnicities including mixed race, Asian or Polynesian. Athletes competed in a total of 18 different sporting disciplines—predominantly soccer (29%), rugby (16%), and cycling (15%)—and exercised for 16.6±6.0 hours per week.

Identification of ECGs Suggestive of Cardiac Disease

One (0.3%) athlete was diagnosed with potentially serious cardiac disease, notably long-QT syndrome (QTc 520 ms). The ECG of this athlete was classified as requiring further evaluation by all 8 cardiologists.

Categorization of ECG Abnormalities in Accordance to ECG Interpretation Criteria

Frequency of ECG Abnormalities

Inexperienced cardiologists more frequently categorized an ECG as abnormal compared with experienced cardiologists for all 3 criteria (Figure 1). Compared with both the 2010 ESC recommendations and the Seattle criteria, the refined criteria reduced the proportion of ECGs categorized as abnormal among all cardiologists.

Interobserver Reliability

Interobserver reliability for categorizing an ECG as abnormal among inexperienced cardiologists was poor for the 2010 ESC recommendations (κ=0.15; 95% CI, 0.12–0.20), fair for the Seattle criteria (κ=0.25; 95% CI, 0.16–0.32), and moderate for the refined criteria (κ=0.41; 95% CI, 0.24–0.50; Figure 2). Among experienced cardiologists, there was moderate reliability for categorizing an ECG as abnormal for all 3 criteria (2010 ESC recommendations: κ=0.40; 95% CI, 0.37–0.45; Seattle criteria: κ=0.53; 95% CI, 0.39–0.64; and refined criteria: κ=0.43; 95% CI, 0.21–0.51).

Interobserver reliability for the presence of a long-QT interval was only fair to moderate (κ=0.21–0.44) among inexperienced cardiologists (Table II in the Data Supplement). Conversely, interobserver reliability for the presence of a long-QT interval among experienced cardiologists improved from fair (κ=0.31) with the 2010 ESC recommendations to good (κ=0.60) with the Seattle and refined criteria. There was

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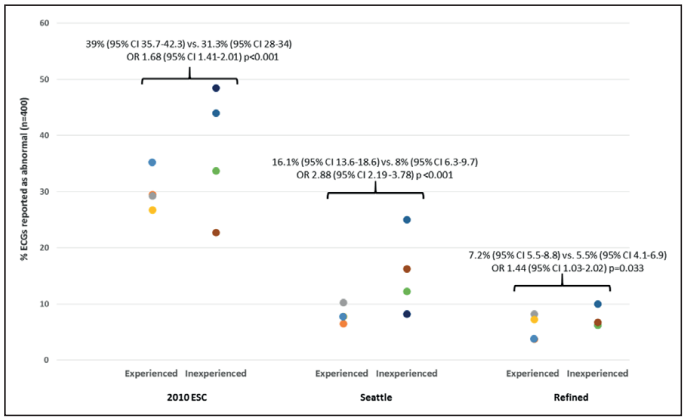

Figure 1. ECGs categorized as abnormal by each cardiologist. Inexperienced cardiologists are more likely to categorize an ECG as abnormal compared with experienced cardiologists irrespective of criteria used. CI indicates confidence interval; and OR, odds ratio.

moderate and good reliability for the presence of abnormal T-wave inversion among inexperienced (κ=0.43–0.54) and experienced cardiologists (κ=0.54–0.64), respectively. The degree of reliability for the presence for other ECG abnormalities ranged from poor to moderate among the cardiologists (Table II in the Data Supplement).

Proportion of Overall and Specific Interobserver Agreement

Proportion of overall interobserver agreement was higher among experienced cardiologists compared with inexperienced cardiologists for all 3 criteria (Table 2). Among both groups, overall agreement was driven specifically by agreement in ECGs categorized as normal. Modification of ECG interpretation criteria improved the overall proportion of interobserver agreement for both inexperienced and experienced cardiologists.

Bivariate Binary Outcome Model

On the basis of the 2010 ESC recommendations, sex (male athletes) and ethnicity (black athletes) proved to be the strongest predictors of disagreement among inexperienced cardiologists as suggested by the bivariate binary mode, whereas sex (male athletes) was the main source of difference in agreement among experienced cardiologists (Table III in the Data Supplement).

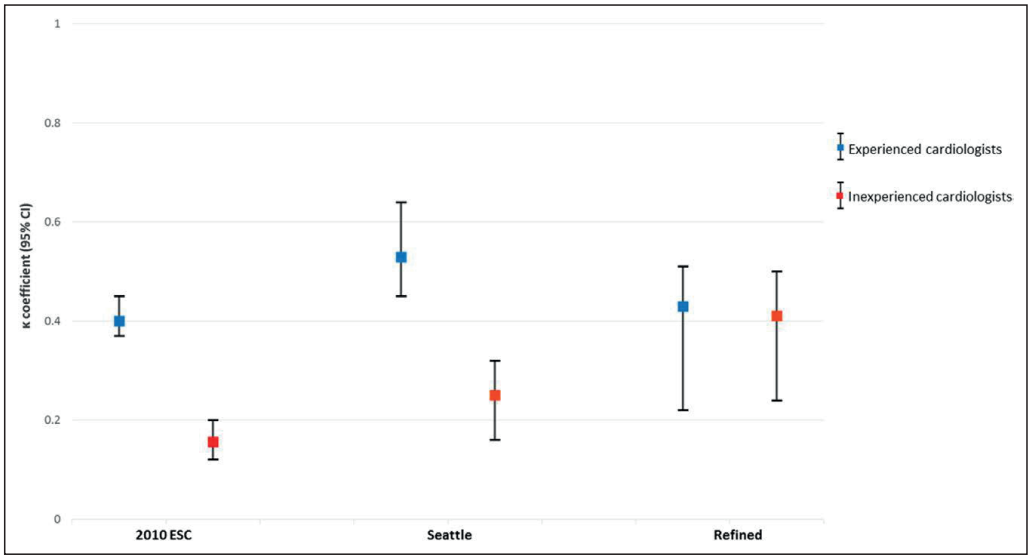

Figure 2. The estimated interobserver reliability among cardiologists for categorizing an ECG as abnormal. Interobserver reliability for an abnormal ECG among experienced cardiologists was moderate for all 3 criteria. Among inexperienced cardiologists, modification of ECG criteria improved interobserver reliability from poor to moderate. CI indicates confidence interval; and ESC, European Society of Cardiology.

MANUSCRIPT 6

Table 2. Proportion of Overall and Specific Agreement for ECG Interpretation Among Cardiologists

	Cardiologists	Overall Agreement (+95% CI)	Agreement for Abnormal (+95% CI)	Agreement for Normal (+95% CI)
2010 ESC recommendations	Inexperienced	0.60 (0.58–0.63)	0.46 (0.44–0.52)	0.68 (0.65–0.71)
	Experienced	0.75 (0.72–0.77)	0.58 (0.53–0.63)	0.82 (0.79–0.82)
Seattle criteria	Inexperienced	0.80 (0.78–0.83)	0.44 (0.29–0.48)	0.88 (0.87–0.90)
	Experienced	0.93 (0.92–0.95)	0.57 (0.45–0.67)	0.96 (0.95–0.97)
Refined criteria	Inexperienced	0.92 (0.90–0.95)	0.46 (0.35–0.56)	0.96 (0.95–0.97)
	Experienced	0.94 (0.92–0.95)	0.46 (0.32–0.58)	0.97 (0.96–0.98)

Further Evaluation and Secondary Investigations

Frequency of Investigations and Interobserver Reliability

Inexperienced cardiologists recommended further evaluation in 17.7% (95% CI, 15.0%–20.0%) of the 400 ECGs and showed fair interobserver reliability with respect to which ECGs required further evaluation (κ=0.23; 95% CI, 0.14–0.30). Experienced cardiologists recommended further evaluation in 7.0% (95% CI, 5.3%–8.8%) of the 400 ECGs, with moderate interobserver reliability (κ=0.40; 95% CI, 0.31–0.53).

Inexperienced cardiologists were likely to recommend a higher proportion of secondary investigations compared with experienced cardiologists, with poor to fair interobserver reliability (Table 3; Figure 3). Interobserver reliability for secondary investigations ranged from fair to moderate among experienced cardiologists.

Proportion of Overall and Specific Interobserver Agreement

Proportion of overall and specific agreement for recommending further evaluation and secondary investigations after ECG interpretation was higher among experienced cardiologists (Table 4). Agreement for familial evaluation was comparable among both groups. In both groups, overall agreement was specifically driven by agreement in not recommending investigations.

Costs Generated by Secondary Investigation

On the basis of the predicted proportions for each group, the cost of secondary investigation among inexperienced cardiologists amounted to $48 697 (95% CI, $35 583–$69 896) and equated to $122 (95% CI, $89–$175) per athlete screened. For experienced cardiologists, the total cost of secondary investigation amounted to $19 123 (95% CI, $11 878–$30 726) and equated to $48 (95% CI, $30–$78) per athlete screened.

Accounting for the initial preparticipation screening costs, the overall cost per athlete equated to $175 (95% CI, $142–$228) and $101 (95% CI, $83–$131) for inexperienced and experienced cardiologists, respectively.

Discussion

The ECG is a relatively cheap investigation that improves the sensitivity for detecting potentially serious cardiac disease in athletes compared with history and examination alone.[11] Recent modification of ECG interpretation recommendations in athletes has significantly reduced false-positive rates without compromising sensitivity.[7,12,13] However, as with any subjective investigation, the effectiveness of the ECG is dependent on the individual interpretation of the test. This study conveys important data pertaining to variation in interpretation of the ECG in a relatively large cohort of highly trained athletes and reveals that there is only moderate reliability in ECG interpretation in athletes among experienced cardiologists. Intuitively, such variation will have significant financial implications on downstream costs of systematic evaluation of athletes.

Impact of Experience in Interpretation of the ECG in Athletes

An important concern about the ECG as a screening tool is the potential for erroneous diagnosis in inexperienced hands. This study reveals that inexperienced cardiologists were at least

Table 3. Estimated Proportions of Further Evaluation and Secondary Investigations Proposed After ECG Interpretation

	Proportion of ECGs Requiring Further Evaluation and Secondary Investigations (n=400) (Marginal Proportions [95% CI])		Odds Ratio (95% CI)	*P* Value
	Inexperienced Cardiologists, %	Experienced Cardiologists, %		
Further evaluation after screening	17.7 (15.0–20.0)	7.0 (5.5–8.8)	4.7 (3.5–6.4)	*P*<0.001
Echocardiography	16.4 (13.8–19.1)	6.5 (4.9–8.1)	4.7 (3.4–6.5)	*P*<0.001
Exercise stress test	6.9 (5.3–8.6)	1.7 (0.9–2.5)	5.9 (3.6–9.6)	*P*<0.001
Holter	6.1 (4.4–7.7)	1.7 (0.9–2.6)	5.5 (3.2–9.2)	*P*<0.001
Cardiac MRI	5.5 (3.8–7.1)	0.9 (0.2–1.5)	12.2 (6.1–24.6)	*P*<0.001
Family screening	0.8 (0.4–1.4)	0.9 (0.4–1.5)	0.9 (0.4–2.0)	*P*=0.84

CI indicates confidence interval; and MRI, magnetic resonance imaging.

MANUSCRIPT 6

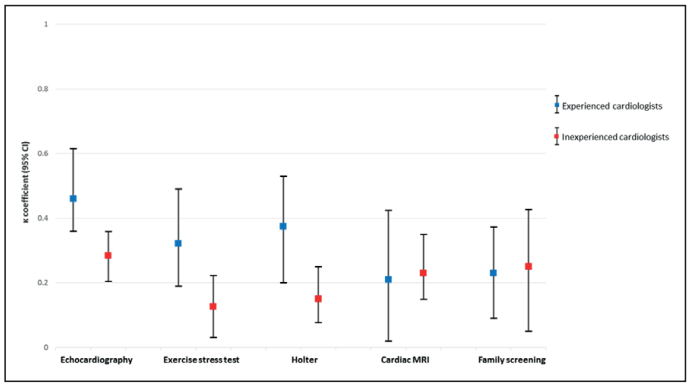

Figure 3. The estimated interobserver reliability among cardiologists for secondary investigations after ECG interpretation. Inexperienced cardiologists demonstrated poorer interobserver reliability for secondary investigations compared with experienced cardiologists. CI indicates confidence interval.

44% more likely to categorize an ECG as abnormal compared with experienced cardiologists (Figure 1). Furthermore, inexperience was associated with poorer interobserver reliability for categorizing an ECG as abnormal.

Reassuringly, the ECG of the athlete harboring potentially serious cardiac disease was identified by all 8 cardiologists. From the clinical point of view, it is arguable that this is certainly the most important aspect of the ECG as a screening tool.

Impact of Modification of Standardized ECG Interpretation Criteria

The impact of recent modification of ECG interpretation criteria on variation in interpretation in highly trained athletes has not been ascertained in a large cohort of highly trained young adult athletes although Berte et al[4] reported a higher overall agreement with the Seattle criteria compared with the 2010 ESC recommendations in a small cohort of adolescent male soccer players. We observed that contemporary ECG interpretation guidelines (Seattle and refined criteria) improve the proportion of overall interobserver agreement by ≤35% and 20% among inexperienced and experienced cardiologists, respectively (Table 2), and reduce the interobserver reliability gap between experienced and inexperienced cardiologists when categorizing an ECG as abnormal (Figure 2).

Impact of ECG Interpretation Variation on Workload and Costs

The workload and cost of secondary investigations required to confirm or refute the diagnosis of cardiac disease after an ECG abnormality are cited as important obstacles to screening young athletes with ECG.[14] We observed that inexperienced cardiologists were 5 times more likely to refer an athlete for further evaluation compared with experienced cardiologists based on ECG interpretation. Specifically, screening by inexperienced cardiologists resulted in a 5-fold increase in number of echocardiograms requested, 6-fold increase in exercise stress tests and Holter monitors, and a 12-fold increase in cardiac magnetic resonance imaging scans compared with experienced cardiologists (Table 3). In addition to the increased

Table 4. Proportions of Overall and Specific Agreement Among Cardiologists for Recommending Further Evaluation and Secondary Investigations After ECG Interpretation

	Cardiologists	Overall Agreement (+95% CI)	Agreement to Recommend (+95% CI)	Agreement Not to Recommend (+95% CI)
Further evaluation after screening	Inexperienced	0.77 (0.74–0.79)	0.38 (0.31–0.44)	0.86 (0.83–0.87)
	Experienced	0.92 (0.89–0.93)	0.45 (0.35–0.55)	0.95 (0.94–0.96)
Echocardiography	Inexperienced	0.81 (0.78–0.84)	0.40 (0.32–0.47)	0.89 (0.87–0.90)
	Experienced	0.94 (0.92–0.95)	0.50 (0.37–0.61)	0.97 (0.96–0.98)
Exercise stress test	Inexperienced	0.89 (0.87–0.91)	0.19 (0.10–0.29)	0.94 (0.93–0.95)
	Experienced	0.98 (0.96–0.99)	0.33 (0.11–0.53)	0.99 (0.98–0.99)
Holter	Inexperienced	0.91 (0.89–0.92)	0.20 (0.12–0.29)	0.95 (0.94–0.96)
	Experienced	0.98 (0.97–0.99)	0.38 (0.07–0.63)	0.99 (0.98–0.99)
Cardiac MRI	Inexperienced	0.92 (0.90–0.94)	0.27 (0.17–0.37)	0.96 (0.95–0.97)
	Experienced	0.99 (0.98–0.99)	0.24 (0.11–0.41)	0.99 (0.98–0.99)
Family screening	Inexperienced	0.99 (0.98–0.99)	0.31 (0.00–0.67)	0.99 (0.99–0.99)
	Experienced	0.98 (0.97–0.99)	0.12 (0.00–0.35)	0.99 (0.99–0.99)

CI indicates confidence interval; and MRI, magnetic resonance imaging.

MANUSCRIPT 6

number of investigations requested, interobserver reliability among inexperienced cardiologists for these secondary investigations ranged from poor to fair (Figure 3). Consequently, ECG-based preparticipation screening conducted by inexperienced cardiologists resulted in an ≈2-fold increase in cost compared with experienced cardiologists.

Experience was associated with a lower frequency of secondary investigations and improvement in proportion of overall agreement (Tables 3 and 4); nevertheless, interobserver reliability among experienced cardiologists for these investigations was only fair to moderate (Figure 3). In real-life practice, cardiovascular screening in athletes is conducted by physicians of varying experience, ranging from general cardiologists, electrophysiologists, and sports physicians. Therefore, the variation in interpretation is likely to fall between the 2 ranges above and will have significant implications on health resources that may preclude financial planning and sustainability of nationwide ECG screening of young athletes.

Despite demonstrating a reduction in the number of positive ECGs with contemporary ECG criteria, inexperienced cardiologists proposed further investigations in 17.7% of the cohort, which is considerably higher than expected based on the authors' experience and existing publications. This finding indicate that modification of ECG interpretation criteria may be associated with a lower positive ECG rate but may still not influence the personal practice among inexperienced cardiologists without further expert guidance.

Strategies to Reduce Variation in ECG Interpretation and Clinical Practice

Despite the success of the Italian athletic screening program in reducing sudden cardiac death, preparticipation screening with ECG remains a contentious issue given the absence of randomized control study evidence demonstrating that early detection of disease translates to lives saved, and consequently, ECG screening is not universally practiced. Nevertheless, ECG screening is endorsed by several major sporting organizations including Fédération Internationale de Football Association and the International Olympic Committee.[2,15] Although our study has shown only moderate reliability for interpretation of the athlete's ECG among experienced cardiologists, we do not aim to deter sporting organizations from screening athletes with ECG. Indeed, the ECG is associated with interobserver reliability rates that are comparable to well-established and generally accepted screening tests such as Papanicolaou smear testing for cervical carcinoma and mammography for carcinoma of the breast.[16–19] Furthermore, the only serious condition conferring increased risk of sudden cardiac death was identified on the basis of an abnormal ECG. By acknowledging the degree and impact of variation in ECG interpretation in athletes, our findings should herald the development of effective educational approaches aimed at reducing this variation. Modification of guidelines for the interpretation of the ECG in athletes from the 2010 ESC recommendations to the Seattle and refined criteria seem to be useful in improving agreement and reliability in ECG interpretation especially in inexperienced cardiologists; however, a better understanding of physiological versus pathological ECG patterns requires appropriate training and education of physicians including cardiologists to potentially minimize variation regardless of whether ECG analysis is being conducted for screening purposes or for diagnostic purposes. Recent small studies have demonstrated significant improvement in ECG interpretation in athletes after online training among inexperienced physicians and hold promise for the future.[20,21]

In comparison to other established and endorsed screening programs in the UK National Health Service (www.gov.uk/topic/population-screening-programmes) with similar rates of positive screening tests, there were no standardized diagnostic pathways for asymptomatic young athletes exhibiting ECG anomalies.[7,8,13,22–28] In this regard, the recently published international recommendations for ECG screening in athletes are unique as they provide guidance to physicians on the minimal set of investigations for each electric abnormality.[29,30] Such guidance will hopefully reduce variation in clinical practice among screening cardiologists, which may improve efficiency.

Limitations

This study has several limitations warranting mention. The definition of experience in interpreting the ECG in athletes was arbitrary, but there is currently no formal accreditation available to quantify this more accurately. We only included adult cardiologists for this study, and hence, the findings may not be readily applicable to organizations whose athletes are screened by pediatric cardiologists, sports physicians, and other healthcare providers. Only 400 athlete ECGs were included to make the study feasible. All 400 athletes were not assessed with echocardiography, and consequently there is no gold-standard reference on which to calculate the interpreter's accuracy for detecting of structural heart disease; however, our study aimed to investigate the level of interobserver variability in ECG interpretation and clinical practice rather than detection of disease. Although all cardiologists were supplied with published documents for all 3 ECG interpretation criteria, we cannot exclude that some may not have strictly adhered to them and reported ECGs based on their own experience. Machine-generated intervals were removed to aptly test the knowledge of the cardiologists in this study, but the impact they present on variation is not known.

Conclusions

Interpretation of the ECG in young athletes and the resultant cascade of downstream investigations is highly physician dependent even in experienced hands, which markedly impacts on the workload and cost of ECG screening. Formal training and development of a standardized diagnostic pathway is essential to support cardiologists involved in cardiovascular screening of young athletes.

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Disclosures

Dr Sharma has been an applicant on previous grants from Cardiac Risk in the Young and British Heart Foundation to study athletes. The other authors report no conflicts.

MANUSCRIPT 6

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MANUSCRIPT 7

Comparison of Three Criteria for Interpretation of Electrocardiogram in the Military

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ABSTRACT Background: Screening of competitive athletes and other individuals exposed to regular and intense physical exercise, such as military personnel, can lead to an early and preclinical identification of cardiac conditions associated with a higher risk for sudden cardiac death. The electrocardiogram (ECG) has been recommended for the precompetitive screening, but its interpretation remains controversial. The aim of this study was to compare three different standardized criteria for interpretation of athletes' ECG applied in military. Methods: Prospective study of 1,380 consecutive healthy military, 249 (18%) also involved in competitive sport, screened with clinical history, physical examination, and ECG. The ECG was interpreted according to the European Society of Cardiology (ESC) recommendations, the Seattle Criteria (SC), and the Refined Criteria (RC). Findings: Independently of the criteria used, the majority of the individuals included had ECG changes, mainly physiological: ESC 55.1%, SC 63.6%, and RC 64.4%. The rate of pathological ECGs was significantly higher with the ESC criteria when compared to SC and RC (ESC 14.8%, SC 5.0% and RC 4.5%; $p < 0.001$). A significant cardiac abnormality was diagnosed with additional investigations in 4 patients (Brugada syndrome Type 1, mitral valve prolapse, bicuspid aortic valve, and Wolff–Parkinson–White pattern). Discussion: Electrical cardiac adaptations are frequent in military personnel, similar to competitive athletes. Some ECG changes, previously considered pathological, could in fact correspond to physiological adaptations. The refinement of the ECG interpretation in this athletic population seems to reduce the rate of false-positive cases. This may have a favorable socioeconomic impact, especially by reducing the health cost burden and number of disability days.

INTRODUCTION

Screening of competitive athletes and other individuals exposed to regular and intense physical exercise, such as military personnel, can lead to an early and preclinical identification of cardiac conditions associated with a higher risk for sudden cardiac death (SCD). Italian data have shown an 89% reduction in the incidence of SCD in competitive athletes after the inclusion of the electrocardiogram (ECG) in screening programs.[1] Despite this, the methodology adopted for precompetitive athlete evaluations remains somewhat controversial. Despite the agreement for the inclusion of clinical history (personal and family) and physical examination in these screening programs, the same is not true for the ECG, emphasizing the dichotomy between European countries and the United States of America, where it is not formally recommended.[2,3]

Among the arguments against the inclusion of the ECG in the evaluation of competitive athletes stands the higher rate of false-positive cases, which lead to unnecessary additional investigations and inappropriate disqualification of healthy individuals from competition. The majority of these false positive cases are related to the higher variability and the absence of standardization in ECG interpretation, with classification of physiological adaptations induced by exercise as pathological changes.[4] Recently, specific criteria were published aiming to standardize and improve the interpretation of athletes' ECG.[5–8]

The active duty military, especially those in Special Forces, is characterized by intense physical exercise, similar to competitive sport, but with some specificities that can increase the risk of complications and clinical events. In this setting, as recommended for the evaluation of competitive athletes, military are frequently evaluated, with clinical history (personal and family), physical examination and 12-lead resting ECG.[9]

The aim of this study was to compare three different specific criteria for the interpretation of athletes' ECG applied in a military population and assess which one associates with higher accuracy and lower rate of false-positive cases.

METHODOLOGY

Population Studied

Prospective cross-sectional study of 1,380 Portuguese Armed Forces military (Army, Navy, and Air Force) consecutively evaluated in the yearly routine clinical evaluation, regularly involved in physical exercise, training at least 4 hours per

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MANUSCRIPT 7

week. Individuals with cardiovascular (CV) symptoms and an established diagnosis of cardiac disease were excluded from this analysis. All the individuals included have given the informed consent for the participation in the study.

Clinical and Sports History

The following baseline data were collected for all individuals: demographics (age, gender, and ethnicity), anthropometric data (weight and height), medical history with focus on the clinical CV risk factors (hypertension, dyslipidemia, smoking, diabetes, and family history of CV disease), medication, exercise-related characteristics, and sports history. Dyslipidemia and diabetes were defined by the presence of an abnormal lipid profile (total cholesterol ≥ 200 mg/dL, low-density lipoprotein ≥ 100 mg/dL, and/or triglyceride ≥ 150 mg/dL), and fasting plasma glucose ≥ 126 mg/dL (annually mandatory in military), respectively, and/or by regular therapy for these conditions. History of smoking was defined as active smoking or cessation in the last year. Family history of CV disease was defined as the occurrence of fatal or nonfatal CV events (sudden death, acute myocardial infarction, or stroke) in first-degree relatives (men <55 years and women <65 years).

Regarding sports history, we assessed the following characteristics: number of training hours per week, type of sport, sportive modalities, intensity of sport, and the number of years at the competitive level. The type of sports were categorized according to the classification proposed by Mitchell.[10]

Electrocardiogram

The 12-lead resting ECG was interpreted according to the following criteria: European Society of Cardiology Criteria[6] (ESC) recommendations, Seattle Criteria[7] (SC), and Refined Criteria[8] (RC) (Fig. 1). The ECGs were assessed by two cardiologists with experience in sports cardiology and classified into three categories: (1) normal, (2) with physiological changes, and (3) with abnormal changes. In the case of doubt or disagreement among the observers, a third cardiologist revised the traces. The individuals with ECGs classified as abnormal by any of the criteria used were referred for evaluation in a sports cardiology clinic, when appropriate with the realization of additional investigations.

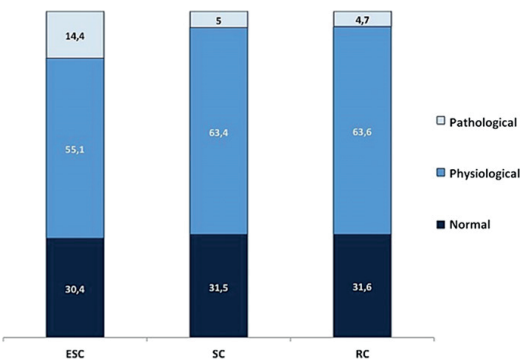

FIGURE 1. ECG classification according to the different criteria.

Statistical Analysis

Continuous variables with normal distribution were expressed as means and standard deviations. Normality was tested with the Kolmogorov–Smrinov test. Categorical variables were expressed as frequencies and percentages. Statistical comparison of the baseline characteristics was performed using the χ^2 test or Fisher's exact test, when appropriate, and Student t or Mann–Whitney tests for continuous variables. To identify independent predictors of abnormal ECG changes, a multivariate analysis using a binary logistic regression model (enter method) was performed. Two-tailed tests of significance are reported. For all comparisons, a p value of <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CIs) were calculated. Statistical analysis was performed with SPSS, version 21.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline Characteristics

Baseline characteristics are depicted in Table I. Briefly, of the 1,380 consecutive military analyzed, the majority were male (88.8%), white (94.8%), and with a mean age of 30.1 ± 8.3 years old (23% veteran athletes). Regarding clinical CV risk factors, smoking was present in almost a quarter of the entire population (24.0%), whereas 6.7% had a family history of CV disease and 3.0% a history of dyslipidemia (3.0%). Concomitant clinical conditions were rare (asthma seen in 0.2% and hypothyroidism in 0.3%). Thirty individuals (2.2%) were on regular pharmacological therapy, mainly statins.

Physical Exercise and Sports History

Data related to exercise habits and sport practice are presented in Table II. The mean number of training hours per week was 6 ± 4 hours and 15.7% of the participants trained at least 10 hours per week. Beyond the exercise performed in the context of military activity, approximately a fifth of the individuals (18.0%) were also involved in competitive sport, whereas 18.7% had been competitive athletes in the past. The large majority of the participants (1,030, 74.6%) were involved in modalities characterized by high dynamic exercise (class C of the Mitchell classification). Among the sports modalities, the most frequent were long distance running (45.0%) and soccer (15.9%).

Electrocardiogram

The most frequent ECG changes were sinus bradycardia (44.0%), isolated QRS voltage for left ventricular hypertrophy (28.0%) and early repolarization (24.7%). Among the potentially abnormal changes, the most frequent were T wave inversion (7.0% in two contiguous leads except III/V1/aVR),

MANUSCRIPT 7

Comparison of 3 Criteria for Interpretation of Electrocardiogram in Military

TABLE I. Baseline Characteristics

Characteristics (N = 1,380)	N (%)
Male Gender	1,226 (88.8)
Age (Years)	30 ± 8
BMI (kg/m^2)	24.4 ± 2.9
Ethnicity	
White	1,308 (94.8)
Black	58 (4.2)
Other	14 (1.0)
CV Risk Factors	
>1 Risk Factor	222 (16.1)
Smoking	331 (24.0)
Dyslipidemia (TC ≥ 200 mg/dL or LDL ≥ 100 mg/dL or TG ≥ 150 mg/dL)	42 (3.0)
Diabetes Mellitus (FPG ≥ 126 mg/dL or HbA1c ≥ 6.5%)	11 (0.8)
Family History of CV	93 (6.7)
Obesity (BMI ≥ 30.0 kg/m^2)	46 (3.3)

BMI, body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

axis deviation (5.6%), pathological Q wave (0.5%), Brugada pattern (Type ½, seen in 3 cases), and ventricular pre-excitation (1 case) (Table III). Independently of the criteria used, the majority of individuals had ECG changes, mainly physiological: ESC 55.1%, SC 63.6%, and RC 64.4%. In contrast, the rate of pathological ECGs was significantly higher using ESC when compared to SC and RC (ESC 14.8%, SC 5.0%, and RC 4.5%; $p < 0.001$). Table IV presents ECG findings according to the criteria used for its interpretation.

Predictors of Pathological ECG changes According to the ESC Recommendations

Independently of the applied criteria, pathological ECG changes were more frequent in younger and Black individuals, training at least 10 hours per week and mainly in those involved in competitive sport. According to the ESC recommendations: age (28 ± 8 vs. 31 ± 8 years; $p < 0.001$), Black ethnicity (32.8% vs. 14.0%; $p < 0.001$), training ≥ 10 hours per week (19.8% vs. 14.3%; $p = 0.040$), and competitive level (19.7% vs. 14.1%; $p = 0.030$); according to the SC: age (27 ± 8 vs. 30 ± 8 years; $p = 0.002$), Black ethnicity (13.8% vs. 4.6%; $p = 0.002$), training ≥ 10 hours per week (9.7% vs. 4.3%; $p = 0.001$), and competitive level (19.7% vs. 14.1%; $p = 0.030$); according to the RC: age (27 ± 8 vs. 30 ± 8 years; $p = 0.002$), Black ethnicity (15.5% vs. 4.0%; $p < 0.001$), training ≥ 10 hours per week (7.4% vs. 4.2%; $p = 0.042$), and competitive level (8.4% vs. 3.8%; $p = 0.002$).

By multivariate analysis, age (odds ratio [OR] 0.97, 95% CI 0.95–0.99; $p = 0.003$) and Black ethnicity (OR 2.71, 95% CI 1.48–4.98; $p = 0.001$) remained independent predictors of pathological ECG changes.

TABLE II. Sport History

Characteristics (N = 1,380)	N (%)
Training Hours/Week	6 ± 4
≥ 10 h/Week	217 (15.7)
Competitive Sport	249 (18.0)
Competitive Sport in the Past	258 (18.7)
Sports Activity	
High Dynamic Sport (*Mitchell* Class C)	1,030 (74.6)
Multimodality	604 (43.8)
Long Distance Running (>10 km)	621 (45.0)
Soccer	219 (15.9)
Weightlifting	130 (9.4)
Cycling	99 (7.2)
Swimming	44 (3.2)

TABLE III. Main Electrocardiographic Changes

ECG Findings (N = 1,380)	N (%)
Sinus Bradycardia	607 (44.0)
Isolated QRS Voltage for Left Ventricular Hypertrophy	386 (28.0)
Early Repolarization	341 (24.7)
T Waves Inversion[a]	97 (7.0)
Incomplete Right Bundle Branch Block	72 (5.2)
First-Degree Atrioventricular Block	47 (3.4)
Right Axis Deviation	47 (3.4)
Left Axis Deviation	31 (2.2)
QTc > 440 Milliseconds in Males or >460 Milliseconds in Females	17 (1.2)
Intraventricular Conduction Delay (QRS >120 Milliseconds)[b]	8 (0.6)
Pathological Q Waves	7 (0.5)
Right Ventricular Hypertrophy	7 (0.5)
QTc < 380 Milliseconds	6 (0.4)
Second-Degree Atrioventricular Block Mobitz I	3 (0.2)
Premature Ventricular Contractions[c]	3 (0.2)
Brugada Pattern (Type 1/2)	3 (0.2)
Ventricular Pre-Excitation	1 (0.1)

[a]Except III/V1/aVR. [b]3 left bundle branch block and one right bundle branch block. [c]Isolated in all the cases.

Additional Investigations

Approximately 7% of the population (N = 97) was evaluated in a sports cardiology clinic: 83 were submitted to a transthoracic echocardiogram, 77 had a treadmill stress test, 11 had 24-hour Holters, 7 had a cardiac magnetic resonance, and 5 had a computed tomography angiography. One

TABLE IV. Predictors of Pathological ECG Changes According to the ESC Recommendations

Univariate Analysis			
Characteristics	With Pathological Changes	Without Pathological Changes	
Age	20.8 ± 8.3	31.0 ± 8.0	<0.001
Black Ethnicity	14 (8.1)	35 (3.4)	0.011
Competitive Sport	39 (24.4)	167 (18.0)	0.057
Multivariate Analysis			
Characteristics	OR	CI 95%	p Value
Age	0.97	0.95–0.99	0.003
Black Ethnicity	2.71	1.5–5.0	0.001

MANUSCRIPT 7

individual was also submitted to a flecainide drug challenge test because of a baseline Type 2 Brugada pattern, which was negative. After these evaluations, we confirmed cardiac disease in 2 cases—1 patient with Brugada syndrome and 1 with the Wolff–Parkinson–White syndrome. These individuals were excluded from exercise practice, the former permanently and the last temporarily until percutaneous ablation. Other relevant findings evidenced in the additional investigations included 1 case of mitral valve prolapse and 1 bicuspid aortic valve, both without significant functional repercussion.

DISCUSSION

The application of more restrictive criteria for the interpretation of athletes' ECG (SC and RC) was associated with a significant reduction in the rate of false-positive cases (approximately two-thirds) when compared to the ESC recommendations. The majority of the young military included in this study had physiological ECG changes and only two individuals were diagnosed with a relevant cardiac disease (primary arrhythmic diseases).

Precompetitive Evaluation

The diagnosis of cardiac conditions associated with an increased risk of SCD represents the main objective of precompetitive screening of athletes and other individuals under intense exercise training, as the case of military. In this setting, the evaluation should focus on the preclinical identification of CV disease, the main cause of SCD in these populations. Although the inclusion of the clinical history and physical examination in these screening programs seems relatively straightforward, the inclusion of the ECG remains controversial, mainly as a result of the dichotomy between European countries and the United States of America, where it is not formally recommended.[9,11] There are several arguments pro-ECG inclusion in precompetitive evaluation, such as its accessibility and the fact that approximately two-thirds of SCD in young athletes are caused by conditions manifested with ECG changes.[4] Otherwise, the main con for the ECG in the context of athletes evaluation is the higher rate of false-positive cases.

Exercise-Induced Cardiac Adaptations

Exercise training is responsible for several physiological cardiac adaptations: structural, functional, and electrical. The differentiation of these physiological adaptations with pathological changes is often challenging because of the overlap with common findings in cardiac conditions, as cardiomyopathies and primary arrhythmic diseases.[4] Nevertheless, physiological changes should be well differentiated from pathological abnormalities to reduce the risk of unnecessary investigations and disqualification of healthy individuals from competition. However, ECG changes in athletes or individuals that exercise regularly are more frequent and exuberant in the presence of specific demographic and exercise-related characteristics.[12–14] As previously reported, our study showed more pathological ECG changes in younger and black individuals.

Interpretation of Athletes' ECG

Recent investigations have showed that some ECG changes which were previously considered pathological could in fact correspond to physiological adaptations. In a study performed by Gati et al[15] in competitive athletes, 43% of the ECGs changes were axis deviation or voltage criteria for atria dilation, findings that were not associated with cardiomyopathies and contributed to the higher rate of false-positive cases. In this context, the reclassification of some changes, as proposed in SC and RC, improves specify in the interpretation of athletes' ECG. The evaluation of T wave inversion, long QT interval, axis deviation, and isolated voltage criteria for ventricle hypertrophy (left or right) are examples of these changes.[16]

Our study reveals that ESC recommendations are responsible for an unacceptable higher rate of false-positive cases when compared with the more recent criteria for ECG interpretation in athletes. This has been reported in several studies since the publication of the SC. Brosnan et al[16] showed a similar reduction in the false-positive rate using SC vs. ESC recommendations (4.5% vs. 17.3%; $p < 0.001$). The RC, proposed by Sheikh et al,[8] also associated with a significant reduction of false-positive rate, including when compared with the SC. It should be highlighted that this study included a significant number of Black athletes in whom the RC were shown to be more accurate. Additionally, it was shown that, independently of the criteria used, when applied in a population of young patients with hypertrophic cardiomyopathy, the sensitivity to detect cardiac abnormalities did not decrease.[8]

Particularities of the Military Activity

Military activity is characterized by a high intensity and volume of exercise, similar to that performed by some competitive athletes. However, the evidence resultant from specific studies in military population is scarce when compared with the large number of studies in athletes. Still, studies have shown similar incidence and causes of SCD in both populations. A landmark study by Eckart et al[17] analyzed cases of SCD in 6.3 millions of military recruited in United States of America during approximately 25 years (1977–2001). This study showed that nontraumatic SCD was a rare event ($N = 126$), mainly occurring as the result of a CV cause (more frequently resulting from a coronary anomaly, followed by myocarditis and hypertrophic cardiomyopathy), in male and during exertion. However, it is important to highlight that military activity has specificities that increase the risk of exercise-related injuries.[18] Military personnel are exposed to extreme meteorological and geographic conditions that can give rise to complications such as

MANUSCRIPT 7

hypothermia, heat shock, or rhabdomyolysis with subsequent dehydration and hydroelectrolyte disturbances that can precipitate malignant arrhythmias.[18] The life-threatening conditions in military operations, nuclear, biological, chemical, and radiological threat, the contact with explosives, weapons used, type of equipment, isolation, and emotional stress are factors that exponentially increase the risk—"continuum of operational stress."[19] On the other hand, military training, in which resistance, mobility, strength, and flexibility are essential components, has simultaneously characteristics of isotonic and isometric exercise. This may increase the difficulty in differentiating physiological vs. pathological changes. In this setting, the military should be periodically evaluated as thoroughly as competitive athletes, focusing on the preclinical identification of conditions potentially associated with an increased risk of SCD.

Limitations

This study presents some limitations. First, military are submitted to frequent medical examinations, including at admission in Armed Forces, before entry in specific courses and periodically (at least annually). It follows that the majority of the individuals included in this analysis had been assessed multiple times and therefore our study represents a healthier cohort which is not necessarily representative of a hypothetical population of individuals being initially considered for military training. Second, the Portuguese Armed Forces representativity in the sample is reduced, mostly because of the lower number of female military or non-whites, limiting the extension of the results. Third, as a result of the broad spectrum of the military, from members of Special Forces to occupations which are considered sedentary, it would have been nice to include a control group, to directly compare the ECG results of the studied population, to ascertain whether the rate of the observed ECG anomalies was truly different compared with a civilian population. Fourth, this sort of mass screening is not practical in military clinical settings because of limitations of staffing and equipment, but it would be possible in larger hospitals.

Fifth, as further investigations were only performed in individuals with abnormal ECGs, it was not possible to assess the false-negative rate. Finally, although the sample size is not negligible, given the lower frequency of pathological changes detected in this population a larger sample size may be necessary for stronger conclusions.

CONCLUSIONS

Electrical cardiac adaptations are frequent in military personnel. As in competitive athletes, the refinement of the ECG interpretation in this athletic population seems to reduce the rate of false-positive cases. This result may have a favorable socioeconomic impact by reducing the health cost burden and the number of disability days.

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MANUSCRIPT 8

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ORIGINAL ARTICLE

Exercise-induced cardiac remodeling in athletes and in special forces soldiers☆

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KEYWORDS
Physical exercise;
Cardiac remodeling;
Myocardial mechanics

Abstract
Introduction: Exercise-induced cardiac remodeling is frequent in athletes. This adaptation is structurally manifested by an increase in cardiac dimensions and mass. Soldiers are also subject to intense physical exercise, although with different characteristics.
Objective: To compare exercise-induced cardiac remodeling in competitive athletes and in soldiers on a special forces training course.
Methods: We studied 17 soldiers (all male and Caucasian, mean age 21±3 years) who completed a special forces course and 17 basketball players (47.3% male, 64.7% Caucasian, mean age 21±3 years). Assessment included a transthoracic echocardiogram and analysis of myocardial mechanics. This assessment was performed at the beginning and end of the military course and the sports season, respectively.
Results: Cardiac remodeling was observed in both groups. The soldiers presented a predominantly eccentric pattern, with increased left ventricular (LV) size (49.7±3.2 vs. 52.8±3.4 mm; p<0.01), increased LV mass (93.1±7.7 vs. 100.2±11.4 g/m^2; p<0.01) and decreased relative wall thickness (0.40±0.1 vs. 0.36±0.1; p=0.05). The basketball players showed a concentric pattern, with decreased LV size (52.0±4.7 vs. 50.4±4.7 mm; p=0.05), and increased relative wall thickness (0.33±0.1 vs. 0.36±0.1; p=0.05). Although there was no significant difference in LV myocardial strain in the groups separately, when compared there was a significant decrease (-20.2±1.6% vs. -19.4±2.1%; p=0.03).

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MANUSCRIPT 8

Conclusion: Cardiac remodeling was frequent, with an eccentric pattern in soldiers and a concentric pattern in basketball players. Myocardial deformation may represent a physiological adaptation to physical exercise.

PALAVRAS-CHAVE
Exercício físico;
Remodelagem cardíaca;
Deformação miocárdica

Remodelagem cardíaca induzida pelo exercício físico em atletas de nível competitivo e militares de forças especiais

Resumo
Introdução: A remodelagem cardíaca induzida pelo exercício físico é frequente em atletas. Esta adaptação manifesta-se a nível estrutural com o aumento das dimensões e massa cardíacas. Os militares também são sujeitos a exercício físico intenso, com especificidades distintas.
Objetivo: Comparar a remodelagem cardíaca induzida pelo exercício físico em atletas de competição e pelo treino militar em militares a frequentar um curso de forças especiais.
Metodologia: Estudámos 17 militares (género masculino e caucasianos, idade média 21 ± 3 anos) que ingressaram no curso de Comandos e 17 basquetebolistas (47,3% do género masculino, 64,7% caucasianos, idade média 21 ± 3 anos). A avaliação incluiu um ecocardiograma transtorácico com análise da mecânica miocárdica. Esta avaliação foi realizada no início e no final do curso militar e da época desportiva, respetivamente.
Resultados: A remodelagem cardíaca teve características distintas: os militares apresentaram um padrão predominantemente excêntrico, com aumento das dimensões do ventrículo esquerdo (49,7 ± 3,2 *versus* 52,8 ± 3,4 mm; p < 0,01) e da massa (93,1 ± 7,7 *versus* 100,2 ± 11,4 g/m²; p < 0,01) e diminuição da espessura relativa das paredes (0,40 ± 0,1 *versus* 0,36 ± 0,1; p = 0,05); os basquetebolistas apresentaram um padrão concêntrico, com diminuição das dimensões do ventrículo esquerdo (52,0 ± 4,7 *versus* 50,4 ± 4,7 mm; p = 0,05) e da espessura relativa das paredes (0,33 ± 0,1 *versus* 0,36 ± 0,1; p = 0,05). Apesar da deformação miocárdica global do ventrículo esquerdo não apresentar diferenças significativas entre os grupos, quando analisados em conjunto o seu valor diminuiu (-20,2 ± 1,6% *versus* -19,4 ± 2,1%; p = 0,03).
Conclusão: A remodelagem cardíaca foi frequente, com padrão excêntrico nos militares e concêntrico nos atletas. A mecânica miocárdica poderá representar uma adaptação fisiológica induzida pelo exercício físico.

Introduction

Intense and prolonged physical exercise leads to changes in cardiovascular physiology known as 'athlete's heart'. Chief among these alterations are increased cardiac size, volumes and mass and improved functional parameters, particularly diastolic function.[1] Classically, two forms of cardiac remodeling have been described: concentric remodeling associated with static exercise, and eccentric remodeling associated with dynamic exercise.[2] For example, marathon runners present eccentric remodeling due to volume overload resulting from increased cardiac output, while weightlifters show concentric remodeling due to pressure overload.[3] It should be noted that this distinction is not absolute, since most sports involve both static and dynamic exercise, and hence lead to mixed remodeling.[4]

However, athletes are not the only individuals who undergo high-intensity training. Soldiers, especially in the special forces, also undergo physically demanding training that involves various forms of both static and dynamic exercise. Overall, the volume of exercise required of these soldiers can be compared to that of competitive athletes, and may often be even higher. However, military training is unique with regard to the methodologies used and the influence of other variables arising from military life.[5]

The manifestations of exercise-induced cardiac remodeling can overlap with those of pathological conditions, especially cardiomyopathy, and differential diagnosis is often challenging.[6] In this context, pre-participation screening of athletes and interpretation of diagnostic exams in this population are of great importance. In the last decade, new imaging techniques have been developed that enable detailed myocardial assessment, such as analysis of myocardial mechanics by transthoracic echocardiography (TTE).[7]

The main aim of this study was to characterize and compare cardiac remodeling in professional basketball players

MANUSCRIPT 8

List of abbreviations

BMI	body mass index
BP	blood pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
FM	fat mass
GLS	global longitudinal strain
HR	heart rate
IVS	interventricular septum
LA	left atrial
LV	left ventricular
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
MM	muscle mass
RWT	relative wall thickness
SBP	systolic blood pressure
TAPSE	tricuspid annular plane systolic excursion
TTE	transthoracic echocardiography
Δ	difference

over the course of a season and in soldiers on a special forces course.

Methods

This observational, longitudinal, case-control study assessed special forces soldiers and competitive athletes at the beginning and end of a military training course and a sports season, respectively. Male and female individuals between the ages of 18 and 35 years were included. The soldiers were selected from those who enrolled in a Portuguese Army commando course and were assessed between January and June 2016. The athletes belonged to two professional basketball teams, one men's and the other women's, competing in the national men's Division 1 and the national women's league, respectively, and were assessed in October 2015 and March/April 2016. Thus, both groups were assessed over a period of about six months. The group of soldiers consisted of the 17 out of 76 trainees (54 dropouts, approximately 70% of trainees) who successfully completed the course and met the inclusion criteria. All of these soldiers had previously participated in competitive sports. The athlete population was composed of 17 basketball players, eight male and nine female.

All of the study subjects were volunteers and gave their informed consent to participate in the study. The protocol was approved by the Ethics Committee of the Medical School of the University of Coimbra (reference protocol 087/2015).

Characteristics of physical exercise in the study population

The commando course involves high-intensity physical exercise intended to develop aerobic and anaerobic capacity. To this end, the soldiers undergo dynamic and static physical training, including various sports including running, swimming, gymnastics and weightlifting. In addition, they undergo military physical training, which aims to instill and develop psychomotor techniques and abilities that enable soldiers to perform their duties under adverse conditions. This physical training involves obstacle courses, intense running interspersed with marching, carrying loads, and similar activities. The training program is divided into two stages: the first stage consists of 10 weeks of vigorous-intensity physical exercise (77-95% of maximum heart rate [HR]),[8] five times per week with a mean duration of four hours per day, while the second phase consists of 15 weeks of vigorous-intensity physical exercise (77-95% of maximum HR) interspersed with periods of near maximal- or maximal-intensity exercise (≥96% of maximum HR),[8] five times per week for a mean of four hours per day. In addition to this scheduled training, the soldiers are under constant physical, psychological and emotional strain, which is difficult to quantify.

Basketball involves numerous movements that require speed, skill and strength and involve dynamic and static exercise, with a general component and a specific component. The general component is provided by continuous running at speed and with changes in direction, and gymnastic and flexibility exercises. The specific component consists mainly of training in coordination by learning and practicing technical maneuvers. The players train four times a week and play one game a week. The mean duration of each training session is three hours, divided into three separate periods: warmup, basketball training with general and specific exercises, and cooldown. The players are subject to periods of vigorous- to near maximal-intensity exercise, with other periods of low- to moderate-intensity exercise. Overall, the training sessions for these athletes can be classified as vigorous-intensity (77-95% maximum HR).[8]

Clinical assessment

All participants underwent a full physical examination and thorough collection of medical history, performed by a sports medicine physician or a cardiologist. Emphasis was placed on cardiovascular risk factors, dietary habits, medications, and sports history, including the number of hours of training and of sleep during the course or season.

Anthropometric assessment

The anthropometric assessment was performed by a nurse and a health technician. Height was measured using a tape measure, and weight, percentage fat mass (FM) and muscle mass (MM) were measured using a digital full-body composition monitor (Omron® HBF-510W) using bioelectrical impedance. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were assessed using an upper arm blood pressure (BP) monitor (Omron® HEM-7113), in accordance with current guidelines.[9] Changes (Δ) in variables (weight, MM, FM, SBP, and DBP) were calculated according to the following formula: (final value - initial value)/initial value×100.

MANUSCRIPT 8

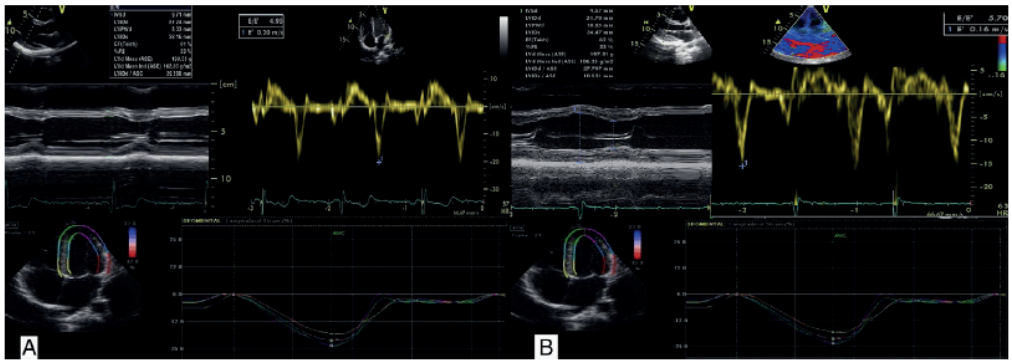

Figure 1 (A) Transthoracic echocardiographic images of a soldier following the special forces course, showing no left ventricular (LV) wall thickening and LV end-diastolic diameter near the upper normal limit, above-normal diastolic function parameters and normal global longitudinal strain (GLS) values; (B) transthoracic echocardiographic images of a basketball player after the sports season, with LV wall thickening near the upper normal limit and normal diastolic function parameters and GLS.

Electrocardiographic assessment

All individuals underwent a 12-lead electrocardiogram (ECG) (Norav® 1200HR), analyzed by two cardiologists and interpreted according to the 'refined' criteria.[10]

Echocardiographic assessment

All transthoracic echocardiograms were performed by a cardiologist with a Vivid 7 ultrasound system (GE Healthcare®), and included the various echocardiographic views and techniques recommended by the European Society of Cardiology (two-dimensional; M-mode; color, pulsed wave, continuous wave and tissue Doppler; and myocardial strain assessed by speckle tracking).[11]

Wall thickness and left ventricular (LV) dimensions were measured via parasternal long-axis view. Relative wall thickness (RWT) was calculated using the formula (2×LV posterior wall thickness/LV end-diastolic diameter [LVEDD]) and LV mass was calculated using the Devereux formula.[12] LV volume and left atrial (LA) volume were determined using the modified Simpson's rule, with images obtained in apical 4- and 2-chamber views. The LA volume index was obtained by indexing to body surface area. LV ejection fraction (LVEF) was determined using Simpson's method. Pulsed wave Doppler was acquired in apical 4-chamber view, and peak E and A wave velocities and E/A ratio were measured. Tissue Doppler images of the mitral and tricuspid annuli were obtained to measure the E and E′ waves, and to measure S′ wave velocities, respectively. Tricuspid annular plane systolic excursion (TAPSE) was determined by M-mode. Speckle tracking was used to calculate LV global longitudinal strain (GLS) using images from apical 4-, 2- and 3-chamber views and an 18-segment model. Cardiac cycles were acquired during the same respiratory phase (exhalation). Three consecutive cycles were recorded and mean sinus rhythm was calculated with a frame rate >60 frames per second. The quality of the exam was considered good when no more than two segments were excluded, and excellent when all segments were analyzed.

Figure 1 shows examples of TTE of a soldier and of an athlete after the course or season, respectively.

Statistical analysis

Categorical variables were presented as frequency and percentage, and compared with the chi-square and Fisher's tests as appropriate. The Kolmogorov-Smirnov test was used to test continuous variables for normality of distribution. Variables with a normal distribution were expressed as mean and standard deviation, and the Student's t test was used for group comparisons. Levene's test was used to assess the homogeneity of variance of individual variables. Variables with a non-normal distribution were expressed as median and interquartile range, and the groups were compared using the Mann-Whitney and Kruskal-Wallis tests. Pearson's correlation was used to analyze associations between MM and FM and echocardiographic parameters. For all comparisons, a p-value <0.05 was considered statistically significant with a 95% confidence interval. All data were calculated and analyzed using SPSS version 20 (IBM SPSS® Inc., Chicago, IL, USA).

Results

Population characteristics

The characteristics of the study population are shown in Table 1. Briefly, the mean age of the two groups was similar, but there were significant differences in terms of gender and race. The soldiers played competitive sports for less time and had a higher body mass index. During the study period, the soldiers completed more hours of scheduled exercise per day and had fewer hours of sleep and fewer meals. Nearly a quarter of the population (20.6%) had at least one cardiovascular risk factor, of which smoking was the most common and was exclusive to the soldiers (17.6%), followed by dyslipidemia, which was also more common in the soldiers (5.9%

MANUSCRIPT 8

Table 1 Baseline characteristics of the study population.

	Soldiers (n=17)	Basketball players (n=17)	p
Demographic			
Age (years)	21±3	21±3	0.71
Male (%)	17/17 (100)	8/17 (47.1)	<0.01
Caucasian (%)	17/17 (100)	11/17 (64.7)	<0.01
Anthropometric			
BMI (kg/m^2)	25.3±2.7	23.1±2.7	0.03
FM (%)	19.1±3.3	25.1±12.1	0.56
MM (%)	41.3±2.1	35.0±7.8	0.09
SBP (mmHg)	128±10	131±13	0.35
DBP (mmHg)	73±7	64±13	0.90
HR (bpm)	65±12	73±7	0.81
Sports history			
Years of competition	7.4±3.4	10.4±5	0.04
Hours of training per day (course/season)	4.0±0.5	2.9±1.1	<0.01
Hours of sleep per day (course/season)	5.5±0.5	7.4±0.8	<0.01
Number of meals per day (course/season)	4.0±1.0	4.7±1.0	<0.01

BMI: body mass index; DBP: diastolic blood pressure; FM: fat mass; HR: heart rate; MM: muscle mass; SBP: systolic blood pressure.

Table 2 Changes in anthropometric data.

	Soldiers (n=17)			Basketball players (n=17)		
	Initial	Final	p	Initial	Final	p
Weight (kg)	75.2±7.8	77.4±6.6	<0.01	76.7	76.3	0.63
MM (%)	41.3±2.1	44.4±1.8	<0.01	35.0±7.8	35.6±7.5	<0.01
FM (%)	19.1±3.3	13.1±3.5	<0.01	25.1±12.1	24.9±11.6	0.88
SBP (mmHg)	128±10	122±7	<0.01	132±13	133±12	0.54
DBP (mmHg)	73±7	66±5	<0.01	73±7	74±9	0.64
HR (bpm)	66±12	59±6	<0.01	65±13	61±11	0.19

DBP: diastolic blood pressure; FM: fat mass; HR: heart rate; MM: muscle mass; SBP: systolic blood pressure.

vs. 2.9%, p=0.32). The study population had no family history of cardiovascular disease, hypertension or diabetes.

Changes in anthropometric data

The soldiers experienced significant weight gain, with increased MM, and more marked decreases in FM, SBP, DBP and HR than the basketball players (Table 2). The increase in MM and decrease in FM were seen in all male subjects.

The percentage difference between the two groups in the changes in anthropometric data was statistically significant for weight, SBP, DBP, MM and FM (Figure 2). Unlike the basketball players, the soldiers gained weight (3.1±3.3 vs. -0.2±3.2%; p<0.01), with an increase in MM (7.5±4.1 vs. 1.7 ±2.4%; p<0.01) and greater decrease in FM (-31.4±15.7 vs. -0.8±14.9%; p<0.01). The soldiers experienced reductions in SBP (-4.8±3.0 vs. 1.4±7.4%; p<0.01) and DBP (-8.6±7.4 vs. 1.5±10.5%; p<0.01).

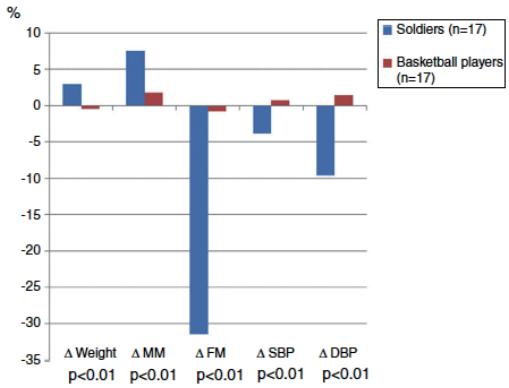

Figure 2 Percentage differences in changes in anthropometric data between the study groups. DBP: diastolic blood pressure; FM: fat mass; MM: muscle mass; SBP: systolic blood pressure.

Electrocardiographic assessment

All ECGs showed sinus rhythm and were considered normal or with only physiological alterations. The most common physiological alteration was sinus bradycardia (41.2%), followed by early repolarization (29.4%), LV hypertrophy

MANUSCRIPT 8

Table 3 Changes in echocardiographic parameters.

	Soldiers (n=17)			Basketball players (n=17)		
	Initial	Final	p	Initial	Final	p
IVS (mm)	9.7±1.0	9.9±1.0	0.39	8.3±1.5	9.1±1.5	0.03
PW (mm)	9.7±0.9	9.6±0.8	0.39	8.5±1.3	9.2±1.1	0.06
LVMI (g/m^2)	93.1±7.7	100.2±11.4	<0.01	82.3±15.9	87.1±18.4	0.18
RWT	0.40±0.1	0.36±0.1	0.05	0.33±0.1	0.37±0.1	0.03
LVEDD (mm)	49.7±3.2	52.8±3.4	<0.01	52.0±4.7	50.4±4.7	0.05
LVESD (mm)	33.2±3.3	35.1±2.6	0.04	34.6±3.9	34.1±3.6	0.47
LA volume (ml)	63.4±10.5	71.2±12.1	0.02	54.1±10.0	56.6±11.6	0.29
LVEF (%)	60±6	55±6	<0.01	58±5	58±6	0.15
Lateral E′ (cm/s)	19±3	19±3	0.92	18±3	17±4	0.18
E/E′	5.3±1.0	5.3±0.9	0.61	5.1±1.3	5.6±0.7	0.14
S′ (cm/s)	15±2	17±2	<0.01	13±2	14±2	<0.01
TAPSE (mm)	25±4	26±5	0.34	24±3	25±3	0.41
GLS (%)	-21.3±0.9	-20.5±1.9	0.11	-19.0±1.2	-18.3±1.2	0.15

GLS: global longitudinal strain; IVS: intraventricular septum thickness; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVESD: left ventricular end-systolic diameter; PW: posterior wall; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion.

(20.6%), incomplete right bundle branch block (11.8%), and first-degree atrioventricular block (2.9%).

Echocardiographic assessment

TTE revealed different structural patterns of cardiac remodeling (Table 3). In the soldiers, there was an increase in left chamber size, of both the left ventricle (49.7±3.2 vs. 52.8±3.4 mm; p<0.01) and the left atrium (63.4±10.5 vs. 71.2±12.1 ml; p=0.02), and a decrease in RWT (0.40±0.1 vs. 0.36±0.1; p=0.05). In the athletes, LV size decreased (52.0±4.7 vs. 50.4±4.7 mm; p=0.05), and interventricular septum (IVS) thickness (8.3±1.5 vs. 9.1±1.5 mm; p=0.03) and RWT (0.33±0.1 vs. 0.36±0.1; p=0.05) both increased. With regard to functional parameters, there was a reduction in resting LVEF in the soldiers (60±6 vs. 55±6%; p<0.01), and an increase in the S′ wave in both the soldiers (15±2 vs. 17±2 cm/s; p<0.01) and the basketball players (13±2 vs. 14±2 cm/s; p<0.01).

When male participants were assessed separately, the different types of remodeling described above applied, with significant differences in LA volume (51.8±8.1 vs. 58.4±10.9 ml; p=0.05) and GLS (-19.4±1.3 vs. -17.6±1.7%; p=0.03) in the basketball players. Although there were no significant differences in GLS in the two groups at the beginning and end of the course or season, there was a significant difference when the two groups were compared (-20.2±1.6% vs. -19.4±2.1%; p=0.03). The echocardiographic findings in the two groups demonstrated differences in LVEDD, RWT, LVEF and S′ wave (Figure 3). Alterations in RWT and LVEDD were opposite: for the soldiers, RWT decreased (-10.0±14.3% vs. 12.1±22.5%; p<0.01) and LVEDD increased (6.2±11.3% vs. -3.1±6.1%; p<0.01), while for basketball players both RWT and LVEDD increased during the season. These findings are similar when only male soldiers and basketball players are compared, with significant differences in RWT (-10.0±14.3% vs. 21±25.3%; p=0.02), LVEDD (6.2±11.3% vs. -3.1 ±4.2%; p<0.01) and LVEF (-5.5±12.8% vs. 4.9±10.5; p<0.01).

Figure 3 Percentage differences in echocardiographic parameters between the study groups. GLS: global longitudinal strain; IVS: interventricular septum thickness; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; RWT: relative wall thickness.

Discussion

This study demonstrated the occurrence of anthropometric and cardiovascular remodeling in both soldiers and basketball players. These adaptations had different characteristics in the two groups. In anthropometric terms, the soldiers had a greater increase in body weight, with gains in MM and reductions in FM. Echocardiographic assessment revealed different patterns of remodeling, with the soldiers developing predominantly eccentric and the basketball players developing mainly concentric adaptations.

The alterations in anthropometric data and vital signs following the military course or sports season were more significant in the soldiers' group, even when a sub-analysis was performed (data not shown) comparing the soldiers with the Caucasian male athletes. There was a marked transformation in the body composition of the former group, with mean MM gains of 7.5% and mean FM reductions of around 30%. The

MANUSCRIPT 8

differences in adaptation in the two groups may be related to the different characteristics of exercise in military training and in basketball, particularly the longer duration and greater intensity of exercise in military training, as well as specific features of the methodologies used. These differences likely explain the more marked adaptations in the soldiers. It has been shown that high-intensity interval training, in this case applied to the soldiers, achieves better results and greater adaptation.[13] The mechanisms underlying this adaptation are still unclear, but this type of training is thought to enhance capacity for aerobic and anaerobic metabolism and to increase oxidative enzyme activity.[14] Although there were no individuals with hypertension in either group, intense physical exercise led to reductions in the soldiers of around 4% and 9% in SBP and DBP, respectively. These results are in agreement with the literature.[15]

Cardiac remodeling occurred in both groups, but had different characteristics. In the soldiers, eccentric remodeling occurred with an increase in left chamber size and a decrease in RWT. At the end of the course, the proportion of soldiers with eccentric ventricular hypertrophy had doubled, from 5.9% to 11.8%.[16] In the basketball players predominantly concentric remodeling was observed, with increases in LV wall thickness, particularly of the IVS, and RWT, and a slight decrease in LVEDD. One possible explanation for these different types of cardiac remodeling is the intensity of the exercise performed. Moderate- to high-intensity exercise is initially associated with concentric hypertrophy due to the stimulus of pressure overload.[17] Vigorous- to near maximal- or maximal-intensity exercise leads to eccentric remodeling, due to volume overload from increased cardiac output, resulting from higher HR and increased ejection volumes, with only a moderate increase in BP.[17,18] This moderate increase in BP seems to be associated with acetylcholine-induced endothelium-dependent vasorelaxation, which plateaus with moderate to vigorous levels of exercise.[19] Thus, when the level of exercise increases from vigorous-intensity to near maximal- or maximal-intensity, there is a greater increase in cardiac output that is not accompanied by a proportional increase in BP, and this may lead to dilatation of the heart chambers that is disproportionate to the observed wall hypertrophy.

Despite the extent of the adaptations observed over the course or season, the changes were still within the upper limit of normal (no athlete with IVS >13 mm and only one with LVEDD >60 mm [61.4 mm]). There were also no statistically significant changes in parameters of diastolic function during the study. However, it should be noted that both soldiers and athletes already had above-normal values, as described in similar populations.[20,21]

Exercise-induced changes in functional parameters were also different in the two groups. In the soldiers, there was a decrease in resting LVEF, while in the basketball players this parameter remained similar to baseline values. The literature reports that elite athletes who are subject to intense and prolonged exertion may have slightly lower resting LVEF, with mean values of 50-55%, which increases as required when prompted by effort.[22,23] In the soldiers, no individual had an LVEF <50% on the baseline or final echocardiogram; however, 12 soldiers (70% of the population) had an LVEF of 50-55% on the final exam.

Both the soldiers and the basketball players had GLS values within normal limits,[7] with a trend toward reduction after the exercise program. This decrease was not significant when the two groups were analyzed separately. However, when they were compared, GLS decreased significantly. This behavior is consistent with that described in the literature,[7] and may represent an exercise-induced physiological adaptation and another characteristic that distinguishes 'athlete's heart' from heart disease, particularly hypertrophic cardiomyopathy.[24,25] However, the current scarcity of data in this area indicates a need for further studies designed to study the effect of physical exercise on this parameter.

Limitations

The main limitation of this study is the small sample size for both special forces soldiers and athletes. The heterogeneity of the populations with regard to gender and race also limits the results, mainly because no female soldiers participated in the special forces course. Another limitation is the inability to objectively quantify unscheduled physical exercise performed by the soldiers during the course. These individuals are constantly involved in activities and assessments, in which the physical component is central, even when they are not performing conventional or scheduled exercise. Finally, although all of the participants strongly denied using stimulants, the study protocol did not enable this denial to be confirmed.

Conclusion

In this study, anthropometric and cardiac remodeling occurred in both special forces soldiers and competitive basketball players following a military course or sports season. This remodeling had different characteristics in the two groups, being predominantly eccentric in the soldiers and concentric in the basketball players. New echocardiographic techniques, particularly myocardial strain analysis, may reveal patterns that are compatible with physiological adaptation to exercise, and may help to differentiate between 'athlete's heart' and heart disease.

Conflicts of interest

The authors have no conflicts of interest to declare.

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MANUSCRIPT 9

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ORIGINAL PAPER

Myocardial deformation and volume of exercise: a new overlap between pathology and athlete's heart?

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Abstract
Regular physical exercise induces cardiac adaptations that can overlap pathological conditions. Controversy still persists about the variability of myocardial deformation in different types and intensity of exercise. The aim of this study was to assess myocardial longitudinal deformation in athletes with different level of exercise. Two groups of young athletes involved in endurance sports characterized by high intensity dynamic component were enrolled. According to the level and the number of exercise training hours/week, two groups were defined: *Group 1*—high level (national/international and ≥ 20 training-hours/week; N = 60); *Group 2*—low level (recreational/regional and < 10 training-hours/week; N = 48). A comprehensive transthoracic echocardiogram including evaluation of global longitudinal strain (GLS) assessed by 2D speckle-tracking was performed. Athletes in Group 1 showed more pronounced cardiac remodeling and enhanced diastolic function. No significant differences were evident in left ventricle ejection fraction (LVEF) between groups. Overall, GLS (absolute values) was 18.0 ± 2.5%, but significantly lower in Group 1 compared to Group 2 (17.3 ± 2.6% vs. 18.9 ± 2.1%; p = 0.001). Thirty-three (31%) athletes had GLS below 17%, more frequently in Group 1 (79% vs. 45%; p = 0.001), with higher LV and left atrium volumes, lower *E* wave and *A* wave peak velocities and *E*/*e*′ ratio. In a multivariate analysis to belong to Group 1 was the only independent variable associated with GLS < 17% (OR 6.5; 95% CI 2.4–17.4; p < 0.001). The athletes with a GLS < 17% were all men, more frequently involved in high level exercise, with higher chamber volumes and lower *E*/*e*′ ratio. Left ventricular global myocardial longitudinal deformation evaluated by GLS was significantly lower in athletes with higher level of exercise. Although GLS in athletes overlap several pathological conditions, these lower values are associated with an enhanced diastolic performance that allows discrimination between physiologic adaptations and pathology.

Keywords Exercise training · Athletes · Myocardial deformation · Global longitudinal strain

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Introduction

Regular exercise training induces several cardiac physiological adaptations aimed to obtain a state of enhanced cardiovascular performance. Structurally, this remodelling is characterized by homogeneous chamber enlargement, increased mass and ventricular wall thickness, always correlated with several demographic and exercise-related characteristics. Because these adaptations may overlap with findings of pathological conditions, the differential diagnosis based on morphological data is often challenging [1, 2].

Beyond enhanced left ventricular (LV) diastolic function, functional adaptations to exercise in athletes are less described and incompletely understood. Although LV ejection fraction (LVEF) is usually normal and not significantly different from non-athletes, additional scientific data on myocardial performance at rest remains scarce [3, 4]. New

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MANUSCRIPT 9

advances in echocardiography, first with tissue Doppler imaging and more recently myocardial deformation analysis, may allow the identification of subclinical myocardial dysfunction despite normal LVEF and become useful to distinguish physiological adaptations from pathology [5–10]. The most clinically validated strain-based parameter is global longitudinal strain (GLS), assessed by two-dimensional (2D) speckle-tracking echocardiography (STE).

Though several cross-sectional studies have already attempted to establish the normal range of GLS in athletes, evidence has been conflicting among them, with undefined reference values and controversial results. Some of these studies reported lower values of GLS in athletes comparing to healthy controls, hypothetically explained as a consequence of physiological adaptation to exercise [11–16]. Additionally, other studies proposed that deformation parameters could also be useful to distinguish the physiological adaptations of the heart in different sport disciplines with different patterns of dynamic and static exercise, not possible with conventional echocardiography [17].

The aim of this study was to assess 2D-STE derived GLS in athletes with different level of exercise.

Materials and methods

Study population

Consecutive young athletes (< 35 years old) involved in endurance sports characterized by high intensity dynamic component (Class C of Mitchell classification) [18] were enrolled. According to the training regimens, namely the level and the number of exercise training hours/week, a surrogate measure of exercise volume, two groups were defined: *Group 1*—high level (national/international and ≥ 20 training-hours/week; N = 60); *Group 2*—low level (recreational/regional and < 10 training-hours/week; N = 48). Athletes had previously a clinical evaluation (detailed personal and family history, physical examination and resting 12-lead electrocardiogram) and the ones considered eligible performed a comprehensive transthoracic echocardiogram (TTE), before the competitive season. Positive personal or family history for cardiovascular disease, known cardiovascular risk factors, cardiac symptoms, positive findings in physical examination, abnormal changes in electrocardiogram, use of enhancing performance substances and TTE with inadequate image quality were exclusion criteria.

Echocardiographic evaluation

TTE exams were performed using a high-quality echocardiograph Vivid E9 (GE Vingmed Ultrasound AS, Horten, Norway) in accordance with the current recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19]. LV linear measurements were achieved by 2D echocardiography from parasternal long axis views, while volumes and LVEF were obtained by biplane modified Simpson's method. Diastolic function was assessed from apical four-chamber view, with pulsed-wave Doppler transmitral flow and tissue Doppler velocities, recorded with the sample in the mitral annulus (interventricular septum and LV lateral wall). GLS was evaluated in the three standard apical views and averaged after three consecutive cardiac cycles for each view. The tracking quality was maximized with a frame rate > 55 fps, avoiding foreshortening. Measurements began with the apical long-axis view to visualize aortic valve closure, using opening and closing clicks. Semiautomatic border detection was used to identify the interface between the LV walls and cavity, while manual corrections were subsequently performed to ensure correct tracing of the endocardial and epicardial border and the correct segmentation of the LV. Automated function imaging (AFI) objectively analyzes myocardial wall motion by tracking features (natural acoustic tags) in the ultrasonic image in two dimensions. GLS was calculated by averaging all regional values of peak systolic deformation, measured in each segment of the three apical views before aortic valve closure in a LV 17-segment model. In this paper, all references to GLS changes are mentioned as an increase or decrease in the absolute value. For subsequent analysis, the lower limit of normal range was defined as 17% [19]. Analyses were performed offline using a dedicated software package (EchoPac PC version BT13, GE Medical Systems, Faireld, CT, USA) by two experienced cardiologists with level III training.

Statistical analysis

All analyses were performed using SPSS for Mac version 23.0 (SPSS, Inc., Chicago, IL). Continuous variables with normal distribution were expressed as means and standard deviation (SD). Normality was tested with the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages. Statistical comparison among the groups was performed using the Chi square test or Fisher's exact test, when appropriate, for categorical variables and Mann–Whitney or Kruskal–Wallis test for continuous variables. Pearson analysis was performed to evaluate the correlations between GLS and others echocardiographic parameters. Binary logistic multivariate analysis was performed for identification the independent predictors of GLS < 17%. A p value < 0.05 was considered statistically significant. To assess interobserver variability, the agreement between two measurements (HD e LM) was expressed using the 95% confidence interval and determined

MANUSCRIPT 9

The International Journal of Cardiovascular Imaging

as the mean of the differences + 1.96 SD, as described by Bland–Altman [20].

Results

Clinical characteristics

Baseline data are showed in Table 1. Group 1 individuals were national/international elite athletes, involved in football (N = 58) and swimming (N = 2), training 20.0 ± 0.6 h/week. Group 2 individuals were recreational/regional competitive athletes, involved in middle-distance running (N = 30), basketball (N = 17) and tennis (N = 1), training 5.3 ± 2.4 h/week. Overall, age, body surface area and ethnicity were comparable between the two groups, but athletes in Group 1 were more frequently male (98% vs. 83%; p = 0.005) and had lower rest heart rate (58 ± 12 beats/min vs. 65 ± 13 beats/min; p = 0.006).

Echocardiographic results

No athlete showed structural abnormalities suspected to be pathological. Regarding the echocardiographic data (Table 2), athletes with high level (Group 1) showed a more pronounced structural remodelling, with significant higher LV mass, LV diastolic diameter, LV volumes and left atrium (LA) volume (Table 2). Although there was no difference on LVEF among both groups, the blood pool PWD E/A ratio was higher in Group 1 athletes, with a non-significant trend to a lower *E*/*e'* value.

The mean GLS in the entire population was 18.0 ± 2.5%, significantly lower in Group 1 (17.3 ± 2.6% vs. 18.9 ± 2.1%; p = 0.001). Semi-automatic tracking was possible in 98.4% of the segments (1807/1836) and the interobserver variability was 0.26 ± 1.71% for the GLS. Figure 1 represents the mean values and standard deviations of GLS in both groups

Table 1 Study populations characteristics

Variable	Group 1 (N = 60) High level	Group 2 (N = 48) Low level	p value
Age (years)	24.2 ± 4.5	23.9 ± 8.2	0.810
Male, *N* (%)	59 (98)	40 (83)	0.005
Caucasian, *N* (%)	44 (73)	39 (81)	0.332
Weight (kg)	78 ± 9	79 ± 12	0.621
Height (cm)	183 ± 8	178 ± 8	0.004
BSA (m^2)	1.99 ± 0.15	1.96 ± 0.17	0.382
HR (beats/min)	58 ± 12	65 ± 13	0.006
Training-hours/week	20.0 ± 0.6	5.3 ± 2.4	<0.001

BSA body surface area, *HR* heart rate

Table 2 Echocardiographic features

Variable	Group 1 (N = 60) High level	Group 2 (N = 48) Low level	p value
IVS (mm)	9.5 ± 1.5	9.1 ± 1.4	0.276
PWT (mm)	9.5 ± 1.5	9.4 ± 1.3	0.534
RWT	0.36 ± 0.07	0.37 ± 0.07	0.494
LVMI (g/m^2)	99 ± 19	90 ± 14	0.009
LVEDD (mm)	54 ± 5	51 ± 4	0.001
LVESD (mm)	33 ± 4	33 ± 4	0.713
LVEDV (ml)	160 ± 24	129 ± 32	<0.001
LVESV (ml)	63 ± 15	53 ± 16	0.003
LVEF (%)	62 ± 6	62 ± 7	0.647
LAVI (ml/m^2)	38 ± 9	23 ± 8	<0.001
Peak *E* velocity (m/s)	0.80 ± 0.18	0.90 ± 0.14	0.004
Peak *A* velocity (m/s)	0.42 ± 0.10	0.54 ± 0.16	<0.001
E/*A* ratio	2.0 ± 0.6	1.7 ± 0.5	0.011
E-wave DT (m/s)	197 ± 50	175 ± 40	0.023
E' (m/s)	0.14 ± 0.03	0.14 ± 0.03	0.334
E/*e'* ratio	5.2 ± 1.2	5.5 ± 1.6	0.232
GLS (%)	17.3 ± 2.6	18.9 ± 2.1	0.001
GLS < 17%, *N* (%)	26 (43)	7 (15)	0.001

DT deceleration time, *GLS* global longitudinal strain, *HR* HEART RATE, *IVST* interventricular septum thickness, *LAVI* left atrium volume indexed, *LVEDD* left ventricular end-diastolic dimension, *LVESD* left ventricular end-systolic dimension, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass indexed, *PWT* posterior thickness, *RWT* relative wall thickness

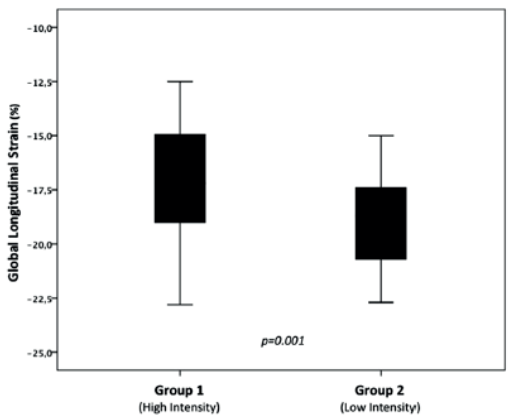

Fig. 1 Comparison of the mean GLS among the two groups of athletes (Group 1: 17.3 ± 2.6% vs. Group 2: 18.9 ± 2.1%; p = 0.001)

MANUSCRIPT 9

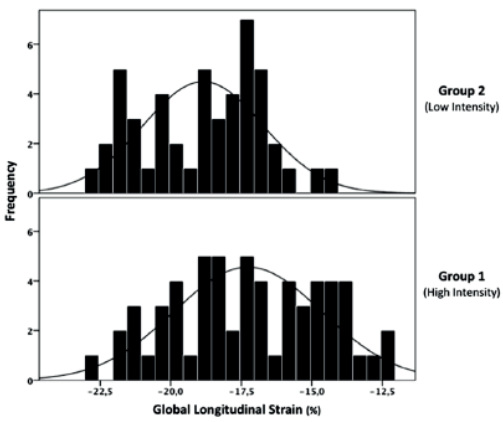

Fig. 2 Distribution and range of values of GLS in the two groups of athletes

and Fig. 2 shows the histograms for the distribution of the GLS values. In the entire population, GLS showed weak but significant correlations with LA indexed volume ($r=0.484$, $p<0.001$), LV end-diastolic volume ($r=0.449$, $p<0.001$), LV end-systolic volume ($r=0.399$, $p<0.001$) and peak *E* wave velocity ($r=-0.478$, $p<0.001$) (Fig. 3).

Thirty-three (31%) athletes had GLS below 17%, mainly in Group 1 (43% vs. 15%; $p=0.001$). All of these GLS < 17% athletes were men, more frequently involved in high level exercise, with higher LV and LA volumes, *E/A* ratios and lower *E/e'* ratio, *E* wave and *A* wave peak velocities. In Table 3 the baseline and echocardiographic variables according to the cut-off of 17% for GLS are reported. Including these statistically significant variables in a binary logistic model for multivariate analysis, high level of exercise training (Group 1) was the only parameter that remained independently associated with GLS < 17% (OR 6.5; 95% CI 2.4–17.4; $p<0.001$).

Discussion

Cardiac adaptations induced by exercise training vary in accordance with the characteristics of athlete and exercise. The classical Morganroth hypothesis postulates that isotonic exercise, linked to endurance sports, is responsible for chronic volume overload leading to eccentric hypertrophy, while isometric exercise, typical of strength disciplines, is responsible for concentric hypertrophy [3]. However, athletes involved in high-level sports usually show combined adaptations due to the simultaneous influence of both types of exercise.

Most of the times, the evaluation of 'athletes' heart' reveals to be challenging, mainly due to the overlap between physiological adaptations and findings present in pathological conditions [1]. In this setting, a comprehensive assessment of cardiac function and structure with TTE should be performed using several modalities, that combines the standard M-mode, 2D, tissue Doppler and more advanced approaches as 2D-STE. Theoretically, the assessment of GLS in athletes could assume a cornerstone position in order to define landmarks between 'athlete's heart' and pathological conditions [21]. However, this hypothesis remains controversial as the normal values of GLS in athletes and the impact of exercise training on LV systolic mechanics at rest remains unclear.

In the present study, athletes with higher level of exercise training had significant higher LV volumes, LV mass, LA volumes and *E/A* ratio than low level exercise-training athletes. Although there was a lower absolute *E/e'* in the high intensity training athletes, it failed to achieve statistical significance. On the other hand, Group 1 athletes showed lower values of GLS and a significant proportion had absolute values considered below the normal range [19]. It is noteworthy that the high level of exercise (national/international athletes with ≥ 20 training-hours/week) was the only variable independently associated with GLS < 17%.

In the absence of disease, as evidenced in these two groups of athletes, the explanation for the high number (79%) of GLS < 17% in Group 1 compared to the respective low number (21%) in Group 2 athletes seems not difficult to find. As previously shown, GLS depends on heart rate, pre-load, after-load and LV mass [22]. Comparing two different sized ventricles, it seems logical that the one with the larger volume needs less systolic deformation to eject the same stroke volume than the other with a smaller volume. In our study the left ventricles of athletes with GLS less than 17% had higher indexed volumes and supernormal diastolic function (lower *E/e'* ratio). The low GLS found in athletes with high volume ventricles seem again to belong to the spectrum of the healthy physiology typical of 'athlete's heart'. Accordingly, in the presence of lower GLS in highly trained athletes, a normal or enhanced diastolic function may become the key to distinguish healthy adaptation from disease, as previously proven [23]. Without compromising the diastolic performance the higher exercise level, induces higher volumes and lower systolic deformation.

Although a recent systematic review and meta-analysis (with only one study with more than 45 athletes) [24] concluded that GLS in athletes is similar to controls, suggesting that exercise training has no impact on GLS, other studies showed similar results to our study. Santoro et al. [25] found a mean GLS around 17%, both in strength and endurance athletes, without significant differences between groups (endurance 17.1 ± 1.3% vs. strength 17.4 ± 1.3% vs. controls

MANUSCRIPT 9

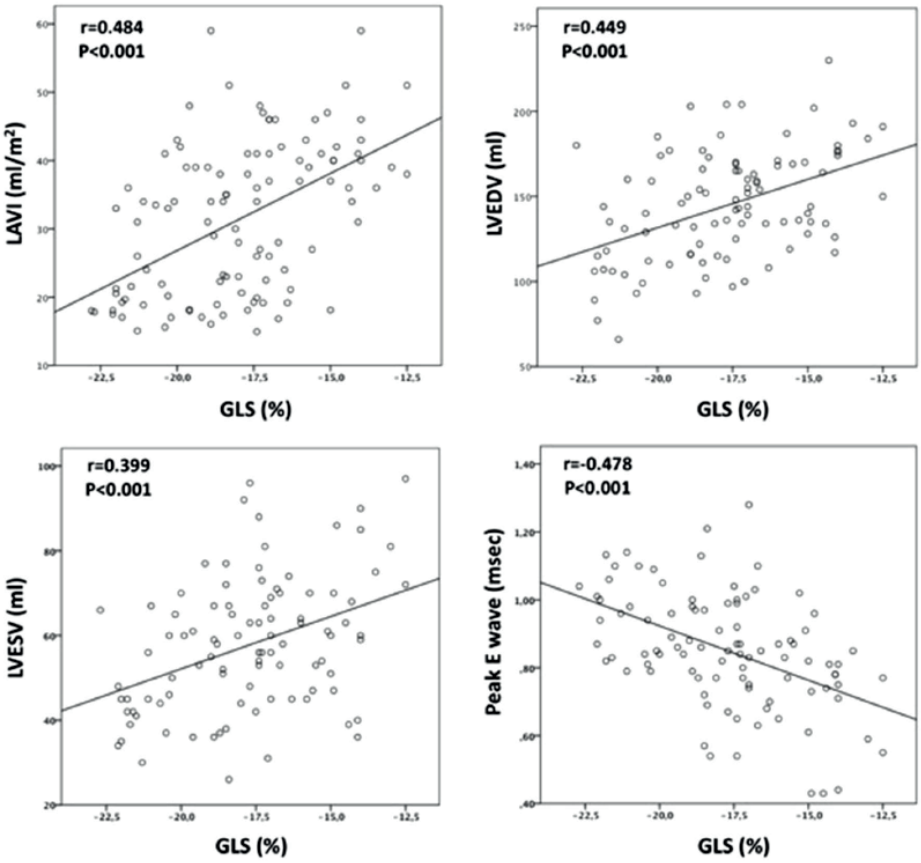

Fig. 3 Statistically significant correlations between GLS and other echocardiographic parameters

18.4 ± 1.8%). The small number of individuals included (33 endurance athletes, 36 strength athletes and 17 controls) can justify this fact. A larger analysis performed by D'Andrea et al. [12] in 370 endurance and 280 power athletes, showed a mean GLS of 17.2 ± 3.1 and 18.6 ± 3.7%, respectively, close to the results of our study. On the other hand, in 200 athletes evaluated by Caselli et al. [11], the mean GLS were not statistically different from controls and remained in the normal reference range stated in the last recommendations [19] (athletes 18.2 ± 2% vs. controls 19.4 ± 2%). However, the results of this study should be interpreted with caution, since contrary to our population, only 61% of the athletes were men and 25% were skill (class A1 of Mitchell classification) [18]. Indeed, when evaluated separately the mean GLS in male athletes was 17.8 ± 2%, even including a significant percentage of those involved in low dynamic and strength exercise.

In this setting, several authors concluded that a lower value of GLS in athletes can be a marker of myocardial adaptation to exercise induced by volume overload in increased preload states [14, 26–29]. The same conclusion can be extracted from the current study, since athletes involved in high dynamic sports are submitted to higher volume overload.

As far is our knowledge this is the first study that compares GLS by 2D-STE between different levels of exercise training, introducing insight into the physiologic adaptation to high level exercise.

Limitations

Most of the athletes included in this study were male, limiting the extrapolation of the results to both genders. Although the athletes were involved in sports with high

MANUSCRIPT 9

Table 3 Comparison of the studied variables according to the value of GLS (< 17% or ≥ 17%)

Variable	GLS < 17% (N = 33)	GLS ≥ 17% (N = 75)	p value
Baseline characteristics			
Age (years)	23.8 ± 2.2	24.2 ± 7.1	0.718
Male, N (%)	33 (100)	66 (88)	0.038
Caucasian, N (%)	24 (73)	59 (79)	0.500
Weight (kg)	79 ± 11	78 ± 10	0.472
Height (cm)	184 ± 7	172 ± 8	0.002
BSA (m^2)	2.01 ± 0.16	1.95 ± 0.15	0.078
HR(beats/min)	60 ± 11	61 ± 13	0.779
Training-hours/week	17 ± 6	12 ± 8	0.114
Group 1, N (%)	26 (79)	34 (45)	< 0.001
Echocardiographic characteristics			
IVS (mm)	9.5 ± 1.3	9.2 ± 1.6	0.455
PWT (mm)	9.2 ± 1.5	9.6 ± 1.4	0.214
RWT	0.35 ± 0.07	0.37 ± 0.07	0.126
LVMI (g/m^2)	94 ± 18	95 ± 18	0.835
LVEDD (mm)	53 ± 4	52 ± 5	0.371
LVESD (mm)	34 ± 4	32 ± 4	0.068
LVEDV (ml)	159 ± 28	137 ± 32	0.002
LVESV (ml)	63 ± 15	55 ± 16	0.032
LVEF (%)	61 ± 7	62 ± 6	0.586
LAVI (ml/m^2)	38 ± 10	29 ± 11	< 0.001
Peak *E* velocity (m/s)	0.76 ± 0.17	0.90 ± 0.15	< 0.001
Peak *A* velocity (m/s)	0.44 ± 0.12	0.50 ± 0.15	0.041
E/A ratio	1.9 ± 0.5	1.9 ± 0.6	0.698
E-wave DT (m/s)	193 ± 57	183 ± 40	0.309
E' (m/s)	0.14 ± 0.03	0.14 ± 0.03	0.225
Mean *E*/*e'*	4.9 ± 1.2	5.5 ± 1.4	0.043

BSA body surface area, *DT* deceleration time, *GLS* global longitudinal strain, *HR* heart rate, *IVST* interventricular septum thickness, *LAVI* left atrium volume indexed, *LVEDD* left ventricular end-diastolic dimension, *LVESD* left ventricular end-systolic dimension, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass indexed, *PWT* posterior thickness, *RWT* relative wall thickness

level of dynamic component, the different modalities can be associated with different LV dynamics patterns, so these results cannot be generalized for other types of sports. As transmitral inflow velocities are not only dependent on ventricular compliance, but largely influenced by heart rate and preload conditions, it depends on the training effort, duration and time between the end of exercise and the echocardiographic evaluation. In order to prevent hemodynamic bias, all the intensive training level athletes performed the echocardiogram in a day off in the pre-competition season, but inherent to the recreation pattern of the exercise in Group 2 it was not possible to obtain it in the same conditions.

Conclusions

LV myocardial deformation evaluated by GLS was significantly lower in athletes with higher level of exercise training. Although GLS in athletes overlap several pathological conditions, these lower values are always associated with a normal/enhanced diastolic performance that allows discrimination between physiologic adaptations and pathology.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

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MANUSCRIPT 9

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MANUSCRIPT 10

Case Report

Symptomatic Exercise-induced Intraventricular Gradient in Competitive Athlete

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Case Report

We describe the case of a 17-year-old caucasian male tennis player, training a mean of 20-24h/week, refereed for evaluation in Sport's Cardiology clinic due to symptoms of dizziness on strenuous exercise, relieving soon after decubitus. The athlete denied other concomitant complaints, namely thoracic pain, palpitations, syncope or decrease in physical performance. Although this is the most symptomatic episode, he revealed other prior episodes with similar presentation, but less intense and occurring in environments with high temperatures. Personal/family history was unremarkable and all pre-competitive evaluations were normal and without restrictions for competitive sport. Physical examination did not show significant findings – cardiac evaluation was normal, heart rate and blood pressure at rest were 52 bpm 121/64mmHg respectively.

The 12-lead electrocardiogram and transthoracic echocardiogram did not show pathological findings, only cardiac physiological adaptations to exercise (Figure 1). Subsequently the athlete underwent a treadmill exercise stress echocardiogram revealing an excellent functional capacity (19'09'' of Bruce protocol, 19.3METs), but with reproduction of symptoms (dizziness) in the peak of exercise with simultaneous decrease in systolic blood pressure (185 →90mmHg) and detection of intraventricular gradient (IVG) – at least 69mmHg (Figure 2). In the first minute of recovery the symptoms disappeared and blood pressure normalized.

The athlete was advertised to stop the sportive practice. An ambulatory 24h-Holter monitoring and cardiac magnetic resonance were subsequently performed, not showing pathological changes, namely arrhythmias or structural cardiac abnormalities.

After these investigations the case was discussed with involvement of the athlete, parents and coach. It was decided to reinitiate exercise with a gradual increase in intensity and volume of training, with the special advertising to increase hydration (apparently suboptimal according to the coach report) and to begin beta-blocker therapy if the symptoms persist. After 18 months of follow-up the athlete remain asymptomatic, with excellent performance and without need of pharmacologic therapy.

Keywords

Athletes; Echocardiography, Stress; Heart Ventricles/physiopathology; Exercise Test/adverse effects; Ventricular Dysfunction/etiology.

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Discussion

The development of significant exercise-induced IVG (>30mmHg at rest or >50mmHg with exercise) is uncommon, but can lead to several and unspecific symptoms such as dizziness, thoracic pain, or even ventricular repolarization changes and arrhythmias during exercise test.[1,2] This condition is usually associated to global or segmental left ventricular hypertrophy or an abnormal implantation of the papillary muscles, but the pathophysiological mechanisms are not well established. Three potential mechanisms are purposed for the development of IVG:

a) Increase of physiological non-obstructive IVGs;

b) End-systolic obstruction secondary to ventricular cavity obliteration;

c) Mid-systolic obstruction due to systolic anterior motion of the mitral valve with restriction of ejection flow.[3,4]

In a study performed by Zywca et al.[5] the independent predictors of dynamic left ventricular outflow tract obstruction in individuals without hypertrophic cardiomyopathy were: chordal systolic anterior motion, smaller left ventricle at end-systole, higher systolic blood pressure at peak, younger individuals and increased septal wall thickness.[5] However, as in the case reported, IVG can occur without structural cardiac changes, namely of the mitral valve apparatus, and eventually justified by extreme myocardial deformation in response to load conditions.[3] In this context, IVG is more frequently described in athletes or in situations with increased inotropic stimuli as during dobutamine stress echocardiogram.[6,7] Exercise stress echocardiogram plays a relevant role in the evaluation of symptomatic athletes, with reproduction of symptoms and the potential detection of significant IVGs.[1,8]

The clinical significance of IVG remains unknown – it could be one extreme physiological adaptation to exercise, one isolated pathological entity or in the other hand corresponds to a pre-phenotypic finding of cardiomyopathy.

Regarding the preventive/therapeutic measures to adopt in the presence of an athlete with IVG, maintenance adequate hydration during exercise is crucial, often sufficient for the remission of symptoms. Exercising under higher temperatures without adequate hydration can increase the gradient secondary to left ventricle cavity obliteration. Among the pharmacological therapy, the evidence indicates a significant effectiveness of beta-blocker therapy, both in the remission of symptoms and in the remission/disappearance of IVG.[1,9]

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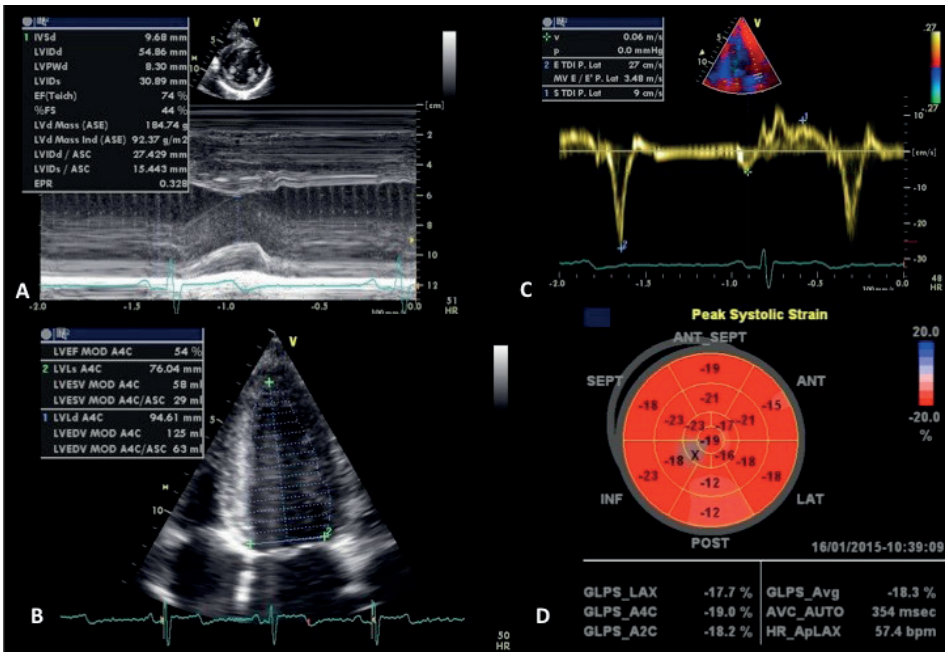

Figure 1 - *Transthoracic echocardiogram at rest without evidence of significant morfo-functional abnormalities – left ventricle dimensions (LV) by M Mode (A), volumes and LV ejection fraction (B), tissular Doppler at mitral ring (C) and global longitudinal strain (D).*

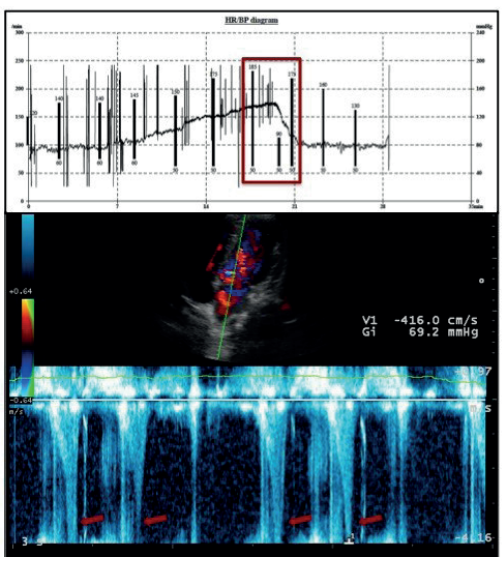

Figure 2 - *Exercise stress echocardiogram performed in treadmill with Bruce protocol, revealing a significant decrease in systolic blood pressure (185 → 90mmHg) in peak of exercise, with concomitant detection of IVG (bottom picture).*

MANUSCRIPT 10

Case Report

The small published data and the short follow-up of athletes with IVG did not permit definite conclusions regarding the prognostic impact, but there are not described fatal clinical events in athletes with IVG without structural cardiac changes. In this setting there are not specific recommendations relatively to competitive sport in athletes with IVG.[10,11] In general, if an athlete is still symptomatic despite the stressed preventive/therapeutic measures, it is not advised to maintain sportive practice, especially with the intensity of exercise that precipitates the symptoms, and this should be regularly evaluated during follow-up.

Shortly, in the presence of an athlete with exercise-induced symptoms, IVG should be taken in consideration. The exclusion of potential pathologies associated to an increased risk for sudden cardiac death is fundamental in the reproduction of symptoms, in which exercise stress echocardiogram plays an important role. IVG remains poorly clarified and some questions unanswered:

- Which is the etiology/pathophysiology of IVG (physiologic versus pathologic)?

- Which is the clinical impact at long-term of IVG?

- Which should be the recommendations regarding the eligibility for competitive sport of athletes with IVG?

- Which should be the surveillance/follow-up of athletes with IVG?

Author contributions

Conception and design of the research: Dores H, Mendes L; Acquisition of data: Dores H, Mendes L, Ferreira A; Writing of the manuscript: Dores H; Critical revision of the manuscript for intellectual content: Dores H, Mendes L, Ferreira A, Santos JF.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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MANUSCRIPT 11

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ORIGINAL PAPER

Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited

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Abstract (1) To study the prevalence and severity of coronary artery disease (CAD) in diabetic patients. (2) To provide a detailed characterization of the coronary atherosclerotic burden, including the localization, degree of stenosis and plaque composition by coronary computed tomography angiography (CCTA). Single center prospective registry including a total of 581 consecutive stable patients (April 2011–March 2012) undergoing CCTA (Dual-source CT) for the evaluation of suspected CAD without previous myocardial infarction or revascularization procedures. Different coronary plaque burden indexes and plaque type and distribution patterns were compared between patients with (n = 85) and without diabetes (n = 496). The prevalence of CAD (any plaque; 74.1 vs. 56 %; $p = 0.002$) and obstructive CAD (≥50 % stenosis; 31.8 vs. 10.3 %; $p < 0.001$) were significantly higher in diabetic patients. The remaining coronary atherosclerotic burden indexes evaluated (plaque in LM-3v-2v with prox. LAD; SIS; SSS; CT-LeSc) were also significantly higher in diabetic patients. In the *per segment* analysis, diabetics had a higher percentage of segments with plaque in every vessel (2.6/13.1/7.5/10.5 % for diabetics vs. 1.4/7.1/3.3/4.4 % for nondiabetics for LM, LAD, LCx, RCA respectively; $p < 0.001$ for all) and of both calcified (19.3 vs. 9.2 %, $p < 0.001$) and noncalcified or mixed types (14.4 vs. 7.0 %; $p < 0.001$); the ratio of proximal-to-distal relative plaque distribution (calculated as LM/proximal vs. mid/distal/branches) was lower for diabetics (0.75 vs. 1.04; $p = 0.009$). Diabetes was an independent predictor of CAD and was also associated with more advanced CAD, evaluated by indexes of coronary atherosclerotic burden. Diabetics had a significantly higher prevalence of plaques in every anatomical subset and for the different plaque composition. In this report, the relative geographic distribution of the plaques within each subgroup, favored a more mid-to-distal localization in the diabetic patients.

Keywords Diabetes · Coronary artery disease · Atherosclerotic burden · Coronary CT angiography

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Introduction

Patients with diabetes are considered to be at an increased risk of cardiovascular events and therefore it has been recommended by many guidelines a more aggressive management of this subset of patients, especially for those with established cardiovascular disease [1, 2].

By contrast, on a primary prevention unselected population level, some of the preventive measures for diabetic patients, like the use of antiplatelets, have failed to demonstrate a clear clinical benefit [3] and are no longer recommended in the absence of clinical evidence of atherosclerotic disease [4]. The reason for the lack of

MANUSCRIPT 11

benefit of aspirin in diabetic patients is likely related to the fact that diabetic patients represents an heterogeneous subset in what concerns the prevalence and severity of atherosclerotic coronary burden.

This illustrates the need for risk stratification of diabetic patients to identify the ones that can benefit from a more aggressive management at earlier stages. This is an opportunity for noninvasive imaging modalities, such as coronary computed tomography angiography (CCTA), which provides a detailed and comprehensive evaluation of the presence and extent of coronary artery disease (CAD), and can play an important role identifying the diabetic patients that could benefit from a more aggressive prevention of cardiovascular events.

Since CCTA is used mainly as a gatekeeper for the exclusion of significant CAD [5], most of the referred patients are at low to intermediate risk, this provides a good setting to study atherosclerotic disease at an earlier stage.

Therefore the aim of this study is two-folded:

1. To study the prevalence and severity of CAD in diabetic patients at earlier stages of CAD, to further evaluate the concept of CAD equivalent.
2. To provide a detailed characterization of the coronary atherosclerotic burden in diabetic patients, using the comprehensive information derived from CCTA on the localization, degree of stenosis and plaque composition.

Methods

Population

Single center prospective registry, including a total of 772 consecutive patients undergoing CCTA (with Dual source CT), from April 2011 to March 2012.

Patients were excluded if: (1) previous history of myocardial infarction and/or revascularization procedures (n = 70); (2) referred for Cardiac CT for other indications than the evaluation of possible CAD (cardiac CT for atrial fibrillation ablation or transcatheter aortic valve implantation procedures; n = 88); (3) referred for suspected acute coronary syndromes (n = 24); (4) with atrial fibrillation or other significant arrhythmias during scan acquisition that compromised image quality (n = 9). This resulted in a 24.7 % of the total population being excluded.

For the purpose of this study, 581 stable patients referred for suspected CAD were included in the context of: (1) Previous equivocal or inconclusive stress tests or discordant with the clinical evaluation (n = 417, 71.8 %); (2) Cardiac CT as 1st line investigation of possible CAD (n = 136, 23.4; %); 3) Preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 17; 2.9 %); (4) Evaluation of possible CAD in cardiomyopathies (Dilated or Hypertrophic) (n = 11; 1.9 %) (Fig. 1: Patient selection and study design).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history by means of a risk factors questionnaire was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents) [6]; (2) Dyslipidemia (defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) [7]; (3) Hypertension (defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medication) [8]; (4) Obesity (body mass index ≥30 kg/m^2); (5) positive family history of premature CAD [defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years of age] [9]; (6) smoking (defined as previous <1 year) or current smoker.

Pre-test probability of CAD was determined using both the Diamond and Forrester extended CAD consortium method (DF–CAD consortium model) [10] and the Morise score [11]. The cardiovascular risk was assessed with the HeartScore [4]. For the DF–CAD consortium probability model, as the CAD probability and CV risk of our population was shifted to lower probability (less that 2 % had a ≥70 % DF probability), the DF–CAD consortium model categories ≥30–70 % and ≥70 % were gathered in a intermediate to high (≥30 %) probability group. For the Morise, the original described cut-off points (for low, intermediate and high probability) were used, and for the HeartScore the established high risk cut-off of ≥5 % was used.

Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >65 beats/min.

During the scan acquisition, a bolus of iodinated contrast (Visipaque, GE Healthcare, USA) was injected at a 6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time + 6 s delay) x flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever

MANUSCRIPT 11

Int J Cardiovasc Imaging (2013) 29:1105–1114

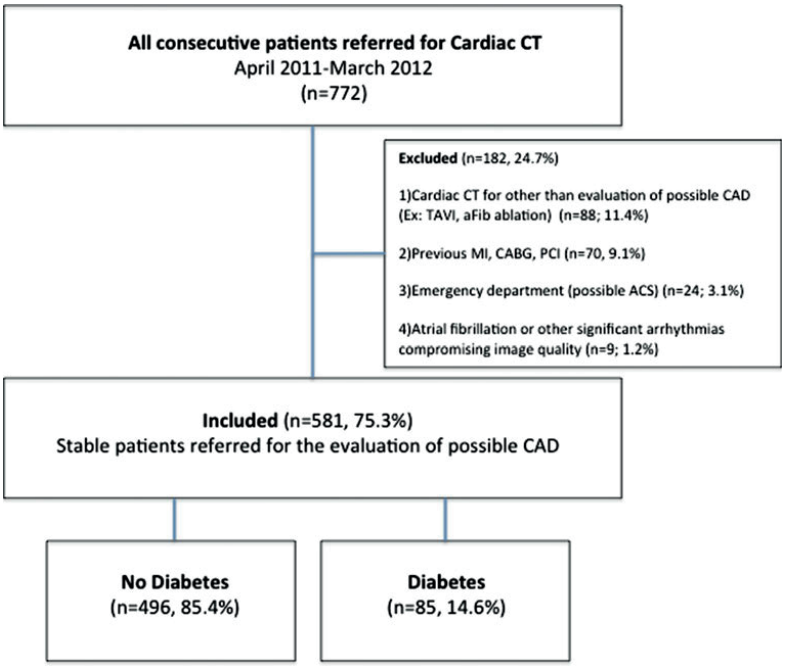

Fig. 1 Patient selection and study design. *CAD* coronary artery disease, *TAVI* transcatheter aortic valve implantation, *aFib* atrial fibrillation, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *ACS* acute coronary syndromes

feasible. Mean estimated radiation dose was 4.6 ± 3.7 mSv, contrast dose was 98.9 ± 14.4 ml and heart rate was 65.6 ± 10.6 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments.

Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III—equivalent experience. The Society of Cardiovascular Computed Tomography (SCCT) recommended classification was used regarding segmentation (16 segments), stenosis severity (<25; 25–49; 50–69; 70–99; 100 %) and plaque composition (calcified, noncalcified, mixed plaque) [12]. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. [13] Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque.

In the detailed *per segment* analysis, for the distribution of plaque on the 3 main coronary vessels, this rules were applied: plaques in the diagonal branches were counted as belonging to the left anterior descending (LAD); plaques in the obtuse marginal an intermediate branch were counted as belonging to the LCx; plaques in the posterior descending and right postero-lateral were counted as belonging to the right coronary artery (RCA). For the last two, coronary dominance was taking into account. The ratio of "proximal-to-distal relative plaque distribution" was calculated as the proportion of plaques between these two subgroups: (1) Left main and proximal segments of the LAD, LCx and RCA; (2) Mid and distal segments of LAD and RCA, distal LCx and all evaluable coronary branches.

Definition of the coronary atherosclerotic burden indexes

The following coronary atherosclerotic burden indexes were evaluated and compared between patients with and

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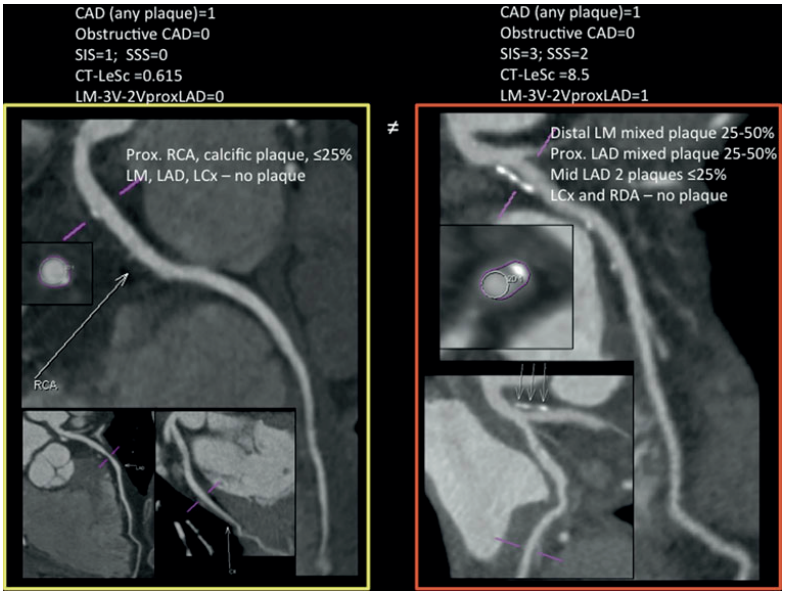

Fig. 2 Two case examples of diabetic patients with nonobstructive CAD. The different plaque burden indexes are shown. *CAD* coronary artery disease, *SIS* segment involvement score, *SSS* segment stenosis score, *CT-LeSc* CT Leaman score, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery, *LM-3 V-2VproxLAD* plaque in left main or 3 vessels or 2 vessels with proximal LAD

without diabetes: (1) Coronary artery disease (CAD)—presence of any plaque in the coronary tree; (2) "Obstructive CAD"—presence of at least one plaque with ≥50 % stenosis; (3) "LM-3v-2v with proximal LAD"—Plaque in the left main or in the 3 main epicardial vessels or in 2 main epicardial vessels including the proximal left anterior descending (LAD); (4) "SIS"—segment involvement score, obtained as the total number of segments with plaque; (5) "SSS"—segment stenosis score, obtained by grading the stenosis severity of each segment with plaque, as was previously described [13]. For these last two, the prognostically validated cut-offs (>5) were used [13]

(6) "Calcium score (CaSc) ≥100"; (7) "CaSc ≥75th percentile" (according to published nomograms [14]; (8) CCTA-adapted Leaman score (CT-LeSc)—this score was calculated taking in account 3 weighting factors (localization, plaque composition and stenosis severity) according to previously described methodology and the same cut-off for high plaque burden (≥8.3) was used (provided as additional information to the reviewers, since the manuscript, where it is originally described, is under consideration elsewhere). In Fig. 2, two case examples of diabetic patients with nonobstructive CAD are shown, with the different plaque burden indexes.

Statistical analysis

Continuous variables are presented as mean ± SD or medians (interquartile range) and categorical variables as frequencies with percentages.

The non-parametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables. Chi square test was used to evaluate differences in frequencies. Differences were regarded significant when $p < 0.05$ (two-tailed).

Multivariate analyses (binary logistic regression model—enter method) were performed to identify independent predictors of CAD (any plaque and obstructive) using the demographic and clinical variables presented in Table 1, that were significant in univariate analysis ($p < 0.05$). A second multivariable analyses was performed to identify independent predictors among the clinical scores of CAD probability (Diamond-Forrester CAD consortium model and Morise score) and the CV risk score HeartScore. For the detailed *per segment* analysis, the unit of measure was each segment and there were no adjustments or corrections made for the serial correlation between segments.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

MANUSCRIPT 11

Int J Cardiovasc Imaging (2013) 29:1105–1114

Results

Study population

In the final study population (n = 581), 85 patients were diabetics (14.6 %).

Regarding the demographic and clinical variables, diabetic patients were older (mean age 61.4 ± 8.7 vs. 56.9 ± 11.3) and had a higher prevalence of obesity (28.6 % vs. 17.4 %) and hypertension (84.7 vs. 58.9 %). This was predominantly a population with low to intermediate CAD probability, more so in the nondiabetic population since 61.7 % had a DF–CAD consortium <30 and 90.7 % had a Morise score <16. The cardiovascular risk, as estimated with the HeartScore (≥5 %), was significantly higher in the patients with diabetes (42.4 vs. 22.6 %) (Table 1).

Independent predictors of CAD

Diabetes was an independent predictor of both the presence of plaque (OR 1.81; 95 % CI 1.02–3.21; $p = 0.041$) and of obstructive CAD (OR 3.69; 95 % CI 2.08–6.53; $p < 0.001$). The other independent predictors of the *presence of plaque* were age ≥65 years (OR 3.42; 95 % CI 2.15–5.45; $p < 0.001$), male sex (OR 2.72; 95 % CI 1.85–4.01; $p < 0.001$), hypertension (OR 1.82; 95 % CI 1.23–2.67; $p = 0.002$), dyslipidemia (OR 1.89; 95 % CI 1.29–2.77; $p = 0.001$), chest pain (OR 0.62; 95 % CI 0.42–0.91; $p = 0.014$) an DF–CAD consortium ≥30 % (OR 2.62; 95 % CI 1.70–4.05; $p < 0.001$), a Morise score ≥16 (OR 2.55; 95 % CI 1.57–4.14; $p < 0.001$), and an HeartScore ≥5 % (OR 3.90; 95 % CI 2.19–6.94; $p < 0.001$). The other independent predictors of *obstructive CAD* were age ≥65 years (OR 1.98; 95 % CI 1.16–3.37; $p = 0.012$), male sex (OR 2.94; 95 % CI 1.68–5.15; $p < 0.001$), an DF–CAD consortium ≥30 % (OR 1.88; 95 % CI 1.04–3.42; $p = 0.038$), a Morise score ≥16 (OR 1.84; 95 % CI 1.06–3.20; $p = 0.031$), and an HeartScore ≥5 % (OR 2.71; 95 % CI 1.50–4.88; $p = 0.001$).

Coronary artery disease prevalence, severity and coronary atherosclerotic burden indexes—*per patient* analysis

The prevalence of plaques in the coronary arteries was high in the overall study population, but this was significantly higher for diabetic patients, as almost 3 out of 4 diabetic patients (74.1 %) had plaques in the coronary arteries.

Table 1 Demographic and clinical characteristics of the study population

	No diabetes (n = 496)	Diabetes (n = 85)	*p*
Demographic			
Age	56.9 ± 11.3	61.4 ± 8.7	<0.001
Male sex	277 (55.8)	47 (55.3)	1.000
Risk factors			
Obesity (BMI ≥30)	85 (17.4)	24 (28.6)	0.023
Hypertension	292 (58.9)	72 (84.7)	<0.001
Dyslipidemia	301 (60.7)	59 (69.4)	0.147
Smoking	118 (23.8)	20 (23.5)	1.000
Family history of premature CAD	168 (33.9)	26 (30.6)	0.619
Chest pain	265 (54.3)	46 (54.1)	1.000
CAD probability			
DF–CAD consortium ≥30 %	189 (38.1)	42 (49.4)	0.049
DF–CAD consortium <30 %	307 (61.9)	43 (50.6)	
Morise score ≥16	46 (9.3)	26 (30.6)	<0.001
Morise score 9–15	316 (63.7)	53 (62.4)	
Morise score 0–8	134 (27.0)	6 (7.1)	
CV risk			
HeartScore ≥5 %	112 (22.6)	36 (42.4)	<0.001

Values are mean ± SD or n (%)

CAD coronary artery disease, *BMI* body mass index, *DF–CAD* consortium diamond-forrester CAD consortium model, *CV* cardiovascular

Table 2 Calcium score and CCTA characteristics of the study population

	No diabetes (n = 496)	Diabetes (n = 85)	*p*
Calcium score			
Median	0 (0-67)	68 (0-311)	<0.001
CaSc ≥100	96 (19.4)	40 (47.1)	<0.001
CaSc ≥75th percentile	60 (12.1)	23 (27.1)	0.001
CCTA			
Normal/No plaque	217 (43.8)	22 (25.9)	<0.001
Nonobstructive CAD	228 (46.0)	36 (42.4)	
Obstructive CAD	51 (10.3)	27 (31.8)	
Coronary atherosclerotic burden indexes			
Plaque in LM-3v-2v with prox. LAD	178 (35.9)	53 (62.4)	<0.001
Segment involvement score >5	66 (13.3)	31 (36.5)	<0.001
Segment stenosis score >5	25 (5.0)	21 (24.7)	<0.001
CT-Leaman Score ≥8.3	79 (15.9)	35 (41.2)	<0.001
Technical data			
Heart rate (bpm)	65.3 ± 10.6	67.0 ± 10.2	0.172
Contrast dose (ml)	99.3 ± 14.7	96.7 ± 12.3	0.119
Radiation dose (mSv)	4.7 ± 4.9	5.7 ± 3.8	0.069

Values are mean ± SD, median (IQR) or n (%)

CaSc calcium score, *CCTA* coronary computed tomography angiography, *CAD* coronary artery disease, *LM-3v-2v* left main, 3 vessel, 2 vessel, *LAD* left anterior descending, *bpm* beats per minute, *mSv* milisievert

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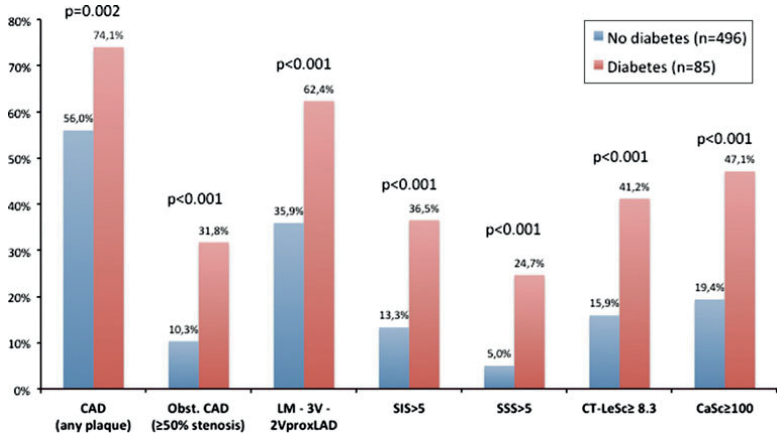

Fig. 3 Diabetes and indexes of coronary atherosclerotic burden. *CAD* coronary artery disease, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *LM-3 V-2VproxLAD* plaque in left main or 3 vessels or 2 vessels with proximal LAD, *SIS* segment involvement score, *SSS* segment stenosis score, *CT-LeSc* CT Leaman score

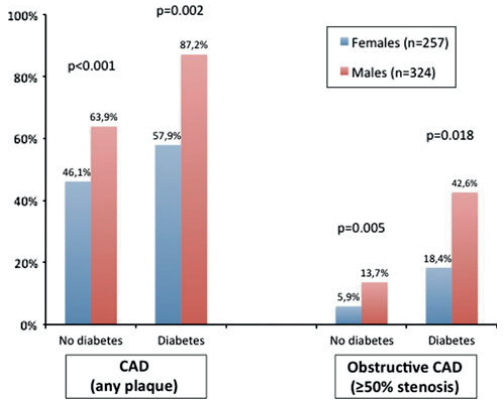

Fig. 4 Prevalence of coronary artery disease (any plaque and obstructive) across the different diabetes and sex subgroups. *CAD* coronary artery disease

All the indexes of coronary atherosclerotic burden were significantly higher in diabetics as compared to nondiabetics (Table 2; Fig. 3).

For some of these indexes, like the presence of obstructive disease, and the SSS, the prevalence was 3–5 times higher in diabetics.

By gender, male diabetics had more often coronary artery disease (any plaque and obstructive), as compared to their counterparts (Fig. 4).

Prevalence, localization and type of plaques—*per segment* analysis

For the analysis of the atherosclerotic burden indexes, 8,136 coronary segments were evaluated for the presence of plaque, degree of stenosis and type of plaque. Because of small size (<2 mm) or insufficient image quality related to artifacts or severe calcification, 866 (10.6 %) segments were excluded (n = 723–10.4 % in nondiabetics; n = 143–12.0 % in diabetics).

On a *"per evaluable segment"* analysis, diabetics had significantly more segments with plaque and this was observed in the left main as well as in the other 3 coronary territories and in both more proximal and more distal locations (Table 3; Fig. 5). The prevalence of obstructive plaque was also significantly higher in patients with, as compared to patients without diabetes (11.6 vs. 6.9 %, $p < 0.001$).

On a *"per segment with plaque"* analysis, nondiabetics had an almost equal distribution of plaques between more proximal (LM/proximal segments) and more mid-to-distal (Mid/distal/branches) localization (ratio of 1.04), but the opposite was seen in patients with diabetes, in whom more plaques were found in the more mid-to-distal segments, as reflected by a ratio of "proximal-to-distal relative plaque distribution" of 0.75 (Table 3).

Regarding plaque composition, diabetics had also a higher percentage of all types of plaques (both calcified and noncalcified or mixed plaques) per evaluable segment (Table 4).

Discussion

The main findings of this study are:

1. Although diabetic patients had a higher prevalence of coronary artery disease, coronary atherosclerotic plaques were commonly observed in both patients with and without diabetes.

MANUSCRIPT 11

Int J Cardiovasc Imaging (2013) 29:1105–1114

Table 3 Prevalence, and localization of plaques—*per segment* analysis

	No diabetes (n = 496; 6,957 segments)	Diabetes (n = 85; 1,187 segments)	*p*
All evaluable segments	6,234 (89.6)	1,044 (88.0)	0.093
Segments with any plaque	1,008 (16.2)	352 (33.7)	<0.001
Coronary artery distribution			
Any plaque in the LM	87 (1.4)	27 (2.6)	0.007
Any plaque in the RCA	276 (4.4)	110 (10.5)	<0.001
Any plaque in the LAD	441 (7.1)	137 (13.1)	<0.001
Any plaque in the LCx/Ramus	204 (3.3)	78 (7.5)	<0.001
Proximal versus distal distribution			
Any plaque in LM/Proximal	514 (8.2)	151 (14.5)	<0.001
Any plaque in Mid/Distal/Branches	494 (7.9)	201 (19.3)	<0.001
"Ratio of proximal-to-distal relative plaque distribution"	1.04 (514/494)	0.75 (151/201)	0.009

"Ratio of proximal-to-distal relative plaque distribution"—proportion of plaques in the "LM/Proximal" versus "Mid/Distal/branches"

LM left main, *RCA* right coronary artery, *LAD* left anterior descending, *LCx* left circunflex, *Ramus* intermediate branch, "*LM/Prox*" left main or proximal segments of the LAD, LCx or RCA, "*Mid/Distal/Branches*" mid or distal segments of the LAD and RCA, distal segment of the LCx, and branches

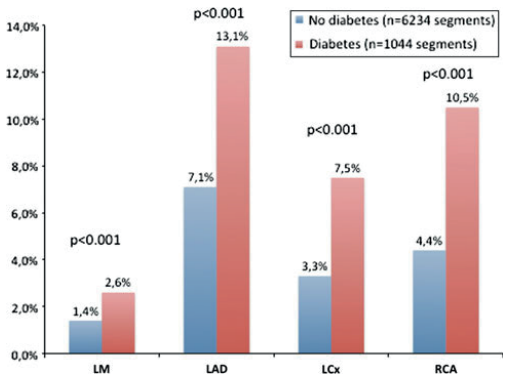

Fig. 5 Prevalence and localization of plaques (any plaque) on a *per segment* analysis. *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery

2. Several different coronary atherosclerotic burden indexes were more prevalent in diabetics, indicating more diffuse and severe CAD, and this was especially true for males.
3. In the detailed per segment analysis, diabetics had a higher percentage of segments with plaque in every vessel and of both calcified and noncalcified or mixed types; ratio of proximal-to-distal relative plaque distribution suggested an anatomical gradient in the geographic distribution, with higher proportion of disease involvement in the mid/distal/branches segments in diabetic patients.

Diabetes as an heterogeneous group—not all diabetics have the same CV risk

For many years, diabetic patients have been considered as a subset at higher risk of cardiovascular events. Nevertheless,

Table 4 Type of plaques—*per segment* analysis

	No diabetes (n = 496; 6,957 segments)	Diabetes (n = 85; 1,187 segments)	*p*
All evaluable segments	6,234 (89.6)	1,044 (88.0)	0.093
Segments with any plaque	1,008 (16.2)	352 (33.7)	<0.001
Calcified plaque			
All segments	571 (9.2)	202 (19.3)	<0.001
LM/Proximal	291 (4.7)	83 (8.0)	<0.001
Mid/Distal/Branches	280 (4.5)	119 (11.4)	<0.001
Noncalcified or mixed plaques			
All segments	437 (7.0)	150 (14.4)	<0.001
LM/Proximal	223 (3.6)	68 (6.5)	<0.001
Mid/Distal/Branches	214 (3.4)	82 (7.9)	<0.001

LM left main, *RCA* right coronary artery, *LAD* left anterior descending, *LCx* left circunflex, *Ramus* intermediate branch, "*LM/Proximal*" left main or proximal segments of the LAD, LCx or RCA, "*Mid/Distal/Branches*" Mid or distal segments of the LAD and RCA, distal segment of the LCx, and branches

MANUSCRIPT 11

it has been difficult to prove a clear benefit of some primary prevention measures, like is the case of aspirin in the primary prevention of cardiovascular events. This inconsistent benefit of aspirin in the absence of clinical manifestations of cardiovascular disease, can be related to the fact that it is less effective in these patients [15] or more likely that diabetic patients are an heterogeneous group in terms of cardiovascular disease presence and extent. This way, without risk stratification, we could be overtreating some low risk diabetic patients, exposing them to the risk of side effects that could offset the reduction in expected atherothrombotic events rate.

Of note, there has been a more consistent beneficial effect of aspirin as primary preventive measure in males, for reducing the risk of myocardial infarction [3] and this is in line with our findings of higher prevalence of coronary plaques and obstructive CAD in this subgroup, as compared to females.

Recently, Saely et al. [16] revisited the concept of diabetes as a CAD equivalent in a study comparing the vascular event rate of patients according to the presence of diabetes and/or CAD. In this study, diabetes was not per se a CAD risk equivalent, since diabetic patients without significant CAD had a lower event rate than nondiabetic patients with significant CAD.

CCTA derived coronary atherosclerotic burden indexes

Scores derived from invasive angiography have previously demonstrated to further stratify diabetic patients with more advanced CAD [17]. We hypothesized that this could also be the case for diabetics with less severe CAD, using the comprehensive information derived from CCTA on the presence, localization, degree of stenosis and plaque composition.

Several different aspects of coronary disease are reflected in these scores: prevalence and severity (*any plaque and obstructive CAD*), number of plaques (*SIS*), number and distribution (*plaque in LM-3v-2v with prox. LAD*), number and stenosis severity (*SSS*), absolute and relative amount of calcified plaque (CaSc ≥100 and ≥75th percentile) and localization, stenosis severity and type of plaque (CT-Le score). All the coronary atherosclerotic burden indexes were significantly higher in diabetics as compared to nondiabetics, reflecting the higher prevalence as well as the more severe coronary disease of this subset of patients and they can be useful as noninvasive imaging tools for risk stratification. Some of these indexes have already been prognostically validated and demonstrated a good correlation with major cardiovascular events [13, 18, 19]. In our view, since the prevalence of plaque is very high, even in this predominantly low-to-intermediate CAD probability population, these coronary atherosclerotic burden indexes can help risk stratify patients and should ideally be included in the CCTA report. However, since they convey information on different aspects of CAD, with some overlap in the information they provide and, in clinical practice, reporting on all of them is not suitable, ideally we should be able to decide in the future which one(s) should be routinely used, based on their prognostic performance.

Anatomical distribution and plaque composition

In this report, the higher prevalence of plaques in diabetic patients was seen in the left main as well as in the other 3 coronary territories and in both proximal and distal locations. Regarding the left main and the other proximal locations, we observed a higher percentage of plaques in diabetics as compared to nondiabetics. This is in line with previous studies linking the geographic distribution of myocardial infarction culprit lesions to more proximal locations in the coronary tree [20] and could explain the higher incidence of coronary events experienced by diabetic patients.

One interesting finding in our study is related to the relative geographic localization of plaques in diabetics as compared to patients without diabetes.

Although in prevalence of evaluable segments, diabetics had more plaques in every location (both proximal and distal) compared to nondiabetics, the relative geographic plaque distribution was different in the two subgroups of patients, since diabetics had a ratio of "proximal-to-distal relative plaque distribution" of 0.75 (vs. 1.04 for nondiabetics), suggesting a higher predisposition to disease involvement of the more distal segments. This finding, on a *per segment* analysis, together with the higher prevalence of a SIS >5 on the *per patient* analysis reflects the more diffuse nature of coronary atherosclerotic burden of diabetic patients.

As diabetic patients are considered to be a model of more advanced CAD, this could suggest that as the coronary atherosclerosis progresses, distal segments become more involved by disease, although serial measurements in time would be the ideal setting to evaluate this hypothesis.

The *per segment* analysis allowed also the evaluation of the plaque composition. Diabetic patients had a significantly higher prevalence of segments with both calcified and noncalcified or mixed plaques, in both more proximal or more distal locations. The proportion of calcified to noncalcified or mixed plaques was the same for both subgroups of patients.

Limitations

There are a number of limitations related to this report:

1. This is a single center data with medium size cohort;

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2. The population included in our study was mainly composed of patients with low to intermediate CAD probability and CV risk, as this reflects daily practice of CCTA being used as a gatekeeper to exclude obstructive CAD and are in line with the recommendations. Since coronary plaques were present in nearly 60 % of the patients, this was an opportunity to evaluate the coronary atherosclerotic burden pattern of DM patients at earlier stages.
3. There were some differences in the baseline characteristics of the two subgroups of patients, that could have contributed to the higher disease extent observed in diabetic patients. Nevertheless, after adjusting for those differences, diabetes remained an independent predictor of both the presence and severity of CAD.
4. Since patients were referred for CCTA because of symptoms and/or the results of stress tests, some referral bias has to be acknowledged.

Conclusions

Diabetes was an independent predictor of CAD and was also associated with more advanced CAD, evaluated by indexes of coronary atherosclerotic burden.

The comprehensive information regarding the presence, severity and type of plaque noninvasively provided by CCTA, has made possible a detailed characterization of the coronary disease pattern of diabetic patients at an earlier stage of disease.

Diabetics had a significantly higher prevalence of plaques in every anatomical subset (type of vessel and both proximal or distal localizations) and for the different plaque composition (both calcified and noncalcified or mixed). In this report, the relative geographic distribution of the plaques within each subgroup, favored a more mid-to-distal localization in the diabetic patients.

Conflict of interest None.

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Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac computed tomography

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Abstract

Background: The relation between body mass index (BMI) and coronary artery disease (CAD) extension remains controversial. The aim of this study was to evaluate the correlation between BMI and CAD extension documented by coronary computed tomography angiography (CCTA).

Methods and results: Prospective registry including 1706 consecutive stable patients that performed CCTA (dual source scanner) for the evaluation of CAD. The population was stratified by BMI: normal 530 (31.1%), overweight 802 (47.0%) and obesity 374 (21.9%). BMI was significantly higher in patients with CAD (27.7 ± 4.3 vs 26.8 ± 4.3 kg/m^2, $p < 0.001$); these patients were also older, more often male and had higher prevalence of diabetes, hypertension and dyslipidemia. By multivariate analysis (logistic regression) BMI remains an independent predictor of CAD (odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.06; $p = 0.012$). Regarding the severity of CAD, BMI was not significantly different among patients with and without obstructive CAD (27.7 ± 4.3 vs 27.2 ± 4.3 kg/m^2, $p = 0.120$). In 319 patients (4516 segments; 4077 evaluable), a detailed atherosclerotic burden was evaluated and compared among BMI classes, defined according to the presence of plaque and the degree of stenosis. Obstructive CAD was identified in 16.9% of the patients and 45.1% had non-obstructive CAD. The discriminative threshold for high burden, established by the segment involvement score (SIS), was >5 segments with plaque (15.4% patients). The prevalence of SIS >5 among the BMI classes was: 18.7%, 13.7% and 13.6% for normal, overweight and obesity respectively (p values for the specific classes versus all other patients: 0.241, 0.450 and 0.663).

Conclusions: In this population of stable patients undergoing CCTA for suspected CAD, BMI was an independent predictor of its presence, but was not correlated with the coronary disease severity.

Keywords

Cardiac computed tomography, body mass index, coronary artery disease

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Introduction

In recent years, obesity has reached epidemic proportions, and is currently a highly prevalent chronic condition associated with significant morbidity and mortality.[1] In the general population, overweight and obesity are associated with an increased risk of cardiovascular disease and all-cause mortality.[2,3] However, among patients with known coronary artery disease

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MANUSCRIPT 12

(CAD), the evidence is contradictory. Several studies have suggested an 'obesity paradox' due to a protective effect of obesity against adverse outcomes, and the correlation between body mass index (BMI) and survival has been described as having a U-shaped curve.[4,5] Additionally, the relationship between obesity and CAD extension remains controversial. Several authors suggest that, paradoxically, obese patients have a lower CAD burden (Duke myocardial jeopardy scores) and lower prevalence of high-risk coronary anatomy (significant left main or triple vessel disease) compared to non-obese patients.[6,7]

Recently, coronary computed tomography angiography (CCTA) has become widely available and adopted in the clinical practice, mainly due to the high negative predictive value to rule out obstructive CAD.[8,9] In addition, CCTA allows also the identification of non-obstructive CAD, providing in this way a noninvasive quantification of the total coronary atherosclerotic burden. As showed in the large CONFIRM Registry,[10] both non-obstructive and obstructive CAD, identified by CCTA, were associated with worse cardiovascular outcomes, while the absence of CAD was associated with a favorable prognosis. To the best of our knowledge, there are no previous published studies evaluating the relationship of BMI with both the presence and extension of CAD, documented by CCTA, and this was the aim of the present study.

Methods

Population

From February 2007 to October 2011 all consecutive stable patients undergoing CCTA (dual source scanner) for the evaluation of possible CAD were included in a single centre prospective registry. Figure 1 shows patient selection and study design. Patients referred from the emergency department (possible acute coronary syndrome) or indications other than evaluation for possible CAD were excluded from this analysis. For the purpose of this study, 1706 patients were included in the context of: previous equivocal or inconclusive stress tests or discordant with the clinical evaluation ($n = 1253$; 73.5%), CCTA as first line investigation of possible CAD ($n = 294$; 17.2%), preoperative CAD assessment prior to non-coronary valvular or aortic surgery ($n = 34$, 2.0%), evaluation of possible CAD in cardiomyopathies ($n = 125$, 7.3%).

A detailed medical history with a risk factors questionnaire was obtained from the patients to assess for the presence of: (a) diabetes mellitus (defined as a fasting glucose level of ≥ 7.0 mmol/l or the need for insulin or oral hypoglycemic agents); (b) dyslipidemia (defined as a total cholesterol level ≥ 5 mmol/l or treatment with lipid-lowering drugs); (c) hypertension (defined as blood pressure $\geq 140/90$ mm Hg or the use of antihypertensive medication); (d) Positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years old); (e) smoking (defined as previous (less <1 year) or current smoker). Weight and height were self-reported by the patients in the questionnaire. The overall population was stratified by the BMI value, according to the World Health Association classification:[11] underweight ($<18.5\,kg/m^2$), normal ($18.5–24.9\,kg/m^2$), overweight ($25.0–29.9\,kg/m^2$) and obesity ($IMC \geq 30.0\,kg/m^2$). Underweight patients were excluded from the present analysis. In a cohort of patients, the detailed atherosclerotic burden was evaluated and compared among the BMI classes. The local ethics committee approved the study and all patients gave written informed consent.

Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition®, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and beta-blockers were administered to lower the heart rate when indicated. During the scan acquisition, a bolus of iodinated contrast (Visipaque®, GE Healthcare, USA) was injected at a 6 ml/s infusion rate, followed by a 50 ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time-+6 s delay) x flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries. Dose reduction strategies-including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering-were used whenever feasible. Mean estimated radiation dose was 5.3 ± 3.7 mSv, contrast dose was 97.1 ± 14.4 ml and heart rate was 67.8 ± 13.3 bpm. Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III-equivalent experience. The Society of Cardiovascular Computed Tomography (SCCT) recommended classification[12] was used regarding segmentation (16 segments), stenosis severity (<25%; 25–49%; 50–69%; 70–99%;

MANUSCRIPT 12

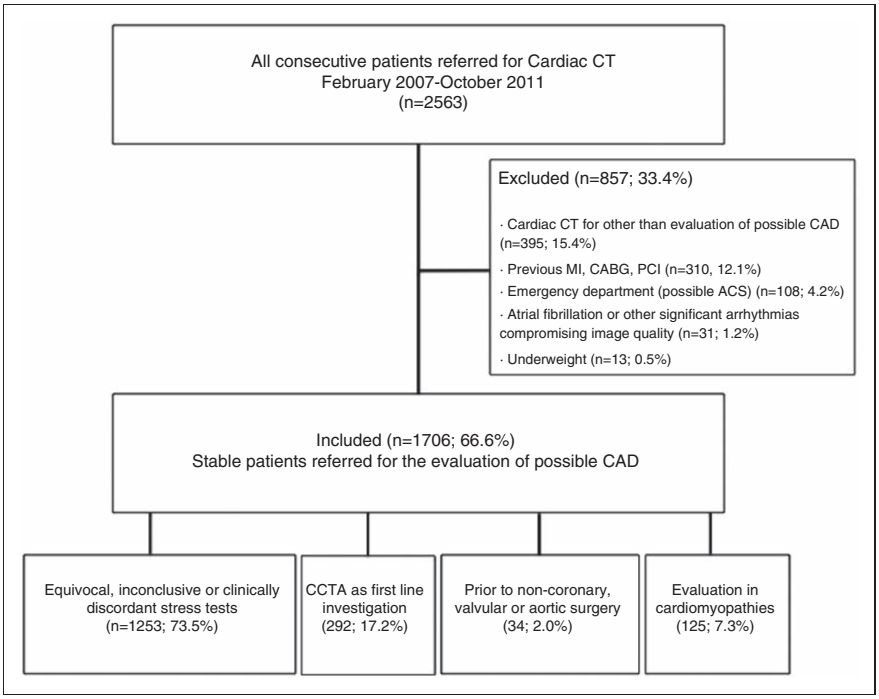

Figure 1. Patient selection and study design.
CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CT: computed tomography; PCI: percutaneous coronary intervention.

100%) and plaque composition (calcified, non-calcified or mixed). CAD was defined as the presence of any coronary plaque identified in CCTA (both obstructive and non-obstructive lesions; including non-calcified plaque). Obstructive CAD was defined as the presence of plaque with $\geq$50% stenosis. The discriminative threshold for high coronary atherosclerotic burden was established as the SIS with the previously tested prognostic threshold of >5 segments with plaque.[13] In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat or the vessel lumen itself. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. The value of the Agatston calcium score was obtained with the analysis of consecutive non-contrast 3 mm slices, with a reconstruction b35f Kernel and a small (cardiac) FOV, with a dedicated software (CaScoring- Siemens^{TM}), where every area at least with 1 mm^2 within a coronary vessel with a density above 130 HU (Hounsfield Units) was selected.[14]

Statistical analysis

Continuous variables with normal distribution were expressed as means and standard deviation (SD), those with non-normal distribution as medians and interquartile range (IQR). Normality was tested with the Kolmogorov-Sminorv test. Categorical variables were expressed as frequencies and percentages. Statistical comparison of baseline characteristics and outcomes was performed using the chi-square test or Fisher's exact test, when appropriate, for categorical variables and the Mann-Whitney or Kruskal-Wallis test for continuous variables. Multivariate analyze (binary logistic regression model - enter method) was performed to identify independent predictors of CAD and independent predictors of obstructive CAD. In this model all the statistically significant variables in the univariate analysis were included. Two-tailed tests of

MANUSCRIPT 12

significance are reported. For all comparisons, a p value of <0.05 was considered statistically significant. When appropriate, a 95% confidence interval (CI) was calculated. Statistical analysis was performed with SPSS version 19.0 (SPSS® Inc., Chicago, Illinois, USA).

Results

Study population

Of the 1706 patients included in the final analysis, the median age was 59.0 (51.0–66.0) years and the majority (57.2%) were male. Demographic and clinical characteristics are depicted in the Table 1. The percentage of patients with diabetes was 15.0% and there was a high prevalence of both hypertension and dyslipidemia (60.5% and 59.8% respectively). The median HeartScore was 2(1–4)%, and 17.2% patients had high cardiovascular risk (HeartScore ≥5%). The median BMI was 26.7 (24.4–29.4) kg/m^2 and the stratification according to the BMI classes was: normal ($n = 530$, 31.1%), overweight ($n = 802$, 47.0%) and obesity ($n = 374$, 21.9%).

CAD burden

In the overall population, the median calcium score was 4(0-100), 58.9% patients had CAD and 19.1% patients had obstructive CAD. By univariate analysis, BMI was significantly higher in patients with CAD (27.7 ± 4.3 vs 26.8 ± 4.3 kg/m^2, $p < 0.001$); these patients were also older, more often male and had higher prevalence of diabetes, hypertension and dyslipidemia. Regarding the presence of obstructive CAD, this was more prevalent in the older patients, in males and in patients with hypertension, diabetes, dyslipidemia and smoking. However, BMI was not significantly different among patients with and without obstructive CAD (27.7 ± 4.3 vs 27.2 ± 4.3 kg/m^2, $p = 0.120$) (Table 2). By multivariate analysis (adjusted for age, male gender, BMI, dyslipidemia, diabetes and hypertension), BMI remain an independent predictor of CAD (OR 1.03, 95% CI 1.01–1.06, $p = 0.012$) (Figure 2).

In a cohort of 319 patients in whom the detailed atherosclerotic burden evaluation was performed (4516 segments; 4077 evaluable), the distribution according BMI classes was: normal ($n = 107$, 33.5%), overweight ($n = 146$, 45.8%) and obesity ($n = 66$, 20.7%). Obstructive CAD was identified in 16.9% of the patients and 45.1% had non-obstructive CAD. The median number of coronary segments with lesions was 1.0 (0.0–4.0) and 15.4% patients had SIS >5. The distribution of the variable SIS >5 among the BMI classes was: 18.7%, 13.7% and 13.6% for normal, overweight and obesity respectively (p values for the specific classes versus all other patients: 0.241, 0.450 and 0.663 respectively).

Table 1. Demographic and clinical characteristics

Variables	All patients ($n = 1706$)
Demographic	
Age, median (IQR) years	59.0 (51.0–66.0)
Male gender, *n* (%)	976 (57.2)
Cardiovascular risk factors, *n* (%)	
Diabetes mellitus	256 (15.0)
Hypertension	1032 (60.5)
Smoking	459 (26.9)
Dyslipidemia	1021 (59.8)
Family history of premature CAD	606 (35.5)
Cardiovascular risk	
HeartScore, median (IQR)	2.0 (1.0–4.0)
HeartScore ≥5%, *n* (%)	293 (17.2)
Chest pain, *n* (%)	
Asymptomatic	836 (49.0)
Non-cardiac	369 (21.6)
Atypical	363 (21.3)
Typical	138 (8.1)
BMI (kg/m^2)	
Median (IQR)	26.7 (24.4–29.4)
Normal, *n* (%)	530 (31.1)
Overweight, *n* (%)	802 (47.0)
Obesity, *n* (%)	374 (21.9)

BMI: body mass index; CAD: coronary artery disease; IQR: interquartile range.

Discussion

Our findings suggest that in this population of stable patients with low to intermediate cardiovascular risk referred for CCTA for suspected CAD, BMI was an independent predictor of CAD presence, but was not correlated with CAD severity. There were no significant differences across different BMI classes in the percentage of patients with obstructive CAD or in the overall coronary atherosclerotic burden, as evaluated by the segment involvement score.

In the general population, obesity is a well-known risk factor for CAD, being associated with poor clinical outcomes. In patients with documented CAD this relationship remains controversial, but the prevalence of obesity is patients with CAD is still increasing and the current management of obesity seems inadequate.[15] Some previous studies described an 'obesity paradox' with better outcomes of obese patients when compared with non-obese, frequently with an U-shaped relationship. This paradoxical association between BMI and

MANUSCRIPT 12

Table 2. Characteristics distribution according to the presence of coronary artery disease and obstructive stenosis

Variables	CAD ($n=1005$)	Non-CAD ($n=701$)	*p* value	Obstructive ($n=326$)	Non-obstructive ($n=1380$)	*p* value
Age (years) (mean ± SD)	61.5 ± 9.9	53.5 ± 11.9	<0.001	62.1 ± 9.9	57.3 ± 11.6	<0.001
Male gender, *n* (%)	648 (64.5)	328 (46.8)	<0.001	239 (73.3)	737 (53.4)	<0.001
Diabetes mellitus, *n* (%)	191 (19.0)	65 (9.3)	<0.001	84 (25.8)	172 (12.5)	<0.001
Hypertension, *n* (%)	669 (66.6)	363 (51.8)	<0.001	226 (69.3)	806 (58.4)	<0.001
Dyslipidemia, *n* (%)	664 (66.1)	357 (50.9)	<0.001	222 (68.1)	799 (57.9)	0.001
Smoking, *n* (%)	287 (28.6)	172 (24.5)	0.065	111 (34.0)	348 (25.2)	0.001
Familiar history of CAD, *n* (%)	362 (36.0)	244 (34.8)	0.607	113 (34.7)	493 (35.7)	0.719
BMI (kg/m^2) (mean ± SD)	27.7 ± 4.3	26.8 ± 4.3	<0.001	27.7 ± 4.3	27.2 ± 4.3	0.120

BMI: body mass index; CAD: coronary artery disease; SD: standard deviation.

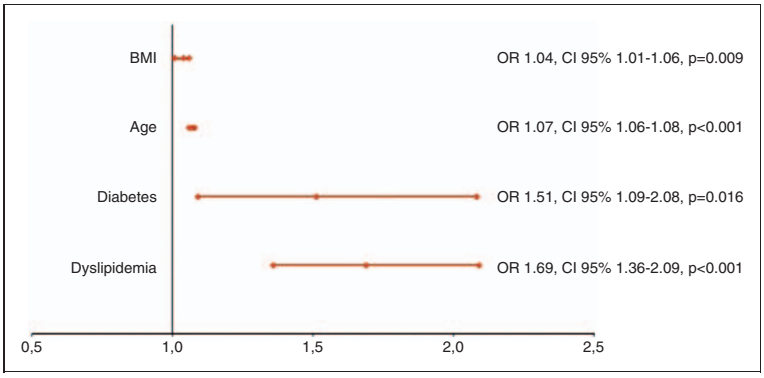

Figure 2. Independent predictors of coronary artery disease (CAD) presence (multivariate analysis).
BMI: body mass index; CI: confidence interval; OR: odds ratio.

survival in patients with CAD occurs irrespectively of the treatment strategy and, in fact, among patients undergoing percutaneous coronary intervention (PCI) an increased BMI was associated with improved survival[4] and a meta-analysis of patients undergoing PCI showed a lower risk of death in patients with higher BMI.[5] Several explanations are frequently given for this paradox. Adipose tissue is a recognized major endocrine organ and obesity is associated with high serum levels of low-density lipoproteins that have anti-inflammatory effect.[4,16] As an example, in patients with heart failure, it has been demonstrated that obese individuals have lower levels of tumor necrosis factor and other inflammatory cytokines.[16] On the other hand, poor clinical outcomes in patients with lower weight can be related to malnutrition or cachexia and prevalence of comorbid conditions, such as occult malignancy and heart failure.[4]

The controversy is not limited to the association between obesity and clinical outcomes, but also occurs with the relationship between obesity and atherosclerotic CAD extension. Studies from Israel performed by Rubinshtein et al.[6] and from the USA by Niraj et al.[7] showed that obesity was associated with less severe CAD among patients undergoing coronary angiography. The better prognosis of obese patients in these studies could be explained by the investigation and treatment at earlier stages in the disease course. Patients with higher BMI are also more frequently submitted to standard medical therapies, diagnostic coronary angiography and revascularization procedures.[17] Among patients undergoing coronary invasive angiography, obese patients are younger and also have a lower prevalence of other cardiovascular risk factors. This evidence contributes to the lower prevalence of high-risk coronary anatomy in patients with higher BMI in some of the previous reports. The Duke jeopardy score was frequently used in these studies, as an estimate of the amount of myocardium at risk according to the coronary artery stenosis location, and provided

independent prognostic information.[18] The association between BMI and CAD assessed by CCTA to our knowledge was not previously reported. CCTA is a noninvasive and accurate method to evaluate CAD, with a good correlation with invasive angiography (QCA) and intravascular ultrasound.[12]

In our study, after adjusting for traditional cardiovascular risk factors including age, gender, hypertension, diabetes, smoking, familiar history of CAD and dyslipidemia, BMI as a continuous variable remained an independent predictor for CAD presence but was not a predictor of CAD severity. One possible explanation for these findings could be related to the baseline characteristics of the population: stable patients (most of them without typical chest pain) and only a minority with high cardiovascular risk, probably representing early stages in the coronary disease evolution. This population is significantly different from those referred for invasive angiography who were included in the previous studies. On the other hand, BMI does not differentiate central and peripheral adiposity. Measurements of abdominal obesity and waist-hip ratio could be more discriminant, as abdominal obesity has been more closely associated with cardiovascular events.[19] In this regard, computed tomography has been recognized as a highly effective, accurate, and reproducible technique for measuring visceral adiposity,[20] and it has been documented by previous authors that there is a correlation between abdominal adiposity and the extent of coronary atherosclerosis.[21]

Limitations

There are some limitations related to this report: (a) single centre data with medium size cohort; (b) use of BMI as the only marker of adiposity, instead of the more specific markers of abdominal obesity that could have a better correlation with CAD severity; (c) studied population predominantly with low-intermediate cardiovascular risk which could have underestimated the coronary disease burden of patients with high BMI; (d) referral bias, since the presence of obesity itself could have played a role in the decision to refer for evaluation, as obese patients are generally considered to be at higher risk of CAD; (e) the risk factors dyslipidemia and hypertension were included in the analysis as categorical variables which could have resulted in some underestimation of their predictive power; (f) lack of follow-up data to evaluate the prognostic impact of BMI in clinical outcomes.

Conclusions

In this population of stable patients undergoing CCTA for suspected CAD, BMI was an independent predictor of the presence of CAD, but was not correlated with severity. There were no significant differences in the percentage of obstructive CAD or in the overall coronary atherosclerotic burden, evaluated by the number of segments with plaque, across the different BMI classes.

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Conflict of interest

None declared.

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MANUSCRIPT 12

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MANUSCRIPT 13

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ORIGINAL ARTICLE

Performance of traditional risk factors in identifying a higher than expected coronary atherosclerotic burden

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KEYWORDS
Atherosclerotic burden;
Risk factor;
Attributable risk;
Calcium score;
CT angiography

Abstract
Objective: To evaluate the performance of traditional cardiovascular (CV) risk factors in identifying a higher than expected coronary atherosclerotic burden.
Methods: We assessed 2069 patients undergoing coronary CT angiography, with assessment of calcium score (CS), for suspected coronary artery disease. A higher than expected atherosclerotic burden was defined as CS >75th percentile (CS >P75) according to age and gender-adjusted monograms. The ability of traditional CV risk factors to predict a CS >P75 was assessed in a customized logistic regression model (''Clinical Score'') and by the calculation of SCORE (Systemic Coronary Risk Evaluation). The population attributable risk (PAR) of risk factors for CS >P75 was calculated.
Results: The median CS was 3.0 (IQR 0.0–98.0); 362 patients had CS >P75. The median SCORE was 3.0 (IQR 1.0–4.0). With the exception of hypertension, all traditional CV risk factors were independent predictors of CS >P75: diabetes, dyslipidemia, smoking and family history (OR 1.3–2.2, $p \leq 0.026$). The areas under the ROC curves for CS >P75 were 0.64 for the Clinical Score (95% CI 0.61–0.67, $p<0.001$) and 0.53 for SCORE (95% CI 0.50–0.56, $p=0.088$). About a quarter of patients with CS >P75 were in the two lower quartiles of the Clinical Score. Altogether, the traditional risk factors explain 56% of the prevalence of CS >P75 (adjusted PAR 0.56).

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MANUSCRIPT 13

Conclusion: Despite the association of CV risk factors with a higher than expected atherosclerotic burden, they appear to explain only half of its prevalence. Even when integrated in scores, the predictive power of these risk factors was modest, exposing the limitations of risk stratification based solely on demographic and clinical risk factors.

PALAVRAS-CHAVE
Carga Aterosclerótica;
Fator de risco;
Score de cálcio;
AngioTC

Desempenho dos fatores de risco clássicos na identificação de uma carga aterosclerótica coronária superior ao esperado

Resumo
Objetivo: O objetivo deste trabalho foi avaliar o desempenho dos fatores de risco cardiovascular (CV) clássicos na identificação de carga aterosclerótica superior ao esperado.
Métodos: Avaliámos 2069 doentes (dts) que realizaram AngioTC cardíaca e ScCa para exclusão de doença coronária. Definiu-se carga aterosclerótica superior ao esperado um ScCa acima do percentil 75 (ScCa>p75) de acordo com nomogramas ajustados para o sexo e idade. A capacidade dos fatores de risco clássicos preverem ScCa>p75 avaliou-se num modelo de regressão logística customizado (*score* clínico) e pelo SCORE. Avaliou-se o Population Attributable Risk (PAR) dos fatores de risco para ScCa>p75.
Resultados: A mediana de ScCa foi 3,0 [IIQ 0,0-98,0]; 362 dts com ScCa>p75. A mediana do HeartScore foi 3,0 [IIQ 1,0-4,0]. Exceto a hipertensão arterial, todos os fatores de risco foram preditores independentes de CaSc>p75: diabetes *mellitus*, dislipidemia, tabagismo e história familiar (OR 1,3-2,2, p≤0,026). As áreas abaixo da curva ROC para SaCa>p75 foram 0,64 para *score* clínico (IC95% 0,61-0,67; p<0,001) e 0,53 para SCORE (IC95% 0,50-0,56, p=0,088). Um quarto dos dts com CaSc>p75 encontravam-se nos dois quartis de *score* clínico mais baixos. No seu conjunto, os fatores de risco clássicos explicam 56% da prevalência de ScCa>p75 (PAR ajustado 0,56).
Conclusão: Apesar de os fatores de risco CV se associarem a uma carga aterosclerótica superior ao esperado, justificam pouco mais de metade da sua prevalência. O poder preditor destes fatores de risco é modesto, mesmo integrados em *scores*, revelando as limitações da estratificação de risco baseada apenas em dados demográficos e fatores de risco clínicos.

Introduction

Coronary artery disease (CAD) remains the single most frequent cause of premature mortality worldwide, reaching epidemic proportions.[1] Primary prevention measures have had a favorable effect on the prognosis of patients with CAD. Estimation of total cardiovascular (CV) risk is a cornerstone of the assessment of patients with suspected CAD, enabling adjustment of the intensity of preventive and therapeutic measures.[2] Risk scores that reflect the interaction of multiple CV risk factors are available for this purpose and are frequently used in clinical practice.

Although modifiable CV risk factors account for most of the risk of myocardial infarction (MI), risk prediction based on scores including only demographic and clinical characteristics have some limitations.[3] The MONICA project[4] showed that only part of the variation in the time trends of coronary event rates could be predicted by trends in risk factors. In fact, CV risk can be higher than indicated by the charts in several settings, for example in asymptomatic individuals with preclinical evidence of atherosclerosis, such as the presence of calcified coronary plaques.

The extent of coronary calcification correlates with total coronary plaque burden, and has a high negative predictive value for ruling out the presence of significant coronary stenosis.[5,6] Additionally, the calcium score (CS) also has a prognostic impact, as it can show increased risk of MI.[7,8] In previous studies, the CS was a predictor for premature CAD independently of traditional clinical CV risk factors, and combining the two appears to change the predicted risk to an extent that may be clinically important, helping to decide how aggressively primary prevention strategies should be implemented.[9,10]

The aim of the present study was to assess the performance of the traditional CV risk factors, alone or associated in scores, in identifying a higher than expected coronary atherosclerotic burden.

Methods

Study design and population

Between February 2007 and September 2012, 3012 consecutive patients undergoing coronary computed tomography

MANUSCRIPT 13

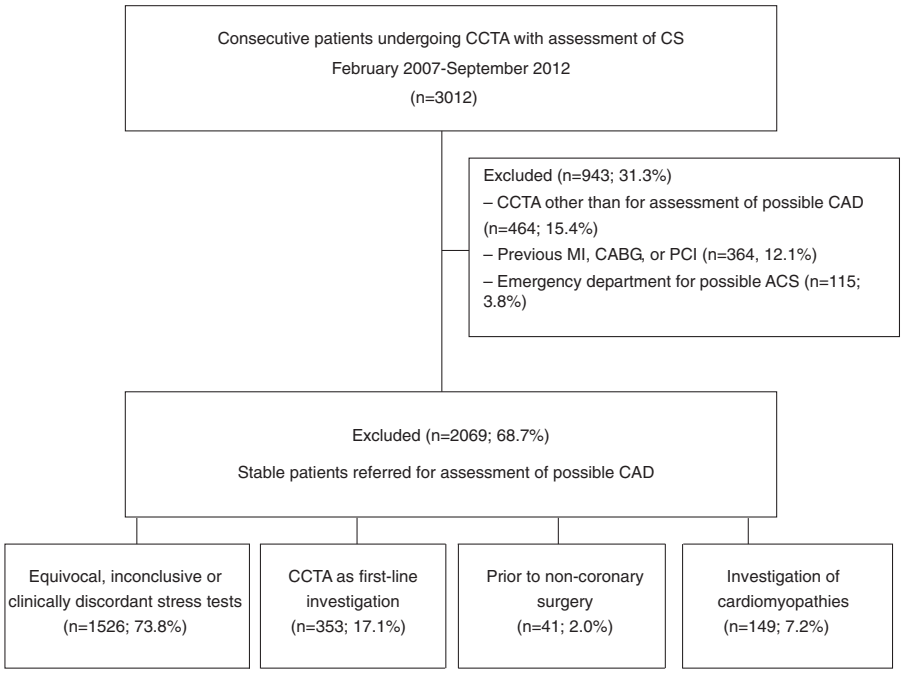

Figure 1 Patient selection and study design. ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CS: calcium score; MI: myocardial infarction; PCI: percutaneous coronary intervention.

angiography (CCTA) for assessment of possible CAD were prospectively enrolled in a single-center registry. Patients referred from the emergency department for possible acute coronary syndrome, those with indications other than assessment for possible CAD, and those without CS assessment were excluded from the present analysis. For the purpose of this study, 2069 patients were included, the majority of them (1526, 73.8%) assessed in the context of previous stress tests that were equivocal, inconclusive or clinically discordant with clinical assessment, while 353 (17.1%) were undergoing first-line investigation of possible CAD. Other exams were performed to investigate possible CAD in patients with cardiomyopathies (149, 7.2%) and for preoperative assessment of CAD prior to non-coronary surgery (41, 2.0%). Patient selection and study design are depicted in Figure 1.

Cardiovascular risk assessment

A detailed medical history, including a CV risk factor questionnaire, was obtained from all patients to assess the presence of: (1) diabetes (defined as fasting plasma glucose ≥7.0 mmol/l or use of oral hypoglycemic agents or insulin); (2) dyslipidemia (defined as total cholesterol ≥5 mmol/l or treatment with lipid-lowering drugs); (3) hypertension (defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medication); (4) family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 [male] or 65 [female] years); and (5) smoking (defined as previous, less than one year, or current smoker).

CV risk was assessed for the overall population using the SCORE (Systemic Coronary Risk Evaluation) system,[2] which estimates the 10-year risk of CV death and is determined by the interaction of various clinical risk factors (gender, age, smoking status, blood pressure and total cholesterol). As recommended in the European guidelines on cardiovascular disease prevention[2] for stratification of the Portuguese population, we used the chart for low-risk countries. The local ethics committee approved the study and all patients gave their written informed consent.

Scan protocol, image reconstruction and calcium score assessment

Scans were performed with a dual-source scanner (SOMATOM Definition®, Siemens Medical Systems, Germany), with the patient in dorsal decubitus and in deep inspiration breathhold. All patients received sublingual nitroglycerin except when contraindicated, and beta-blockers were administered to lower heart rate when indicated. During the scan acquisition, a bolus of iodinated contrast (Visipaque®, GE Healthcare, USA) was infused at 6 ml/s, followed by a 50-ml saline flush. The contrast dose was calculated according to

MANUSCRIPT 13

the following formula: (acquisition time+6 s delay)×flow (6 ml/s). Contrast administration was timed to optimize uniform enhancement of the coronary arteries. Dose reduction strategies – including ECG-gated tube current modulation, reduced tube voltage, and prospective axial triggering – were used whenever feasible. Mean estimated radiation dose was 5.1±3.9 mSv and the contrast dose was 97.0±14.0 ml. Mean heart rate was 67.3±12.7 bpm; 197 (9.5%) patients received beta-blocker therapy before acquisition. Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering. All scans were analyzed in the same session by both a cardiologist and a radiologist with level III-equivalent experience. The CS was calculated by summing the number of coronary segments with calcium. A higher than expected atherosclerotic burden was defined as a CS above the 75th percentile (CS >P75) according to age- and gender-adjusted monograms.

Statistical analysis

Continuous variables with normal distribution were expressed as means and standard deviation (SD) and those with non-normal distribution as medians and interquartile range (IQR). Normality was tested with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages. Statistical comparisons were performed using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the Mann-Whitney or Kruskal-Wallis tests for continuous variables. The ability of traditional CV risk factors to predict a CS >P75 was assessed in a customized logistic regression model (''Clinical Score'') and by calculating SCORE. Areas under the receiver operating characteristic (ROC) curves of both the Clinical Score and SCORE for prediction of CS >P75 were determined. Additionally, the population attributable risk (PAR) of the various clinical risk factors for a higher than expected atherosclerotic burden was calculated. Two-tailed tests of significance are reported. For all the comparisons, a p value <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CI) were calculated. The statistical analysis was performed with SPSS version 21.0 (SPSS® Inc., Chicago, IL, USA).

Results

Baseline population characteristics

Demographic and clinical characteristics are depicted in Table 1. Briefly, the mean age of the 2069 patients studied was 58±11 years and 55.8% were male. Almost two-thirds (65.9%) of the patients had more than one CV risk factor, the most prevalent being hypertension (61.2%), followed by dyslipidemia (59.2%), family history of premature CAD (34.9%), smoking (25.7%) and diabetes (15.0%). Mean body mass index (BMI) was 27.3±4.3 kg/m^2; 24.2% patients were obese (BMI ≥30.0 kg/m^2). The median SCORE was 3.0 (IQR 1.0–4.0); 13.9% patients had high/very high CV risk (SCORE ≥5). Regarding clinical presentation, 44.2% patients were asymptomatic, only 6.6% reporting typical chest pain. The majority of the population had a low-intermediate pre-test probability of CAD as assessed by the Diamond-Forrester and Morise scores (95.2% and 86.1%, respectively). The median CS was 3.0 (IQR 0.0–98.0), with 362 patients (17.5%) having CS >P75.

Table 1 Demographic and clinical characteristics of the study population.

Variables, n (%)	All patients (n=2069)
Demographic	
Age, years (mean ± SD)	58±11
Male	1155 (55.8)
Cardiovascular risk factors	
Diabetes	311 (15.0)
Hypertension	1266 (61.2)
Smoking	532 (25.7)
Dyslipidemia	1222 (59.2)
Family history of premature CAD	723 (34.9)
BMI, kg/m^2 (mean ± SD)	27.3±4.3
Obesity (BMI ≥30.0 kg/m^2)	500 (24.2)
Cardiovascular risk	
SCORE, median (IQR)	3.0 (1.0–4.0)
SCORE ≥5	494 (13.9)
Chest pain	
Asymptomatic	914 (44.2)
Non-cardiac	581 (28.1)
Atypical	437 (21.1)
Typical	137 (6.6)
Low-intermediate pre-test probability	
Diamond-Forrester	1970 (95.2)
Morise (<16)	1781 (86.1)
Calcium score	
Median (IQR)	3.0 (0.0–98.0)
CS >P75	362 (17.5)

BMI: body mass index; CAD: coronary artery disease; CS: calcium score; CV: cardiovascular; IQR: interquartile range; P75: 75th percentile; SD: standard deviation.

Cardiovascular risk factor performance

With the exception of hypertension, all the traditional CV risk factors – diabetes, dyslipidemia, smoking and family history of CAD – were independent predictors of CS >P75, all odds ratio (OR) 1.3–2.2, p≤0.026 (Figure 2). The predictive power of both Clinical Score and SCORE for the presence of CS >P75, as assessed by ROC curves, was low (Figure 3): area under the curve (AUC) 0.64 for the Clinical Score (95% CI 0.61–0.67, p<0.001) and 0.53 for SCORE (95% CI 0.50–0.56, p=0.088). Analyzing the population by quartile of the Clinical Score, a quarter of patients with CS >P75 (24.3%) were in the two lower quartiles (Figure 4). Altogether, the traditional CV risk factors analyzed (hypertension, dyslipidemia, smoking, diabetes and family history of premature CAD, and obesity) explain only 56% of the prevalence of CS >P75 (adjusted PAR 0.56).

MANUSCRIPT 13

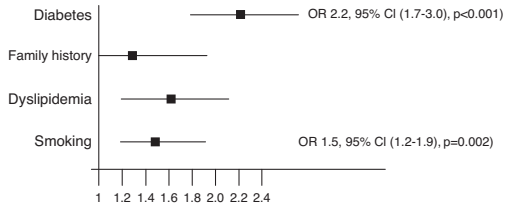

Figure 2 Independent predictors of a higher than expected coronary atherosclerotic burden (calcium score >75th percentile). CI: confidence interval; OR: odds ratio.

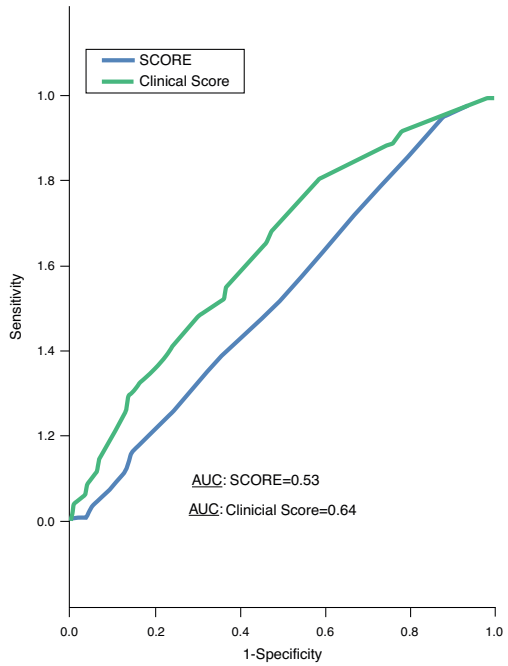

Figure 3 Receiver operating characteristic curves for the prediction of a higher than expected coronary atherosclerotic burden (calcium score >75th percentile) by the Clinical Score and SCORE.

Discussion

The present study shows that despite the association between traditional CV risk factors and a higher than expected atherosclerotic burden, as defined by a CS above the 75th percentile according to age and gender-adjusted monograms, these risk factors appear to explain only 56% of its prevalence. Even when integrated in scores, the predictive power of these traditional CV risk factors was relatively modest, exposing the limitations of risk stratification based solely on demographic and clinical risk factors.

The association of traditional risk factors in scores has emerged as a central step in the stratification of CV risk and

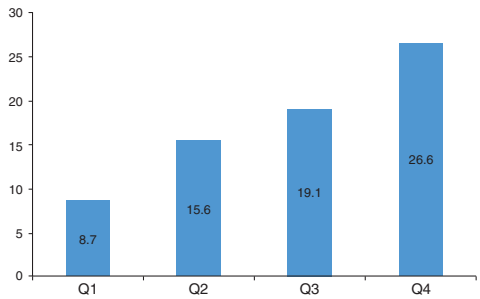

Figure 4 Distribution of patients with higher than expected coronary atherosclerotic burden (calcium score >75th percentile) according to Clinical Score quartile (Q).

subsequent implementation of preventive actions. Several risk assessment algorithms, such as those derived from the Framingham Heart Study in the USA or from the Prospective Cardiovascular Münster (PROCAM) study in Germany, and SCORE, are available for estimating multifactorial absolute risk in clinical practice. In the European guidelines on cardiovascular disease prevention,[2] determination of SCORE is recommended in asymptomatic adults without evidence of CV disease, since risk stratification is an important measure, even in asymptomatic individuals. Sudden cardiac death or acute MI can be the first manifestation of coronary atherosclerosis, highlighting the importance of prevention. However, the identification of asymptomatic individuals with higher risk for CV events remains challenging.

Although several studies and registries, such as the landmark INTERHEART study,[3] show that traditional CV risk factors account for most of the risk of MI, risk prediction based only on demographic and clinical factors appears to have limitations. In a population of more than 120 000 patients enrolled in 14 international randomized clinical trials of coronary heart disease and presenting with acute coronary syndrome or undergoing percutaneous coronary intervention, Khot et al.[11] showed that 58% had none or one of the CV risk factors diabetes, dyslipidemia, smoking and hypertension. Additionally, another analysis by Akosah et al.[12] in a population of young adults with first acute MI showed that only 25% met criteria to qualify for pharmacotherapy. Even in the presence of established clinical CV risk factors, a significant number of coronary events are unpredictable.

The limitations of risk scores based on clinical characteristics highlights the potential utility of direct imaging modalities, such as CCTA, for accurate identification of the presence and extent of coronary atherosclerosis. In this context, CS has emerged as a feasible and easy method for assessment of the presence of CAD. A high CS is indicative of advanced atherosclerotic lesions as identified by histological criteria as fibroatheroma[14]; although it cannot localize lesions that are stenotic or at risk of rupture, it may be able to determine the total coronary atherosclerotic disease burden, and is linearly correlated with the occurrence of hard clinical events.[15,16] Although the absolute prevalence of severely stenotic plaques may be higher than that of mildly stenotic plaques, there are more plaques with

MANUSCRIPT 13

mild than with severe stenosis. Data from the PROSPECT study[17] show that in patients presenting with acute coronary syndrome and undergoing percutaneous coronary intervention, major adverse CV events during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit, frequently angiographically mild, lesions. The CONFIRM registry[18] showed that both obstructive and nonobstructive plaques are associated with higher mortality, with risk profiles differing for age and gender, and the absence of CAD is associated with a favorable prognosis. An interesting finding was that more than two-thirds of patients did not have obstructive disease, and when compared in survival analysis, the prognosis of patients with nonobstructive stenosis was closer to that of those with significant single-vessel disease than that of those with no coronary plaques. In this context, even with low values, determination of CS may help in deciding how aggressive primary prevention strategies should be.

The relationship between CS and traditional CV risk factors, with CS increasing the prognostic value of traditional clinical predictors, has been addressed in several studies. The St. Francis Heart Study,[19] a prospective population-based study including 4613 asymptomatic individuals aged between 50 and 70 and followed for 4.3 years, showed that CS predicted CAD events independently of traditional risk factors and C-reactive protein, was superior to the Framingham score in the prediction of events, and enhanced stratification of those falling into the Framingham categories of low, intermediate, and high risk. Data from a large registry[15] of 25 253 asymptomatic patients followed for 6.8 years revealed that CS provides independent and incremental information in addition to traditional risk factors. In the Rotterdam calcification study,[7] the upper percentile range of CS reflected a 12-fold increased risk of MI, also independently of traditional risk factors, even in elderly people. In the 1330 participants with intermediate risk (assessed by the Framingham score) included in the MESA study,[13] during a median follow-up of 7.6 years, CS, ankle-brachial index, high sensitivity C-reactive protein and family history of CAD were independently associated with incident coronary heart disease. Further analysis of this study showed that the addition of CS to the Framingham risk score plus race caused the highest increase in the AUC and provided superior discrimination and risk reclassification compared with other risk markers. Therefore, CS constitutes a feasible non-invasive tool that may lead to CV risk reclassification of a significant number of individuals, with a number needed to scan for risk reclassification of patients with intermediate risk estimated at 4–6.[20,21]

The discrepancy between clinical data and documented CS was also evident in our study, with the distribution of advanced coronary atherosclerosis showing almost a quarter of patients in the two lower quartiles of the Clinical Score. Indeed, these patients with a known higher than expected coronary atherosclerotic burden could not be identified without determination of the CS.

Although the diagnostic sensitivity of the CS in detecting obstructive CAD is high, the frequency of false negatives (significant CAD in the absence of CS) is not well established. The CONFIRM registry[18] showed nonobstructive CAD in 13% and obstructive CAD in 3.5% of the 10 037 symptomatic patients without known CAD who had CS of zero. In a previously analysis performed in our center[20] of 864 patients with zero CS, 12.4% had coronary plaques on contrast CT (1.6% obstructive). The independent predictors of CAD were age >55 years, hypertension and dyslipidemia, and in the presence of these three variables the probability of having coronary plaques was 21%. However, it is important to emphasize the low rate of clinical events in this population without evidence of CS.[15]

Another important point concerning the CS is the possible effect of CS assessment on reduction of CV risk. This issue was analyzed in the EISNER study,[22] in which asymptomatic patients were randomized to CS scan versus no scan with comparison of the changes in CV risk at four years of follow-up. The group of patients scanned showed a net favorable improvement in risk, including a considerable reduction in mean systolic blood pressure and low-density lipoprotein cholesterol, and reduced waist circumference (WC) for those with increased WC at baseline.

Although the results of the present study and previous published data demonstrate the incremental value of the CS over traditional clinical CV risk factors, the accuracy and cost-effectiveness of this more expensive imaging test in large populations has yet to be determined. Nonetheless, the inclusion of objective tools for identification of subclinical CAD in CV risk stratification schemes seems logical and necessary. This will allow identification of patients with higher risk for fatal CV events, which unfortunately are sometimes the first event. As Eugene Braunwald wrote, ''treating such events is analogous to locking the barn door after the horse has been stolen.''[23]

This study has some limitations: it was a single-center study with a medium-sized cohort; the study population had predominantly low-intermediate cardiovascular risk; the risk factors of dyslipidemia and hypertension were included in the analysis as categorical variables, which could have led to underestimation of their predictive power; and follow-up data to assess the prognostic impact of the studied characteristics on clinical outcomes were lacking.

In conclusion, despite the statistical association of CV risk factors with a higher than expected atherosclerotic burden, in the population studied they appear to explain only half of its prevalence. Even when integrated in scores, the predictive power of these risk factors is relatively modest, exposing the limitations of risk stratification based solely on demographic and clinical risk factors. This study provides additional support for the use of CS as a tool for refining CV risk prediction.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

MANUSCRIPT 13

Conflicts of interest

The authors have no conflicts of interest to declare.

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MANUSCRIPT 14

Original research 1

Low previous cardiovascular risk of patients with ST-elevation myocardial infarction

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Background **Myocardial infarction is frequently the initial form of presentation of coronary artery disease (CAD). Systemic Coronary Risk Estimation (SCORE) risk tables are used in primary prevention and provide an estimate of cardiovascular (CV) risk through known risk factors. The aim of this study was to evaluate the performance of the SCORE, calculated using data previous to the event, to estimate CV risk of a population of patients presenting with ST-elevation myocardial infarction (STEMI) as the first manifestation of CAD.**

Methods and results **From a prospective registry including 3056 patients with STEMI subjected to coronary angiography between 2004 and 2014, 1628 patients with STEMI as the first manifestation of CAD were included after the exclusion of patients with known CAD ($n = 748$, 24.5%), patients with high-risk equivalents ($n = 930$, 30.4%), and patients with normal coronaries ($n = 57$, 1.87%). The individual risk profile was calculated using data previous to the event and patients were classified into three established subgroups: low risk (SCORE < 5%; $n = 1162$, 71.4%), high risk (SCORE 5–10%; $n = 409$, 25.1%), and very high risk (SCORE ≥ 10%; $n = 57$, 3.5%).**

Conclusion **In a population of patients with STEMI as the first manifestation of CAD, the CV risk stratification with the SCORE risk charts, if calculated before the event, would classify as low risk more than two-thirds of the patients (71.4%) and only 3.5% would be classified as very high-risk patients. The high prevalence of low-risk patients indicates the current challenge of CV risk stratification, underlying the need for additional tools in primary prevention to better identify patients at risk.** ***Coron Artery Dis*** **00:000–000**

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Keywords: coronary artery disease, risk stratification, ST-elevation myocardial infarction, Systemic Coronary Risk Estimation

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, and in Europe, CVDs are responsible for about four million deaths annually, over a third of them from coronary artery disease (CAD) [1–3].

Primary prevention has been proven to have a favorable prognostic influence in patients with CAD [4–7]. The Systemic Coronary Risk Estimation (SCORE) charts were developed using epidemiological data from several European countries and reflect the interaction of traditional demographic and clinical risk factors, allowing for the estimation of total cardiovascular (CV) risk [8]. Although this is a useful tool for the primary prevention of CVD, leading to the adjustment of the preventive measures, ST-elevation myocardial infarction (STEMI) is frequently the first manifestation of CAD and many patients were previously asymptomatic and not considered to be at high CV risk [9].

The aim of this study was to evaluate the performance of the SCORE calculated using the demographic and clinical data before the event to estimate CV risk of a population of patients presenting with STEMI as the first manifestation of CAD.

Methods

Study population and design

Between January of 2004 and December of 2014, all consecutive patients submitted to invasive coronary angiography in the context of presumed STEMI were screened ($n = 3056$). For the purpose of the present study, patients with previous manifestations of CAD ($n = 748$, 24.5%), those without CAD ($n = 57$, 1.87%) and individuals with features that admittedly assign an elevated risk requiring an aggressive risk factor control (cerebrovascular and peripheral artery disease, diabetes, or chronic kidney disease; $n = 930$, 30.4%) were excluded. The final population included 1628 patients (Fig. 1).

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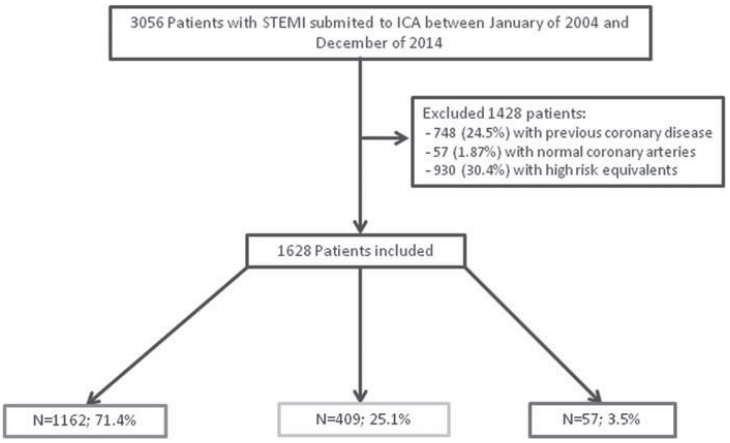
MANUSCRIPT 14

2 **Coronary Artery Disease** 2017, Vol 00 No 00

Fig. 1



Study flowchart. High-risk equivalents are: diabetes mellitus, chronic kidney disease, previous myocardial infarction, bypass surgery or coronary intervention, cerebrovascular disease, peripheral artery disease. ICA, invasive coronary angiography; STEMI, ST-elevation myocardial infarction

Patient information was collected in the ACROSS (Angiography and Coronary Revascularization Registry of Santa Cruz Hospital) Registry, in which demographic, clinical, angiographic, and procedure-related variables are prospectively collected using a dedicated cath-lab-based computer database as we published previously (Cardiobase; Infortucano, Lisbon, Portugal) [10].

Cardiovascular risk stratification

The assumed previous SCORE was retrospectively calculated in the study population using the most recent clinical data before the index hospitalization. When blood samples for the lipid profile were not available, the self-reported previous dyslipidemia and/or used of lipid-lowering drugs was used as a surrogate for high cholesterol and assigned a valued from the middle-up in the chart. The same assumption was made for blood pressure, in case the patient was not aware of previous values. This assumption of using high cholesterol and blood pressure as categorical variables rarely changed the final subgroup of the patient as many were in any case classified in the low-risk subgroup (<5%) on the basis of age and sex. As proposed in the European Guidelines on CVD prevention in clinical practice, the SCORE chart for countries at low CVD risk was used. Patients were stratified into the following risk classes: low-moderate risk (<5%), high risk (≥5%), and very high risk (≥10%) [2,8].

Statistical analysis

Continuous variables with a normal distribution were expressed as mean±SD. Discrete variables were expressed as frequencies and percentages. All the analyses carried out were retrospective. When appropriate, the 95% confidence interval was calculated. Statistical analysis was carried out using the SPSS software (version 21.0; SPSS Inc., Chicago, Illinois, USA).

Results

Of the 3056 patients admitted with STEMI between 2004 and 2014, 1628 patients were included in this analysis. Patients with known coronary disease ($n=748$, 24.5%), with a traditionally known higher risk of CV risk ($n=930$, 30.4%) as a manifestation of vascular disease in other territories (cerebrovascular or peripheral artery disease) or potential equivalents of coronary disease (diabetes or chronic kidney disease), and patients with normal coronaries ($n=57$, 1.87%) were excluded (Fig. 1).

Most of the patients were men ($n=1209$, 74.3%), with a median age of 61.2±13.3 years and a median BMI of 26.4±4 kg/m^2. Hypertension was present in 798 (49%) patients, tobacco abuse in 719 (45%) patients, dyslipidemia in 654 (40.2%) patients, and a family history of premature CVD in 133 (8.2%) patients. All patients and study population baseline characteristics are detailed in Table 1.

The distribution of patients according to the CV risk classes defined by the SCORE was as follows: low-moderate risk: 1162 patients (71.4%), high risk: 409 (25.1%), and very high risk: 57 (3.5%) (Fig. 2).

Discussion

The main findings of our study are as follows: (a) nearly half (53.3%) of the patients presented for coronary angiography with an STEMI, which was the first manifestation of CAD; (b) among these, CV risk stratification using the SCORE risk charts, if calculated before the

MANUSCRIPT 14

Table 1 Baseline characteristics

Characteristics	All patients ($N=3056$)	Excluded patients ($N=1428$)	Study population ($N=1628$)	P value
Sex: male	2243 (73.3)	1034 (72.4)	1209 (74.3)	0.25
Age (years)	62.9 ± 12.9	64.8 ± 12.2	61.2 ± 13.3	< 0.001
Diabetes mellitus	700 (22.9)	700 (49)	–	
Hypertension	1804 (59)	1006 (70.4)	798 (49)	< 0.001
Dyslipidemia	1435 (46.9)	781 (54.7)	654 (40.2)	< 0.001
Smoker	1138 (37.2)	418 (29.3)	719 (45)	< 0.001
Chronic kidney disease	102 (3.3)	102 (7.1)	–	
Peripheral artery disease	125 (4.1)	125 (8.8)	–	
BMI (kg/m^2)	27 ± 4	27.3 ± 4.3	26.4 ± 4	< 0.001
Previous MI	569 (18.6)	569 (39.8)	–	
Previous PCI	527 (17.2)	527 (36.9)	–	
Previous CABG	85 (2.8)	85 (6)	–	
Previous cerebrovascular disease	192 (6.3)	192 (13.4)	–	
Family history of CVD	214 (7)	81 (5.7)	133 (8.2)	0.007

Characteristics are presented in absolute number and percentage; age and BMI are expressed in mean ± SD.
Chronic kidney disease considered if estimated glomerular filtration rate ≤60 ml/min/1.73 m^2.
CABG, coronary artery bypass surgery; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

event, would classify as low risk more than two-thirds of these inaugural patients (71.4%) and only 3.5% would be classified as very high-risk patients.

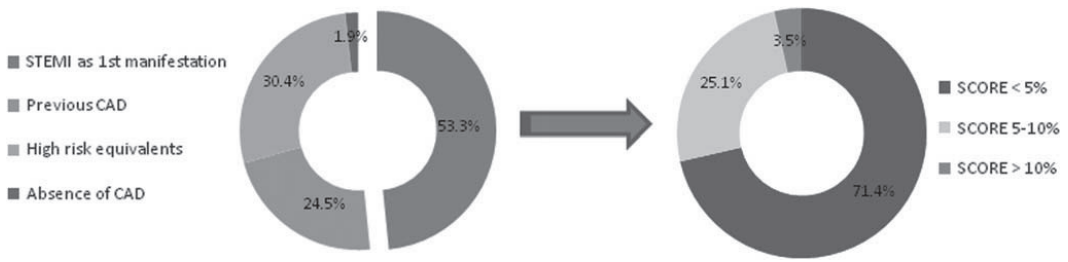
The SCORE risk charts are a useful tool for primary prevention as they reflect the interaction of several traditional demographic and clinical risk factors, allowing for the estimation of total CV risk and subsequent decisions on the level of aggressiveness of preventive measures and surveillance [8].

Although many advances in diagnostic and therapeutic management of CAD have been made in recent years, STEMI is still frequently the first manifestation of CAD and many patients were previously asymptomatic and not considered to be at high CV risk. The identification of patients at risk would be beneficial as they might become eligible for the several available preventive pharmacological measures that are known to lower CV risk, such as statins and antiplatelet agents [11–13].

This strikingly low percentage of STEMI patients with high and very high-risk profile underlines the inability of traditional risk factors, even when optimized in risk scores, to predict CV risk, on the one hand, and the contrast between individual and population risk on the other. In fact, although high-risk patients have a higher relative risk of experience an event, from a population perspective, many events occur in the much larger in number subgroups of low-risk to intermediate-risk populations [14–16].

Several risk scores and predictive models are available for CV population risk stratification, allowing a better selection of patients who might benefit from more aggressive preventive measures [8,17,18]. These tools are based on demographic and clinical risk factors with a proven prognostic impact in population-based analysis. In the European guidelines on CVD prevention in clinical practice, the total risk estimation is recommended using the SCORE for asymptomatic adults without evidence of CVD, but the benefit of these stratification tools is still controversial [2,15]. Although some authors were able to show that the risk stratification with SCORE leads to beneficial changes in medication during follow-up, others failed to find an association between the SCORE and coronary artery calcium [19,20]. In addition, McClelland *et al.* [21] also noted incongruity between calcium scoring and the Framingham risk score, another widely recognized predictive model. In a study by Akosah *et al.* [22] examining the risk profile of a population of young adults with inaugural myocardial infarction, only 25% were identified as having a risk with criteria to qualify for pharmacotherapy. It is noteworthy that in this study, 23% of these young adults with STEMI had low-density lipoprotein cholesterol lower than 100 mg/dl. In another study, Khot *et al.* [23] pointed out that more than half of patients from a population with CVD had less than or

Fig. 2



Study population distribution according to baseline characteristics and SCORE risk subgroups. Risk classification according to SCORE. CAD, coronary artery disease; SCORE, Systemic Coronary Risk Estimation; STEMI, ST-elevation myocardial infarction.

MANUSCRIPT 14

equal to one risk factor. In line with these studies, the MONICA project showed that only part of the variation in the time trends of coronary event rates could be predicted by trends in risk factors [24].

These results emphasize the need for better strategies for risk stratification and one likely candidate might be the identification of atherosclerotic burden by calcium scoring or cardiac computed tomography [16,25,26]. These might provide a better estimation of the risk to proper guide and dose our primary prevention attitude in the future, pending clinical and cost-effectiveness validation of these strategies.

This study has some limitations: (i) this was a single-center retrospective study; (ii) the risk factors of high cholesterol and blood pressure were based on previous laboratory values or measurements, either patient-referred or clinical registries based, and in cases when there were no previous laboratory values and blood pressure specified, they were included in the analysis as categorical variables (meaning having or not the risk factor), which could have led to underestimation of their predictive power. Although this might influence the final value of each patient, it was rarely significant enough to move the patients across some risk category, especially as most of them were of low risk in any case on the basis of their demographic variables.

In this population of patients with myocardial infarction as the first manifestation of CAD, CV risk stratification using the SCORE risk charts, if calculated before the event, would classify as low risk more than two-thirds of the patients (71.4%) and only 3.5% would be classified as very high-risk patients. The high prevalence of low-risk patients indicates the current challenge of CV risk stratification, underlying the need for additional tools in primary prevention to better identify patients at risk.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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MANUSCRIPT 15

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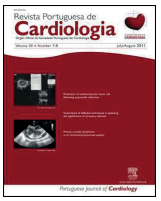

ORIGINAL ARTICLE

Effective radiation dose of three diagnostic tests in cardiology: Single photon emission computed tomography, invasive coronary angiography and cardiac computed tomography angiography

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KEYWORDS
Ionizing radiation;
Single photon emission computed tomography;
Invasive coronary angiography;
Cardiac computed tomography;
Obesity

Abstract
Introduction: Diagnostic tests that use ionizing radiation play a central role in cardiology and their use has grown in recent years, leading to increasing concerns about their potential stochastic effects.

The aims of this study were to compare the radiation dose of three diagnostic tests: single photon emission computed tomography (SPECT), invasive coronary angiography (ICA) and cardiac computed tomography (cardiac CT) and their evolution over time, and to assess the influence of body mass index on radiation dose.

Methods: We assessed consecutive patients included in three prospective registries (SPECT, ICA and cardiac CT) over a period of two years. Radiation dose was converted to mSv and compared between the three registries. Differences over time were evaluated by comparing the first with the fourth semester.

Results: A total of 6196 exams were evaluated: 35% SPECT, 53% ICA and 22% cardiac CT. Mean radiation dose was 10.7±1.2 mSv for SPECT, 8.1±6.4 mSv for ICA, and 5.4±3.8 mSv for cardiac CT ($p<0.001$ for all). With regard to the radiation dose over time, there was a very small

MANUSCRIPT 15

reduction in SPECT (10.7 to 10.5 mSv, p=0.004), a significant increase (25%) in ICA (7.0 to 8.8 mSv; p<0.001), and a significant reduction (29%) in cardiac CT (6.5 to 4.6 mSv, p<0.001). Obesity was associated with a significantly higher radiation dose in all three exams.

Conclusions: Cardiac CT had a lower mean effective radiation dose than invasive coronary angiography, which in turn had a lower mean effective dose than SPECT.

There was a significant increase in radiation doses in the ICA registry and a significant decrease in the cardiac CT registry over time.

PALAVRAS-CHAVE
Radiação;
Cintigrafia de perfusão miocárdica;
Coronariografia invasiva;
Tomografia computorizada cardíaca;
Obesidade

Dose efetiva de radiação de três exames de diagnóstico em cardiologia: cintigrafia de perfusão miocárdica, coronariografia invasiva e tomografia computorizada cardíaca

Resumo

Introdução: Os exames diagnósticos que usam radiação ionizante têm um papel central na cardiologia e a par do seu uso crescente, tem aumentado a preocupação pelos seus potenciais efeitos estocásticos.

Os objetivos deste estudo foram: 1) Comparar a dose de radiação de três exames: Cintigrafia de perfusão miocárdica (SPECT), coronariografia invasiva (CAT) e tomografia computorizada cardíaca (AngioTC) e a sua evolução temporal. 2) Avaliar o impacto do índice de massa corporal na dose de radiação.

Métodos: Doentes consecutivos incluídos em três registos prospetivos (SPECT, CAT e AngioTC) durante dois anos. A dose de radiação foi convertida a mSv e comparada entre os três registos. A evolução temporal foi avaliada por comparação do 1.º e 4.º semestres.

Resultados: Foram avaliados 6196 exames: 35% SPECT, 53% CAT e 22% AngioTC. A dose de radiação foi: 10,7 ± 1,2 mSv para o SPECT; 8,1 ± 6,4 mSv para o CAT; 5,4 ± 3,8 mSv para a AngioTC (p < 0,001 todas comparações).

Evolução temporal da dose de radiação: redução muito ligeira no SPECT (10,7 para 10,5 mSv; p = 0,004); aumento significativo (25%) no CAT (7,0 para 8,8 mSv; p < 0,001); redução significativa (29%) na AngioTC (6,5 para 4,6 mSv; p < 0,001). A obesidade associou-se a níveis de radiação significativamente mais elevados nos três exames.

Conclusão: O exame associado a uma menor dose de radiação foi a AngioTC, seguida do CAT que, por sua vez, foi menor que a do SPECT. Houve um aumento significativo da dose de radiação no registo CAT e uma redução significativa no registo da AngioTC ao longo do tempo.

List of abbreviations

BMI	Body mass index
CAD	coronary artery disease
CT	computed tomography
ICA	invasive coronary angiography
SPECT	single photon emission computed tomography

Introduction

In recent years, the development of imaging techniques using ionizing radiation has resulted in considerable progress in the diagnosis and treatment of heart disease. Three commonly used diagnostic modalities that involve ionizing radiation are used for assessing patients with possible coronary artery disease (CAD): single photon emission computed tomography (SPECT), cardiac computed tomography (cardiac CT) and invasive coronary angiography (ICA), the latter being considered the gold standard for the diagnosis of CAD.[1]

Different radiation doses have been reported for each of these exams, ranging from 5 to 10 mSv for ICA, 6 to 15 mSv for SPECT, and 4 to 21 mSv for cardiac CT.[2–5] With more frequent use of these exams, there have been growing concerns about the radiation's potential secondary effects, especially the stochastic effects of high cumulative doses over time.[6,7]

We have previously reported on the effective radiation dose associated with cardiac CT in a single-center registry, documenting a significant decrease in dose over time, and were able to identify the predictors of higher dose.[8]

New scanners and acquisition protocols have recently been developed which lead to significant reductions in radiation dose associated with cardiac CT.[9,10]

The aims of this study were to evaluate and compare the radiation dose used in three diagnostic tests – SPECT, ICA and cardiac CT – and their evolution over time, and to assess the influence of body mass index on radiation dose.

MANUSCRIPT 15

Table 1 Demographic and clinical characteristics of the study population.

	Cardiac CT (n=1344)	ICA (n=3267)	SPECT (n=1585)
Age (years, mean ± SD)	59±12	66±12	64±9
Male (%)	60%	61%	63%
BMI (kg/m^2)	27.3±4.3	27.3±4.2	27.5±4.4
Diabetes (%)	16%	29%	N/A
Hypertension (%)	57%	72%	N/A
Dyslipidemia (%)	54%	57%	N/A
Smoking (%)	27%	31%	N/A
Previous MI (%)	3%	17%	N/A
Previous PCI (%)	7%	18%	N/A
Previous CABG (%)	3%	7%	N/A

Values are means (SD) or percentages. BMI: body mass index; CABG: coronary artery bypass grafting; CT: computed tomography; ICA: invasive coronary angiography; MI: myocardial infarction; N/A: not available; PCI: percutaneous coronary intervention; SPECT: single photon emission computed tomography.

Methods

From three prospective registries of SPECT, ICA and cardiac CT, we selected for this analysis the exams performed during a two-year period (October 1, 2008 to September 30, 2010) in which the indication was assessment of possible CAD.

The exams were performed with an SMV DST-XL gamma camera using 99m Tc-tetrofosmin with stress/rest or rest/stress protocols (SPECT registry), a Siemens Coroskop TOP/ARTIS dFC system (ICA registry), and a Siemens Somatom Definition dual-source scanner (cardiac CT registry). The effective radiation dose was converted to mSv in accordance with current literature and the manufacturer's product information and compared between the registries. Briefly, a factor of 0.014 mSv/Gy cm was used for the conversion of cardiac CT dose-length product,[9,11] a factor of 0.183 mSv/Gy cm^2 was used for the conversion of ICA dose-area product,[12,13] and factors of 0.0060 mSv/MBq^{-1} (after exercise) and 0.0071 mSv/MBq^{-1} (at rest) were used for the conversion of injected activity in SPECT.[14–16] To evaluate the evolution of radiation doses over time, the study period was divided into four semesters according to the date of the exam and effective radiation dose was compared between the first and last semesters in each registry. All prospectively collected variables in the respective registries were analyzed, looking for predictors of dose change over time.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (unless otherwise specified), and categorical variables as number (n) or frequency (%).

Continuous variables were analyzed using the Mann–Whitney or Kruskal–Wallis nonparametric tests. The chi-square test was used to assess differences in frequencies.

Statistical significance was accepted for two-sided p values <0.05.

The statistical analysis was performed using SPSS Statistics 17.0 for Windows.

Results

During the two-year period of this analysis, 6196 exams were performed: 3267 (52.7%) ICA, 1585 (25.6%) SPECT and 1344 (21.7%) cardiac CT. The demographic and clinical characteristics of the study population are presented in Table 1.

Mean effective radiation dose was 8.2±5.6 mSv for the whole population, 10.7±1.2 mSv for SPECT, 8.1±6.4 mSv for ICA and 5.4±3.8 mSv for cardiac CT (p<0.001 for all comparisons, Figure 1).

Division of the study period into semesters showed that there was a small but significant reduction in mean effective radiation dose over time for SPECT (10.7 to 10.5 mSv; p<0.01). In cardiac CT there was a significant 29% decrease in mean effective radiation dose (6.5 to 4.6 mSv, p<0.001) and in ICA a significant 25% increase (7.0 to 8.8 mSv; p<0.001) (Table 2 and Figure 2).

The factors associated with the 25% increase in mean effective radiation dose with ICA from the first to the fourth semester were the higher proportions of positive exams, radial vascular access and exams performed by fellows in

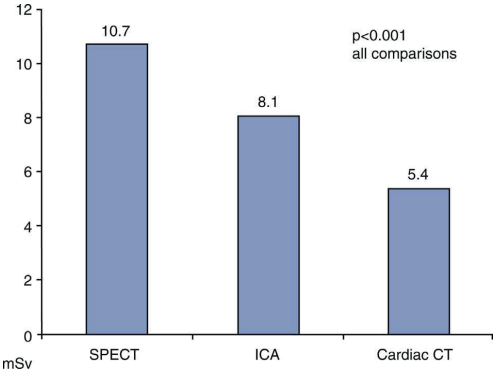

Figure 1 Mean effective radiation dose used in each exam studied. CT: computed tomography; ICA: invasive coronary angiography; SPECT: single photon emission computed tomography.

MANUSCRIPT 15

Table 2 Mean effective radiation dose for each exam over the four semesters.

	1st semester	2nd semester	3rd semester	4th semester	p (1st vs. 4th)
SPECT	10.7 ± 1.1	10.7 ± 1.4	10.7 ± 1.3	10.5 ± 0.9	0.004
ICA	7.0 ± 6.0	7.6 ± 5.6	9.0 ± 6.9	8.7 ± 6.9	<0.001
Cardiac CT	6.5 ± 3.7	6.2 ± 4.2	5.0 ± 4.1	4.6 ± 3.0	<0.001

CT: computed tomography; ICA: invasive coronary angiography; SPECT: single photon emission computed tomography.

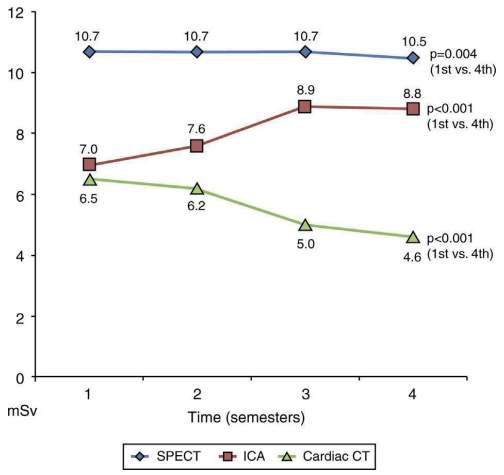

Figure 2 Time trends in mean effective radiation dose used in each exam. CT: computed tomography; ICA: invasive coronary angiography; SPECT: single photon emission computed tomography.

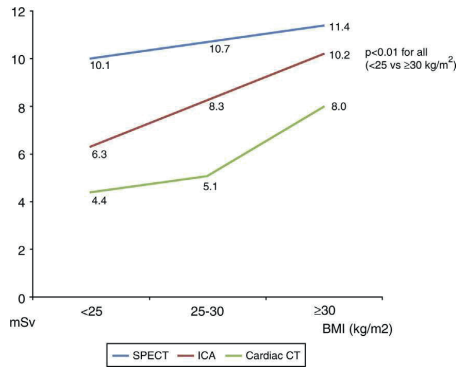

Figure 3 Mean effective radiation doses for each exam and different body mass index classes. BMI: body mass index; CT: computed tomography; ICA: invasive coronary angiography; SPECT: single photon emission computed tomography.

training (Table 3). In the first semester 39% of ICA progressed to percutaneous coronary intervention, while in the fourth semester this proportion increased to 42% (p<0.001). Regarding vascular access, in the first semester only 1% of ICA were performed by radial access, which increased to 46% in the fourth semester. In our population, the use of radial vascular access was associated with a mean increase of 15% in effective radiation dose (from 7.8 mSv with femoral access to 9.0 with radial access, p<0.001). Finally, the proportion of exams performed by trainee operators increased from 26% in the first semester to 52% in the fourth. In this registry, when the exam was performed by a trainee operator there was a mean increase of 29% in effective radiation dose (from 7.3 mSv with a senior operator to 9.4 mSv with a trainee operator, p<0.001).

The only variable associated with the decrease in effective radiation dose for cardiac CT was the use of prospective (step-and-shoot) acquisition: the use of a prospective acquisition protocol was associated with a decrease of 60% in effective radiation dose. In the first semester no exams were performed with this protocol, while in the fourth semester 45% were acquired prospectively (Table 3).

The influence of body mass index on mean effective radiation dose was also evaluated. There was a significantly higher dose in obese patients (BMI ≥30 kg/m^2) compared to overweight patients, which in turn was higher that in patients with normal weight (BMI <25 kg/m^2) (Figure 3).

Discussion

In this analysis, we found significantly different effective radiation doses associated with common diagnostic tests used in cardiology. The dose was highest for SPECT, followed by ICA and lowest for cardiac CT. Furthermore, we found

Table 3 Variables associated with increase in ICA radiation dose and decrease in cardiac CT radiation dose.

		ΔmSv	1st semester	4th semester
	Proportion of patients undergoing PCI	ND	39%	42%
ICA	Exams performed by fellows in training	↑29%	26%	52%
	Proportion of radial vascular access	↑15%	1%	46%
Cardiac CT	Prospective acquisition	↓60%	0%	45%

CT: computed tomography; ICA: invasive coronary angiography.

MANUSCRIPT 15

some time trends in the mean effective radiation dose associated with ICA and cardiac CT related to particular clinical and procedural methodologies.

The biological effects of ionizing radiation are related to the cumulative effective dose, and doses above 100 mSv have been linked to stochastic effects including the development of cancer, while the effects of lower radiation levels, common in diagnostic X-ray imaging, are much less clear.[4,17] Although other theoretical models based on dose-threshold and hormetic effects have been proposed, the more conservative linear no-threshold model, which assumes that no level of radiation is without risk, is widely accepted.[4,17]

On this basis, procedures that use ionizing radiation should be performed in accordance with the ''as low as reasonably achievable'' philosophy, and physicians ordering and performing cardiac imaging diagnostic tests should be familiar with the associated radiation doses and with ways in which they can be minimized.

The mean effective radiation dose we found for each exam is in agreement with previous studies.[3,4,6,18] Furthermore, we confirmed that certain variables influence the effective radiation dose delivered by these exams. For ICA, the effective radiation dose increased with the use of radial access and with less experienced operators, which is in line with published data.[13,19] The higher radiation dose in the ICA registry over time was also associated with a higher proportion of positive exams; although we did not quantify the difference between positive and negative ICA, we can assume that positive tests needed more cine angiograms of the coronary arteries, with a consequent increase in the radiation dose used.

For cardiac CT, the introduction and increasingly frequent use of a prospective protocol during the study period was associated in our experience with a significant decrease in the effective radiation dose for this exam, as has been demonstrated by other authors.[20–22] Finally, for SPECT, the dose change over time was very small, which is to be expected since there were no changes in protocol during the study period.

It is worth noting that during the same period, doses associated with stress-only and rest-only SPECT studies were significantly lower (with mean effective doses of 2.3±0.9 mSv and 5.8±1.0 mSv, respectively) but they were not considered for the purpose of this study, and the small number of patients involved (n=49 and n=63, respectively) would not have had a significant impact on the overall SPECT radiation dose.

Mean effective radiation doses were significantly higher for obese patients in all the exams analyzed. This was especially true for cardiac CT and ICA, with an almost two-fold increase in radiation dose compared to their normal-weight counterparts. In the SPECT registry, the effect of BMI was less pronounced. This should be taken in consideration when selecting the appropriate diagnostic exam, especially for those at higher risk from radiation exposure, like women and younger patients.[23] In line with this, particular attention should be paid to cardiac CT dose, since patients in our registry undergoing cardiac CT were significantly younger than those in the ICA and SPECT registries.

Although the present study focuses on comparison of the radiation dose between three different diagnostic exams, other features should be taken into account when comparing different imaging modalities. As cardiac CT and ICA require the administration of iodinated contrast, care should be taken in the presence of impaired renal function or history of allergies; likewise, the probability of CAD is also an important factor, as SPECT and ICA are more appropriate for patients with higher probability of CAD.[24,25] Thus, all these features (radiation dose, need for iodinated contrast and CAD probability) should be taken into consideration when selecting the most appropriate exam for each patient.

Conclusions

In these registries of diagnostic tests commonly used in cardiology, the mean effective radiation dose used in cardiac CT was lower than that used in ICA, which in turn was lower than the doses used in SPECT. There was a significant increase over time in the mean effective radiation dose associated with ICA, mainly related to the increased use of radial access, and a decrease in cardiac CT doses as a consequence of the implementation of a prospective protocol. Obesity was associated with a significantly higher radiation dose in all three exams.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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MANUSCRIPT 16

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ORIGINAL PAPER

Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden

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Abstract To describe a coronary computed tomography angiography (CCTA)-adapted Leaman score (CT-LeSc) as a tool to quantify total coronary atherosclerotic burden with information regarding localization, type of plaque and degree of stenosis and to identify clinical predictors of a high coronary atherosclerotic burden as assessed by the CT-LeSc. Single center prospective registry including a total of 772 consecutive patients undergoing CCTA (Dual-source CT) from April 2011 to March 2012. For the purpose of this study, 581 stable patients referred for suspected coronary artery disease (CAD) without previous myocardial infarction or revascularization procedures were included. Pre-test CAD probability was determined using both the Diamond–Forrester extended CAD consortium method (DF-CAD consortium model) and the Morise score. Cardiovascular risk was assessed with the HeartScore. The cut-off for the 3rd tercile (CT-LeSc $\geq$8.3) was used to define a population with a high coronary atherosclerotic burden. The median CT-LeSc in this population (n = 581, 8,136 coronary segments evaluated; mean age 57.6 $\pm$ 11.1; 55.8 % males; 14.6 % with diabetes) was 2.2 (IQR 0–6.8). In patients with CAD (n = 341), the median CT-LeSc was 5.8 (IQR 3.2–9.6). Among patients with nonobstructive CAD, most were classified in the lowest terciles (T1, 43.0 %; T2, 36.1 %), but 20.9 % were in the highest tercile (T3). The majority of the patients with obstructive CAD were classified in T3 (78.2 %), but 21.8 % had a CT-LeSc in lower terciles (T1 or T2). The independent predictors of a high CT-LeSc were: Male sex (OR 1.73; 95 % CI 1.04–2.90) diabetes (OR 2.91; 95 % CI 1.61–5.23), hypertension (OR 2.54; 95 % CI 1.40–4.63), Morise score $\geq$16 (OR 1.97; 95 % CI 1.06–3.67) and HeartScore $\geq$5 (OR 2.42; 95 % CI 1.41–4.14). We described a cardiac CT adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA. Male sex, hypertension, diabetes, a HeartScore $\geq$5 % and a Morise score $\geq$16 were associated with a high coronary atherosclerotic burden, as assessed by the CT-LeSc. About one fifth of the patients with nonobstructive CAD had a CT-LeSc in the highest tercile, and this could potentially lead to a reclassification of the risk profile of this subset of patients identified by CCTA, once the prognostic value of the CT-LeSc is validated.

Keywords CCTA · Coronary artery disease · Atherosclerotic burden · Risk scores

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MANUSCRIPT 16

1576 Int J Cardiovasc Imaging (2013) 29:1575–1584

Introduction

Coronary atherosclerosis is the leading cause of mortality and it is expected to remain the most important disease in the upcoming years [1]. Frequently, the first manifestation of coronary disease is an acute coronary syndrome (ACS), and many patients were previously asymptomatic [2]. An early detection of coronary disease is of utmost relevance and a non-invasive diagnostic test is desirable.

In the recent years, coronary computed tomography angiography (CCTA) has become widely available and adopted. The main reason for this is the high predictive accuracy of detection of obstructive coronary artery disease (CAD) compared to conventional invasive coronary angiography [3, 4]. In addition, CCTA allows also the identification of nonobstructive CAD and in this way it can provide a noninvasive quantification of the total coronary atherosclerotic burden. Since the percentage of patients with nonobstructive CAD is very high, there is a need for tools to stratify cardiovascular risk by the degree of plaque burden [5]. The information regarding the localization, severity and composition of coronary plaques identified with CCTA can be collected in scores to reflect the total coronary plaque burden, and some have been already developed and validated [6].

Conventional cardiovascular (CV) risk factors relate to the risk of subsequent CV events and they can be combined in tools as it has been done in the Heart Score [7]. Notwithstanding these observations, accurate prediction of major coronary events on the individual patient level, as opposed to population based studies, remains challenging.

Therefore the aim of this study is two folded: (1) To describe a CCTA-adapted Leaman score (CT-LeSc) as a tool to quantify total coronary atherosclerotic burden including information regarding localization, type of plaque and degree of stenosis and; (2) To identify clinical predictors of a high coronary atherosclerotic burden as assessed by CT-LeSc in a population of stable patients referred for CCTA for suspected CAD.

Methods

Population

Single center prospective registry including a total of 772 consecutive patients undergoing CCTA (with Dual source CT) from April 2011 to March 2012. Patients were excluded if: (1) previous myocardial infarction and/or revascularization procedures (n = 70); (2) referred for Cardiac CT for other indications than the evaluation of possible CAD (cardiac CT for atrial fibrillation ablation or transcatheter aortic valvular implantation procedures; n = 88); (3) referred for suspected ACS (n = 24); (4) with atrial fibrillation or other significant arrhythmias during scan acquisition that compromised image quality (n = 9). This resulted in a 24.7 % of the total population being excluded.

For the purpose of this study, 581 stable patients referred for suspected CAD were included in the context of: (1) Previous equivocal or inconclusive stress tests or discordant with the clinical evaluation (n = 417; 71.8 %); (2) Cardiac CT as 1st line investigation of possible CAD (n = 136; 23.4 %); (3) Preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 17; 2.9 %); (4) Evaluation of possible CAD in cardiomyopathies (DCM or HCM; n = 11; 1.9 %; Fig. 1: Patient selection and study design).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history with a risk factors questionnaire was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents) [8]; (2) Dyslipidemia (defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) [9]; (3) Hypertension (defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medication) [10]; (4) Obesity (body mass index ≥30 kg/m^2); (5) positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 [male] or 65 [female] years of age) [11]; (6) smoking (defined as previous [less <1 year] or current smoker.

Pre-test probability of CAD was determined using both the Diamond and Forrester extended CAD consortium method (DF-CAD consortium model) [12] and the Morise score [13]. The cardiovascular risk was assessed with the HeartScore [7]. As the CAD probability and CV risk of our population was shifted to lower probability and risk, the cut-offs used were: (1) for DF-CAD consortium model categories ≥30–70 and ≥70 % were gathered in a Intermediate to High (≥30 %) probability group.

For the Morise, the population was divided in terciles, and for the HeartScore the established high risk cut-off of ≥5 % was used.

Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >65 beats/min.

During the scan acquisition, a bolus of iodinated contrast (Visipaque, GE Healthcare, USA) was injected at a

MANUSCRIPT 16

Int J Cardiovasc Imaging (2013) 29:1575–1584

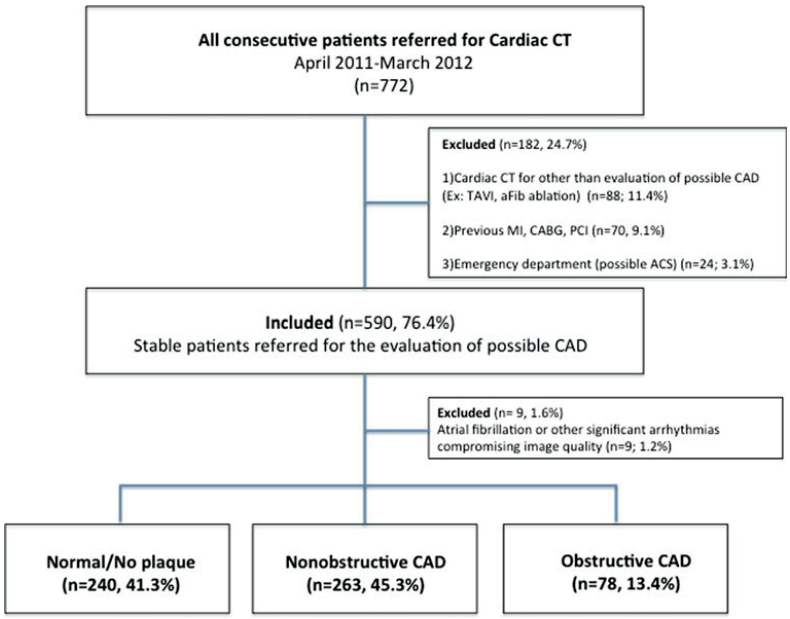

Fig. 1 Patient selection and study design. *CAD* coronary artery disease, *TAVI* transcatheter aortic valve implantation, *aFib* atrial fibrillation, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *ACS* acute coronary syndromes

6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time +6 s delay) × flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible. Mean estimated radiation dose was 4.6 ± 3.7 mSv, contrast dose was 98.9 ± 14.4 ml and heart rate was 65.6 ± 10.6 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments.

Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III-equivalent experience. The Society of Cardiovascular Computed Tomography recommended classification was used regarding segmentation (16 segments), stenosis severity (<25, 25–49, 50–69, 70–99, 100 %) and plaque composition (calcified, non calcified, mixed plaque) [14].

In each coronary artery segment, coronary atherosclerosis was defined as a tissue structure >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [6]. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque.

CCTA adapted Leaman score (CT-LeSc)

For the CT adaptation of the LeSc, we used three sets of weighting factors, all noninvasively provided by CCTA: (1) *localization* of the coronary plaques as originally described [15]. In this study, a modification was made to account for balanced dominance. In cases of balanced dominance, not taken in account in the original Leaman or in the Syntax scores, we assumed an intermediate value between right and left dominance which changed the values for the posterior descending and the proximal, mid and

MANUSCRIPT 16

distal RCA segments as well as for the left main and proximal and distal segments of the circumflex; (2) *type of plaque* (i.e. noncalcified, calcified or mixed plaques). To take in account the cardiac CT added information related to plaque composition, an additional weighting factor of 1.5 was added to predominantly noncalcified of mixed plaques and a factor of 1 to predominantly calcified plaques, reflecting the assumption of less plaque vulnerability of the later ones [16, 17]; (3) *degree of stenosis* (<50 ≥% stenosis). In the presence of obstructive CAD (≥50 % stenosis), the score in each segment was multiplied by 1 and for nonobstructive CAD it was multiplied by a factor of 0.615. This factor reflects the relative proportion in the published hazard ratios for mortality in the large CONFIRM registry [5] for obstructive versus nonobstructive CAD (2.6 vs 1.6 respectively) and it was assumed to reflect the relative prognostic impact of nonobstructive CAD (Table 1).

Table 1 CT-adapted Leaman Score (CT-LeSc) weighting factors

Segment	Right dominance	Left dominance	Balanced
Coronary segments			
RCA proximal	1	0	0.5
RCA mid	1	0	0.5
RCA distal	1	0	0.5
PDA	1	na	0.5
Left main	5	6	5.5
LAD proximal	3.5	3.5	3.5
LAD mid	2.5	2.5	2.5
LAD distal	1	1	1
1st diagonal	1	1	1
2nd diagonal	0.5	0.5	0.5
LCx proximal	1.5	2.5	2.0
1st obtuse marginal	1	1	1
LCx distal	0.5	1.5	1
2nd obtuse marginal	1	1	1
PDA from LCA	na	1	na
PL branch from LCA	na	0.5	0.5
PL branch from RCA	0.5	na	na
Intermediate branch	1	1	1
Stenosis severity			
Obstructive CAD	1		
Nonobstructive CAD	0.615		
Plaque composition			
Non-calcified or mixed	1.5		
Calcified	1		

RCA right coronary artery, *PDA* posterior descending artery, *LAD* left anterior descending, *LCx* left circumflex, *PL* postero-lateral, *CAD* coronary artery disease

The CT-LeSc on a patient level was calculated as the sum of the partial CT-LeSc of all evaluable coronary segments. Two cases examples are shown in Fig. 2.

Statistical analysis

Continuous variables are presented as mean ± SD or medians (interquartile range) and categorical variables as frequencies with percentages.

The non-parametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables, and the Chi square test to evaluate differences in frequencies. Differences were regarded significant when $p < 0.05$ (two-tailed).

Since there are no previous validated cut-offs for the presently described CCTA score, the population with CAD was divided in terciles. A high CT-LeSc was defined with the cut-off for the 3rd tercile (a score ≥8.3, n = 116; 34.8 % of the CAD population) and patients in this group were compared with the remaining population.

Multivariate analyses (binary logistic regression model—enter method) were performed to identify independent predictors of a high CT-LeSc using the demographic and clinical variables presented in Table 2 that had a p value <0.2 at univariate analyses. A second multivariable analyses was performed to identify independent predictors among the clinical scores of CAD probability (Diamond–Forrester CAD consortium model and Morise score) and the CV risk score HeartScore.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

In the final study population of 581 patients, 8,136 coronary segments were evaluated. Segments <2 mm (n = 742; 9.1 %) or with suboptimal image quality related to artefacts or severe calcification (n = 120; 1.5 %) were excluded.

Most of patients were male (55.8 %) and mean age was 57.6 ± 11.1, and 14.6 % were diabetics. This was predominantly a population with low to intermediate CAD probability since 60.1 % had a DF-CAD consortium <30 and 87.6 % had a Morise score <16. A high cardiovascular risk, as assessed by an HeartScore ≥5 %, was present in 25.5 % of the patients. In this population, the median calcium score was 1 (IQR 0–93), 23.4 % had a calcium score (CaSc) ≥100 and 14.3 % had a CaSc ≥75th percentile. In the population with CAD, the median CaSc was 64 (IQR 8–200; Table 2).

CT-LeSc

Overall (n = 581), the median CT-LeSc in this population was 2.2 (IQR 0–6.8). In patients with CAD (n = 341), the

MANUSCRIPT 16

Int J Cardiovasc Imaging (2013) 29:1575–1584

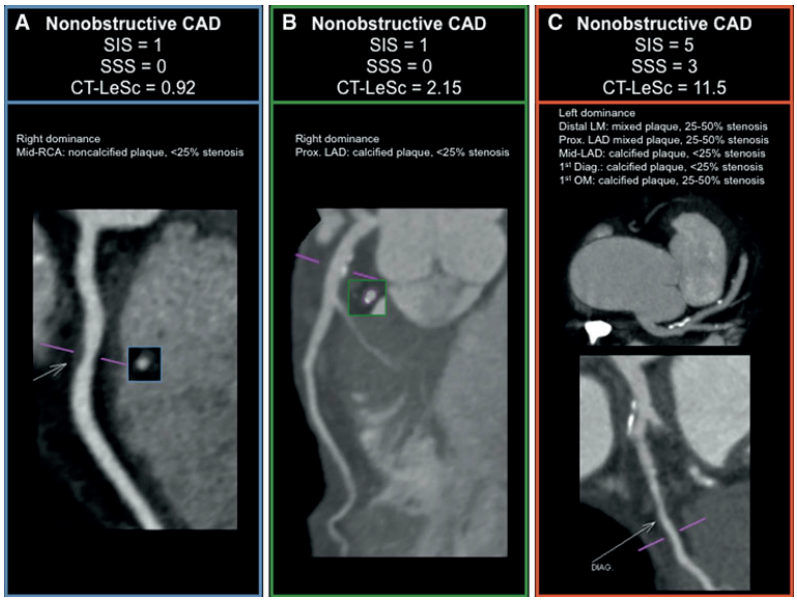

Fig. 2 Three cases examples of patients with nonobstructive CAD stratified by different coronary atherosclerotic burden scores. In panel *A*, a patient with a single lesion in the mid-RCA (weighting for localization × type of plaque × stenosis severity = 1 × 1.5 × 0.615 = 0.92); In panel *B*, a patient with a single proximal LAD lesion (CT-LeSc = 3.5 × 1 × 0.615 = 2.15). In panel *C*, a patient with left dominance and 5 nonobstructive lesions with a total CT-LeSc = LM (6 × 1.5 × 0.615) + prox. LAD (3.5 × 1.5 × 0.615) + mid-LAD (2.5 × 1 × 0.615) + 1st Diag. (1 × 1 × 0.615) + 1st OM (1 × 1 × 0.615) = 11.5. *CAD* coronary artery disease, *CT-LeSc* CT Leaman score, *SIS* segment involvement score, *SSS* segment stenosis score, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery, *1st Diag.* first diagonal branch, *1st OM* first obtuse marginal branch

median CT-LeSc was 5.8 (IQR 3.2–9.6). Within this population the median CT-LeSc in patients with non-obstructive disease (n = 263) was 4.6 (IQR 2.9–7.7) and in patients with obstructive disease (n = 78) it was 11.7 (IQR 8.7–14.4). The terciles in population with CAD were: *T1* ≤*3.7 (0.3–3.7)*; *T2 (3.8–8.3)*; *T3* ≥8.3 (8.3–24.1).

Regarding the distribution of patients with nonobstructive versus obstructive CAD across the CT-LeSc terciles, most of the patients with nonobstructive CAD were in T1 (n = 113, 43.0 %) or T2 (n = 95, 36.1 %), but about one fifth (n = 55, 20.9 %) were in the highest tercile (T3, CT-LeSc ≥8.3). On the other hand, although most of the patients with obstructive CAD were classified in T3, 21.8 % had a CT-LeSc in lower terciles (T1, 2.6 %; T2, 19.2 %; Fig. 3).

The median CT-LeSc was significantly higher in males and in the presence of diabetes and hypertension, as well as in patients with a high cardiovascular risk assessed by an HeartScore ≥5 %. The median CT-LeSc was also significantly higher in patients with a CaSc ≥100 and CaSc ≥75th percentile (Fig. 4: Median CT-LeSc in different patient subgroups).

Univariate predictors

In the univariate analysis, a high CT-LeSc was associated with older age (≥60 years), diabetes and hypertension. The percentage of male patients and patients with dyslipidemia was also higher in the high CT-LeSc group, but not statistically significant. Patients in the high CT group had also a higher pre-test CAD probability (DF-CAD consortium ≥30 % and Morise score ≥16) as well as higher CV risk, reflected in the significantly higher percentage of patients with a HeartScore ≥5 %. Of note, some traditional risk factor as obesity, smoking status and family history of premature CAD were not differently distributed in the two groups, and this was also the case for chest pain (Table 3).

Multivariate predictors

By multivariate analysis, the independent predictors of a high CT-LeSc were: male sex; diabetes, hypertension, Morise score ≥16 and HeartScore ≥5 (Table 4; Fig. 5). Of note, regarding the modifiable risk factors, patients with

MANUSCRIPT 16

Table 2 Demographic, clinical and CCTA characteristics of the study population

	All patients (n = 581)
Demographic	
Age	57.6 ± 11.1
Male sex	324 (55.8)
Risk factors	
Obesity (BMI ≥30)	109 (18.8)
Diabetes	85 (14.6)
Hypertension	364 (62.7)
Dyslipidemia	360 (62.0)
Smoking	138 (23.8)
Family history of premature CAD	194 (33.4)
Chest pain	
Asymptomatic	270 (46.5)
Noncardiac	169 (29.1)
Atypical	109 (18.8)
Typical	33 (5.7)
CAD probability	
DF-CAD consortium ≥70 %	11 (1.9)
DF-CAD consortium 30–70 %	221 (38.0)
DF-CAD consortium <30 %	349 (60.1)
Morise score ≥16	72 (12.4)
Morise score 9–15	369 (63.5)
Morise score 0–8	140 (24.1)
CV risk	
Heart score ≥5 %	148 (25.5)
Calcium score	
Median	1 (0–93)
Median in patients with CAD	64 (8–200)
CaSc ≥100	136 (23.4)
CaSc ≥75th percentile	83 (14.3)
CCTA	
Normal/no plaque	240 (41.3)
Nonobstructive CAD	263 (45.3)
Obstructive CAD	78 (13.4)
Technical data	
Heart rate (bpm)	65.6 ± 10.6
Contrast dose (ml)	98.9 ± 14.4
Radiation dose (mSv)	4.6 ± 3.7

Values are mean ± SD, median (IQR) or n (%)

CAD coronary artery disease, *BMI* body mass index, *DF-CAD consortium* Diamond–Forrester CAD consortium model, *CV* cardiovascular, *CCTA* coronary computed tomography angiography, *CaSc* calcium score, *bpm* beats per minute, *mSv* milisievert

diabetes had a threefold and patients with hypertension a 2.5-fold higher probability of having a high CT-LeSc.

A high HeartScore (≥5 %) and a high Morise score (≥16) were associated respectively with a 2.5 and twofold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc.

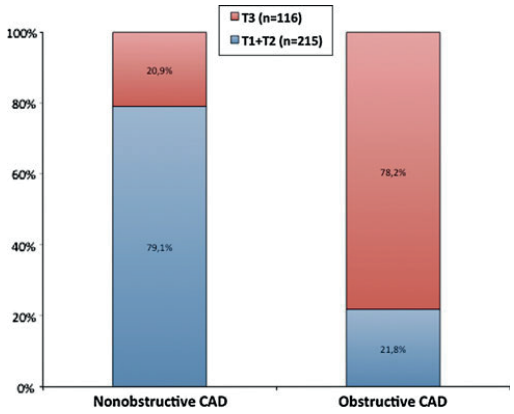

Fig. 3 Distribution of the two subgroups of patients (nonobstructive and obstructive CAD), according to CT-LeSc terciles (T1 + T2 vs T3). *CAD* coronary artery disease, *T1* 1st tercile, *T2* 2nd tercile, *T3* 3rd tercile

Discussion

The main findings of this study are: (1) Calculation of a cardiac CT adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA is feasible; (2) There was a significant association between the CT-LeSc and diabetes, a well recognized subset of advanced coronary atherosclerotic burden. A high CV risk (HeartScore) and a high CAD probability (Morise score) were also both associated with nearly a 2–2.5 fold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc.

Although the exclusion of obstructive CAD remains presently the main indication to refer a patient for CCTA, this noninvasive diagnostic tool can also provide information regarding the presence of nonobstructive plaques, detecting CAD at earlier disease stages. Although on a *per lesion* basis, vulnerability is positively associated with the degree of stenosis, on a *per patient* level most of the acute events come from nonobstructive lesions [18–20]. It is also recognized that many of the nonstenotic lesions can have a high plaque burden, underestimated by luminal angiograms, since they undergo expansive or positive outward enlargement, and such remodeling is a potential surrogate marker of plaque vulnerability [21]. In the multicenter virtual histology intravascular ultrasound (VH-IVUS) PROSPECT study [22], a large plaque burden, a small lumen area and the presence of a thin cap fibroatheroma were independent predictors of future nonculprit lesion major adverse cardiac events (MACE). In this study, lesions that led to MACE had a high plaque burden by

MANUSCRIPT 16

Int J Cardiovasc Imaging (2013) 29:1575–1584

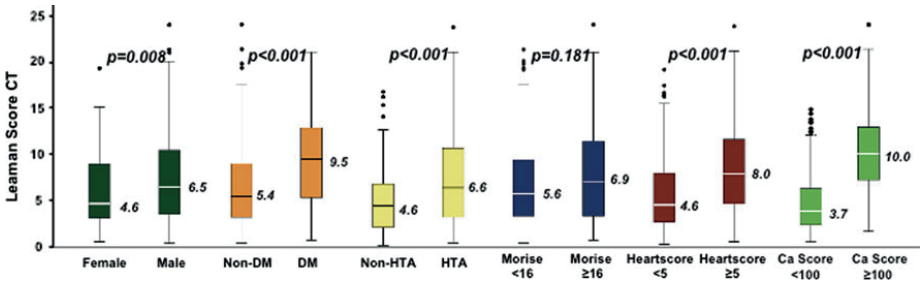

Fig. 4 Median CT-LeSc in different patient subgroups. *DM* diabetes mellitus, *HTA* hypertension, *CA score* calcium score, *CT-LeSc* CT Leaman score

Table 3 Univariate analysis

	CT LeSc T1 + 2 (<8.3)	CT LeSc ≥ T3 (≥8.3)	*p*
Age ≥60	126 (56.0)	79 (68.1)	0.031
Male sex	138 (61.3)	81 (69.8)	0.121
BMI ≥30	41 (18.3)	25 (22.1)	0.404
Diabetes	26 (11.6)	36 (31.0)	<0.001
Hypertension	144 (64.0)	98 (84.5)	<0.001
Dyslipidemia	146 (64.9)	87 (75.0)	0.057
Smoking	53 (23.6)	31 (26.7)	0.520
Family history of premature CAD	77 (34.2)	37 (31.9)	0.666
Chest pain	106 (47.3)	59 (51.3)	0.487
DF-CAD consortium ≥30 %	66 (29.3)	64 (55.2)	<0.001
Morise score ≥16	105 (46.7)	78 (67.2)	<0.001
Heart score ≥5	29 (12.9)	24 (20.7)	0.060

Values are n (%); *CAD* coronary artery disease, *BMI* body mass index, *DF-CAD* consortium-diamond–Forrester CAD consortium model

Table 4 Multivariate analysis—independent predictors of a high CT-LeSc (3rd tercile, score ≥8.3)

	OR	(95 % CI)	*p*
Demographic and clinical variables			
Age ≥60	1.370	0.819–2.291	0.230
Male sex	1.732	1.035–2.901	0.037
Diabetes	2.905	1.612–5.234	<0.001
Hypertension	2.543	1.395–4.634	0.002
Dyslipidemia	1.563	0.919–2.660	0.099
Clinical scores			
Heart score ≥5	2.416	1.411–4.135	0.001
DF-CAD consortium ≥30 %	1.590	0.918–2.754	0.098
Morise ≥16	1.971	1.060–3.666	0.032

OR odds ratio, *DF-CAD consortium* Diamond–Forrester CAD consortium model

IVUS, but were mild by baseline angiography (mean diameter stenosis 32 %). The prognostic value of nonobstructive CAD has also been recently reinforced from large cardiac CT registries (CONFIRM) and meta-analysis [23].

In the large international multicenter CONFIRM registry, all-cause mortality was significantly higher for patients with nonobstructive CAD, as compared with patients without coronary atherosclerosis. One notable finding in this registry is the superimposed survival curves of nonobstructive and 1 vessel obstructive CAD, reinforcing the prognostic impact of nonobstructive coronary lesions [6].

Why a plaque burden CT score?

The main reason is because CAD represents a very heterogeneous condition and there is a need to structure the quantification of the plaque burden and to integrate the most important information collected by CT and finally to homogenize the reporting of CT findings.

There are already some CT scores developed and prognostically validated namely the segment involvement score (SIS) and the segment stenosis score (SSS), but they only reflect some aspects of the coronary atherosclerotic burden, the former only takes into account the number of segments with plaque and the latter the degree of stenosis [6]. The CT-LeSc reflects some of the aspects that are partially included in the SIS (number of segments with plaque) and the SSS (degree of stenosis), and combines these two aspects, and also the localization, on a more comprehensive score.

Why these three components?

Individually, *localization* of the plaque within the coronary tree, *the type of plaques* and *degree of stenosis* are strong predictors of future coronary events.

Since CCTA is able to reliably collect information on these three aspects, a comprehensive score should be able to integrate these components.

MANUSCRIPT 16

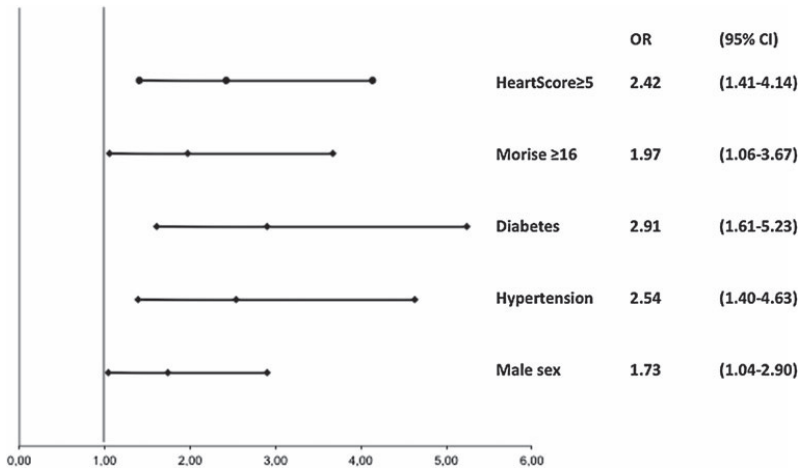

Fig. 5 Independent predictors of a high CT-LeSc (score ≥8.3). *CT-LeSc* CT Leaman score

Regarding *localization*, the original Leaman score was developed as a score to quantify obstructive coronary disease identified with invasive angiography [15]. In this score, with the rational of relative blood supply to the left ventricle, all coronary segments were given a weighting factor, reflecting the relative contribution of blood flow to the left ventricle of each vessel segment, taking also in account the specific right or left dominance systems. Recently, this score was used as the segment weighting factor for the development of the syntax score [24] which has been proven to have a strong prognostic value in different clinical scenarios [25, 26]. In our score, values were also provided for balanced dominance, reflecting more adequately the anatomical variants of the coronary tree.

Plaque composition has been found in both pathological and clinical studies associated with cardiac events [22, 27]. CCTA has shown to be able to characterize plaque composition [28]. Thin cap fibroatheroma is the most common pathological substrate of ACS and in CCTA these plaques appear as noncalcified or mixed plaques [16]. In a recent study by Maurovich-Horvat et al. [16], the frequency of a napkin-ting sign, a CCTA feature of advanced lesions by histology, was similar between noncalcified and mixed plaques, which also reinforces our weighting factor in the CT-LeSc for plaque composition that was the same between these two types (a factor of 1.5), and different from predominantly calcified plaques (a factor of 1).

Regarding the *degree of stenosis*, we assumed in our scoring system a factor reflecting the proportion of the hazard ratios for obstructive versus nonobstructive observed in the recently large scale CONFIRM registry. By gathering all the nonobstructive (<25, 25–49 %) and obstructive (50–69, 70–99, 100 %) in the same risk categories, this scoring system is expected to have a good intra and inter-observer correlation, since the other two weighting factors (localization and plaque calcification) have also an excellent reproducibility and are usually described in CCTA reporting.

Clinical implications

Many tools are already available to help stratifying patients at risk of a CV event and some scores have been already developed gathering the information provided by the different traditional risk factors, like the Framingham score or the HeartScore. Notwithstanding these observations, accurate prediction of major coronary events on the individual patient level, as opposed to population based studies, remains challenging.

The clinical implications of a score that reflect the extent of coronary atherosclerotic burden is related to the fact that this way we can have a tool to quantify and compare this burden, which is particularly useful when reporting a CCTA of a patient without obstructive CAD, but in whom the extent of nonobstructive CAD could lead to a reclassification of his risk profile and thereby his cardiovascular treatment.

Of note in our study is the fact that although the CT-LeSc, by having the degree of stenosis in its composition, tends to favour patients with obstructive CAD, we were able to demonstrate that a significant percentage (20.9 %) of patients with nonobstructive CAD had in fact a CT-LeSc in the highest tercile (T3). Conversely, among patients with obstructive CAD, about one fifth had a coronary

MANUSCRIPT 16

atherosclerotic burden, as assessed by the CT-LeSc, in lower terciles.

The CT-LeSc, by having a weight related to the localization, it reflects not only the extent of CAD but also the expected clinical consequences in case that the more proximal lesions evolve to a significant stenosis or become unstable and trigger a coronary event.

In our study, a high HeartScore and a high Morise score were both associated with nearly a 2–2.5 fold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc. This could be expected for the HeartScore, as it was develop as a tool to predict cardiovascular risk. In the case of the Morise score, is was developed and validated as a clinical tool to estimate the probability of CAD, but it has also been linked to cardiovascular outcomes [29]. The Diamond–Forrester was not an independent predictor of a high CT-LeSc and although we used the recently calibrated CAD consortium model [12], is has been developed and calibrated for obstructive CAD identified with invasive angiography and doesn't take in account the cardiovascular risk factors in its composition.

Limitations

There are a number of limitations related to this report: (1) This is a single center data with medium size cohort; (2) High prevalence of low CAD probability/CV risk patients. The population included in our study was mainly composed of patients with low to intermediate CAD probability and CV risk. Nevertheless, CAD was present in nearly 60 % of the patients and this reflects the daily practice and the recommendations that high CAD probability patients have not an appropriate indication for CCTA [30]; (3) For the weighting factor of plaque composition, we used a multiplication factor of 1.5 for mixed and noncalcified plaques. Although this was an arbitrary factor, this is in line with several CCTA prognostic studies that demonstrated lower hazard ratios for calcified plaques and reflects an assumption of less plaque vulnerability of calcified plaques. (4) Lack of prognostic validation: the aim of this study was to describe a CCTA score to quantify total coronary atherosclerotic burden and to identify its clinical predictors. Future studies will be needed to provide a prognostic validation of this described CT-LeSc.

Conclusions

The calculation of the CCTA-adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA is feasible. There was a significant association between the CT-LeSc and some traditional demographic and clinical risk factors. In face of this association, we expect this score to be a useful tool to quantify the coronary atherosclerotic burden evaluated by CCTA and it is expected to convey prognostic information, and this should be evaluated in future studies.

About one fifth of the patients with nonobstructive CAD had a CT-LeSc in the highest tercile, which could potentially lead to a reclassification of the risk profile of these subset of patients identified by CCTA, once the prognostic value of the CT-LeSc is validated.

Conflict of interest There were no sources of funding and the authors have no conflicts of interest related to this manuscript.

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MANUSCRIPT 17

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ORIGINAL PAPER

Prevalence and predictors of coronary artery disease in patients with a calcium score of zero

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Abstract The absence of coronary calcification is associated with an excellent prognosis. However, a calcium score of zero does not exclude the presence of coronary artery disease (CAD) or the possibility of future cardiovascular events. Our aim was to study the prevalence and predictors of coronary artery disease in patients with a calcium score of zero. Prospective registry consisted of 3,012 consecutive patients that underwent cardiac CT (dual source CT). Stable patients referred for evaluation of possible CAD that had a calcium score of zero (n = 864) were selected for this analysis. The variables that were statistically significant were included in a multivariable logistic regression model. From 864 patients with a calcium score of zero, 107 (12.4 %) had coronary plaques on the contrast CT (10.8 %, n = 93 with nonobstructive CAD and 1.6 %, n = 14 with obstructive CAD). By logistic regression analysis, the independent predictors of CAD in this population were age >55 years [odds ratio (OR) 1.63 (1.05–2.52)], hypertension [OR 1.64 (1.05–2.56)] and dyslipidemia [OR 1.54 (1.00–2.36)]. In the presence of these 3 variables, the probability of having coronary plaques was 21 %. The absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low. In this population, the independent predictors of CAD in the setting of a calcium score of zero were hypertension, dyslipidemia, and age above 55 years. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population.

Keywords Zero calcium score · Coronary artery disease · Noncalcified plaque

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Introduction

Coronary artery disease (CAD) is a major cause of death in developed countries and it is expected to remain the most important disease in the upcoming years [1].

Quantification of coronary artery calcium [calcium scoring (CaSc)] can provide a measure of the atherosclerotic plaque burden, since coronary arterial calcification occurs almost exclusively in atherosclerotic plaques [2, 3]. Also, it has been demonstrated in many large clinical trials, that CaSc is a strong predictor of cardiovascular events [4–7].

On the other hand, the absence of calcium in the coronary arteries, although it does not rule out atherosclerotic disease, is consistent with an excellent long-term prognosis [8] and has a high sensitivity and negative predictive value for excluding obstructive CAD. This fact prompted some recent guidelines to suggest that a calcium score of zero might exclude the need for coronary angiography in symptomatic patients [9]. Nevertheless, in previous studies, a high variation was reported in the incidence of obstructive CAD in patients with a CaSc of zero, ranging from 2 to 32 % [10–15]. For instance, in the recent CONFIRM registry, it was shown that in patients with a CaSc of zero, obstructive CAD is

MANUSCRIPT 17

Int J Cardiovasc Imaging

possible and is associated with increased cardiovascular events [16]. The aim of this study was to assess the prevalence and predictors of coronary artery disease in a population of stable patients referred for evaluation of possible CAD who had a calcium score of zero.

Methods

Study design and patient population

Single center prospective registry including 3,012 consecutive patients undergoing dual source coronary CT angiography (CCTA) from February 2007 to March 2012. For this analysis, 864 stable patients (with symptoms and/or positive or inconclusive stress tests) referred for evaluation of possible CAD that had a calcium score of zero were included.

Exclusion criteria included: (1) preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 51); (2) evaluation of possible CAD in cardiomyopathies (dilated cardiomyopathy or hypertrophic cardiomyopathy) (n = 162); (3) cardiac CT for atrial fibrillation ablation (n = 330); (4) previous myocardial infarction and/or revascularization procedures (n = 257); (5) suspected ACS (n = 70); (6) other indications (n = 102). Patients with atrial fibrillation or other significant arrhythmias during scan acquisition or artifacts that significantly compromised image quality were also excluded, as every patient with a CaSc >0 (Fig. 1).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history with a questionnaire investigating risk factors was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥126 mg/dl or the need for insulin or oral hypoglycemic agents) [17]; (2) Dyslipidemia (defined as a total cholesterol level ≥200 mg/dl or treatment with lipid-lowering drugs) [18]; (3) Hypertension (defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medication) [19]; (4) Obesity (body mass index ≥30 kg/m^2); (5) positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years of age) [20]; (6) smoking (defined as previous (less <1 year) or current smoker).

Pre-test probability of CAD was determined using both the modified Diamond and Forrester [21] and the Morise score [22]. The cardiovascular risk was assessed with the Heart Score [23]. In the modified Diamond–Forrester, patients were classified into very low (<5 %), low (<10 %), intermediate (10–90 %) and high probability (>90 %). For the Morise score, patients were classified into low (scores 0–8), intermediate (scores 9–15) and high probability (scores ≥16). For the Heart Score, the cut-off of ≥5 % (high-risk) was used.

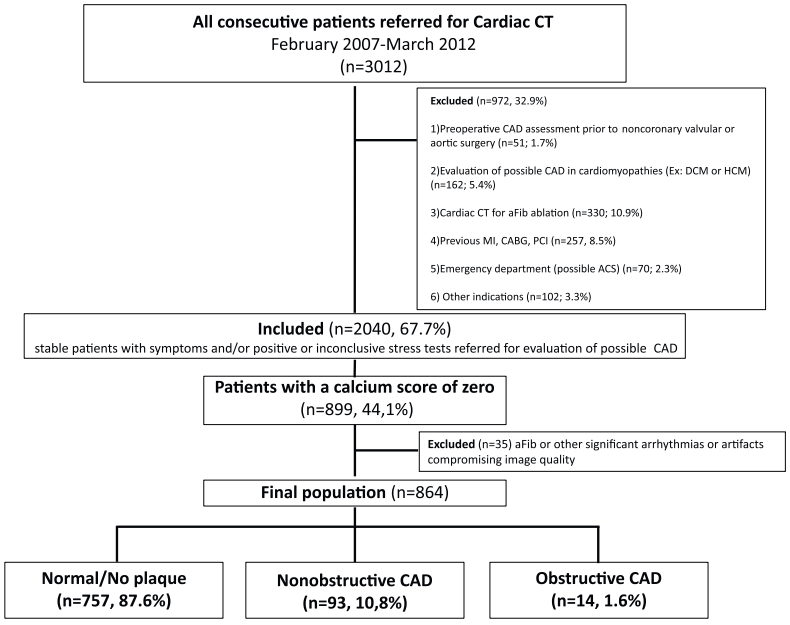

Fig. 1 Patient selection and study design

MANUSCRIPT 17

Int J Cardiovasc Imaging

Scan protocol and image reconstruction

All scans were performed with the first generation of dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold.

The calcium score acquisition consisted of step and shoot—prospective ECG triggering at 70 % of the R–R interval if the heart rate was below 80 beats per min (bpm) or at 40 % of the R–R interval if the heart rate was higher. From the topogram, a cranio-caudal scan was obtained from the carina to the plane just below the heart *silhouette*, with 120 kV and 128 mAs/rot tube current, with CARE-Dose 4D mAs modulation. The value of the calcium score was obtained with the analysis of consecutive non-contrast 3 mm slices, with a reconstruction b35f Kernel and a small (cardiac) FOV, with a dedicated software (CaSc–Siemens), where every area at least with 3 mm^2 within a coronary vessel with a density above 130 HU (Hounsfield Units) was selected.

For CCTA, sublingual nitroglycerin was administered to all patients, except when contraindicated, and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >70 bpm.

During the scan acquisition, a bolus of iodinated contrast was injected at a 6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time + 6 s delay) × flow (6 ml/s). A ROI was defined in the ascending aorta for the bolus trigger technique, set at 120 HU.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible.

Mean estimated radiation dose was 0.8 ± 0.5 mSv for CaSc and 4.6 ± 3.8 mSv for CT scan. Mean contrast dose was 96.2 ± 13.6 ml and heart rate was 67.8 ± 12.9 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique. All scans were analysed independently in the same session by both a cardiologist and a radiologist with level III equivalent experience by the Society of Cardiovascular Computed Tomography. In case of disagreement, a joint reading was performed and a consensus decision was reached.

In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [24]. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. Obstructive CAD was defined by presence of at least one plaque with ≥50 % stenosis.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation. Categorical variables were expressed as percentages and their frequencies were compared with the Chi square test.

Binary logistic regression models were built to elucidate independent predictors of CAD without coronary calcification.

The objective of this model was the assessment of clinical variables that aid to predict the presence of CAD in patients with a calcium score of zero. All the demographic, risk factors and clinical variables present in Table 2 that had a p <0.1 in univariate analysis were included in a multivariate logistic regression model (Enter method).

Statistical analysis was performed with SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline and procedural characteristics

In the final study population of 864 patients, most of the patients were female (55 %) and mean age was 53.8 ± 11.0 years. The prevalence of traditional risk factors was low, with only 9.0 % of patients with diabetes. This was predominantly a low risk population with few high risk patients (only 9.0 % with the Morise score and 3.1 % with the modified Diamond–Forrester had a high CAD probability). Likewise, most of the patients were not considered as high cardiovascular risk, as assessed by the Heart Score (only 11.9 % had a Heart Score ≥5 %)—Table 1.

Coronary plaques were detected on CCTA in 107 patients (12.4 %): 10.8 % (n = 93) with nonobstructive CAD and 1.6 % (n = 14) with obstructive CAD—Fig. 2. Considering the degree of stenosis of the obstructive CAD group, 64 % (n = 9) had a 50–70 % stenosis and 36 % (n = 5) a >70 % stenosis. Considering the extent of disease, all these patients had obstructive CAD in only 1 vessel and 93 % had a single lesion. Regarding the distribution, most of the obstructive CAD lesions were found in proximal or mid segment locations (87 %), and the most affected artery was the right coronary artery 50 % (n = 7).

MANUSCRIPT 17

Table 1 Demographic, clinical and CCTA characteristics of the study population

	All patients (n = 864)
Demographic	
Age	53.8 ± 11.0
Male sex	389 (45.0)
Risk factors	
Obesity (BMI ≥ 30)	160 (18.5)
Diabetes	78 (9.0)
Hypertension	459 (53.1)
Dyslipidemia	454 (52.5)
Smoking	206 (23.8)
Family history of premature CAD	284 (32.9)
Chest pain	
Asymptomatic	441 (51.0)
Noncardiac	194 (22.5)
Atypical	182 (21.1)
Typical	47 (5.4)
CAD probability—Morise	
Score ≥16	78 (9.0)
Score 9–15	446 (51.6)
Score 0–8	340 (39.4)
CAD probability—modified Diamond Forrester	
Very low	188 (21.8)
Low	391 (45.3)
Intermediate	257 (29.7)
High	27 (3.1)
CV risk	
Heart Score ≥5 %	103 (11.9)
CCTA	
Normal/no plaque	757 (87.6)
Non obstructive CAD	93 (10.8)
Obstructive CAD	14 (1.6)
Technical data	
Heart rate (bpm)	67.8 ± 12.9
Contrast dose (ml)	96.2 ± 13.6
Radiation dose—CTA (mSv)	4.6 ± 3.8
Radiation dose—CaSc (mSv)	0.8 ± 0.5

Values are mean ± SD or n (%)

BMI body mass index, *CAD* coronary artery disease, *CV* cardiovascular, *CCTA* coronary computed tomography angiography, *bpm* beats per minute, *mSv* milisievert

Left anterior descendent was affected in 5 patients, while left main was affected in one patient and the circumflex artery in other patient.

There were no significant differences in the prevalence of CAD in patients referred for CCTA because of positive/inconclusive stress tests (93/722 = 12.9 %) versus patients referred without previous stress tests (14/142 = 9.9 %), $p = 0.403$.

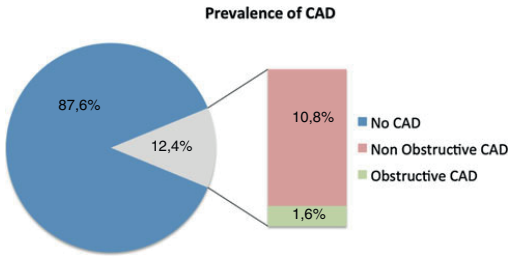

Fig. 2 Distribution of CT angiographic findings

Table 2 Prevalence of CAD according to the pretest probability (Morise)

Pretest probability	Nonobstructive CAD	Obstructive CAD
Low (n = 340)	27 (7.9 %)	6 (1.8 %)
Intermediate (n = 446)	64 (14.3 %)	6 (1.3 %)
High (n = 78)	16 (20.5 %)	2 (2.6 %)
p	0.002	0.708

We further analyzed the distribution of CAD in the different pretest probability subgroups. Using those defined by Morise, the prevalence of CAD (any plaque) was 7.9, 14.3 and 20.5 % in low, intermediate and high pretest probability patients, respectively. Regarding obstructive CAD, a higher prevalence was also found in patients with high pretest probability, but this increase was not statistically significant (Table 2).

Univariate analysis

Patients with CAD were older (prevalence of age ≥55 years 64 vs. 47 %, $p = 0.001$) than patients without CAD and had a higher prevalence of dyslipidemia (65 vs. 51 %, $p = 0.010$) and hypertension (67 vs. 51 %, $p = 0.002$).

The pre-test CAD probability assessed both by the Morise score and the modified Diamond–Forrester was higher in the CAD group and these patients had a 2–4 times higher probability of being of a high CAD probability group. Cardiovascular risk, estimated by the Heart Score, was also significantly higher in patients with CAD. Although there was a trend in this group towards a higher prevalence of diabetes and male gender, these differences were not statistically significant—Table 3.

Multivariate analysis

By multivariate analysis, the independent predictors of CAD in patients with a calcium score of zero were age ≥55 (OR 1.631, 95 % CI 1.054–2.524, $p = 0.028$), hypertension (OR

MANUSCRIPT 17

Int J Cardiovasc Imaging

Table 3 Univariate analysis

	No CAD (n = 757)	CAD (n = 107)	*p*
Demographic			
Age ≥55 years	355 (47.0)	68 (63.6)	**0.001**
Male gender	335 (44.3)	54 (50.5)	0.254
Risk factors			
Diabetes	64 (8.5)	14 (13.1)	0.147
Obesity (BMI ≥ 30)	139 (18.4)	21 (19.6)	0.790
Hypertension	387 (51.1)	72 (67.3)	**0.002**
Dyslipidemia	385 (50.9)	69 (64.5)	**0.010**
Smoking	184 (24.3)	22 (20.6)	0.467
Family history of premature CAD	248 (32.8)	36 (33.6)	0.913
Symptoms			
Chest pain	371 (49.0)	52 (48.6)	1.000
CAD probability—Morise			
Score ≥16	62 (8.2)	16 (15.0)	**0.002**
Score 9–15	382 (50.5)	64 (59.8)	
Score 0–8	313 (41.3)	27 (25.2)	
CAD probability—modified Diamond Forrester			
Very low	171 (22.6 %)	17 (15.9)	**0.005**
Low	342 (45.2)	49 (45.8)	
Intermediate	225 (29.8)	32 (29.9)	
High	18 (2.4)	9 (8.4)	
CV risk			
Heart Score ≥5	79 (10.4)	24 (22.4)	**0.001**

Values are mean ± SD or n (%)

CAD coronary artery disease, *BMI* body mass index, *CV* cardiovascular

Bold indicates *p* value with statistical significance

1.641, 95 % CI 1.051–2.560, $p = 0.029$) and dyslipidemia (OR 1.538, 95 % CI 1.002–2.361, $p = 0.049$) (Fig. 3). In the presence of these 3 variables (n = 176 patients, 20.4 % of the population), the probability of having coronary plaques was 21 % (vs. 12.4 % in the total studied population). We also analyzed the prevalence of CAD according to the presence of none, one, two or three of these risk factors. The results are shown in Table 4.

Discussion

In this single center cohort of stable patients without known CAD, referred for cardiac CT angiography, we found a very low prevalence of obstructive CAD (1.6 %) in the subset with a CaSc of zero. When considering the degree of stenosis, only 0.6 % had a stenosis >70 %.

The prevalence and clinical significance of obstructive CAD on coronary CT angiography among patients with a

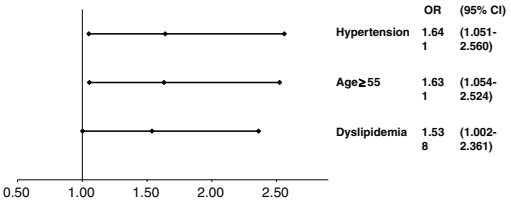

Fig. 3 Independent predictors of CAD in patients with a CaSc of zero

calcium score of zero has been evaluated in several cohorts, but with conflicting results, depending on the population included. Data from Nieman et al. [14], the CONFIRM registry [16], Rubinshtein et al. [13] and Akram et al. [11], are in line with our results, with a low prevalence of obstructive CAD (2, 3.5, 7.2 and 8.2 %, respectively). Our prevalence was even lower, and this might be explained by a high prevalence of patients with a low pretest probability of CAD.

In contrast, in the work of Harberl et al. [10] and Gottlieb et al. [12], there was a high prevalence of CAD (32 and 19.4 %, respectively), which can be related to the fact that these studies included patients referred for conventional angiography, including patients with possible acute coronary syndromes.

In our population, the prevalence of CAD in patients with positive/inconclusive stress tests (exercise electrocardiography in most cases) was not significantly different from that of patients referred to CCTA without previous tests, as in the study from Nieman et al. [14].

Calcium scoring enables a noninvasive quantification of the total coronary atherosclerotic burden, although it underestimates the burden of disease, by not measuring noncalcified plaques [25]. Nevertheless, it has been shown to outperform traditional risk stratification tools, such as clinical risk factor assessment, ankle-brachial index, carotid intima-media thickness and high-sensitivity C-reactive protein, as a predictor of cardiovascular events [4, 5].

Our data suggests that, although the absence of calcium does not exclude the presence of CAD, it was associated with a very low probability of obstructive lesions. This was especially true in cases of low and intermediate pretest CAD probability, as in the study from Werkhoven et al. [15] in which the prevalence of obstructive CAD, in the absence of calcium, was only 3.4 and 3.8 % in patients with low and intermediate pretest CAD probability, respectively. This is in line with the excellent prognosis that has been demonstrated for patients with a calcium score of zero [8].

In our population, older age (≥55 years), hypertension and dyslipidemia were independent predictors of CAD in

MANUSCRIPT 17

Table 4 Prevalence of CAD according to the presence of risk factors found to be independent predictors

Independent preditors	No CAD	Nonobstructive CAD	Obstructive CAD	Total	*p*
0	158 (96.9 %)	5 (3.1 %)	0 (0 %)	163	<0.001
1	210 (86.8 %)	25 (10.3 %)	7 (2.9 %)	242	
2	250 (88.3 %)	28 (9.9 %)	5 (1.8 %)	283	
3	139 (79.0 %)	35 (19.9 %)	2 (1.1 %)	176	
	757	93	14	864	

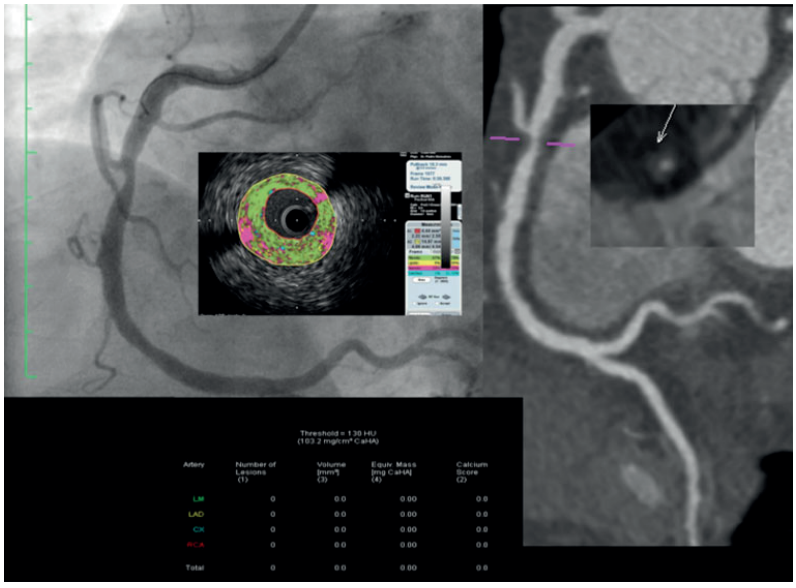

Fig. 4 Non-calcified plaque on cardiac CT (on the *right*) in a patient with a CaSc of zero; the angiography (on the *left*) confirmed the presence of a 50–70 % stenosis in the mid-RCA; intravascular ultrasound with virtual histology (in the *middle*) suggests the presence of microcalcifications

this subset of patients without calcium, and in the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population. Nevertheless, the odds ratios for the independent predictors were rather modest and other traditional CAD risk factors were not found to be independent predictors. This way, we could hypothesize that coronary plaques without calcium could be a different phenotypical subset of CAD. Another possibility could be that these patients with coronary plaques in the absence of calcium represent CAD at earlier stages, since calcium is considered to be associated with more advanced forms of atherosclerotic lesions [2]. In fact, in our population, all the patients with obstructive CAD had only 1 vessel disease, most (93 %) with a single lesion, and only a minority (36 %) had >70 % stenosis.

One last hypothesis could be that these plaques can have microcalcifications below the threshold of cardiac CT spacial resolution, as in the case example (Fig. 4), in which small spots of calcium were only detected by intravascular ultrasound (IVUS) virtual histology.

Limitations

There are a number of limitations related to this report: (1) this is a single center retrospective study with medium size cohort; (2) our population in mainly of low CAD probability and CV risk; the very low percentage of obstructive CAD found can not be extrapolated to cohorts with more patients with higher CAD probability and CV risk (3) the definition of CAD was made using CCTA and not invasive angiography, which may lead to false-positive findings, although this is unlikely in the absence of calcium; (4) lack of prognostic information, since we did not evaluate the prognostic importance of obstructive CAD in patients with a CaSc of zero.

MANUSCRIPT 17

Int J Cardiovasc Imaging

Conclusions

In this population of stable patients referred for evaluation of possible CAD that had a calcium score of zero, 12.4 % had coronary plaques and 1.6 % had obstructive (≥50 %) CAD.

Therefore, and despite the known high negative predictive value of CaSc for coronary events, the absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low.

In this population, we found that age ≥55, hypertension, dyslipidemia were independent predictors of CAD in the setting of a calcium score of zero. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the total studied population.

Conflict of interest All the authors declare that they have no conflict of interest.

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MANUSCRIPT 18

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CASO CLÍNICO

Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular

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PALAVRAS-CHAVE
Tomografia computorizada cardíaca;
Doença coronária não obstrutiva;
Exercício físico

Resumo A tomografia computorizada cardíaca (angioTC cardíaca) permite documentar a presença de doença coronária, independentemente do seu grau de estenose. Recentemente, foi validado o valor prognóstico da doença coronária não obstrutiva documentada por angioTC cardíaca. No entanto, não existem ainda recomendações claras acerca da abordagem destes doentes, nomeadamente sobre o início de medidas farmacológicas mais agressivas em prevenção primária. A abordagem destes doentes permanece controversa, sobretudo nos casos em que existe uma discrepância entre o risco cardiovascular e a carga aterosclerótica objetivada na angioTC.

Os autores descrevem o caso de um doente com discrepância entre a extensão da aterosclerose coronária objetivada e a sua estimativa de acordo com os *scores* de probabilidade pré-teste e de eventos cardiovasculares. Tratando-se de um indivíduo com documentação de aterosclerose coronária acima do esperado - *score* de cálcio superior ao percentil 90 e doença coronária não obstrutiva na angioTC cardíaca, mas por outro lado, assintomático e sem fatores de risco nem antecedentes cardiovasculares, com uma estimativa de risco cardiovascular muito baixa e atleta de competição, torna-se difícil decidir acerca do risco/benefício de medidas farmacológicas de prevenção primária.

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MANUSCRIPT 18

KEYWORDS
Cardiac computed tomography;
Non-obstructive coronary artery disease;
Physical exercise

Non-obstructive coronary artery disease documented by cardiac computed tomography: Discrepancy between atherosclerotic burden and cardiovascular risk

Abstract Cardiac computed tomography (CT) documents the presence of coronary artery disease, regardless of the degree of stenosis. The prognostic value of non-obstructive coronary artery disease documented by cardiac CT has recently been validated. However, there are still no clear guidelines on the management of such patients, particularly concerning initiation of more aggressive pharmacological measures for primary prevention. The approach to these patients remains controversial, especially in cases in which there is a discrepancy between cardiovascular risk and the atherosclerotic burden as documented by cardiac CT.

The authors describe the case of a patient with a discrepancy between the extent of documented coronary atherosclerosis and that estimated according to pretest probability and cardiovascular risk scores. As this individual had more severe coronary atherosclerosis than expected (calcium score above the 90th percentile and non-obstructive coronary artery disease on cardiac CT) but was a competitive athlete and otherwise asymptomatic and without risk factors or cardiovascular history, with a very low estimated cardiovascular risk, it was difficult to decide on the risks and benefits of pharmacological primary prevention.

Caso clínico

Descreve-se o caso de um homem de 47 anos, sem fatores de risco cardiovascular ou antecedentes pessoais/familiares relevantes, desportista de alta competição, praticante de *Ironman* – triatlo de longas distâncias composto por natação (3 800 m), ciclismo (180 km) e corrida (42,2 km). O doente negava a toma de medicação regular e o abuso de substâncias aditivas como tabaco, álcool ou estimulantes como sendo esteroides anabolizantes. Na sequência de um quadro de infeção respiratória e a pedido do seu médico assistente (Medicina Geral e Familiar), realizou uma tomografia computorizada (TC) torácica, em que foi relatada como achado extrapulmonar a presença de «calcificação das artérias coronárias». Por este motivo, realizou uma angioTC cardíaca para quantificação da calcificação coronária e exclusão da presença de doença coronária obstrutiva. O *score* de cálcio foi de 226, distribuído por todas as artérias coronárias epicárdicas, com predomínio na artéria descendente anterior proximal (Figura 1). De acordo com os normogramas publicados[1], este valor estava muito acima do esperado para o sexo masculino nesta faixa etária (superior ao percentil 90). Este valor seria o expectável (percentil 50) para um indivíduo na sexta década de vida.

Na aquisição com contraste foi possível excluir doença coronária obstrutiva. Documentou-se a presença de placas mistas, mas predominantemente calcificadas, dispersas por toda a árvore coronária, sobretudo no tronco comum e no segmento proximal da artéria descendente anterior. Foram evidentes placas com remodelagem positiva (Figuras 2 e 3).

Com o resultado deste exame, o doente recorreu a consulta de cardiologia. Encontrava-se assintomático e, ao exame objetivo, não apresentava alterações relevantes: TA 140/80 mmHg, FC 60 bpm, IMC 23,7 kg/m^2; auscultação cardíaca com S1S2 rítmicos, sem sopros e auscultação pulmonar com murmúrio vesicular mantido, simétrico e sem ruídos adventícios audíveis; membros sem edemas periféricos, pulsos distais palpáveis, amplos e simétricos.

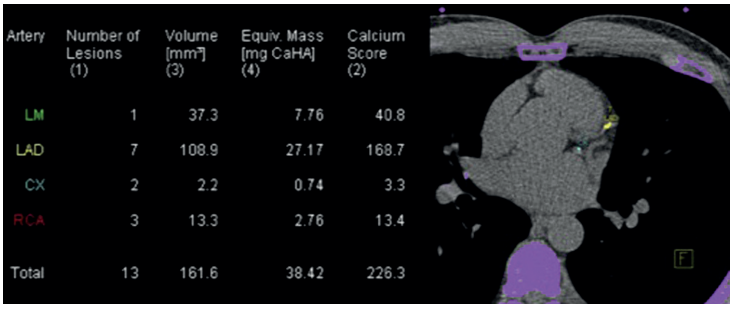
O doente tinha realizado recentemente (há menos de 6 meses) exames laboratoriais, prova de esforço e ecocardiograma, pedidos no âmbito de avaliação em medicina do trabalho. Nos *exames laboratoriais* havia a destacar: hemoglobina 14,0 g/dl, glicemia em jejum 84 mg/dl, colesterol total 217 mg/dl, colesterol LDL 116 mg/dl, colesterol HDL 116 mg/dl e triglicéridos 70 mg/dl. A *prova de esforço* foi efetuada segundo o protocolo Bruce, teve a duração de 21 min, atingiu 19,3 MET, normal evolução cronotrópica (101% da FC máxima prevista) e normal evolução tensional (TA basal 130/80 mmHg e 200/80 mmHg no pico de esforço). Não apresentou queixas durante a realização da prova, nomeadamente angor, nem ocorreram alterações electrocardiográficas sugestivas de isquemia nem disritmias. O *ecocardiograma* revelou alterações típicas de coração de atleta – hipertrofia ventricular esquerda excêntrica ligeira, sem dilatação ventricular, com fração de ejeção e função diastólica normais, assim como dilatação auricular esquerda ligeira (Figura 4).

Pelo cálculo de *scores* de probabilidade de doença coronária, o doente encontra-se numa categoria de baixa probabilidade, sobretudo atendendo à idade e à ausência de sintomas: *Score* de *Diamond-Forrester* – baixa probabilidade; *Score* de *Morise* – *score* 6 (baixa probabilidade se < 8).

O risco de eventos cardiovasculares estimado foi igualmente baixo: *HeartScore* – 1%; *Framingham* – 4%, nomeadamente atendendo à idade, à ausência de fatores de risco e a um perfil lipídico favorável.

Apesar de se tratar de um indivíduo assintomático e com baixo risco cardiovascular, pela presença de doença aterosclerótica coronária na angioTC cardíaca com um *score* de cálcio elevado, além da manutenção de medidas preventivas para o controlo dos fatores de risco cardiovascular, optou-se por iniciar terapêutica farmacológica com estatina (rosuvastatina 5 mg/d). Foi também recomendada a redução da intensidade da prática desportiva, nomeadamente em contexto de alta competição.

MANUSCRIPT 18



Artery	Number of Lesions (1)	Volume [mm³] (3)	Equiv. Mass [mg CaHA] (4)	Calcium Score (2)
LM	1	37.3	7.76	40.8
LAD	7	108.9	27.17	168.7
CX	2	2.2	0.74	3.3
RCA	3	13.3	2.76	13.4
Total	13	161.6	38.42	226.3

Figura 1 *Score* de cálcio – distribuição pelas artérias coronárias epicárdicas. Cx: circunflexa; LAD: descendente anterior; LM: tronco comum; RCA: coronária direita.

Discussão

O caso apresentado descreve um quadro clínico com uma importante discrepância entre a carga aterosclerótica coronária objetivada na angioTC cardíaca e o baixo risco cardiovascular estimado. Este caso levanta várias questões controversas e com resposta ainda inconclusiva, nomeadamente em relação à indicação para realização de angioTC cardíaca e à abordagem de doentes em que se documenta doença coronária não obstrutiva, sendo representativo de um subgrupo de doentes com que cada vez mais somos confrontados e para os quais ainda não existem recomendações claras.

O primeiro passo a adotar na avaliação de um doente com suspeita de doença coronária deve ser a avaliação clínica exaustiva com o cálculo da probabilidade pré-teste para a presença de doença coronária e a estimativa da ocorrência de eventos cardiovasculares. Existem inúmeros *scores* que permitem fazer esta estratificação de risco, sendo os mais usados na determinação da probabilidade pré-teste para a presença de doença coronária o *Diamond-Forrester* e o *Morise* e na estimativa da probabilidade para a ocorrência

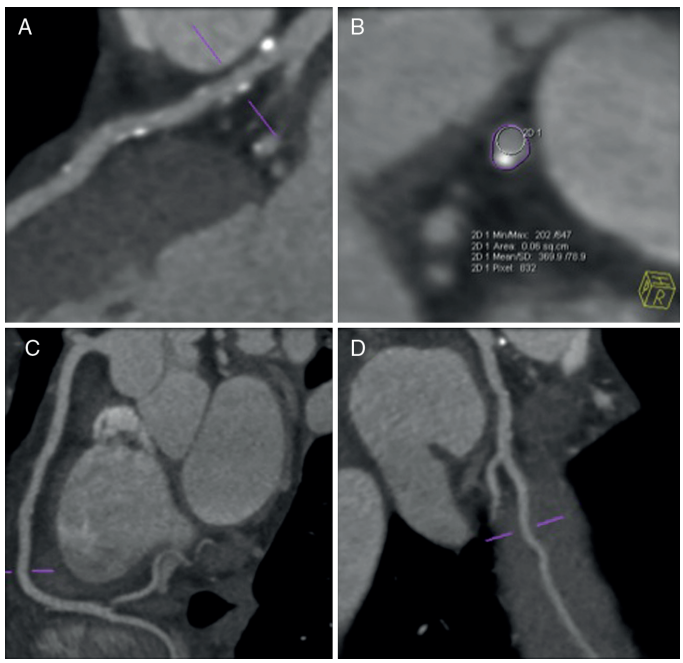


Figura 2 AngioTC cardíaca: A – placas predominantemente calcificadas dispersas no segmento proximal da artéria descendente anterior, sem condicionar estenose significativa; B – placa mista, excêntrica, com remodelagem positiva; C e D – artérias circunflexa e coronária direita (vaso dominante) com placas mistas *minor*, sem estenoses significativas.

MANUSCRIPT 18

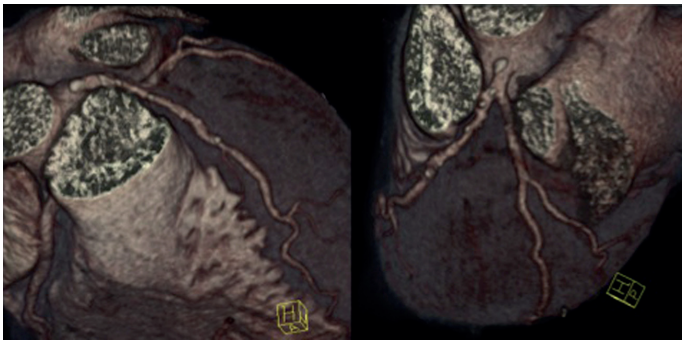


Figura 3 Imagens de reconstrução volumétrica da árvore coronária demonstrando placas ateroscleróticas dispersas na coronária esquerda, não condicionando estenoses significativas.

de eventos cardiovasculares o *HeartScore* e o *Framingham*. O doente em causa, de acordo com todos estes *scores*, encontra-se na categoria de baixa probabilidade de doença coronária e de baixo risco para eventos cardiovasculares.

No caso descrito, o primeiro ponto que importa analisar e discutir é a indicação deste doente para o cálculo do *score* de cálcio e a realização de angioTC cardíaca. Nos doentes assintomáticos e com baixo risco cardiovascular não está indicada a avaliação do *score* de cálcio nem a realização de angioTC cardíaca. Nas recomendações para a avaliação do risco cardiovascular em adultos assintomáticos da *American Heart Association*, neste contexto, ambos os exames têm classe de recomendação III, não devendo, portanto, ser realizados[2]. A maior acessibilidade existente atualmente para o pedido e a realização de exames complementares de diagnóstico leva a que, por vezes, estes sejam realizados de forma indiscriminada e sem indicação, sendo difícil a interpretação dos seus resultados. No caso descrito, após a realização destes exames, o doente passou para um patamar de risco superior ao indicado pelos *scores* de avaliação e de predição de risco cardiovascular. Por um lado, o valor do *score* de cálcio associa-se diretamente a maior mortalidade a longo prazo[3]. Por outro lado, além do pior prognóstico comprovado pela presença de doença coronária obstrutiva determinada

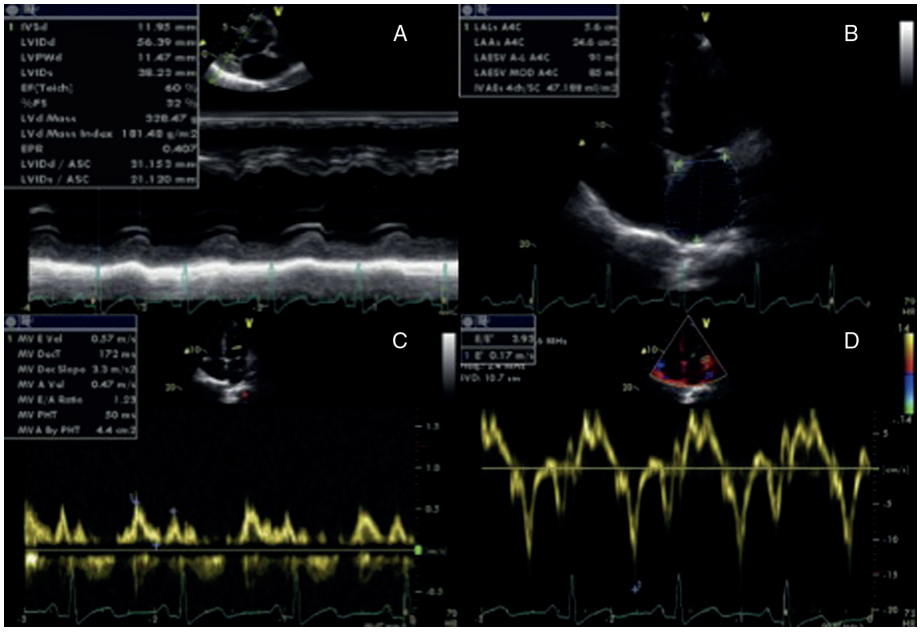


Figura 4 Ecocardiograma transtorácico revelando hipertrofia ventricular esquerda excêntrica (A), dilatação auricular esquerda (B), fluxo Doppler transmitral e padrão de enchimento normais (C e D).

MANUSCRIPT 18

pela angioTC cardíaca, também a presença de doença não obstrutiva se associa a maior mortalidade, comparativamente aos doentes sem estenoses coronárias. Estes dados foram comprovados pelo registo multicêntrico CONFIRM, recentemente publicado, após a análise de 23 854 doentes[4]. Portanto, as alterações encontradas neste doente, *score* de cálcio elevado e placas não obstrutivas, terão impacto negativo no seu prognóstico.

Com estes dados, surge também a questão sobre quais deverão ser as medidas preventivas a implementar. A presença de doença aterosclerótica representa uma manifestação subclínica de doença coronária e pode ser considerada como um *qualifier*, colocando o doente num patamar de risco superior, com indicação para estratégias preventivas diferentes dos doentes com o mesmo perfil de risco, mas sem estas alterações[5]. Independentemente do perfil lipídico, que neste caso é normal, salientando-se mesmo o elevado valor do colesterol HDL, comum em atletas, poderá estar indicado o início de terapêutica farmacológica com estatina, além das medidas preventivas comuns de controlo dos fatores de risco cardiovascular[6,7]. Assim, além do controlo destes fatores de risco através da manutenção de hábitos de vida saudáveis, a estratégia adotada incluiu o início de terapêutica com estatina. Esta atitude advém da comprovada redução do grau de estenose e do volume da placa aterosclerótica nos doentes medicados com estatina[8]. Outra classe farmacológica com benefício comprovado em doentes com doença coronária conhecida são os antiagregantes plaquetários. No entanto, segundo as recomendações da Sociedade Europeia de Cardiologia para a prevenção da doença cardiovascular, deverão ser apenas prescritos aos doentes com doença coronária estabelecida ou risco cardiovascular elevado (*HeartScore* > 10%)[5]. Neste sentido e adicionalmente aos efeitos adversos não desprezíveis destes fármacos, sobretudo num doente potencialmente exposto a eventuais complicações hemorrágicas pelo tipo de desporto que pratica, optou-se pela sua não prescrição.

Outro ponto importante é avaliar a indicação para a suspensão ou redução do exercício físico, nomeadamente em contexto de alta competição. O triatlo, segundo a 36.ª Conferência de *Bethesda*, é um desporto caracterizado tanto por uma elevada intensidade dinâmica como estática[9]. Por outro lado, o *Ironman* (triatlo levado ao extremo) corresponderá a cargas de intensidade ainda mais elevadas. Segundo esta conferência, os atletas de baixo risco cardiovascular com doença coronária, como o caso do doente apresentado, podem realizar desporto competitivo de baixa intensidade dinâmica e de baixa/moderada intensidade estática, mas deverão evitar provas com intensidade competitiva elevada. Nas mesmas recomendações releva-se também o papel do *score* de cálcio na avaliação dos atletas, devendo os cuidados ser acrescidos quando os valores são superiores a 100[9]. Assim, o doente foi aconselhado a suspender provas de alta competição e a reduzir a intensidade do exercício efetuado.

Conclusão

A determinação do risco cardiovascular e da probabilidade pré-teste constituem o primeiro passo na avaliação dos doentes com suspeita de doença coronária. A presença de doença coronária não obstrutiva tem impacto prognóstico, devendo estes doentes, mesmo com risco cardiovascular baixo, ser alvo de medidas preventivas mais intensas. Contudo, a melhor abordagem a adotar, especialmente iniciar terapêutica farmacológica, permanece mal definida. Adicionalmente, na presença de doentes que praticam desporto de alta competição, a controvérsia estende-se ao tipo de recomendação relativamente à redução da sua prática. Provavelmente, a melhor atitude deverá ser a avaliação de cada doente caso a caso, de acordo com o tipo de desporto efetuado e a intensidade do mesmo.

Responsabilidades éticas

Proteção dos seres humanos e animais. Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com os da Associação Médica Mundial e da Declaração de Helsínquia.

Confidencialidade dos dados. Os autores declaram ter seguido os protocolos de seu centro de trabalho acerca da publicação dos dados de pacientes e que todos os pacientes incluídos no estudo receberam informações suficientes e deram o seu consentimento informado por escrito para participar nesse estudo.

Direito à privacidade e consentimento escrito. Os autores declaram ter recebido consentimento escrito dos pacientes e/ou sujeitos mencionados no artigo. O autor para correspondência deve estar na posse deste documento.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

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MANUSCRIPT 18

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MANUSCRIPT 19

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REVIEW ARTICLE

Coronary artery disease in athletes: An adverse effect of intense exercise?

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KEYWORDS
Veteran athletes;
Dose of exercise;
Coronary artery disease;
Coronary computed tomography angiography

Abstract Regular physical exercise is responsible for various health benefits, and is recommended for primary and secondary cardiovascular (CV) prevention. Despite these recognized benefits, various clinical events can occur in athletes, including acute myocardial infarction and sudden cardiac death (SCD); the main cause of SCD in veteran athletes is coronary artery disease (CAD). The relationship between intense exercise training and CAD is controversial, and a U-shaped association has been hypothesized. If this is the case, screening for subclinical CAD in older athletes may be justified, and various different methodologies have been proposed. However, the methodology for screening veteran athletes is not consensual, and several markers of CAD, in addition to clinical CV risk factors, could improve risk stratification in this population. In the present paper we review the published data on CAD in athletes, focusing on the relationship between the dose of exercise and CAD, as well as the implications for pre-participation screening of veteran athletes.

PALAVRAS-CHAVE
Atletas veteranos;
Dose de exercício;
Doença das artérias coronárias;
Angiografia coronária por tomografia computorizada

Doença coronária em atletas: «efeito adverso do exercício físico intenso?»

Resumo O exercício físico associa-se a múltiplos benefícios para a saúde, estando recomendado na prevenção cardiovascular (CV) primária e secundária. Apesar dos benefícios comprovados, diversos eventos clínicos podem ocorrer em atletas, incluindo enfarte agudo do miocárdio e morte súbita, nos atletas veteranos maioritariamente devido a doença das artérias coronárias (DAC). A relação entre exercício físico intenso e DAC permanece controversa, colocando-se a hipótese de associação tipo «curva em U». Neste contexto, a deteção subclínica de DAC em atletas veteranos pode ser justificada, estando propostas algumas metodologias.

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MANUSCRIPT 19

No entanto, a metodologia para a avaliação pré-competitiva dos atletas veteranos não é consensual e diversos marcadores de risco, adicionais aos fatores de risco CV clínicos tradicionais, poderão melhorar a estratificação de risco nesta população. Neste artigo revêm-se os dados publicados sobre DAC em atletas, com relevância para a relação entre a dose de exercício e DAC, bem como as implicações para a avaliação pré-competitiva de atletas veteranos.

Introduction

Regular physical activity and exercise training have various health benefits, and are recommended for primary and secondary cardiovascular (CV) prevention.[1,2] The benefits of exercise are mediated by multiple mechanisms, with favorable impact both in the general population and in patients with established CV disease in the context of cardiac rehabilitation. Among these effects are the prevention and control of various CV risk factors, including reduction in the incidence of obesity and diabetes and improved lipid and blood pressure profiles, as well as reduction of acute coronary events and increased survival.[2]

In response to the constant campaigns promoting the benefits of physical activity and exercise training, the number of people participating regularly in sports has grown in recent decades. Consequently, the spectrum of athletes has widened to include not only young adults, but also children and the elderly, with more individuals taking up regular exercise in middle age and continuing until late in life. Evidence of this tendency is the large number of veteran athletes involved in high dynamic component disciplines such as cycling, marathon, triathlon and Ironman races.[3,4]

Although much is now known about exercise-induced physiological cardiac adaptations, the long-term effects of prolonged and excessive intense exercise training remain unclear. Recent evidence points to a potential U-shaped relationship between the dose of exercise and the occurrence of clinical CV events, which could be related to the presence and severity of coronary artery disease (CAD). This is an important issue, since CAD is responsible for the greatest proportion (approximately 80%) of sudden cardiac death (SCD) in veteran athletes, a less studied athletic population.

The recent development of new CV imaging tests, including non-enhanced cardiac computed tomography (CT) with calcium scoring (CS) and enhanced cardiac CT (coronary CT angiography [CCTA]), has enabled non-invasive detection and better characterization of the presence and severity of CAD.[5] This could be a game-changer for risk stratification in veteran athletes, changing the paradigm from traditional stratification based on clinical CV risk factors and exercise electrocardiographic testing, which has well-known limitations.[6]

In the present paper we review the published data on CAD in athletes, focusing on the relationship between the dose of exercise and CAD, the potential mechanisms involved and the implications for pre-participation screening of veteran athletes, highlighting the role of CS and CCTA.

The paradox of sudden cardiac death in athletes

Despite the proven benefits of regular physical exercise and although athletes are the paradigm of healthy individuals, this population is not risk-free and can suffer severe clinical conditions including SCD.[5,7] Although SCD is uncommon in young athletes (incidence 2-5/100 000 per year), it is a tragic event, with high visibility due to media attention. Most sports-related cardiac arrests occur in individuals not performing regular exercise, and in epidemiological terms, SCD during sports accounts for only a small proportion of cases in the general population.

Several studies have confirmed both the increased risk of exercise-associated myocardial infarction and SCD and the beneficial effect of regular exercise in risk reduction. Data from Italy revealed a 2.8-fold greater risk of SCD in young competitive athletes compared to non-athletes.[8] However, it should be stressed that exercise is not the cause of death, but is a precipitating factor in susceptible individuals with previously undiagnosed cardiac disease. It should also be recognized that the overall beneficial effects of exercise in the population outweigh the increased risk.

In young athletes the most common causes of SCD are hereditary diseases, mainly cardiomyopathies and primary arrhythmic diseases, while in veteran athletes the great majority is caused by CAD.[5,9–12] For the purpose of this paper, we define a veteran athlete as an individual more than 35 years old participating in sports at a competitive level or as a leisure activity. The majority of sports-related SCD occurs in older athletes, but as many of the deaths are unwitnessed, the magnitude of the problem is probably underestimated.[12] Beyond the difference in the athletes' age, other important epidemiological features of SCD in athletes are the higher frequency in males (9:1 to females) and occurrence during or immediately after exercise and mainly in high dynamic component sports.[5]

Identification of athletes with higher CV risk is a crucial goal of pre-participation screening.[13,14] Although controversial, due to the long-standing disagreement between Europe and the US, the methodology recommended by the European Society of Cardiology (ESC) for screening of young athletes includes medical history (personal and family), physical examination, and 12-lead electrocardiogram (ECG).[13] Central to the disagreement is the ECG, due to the high rate of false positive results. The main question is not whether the ECG should be included, but how it should be interpreted; the adoption of more restrictive criteria decreases the false-positive rate without reducing sensitivity and with

MANUSCRIPT 19

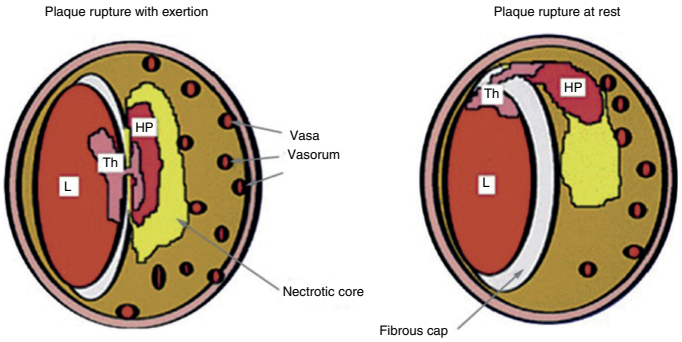

Figure 1 Comparison between coronary plaque rupture with exertion and at rest (reprinted from Burke et al.[22]). HP: hemorrhage into plaque; L: lumen; Th: thrombus.

a favorable impact on cost-effectiveness.[15–19] Regarding the pre-participation screening of veteran athletes the controversy is greater, as will be discussed below.

Coronary artery disease in athletes

SCD or acute myocardial infarction may be the first clinical presentation of CAD. The rupture of non-obstructive coronary plaques is the most common pathophysiological mechanism involved, which explains the previous absence of symptoms such as angina, usually present in individuals with obstructive CAD.[9,20,21] Superficial plaque erosion and intraplaque hemorrhage are other mechanisms associated with coronary plaque instability, but ischemia due to an imbalance between oxygen supply and demand has also been described as one of the main causes of acute exercise-related cardiac arrest.[20]

Plaque rupture during exertion typically occurs in the central part of a thin fibrous cap with numerous vasa vasorum, while plaque rupture at rest occurs more in the periphery, at the junction between the fibrous cap and the arterial wall (Figure 1).[12,22]

Although the concept of advanced atherosclerosis in veteran athletes is somewhat counter-intuitive, various stress factors and pathophysiological mechanisms induced by chronic and extreme endurance exercise may play a critical role.

Among the potential mechanisms triggering exertion-related acute coronary syndromes are increased thrombogenicity, sympathetic activation, electrolyte imbalance, hyperdynamic circulation, shear stress and imbalance between the antioxidative and oxidative effects of exercise.[12] An analysis performed in men with CAD exposed to physical exercise showed an improvement in antioxidant and vascular effects, a benefit which can be blunted with increased exercise intensity.[23] Intense and prolonged exercise increases oxidative stress and release of inflammatory mediators such as oxygen free radicals and cytokines, a process documented in patients with CAD. Beyond the potential involvement of these exercise-related factors, it should be borne in mind that, as in the general population, the development of CAD in athletes is multifactorial, and can be affected by clinical CV risk factors, genetic predisposition, normal aging processes, infections and toxins (Figure 2).

Exercise training leads to the release of cardiac biomarkers, particularly troponin, an invaluable tool for the assessment of patients with myocardial infarction. In the context of exertion, this appears to be a benign process, but the underlying mechanisms are still poorly understood. Troponin elevation is likely to result from increased myocyte turnover, cellular release of proteolytic troponin degradation products, cellular wall permeability and formation and release of membranous blebs.[24–26] Interestingly, the extent of troponin release is strongly related to intensity of exercise, and it is not clear if recurrent episodes would lead to long-term adverse cardiac effects.

Even with lower incidences, it is important to emphasize that besides the atherosclerotic process, there are other coronary abnormalities associated with SCD in athletes that should be considered and excluded, such as anomalous coronary artery origin, vasospasm, bridging, coronary dissection and vasculitis, which are beyond the scope of the present review.[27,28]

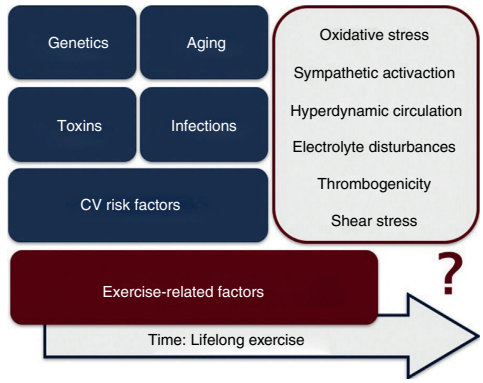

Figure 2 Factors potentially involved in the development of coronary artery disease in athletes. CV: cardiovascular.

MANUSCRIPT 19

Potential CV effects of intense exercise	
Acute CV risks	↑ Risk for SCD
	↑ Risk for acute myocardial infarction
	↓ Ventricular systolic function
Myocardial injury	↑ Release of cardiac enzymes
	↑ Release of natriuretic peptides
	↑ Myocardial fibrosis
Cardiac remodeling	↑ Left and right ventricular dimensions
	↑ Left and right atrial dimensions
	↑ Ventricular wall thickness
Clinical implications	↑ CAD
	↑ Risk for atrial fibrillation
	↑ Exercise-induced ARVC
	↓ Risk for CV mortality

Figure 3 Potential cardiovascular effects of regular intense exercise training. ARVC: arrhythmogenic right ventricular cardiomyopathy; CAD: coronary artery disease; CV: cardiovascular; SCD: sudden cardiac death.

Relationship between amount of exercise and coronary artery disease

The relationship between amount of exercise and CAD is still not well established. In principle, as a drug becomes ineffective at a dose below that recommended, or toxic in the case of overdose, the same could happen with physical exercise. It is known that relatively modest doses of regular exercise are sufficient to induce benefits, but the upper limit above which the adverse effects outweigh the benefits has not been determined.[29–32] There is emerging evidence that with increasing doses of exercise, the relative benefits decrease.[30] Humans may not be genetically adapted for sustained intense exercise, and if so, it is worth considering how much exercise could actually be harmful and what the desired therapeutic window of exercise would be.

Extreme exercise leads to various cardiac changes (histological, structural and functional). These are mainly physiological adaptations, but maladaptation can also occur, increasing susceptibility to atrial and ventricular arrhythmias. Myocardial fibrosis, inflammation, marked ventricular remodeling and accumulation of coronary calcium are potentially related to extreme exercise (Figure 3).

Some authors have argued that there exists a type of cardiotoxicity induced by extreme exercise, and the relationship between dose of exercise and incidence of clinical events has been described as a U-shaped curve.[33,34] Moderate exercise appears to be better than none, but vigorous exercise may actually be harmful, at least for some individuals. From a public health perspective, we emphasize that although these findings raise some concerns about the benefits of high-end endurance sports, they do not undermine the substantial beneficial effects of regular exercise on all-cause mortality in the vast majority of older athletes.

Regarding mortality, this U-shaped relationship is clear for running distances, speeds and frequencies.[35] In the Copenhagen City Heart Study,[36] moderate joggers had lower

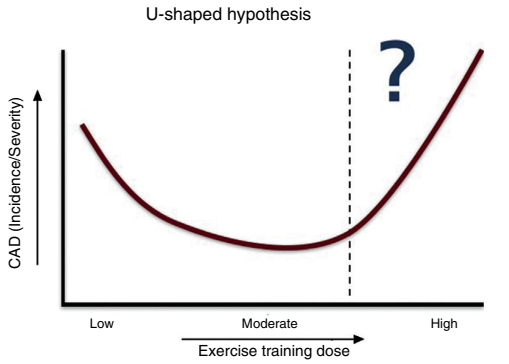

Figure 4 Hypothetical representation of the relationship between the dose of exercise and the incidence and severity of coronary artery disease. CAD: coronary artery disease.

mortality than sedentary nonjoggers and strenuous joggers. Although the evidence is weaker, the same relationship has been proposed for the presence and severity of CAD (Figure 4). In fact, the dose of exercise has a central role, as most cardiac arrests during marathons occur in the last quartile of races, although this could also be explained by cumulative electrolyte disturbances during the race.[37]

In daily clinical practice, it is not uncommon to identify athletes with a higher than expected atherosclerotic burden. Figure 5 illustrates a CCTA of an asymptomatic 47-year-old male competitive Ironman athlete, with a discrepancy between total CV risk based on SCORE (<1%) and extent of CAD.[38]

The potential association between intense exercise training and CAD does not appear to be an incidental finding. In recent years, several authors have described a higher than expected CAD incidence and severity in veteran athletes involved in endurance sports. Mohlenkamp et al.[39] studied 108 veterans who ran at least five marathons over the previous three years, compared with a control group of non-athletes. CS was similar in both groups with adjustment for age, but significantly higher in the athletes after adjustment for Framingham risk score (mean CS: 36 vs. 12, p=0.02; CS ≥100: 36% vs. 22%, p=0.01; CS >percentile 75: 25% vs. 15%, p=0.01). During a mean follow-up of 21 months, athletes with CS ≥100 had a higher rate of CV events. Tsiflikas et al.[40] studied male marathoners aged over 45 years and detected CAD in half of them, including 24% with plaques in the proximal coronary segments. Merghani et al.[41] documented a U-shaped curve for the relationship between dose of exercise and CS in veteran athletes. A CS >percentile 70 was two or three times more frequent in athletes training >30 miles/week vs. <20 miles/week (39% vs. 13%; p=0.037). In the recent published MARC study,[42] CCTA detected occult CAD in almost one in five asymptomatic sportsmen aged ≥45 years after a normal sports medical evaluation that included resting and exercise ECG. The number needed to treat in order to prevent one CV event compares favorably to that of other screening tests.

Despite these findings, several questions remain unanswered. These results imply that endurance athletes may not be protected from accumulation of coronary calcium,

MANUSCRIPT 19

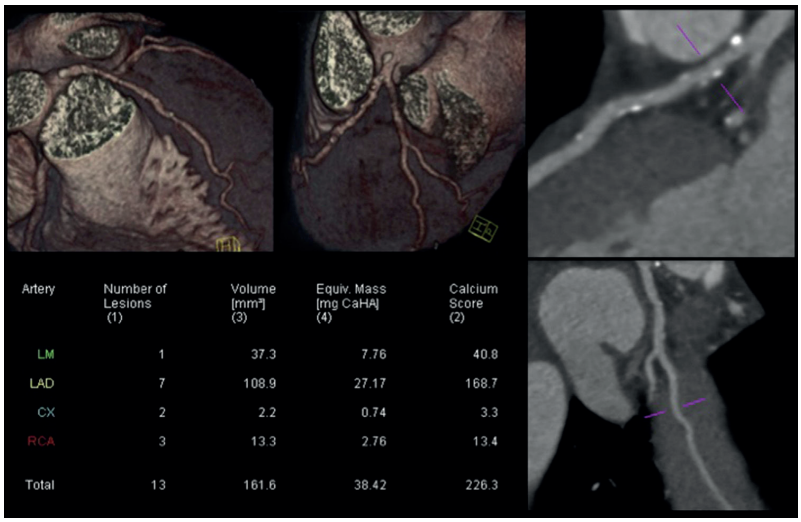

Figure 5 Coronary computed tomography angiography of a competitive Ironman veteran athlete with low cardiovascular risk based on SCORE (<1%), but with a higher than expected atherosclerotic burden (calcium score >percentile 90), with plaques in all the epicardial coronaries, including >5 segments with plaque (segment involvement score >5) and involvement of the left main and proximal left anterior descending arteries (adapted from Dores et al.[38]).

but it is important to recognize that the evidence does not show that endurance athletics has an adverse impact on either CS or CV events.[12] It should also be emphasized that as well as being few in number, the published studies show inconsistencies: different inclusion criteria, regular exercise training begun at different ages, small samples, and different characterizations of exercise training.[43] This issue requires a thorough analysis and more evidence, and is an emerging area of research in sports cardiology.

Cardiovascular risk stratification of veteran athletes

The epidemiological differences between young and veteran athletes justify the adoption of different pre-participation screening methodologies in the two groups. The large number of middle-aged individuals engaged in leisure-time sports makes the screening of this population an emerging task. Although the main cause of SCD in veteran athletes is coronary events, the focus of this screening should rule out subclinical CAD.[12,44] Currently, a stepwise approach is suggested for the assessment of middle-aged/senior individuals involved in leisure or competitive sports:

- Step 1: Self-assessment using pre-specified questionnaires;
- Step 2: Assessment by a physician (personal and family history, physical examination, SCORE calculation and resting ECG);
- Step 3: Maximal exercise testing.

The identification and management of CAD in asymptomatic individuals (athletes or non-athletes) is a difficult task and there is still no agreement on the correct approach to adopt.[45] Total risk estimation using multiple risk factors is recommended by the ESC for asymptomatic adults without evidence of CV disease (class I, level of evidence C).[2] However, the predictive capacity of this conventional methodology based on clinical scores such as the Framingham risk score and SCORE is modest, failing to identify a significant proportion of individuals with established CAD. If these scores had been calculated on the day before an acute myocardial infarction, most patients would have had low-moderate risk, without indication for the implementation of preventive or therapeutic measures.[46–48]

Regarding the CV assessment of middle-aged/senior individuals engaged in leisure-time sports, the ESC recommends self-assessment of habitual physical activity level and risk factors, followed by SCORE calculation. Individuals with an increased risk for coronary events embarking on moderate/intense physical activity should undergo a maximal exercise test and possibly further cardiac investigation.[49] Although this methodology may be valid in veteran athletes, it does not take into consideration specific characteristics such as dose of exercise, type of sport and length of exercise training. It seems obvious that more intensive investigation should be performed in athletes with moderate-high CV risk, particularly for those who are naïve or involved in high-level endurance sports. The main question is which further investigations should be performed.

Despite its recognized prognostic value, the utility of the ECG for screening asymptomatic subjects without known CAD is limited. Up to half of individuals with angiographically normal coronary arteries show changes on the ECG, one-third of those with CAD have normal baseline ECG, and the majority of coronary events occur in the absence of prior electrocardiographic abnormalities. In addition, all stress

MANUSCRIPT 19

tests, by definition, depend on the presence of obstructive CAD and therefore they are not designed to detect nonobstructive CAD, which has been associated with worse CV outcome in several CCTA studies.[50–54]

Usually, athletes with high CV risk undergo an exercise ECG test, an exam of established prognostic value, widespread availability and low cost. Several studies have reported an increased relative risk of coronary death for asymptomatic subjects with a positive test. However, the accuracy of exercise testing for CAD detection in populations with low pretest probability, such as asymptomatic athletes involved in high-intensity sports, is limited.[55–57] To overcome some of these limitations the measurement of biomarkers (e.g. high-sensitivity C-reactive protein and natriuretic peptides) has been proposed, but the gain in CAD detection and the practical applicability were low.[58,59]

Apart from the conventional scores based on clinical risk factors, it is known that some risk modifiers detected by emerging tests such as CS and carotid atherosclerotic plaque detection can improve the calculation of total CV risk.

The role of calcium score and cardiac computed tomography in screening veteran athletes

Determination of total atherosclerotic burden is an option for screening veteran athletes, helping to detect coronary calcifications, a recognized marker of subclinical atherosclerosis. CS is a non-invasive marker of CAD with proven prognostic impact, predicting CV events and death, independently of and incremental to conventional risk factors.[60–63] CS is a risk modifier that can be considered in individuals with SCORE around 5%-10%. In the PESA study[64] in individuals aged 40-54 years, 63% had subclinical atherosclerosis after assessment of multivascular territories, and CAD was detected in 18% of individuals, most of them with low SCORE. The landmark MESA study[65] showed superior discrimination and reclassification of CV risk in intermediate-risk individuals using subclinical markers. CS had higher predictive power than other markers such as carotid intima-media thickness and ankle-brachial index, in agreement with the results of the Rotterdam study.[66] Additionally, CS improves the adoption of preventive measures, leading to better control of several CV risk factors, as shown in the EISNER study.[67,68]

It is important to stress that not all coronary plaques are calcified, nor is CS an indicator of plaque instability. Moreover, although much less frequent than calcified or mixed plaques, non-calcified plaques are more prone to instability leading to acute coronary events. In this context, CCTA provides useful additional information, enabling better characterization of the coronary tree and plaques.[26,69] Beyond obstructive CAD, the presence and quantity of non-obstructive plaques also has prognostic value, as shown in the CONFIRM registry[70] and in other CCTA studies using atherosclerotic burden indices like the segment involvement score[53] or the CT-adapted Leaman score (CT-LeSc).[54] The comprehensive information provided by CCTA, including location, type and number of plaques, can be clustered in CCTA atherosclerotic burden scores like the CT-LeSc,[71] which can help identify individuals with nonobstructive CAD at higher risk of CV events and therefore contribute to risk stratification.[54]

A recent study by Ermolao et al.[57] in asymptomatic middle-aged athletes with ST-segment anomalies during maximal exercise test (diagnostic or equivocal) revealed CAD in only 32% of the subjects. In the MARC study,[42] in 318 middle-aged sportsmen with low SCORE who underwent CCTA following normal pre-participation screening, 94% had low CV risk and 18.9% had CAD (CS ≥100 or ≥50% luminal

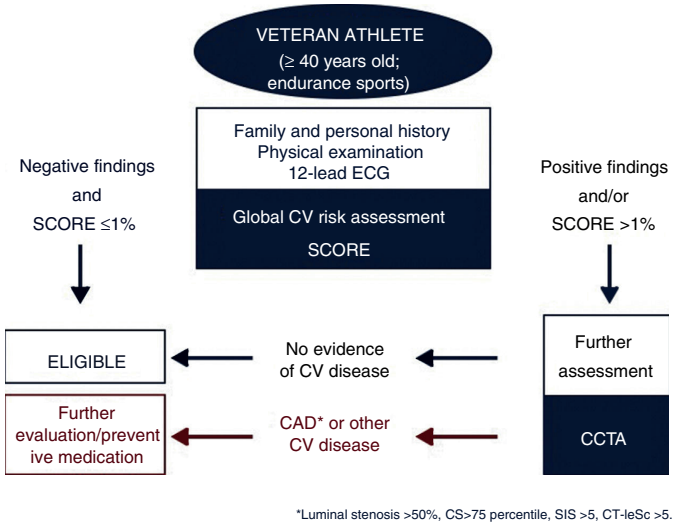

Figure 6 Algorithm proposed for veteran athlete screening. CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CT-LeSc: computed tomography-adapted Leaman score; CV: cardiovascular; ECG: electrocardiogram; SIS: segment involvement score.

MANUSCRIPT 19

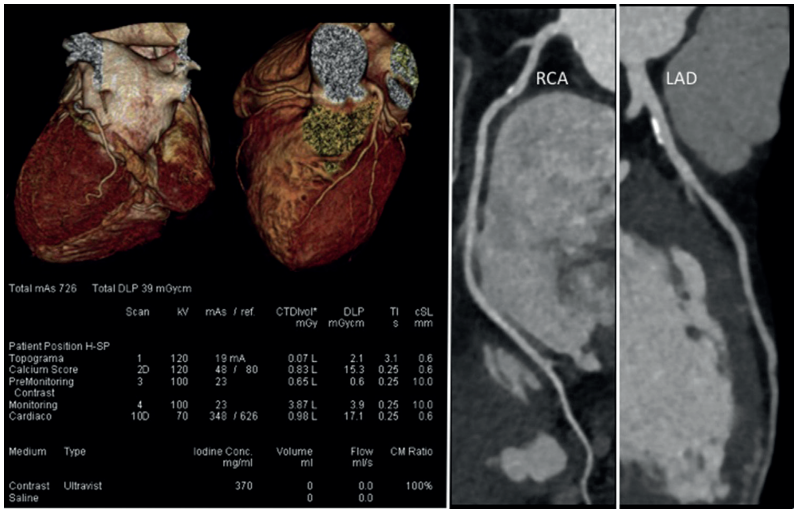

Figure 7 Coronary computed tomography angiography of a non-competitive athlete performed with a new-generation scanner (SOMATOM Force, Siemens Healthcare), using an ultra-low radiation dose of 0.5 mSv. Left: volume rendering technique images and study protocol; middle: nonobstructive mixed plaque in the proximal segment of the right coronary artery; right: nonobstructive calcified plaque in the proximal left anterior descending artery. LAD: left anterior descending artery; RCA: right coronary artery.

stenosis), almost one in five individuals. In this setting, some authors have proposed the inclusion of CCTA in the screening of veteran endurance athletes with moderate-high CV risk. However, as Braber et al.[42] showed, even veteran athletes with low CV risk could benefit from CCTA, increasing the controversy concerning the target population of this exam. Based on these data, mainly derived from studies performed in athletes aged >40 years involved in endurance sports and with a wide spectrum of CV risk (including low risk), a hypothetical flowchart for veteran athletes screening is proposed in Figure 6.

Another important feature of CCTA is the ability to detect other important coronary abnormalities in the screening of athletes, such as malignant variants of anomalous origin of the coronaries and coronary bridging, both described as possible causes of SCD in athletes.

In addition, and also of considerable importance, recent technological developments in scanner technology (both hardware and software) have led to impressive reductions in radiation dose, the main limitation of CCTA.[72,73] Figure 7 presents an example of a CCTA performed with a new-generation scanner, showing high image quality with ultra-low radiation and contrast doses (0.5 mSv and 50 cc, respectively).

Finally, although we have reviewed the published evidence linking physical exercise and the presence and severity of CAD, several issues remain unanswered and warrant further research. It is the view of the authors that although CV risk stratification of veteran athletes is at present still based on traditional risk factors and rest ECG, cardiac CT may play a role in the future. To clarify this important issue, further research is needed focusing on three lines of investigation: first, to explore the possible U-shaped association between the dose of exercise and CAD; second, to establish the added value of CS and CCTA in screening of veteran athletes; and third, to demonstrate that the use of these newer CT-based imaging modalities can further improve risk stratification of this important subset of presumed healthy individuals, who may in fact be at risk of CV events.

Conclusions

The benefits of exercise in the overall population are indisputable, but in athletes with CV disease exercise can also be associated with adverse clinical events, including SCD. In veterans, a growing group of athletes, CAD is the most common cause of SCD, and there appears to be an U-shaped relationship with the dose of exercise. Detection of subclinical CAD should be the main objective of veteran athlete screening, since the performance of classical CV risk stratification based on clinical factors appears to be suboptimal. Emerging data show an important role for CS and CCTA in this setting. Coupled with the impressive technical improvements in scanner technology in recent years, these have the potential to make cardiac CT a game-changer in the risk stratification of veteran athletes, with the ultimate goal of reducing the burden of CV events in this population, and should be the focus of further investigation in the near future.

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MANUSCRIPT 20

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Coronary atherosclerotic burden in recreational male veteran athletes with low to intermediate cardiovascular risk

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Abstract:	Background Although the evidence describing a significant proportion of veteran athletes with coronary atherosclerotic disease (CAD), its prevalence in recreational athletes with low-intermediate cardiovascular (CV) risk is not established. This study sought to characterized the coronary atherosclerotic burden in recreational veteran male athletes with low-intermediate CV risk. Methods Asymptomatic male athletes aged ≥40 years old with low-intermediate risk, who exercised >4 hours/week for >5 years, underwent cardiac computed tomography (CT) - coronary artery calcium (CAC) score and angiography. High coronary atherosclerotic burden was defined as at least one of: CAC score >100; CAC score ≥75th percentile; obstructive CAD; disease involving left main, 3-vessels or 2-vessels including proximal anterior descending artery; segment involvement score >5; CT-adapted Leaman score ≥5. Athletes were categorized by tertiles of volume of exercise, calculated by Metabolic Equivalent Task (MET) scores. Results

MANUSCRIPT 20

	A total of 105 athletes were included, all with SCORE <4%, mainly engaged in high-dynamic sports. The median volume of exercise was 66 [44; 103] METs/h/week, with 8±5 hours-training/week and 17±10 years of exercise. A high coronary atherosclerotic burden was present in 27 (25.7%) athletes. Ten (9.5%) athletes had CAC score >100, 13 (12.4%) ≥75th percentile and 6 (5.7%) obstructive lesions. The extension and severity of coronary plaques did not differ according to the volume of exercise. Conclusions The prevalence of subclinical CAD detected by cardiac CT in recreational male veteran athletes with low-intermediate CV risk was high. Up to a quarter of our cohort had a high coronary atherosclerotic burden.

MANUSCRIPT 20

Coronary atherosclerotic burden in recreational male veteran athletes with low to intermediate cardiovascular risk

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MANUSCRIPT 20

Conflits of interest statement

- All the authors declare **NO** conflits of interest regarding this study.

MANUSCRIPT 20

Abstract

Background: Although the evidence describing a significant proportion of veteran athletes with coronary atherosclerotic disease (CAD), its prevalence in recreational athletes with low-intermediate cardiovascular (CV) risk is not established. This study sought to characterized the coronary atherosclerotic burden in recreational veteran male athletes with low-intermediate CV risk.

Methods: Asymptomatic male athletes aged ≥40 years old with low-intermediate risk, who exercised >4 hours/week for >5 years, underwent cardiac computed tomography (CT) - coronary artery calcium (CAC) score and angiography. High coronary atherosclerotic burden was defined as at least one of: CAC score >100; CAC score ≥75th percentile; obstructive CAD; disease involving left main, 3-vessels or 2-vessels including proximal anterior descending artery; segment involvement score >5; CT-adapted Leaman score ≥5. Athletes were categorized by tertiles of volume of exercise, calculated by Metabolic Equivalent Task (MET) scores.

Results: A total of 105 athletes were included, all with SCORE <4%, mainly engaged in high-dynamic sports. The median volume of exercise was 66 [44; 103] METs/h/week, with 8±5 hours-training/week and 17±10 years of exercise. A high coronary atherosclerotic burden was present in 27 (25.7%) athletes. Ten (9.5%) athletes had CAC score >100, 13 (12.4%) ≥75th percentile and 6 (5.7%) obstructive lesions. The extension and severity of coronary plaques did not differ according to the volume of exercise.

Conclusions: The prevalence of subclinical CAD detected by cardiac CT in recreational male veteran athletes with low-intermediate CV risk was high. Up to a quarter of our cohort had a high coronary atherosclerotic burden.

Key-words: Veteran Athletes; Coronary Artery Disease; Risk Stratification.

MANUSCRIPT 20

Introduction

The cardiovascular (CV) benefits of physical activity and exercise training are established.[1,2] Participation in organized sports activities at recreational and competitive level, has grown among middle age individuals in the last decade. Additionally, the number of veteran athletes engaging in lifelong high dynamic sports is increasing.[3]

There is emerging evidence that veteran athletes (>40 years old) with a low atherosclerotic risk profile have a higher coronary artery calcium (CAC) score compared with relatively sedentary counterparts of similar age and atherosclerotic risk profile.[4]

Additionally, recent studies report a positive relationship between the prevalence of atherosclerotic coronary artery disease (CAD) and intensity of exercise. These studies have focused largely in competitive athletes of whom many have achieved national or international recognition, but most deaths in sport occur in recreational male athletes in the 5th decade and up to 80% are accounted by CAD.[5-8] The prevalence of CAD in recreational veteran athletes with a low to intermediate risk profile has not been characterized, but the CAC score in individuals with an intermediate atherosclerotic risk has a significant prognostic value compared with conventional clinical risk factors.[9-15]

This study aimed to characterize the coronary atherosclerotic burden by cardiac computed tomography (CT) in veteran athletes with low to intermediate CV risk.

Methods

Study design and population

Male veteran athletes (≥40 years old) who have been participating in regular systematic recreational exercise for at least 4 hours/week for a minimum of 5 years, were enrolled in this observational study performed in two centers. Athletes with symptoms, diabetes mellitus, a Systematic Coronary Risk Estimation (SCORE) ≥5%, renal impairment or previous allergy to iodinated contrast agents were excluded. The initial assessement regarding eligibility to participate was performed in a sports cardiology clinic, with physical evaluation, documentation of demographic, anthropometric, atherosclerotic risk factors, family history and sports history. The CV risk factors included were: family history of premature CV disease (first degree relatives <50 years old), smoking (current if smoking in the last year), hypertension (≥140/90mmHg or treatment with antihypertensive

MANUSCRIPT 20

medications) and dyslipidemia (LDL cholesterol ≥115mg/dl or treatment with lipid lowering medications). These characteristics were evaluated and integrated in the SCORE charts.[16] All athletes underwent blood tests, 12-lead resting electrocardiogram, transthoracic echocardiogram and exercise testing. The study was approved by the ethics committees and all individuals gave their informed consent for participation.

Exercise evaluation

The volume of exercise was calculated by the Metabolic Equivalent Task Score (MET-hour/week), representing the product of intensity, frequency and duration of exercise. The intensity of exercise was established by the METs for each reported sport according to the Compendium of Physical Activities.[17] The frequency of exercise was defined as the number of training sessions performed per week, whereas the duration was defined by the number of hours spent in each workout. The volume of exercise training was classified by tertile. Sports disciplines were grouped according to the Mitchell classification[18], being especially registered the sports characterized by high dynamic (class C) and high static (class III) components. We also registerd the participation in organized competitions and the number of years of continuous exercise training, being specifically identified the athletes exercising more than 20 years.

Coronary CT Angiography

Coronary atherosclerotic burden was evaluated by CAC score and coronary CT angiography (CCTA), using multi-detector row CT scanners consisting of 64-rows or greater (Somatom Force and Somatom Perspective, Siemens Healthcare, Inc), in order to minimize the dose of radiation and contrast. Except in the presence of contraindications, sublingual nitroglycerin (0.5mg) was administered, and beta-blockers when appropriate (heart rate >65bpm). Both a cardiologist and a radiologist with level III-equivalent experience analyzed all scans processed on a workstation (Syngo.via, Siemens, Healthcare, Inc); abnormal findings were reviewed by consensus.

CAC score was analysed in absolute terms and also expressed as a percentile value, according to normograms adjusted for age, gender and ethnicity.[19] The presence of coronary plaque, plaque morphology, plaque distribution (Society of Cardiovascular Computed Tomography classification[20]) and degree of stenosis was ascertained with CCTA to calculate

MANUSCRIPT 20

the segment involvement score (SIS) and CT-adapted Leaman score (CT-LeSc).[21-23] SIS is a semiquantitative measure of atherosclerotic burden, representing the number of coronary segments with plaques, being considered significant if involving more than five segments. As previously described, CT-LeSc calculation is based on three sets of weighting factors provided by CCTA: 1) localization of plaques in the coronary tree, taking into account the dominance; 2) type of plaque; 3) degree of stenosis.[22] A CT-LeSc ≥5 was defined as a significant value. To identify the athletes with higher atherosclerotic burden, it was created a variable combining the presence of at least one of the following characteristics: CAC score >100 Agatston Units (AU); CAC score >75th percentile; obstructive CAD (luminal stenosis ≥50%); presence of plaques in left main, three vessels or two vessels involving the proximal anterior descending artery (LM-3v-2vpLAD); SIS >5; CT-LeSc ≥5.

Statistical analysis

All analyses were performed using SPSS for Mac version 23.0 (SPSS, Inc., Chicago, IL). Normality was tested with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as means and standard deviation and non-normal variables as median (interquartile range [IQR]). Categorical variables were expressed as frequencies and percentages. Statistical comparison was performed using the chi-square test or Fisher's exact test, when appropriate for categorical variables, and Mann-Whitney or Kruskal-Wallis test for continuous variables. A p value <0.05 was considered statistically significant.

Results

Demographics, clinical and exercise history

A total of 105 athletes were studied (Table 1). Almost all athletes (98.1%) were white. The mean age was 48±6 (41-61) years old, 60% aged between 40 years-old and 50, and 40.0% above 50 years-old. The majority of athletes (N=56; 53.3%) had low CV risk (SCORE=0), while the remainder had an intermediate risk SCORE between 1-3% (SCORE=1 in 73%). Forty-nine (46.7%) athletes had at least one CV risk factor, mainly dyslipidemia which was present in 43 (41.0%). Most athletes were engaged in sports modalities characterized by high-dynamic exercise (N=88; 83.8%), especially running (N=67 - 9 short, 41 middle and 17 long distance), cycling (N=11) and weight lifting (N=10); approximately a quarter (N=26;

MANUSCRIPT 20

exercise was 66 [44; 103] METs/h/week, with a mean number of 8±5 hours-training/week (16.2% >10 hours) and a mean number of 17±10 years (31.4% with continuous training >20 years).

Cardiac computerised tomography

The total average dose of radiation and contrast were 2.7±1.8mSv and 110±19ml, respectively. There were no major adverse reactions during CCTA. Cardiac CT results are shown in Table 2. Sixty-two (59.0%) athletes had zero CAC score. Ten (9.5%) athletes had a CAC score >100 AU and 13 (12.4%) had a CAC score exceeding the 75th percentile. Forty-four (41.9%) athletes had coronary plaques of which 6 (5.7%) had obstructive lesions. Among athletes with CAD, 10 (22.7%) had LM disease (7 with concomitant lesions in other arteries), 4 (9.1%) had 3-vessel disease, 10 (22.7%) had 2-vessel disease and 20 (45.5%) had single-vessel disease. Twenty-four (22.9%) athletes had lesions in LM-3v-2vpLAD.

A total of 107 plaques were distributed throughout the coronary tree, 51 (47.7%) in LAD, 26 (24.3%) in right coronary artery, 20 (18.7%) in circumflex and 10 (9.3%) in LM. The majority of these coronary plaques were calcified (73.8%), while 23.4% were of mixed morphology and 2.8% were non-calcified. The median SIS was 2 segments and median CT-LeSc 3.1 [2.2; 5.4]; 4 (3.8%) athletes had SIS >5 and 16 (15.2%) had CT-LeSc ≥5.

In combination, a high coronary atherosclerotic burden was present in 27 (25.7%) athletes (Figure 1). Among athletes with this high coronary atherosclerotic burden, 11 (40.7%) had at least one CV risk factor and only 6 (22.2%) had significant abnormal findings on exercise testing, of which 3 (11.3%) were positive for myocardial ischemia.

Althought not statistical significant, a high coronary atherosclerotic burden was more common in the 1st and 3rd tertiles of the volume of exercise (1st tertile <50METs/h/week, 2nd tertile 50-99METs/h/week and 3rd tertile ≥100METs/h/week) (Figure 2). The distribution of plaques in coronary tree (Figure 3) and the several cardiac CT-derived indices (Figure 4) were not significant different according to the volume of exercise - low (1st tertile) *Vs.* high (3rd tertile).

CCTA detected anomalous origin of coronary arteries in two athletes (right coronary artery with origin in left ostia and interarterial course; circumflex artery with origin in right ostia with shared ostium) and myocardial bridging in three athletes, all located in median segment of LAD.

MANUSCRIPT 20

Athletes with higher than expected coronary atherosclerotic burden were given lifestyle recommendations and advised to contact their general practioner. Thirteen athletes were commences on a statin. Participants with obstructive lesions underwent myocardial perfusion scintigraphy and no myocardial ischemia was detected. In general, athletes who were found significant CAD were not discouraged from continuing exercising, but were advised to to refrain from vigorous exercise. The athlete with malignant origin of coronary artery had not documented ischemia and was advised to limit exercise training to sports with low intensities.

Discussion

In the present study of predominantly recreational male veteran athletes and with a low to intermediate atherosclerotic risk profile, the prevalence of subclinical CAD detected by cardiac CT was relatively high. A quarter of the population had high coronary atherosclerotic burden.

Prevalence of CAD in veteran athletes

This paradoxical high prevalence of CAD in athletes has also been reported in previous studies. The Marathon Study[4] performed in 108 marathon runners showed higher CAC scores compared with non-runners when matched for Framingham risk score. In this study, a significant proportion of athletes had established risk factors for CAD.

Among 50 male marathon runners studied by Tsiflikas et al[5], half had CAD, 8% had moderate to significant disease and 10% had CAC score >100 AU, which is similar to our results. Since athletes completing only one marathon were also included in this study, the results may be more transferable to the real life situation, as individuals with none or minimal long-distance running experience constitute a relevant group of participants in endurance events. In our study, we evaluated recreational athletes involved in regular exercise training, frequently with high volumes. However, the populations have significant differences in baseline characteristics that limit comparisons, with older athletes (>45 years old) and higher prevalence of CV risk factors, as smoking and family history of CV disease, than in our study.

Of 318 asymptomatic sportsmen included in MARC study[6], 16.4% had CAC score ≥100 AU and 63.2% atherosclerosis in CCTA (5.3% stenosis ≥50%). Overall, significant CAD (CAC score ≥100 AU or luminal stenosis ≥50%) was present in almost one in five individuals. The higher prevalence of CAD in this population may be related to older age (55±6 years old)

MANUSCRIPT 20

and higher risk profile. Although a SCORE <5% was present in the majority of the participants, patients with diabetes were not excluded and the frequency of other risk factors, namely family history of CV disease and former smoking, was considerably higher than our study and the others discussed above.

Merghani et al,[7] studied 152 master athletes without CV risk factors (aged 54±9 years old, 70% male), mainly runners with lifelong exposure to exercise. Among male athletes, 19% had CAC score ≥100 AU, while on CCTA 42% were identified with CAD (any plaque), 22% multivessel disease and 7.5% obstructive CAD. Similar to our findings, most coronary plaques were calcified and located in the LAD. The results of this study performed in high level athletes without CV risk factors, suggest that the higher atherosclerotic burden in previous studies may reflect a higher atherosclerotic risk profile rather than a potential deleterious exercise effect. Recently, a study performed by Aengevaeren et al[9] in 283 veteran (55±7 years old) athletes also showed a high atherosclerotic burden, with CAC present in 53% of them.

The differences in the populations included and the methodologies adopted for evaluation of exercise and atherosclerotic burden limit direct comparisons and extrapolations. Our study is the only in which several prognostically validated cardiac CT-derived indices were applied, performing a detailed characterization of the coronary atherosclerotic burden.[21,23] This more detailed evaluation may offer advantage in risk stratification and early identification of athletes with accelerated atherosclerosis, more prone to have acute coronary events.

Relationship between exercise-related characteristics and CAD

Some authors have described a 'U-shaped' curve for the relationship between volume of exercise and development of several clinical conditions as CAD.[9, 24-26] To date, this hypothesis has not been rigorously tested, and causal mechanisms remain unknown, with several limitations and inconsistences among the studies. In the Copenhagen City Heart Study,[27] jogging in moderate volume was associated to lower mortality when compared with sedentary life style or jogging in higher volumes. In contrast, The Fit study[28] showed a significant reduction in all-cause mortality in middle-age individuals exercising in strenuous workloads compared with those exercising at a lower workload, conventionally associated with maximal benefit. A meta-analysis comprising more than 650.000 individuals with a median age of 62 years old, exercising up to 10 times the recommended levels was not associated with increased mortality.[29]

MANUSCRIPT 20

A previous study revealed a significant higher CAC score in athletes than controls after adjustment for Framingham Risk Score, but did not show a significant relationship between CAD and measures of physical activity.[4] In the study performed by Merghani et al[7] the number of years of training was an independent predictor of significant CAD in male athletes, but there was no significant relationship between the volume of exercise and coronary atherosclerosis. Our study revealed a higher frequency of high coronary atherosclerotic burden in 1st and 3rd tertiles of volume of exercise but we were also unable to demonstrate significant differences.

As with two previous studies, we also demonstrated that most of our athletes with significant CAD plaques had calcified plaques in athletes which may indicate different pathophysiological mechanisms may be responsible plaque formation versus sedentary individuals. The stable nature of the plaques could mitigate the risk of plaque rupture, explaining the increased longevity of athletes despite the great proportion of coronary plaques in the most active.[7,9]

Role of cardiac CT in pre-participation evaluation

The main objective in the evaluation of veteran athletes is CV risk stratification, focusing early detection of CAD, the leading cause of sudden cardiac death in this population. Risk stratification based on clinical characteristics has limitations, and more objective markers have beeen advocated to improve the detection of individuals with higher risk.[9,10] In our study, the presence of risk factors and positive exercise testing for myocardial ischemia had a low discriminative value to identify individuals with higher atherosclerotic burden. With respect to cardiac CT, CCTA showed an incremental value over CAC score to identify individuals with subclinical CAD. Our results showing a high coronary atherosclerotic burden in a significant proportion of athletes with low to intermediate CV risk, give new insights about the evaluation and characterization of coronary atherosclerotic burden with application of several cardiac CT-derived indices previously validated in other populations.

The prognostic impact of CAC score in prediction CV events is well know, being independent and incremental to conventional risk factors.[12,13] In MESA study[15] CAC score showed a higher predictive power than other markers in discrimination and reclassification of CV risk in intermediate-risk individuals. Additionally, CAC score improves the adoption of preventive measures, leading to better control of several risk factors. Beyond detection of obstructive CAD, CCTA provides additional information with prognostic impact, as nonobstructive plaques, shown in the landmark CONFIRM Registry, and markers of

MANUSCRIPT 20

atherosclerotic burden such as SIS and CT-LSc.[21,23,30] Clustering information as localization, type of plaque, degree of luminal stenosis and number of plaques in these atherosclerotic burden scores, as performed in the present study may identify athletes who may potentially be at higher risk of CV events.[31]

Limitations

Our study has several limitations. We did not include controls or female athletes. We focused predominantly on dynamic sports. Although we performed more detailed and objective characterization of the volume of exercise than in previous studies, this evaluation was based on athlete recall. The size of our cohort may have been underpowered to test the relationship between the volume of exercise training and the prevalence or severity of CAD. It is also possible that the increased CAD burden in some of our athletes may have been due to previous risk factors for atherosclerosis which improved with exercise training. This study was cross-sectional and cannot infer that the increased atherosclerotic risk burden equates to an increased risk of adverse cardiac events. Finally, we did not test for the use of performance enhancing agents which may have contributed to our findings.

Conclusions

In the present study of middle aged recreational male athletes and with a low to intermediate atherosclerotic risk profile, the prevalence of subclinical CAD detected by cardiac CT was high. A quarter of the population had high coronary atherosclerotic burden. The extension and severity of CAD was not associated with exercise duration or intensity.

MANUSCRIPT 20

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MANUSCRIPT 20

Figures

Figure 1. Prevalence of CAD (any plaque) and high coronary atherosclerotic burden.

Figure 2. Relationship between tertiles of the volume of exercise and the presence of higher coronary atherosclerotic burden.

Figure 3. Relationship between the distribution of plaques across the coronary tree and volume of exercise (1st tertile and 3rd tertile; all p>0.05).

Figure 4. Distribution of cardiac CT-derived indices according to the volume of exercise (1st tertile and 3rd tertile; all p>0.05).

Figure 1

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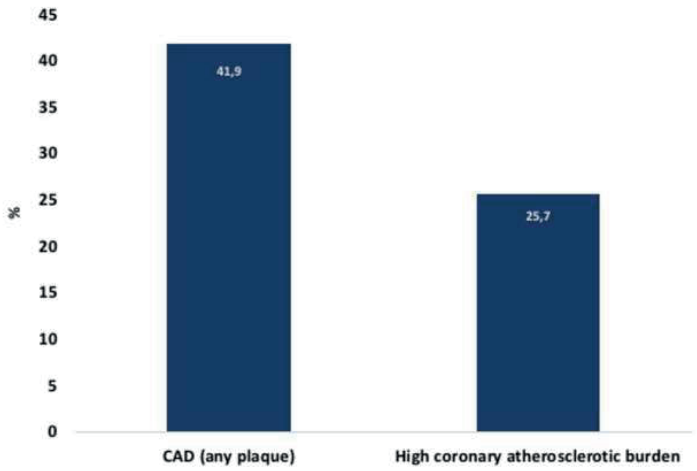

Figure 2

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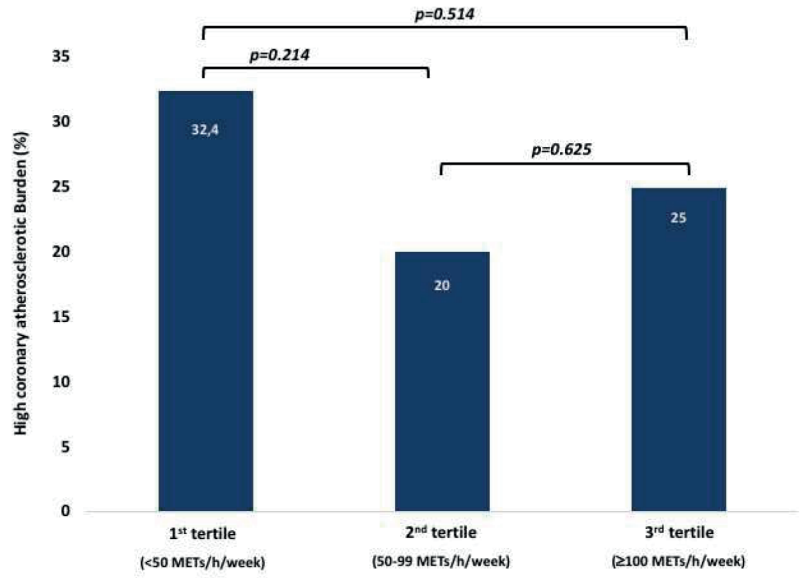

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Figure 3

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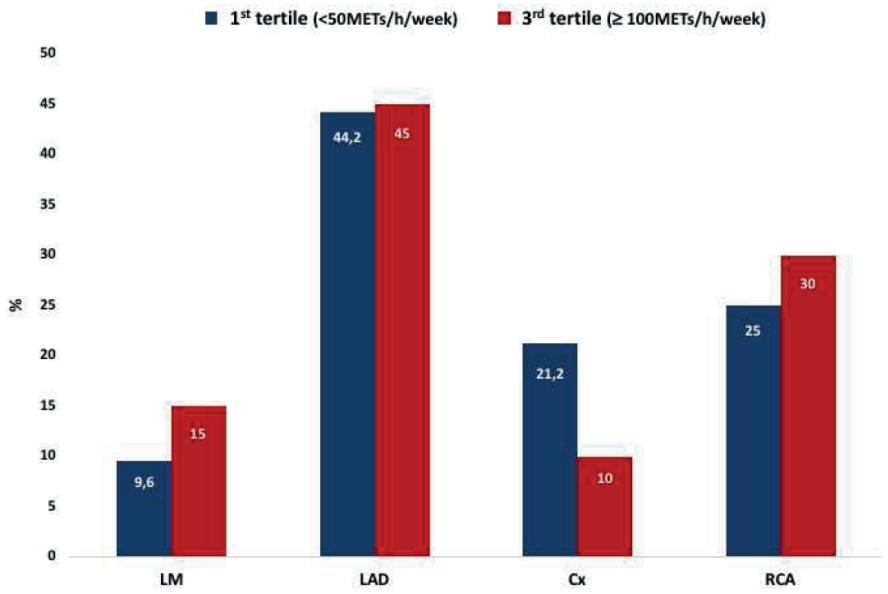

Figure 4

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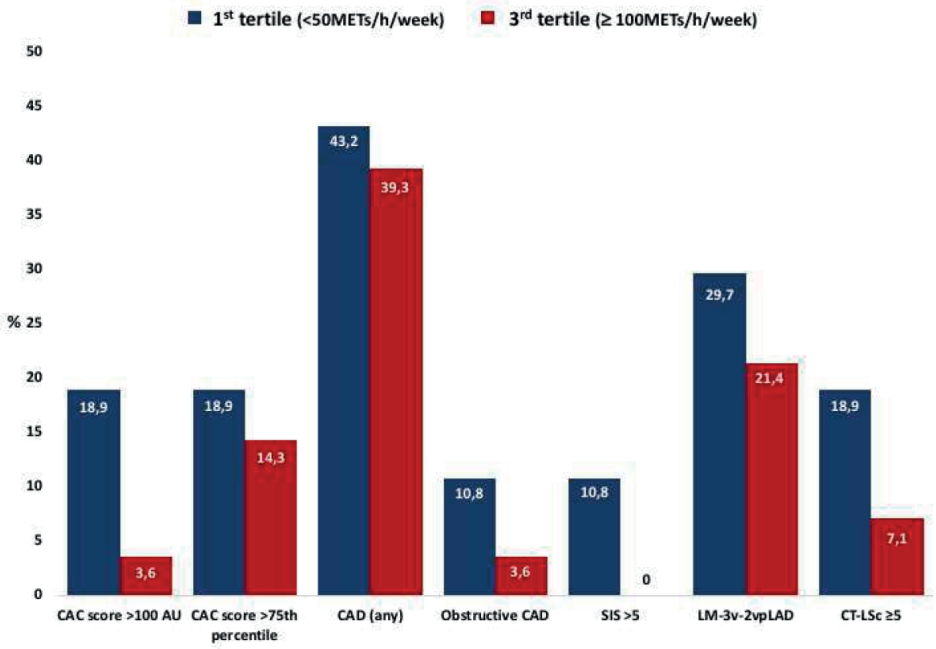

MANUSCRIPT 20

Table 1. Baseline and exercise-related characteristics (N=105).

Demographics and Clinical	
Caucasians, n (%)	103 (98.1)
Age, years old	48±6
Height, cm	176±6
Weight, kg	76±9
BSA, m^2	1.9 [1.8; 2.0]
SBP, mmHg	125±11
DBP, mmHg	78±8
Heart rate, bpm	57±8
CV risk factors	
Family history of premature CV disease, n (%)	3 (2.9)
Current smoking, n (%)	8 (7.6)
Former smoking, n (%)	10 (9.5)
Hypertension, n (%)	9 (8.6)
Dyslipidemia, n (%)	43 (41.0)
LDL cholesterol, mg/dl	124±31
Lipid-lowering medication, n (%)	7 (6.7%)
≥1 CV risk factor, n (%)	49 (46.7)
Low risk (SCORE <1%), n (%)	56 (53.3)
Exercise-related characteristics	
High dynamic sport (class C) , n (%)	88 (83.8)
High static sport (class III) , n (%)	32 (30.5)
Hours of training/week (hours)	8±5
>10 hours of training/week, n (%)	17 (16.2)
Volume of exercise, METs/h/week	66 [44; 103]
Years of continuos exercise, years	17±10
>20 years of continuous exercise, n (%)	33 (31.4)

CV: Cardiovascular; BSA: Body Surface Area; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure.

MANUSCRIPT 20

Table 2. Cardiac CT results (N=105).

Overall CAC score	0 [0; 13]
CAC score in athletes with coronary calcium	34 [2; 81]
CAC score 0 AU, n (%)	62 (59.0)
CAC score 1-10 AU, n (%)	17 (16.2)
CAC score 10-100 AU, n (%)	16 (15.2)
CAC score >100 AU, n (%)	10 (9.5)
CAC score >75th percentile, n (%)	13 (12.4)
CAD, n (%)	44 (41.9)
Obstructive CAD, n (%)	6 (5.7)
Non Obstructive CAD, n (%)	38 (36.2)
Athletes with non-calcified/mixed plaques, n (%)	15 (14.3)
>1 Coronary plaque, n (%)	30 (28.6)
SIS in athletes with coronary plaques	2 [1; 3]
SIS >5, n (%)	4 (3.8)
LM-3v-2vpLAD, n (%)	24 (22.9)
CT-LeSc	0 [0; 2.8]
CT-LeSc in athletes with coronary plaques	3.1 [2.2; 5.4]
CT-LeSc ≥5, n (%)	16 (15.2)
High coronary atherosclerotic burden, n (%)	27 (25.7)

AU: Agatston Unit; CAD: Coronary Artery Disease; CAC: coronary artery calcium; CT-LeSc: Computed Tomography-adapted Leaman score; LM-3v-2vpLAD: left main disease, three vessels or two vessels involving the proximal anterior descending artery; SIS: Segment Involvement Score.

MANUSCRIPT 21

Original article

Subclinical coronary artery disease in veteran athletes: is a new preparticipation methodology required?

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ABSTRACT

Objective Preparticipation evaluation of veteran athletes should focus on accurate cardiovascular (CV) risk stratification and subclinical detection of coronary artery disease (CAD), which is the main cause of sudden cardiac death in this population. We aimed to investigate the effectiveness of current preparticipation methodology used to identify veteran athletes with high coronary atherosclerotic burden.

Methods A total of 105 asymptomatic male athletes aged ≥40 years old, with low to moderate CV risk (Systematic Coronary Risk Estimation <5%) who trained ≥4 hours/week for at least 5 years, were studied. The screening protocol included clinical evaluation, ECG, transthoracic echocardiogram and exercise testing. Cardiac CT was performed to detect CAD, defined as a high atherosclerotic burden according to coronary artery calcium score and coronary CT angiography.

Results The majority of the athletes (n=88) engaged in endurance sports, with a median volume of exercise of 66 (44; 103) metabolic equivalent task score/hour/week. Exercise testing was abnormal in 13 (12.4%) athletes, 6 (5.7%) with electrocardiographic criteria for myocardial ischaemia and 7 (6.7%) with exercise-induced ventricular arrhythmias. A high coronary atherosclerotic burden was present in 27 (25.7%) athletes, of whom 11 (40.7%) had CV risk factors and 6 had abnormal exercise tests, including 3 who were positive for myocardial ischaemia.

Conclusions Conventional methodology used in preparticipation evaluation of veteran athletes, based on clinical CV risk factors and exercise testing, was poor at identifying significant subclinical CAD. The inclusion of more objective markers, particularly data derived from cardiac CT, is promising for more accurate CV risk stratification of these athletes.

What are the findings?

- Subclinical coronary artery disease (CAD) is common among veteran athletes.
- Preparticipation evaluation based on clinical cardiovascular risk factors and exercise testing has limitations when identifying athletes with a high burden of coronary atherosclerosis.
- Cardiac CT can detect CAD at an early stage and allow detailed characterisation of the total coronary atherosclerotic burden in veteran athletes.

How might it impact on clinical practice in the future?

- Preparticipation evaluation of veteran athletes should focus on early detection of CAD.
- Data derived from cardiac CT are promising for more accurate cardiovascular risk stratification of these athletes.
- Inclusion of more objective markers in the preparticipation evaluation of veteran athletes may lead to a more effective way of identifying those at the highest risk.

INTRODUCTION

The number of middle-aged participating in lifelong regular exercise training has progressively increased over the past few decades. Despite the well-established benefits from a cardiovascular (CV) perspective, in a small but significant proportion of susceptible individuals, exercise can precipitate adverse events including sudden cardiac death (SCD). Coronary artery disease (CAD) represents the most common cause of SCD in veteran athletes, accounting for approximately two-thirds of all cases.[1] Additionally, several studies have shown a higher than expected prevalence of CAD in veteran athletes, reinforcing the importance of accurate risk stratification and early detection of CAD in this population.[2–5]

The traditional approach for preparticipation evaluation of veteran athletes is based on CV risk factors and exercise testing. Such practice, however, does have limitations, including the low sensitivity of exercise testing to identify individuals with established CAD.[6–8] Consequently, inclusion of more objective markers may improve CV risk stratification in these athletes. Cardiac CT, from which coronary artery calcium (CAC) score and coronary CT angiography (CCTA) are acquired, can be useful in this evaluation. CAC score when performed in low to intermediate risk populations has been shown to add an incremental value in risk prediction compared with conventional clinical risk factors, while CCTA provides additional information with prognostic impact beyond obstructive plaques.[9–15]

Our hypothesis is that conventional CV risk assessment has low sensitivity in the detection of CAD in veteran athletes and may be improved by the addition of data derived from cardiac CT. The aim of this study was to analyse the effectiveness of current preparticipation methodology used to

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MANUSCRIPT 21

Original article

identify veteran athletes with high coronary atherosclerotic burden.

METHODS

Study design and population

Male veteran athletes (≥40 years old) who were participating in regular exercise for at least 4 hours/week for a minimum of 5 years were included. Individuals with symptoms, diabetes mellitus, a Systematic Coronary Risk Estimation (SCORE) ≥5%, renal impairment or previous allergy to iodinated contrast agents were excluded. The evaluation of athletes was performed at a dedicated sports cardiology clinic, with documentation of demographic, anthropometric, atherosclerotic risk factors and sports history, and physical evaluation. CV risk factors included family history of premature CV disease (first-degree relatives <50 years old), smoking (current if smoking in the last year), hypertension (≥140/90 mm Hg or treatment with antihypertensive medications) and dyslipidaemia (low-density lipoprotein (LDL) cholesterol ≥115 mg/dL or treatment with lipid-lowering medications). These risk factors were noted in isolation and integrated in the SCORE charts.[16] The volume of exercise was calculated by the metabolic equivalent task score (MET/hour/week), representing the product of intensity (METs for each sport according to the Compendium of Physical Activities[17]), frequency of exercise (number of training sessions per week) and duration of exercise (hours in each workout). Sporting disciplines were grouped according to the Mitchell classification,[18] with particular attention placed on those participating in sports characterised by high dynamic (class C) and high static (class III) components. Participation in organised competitions and the number of years of continuous exercise training were also registered.

Further assessment

Further testing included blood tests (complete blood count, lipid profile, fasting glycaemia, glycated haemoglobin and renal function), 12-lead resting ECG, interpreted according to the International Recommendations for Electrocardiographic Interpretation in athletes,[19] transthoracic echocardiogram (TTE; M-mode, two-dimensional, colour, pulsed, continuous and tissue Doppler, speckle tracking), exercise testing (maximal or limited by symptoms and performed on a treadmill according to the Bruce protocol) and cardiac CT to evaluate the coronary atherosclerotic burden (CAC score and CCTA).

Cardiac CT was performed in multidetector row CT scanners consisting of 64 rows or greater (Somatom Force and Somatom Perspective, Siemens Healthcare), in order to minimise the dose of radiation and contrast. Except in the presence of conventional contraindications, sublingual nitroglycerin (0.5 mg) was administered, as were beta-blockers when appropriate to achieve a heart rate <65 beats per minute. CT scans were processed on a workstation (Syngo.via, Siemens Healthcare) and assessed by an experienced cardiologist and radiologist. Abnormal findings were reviewed in a multidisciplinary team meeting. CAC score was analysed in absolute terms and percentiles, according to normograms adjusted for age, gender and ethnicity. The presence of coronary plaque, plaque morphology, plaque distribution (according to the Society of Cardiovascular Computed Tomography classification[20]) and the degree of stenosis were ascertained with CCTA to calculate the Segment Involvement Score (SIS) and CT-adapted Leaman score (CT-LeSc).[21–23] SIS is a semi-quantitative measure of atherosclerotic burden, representing the number of coronary segments with plaques, and is considered significant if more than five segments are involved. CT-LeSc calculation is based on three sets of weighting factors provided by CCTA: (1) localisation of plaques in the coronary tree, taking into account the dominance; (2) type of plaque; and (3) degree of stenosis.[22] A CT-LeSc ≥5 was defined as a significant value.[22] A high atherosclerotic burden was defined in the presence of at least one of the following characteristics: CAC score >100 Agatston units (AU); CAC score >75th percentile; obstructive CAD (luminal stenosis ≥50%); plaques in the left main, three vessels or two vessels including the proximal anterior descending artery; SIS >5; or CT-LeSc ≥5.

Table 1 Baseline characteristics (n=105)

Demographics and clinical characteristics	
Caucasians, n (%)	103 (98.1)
Age (years)	48±6
Height (cm)	176±6
Weight (kg)	76±9
BMI (kg/m^2)	24.5±2.5
BSA (m^2)	1.9 (1.8; 2.0)
SBP (mm Hg)	125±11
DBP (mm Hg)	78±8
Heart rate (beats per minute)	57±8
CV risk factors	
Family history of premature CV disease, n (%)	3 (2.9)
Current smoking, n (%)	8 (7.6)
Former smoking, n (%)	10 (9.5)
Hypertension, n (%)	9 (8.6)*
Dyslipidaemia, n (%)	43 (41.0)
LDL cholesterol (mg/dL)	124±31
Lipid-lowering medication, n (%)	7 (6.7)
≥1 CV risk factor, n (%)	49 (46.7)
Low risk (SCORE=0), n (%)	56 (53.3)

*All patients under treatment with antihypertensive medication.
BMI, body mass index; BSA, body surface area; CV, cardiovascular; DBP, diastolic blood pressure; LDL, low-density lipoprotein; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Estimation.

Statistical analysis

All analyses were performed using SPSS V.23.0 for Mac. Normality was tested with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean and SD, and non-normal variables as median (IQR). Categorical variables were expressed as frequencies and percentages. Statistical comparison was performed using X^2 test or Fisher's exact test, when appropriate for categorical variables, and Mann-Whitney or Kruskal-Wallis test for continuous variables. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Demographic, clinical and exercise-related characteristics are shown in table 1. Of the 105 athletes included, 103 (98.1%) were Caucasian with a mean age of 48±6 years old. Forty-nine (46.7%) athletes had at least one CV risk factor, which was most commonly dyslipidaemia, present in 43 (41.0%) athletes, with a mean LDL cholesterol of 124±31 mg/dL. Current or former smoking was the second most common risk factor, present in 18 (17.1%) athletes. All athletes had low to intermediate CV risk with SCORE ≤3, with over half (n=56; 53.3%) classified as low risk (SCORE=0). The mean hours-training/week was 8±5 hours and the median volume was 66 (44; 103) METs/hour/week.

MANUSCRIPT 21

Most athletes practised high-dynamic endurance sports (n=88; 83.8%), especially running (n=67) and cycling (n=11), while a quarter (24.8%) were involved in competitive sport.

Further investigations

Regarding the 12-lead resting ECG, most athletes had normal traces (n=44; 41.9%) or physiological findings (n=48; 45.7%), while 11 (10.5%) had borderline characteristics and 5 (4.8%) had pathological findings (3 athletes had a QTc interval ≥470 ms and 2 athletes revealed pathological T-wave inversion). TTE showed frequent structural adaptations, mainly left atrial (LA) enlargement (n=53; 50.5%), with a mean LA volume index of 36±9 mL/m^2, and left ventricular (LV) hypertrophy (n=37; 35.2%), predominantly eccentric, with a mean indexed LV mass of 111±30 g/m^2, and LV end-diastolic and end-systolic volume index of 69±13 mL/m^2 and 27±7 mL/m^2, respectively. Functional evaluation revealed normal mean values of LV ejection fraction (61%±7%), LV global longitudinal strain (−18.3±2.0%), E/A ratio (1.4±0.4), E/e' ratio (6.6±1.7), tricuspid annular plane systolic excursion (26±4 mm) and tissue Doppler imaging of tricuspid annulus (0.14±0.03 ms). Two athletes had significant findings (bicuspid aortic valve and mitral valve prolapse, both without significant functional repercussion), but no cardiomyopathies were identified.

CAD evaluation with cardiac CT and exercise testing

The cardiac CT results are presented in figure 1 and table 2. The average dose of radiation was 2.7±1.8 mSv and the contrast used was 110±19 mL. Forty-two (41.9%) athletes revealed coronary plaques, 36 (34.3%) had non-obstructive plaques and 6 (5.7%) individuals demonstrated obstructive plaques. The vast majority of plaques were calcified in nature (73.8%), mixed in 23.4% and non-calcified in 2.8%. A high coronary atherosclerotic burden was present in a quarter of the population (n=27; 25.7%). Figure 2 shows an example of an athlete with high coronary atherosclerotic burden on cardiac CT.

Exercise testing was maximal or to voluntary exhaustion in all individuals (mean duration 16.2±2.9 min; 16.1±2.5 METs). The majority of athletes (n=92; 87.6%) had a negative test for myocardial ischaemia, while in six (5.7%) showed findings that were compatible with myocardial ischaemia according to electrocardiographic criteria, and seven (6.7%) showed frequent ventricular extra beats during exercise (non-sustained ventricular tachycardia in three cases).

Among the athletes with high atherosclerotic burden (n=27), only six had significant abnormal findings on exercise testing (figure 3), of whom three (11.3%) were positive for myocardial ischaemia, two equivocal for myocardial ischaemia (upsloping ST segment) and one had non-sustained ventricular tachycardia

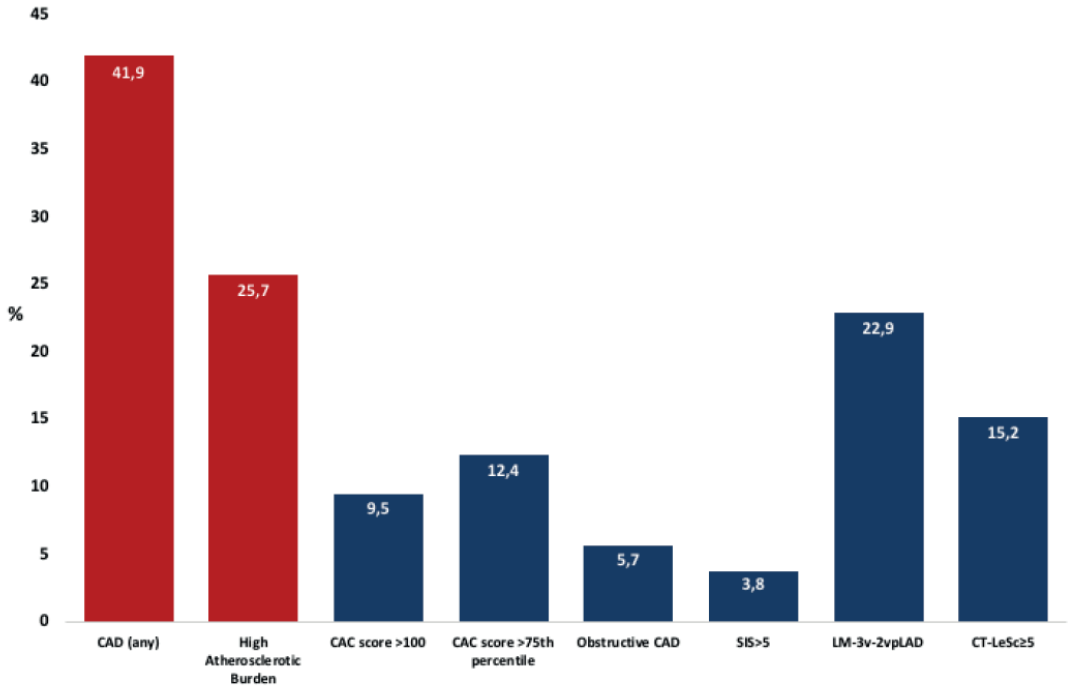

Figure 1 Main cardiac CT results (n=105). CAC, coronary artery calcium; CAD, coronary artery disease; CT-LeSc, CT-adapted Leaman score; LM-3v-2vpLAD, left main, three vessels or two vessels involving the proximal anterior descending artery; SIS, Segment Involvement Score.

MANUSCRIPT 21

Original article

Table 2 Cardiac CT results (n=105)

Overall median CAC score	0 (0; 13)
CAC score 0 AU, n (%)	62 (59.0)
CAC score >100 AU, n (%)	10 (9.5)
CAC score >75th percentile, n (%)	13 (12.4)
CAD (any plaque), n (%)	44 (41.9)
>1 Coronary plaque, n (%)	30 (28.6)
Obstructive CAD, n (%)	6 (5.7)
Non-obstructive CAD, n (%)	38 (36.2)
Median SIS in athletes with coronary plaques	2 (1; 3)
SIS >5, n (%)	4 (3.8)
Median CT-LeSc	0 (0; 2.8)
CT-LeSc≥5, n (%)	16 (15.2)
LM-3v-2vpLAD, n (%)	24 (22.9)
High coronary atherosclerotic burden	27 (25.7)

AU, Agatston unit; CAC, coronary artery calcium; CAD, coronary artery disease; CT-LeSc, CT-adapted Leaman score; LM-3v-2vpLAD, left main disease, three vessels or two vessels involving the proximal anterior descending artery; SIS, Segment Involvement Score.

during exercise. Only one of the athletes with features of myocardial ischaemia on exercise testing had obstructive CAD. In the same subgroup of athletes with high atherosclerotic burden, only 11 (40.7%) had at least one CV risk factor.

DISCUSSION

A significant proportion of male veteran athletes with low to intermediate CV risk had subclinical CAD, including a high coronary atherosclerotic burden, present in a quarter. Conventional methodology used in preparticipation evaluation, based on clinical risk factors and exercise testing, was poor at correct identification of these athletes. As CAD is the most common cause of SCD among veteran athletes, it should be the main factor to detect through preparticipation evaluation. Cardiac CT is a promising tool to identify CAD in these individuals.

A similarly high prevalence of CAD in veteran athletes was previously shown in several studies. The Marathon study[2] showed a CAC score ≥100 AU and >75th percentile in 36% and 25% of veteran marathon runners, respectively. Another study revealed CAD in half the middle-aged marathon runners analysed.[3] The Measuring Athlete's Risk of Cardiovascular Events study[5] showed significant CAD (CAC score ≥100 AU or luminal stenosis ≥50%) in almost a fifth of 318 veteran athletes.

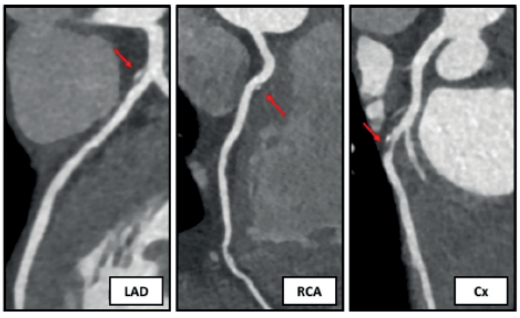

Figure 2 Coronary CT angiography of a veteran athlete showing coronary plaques (arrows)—non-obstructive plaques in the left anterior descending (LAD) artery and right coronary artery (RCA), obstructive in circumflex (Cx).

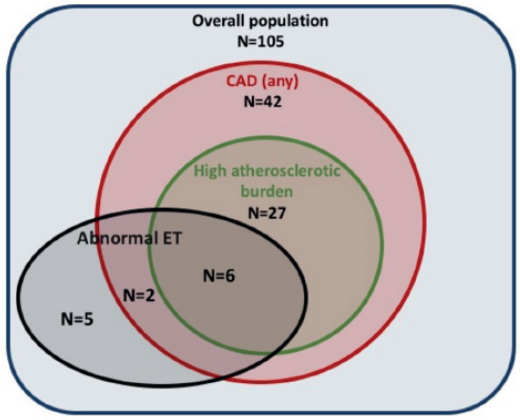

Figure 3 Relationship between the presence of coronary artery disease (CAD) and high coronary atherosclerotic burden with abnormal exercise testing (ET).

Similarly, two recent studies of predominantly marathon runners and endurance cyclists showed CAD in 42% to 53% of veteran athletes respectively.[4 24]

The heterogeneity of the inclusion criteria used in the aforementioned studies, namely the age range and the frequency of CV risk factors, makes direct comparisons with our study more difficult. We analysed an under-represented population compared with the other studies, namely recreational athletes, and incorporated a more detailed analysis of coronary atherosclerotic burden using cardiac CT. An updated and controversial topic is the relationship between the volume of exercise and the development of CAD in athletes, with some exercise-related mechanisms potentially involved.[25 26]

The actual methodology applied in preparticipation evaluation of veteran athletes is based on traditional clinical CV risk factors and data derived from exercise testing. However, this strategy has some limitations, underestimating the prevalence of significant CAD. More objective markers may add incremental value in identifying individuals with higher risk.[7] In our study, cardiac CT increased such identification of individuals with subclinical CAD. The presence of CV risk factors and significant findings on exercise testing had low discriminative value to identify the individuals with high coronary atherosclerotic burden detected by cardiac CT.

While exercise testing has established prognostic value and is widely available, the accuracy of exercise testing to detect CAD in populations with low to intermediate pretest probability is limited.[27 28] A recent study performed in asymptomatic middle-aged athletes with ST segment anomalies during maximal exercise testing revealed CAD in only 32% of the subjects.[29] Indeed, any stress test relieson the presence of obstructive CAD and does not detect non-obstructive CAD, which has been associated with worse CV outcomes in several studies.[21 23 30]

Several parameters of CCTA and CAC score have shown an incremental prognostic impact over the conventional CV risk factors.[10 11 31 32] For example, the landmark Multi-Ethnic Study of Atherosclerosis[13] revealed a higher predictive power of CAC score in risk stratification compared with other markers, reclassifying a significant number of individuals with intermediate risk. Additionally, CCTA provides the unique ability to detect markers with proved prognostic impact, for example, the presence of

MANUSCRIPT 21

non-obstructive plaques and calcified plaques.[15 22 31] Although we demonstrated a high prevalence of predominantly non obstructive CAD disease in our cohort of recreational middle-aged endurance athletes, we must be mindful to the multiple health benefits associated with moderate amouunts habitual physical exercise. Non-obstructive CAD in asymptomatic athletes is not a contraindication for exercise training. Indeed, future investigations are needed to analyse the dichotomy between the potential association of lifelong extreme exercise with the development of CAD and the benefits of exercise in the reduction of coronary events. It may be the case that by doing regular exercise these athletes may indeed show a lower atherosclerotic burden than if the same individuals had a sedentary lifestyle, but this is difficult to prove without longitudinal long-term follow-up studies. Cardiac CT has the ability to detect CAD in an early stage and to perform a deeper characterisation of the total coronary atherosclerotic burden, which may lead to the implementation of preventive measures in high-risk athletes, among which exercise has a central role. Our data can contribute to future research on this topic.

The present study has some limitations that should be highlighted. Our data do not apply to women and may not be representative of all sports modalities, as we cannot exclude recruitment bias. The sample size may be underpowered to test the methodology used. It is also possible that increased CAD burden in some athletes may have been due to previous risk factors for atherosclerosis which improved with exercise training. As the study was cross-sectional, one cannot infer that the increased atherosclerotic risk burden equates to an increased risk of adverse cardiac events.

CONCLUSIONS

In this study of asymptomatic male veteran athletes, a quarter had a high coronary atherosclerotic burden. Conventional methodology used in preparticipation evaluation of veteran athletes, based on clinical CV risk factors and exercise testing, was limited in identifying significant subclinical CAD. The inclusion of more objective markers, particularly data derived from cardiac CT, can improve correct CV risk stratification of these athletes.

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MANUSCRIPT 21

Original article

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KEY RESULTS AND CLINICAL IMPLICATIONS

KEY RESULTS AND CLINICAL IMPLICATIONS

The main results and clinical implications of the original manuscripts presented in this document were as follows:

- Anterior T-wave inversion was present in 2.3% of young white population, more commonly in women and athletes. Almost 80% was confined to leads V1-V2 and had a poor diagnostic yield for cardiac pathology, implying that this pattern could be a normal variant or physiological phenomenon in asymptomatic white individuals without a family history of cardiomyopathy or premature SCD. In contrast, anterior T-wave inversion beyond V2 was rare, particularly in men, and may warrant investigation.

- There was a positive correlation between greater intensity and level of sport with increased prevalence of ECG abnormalities. Although the lower frequency of abnormal ECGs, this relationship persisted with the use of more restrictive criteria for ECG interpretation in athletes ('refined criteria'). Exercise-related characteristics should be known and taken into account during the evaluation of athletes to help early identification of those who may be more prone to develop ECG abnormalities and to prevent unnecessary subsequent investigations and unwarranted disqualification from competitive sport.

- The interpretation of ECG in athletes among physicians, mainly cardiologists, was suboptimal. A quarter of the ECGs were not correctly assessed and the variability in interpretation was high. Specific criteria for the interpretation of ECG in athletes were applied by less than half of the physicians. Standardization of ECG interpretation in athletes is needed to improve the accuracy of this exam in preparticipation evaluation and to reduce the rate of false positive cases.

- Even among experienced cardiologists, the reliability in interpretation of ECGs in a large cohort of highly trained young athletes was only moderate. The resultant cascade of downstream investigations was highly physician dependent, which

- Electrical cardiac adaptations were frequent in a population of young military. The application of more restrictive criteria for interpretation of ECG - Seattle criteria and 'refined' criteria, reduced significantly the rate of false-positive cases compared to the ESC recommendations, less restrictive (approximately two thirds, from 15% to 5%). The application of specific criteria may have a favorable socioeconomic impact reducing the health cost burden and the number of disability days.

- Exercise training induced different structural LV remodeling in young special forces soldiers and competitive athletes - eccentric in military and concentric in basketballers. Although the LV myocardial mechanics did not show a significant difference in the two groups separately, when analyzed together there was a significant decrease in GLS. Knowledge of the characteristics of exercise should be considered during the echocardiographic evaluation of athletes. Among the several echocardiographic modalities, new parameters as GLS are promising.

- The GLS was significantly lower in athletes with higher level of exercise training (national or international and ≥20 training-hours per week). Thirty-one percent of the athletes had GLS below 17%, more frequently in the group of higher level of exercise training, with higher LV and left atrium volumes, lower *E* wave and *A* wave peak velocities and *E/e'* ratio. Although the value of GLS in athletes may overlap pathological conditions, the association between lower values and enhanced diastolic performance allows the discrimination between physiologic adaptations and pathology.

- The comprehensive information regarding the presence, severity and type of coronary plaques noninvasively provided by CCTA made possible a detailed characterization of the CAD pattern in diabetic patients at earlier stage of disease. This feature of CCTA is promising for subclinical detection of CAD and deeper characterization of coronary atherosclerotic burden in other populations.

- In a population of stable patients undergoing CCTA for suspected CAD, body mass index was an independent predictor of CAD, but was not correlated with

obstructive CAD or in overall coronary atherosclerotic burden across the different body mass index classes. CCTA led to a better clarification of the controversial relationship between some CV risk factors as overweight and obesity and severity of CAD.

- Despite the association of several clinical CV risk factors with a higher than expected coronary atherosclerotic burden evaluated by cardiac CT, they explained only half of its prevalence. Even when integrated in scores, the predictive power of these risk factors is relatively modest, exposing the limitations of risk stratification based solely on demographic and clinical characteristics.

- In patients with myocardial infarction as the first manifestation of CAD, CV risk stratification using the SCORE, if calculated before the event, classified more than two-thirds of the patients as low risk and a minority as very high risk. The high prevalence of low risk patients indicates a current challenge of CV risk stratification, underlying the need for additional tools in primary prevention to better identify patients at risk.

- The mean effective radiation dose used in cardiac CT was lower than in invasive coronary angiography, which in turn was lower than in single photon emission computed tomography. There was a significant reduction over time in mean effective radiation dose associated with cardiac CT after implementation of a prospective protocol. Beyond these software improvements, the 'new' generation CT scanners made possible the acquisition of cardiac CT exams at ultra-low radiation dose, which is of utmost importance if CCTA is to be included in clinical practice to evaluate populations with lower CV risk.

- The calculation of CT-LeSc, as a tool to quantify total coronary atherosclerotic burden (obstructive and non-obstructive), reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA, was feasible. There was a significant association between the CT-LeSc and some traditional demographic and clinical risk factors, being expected to

obstructive CAD had CT-LeSc in the highest tercile, which could potentially lead to a reclassification of the risk profile of these apparently low risk individuals.

- In stable patients with zero CAC score, 12.4% had coronary plaques, but only 1.6% had obstructive CAD. Age over 55 years old, hypertension and dyslipidemia were independent predictors of CAD in the setting of zero CAC score. In the presence of these predictors, the probability of CAD was almost two times higher than in the total studied population.

- The prevalence of subclinical CAD detected by cardiac CT in middle-aged male veteran athletes with low to intermediate CV risk was high (42%). A quarter of the athletes had high coronary atherosclerotic burden, defined as the conjugation of several variables derived from the CAC score and CCTA. The extension and the severity of CAD did not significantly differ according to the volume of exercise.

- The majority of the veteran athletes with high coronary atherosclerotic burden evaluated by CCTA had no CV risk factors or significant changes in exercise testing. Since CAD is the leading cause of SCD in this subset of athletes and due to the limitations of risk stratification limited to clinical factors and exercise testing, adjustments of preparticipation methodology are probably required. Inclusion of more objective markers as parameters derived from cardiac CT may be useful in early detection of CAD in veteran athletes, leading to risk reclassification and early implementation of preventive measures.

CONCLUSIONS AND FUTURE PERSPECTIVES

CONCLUSIONS AND FUTURE PERSPECTIVES

CV risk assessment is essential to identify athletes with increased risk or subclinical disease associated with the occurrence of clinical events including SCD. Though uncommon, SCD is the most devastating sport related event, widely publicized by the media with the implication that such a fatality can be preventable. Despite the different methodologies adopted by several countries and sports organizations, preparticipation evaluation of athletes is globally mandatory.

The interpretation of ECG in athletes is frequently challenging and limited by false positive cases related with physiological adaptations induced by exercise training. Understanding these adaptations and its association with demographics and sports-related characteristics is very important. The use of specific and more restrictive criteria for the interpretation of ECG in athletes can overcome some limitations, improving the accuracy in preparticipation evaluation and leading to socioeconomic benefits.

Although the progressive advances regarding the ECG in athletes, several points remain to clarify, as the association between some specific electrocardiographic patterns with pathological conditions and its prognostic impact. Larger populations of athletes with different demographic characteristics (e.g. children, women) and involved in sports usually under-represented (e.g. isometric sports) should be further investigated. Formal medical training and development of a standardized diagnostic pathway for ECG interpretation is essential to support physicians involved in athletes' evaluation.

Structural cardiac remodelling, the most typical feature of the 'athlete's heart', varies according to the type of exercise training. Since some physiological adaptations can overlap findings present in pathological conditions, namely cardiomyopathies, a comprehensive evaluation is needed to improve this differential diagnosis. Echocardiography remains the most useful imaging test for this purpose and advanced modalities such as myocardial deformation may improve the early recognition of pathology. However, GLS should be interpreted with caution because the normal values in athletes are not established and a 'grey zone' may exist, potentially representing

echocardiographic tools in athlete's evaluation is promising, but it should be deeply tested. The role of cardiac magnetic resonance as the gold-standard imaging test for structural and functional cardiac evaluation should be studied, being a potential line of research to follow.

CV risk stratification based on clinical risk factors, isolated or integrated in scores, has some limitations. The relatively modest predictive power of this methodology has been highlighted in patients presenting with STEMI as first manifestation of CAD. Cardiac-CT (CAC score and CCTA) is useful to quantify the total coronary atherosclerotic burden, leading to the reclassification of risk profile in some individuals. Several CT derived scores are validated and allow a detailed characterization of the coronary atherosclerotic burden.

As CAD is the leading cause of SCD in veteran athletes, preparticipation evaluation of these athletes should focus CV risk stratification and early detection of CAD. Cardiac CT demonstrated a higher than expected prevalence of CAD in veteran athletes, approximately one fourth with high coronary atherosclerotic burden. The association between volume of exercise and CAD, with the potential influence of some exercise-related characteristics in the development of CAD, deserve further investigation.

The conventional methodology of veteran athlete's evaluation based on CV clinical risk factors and exercise testing seems to limit the identification of individuals with established and significant CAD. Inclusion of more objective markers in preparticipation evaluation of these athletes, as data derived from cardiac CT, is promising for more early and accurate risk stratification. Such understanding will become of utmost importance and will provide a more effective way to identify the individuals at the highest risk.

Despite the advances over the last years in the field of sports cardiology, there is still a lot to be learned about CV risk assessment in athletes. Beyond this issue, sports cardiology covers an emerging broad range of areas that remain to clarify and will certainly mark the clinical research in near future.

This is not the end, but just a new beginning, since we believe that several doors were opened, providing future research opportunities!

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BIBLIOGRAPHY

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APPENDICES

APPENDIX A - Ethics committees and institutional approvals

Decisão final sobre o projecto "Relação entre exercício físico e doença coronária em atletas"

A Comissão de Ética da NMS|FCM-UNL (CEFCM) decidiu, por unanimidade, aprovar o projecto de investigação intitulado "Relação entre exercício físico e doença coronária em atletas" (nº41/2016/CEFCM), submetido por Dr. Hélder Dores.

Lisboa, 09 de Maio de 2017

O Presidente da Comissão de Ética,

(Prof. Doutor Diogo Pais)

TO WHOM IT MAY CONCERN

The Ethics Research Committee NMS|FCM-UNL (CEFCM) has unanimously approved the Project entitled "Relação entre exercício físico e doença coronária em atletas" (nr.41/2016/CEFCM), submitted by Dr. Hélder Dores.

Lisbon, May 09th, 2017

The Chairman of the Ethics Research Committee,

(Diogo Pais, MD, PhD)

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MINISTÉRIO DA DEFESA NACIONAL

HOSPITAL DAS FORÇAS ARMADAS
POLO DE LISBOA

Exmo Senhor
Capitão Médico
Hélder Alexandre Correia Dores
HFAR

Assunto: Parecer da Comissão de Ética para a Saúde

Tendo sido apresentado o pedido de parecer sobre a proposta de projeto de Tese de Doutoramento em Medicina intitulado: **"Relação entre exercício físico e doença coronária em atletas"** apresentada pelo Capitão Médico Hélder Alexandre Correia Dores, após a sua análise, esta comissão decidiu emitir parecer favorável à sua realização, considerando o seu interesse científico ao poder alcançar evidência sobre os riscos e benefícios do exercício físico, podendo trazer benefícios de prevenção de risco para os próprios participantes no estudo.
Acresce que se trata de um estudo analítico e observacional, sem intervenção terapêutica, sendo obtido consentimento informado dos participantes, com obediência aos princípios da bioética.

Lisboa, 13 de Outubro de 2016
O Presidente da Comissão de Ética para a Saúde

José Carlos Nunes Marques
MGen Ref

Azinhaga dos Ulmeiros - 1649-020 LISBOA
Telefone: 217519676 - Fax: 217519689

HOSPITAL DA LUZ
ESPÍRITO SANTO SAÚDE

Comissão de Investigação Clínica – Director Clínico

Hospital da Luz

Exmo. Sr.

Dr. Helder Dores

Hospital da Luz

Lisboa, 03 de Janeiro de 2017

Assunto: **Parecer ao Estudo "Relação entre exercício físico e doença coronária em atletas"**

A Comissão de Investigação do Hospital da Luz informa que o parecer foi **positivo** relativo à realização do Estudo **Relação entre exercício físico e doença coronária em atletas.**

Pel'A Comissão de Investigação

Prof. Jose Roquette, Director Clinico

REPÚBLICA PORTUGUESA
SAÚDE

ceic
Comissão de Ética para a Investigação Clínica
National Ethics Committee for Clinical Research

Exma. Sr.ª
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Data: 31/01/2017

Nossa Ref.: 2016_PC_13 (CEIC/5147)

Assunto: Pedido de classificação do estudo com o Título *Relação entre exercício físico e doença coronária em atletas*

Exmos. Senhores,

Em resposta ao seu pedido de classificação do estudo clínico com o título: *Relação entre exercício físico e doença coronária em atletas*, envia-se a V. Exa. a fundamentação da decisão, conforme documento em anexo.

Com os melhores cumprimentos,

A Comissão de Ética para a Investigação Clínica

RS

Anexo: Fundamentação do parecer.

CEIC - Parque de Saúde de Lisboa
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REPÚBLICA PORTUGUESA
SAÚDE

ceic
Comissão de Ética para a Investigação Clínica
National Ethics Committee for Clinical Research

Fundamentação do parecer

Esta solicitação prende-se especificamente com a interpretação do Artigo 2º, alínea p), da Lei 21/2014 de 16 de abril.

A Lei 21/2014 de 16 de abril, relativa ao regime jurídico aplicável à realização de estudos clínicos, explicita os critérios para a definição e caracterização de um estudo sem intervenção, entre os quais se salientam os seguintes:

i) Os medicamentos sejam prescritos ou os dispositivos médicos sejam utilizados de acordo com as condições previstas na autorização de introdução no mercado ou no procedimento de avaliação de conformidade, respetivamente;

Os testes de diagnóstico são efetuados em condições padronizadas, mas acordo com as condições previstas de utilização

ii) A inclusão do participante numa determinada estratégia terapêutica não seja previamente fixada por um protocolo de estudo, mas dependa da prática corrente;

A inclusão depende do protocolo do estudo, e existe exame (angio-TAC) que em condições habituais não serão efetuados de forma rotineira na prática clínica. Por outro lado, há alguma evidência que sugere a realização de angio-TAC a atletas acima dos 40 anos para despiste de doença coronária.
No contexto do angio-TAC, pode afirmar-se que não será testada a fiabilidade intrínseca do aparelho e da técnica enquanto dispositivo médico, mas o que está em causa são outros aspetos, como por ex., a potencialidade enquanto teste diagnóstico preditor de doença coronária acima dos 40 anos, em atletas.

Iii) A decisão de prescrever o medicamento ou utilizar um dispositivo médico esteja claramente dissociada da decisão de incluir ou não o participante no estudo;

Formalmente a decisão de aplicar a angio-TAC depende da inclusão no estudo

iv) Não seja aplicado aos participantes qualquer outro procedimento complementar de diagnóstico ou de avaliação e sejam utilizados métodos epidemiológicos para analisar os dados recolhidos;

RS

Anexo: Fundamentação do parecer.

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Há a realização de procedimentos estandardizados de diagnóstico que vão permitir aferir a potencialidade do angio-TAC enquanto teste de diagnóstico numa condição específica.

A aplicação da Lei 21/2014 permite concluir que se classifica como estudo com intervenção.

A questão essencial é se sendo estudo com intervenção será um ensaio clínico ao abrigo da Lei 21/2014 (Lei de investigação clínica) (LIC), ou pode configurar tratar-se de "estudo clínico com intervenção", previsto na LIC.

Na LIC configura-se uma entidade, não existente na Lei 46/2004, e que será a do "estudo clínico com intervenção", no qual se define como (selecionadas as partes da definição que interessam ao estudo em avaliação) "qualquer investigação que preconize uma alteração, influência ou programação dos …comportamentos ou dos conhecimentos dos participantes… com a finalidade de descobrir ou verificar efeitos na saúde, incluindo a exposição a medicamentos, a utilização de dispositivos médicos, a execução de técnicas cirúrgicas, …".

Em conclusão, considera-se que o protocolo apresentado tem caráter interventivo, mas que não envolve o dispositivo médico enquanto objeto específico de estudo, mas como meio de diagnóstico., pelo que, em conformidade com a legislação portuguesa (art. 16º Lei 21/2016 de 16 de abril), a sua avaliação compete às CES.

RS

Anexo: Fundamentação do parecer.

3

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Autorização n.º 10534/ 2016

Helder Alexandre Correia Dores notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realizar um Estudo Clínico sem Intervenção, denominado Relação entre exercício físico e doença coronária em atletas .

A investigação é multicêntrica, decorrendo, em Portugal, nos centros de investigação identificados na notificação.

Existe justificação específica, validada pela Comissão de Ética Competente (CEC), para o tratamento do dado pessoal raça/etnia.

O participante é identificado por um código especificamente criado para este estudo, constituído de modo a não permitir a imediata identificação do titular dos dados; designadamente, não são utilizados códigos que coincidam com os números de identificação, iniciais do nome, data de nascimento, número de telefone, ou resultem de uma composição simples desse tipo de dados. A chave da codificação só é conhecida do(s) investigador(es).

É recolhido o consentimento expresso do participante ou do seu representante legal.

A informação é recolhida diretamente do titular e indiretamente do processo clínico.

As eventuais transmissões de informação são efetuadas por referência ao código do participante, sendo, nessa medida, anónimas para o destinatário.

A CNPD já se pronunciou na Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios aplicáveis para o correto cumprimento da Lei n.º 67/98, de 26 de outubro, alterada pela Lei n.º 103/2015, de 24 de agosto, doravante LPD, bem como sobre as condições e limites aplicáveis ao tratamento de dados efetuados para a finalidade de investigação clínica.

No caso em apreço, o tratamento objeto da notificação enquadra-se no âmbito daquela deliberação e o responsável declara expressamente que cumpre os limites e condições aplicáveis por força da LPD e da Lei n.º 21/2014, de 16 de abril, alterada

pela Lei n.º 73/2015, de 27 de junho – Lei da Investigação Clínica –, explicitados na Deliberação n.º 1704/2015.

O fundamento de legitimidade é o consentimento do titular.

A informação tratada é recolhida de forma lícita, para finalidade determinada, explícita e legitima e não é excessiva – cf. alíneas a), b) e c) do n.º 1 do artigo 5.º da LPD.

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do artigo 30.º da LPD, bem como do n.º 3 do artigo 1.º e do n.º 9 do artigo 16.º ambos da Lei de Investigação Clínica, com as condições e limites explicitados na Deliberação da CNPD n.º 1704/2015, que aqui se dão por reproduzidos, autoriza-se o presente tratamento de dados pessoais nos seguintes termos:

Responsável – Helder Alexandre Correia Dores

Finalidade – Estudo Clínico sem Intervenção, denominado Relação entre exercício físico e doença coronária em atletas

Categoria de dados pessoais tratados – Código do participante; idade/data de nascimento; género; raça/etnia; dados antropométricos; sinais vitais; dados da história clínica; dados dados de exame físico; dados de meios complementares de diagnóstico; medicação prévia concomitante; relativos à atividade profissional com conexão com a Investigação

Exercício do direito de acesso – Através dos investigadores, por escrito

Comunicações, interconexões e fluxos transfronteiriços de dados pessoais identificáveis no destinatário – Não existem

Prazo máximo de conservação dos dados – A chave que produziu o código que permite a identificação indireta do titular dos dados deve ser eliminada 5 anos após o fim do estudo.

Da LPD e da Lei de Investigação Clínica, nos termos e condições fixados na presente Autorização e desenvolvidos na Deliberação da CNPD n.º 1704/2015, resultam

obrigações que o responsável tem de cumprir. Destas deve dar conhecimento a todos os que intervenham no tratamento de dados pessoais.

Lisboa, 04-10-2016

A Presidente

Filipa Calvão

MINISTÉRIO DA DEFESA NACIONAL

ESTADO-MAIOR-GENERAL DAS FORÇAS ARMADAS

HOSPITAL DAS FORÇAS ARMADAS

Exmo. Senhor
Major Médico
Hélder Alexandre Correia Dores
HFAR

Assunto: Parecer da Comissão de Ética para a Saúde

Tendo sido apresentado o pedido de parecer relativo ao registo e à utilização dos dados clínicos de militares avaliados no HFAR nos trabalhos de investigação que compõem a tese intitulada ***"Cardiovascular Risk Assessment in Athletes: the role of Electrocardiography and Imaging"*** do Major Médico Hélder Dores, decide-se emitir um parecer favorável.

Os vários trabalhos apresentados e publicados, destacando-se o artigo *"Comparison of Three Criteria for Interpretation of Electrocardiogram in the Military"*, possuem elevado interesse científico para a Instituição, resultando de estudos observacionais, sem intervenção terapêutica e que seguiram os princípios da bioética.

Lisboa, 26 de outubro de 2018

O Presidente da Comissão de Ética para a Saúde

José Carlos Nunes Marques
MGen Ref

MINISTÉRIO DA DEFESA NACIONAL

ESTADO-MAIOR-GENERAL DAS FORÇAS ARMADAS
HOSPITAL DAS FORÇAS ARMADAS

DIREÇÃO

Assunto: **Registo e utilização de dados clínicos para investigação**

Exmo. CAP MED Hélder Dores;

Em resposta ao pedido de autorização para o registo dos dados clínicos e dos exames complementares de diagnóstico efetuados a militares avaliados no HFAR-PL na consulta de Cardiologia Desportiva e no âmbito de Pré-Participação, e à sua utilização na investigação *"Comparison of Three Criteria for Interpretation of Electrocardiogram in the Military"*, o parecer é favorável.

Pelo carácter descritivo e não interventivo do estudo, o registo regular de dados já realizado em militares e o interesse desta investigação para o HFAR, não se solicita avaliação específica em sede de Comissão de Ética.

Reforça-se a necessidade de obediência aos princípios de bioética e manutenção de boas práticas, nomeadamente o dever de confidencialidade, a não transmissão de resultados sem avaliação e a aprovação militar interna, bem com o registo de dados em questionário próprio com autorização voluntária dos participantes.

Lisboa, 15 de outubro de 2015

José Carlos Monge
TCOR MED

· U C ·

FMUC FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

COMISSÃO DE ÉTICA DA FMUC

Of. Refª **077-CE-2015**

Data 27/7/**2015**

C/conhecimento ao aluno

Exmo Senhor

Prof. Doutor Armando Carvalho

Coordenador do Gabinete de Estudos Avançados da FMUC

Assunto: Projecto de Investigação no âmbito do Mestrado em Medicina do Desporto (refª CE-087/2015)

Candidato(a): Paulo Jorge Gomes Dinis

Título do Projecto: *"Atletas e militares: Diferente treino condiciona diferente remodeling?".*

A Comissão de Ética da Faculdade de Medicina, após análise do projecto de investigação supra identificado, decidiu emitir o parecer que a seguir se transcreve: ***"Parecer favorável".***

Queira aceitar os meus melhores cumprimentos.

O Presidente,

Prof. Doutor João Manuel Pedroso de Lima

GC

SERVIÇOS TÉCNICOS DE APOIO À GESTÃO - STAG • COMISSÃO DE ÉTICA
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HOSPITAL DA LUZ

ESPÍRITO SANTO **SAÚDE**

HOSPITAL DA LUZ
COMISSÃO DE ÉTICA PARA A SAÚDE

Exmo. Sr.
Dr. Pedro Gonçalves
Unidade de Cardiologia
Hospital da Luz

Assunto: **Utilidade da Tomografia Computorizada Cardíaca na Avaliação da Doença Coronária**

CC.: Director Clínico / Conselho de Administração

A **Comissão de Ética para a Saúde** do Hospital da Luz, reunida a 25 de Fevereiro de 2011 aprovou por unanimidade a realização do estudo clínico **Utilidade da Tomografia Computorizada Cardíaca na Avaliação da Doença Coronária,** de que V. Exa. é investigador principal.

Com os melhores cumprimentos

Lisboa, 25/02/2011

Pel'A Comissão de Ética para a Saúde

João Sá, Presidente

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HL MOD.1

North & Mid Essex Local Research Ethics
Committee
2nd Floor
8 Collingwood Road
Witham
Essex
CM8 2TT
Tel: 01376 302224
Fax: 01376 302119

Our Ref: MH 532A-2-04
Your Ref:

Dr Sanjay Sharma
University Hospital Lewisham
Lewisham High Street
Lewisham
London
SE13 6LH

24 March 2004

Dear Dr Sharma

Re: MH532A-02-04: The role of the ECG as a useful tool in detecting cardiac abnormalities in young apparently healthy people

Thank you for your letter of 18 March 2004 enclosing amended documentation. Following further review by the Chair, we are satisfied that your resubmitted application conforms to the requirements of the committee. This study is now given Local Research Ethics Committee approval to proceed. Please ensure that any future correspondence includes our reference number.

You will no doubt realise that even when the LREC has given approval for your project on ethical grounds, it is still necessary for you to obtain approval, *if you have not already done so*, from the Trusts in which the work will be carried out.

- It is condition of the approval that all raw data is the responsibility of the Principal Investigator. Such data is to be retained for 5 years post completion of the study, and kept in a safe, secure environment.
- It is a condition of the approval that the Committee is advised of research progress annually (a form is enclosed for your use) and that a final report is submitted within three months of completion of the study.
- If the research is terminated prematurely a report is required within 15 days of the termination date giving details of the reason for the early finish.
- Any deviation from, or changes to, the protocol must be submitted to the Research Ethics Committee in writing for consideration *prior to being implemented.*
- The Committee must be advised of any unusual or unexpected results that raise questions about the safety of the research.
- If the research has not started within two years of the date of this letter Local Research Ethics approval will be withdrawn and it is essential that the application be resubmitted.

I wish you every success with your project.

Yours sincerely

MARTIN HARRISON
Chair
North & Mid Essex Local Research Ethics Committee
Email: nmelrec@essexsha.nhs.uk

NHS
National Patient Safety Agency
National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:

Name: Prof. Sanjay Sharma BSc (Hons), MD, FRCP (UK), FESC
Address: Prof. Sanjay Sharma BSc (Hons), MD, FRCP (UK), FESC
Division of Cardiac and Vascular Sciences,
St George's University of London
Cranmer Terrace
London SW17 0RE

Telephone: 07930 407 772
Email: ssharma21@hotmail.com
Fax: 01737 363 444

Full title of study:	**Evaluation of the 12 lead ECG as a useful tool in identifying young apparently healthy individuals with cardiac disease.**
Name of main REC:	Essex 2 Research Ethics Committee EoE REC Office (3) 9th Floor Terminus House The High, Harlow Essex CM20 1XA
REC reference number:	MH532A-02-04
Date study commenced:	24th March 2004
Protocol reference *(if applicable)*, current version and date:	Version 5 from 8/03/04

Amendment number and date:	5 – 19.03.2010.

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

No

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

Notice of amendment (non-CTIMP), version 3.1, November 2005

1. Doctor present on the day

To fast track any cases that require immediate treatment: to carry out further investigations on the day to reduce false positives; to carry out a consultation with each patient and address any concerns they have; to provide instant information relating to their result.

2. ECHO performed on the day

When ECGs are abnormal a follow up Echocardiogram is required. With a Doctor present on the day it is possible to identify abnormal ECGs and conduct ECHO (Echocardiogram) on the day. When Echocardiograms are conducted on the day this will significantly reduce the number of false positives and number of people who will be required to be referred to follow up tests (from approximately 10% to 2- 4%).

This also improves the experience of a significant percentage (up to 6%) of participants that will not have to wait between having an abnormal ECG and the follow up ECHO.

With a Doctor present on the day it is also possible to confirm with the patient that the ECG was not abnormal and no further tests are required.

3. Sending out of the results

To send all abnormal results recorded delivery to ensure that the letters are received.

4. Online booking of screening appointment

To enable people to book their appointment online giving their home and GP's details online. This is a secure service that reduces school administration and enables result letters to be sent to the patients more quickly. This reduces the potential for administrative error where by the individual types in their personal and GP's details. The quality of data is not dependent on the person's ability to read other people's writing.

There is a reduction in administrative time required to contact participants to clarify their personal details.

The online system enables mandatory fields to be set to ensure that people have to find out the correct information prior to the testing, rather than to turn up with the incomplete fields on their medical questionnaire, usually their GP's address.

The NSF chapter 8 guidelines state that a person with a family history of young sudden cardiac death should be referred directly to a specialist cardiologist for a full review. The online booking system also enables administrators to identify any people with a family history of young sudden death prior to the testing and advice them accordingly. Should they still choose to attend the testing, the Dr will be advised of their family history prior to the event.

5. Ongoing evaluation of the impact of the programme

On occasion, participants identified with an abnormality are referred by their GP to a cardiologist who does not forward a copy of their final diagnosis to Professor Sharma. For

Notice of amendment (non-CTIMP), version 3.1, November 2005

this reason we have incorporated some text into the informed consent that will open the opportunity for participants to be contacted at a later date to confirm that they were referred correctly ("CRY may contact you in the future for information about any follow up tests you may require").

As with every screening programme there is possibility for false negatives. Currently there are no publications that evaluate the impact of false negatives. For this reason we will give some people the opportunity to be tested on a second occasion. We have introduced an opt-out question on the informed consent whereby they can choose for us not to contact them in the future for the repeat testing ("CRY may contact you in the future to have your tests repeated for research purposes. If you would prefer not to be contacted to be offered repeat testing, please tick the box" ☐).

6. Increase sample size to 20,000 and extend the duration of the study by 3 years

CRY has £730,000 ringfenced for screening throughout the UK. This will fund the cost of testing a further 20,857 young people (aged 14-35) (£35/person). CRY has recently awarded a grant of £500,000 to Professor Sharma at St George's Hospital, London, for clinical fellowship grants to facilitate the testing and follow up appointments of the CRY screening programme. CRY currently tests over 6,500 young people per year. We would therefore expect the testing of 20,000 people to take 3 years to complete.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

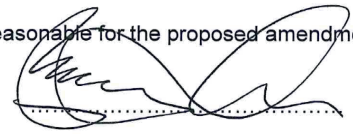
List of enclosed documents

Document	*Version*	*Date*
Protocol	5	19.03.2010
Consent form	5	19.03.2010
Health Questionnaire	5	19.03.2010
Information letter	5	19.03.2010
Leaflet	5	19.03.2010
All-clear example result	5	19.03.2010
Information letter for Parent/Guardian	5	19.03.2010
Changes to the Protocol document		19.03.2010

Notice of amendment (non-CTIMP), version 3.1, November 2005

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: 

Print name: Prof. Sanjay Sharma

Date of submission: 23/03/10

Notice of amendment (non-CTIMP), version 3.1, November 2005

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Proc. 11203/2008

Autorização n.º 2391 /2010

Centro Hospitalar de Lisboa Ocidental, EPE notificou um tratamento com a finalidade declarada de gestão de doentes do serviço de cardiologia

Declara as seguintes categorias de dados pessoais:

Dados de Identificação: Nome, idade, sexo, morada, sistema de saúde, n.º do Serviço Nacional de Saúde e de beneficiário, NIF e contactos telefónicos;

Dados Clínicos: Antecedentes pessoais de saúde, diagnóstico, terapêutica, resultados laboratoriais e meios auxiliares de diagnóstico.

O n.º 4 do art. 7º da Lei n.º 67/98, de 26 de Outubro admite o tratamento de dados de saúde quando for necessário para efeitos de medicina preventiva, diagnóstico médico, prestação de cuidados ou tratamentos médicos ou para gestão dos serviços de saúde, desde que o tratamento desses dados seja efectuado por profissional de saúde sujeito a sigilo médico ou por outra pessoa obrigada a segredo profissional de saúde e desde que estejam garantidas medidas de segurança da informação.

A informação tratada é recolhida de forma lícita (art.º 5º, n.º1 al. a) da Lei 67/98), com consentimento do titular, para finalidades determinadas, explícitas e legítimas (cf. al. b) do mesmo artigo) e a informação recolhida não é excessiva.

Assim, nos termos dos artigos 27º, n.º1 e 30º da Lei de Protecção de Dados regista-se, nos exactos termos declarados, o tratamento nos seguintes termos e com as seguintes condições:

1. **Responsável:** Centro Hospitalar de Lisboa Ocidental, EPE
2. **Categorias de dados pessoais tratados:**

   Dados de Identificação: Nome, idade, sexo, morada, sistema de saúde, n.º do Serviço Nacional de Saúde e de beneficiário, NIF e contactos telefónicos;

   Dados Clínicos: Antecedentes pessoais de saúde, diagnóstico, terapêutica, resultados laboratoriais e meios auxiliares de diagnóstico.
3. **Finalidade:** gestão de doentes do serviço de cardiologia
4. **Entidades a quem podem ser transmitidos:** Não há comunicação de dados.
5. **Forma de exercício do direito de acesso e rectificação:** Por solicitação escrita ou pessoal. A informação é revelada por «intermediação médica» (cf. artigo 11.º n.º 5 da Lei 67/98).
6. **Interconexões** : Não existem

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21 393 00 39
LINHA PRIVACIDADE
Dias úteis das 10 às 13 h
duvidas@cnpd.pt

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

7. Transferências de dados para países terceiros : Não há.

8. Tempo de conservação:

a) Dados de saúde – Nos termos da Portaria n.º 247/2000, de 8 de Maio;

b) ***Dados para facturação*** – 10 anos.

Aos titulares dos dados deve ser assegurado o direito de Informação previsto no art. 10º da referida lei;

O responsável deve assegurar as medidas de segurança necessárias à sensibilidade da informação tratada, designadamente a separação lógica entre os dados administrativos e os dados de saúde (cf. Art.º 15º n.º 3 da referida lei), devendo ser adoptadas medidas de segurança que impeçam o acesso à informação por pessoas não autorizadas. A informação de saúde deverá ser de acesso restrito aos médicos e técnicos de saúde ou, sob a sua direcção, a outros profissionais obrigados a segredo profissional (n.º 4 do citado art.º 7º). O sistema deve ser dotado de *passwords* de acesso diferenciado para assegurar as exigências supra especificadas;

Lisboa, 7 de Junho de 2010

Ana Roque, Carlos Campos Lobo, Luís Paiva de Andrade, Helena Delgado António, Luís Barroso (Relator), Vasco Almeida

Luís Lingnau da Silveira (Presidente)

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APPENDIX B - Informed consents and participation authorizations

CONSENTIMENTO INFORMADO

ESTUDO: Relação entre Exercício Físico e Doença Coronária

Por favor, leia com atenção todo o conteúdo deste documento e não hesite em solicitar mais informações se não estiver completamente esclarecido.
Verifique se todas as informações estão corretas e se aceitar participar, pedir-lhe-emos que assine o seu consentimento, do qual lhe será dada uma cópia.

A informação colhida será mantida sempre estritamente confidencial, de acordo com os princípios legais. Será introduzida numa base de dados para análise pelos investigadores responsáveis, estando abrangidos pelo obrigatório 'segredo médico profissional'. Não será possível a ninguém que não esteja ligado ao estudo aceder a qualquer informação pessoal ou de índole médica.

O **OBJETIVO PRINCIPAL** deste estudo é avaliar a relação entre a prática regular de exercício físico com a presença e a gravidade de doença coronária. Foi selecionado e é convidado a participar de forma voluntária porque preenche os critérios de inclusão, nomeadamente ter pelo menos 40 anos de idade, praticar exercício físico regularmente (pelo menos 4h por semana e de forma continua há 5 ou mais anos), não apresentar sintomas relacionados com o exercício físico (ex. dor no peito, palpitações, falta de ar ou desmaios) e não ter doenças cardiovasculares conhecidas ou outras que limitem o exercício físico.

A participação neste estudo, além da história clínica e da avaliação física realizada em consulta específica, implica a realização de **exames complementares de diagnóstico**: tomografia computorizada cardíaca (Angio-TC), ecocardiograma transtorácico, análises sanguíneas, eletrocardiograma e prova de esforço em tapete rolante.

A **ANGIO-TC CARDÍACA** é realizada no âmbito do protocolo de **investigação** do estudo, não estando recomendada por rotina na avaliação desta população. Este exame é efetuado com recurso a radiação ionizante (raios-X). Para maior segurança utilizamos técnicas e equipamentos que reduzem ao máximo a dose a que o doente fica exposto. Este exame implica a administração de contraste iodado (endovenoso), de um medicamento sublingual (nitrato) e quando indicado, de outro por via oral ou endovenosa (betabloqueante) visando melhorar a sua qualidade. Antes do exame serão excluídas as suas principais contraindicações, nomeadamente insuficiência renal ou história de reações alérgicas a contraste iodado. Estas reações adversas ao contraste podem ocorrer, mas na grande maioria dos casos são leves (ex. reações cutâneas e náuseas), enquanto as graves (com risco de vida) são extremamente raras. Caso ocorram poderá ser necessário administrar medicamentos endovenosos com o objetivo de as reverter.

O participante

Fui informado do objetivo de estudo e dos exames complementares de diagnóstico que é necessário realizar, nomeadamente a Angio-TC cardíaca. Fui esclarecido dos cuidados que deverei ter durante e após este exame, a fim de aumentar a sua eficácia e prevenir eventuais complicações. Autorizo a equipa médica e os seus assistentes a realizarem tudo o que considerarem necessário para a concretização deste procedimento, ou de medidas adicionais que visem o tratamento de complicações do mesmo.

Declaro ter compreendido quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada a oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre a proposta.

ACEITO ☐ **NÃO ACEITO** ☐ *(assinalar com X a opção escolhida)* participar voluntariamente neste estudo, bem como realizar os exames complementares que são solicitados e outros procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas devidamente fundamentadas.

Nome:_____

Assinatura: _____ Data: _____/_____/_____

Nome legível do profissional de saúde: _____

Assinatura: _____ Data: _____/_____/_____

Ministério da Defesa Nacional

Hospital das Forças Armadas - PL

Serviço de Imagiologia

TERMO DE RESPONSABILIDADE DE CONSENTIMENTO LIVRE E ESCLARECIDO

ANGIO TC CARDÍACA E DOS VASOS PERIFÉRICOS

A Angio TC é uma técnica de diagnóstico de imagem que usa Radiação X para visualização de estruturas vasculares. Antes da realização deste exame deverá ter em consideração as seguintes indicações:

- Jejum de 4 horas
- Trazer análises recentes
- Não interromper a medicação habitual salvo por indicação médica.
- Não consumir substâncias excitantes (ex.: café, chá verde, bebidas energéticas) 12 horas antes do exame
- Não realizar exercício físico no dia do exame

A qualidade do exame depende do controlo da frequência cardíaca (valores inferiores a 65bpm), podendo ser necessário administrar um medicamento (beta-bloqueante) oral ou endovenoso, em geral bem tolerado, mas por via oral poderá aumentar o tempo de espera em aproximadamente 2 horas.

A visualização das estruturas vasculares implica a administração de contraste que poderá provocar reações adversas, quase sempre ligeiras (ex.: sensação de calor no corpo, sabor a ferro e náuseas), que passam em segundos e que normalmente não necessitam de terapêutica. No entanto, podem ocorrer outras reações, principalmente cutâneas (ex.: borbulhas, comichão e vermelhidão), que justificam terapêutica e acompanhamento adequado. Muito raramente ocorrem reações mais graves (um caso em cada 75000) com necessidade de apoio médico urgente.

Para reduzir a possibilidade da ocorrência e o nível de gravidade destas reações é conveniente respeitar as indicações tidas na preparação do exame e preencher o seguinte questionário.

Para esclarecimentos adicionais contacte o Serviço de Imagiologia pelo número 217714000 entre as 9 as 18 horas.

QUESTIONÁRIO

(assinale a opção correta)

	SIM	NÃO
TEM ALERGIA A ALGUM MEDICAMENTO?	☐	☐
Se sim, a qual/quais? _____		
TEM ALERGIA A ALGUM ALIMENTO?	☐	☐
Se sim, a qual/quais? _____		
TEM ALERGIA AOS ÁCAROS, POLÉN OU PÓ?	☐	☐
TEM ASMA OU RINITE ALÉRGICA?	☐	☐
Se sim, que medicação faz? _____		
TEM DIABETES?	☐	☐
FAZ METFORMINA?	☐	☐
Ex. Risidon, Stagid, Zomarist, Icandra, Eucreas, Janumet, Velmetia.		
JÁ FOI OPERADO/A?	☐	☐
Se sim, que cirurgia? _____		
TEM ALGUMA DOENÇA RENAL?	☐	☐
Se sim, qual? _____		
TEM HIPERTIROIDISMO?	☐	☐
***Se mulher*, PODERÁ ESTAR GRÁVIDA?**	☐	☐
***Se homem*, FEZ NAS ÚLTIMAS 48H MEDICAÇÃO PARA DISFUNÇÃO ERÉCTIL?**	☐	☐
JÁ FEZ ALGUMA VEZ EXAMES COM CONTRASTE?	☐	☐
SE SIM, TEVE ALGUMA REAÇÃO ALÉRGICA?	☐	☐
Qual? _____		

PESO_____kg **ALTURA** _____m **TENSÃO ARTERIAL** _____/_____ mmHg **FREQUÊNCIA CARDÍACA**_____bpm

Eu abaixo assinado, estou devidamente esclarecido e consinto a realização do exame **com** contraste

_____

(assinatura por extenso)

Data _____/_____/_____

CONSENTIMENTO INFORMADO

De acordo com a Declaração de Helsínquia da Associação Médica Mundial e suas atualizações:

1. Declaro ter lido este formulário e aceito de forma voluntária participar neste estudo.
2. Fui devidamente informado(a) da natureza, objetivos, riscos, duração provável do estudo, bem como do que é esperado da minha parte.
3. Tive a oportunidade de fazer perguntas sobre o estudo e percebi as respostas e as informações que me foram dadas.

   A qualquer momento posso fazer mais perguntas ao médico responsável do estudo. Durante o estudo e sempre que quiser, posso receber informação sobre o seu desenvolvimento. O médico responsável dará toda a informação importante que surja durante o estudo que possa alterar a minha vontade de continuar a participar.
4. Aceito que utilizem a informação relativa à minha história clínica e os meus tratamentos no estrito respeito do segredo médico e anonimato. Os meus dados serão mantidos estritamente confidenciais. Autorizo a consulta dos meus dados apenas por pessoas designadas pelo promotor e por representantes das autoridades reguladoras.
5. Aceito seguir todas as instruções que me forem dadas durante o estudo. Aceito em colaborar com o médico e informá-lo(a) imediatamente das alterações do meu estado de saúde e bem-estar e de todos os sintomas inesperados e não usuais que ocorram.
6. Autorizo o uso dos resultados do estudo para fins exclusivamente científicos e, em particular, aceito que esses resultados sejam divulgados às autoridades sanitárias competentes.
7. Aceito que os dados gerados durante o estudo sejam informatizados pelo promotor ou outrem por si designado.

Eu posso exercer o meu direito de retificação e/ ou oposição.

8. Tenho conhecimento que sou livre de desistir do estudo a qualquer momento, sem ter de justificar a minha decisão e sem comprometer a qualidade dos meus cuidados médicos. Eu tenho conhecimento que o médico tem o direito de decidir sobre a minha saída prematura do estudo e que me informará da causa da mesma.
9. Fui informado que o estudo pode ser interrompido por decisão do investigador, do promotor ou das autoridades reguladoras.

Nome do Participante_____

Assinatura:_____ _____

Data:_____/_____/____

Nome de Testemunha / Representante Legal:_____

Assinatura:_____ _____

Data:_____/_____/____

Confirmo que expliquei ao participante acima mencionado a natureza, os objetivos e os potenciais riscos do Estudo acima mencionado.

Nome do Investigador:_____

Assinatura:_____ _____

Data:_____/_____/____

MINISTÉRIO DA DEFESA NACIONAL

HOSPITAL DAS FORÇAS ARMADAS
POLO DE LISBOA

SERVIÇO DE CARDIOLOGIA

CARDIOLOGIA DESPORTIVA

NOME: _____

DATA DE NASCIMENTO: ____/____/_____ **IDADE:** _____ **anos**

GÉNERO: masculino □ feminino □ **PESO:** _____ **kg** **ALTURA:** _____ **cm**

ETNIA: Caucasiana (branca): □ Negra: □ Oriental: □ Outra: _____

MILITAR NO ATIVO: sim □ não □

Se sim, POSTO: _____ **UNIDADE:** _____

CONTACTO TELEFÓNICO: _____

Antecedentes clínicos:

HIPERTENSÃO ARTERIAL: sim □ não □

DIABETES: sim □ não □

COLESTEROL ELEVADO: sim □ não □

TABAGISMO ATIVO: sim □ não □ **Número de cigarros/dia:** _____ **cigarros**

HISTÓRIA FAMILIAR DE DOENÇA CARDÍACA: sim □ não □

(Ex. Enfarte agudo do miocárdio, AVC, morte súbita em familiares de primeiro grau – pai com <55 anos e mãe com <65 anos)

OUTRO ANTECEDENTE RELEVANTE: _____

MEDICAÇÃO HABITUAL: _____

História desportiva:

PRATICA REGULARMENTE EXERCÍCIO FÍSICO? sim □ não □

Modalidade(s): _____

NÚMERO DE HORAS DE TREINO SEMANAL: _____ **horas**

PARTICIPA ATUALMENTE EM COMPETIÇÕES (nível federado ou recreativo)? sim □ não □

Há quantos anos pratica desporto competitivo? _____ **anos**

SE NÃO PARTICIPA ATUALMENTE EM COMPETIÇÕES MAS JÁ O FEZ NO PASSADO,

Quantos anos praticou?_____ **anos.**

Em que modalidade(s) praticou? _____

TEM SINTOMAS RELACIONADOS COM A PRÁTICA DESPORTIVA: sim □ não □

Se sim, especificar: _____

(Ex. Dor torácica, palpitações, desmaio ou cansaço exagerado para a intensidade de exercício realizada)

Data: ____/____/_____

Assinatura: _____

Questionário angioTCs cardíacas

Foi-lhe solicitada pelo seu medico assistente a realização de uma angioTC cardíaca. O centro de Imagiologia do Hospital da Luz é uma referencia nesta área, fruto não só do elevado numero de exames mas sobretudo da investigação científica, apresentada regularmente em reuniões nacionais e internacionais de Cardiologia e de Imagiologia e estando em curso 2 teses de doutoramento nesta área.
Para este efeito, gostaríamos de pedir a sua colaboração no preenchimento deste questionário, cuja informação (bem como a do resultado do seu exame) será introduzida numa base de dados, para análise pelos médicos responsáveis pelos exames de angioTC cardíaca. Será sempre respeitada a sua confidencialidade, retirada a sua identificação de qualquer imagem que possa vir a ser apresentada e/ou publicada, estando estes dados abrangidos pelo obrigatório "segredo médico profissional".

Tem tensão arterial elevada ou toma medicação para a tensão arterial ?

☐ SIM ☐ NÃO

Tem o colesterol elevado ou toma medicação para o colesterol ?

☐ SIM ☐ NÃO

Tem diabetes?

☐ SIM ☐ NÃO

É fumador (ou ex-fumador há menos de 1 ano)?

☐ SIM ☐ NÃO

Tem história de doença cardiovascular na família (enfarte do miocárdio ou acidente vascular cerebral - AVC)?

☐ SIM ☐ NÃO

Se sim, esses antecedentes são num familiar directo (Pai, Mãe, Irmãos) e em idade prematura (num homem <55 anos; numa mulher <65 anos)?

☐ SIM ☐ NÃO

Sabe o nome dos medicamentos que toma regularmente?

_____

_____

Autorizo que os meus dados sejam incluídos em bases de dados para investigação científica e aceito ser eventualmente contactado telefonicamente de futuro para seguimento e atualização da minha situação clinica.

*Data*____/____/_____*Assinatura*_____

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

CENTRO DE REFERÊNCIA

Serviço Cardiologia - CHLO

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

Para Atos / Intervenções de Saúde nos termos

da norma N. 015/2013 da Direcção Geral de Saúde

CATETERISMO CORONÁRIO E REVASCULARIZAÇÃO PERCUTÂNEA DE DOENÇA CORONÁRIA (ANGIOPLASTIA)

1. Diagnóstico / descrição da situação clínica:

.....
.....
.....

2. Descrição do ato/ intervenção: A revascularização coronária percutânea ou angioplastia é uma intervenção que se inicia pela punção (picada) duma artéria do braço ou da perna, sob anestesia local, sendo depois inserido um tubo pequeno e fino (chamado de catéter) até às artérias do coração (coronárias). Através deste catéter administram-se pequenas quantidades de contraste opaco aos Raios-X, permitindo a visualização do interior das artérias do coração e a identificação de possíveis obstruções (isto consiste na angiografia coronária). Após a identificação e caracterização das obstruções é possível desobstruí-las, primeiro com um balão que é insuflado na obstrução, e depois colocando uma malhinha metálica (chamada de *stent* coronário), que permite manter a artéria aberta, com um fluxo normal de sangue para o coração. O procedimento é habitualmente indolor, embora por vezes possa surgir, nalguns casos, algum desconforto no peito durante e após o exame.

3. Benefícios: A angioplastia permite o alívio de obstruções ao fluxo de sangue nas artérias coronárias, melhorando na grande maioria dos doentes os seus sintomas e/ou o prognóstico a longo prazo. A sua realização evita, na maioria dos doentes, o recurso à revascularização por cirurgia convencional (cirurgia de bypass), que pode acarretar riscos desnecessários para o doente.

4. Riscos graves e riscos frequentes: As complicações mais frequentes são vasculares, ou seja, relacionadas com as artérias picadas no início do procedimento, e podem ser: hematoma, oclusão aguda (redução do fluxo de sangue a passar nessa artéria) ou hemorragia, embora com o uso habitual das artérias do braço estas complicações são mais raras (<2%). A maior parte destas complicações não são graves e habitualmente regridem em poucos dias após a intervenção.
No caso do tratamento das artérias do coração (angioplastia), a complicação mais grave consiste na obstrução da artéria coronária logo após o procedimento (<1%), sendo minimizada pelo uso de medicamentos que previnem a formação de trombos e tratada com nova angioplastia urgente. A ocorrência de dissecção coronária ou aórtica (em que ocorre uma lesão da parede do vaso com acumulação de sangue na parede) é uma complicação rara (<1%). A necessidade de injecção de contraste iodado poderá desencadear uma reação alérgica (<1%) ou aumentar o risco de agravamento da função renal, sobretudo em doentes com insuficiência renal prévia (<5%). Outras complicações imponderáveis podem ocorrer.
Riscos particulares deste doente: .....

5. Alternativas: A cirurgia de bypass pode ser uma alternativa com eficácia semelhante à angioplastia coronária, embora tenha riscos associados maiores e um tempo de recuperação mais prolongado. O uso de medicamentos pode melhorar os sintomas do doente embora a sua eficácia seja mais limitada, não permitindo restabelecer o fluxo sanguíneo nas artérias coronárias obstruídas como a angioplastia coronária ou a cirurgia convencional.

6. Riscos de não tratamento: A não realização de revascularização coronária percutânea poderá ter implicações no seu prognóstico e na sua qualidade de vida.

REPÚBLICA PORTUGUESA SAÚDE — SNS SERVIÇO NACIONAL DE SAÚDE — CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E. — CENTRO DE REFERÊNCIA

Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao acto a que este documento se refere. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti ao doente (ou aos seus representantes) que em caso de recusa lhe serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: ..... Assinatura: .....

Data ... .../... .../.... Contacto institucional: ..... Nº OM ou mecanográfico: .....

Dúvidas e esclarecimentos: Serviço de Cardiologia do CHLO

Contactos telefónicos: 210433166 (HSC), 210431099 (HSFX) e 210432508 (HEM) Horário de Atendimento: 9h às 16h

Contacto telefónico fora do horário de atendimento: 210433000

À pessoa / representante: Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

Declaro ter compreendido os objectivos do exame e/ou intervenção que me foi proposto(a) e explicado(a) pelo profissional de saúde que assina este documento. Foi-me dada oportunidade para fazer todas as perguntas que entendi necessárias sobre o assunto e obtive resposta esclarecedora para todas elas. Foi-me assegurado que não haverá prejuízo para os meus direitos assistenciais se recusasse esta solicitação e foi-me concedido tempo suficiente para reflectir sobre esta proposta.

Autorizo o acto indicado, bem como os procedimentos com ele directamente relacionados que sejam necessários no meu próprio interesse se justificados por razões clínicas fundamentadas.

Autorizo o registo das imagens (fotografia ou filme) relativos ao exame e/ou intervenção e a sua utilização, assim como de outra documentação relativa a este episódio, para revisão ou formação de profissionais, após devidamente anonimados e autorizados, de acordo com o tipo de Estudo, por um ou vários dos seguintes Órgãos: Direcção do Serviço, Comissão de Ética e Departamento de Investigação.

Nome: |_____| ... / ... / ..... (data) Assinatura ... ...

Se não for o próprio a assinar por menoridade ou incapacidade (se o menor tiver discernimento deve também assinar acima):

Nome: ... ... Doc. Identificação N º ..... Data ou Validade ..... /..... /...

Parentesco ou tipo de representação: ..... REPRESENTAÇÃO: .....

Nos termos da norma 015/2013 da DGS este documento tem duas vias: uma para o processo clínico e outro para ficar na posse do doente/representante.

REFERÊNCIAS BIBLIOGRÁFICAS:

- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal 2014; 35: 2541-2619.
- Levine G, Bates E, Blankenship J, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. JACC 2011; 58(24): e44-122.

CRY

CARDIAC RISK IN THE YOUNG

HEAD OFFICE: Unit 1140B, The Axis Centre, Cleeve Road, Leatherhead, KT22 7RD.
Tel: 01737 363 222 **Fax:** 01737 363 444 **E-mail:** cry@c-r-y.org.uk **Websites:** www.c-r-y.org.uk www.sads.org.uk

Name of Client
Address of Client

Dear xxxxxx,

Many thanks for attending cardiac screening conducted by Cardiac Risk in the Young (CRY) on xx/xx/xx in xxxxxxx. We had recommended that you would benefit from further evaluation and testing after the CRY screening event. We had written to your GP regarding this. We hope you are keeping well.

Cardiac Risk in the Young (CRY) has been working to reduce the frequency of sudden cardiac death in young individuals. This includes developing and promoting research both in elite athletes and the general population. Research through CRY has already contributed significantly to the understanding of cardiac conditions in young individuals globally.

We take this opportunity to invite you to participate in our research which we envisage will lead to an even greater understanding of such conditions as well as potentially reduce the frequency of sudden cardiac death in the young.

What is the purpose of this investigation?

The vast of majority of conditions that can cause sudden cardiac death in young individuals can be detected during life and are potentially treatable.

We are collecting information relating to the long-term cardiac health and well-being of individuals who have been screened by CRY. We aspire that such information may result in a reduction in the frequency of sudden cardiac death in the young by:

1. Establishing the precise frequency of cardiac disorders capable of causing sudden death in asymptomatic and apparently healthy young individuals
2. Gaining a greater understanding of the conditions associated with sudden cardiac death in young individuals
3. Determining the effectiveness of screening for cardiac conditions in the young

Do you have to take part?

Participation in research with CRY is completely voluntary. You are free to withdraw consent and discontinue participation in any procedures at any time without giving a reason. Not participating in research will not affect the care you receive in the future in any way.

What will you do in the project?

This research project does not require your active participation or any further tests. Should you wish to participate, we would ask you to sign the consent form below and return it to us. Signing this form indicates that you agree for the CRY team to contact your GP and for your GP to release the results of your cardiac investigations to CRY. Please note that we will only collect data relating to your cardiac health.

Why have you been invited to take part?

You have been invited to participate in this research because you have undergone cardiac screening through CRY.

What happens to the information in the project?

Any information collected about you during the course of the study will be kept strictly confidential and held securely and be used for research purposes only. All data collected will be "anonymised"- that is, any information collected that leaves the study office will have all names and addresses removed so that individuals cannot be recognised from it.

Thank you for reading this information – please ask any questions if you are unsure about what is written here.

Further information

Please kindly return the signed form to CRY using the pre-paid envelope attached. Should we not hear from you in one month, we will attempt to contact you via telephone. The purpose of telephoning you will only be to find out whether you received the patient information sheet, and give you an opportunity to ask questions if you have any queries about the research. The person telephoning you will not pressure you to take part in the study, and will ring back at a different time if it is not convenient for you to speak at the time they ring you initially, or if you have not had sufficient time to study the patient information sheet.

If you have any questions concerning the resarch, please contact Dr. Harshil Dhutia, the Study Co-ordinator on 01737 363 222 or email at hdhutia@c-r-y.org.

If you have any comments, concerns or complaints about any aspect of the way you have been approached or treated during the course of this research, you can write to Dr Steve Cox, CRY, Unit 1140B, The Axis Centre, Cleeve Road, Leatherhead, KT22 7RD or telephone 01737 363 222.

CRY

CARDIAC RISK IN THE YOUNG

HEAD OFFICE: Unit 1140B, The Axis Centre, Cleeve Road, Leatherhead, KT22 7RD.
Tel: 01737 363 222 **Fax:** 01737 363 444 **E-mail:** cry@c-r-y.org.uk **Websites:** www.c-r-y.org.uk www.sads.org.uk

CONSENT FORM FOR CRY RESEARCH

1. I undwerwent further cardiac testing after the CRY screening and agree for CRY to access my test results through my GP ☐

2. I did not undergo any further testing after the CRY screening ☐

Signature.....

Name of Client.....

Contact Telephone number.....

Parents Signature..... **Date**.....
(Required if individual is under 16 years of age)