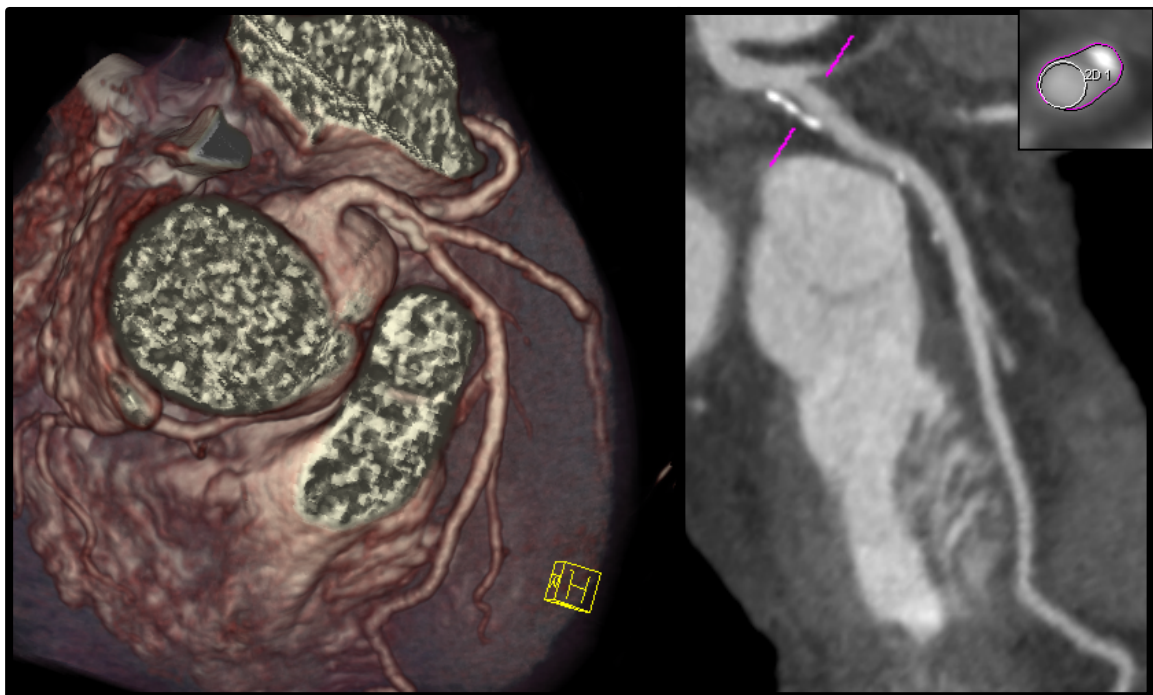


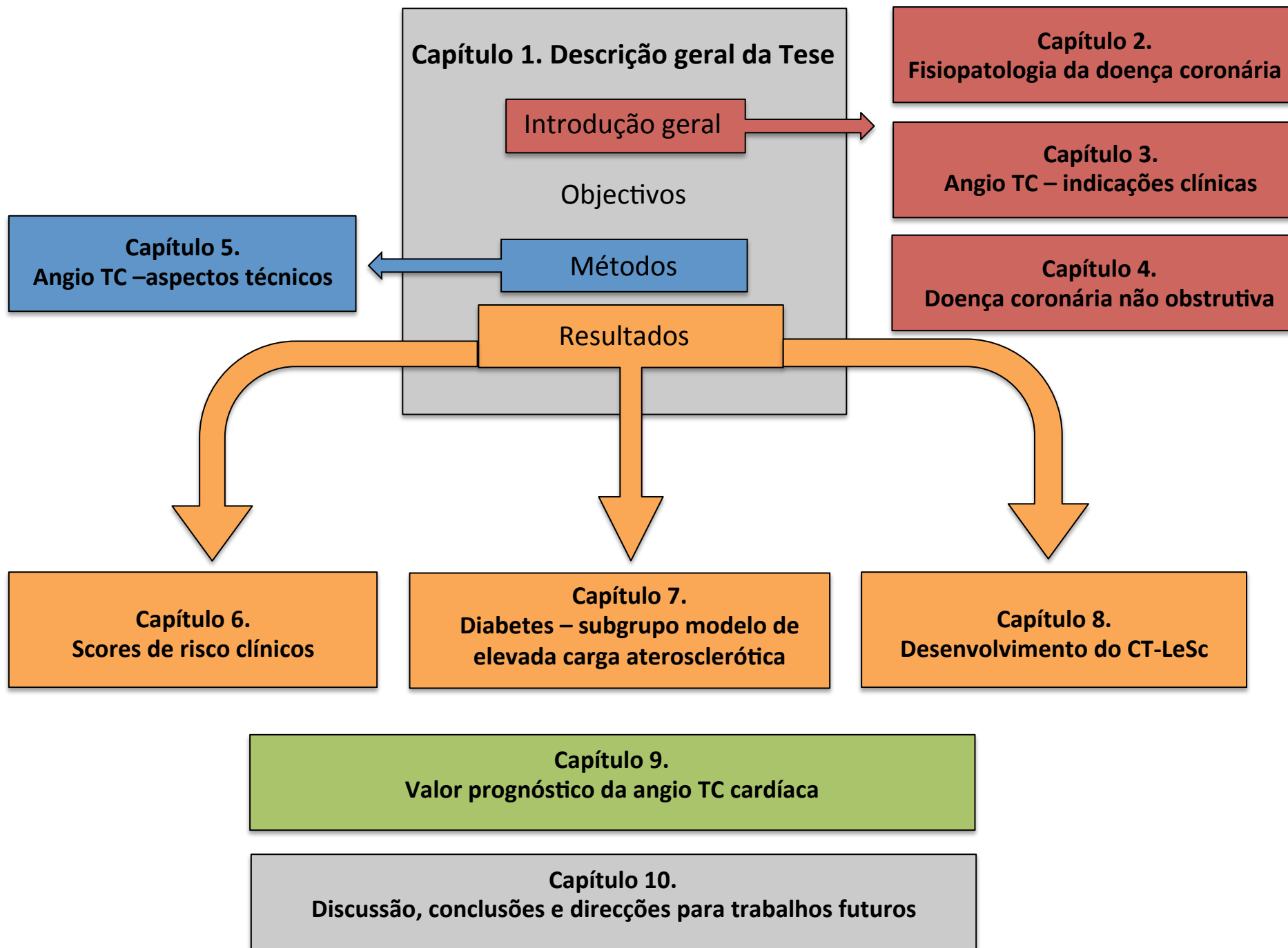
PEDRO ALEXANDRE CASTRO DE ARAÚJO GONÇALVES

Utilidade da tomografia computadorizada cardíaca na avaliação da doença coronária



DISSERTAÇÃO DE DOUTORAMENTO EM MEDICINA, INVESTIGAÇÃO CLÍNICA
FACULDADE DE CIÊNCIAS MÉDICAS, UNIVERSIDADE NOVA DE LISBOA

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DISSERTAÇÃO DE DOUTORAMENTO

TÍTULO DA TESE:

Utilidade da tomografia computadorizada cardíaca na avaliação da
doença coronária

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Aos meus Mestres

À Sílvia, à Rita e ao Pedro

*"The trouble with heart disease
is that the first symptom is often
hard to deal with: death."*

Michael Phelps

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LISTA DE ABREVIATURAS

Angio TC cardíaca	Tomografia computadorizada cardíaca
AI	Angina instável
Bpm	Batimentos por minuto
CaSc	Score de cálcio
CABG	Cirurgia de revascularização miocárdica
CD	Coronária direita
QCA	Análise coronária quantitativa
CX	Circunflexa
CT-LeSc	Score de <i>Leaman</i> adaptado à angioTC cardíaca
CV	Cardiovascular
DA	Descendente anterior
DF	<i>Diamond-Forrester</i>
DC	Doença coronária
EAM	Enfarte agudo do miocárdio
FA	Fibrilhação auricular
HR	<i>Hazard ratio</i>
ICP	Intervenção coronária percutânea
IMC	Índice de massa corporal
IVUS	Ecografia intravascular
IVUS-VH	Ecografia intravascular com histologia virtual
mSv	<i>Milisievert</i>
NCEP-ATPIII	<i>National Cholesterol Educational Program-Adult Treatment Panel III</i>
NICE	<i>National Institute for Health and Clinical Excellence</i>
NRS	<i>Napkin-ring sign</i>
OCT	Tomografia de coerência óptica
OR	<i>Odds ratio</i>
Placa TC-3v-2vDAp	Placa no TC, em 3 vasos ou em 2 vasos com envolvimento DA proximal
SCA	Síndrome coronário agudo
SCCT	<i>Society of Cardiovascular CT</i>
SIS	<i>Segment involvement score</i>
SSS	<i>Segment stenosis score</i>
TA	Tensão arterial
TC	Tronco comum
TCFA	Fibroateroma de cápsula fina
UH	Unidades de Hounsfield
VAP	Válvula aórtica percutânea

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*“Um cavalo nunca corre tão depressa como quando
tem outros cavalos para perseguir”.*

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*“If you can't explain it to a six year old,
you don't understand it yourself.”*

Albert Einstein

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RESUMO

Apesar de toda a evolução farmacológica e de meios complementares de diagnóstico possível nos últimos anos, ***o enfarte agudo do miocárdio e a morte súbita continuam a ser a primeira manifestação da aterosclerose coronária*** para muitos doentes, que estavam previamente assintomáticos.

Os exames complementares de diagnóstico tradicionalmente usados para avaliar a presença de doença coronária, baseiam-se na ***documentação de isquémia do miocárdio*** e por este motivo a sua positividade depende da presença de lesões coronárias ***obstrutivas***.

As lesões coronárias ***não obstrutivas*** estão também frequentemente implicadas no desenvolvimento de eventos coronários. Apesar de o risco absoluto de instabilização por placa ser superior para as lesões mais volumosas e obstrutivas, estas são menos prevalentes do que as placas não obstrutivas e assim, por questões probabilísticas, os eventos coronários resultam com frequência da rotura ou erosão destas últimas.

Estudos recentes de ***imagiologia intracoronária*** avançada forneceram evidência de que apesar de ser possível identificar algumas características de vulnerabilidade em placas associadas ao desenvolvimento subsequente de eventos coronários, a sua sensibilidade e especificidade é muito baixa para aplicação clínica. Mais do que o risco associado a uma placa em particular, para o doente poderá ser mais importante o risco global da sua árvore coronária reflexo da soma das probabilidade de todas as suas lesões, sendo que quanto maior for a carga aterosclerótica maior será o seu risco.

A ***angio TC cardíaca*** é a mais recente técnica de imagem não invasiva para o estudo da doença coronária e surgiu nos últimos anos fruto de importantes avanços na tecnologia de TC multidetectores. Estes avanços, permitiram uma progressiva melhoria da resolução espacial e temporal, contribuindo para a melhoria da qualidade dos exames, bem como uma significativa redução da dose de radiação. A par desta ***evolução tecnológica***, foi aumentando a experiência e gerada mais evidência científica, tornando a angio TC cardíaca cada vez mais robusta na avaliação da doença coronária e aumentando a sua ***aplicabilidade clínica***.

Mais recentemente apareceram vários trabalhos que validaram o seu ***valor prognóstico***, assinalando a sua chegada à idade adulta.

Para além de permitir excluir a presença de doença coronária e de identificar a presença de estenoses significativas, a angio TC cardíaca permite identificar a presença de ***lesões coronárias não obstrutivas***, característica impar desta técnica como modalidade de imagem não invasiva. Ao permitir identificar a totalidade das lesões ateroscleróticas (obstrutivas e não obstrutivas), a

angio TC cardíaca poderá fornecer uma **quantificação da carga aterosclerótica coronária total**, podendo essa identificação ser útil na estratificação dos indivíduos em risco de eventos coronários.

Neste trabalho foi possível identificar **preditores demográficos e clínicos** de uma elevada carga aterosclerótica coronária documentada pela angioTC cardíaca, embora o seu poder discriminativo tenha sido relativamente modesto, mesmo quando agrupados em scores clínicos. Entre os vários scores, o desempenho foi um pouco melhor para o score de risco cardiovascular Heartscore. Estas limitações espelham a dificuldade de prever apenas com base em variáveis clínicas, mesmo quando agrupadas em scores, a presença e extensão da doença coronária.

Um dos factores de risco clássicos, a **obesidade**, parece ter uma relação paradoxal com a carga aterosclerótica, o que pode justificar algumas limitações da estimativa com base em scores clínicos

A **diabetes mellitus**, por outro lado, foi um dos preditores clínicos mais importantes, funcionando como modelo de doença coronária mais avançada, útil para avaliar o desempenho dos diferentes índices de carga aterosclerótica.

Dada a elevada prevalência de placas ateroscleróticas identificáveis por angio TC na árvore coronária, torna-se importante desenvolver ferramentas que permitam quantificar a carga aterosclerótica e assim identificar os indivíduos que poderão eventualmente beneficiar de medidas de prevenção mais intensivas.

Com este objectivo, foi desenvolvido um índice de carga aterosclerótica que reúne a informação global acerca da localização, do grau de estenose e do tipo de placa, obtida pela angio TC cardíaca, o **CT-LeSc**. Este score poderá vir a ser uma ferramenta útil para quantificação da carga aterosclerótica coronária, sendo de esperar que possa traduzir a informação prognóstica da angio TC cardíaca.

Por fim, o conceito de **árvore coronária vulnerável** poderá ser mais importante do que o da placa vulnerável e a sua identificação pela angio TC cardíaca poderá ser importante numa estratégia de prevenção mais avançada. Esta poderá permitir **personalizar as medidas de prevenção primária**, doseando melhor a sua intensidade em função da carga aterosclerótica, podendo esta vir a constituir uma das mais importantes indicações da angio TC cardíaca no futuro.

ABSTRACT

Despite the significant advances made possible in recent years in the field of pharmacology and diagnostic tests, ***acute myocardial infarction and sudden cardiac death remain the first manifestation of coronary atherosclerosis*** in a significant proportion of patients, as many were previously asymptomatic.

Traditionally, the diagnostic exams employed for the evaluation of possible coronary artery disease are based on the ***documentation of myocardial ischemia*** and, in this way, they are linked to the presence of ***obstructive*** coronary stenosis.

Nonobstructive coronary lesions are also frequently involved in the development of coronary events. Although the absolute risk of becoming unstable *per plaque* is higher for more obstructive and higher burden plaques, these are much less frequent than nonobstructive lesions and therefore, in terms of probability *for the patient*, coronary events are often the result of rupture or erosion of the latter ones.

Recent ***advanced intracoronary imaging*** studies provided evidence that although it is possible to identify some features of vulnerability in plaques associated with subsequent development of coronary events, the sensitivity and sensibility are very limited for clinical application.

More important than the individual risk associated with a certain plaque, for the patient it might be more important the global risk of the total coronary tree, as reflected by the sum of the different probabilities of all the lesions, since the higher the coronary atherosclerotic burden, the higher the risk for the patient.

Cardiac CT or Coronary CT angiography is still a young modality. It is the most recent noninvasive imaging modality in the study of coronary artery disease and its development was possible due to important advances in ***multidetector CT technology***. These allowed significant improvements in temporal and spatial resolution, leading to better image quality and also some impressive reductions in radiation dose. At the same time, the increasing experience with this technique lead to a growing body of scientific evidence, making cardiac CT a robust imaging tool for the evaluation of coronary artery disease and increased its ***clinical indications***. More recently, several publications documented its ***prognostic value***, marking the transition of cardiac CT to adulthood.

Besides being able to exclude the presence of coronary artery disease and of obstructive lesions, Cardiac CT allows also the identification of ***nonobstructive lesions***, making this a unique tool in the field of noninvasive imaging modalities.

By evaluating both obstructive and nonobstructive lesions, cardiac CT can provide for the quantification of **total coronary atherosclerotic burden**, and this can be useful to stratify the risk of future coronary events.

In the present work, it was possible to identify significant **demographic and clinical predictors** of a high coronary atherosclerotic burden as assessed by cardiac CT, but with modest odds ratios, even when the individual variables were gathered in clinical scores.

Among these different clinical scores, the performance was better for the Heartscore, a cardiovascular risk score.

This modest performance underline the limitations on predicting the presence and severity of coronary disease based only on clinical variables, even when optimized together in risk scores, One of the classical risk factors, **obesity**, had in fact a paradoxical relation with coronary atherosclerotic burden and might explain some of the limitations of the clinical models.

On the opposite, **diabetes mellitus** was one of the strongest clinical predictors, and was considered to be a model of more advanced coronary disease, useful to evaluate the performance of different plaque burden scores.

In face of the high prevalence of plaques that can be identified in the coronary tree of patients undergoing cardiac CT, it is of utmost importance to develop tools to quantify the total coronary atherosclerotic burden providing the identification of patients that could eventually benefit from more intensive preventive measures.

This was the rational for the development of a coronary atherosclerotic burden score, reflecting the comprehensive information on localization, degree of stenosis and plaque composition provided by cardiac CT – **the CT-LeSc**.

This score may become a useful tool to quantify total coronary atherosclerotic burden and is expected to convey the strong prognostic information of cardiac CT.

Lastly, the concept of **vulnerable coronary tree** might become more important than the concept of the vulnerable plaque and his assessment by cardiac CT might become important in a more advanced primary prevention strategy. This could lead to a more **custom-made primary prevention**, tailoring the intensity of preventive measures to the atherosclerotic burden and this might become one of the most important indications of cardiac CT in the near future.

Capítulo 1.

Descrição geral da tese

RESUMO:

Neste capítulo é feita uma introdução geral ao tema da tese, a utilidade da angio TC cardíaca na avaliação da doença coronária. Apesar de a principal indicação da angio TC ser a exclusão de doença obstrutiva, fruto do seu elevado valor preditor negativo, esta é uma técnica que permite também documentar a presença de lesões não obstrutivas e assim a presença e a extensão da aterosclerose coronária desde as suas fases iniciais.

Na presente tese é dado um particular ênfase a esta capacidade da angio TC objectivar a carga aterosclerótica coronária que se espera poder vir a contribuir no futuro para uma mudança no paradigma de avaliação da doença coronária.

A possibilidade de se poder identificar os indivíduos em risco de eventos poderá contribuir para mudar a dramática forma de apresentação inaugural da doença coronária que, para muitos doentes, continua a ser o enfarte agudo do miocárdio e a morte súbita.

Após esta introdução teórica, são descritos os objectivos, a metodologia empregue, bem como os principais resultados da população incluída na tese.

Por fim, é feita uma descrição sumária dos diferentes capítulos incluídos na tese.

ABSTRACT:

In this chapter, a general introduction to the subject of the present thesis, the use of cardiac CT in the evaluation of coronary artery disease, is provided.

Although the main indication for cardiac CT is the exclusion of obstructive disease, due to its high negative predictive value, this is a technique that enables the visualization of nonobstructive lesions and, therefore, the presence and extension of coronary atherosclerosis even at earlier stages.

In the present thesis, this ability of cardiac CT to document the coronary atherosclerotic burden is emphasized and it is expected that it might lead in the future to a paradigm shift in the evaluation of coronary artery disease.

The potential for the identification of patients at risk of acute events might contribute to change the dramatic initial presentation of coronary artery disease that for many patients is still and acute myocardial infarction or sudden cardiac death.

After this theoretical introduction, the objectives and the methodology of the thesis are described, as well as the main results of the studied population.

Finally, a brief overview of the different chapters included in the thesis is provided.

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1.5 DESCRIÇÃO SUMÁRIA DA TESE

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1.7 ANEXOS

1.1 INTRODUÇÃO GERAL

Apesar dos avanços que temos vindo a acompanhar nos últimos anos no diagnóstico e tratamento das doenças CV, estas continuam a ser a **principal causa de morte** nos países desenvolvidos, sendo responsáveis por mais de 4 milhões de mortes por ano na Europa e contribuindo com uma elevada percentagem (47%) de todas as causas de morte, de acordo com estatísticas europeias recentes (1).

Neste campo, a doença coronária (DC) é o principal protagonista, não só pelo contributo relativo para a fatia das doenças CV, mas sobretudo pela sua dramática e frequente forma de apresentação inaugural que numa percentagem elevada dos doentes continua a ser o EAM e a morte súbita. A DC é responsável por cerca de 75% dos casos de morte súbita cardíaca e em 2/3 dos casos nas mulheres e 50% dos casos nos homens não existia história prévia de doença cardíaca (2). Estes eventos clínicos irreversíveis são assim a **primeira manifestação** de DC numa significativa percentagem de doentes, que previamente ao evento estavam assintomáticos e muitos deles não seriam considerados de elevado risco de acordo com a actual metodologia de estratificação clínica. Num estudo realizado após a divulgação das recomendações do NCEP-ATPIII (3), foi feita a avaliação retrospectiva do perfil de risco clínico de doentes que sofreram um EAM inaugural, sendo concluído que apenas 25% dos homens e 18% das mulheres seriam classificados como de alto risco, definido por essas recomendações como tendo um risco de eventos CV a 10 anos >20% (4). Num outro trabalho, foi caracterizado o risco CV numa população de 1113 doentes com um EAM inaugural usando o Heartscore. Nesta população, mais de metade não seria classificada como de elevado risco previamente ao evento, sendo que apenas 28% tinha um Heartscore entre 5 e 10%, só 14,6% teriam um Heartscore $\geq 10\%$ e a prevalência de outros qualificadores de alto risco como a diabetes (19,4%), doença vascular periférica (2,6%) e doença cérebro-vascular (4,5%) era igualmente baixa (5).

Numa publicação mais recente, foi avaliada a evolução temporal do perfil demográfico e de factores de risco em 138.122 doentes com EAM incluídos no registo da “American Heart Association Get With the Guidelines Coronary Artery Disease program” (AHA GWTG-CAD), entre 2003 e 2008, verificou-se uma redução significativa da idade média dos doentes, com um aumento da percentagem de doentes com enfarte abaixo dos 45 anos que já representavam 11% no último ano deste estudo e mais de metade dos doentes (60% no último ano do registo) tinham <65 anos (6).

Assim, existem presentemente limitações na identificação dos indivíduos em risco com base no perfil demográfico e clínico, mesmo quando agrupados em scores clínicos (tema do [capítulo 5](#)), sendo este o racional para o desenvolvimento de métodos para identificação e estratificação dos indivíduos em risco de eventos CV.

Nos últimos anos, com os avanços tecnológicos na área da tomografia computadorizada, com melhorias progressivas da resolução espacial e temporal, tornou-se possível a avaliação das estruturas cardíacas por TC, nomeadamente permitindo a realização de uma coronariografia de

modo não invasivo, bem como uma progressiva redução da dose de radiação (aspectos melhor desenvolvidos no [Capítulo 5](#)). Na sua fase inicial, a **angio TC cardíaca** foi validada por comparação com a coronariografia por cateterismo cardíaco, tendo sido demonstrado o seu elevado valor preditor negativo, tornando assim esta técnica particularmente útil para exclusão de DC obstrutiva (7). Esta é uma das actuais indicações para esta técnica, sendo as suas indicações clínicas abordadas no [Capítulo 3](#).

No entanto, desde cedo percebeu-se que nas imagens de tomografia obtidas na angio TC cardíaca, era possível identificar não só o lúmen opacificado por contraste, mas também a parede vascular, permitindo assim avaliar a presença de DC não obstrutiva. Assim, ficou claro que esta era uma técnica que permitia identificar a presença e a extensão da aterosclerose coronária, fornecendo informação acerca da localização das lesões, grau de obstrução e tipo de placas ateroscleróticas (calcificadas, não calcificadas ou mistas).

Esta informação global da carga aterosclerótica coronária é uma característica particular da angio TC cardíaca, sendo a única técnica que a pode avaliar de modo não invasivo, uma vez que os habituais exames de diagnóstico empregues para avaliar a presença de DC baseiam-se na documentação de isquémia do miocárdio. Esta, para ocorrer, depende da presença de estenoses coronárias significativas não detectando assim placas ateroscleróticas, mesmo de volume importante, mas cujo *remodeling* positivo faz com que ainda não condicionem uma redução significativa do lúmen vascular (8).

No entanto é muito frequente encontrar placas ateroscleróticas na árvore coronária mesmo numa população sem antecedentes de DC. Num estudo recente, numa população referenciada para angioTC cardíaca para avaliação de eventual DC, só 44% dos doentes sem diabetes e 26% dos doentes com diabetes apresentavam uma árvore coronária sem placas identificáveis por angioTC cardíaca (9). Assim, torna-se importante desenvolver índices que permitam quantificar a carga aterosclerótica coronária, identificando em que casos se poderá justificar uma prevenção mais agressiva, mesmo na ausência de DC obstrutiva – tema desenvolvido no [Capítulo 8](#).

1.2 OBJECTIVOS

1. Identificar preditores demográficos, clínicos e de scores de risco para uma elevada carga aterosclerótica, avaliada pela angioTC cardíaca.
2. Avaliar o desempenho de 3 scores clínicos (HeartScore, Morise e Diamond-Forrester) na identificação da presença e da gravidade da DC (obstrutiva e não obstrutiva) documentada por angioTC cardíaca.
3. Desenvolver um índice de carga aterosclerótica que reúna a informação global acerca da localização, do grau de estenose e do tipo de placa, obtida pela angioTC cardíaca.

1.3 MÉTODOS

1.3.1 – População estudada

Foram incluídos doentes consecutivos que realizaram angio TC cardíaca durante 1 ano (de 1 de Abril de 2011 a 31 de Março de 2012) no Centro de Imagiologia do Hospital da Luz.

O estudo foi aprovado pela comissão de ética (*anexo 1*) e os doentes deram o seu consentimento informado (*anexo 2*).

Foram excluídos os doentes em fibrilhação auricular ou outras arritmias significativas durante o exame que levassem a compromisso significativo da qualidade do exame, bem como os doentes referenciados para realização isolada de score de cálcio. Foram igualmente excluídos os doentes referenciados para angio TC cardíaca nos quais se optou pela não administração de contraste iodado, nomeadamente doentes com antecedentes alérgicos e doentes com score de cálcio elevado (em absoluto na árvore coronária e/ou com distribuição preferencial concêntrica e em segmentos proximais).

Foi realizado um questionário para caracterização detalhada dos factores de risco e colhida uma história clínica sumária para avaliar a presença e tipo de dor torácica, bem como os antecedentes cardíacos, nomeadamente de enfarte do miocárdio e de procedimentos de revascularização. Foi feita ainda uma consulta das análises laboratoriais e dos exames complementares de diagnóstico previamente realizados. A informação foi recolhida numa folha de colheita de dados, onde foi igualmente preenchida a informação acerca do protocolo nomeadamente: kilovoltagem da ampola, tipo de aquisição (prospectiva ou retrospectiva), dose de contraste, dose de radiação, frequência e ritmo cardíaco durante a aquisição. Foi ainda feito o registo do peso, da altura e da tensão arterial do doente (*anexo 3*).

Esta informação recolhida permitiu assim:

a) Caracterizar a dor torácica em 3 tipos:

-*Típica*, na presença das 3 seguintes características

- 1- Dor ou desconforto retroesternal
- 2- Desencadeada pelo esforço físico ou stress emocional
- 3- Aliviada com o repouso e/ou com uso sublingual de nitratos

-*Atípica*, na presença de 2 das anteriores características

-*Toracalgia inespecífica*, na presença de apenas uma ou nenhuma das anteriores (10, 11)

b) Colheita dos factores de risco:

-Diabetes mellitus, definida como glicemia em jejum ≥ 126 mg/dl ou uso de antidiabéticos orais e/ou insulina.

-Dislipidemia, definida como colesterol total ≥ 190 mg/dl ou uso de fármacos hipolipemiantes.

-Hipertensão arterial, definida como TA $\geq 140/90$ mmHg ou uso de fármacos hipotensores.

-Obesidade, definida como IMC ≥ 30 kg/m².

-Tabagismo, considerado se corrente ou ex-fumador < 1 ano.

-História familiar de doença CV prematura, definida como antecedentes de DC em familiares de 1º grau antes dos 55 anos (homens) ou dos 65 anos (mulheres).

c) Classificação da indicação para a realização do exame.

Para a presente análise foram **incluídos** os doentes que realizaram a angio TC cardíaca pelas seguintes indicações clínicas:

- Avaliação de eventual DC no contexto de exames prévios duvidosos, inconclusivos ou discordantes com a avaliação clínica.
- Avaliação de possível DC sem exames de isquémia prévios.
- Avaliação de DC no estudo prévio a cirurgia cardíaca não coronária (valvular e/ou aorta).
- Avaliação de possível DC em cardiomiopatias (dilatada ou hipertrófica).

Foram **excluídos** os doentes com

- Antecedentes de enfarte do miocárdio e/ou revascularização (angioplastia ou cirurgia coronária).
- Angio TC cardíaca realizada no contexto do serviço de urgência (suspeita de Síndrome coronário agudo e/ou miocardite).
- Angio TC cardíaca realizada por outro motivo que não para avaliação de DC (Ex: estudo prévio a ablação de fibrilhação auricular ou implantação percutânea de válvula aórtica)

d) Cálculo dos índices de probabilidade pré-teste de doença coronária (Score de Diamond-Forrester e Score de Morise) e de risco cardiovascular (HeartScore).

O *score de Diamond-Forrester* foi calculado a partir da informação demográfica (sexo, idade) e características da dor, de acordo com a metodologia originalmente descrita (12) e a recente calibração do CAD-consortium (13), tendo sido utilizada a calculadora online disponibilizada para este efeito (14). Uma vez que a população incluída era predominantemente de baixa probabilidade, optou-se por agrupar as categorias 30-70% e >70% numa única classe de probabilidade intermediária a alta (limiar discriminativo $\geq 30\%$).

O *score de Morise*, foi calculado a partir da informação demográfica (sexo, idade), características da dor e factores de risco (diabetes, HTA, dislipidémia, tabagismo, IMC > 27 kg/m²). Uma das variáveis incluídas neste score diz respeito ao estado estrogénico, tendo sido considerado positivo nas mulheres pré-menopausicas ou sob terapêutica hormonal de substituição). A população foi dividida nos 3 grupos de probabilidade de acordo com o score originalmente descrito (15): probabilidade baixa (scores 0-8); probabilidade intermédia (scores 9-15); probabilidade alta (scores ≥ 16).

O *Heartscore* foi calculado a partir dos dados demográficos (sexo e idade) e factores de risco (tabagismo, dislipidemia, hipertensão arterial), sendo usada a tabela adequada para países de baixo risco CV. Foi usado o limiar estabelecido de $\geq 5\%$ para definir a população de elevado risco CV (16).

De acordo com o resultado da angio TC cardíaca, os doentes foram classificados em 3 subgrupos:

- 1- Sem doença coronária identificável.
- 2- Doença coronária não obstrutiva.
- 3- Doença coronária obstrutiva (definida como estenoses $\geq 50\%$).

1.3.2 – Angio TC cardíaca – aparelho, protocolo de aquisição e reconstrução das imagens

Os exames foram realizados num aparelho de 64 cortes e dupla ampola (Dual-Source CT - Somaton Definition®, Siemens-Medical). Na preparação prévia do doente, foi feito ensino da respiração e a administração de nitroglicerina sublingual e/ou betabloqueantes endovenosos, excepto quando contraindicados.

O contraste iodado (Visipaque, GE Healthcare, USA) foi injectado a 6 ml/s seguido de um bólus de 50ml de soro fisiológico. A dose total foi calculada pela seguinte fórmula: (tempo de aquisição + 6 s) x débito da injeção (6 ml/s).

Sempre que possível foram utilizadas as estratégias disponíveis para redução da dose de radiação (modulação pelo ECG; redução da kilovoltagem da ampola para 100Kv; aquisição com protocolo prospectivo ou adaptativo). As imagens transaxiais foram reconstruídas com uma resolução temporal de 83ms, uma espessura de cortes de 0,75mm, com incrementos de 0,4mm. O pós-processamento foi realizado numa estação de trabalho dedicada com o software Circulation® (Siemens-Medical), tendo sido realizadas reconstruções multiplanares (MPR), reconstruções de projecção de intensidade máxima (MIP) e de técnica volumétrica (VRT).

1.3.3 - Análise da árvore coronária

Todos os exames foram revistos por 2 médicos (1 Cardiologista e 1 Radiologista) com experiência em angio TC cardíaca (equivalência nível III da *Society of Cardiovascular Computed Tomography - SCCT*) (17).

Foi feita uma análise detalhada da árvore coronária, sendo seguidas as recomendações da SCCT (18) para classificação da localização, grau de estenose e tipo de placa:

-**Localização** de acordo com esquema de segmentação coronária em 18 segmentos proposto pelo SCCT (**Figura 1**).

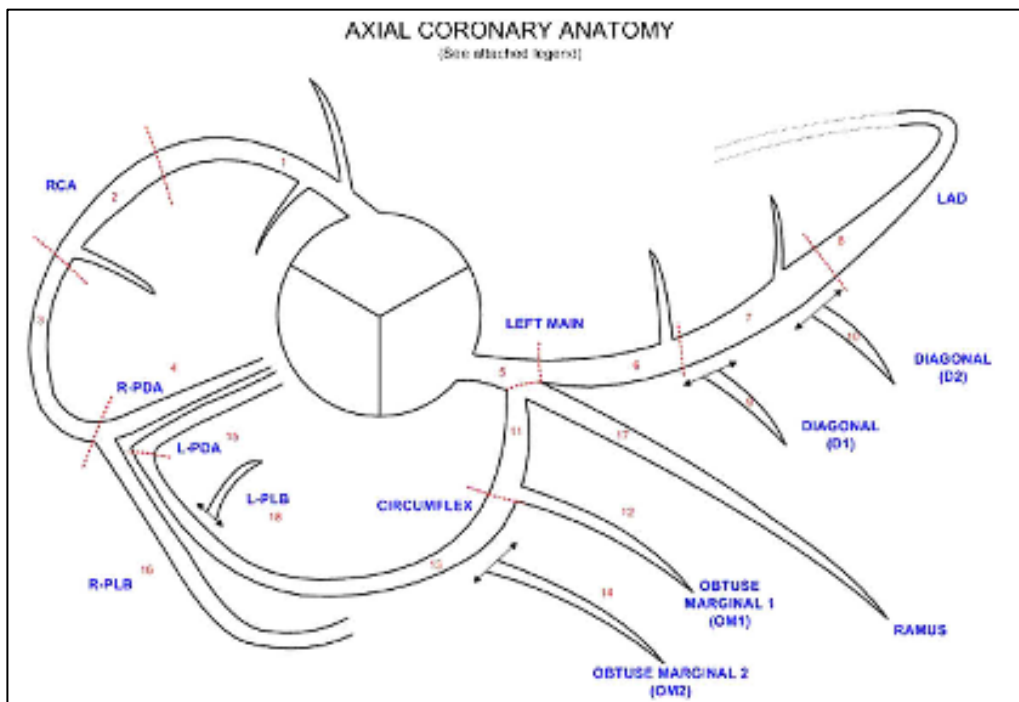


Figura 1: Esquema recomendado pela SCCT para classificação da árvore coronária em 18 segmentos.

-**Grau de estenose:** A avaliação do grau de estenose foi feita de acordo com a percentagem de obstrução do lúmen artéria coronária, por comparação com o diâmetro do vaso sem doença imediatamente abaixo da placa por estimativa visual e pela graduação proposta pela SCCT: sem placa ou muito ligeira (<25%); estenose ligeira (25-49%); estenose moderada (50-69%); estenose severa (70-99%); oclusão (100%).

-**Tipo de placa:** A presença de placa foi definida como uma densidade no lúmen vascular ou adjacente a este, com densidade diferente do lúmen vascular e do tecido e gordura epicárdicos, com pelo menos 1mm² de área. As placas foram classificadas em calcificadas, não calcificadas e mistas.

1.3.4 – Índices de carga aterosclerótica coronária

A presença e gravidade da DC foi objectivada pelos seguintes índices de carga aterosclerótica coronária:

1- **Segment involvement score (SIS)**. Este índice traduz o número de segmentos envolvidos por doença, sendo obtido pela soma do número de segmentos com qualquer placa - mínimo 0, máximo 17. Foi usado o limiar discriminativo > 5 segmentos com placa, uma vez que já foi validado o seu valor prognóstico em estudos prévios (19, 20).

2- **Segment stenosis score (SSS)**. O score de número de segmentos com placa indexado ao grau de estenose foi obtido pela soma de cada placa de acordo com o seu valor ponderal (<25%=0; 25-50%=1; 50-70%=2; >70%=3). Este score pode variar potencialmente entre 0 e 51 (17 segmentos x valor ponderal 3). Foi usado o limiar discriminativo > 5, cujo valor prognóstico já foi validado por outros autores (19, 20)

3- Presença de placa no tronco comum, nos 3 vasos epicárdicos ou em 2 vasos com envolvimento da descendente anterior proximal (**Placa TC-3v-2vDAp**). Foi criado este índice para reflectir DC mais extensa, por analogia com a DC obstrutiva avaliada na coronariografia invasiva onde este tipo de envolvimento associa-se a mau prognóstico e a um benefício prognóstico da revascularização miocárdica (21, 22).

4- Score de Leaman adaptado à angioTC (**CT-LeSc**). O desenvolvimento deste score foi um dos objectivos centrais da tese e é descrito em detalhe no [Capítulo 8](#).

5- Como índices de elevada carga aterosclerótica foram ainda testadas 2 variáveis determinadas a partir do score de cálcio, obtido em todos os doentes previamente à administração de contraste. Foram criadas as variáveis **CaSc >100** (*valor absoluto*) e a variável **CaSc >p75** (*valor relativo*), esta última traduzindo um grau de calcificação acima do esperado para o percentil 75 de acordo com os normogramas estabelecidos para a idade e o sexo (23).

1.3.5 - Base de dados e análise estatística

Os dados demográficos, factores de risco, antecedentes CV, indicação para a realização da angio TC, dados técnicos respeitantes à aquisição do exame, bem como do seu resultado após processamento das imagens adquiridas (presença e extensão da doença) foram colhidos numa folha especificamente elaborada para este motivo ([anexo 3](#)) e posteriormente introduzidos numa base de dados.

A análise estatística foi realizada no programa SPSS statistics v17 Windows e v19 Mac Os.

As variáveis contínuas são apresentadas como médias e desvio padrão ou medianas e intervalo interquartil e as variáveis categóricas como frequências e percentagens.

Foram usados testes não paramétricos (Mann-Whitney ou Kruskal-Wallis) para comparar as variáveis contínuas e o teste de Qui quadrado para comparar variáveis categóricas. As diferenças foram consideradas significativas quando o p era $<0,05$.

Foram construídas curvas ROC (receiver operating characteristics) para avaliar o desempenho dos scores de risco clínicos, traduzido pela área abaixo da curva ou estatística-C.

Foi realizada análise multivariável (regressão logística binária – método “enter”) para identificar os preditores independentes de DC (presença de qualquer placa e doença obstrutiva), usando as variáveis demográficas e clínicas apresentadas na tabela 1, que foram significativas na análise univariável ($p<0.05$).

Foi feita uma segunda análise multivariável para identificar os preditores independentes entre os scores clínicos de probabilidade pré-teste de DC (Diamond-Forrester e Morise) e de risco CV (Heartscore).

1.4 RESULTADOS

1.4.1 - População incluída

Dos 772 doentes que realizaram angioTC cardíaca durante o período de inclusão de 1 ano, 581 foram **incluídos** na análise, distribuídos pelas seguintes indicações:

- Avaliação de eventual DC no contexto de exames prévios duvidosos, inconclusivos ou discordantes com a avaliação clínica, $n= 417$, 71,8%.
- Avaliação de possível DC sem exames de isquémia prévios, $n=136$, 23,4%.
- Avaliação de DC no estudo prévio a cirurgia cardíaca não coronária (valvular e/ou aorta), $n=17$, 2,9%.
- Avaliação de possível DC em cardiomiopatias (dilatada ou hipertrofica), $n=11$, 1,9%.

Foram **excluídos** da análise 191 doentes (24,7%) pelos seguintes motivos (figura 2):

- Antecedentes de EAM e/ou revascularização (ICP ou CABG), n=70.
- Angio TC cardíaca realizada no contexto do serviço de urgência (suspeita de SCA e/ou Miocardite), n=24.
- Angio TC cardíaca realizada por outro motivo que não para avaliação de DC (Ex: estudo prévio a ablação de fibrilhação auricular ou implantação percutânea de válvula aórtica), n=88.
- Em fibrilhação auricular ou com outras arritmias importantes comprometendo significativamente a qualidade da imagem, n=9.

A distribuição dos doentes de acordo com a presença e a gravidade da DC foi a seguinte (**Figuras 2 e 3**):

- Normal/Sem placas identificáveis (n=240, 41,3%);
- Doença coronária não obstrutiva (n=263; 45,3%);
- Doença coronária obstrutiva (n=78, 13,4%).

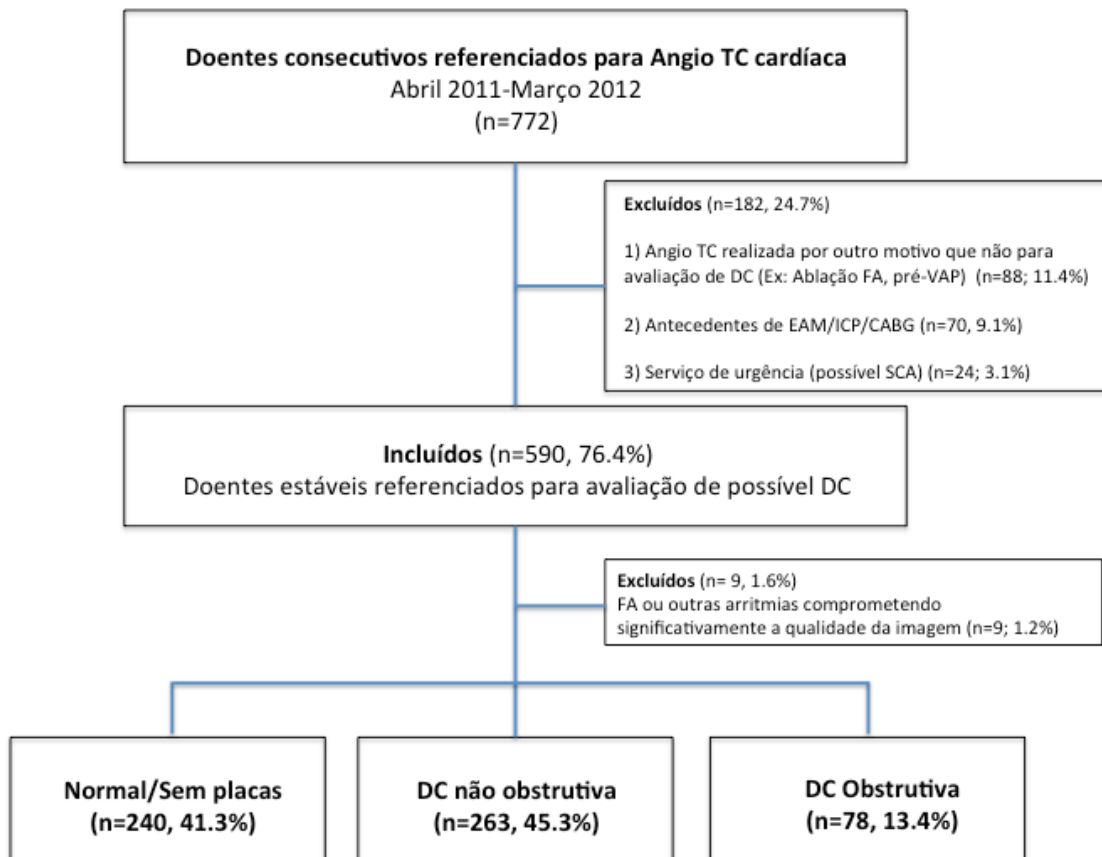


Figura 2: População incluída.

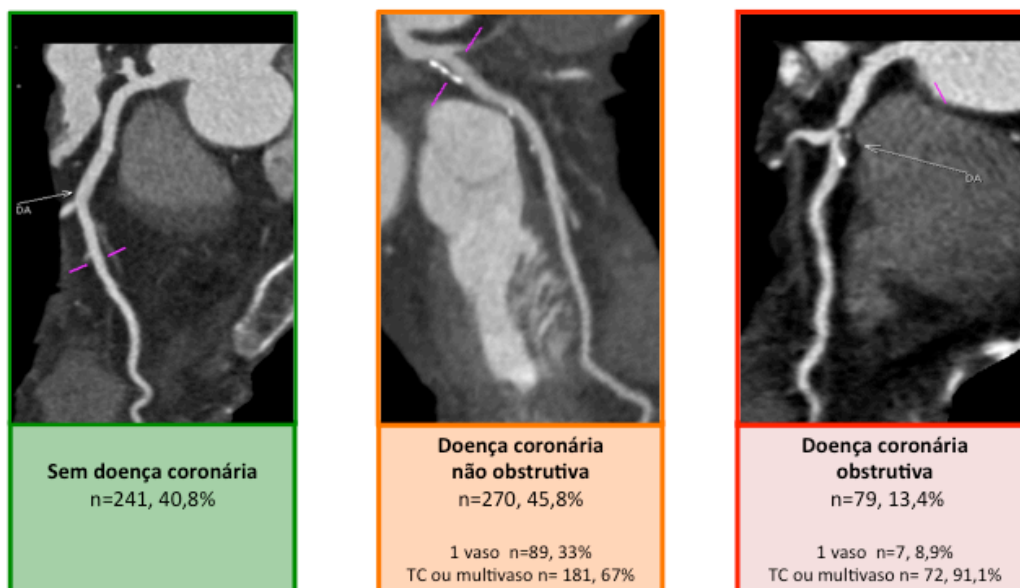


Figura 3: Distribuição de acordo com a presença e gravidade da doença coronária.

Nesta população final (n=581 doentes), foram avaliados 8136 segmentos da árvore coronária. Os segmentos com $\leq 1,5\text{mm}$ (n=742; 9,1%) ou com qualidade de imagem subótima por artefactos ou calcificação severa (n=120; 1,5%) foram excluídos.

A idade média da população foi de 57.6 ± 11.1 , a maioria era do sexo masculino (55,8%) e a prevalência de diabetes foi de 14,6%. A população incluída era predominantemente de baixa a intermédia probabilidade de DC, uma vez que 60,1% tinha um score de Diamond-Forrester $<30\%$ e 87,6% um score de Morise <16 . Cerca de $\frac{1}{4}$ dos doentes tinham um risco CV elevado (HeartScore $\geq 5\%$ em 25,5% dos doentes) - **tabela 1**.

A dose média estimada de radiação foi de 4.6 ± 3.7 mSv, de contraste foi de 98.9 ± 14.4 ml e a frequência cardíaca na aquisição foi de 65.6 ± 10.6 bpm - **tabela 2**.

1.4.2 – Preditores da presença de doença coronária

Foram avaliados os preditores da presença de DC (qualquer placa) e os preditores da presença de DC obstrutiva (estenoses $\geq 50\%$) em análise univariável (tabelas 3 e 4) e multivariável (tabelas 5 e 6).

Nesta análise, destaca-se de entre os vários factores de risco, para além dos não modificáveis idade e sexo masculino, a diabetes surgiu como um importante preditor da presença de DC não obstrutiva, justificando-se assim a sua análise mais detalhada apresentada no [Capítulo 7](#). A obesidade (IMC $>30\text{kg/m}^2$) não foi um preditor da presença de DC, aspecto discutido no [Capítulo 6](#).

De entre os scores clínicos, um Heartscore $\geq 5\%$, apesar de não ser influenciado pela presença e características da dor torácica foi o preditor independente mais importante não só da presença de DC mas também de DC obstrutiva. O desempenho do Heartscore e dos scores de probabilidade pré-teste é discutido no [Capítulo 6](#).

Tabela 1: Características demográficas e clínicas da população incluída.

	População total (n=581)
Demográficas	
Idade	57,6 ± 11,1
Sexo masculino	324 (55,8)
Factores de risco	
Obesidade (IMC ≥30)	109 (18,8)
Diabetes mellitus	85 (14,6)
Hipertensão arterial	364 (62,7)
Dislipidémia	360 (62,0)
Tabagismo	138 (23,8)
História familiar de DC prematura	194 (33,4)
Dor torácica	
Assintomático	270 (46,5)
Toracalgia inespecífica	169 (29,1)
Atípica	109 (18,8)
Típica	33 (5,7)
Probabilidade de doença coronária	
DF-CAD consortium ≥70%	11 (1,9)
DF-CAD consortium 30-70%	221 (38,0)
DF-CAD consortium <30%	349 (60,1)
Score Morise ≥ 16	72 (12,4)
Score Morise 9-15	369 (63,5)
Score Morise 0-8	140 (24,1)
Risco cardiovascular	
HeartScore ≥5%	148 (25,5)

Valores apresentados em média ± desvio padrão ou n (%).

Tabela 2: Resultado global da angioTC cardíaca, do score de cálcio e dados técnicos da população incluída.

	População total (n=581)
Resultado da angioTC cardíaca	
Normal/Sem placas identificáveis	240 (41,3)
Doença não obstrutiva	263 (45,3)
Doença obstrutiva	78 (13,4)
Score de cálcio	
Mediana	1 (0-93)
Mediana nos doentes com DAC	64 (8-200)
CaSc $\geq$ 100	136 (23,4)
CaSc $\geq$ percentil 75	83 (14,3)
Dados técnicos	
Frequência cardíaca (bpm)	65,6 $\pm$ 10,6
Dose de contraste (ml)	98,9 $\pm$ 14,4
Dose de radiação (mSv)	4,6 $\pm$ 3,7

Valores apresentados em média $\pm$ desvio padrão, mediana (IQ) ou n (%).

Tabela 3: Preditores da presença de doença coronária (qualquer placa) - análise univariável

	Sem DC (n=240)	DC (qualquer placa) (n=341)	p
Idade ≥ 65	34 (14.2)	124 (36.4)	<0.001
Sexo masculino	106 (44.2)	218 (63.9%)	<0.001
IMC ≥30	42 (17.9)	67 (19.9)	0.589
Diabetes mellitus	22 (9.2)	63 (18.5)	0.002
Hipertensão arterial	122 (50.8)	242 (71.0)	<0.001
Dislipidemia	126 (52.5)	234 (68.6)	<0.001
Tabagismo	55 (22.9)	83 (24.3)	0.767
História familiar de DC prematura	80 (33.3)	114 (33.4)	1.000
Dor torácica	145 (62.0)	166 (49.0)	0.002
DF-CAD consortium ≥30%	50 (20.8)	181 (53.1)	<0.001
Morise ≥ 16	29 (12.3)	89 (26.4)	<0.001
HeartScore ≥5	19 (7.9)	129 (37.8)	<0.001

Valores apresentados em n (%).

Tabela 4: Preditores da presença de doença coronária obstrutiva – análise univariável

	Sem DC obstrutiva n=503	DC obstrutiva (estenose ≥50%) n=78	p
Idade ≥ 65	126 (25,0)	32 (41,0)	0.006
Sexo masculino	266 (52,9)	58 (74,4)	<0.001
IMC ≥30	93 (18,8)	16 (20,8)	0.643
Diabetes mellitus	58 (11,5)	27 (34,6)	<0.001
Hipertensão arterial	304 (60,4)	60 (76,9)	0.005
Dislipidemia	305 (60,6)	55 (70,5)	0.104
Tabagismo	114 (22,7)	24 (30,8)	0.118
História familiar de DC prematura	166 (33,0)	28 (35,9)	0.608
Dor torácica	274 (55,4)	37 (47,4)	0.222
DF-CAD consortium ≥30%	181 (36,0)	50 (64,1)	<0.001
Morise ≥ 16	94 (19,0)	24 (31,2)	0.022
HeartScore ≥5	107 (21,3)	41 (52,6)	<0.001

Valores apresentados em n (%).

Tabela 5: Preditores independentes da presença de doença coronária (qualquer placa) - análise multivariável

Variáveis demográficas e clínicas

	OR	(IC 95%)	p
Idade ≥ 65	3,417	2,145-5,445	<0,001
Sexo masculino	2,722	1,849-4,008	<0,001
Diabetes mellitus	1,812	1,024-3,205	0,041
Hipertensão arterial	1,816	1,234-2,672	0,002
Dislipidemia	1,893	1,295-2,768	0,001
Dor torácica	0,620	0,424-0,906	0,014

Scores clínicos

	OR	(IC 95%)	p
HeartScore≥5	3,896	2,189-6,935	<0,001
DF-CAD consortium ≥30%	2,623	1,697-4,052	<0,001
Morise ≥16	2,549	1,568-4,144	<0,001

Tabela 6: Preditores independentes da presença de doença coronária obstrutiva - análise multivariável

Variáveis demográficas e clínicas

	OR	(IC 95%)	p
Idade ≥ 65	1,976	1,159-3,369	0,012
Sexo masculino	2,942	1,679-5,154	<0,001
Diabetes mellitus	3,686	2,079-6,533	<0,001
Hipertensão arterial	1,543	0,851-2,798	0,154

Scores clínicos

	OR	(95% CI)	p
HeartScore≥5	2,709	1,503-4,880	0,001
DF-CAD consortium ≥30%	1,884	1,036-3,424	0,038
Morise ≥16	1,838	1,057-3,197	0,031

1.4.3 – Desempenho dos scores de risco clínicos

A partir dos dados demográficos, de factores de risco e tipo de dor torácica, foram calculados diferentes índices (scores) clínicos e testado o seu desempenho para prever a presença e a gravidade da DC documentada na angioTC cardíaca.

Esta análise é descrita no *Capítulo 6*.

1.4.4 –Análise dos doentes com diabetes mellitus

Foi feita uma análise detalhada do subgrupo de doentes com diabetes mellitus, como subgrupo modelo de doença aterosclerótica mais avançada. Esta análise é descrita no *Capítulo 7*.

1.4.5. Desenvolvimento de um score de carga aterosclerótica quantificada por angioTC cardíaca - CT-LeSc.

Foi desenvolvido um score para quantificar a carga aterosclerótica coronária identificada pela angioTC cardíaca, englobando informação acerca da localização, grau de estenose e tipo de placa. Este score, o CT-Leaman score, é um dos objectivos centrais desta tese e é descrito no *Capítulo 8*.

1.5 DESCRIÇÃO SUMÁRIA DA TESE

Esta tese está dividida em 10 capítulos, cuja organização é ilustrada pela **Figura 4**:

No presente capítulo, o **capítulo 1**, faz-se uma introdução ao tema da doença coronária, contextualizando a sua importância epidemiológica, a sua forma de apresentação frequentemente dramática, que justifica o esforço no desenvolvimento de novos métodos para a correcta identificação dos indivíduos em risco e do potencial da angio TC cardíaca como meio de diagnóstico não invasivo. Neste capítulo são descritos os objectivos e a metodologia da tese, bem como os resultados da análise geral da população incluída.

Por fim é feita uma descrição sumária dos diferentes capítulos que a compõe.

Os **capítulos 2, 3 e 4** prolongam a *introdução*, abordando em mais detalhe alguns aspectos particulares da doença coronária, para melhor contextualização do tema da tese.

No **capítulo 2**, faz-se uma revisão da Fisiopatologia da doença coronária com ênfase nos SCA e na placa vulnerável.

No **capítulo 3** é feita uma revisão das indicações clínicas actuais da angio TC cardíaca.

No **capítulo 4** é descrita a capacidade da angioTC cardíaca identificar a presença da doença coronária não obstrutiva, característica impar entre os vários exames de diagnóstico não invasivos em Cardiologia. Neste capítulo é feita uma revisão dos diferentes marcadores de aterosclerose subclínica.

O **capítulo 5** é um complemento à descrição da *metodologia* da tese, sendo descritos os aspectos técnicos da angio TC cardíaca, destacando-se em particular o uso e dose de radiação ionizante associada a estes exames, com os potenciais efeitos estocásticos para a saúde e as estratégias desenvolvidas que conduziram a uma progressiva redução da dose de radiação nestes exames, importante para a sua aplicabilidade clínica.

Nos **capítulos 6, 7 e 8** são descritos e discutidos os *resultados* mais importantes da Tese.

No **capítulo 6** faz-se uma análise do desempenho dos scores de risco clínicos na identificação da presença e da gravidade da doença coronária documentada por angio TC cardíaca.

No **capítulo 7** é descrita a utilidade da angioTC cardíaca na avaliação dos doentes com diabetes mellitus, aparecendo aqui a diabetes como um subgrupo modelo de doença coronária mais avançada, útil para avaliar o desempenho de diferentes scores de carga aterosclerótica.

No **capítulo 8** é apresentado o score de carga aterosclerótica coronária quantificada por angioTC cardíaca, desenvolvido nesta tese, o CT-LeSc.

No **capítulo 9**, é feita uma revisão do valor prognóstico da angioTC cardíaca, desde os estudos iniciais de validação prognóstica, passando pelas meta-análises e estudos multicêntricos, a validação a longo prazo e finalmente o seu valor incremental e comparação com outros métodos de imagem não invasivos.

No **Capítulo 10** faz-se uma discussão final conjunta, descrevem-se as conclusões e apresentam-se possíveis direcções para trabalhos futuros.

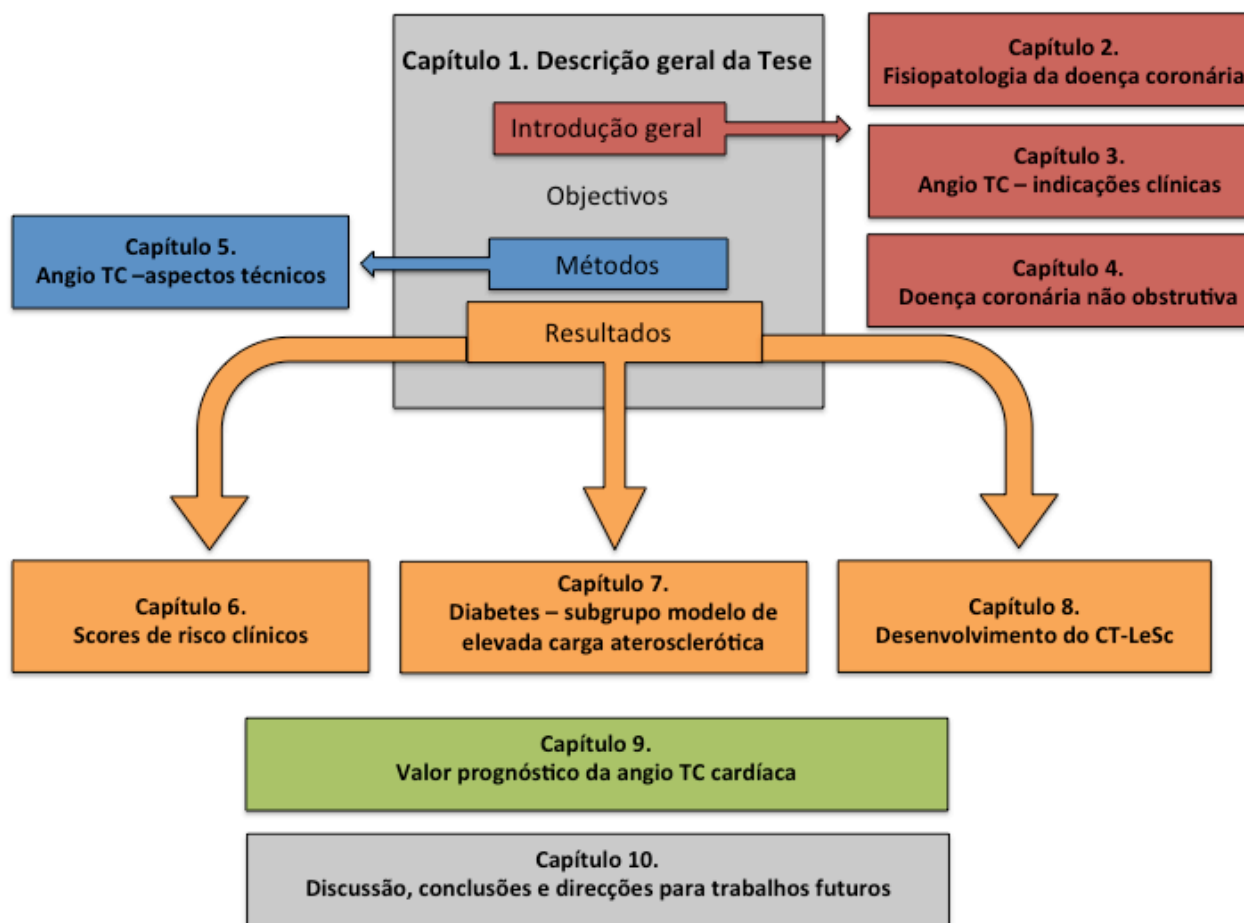


Figura 4: Organização dos diferentes capítulos da Tese.

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1.7 ANEXOS

Anexo 1: Parecer da comissão de ética



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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Anexo 2: Questionário para o doente e consentimento

Questionário angioTCs cardíacas

Foi-lhe solicitada pelo seu médico assistente a realização de uma angioTC cardíaca. O centro de Imagiologia do Hospital da Luz é uma referência nesta área, fruto não só do elevado número 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 clínica.

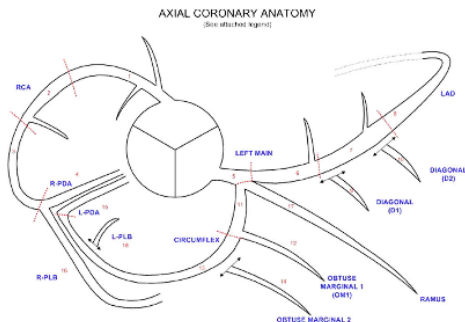
Data ____/____/____ Assinatura _____

Anexo 3: Folha de colheita de dados



Exame									
NHC	Data		/	/	Referenciador				
Identificação									
1. M 0. F	Idade	DN	/	/	Nome				
Biometria									
PAS	PAD				Peso	Altura			
Factores de risco		Antecedentes			Scores		ECG		
DM		Enfarte			Heart.Sc ____		1. Sinusal		
HTA		Cateterismo Stents			Duke ____		2. FA		
Dislipidémia		Cirurgia cardíaca					3. ESSV/EV		
Tabagismo		Bypass			Prob Pré T:		4. Pacing		
Hist. Fam. (♂≤55; ♀≤65)		Asma			Diam.Forr ____		FC Min ____		
Dor		0. Assintomático			1. Toracalгия não anginosa (0 / 1 critério)		FC Med ____		
		2. Angina Atípica (2 critérios)			3. Angina típica (3 critérios)		Morise: ____ FC Max ____		
Critérios: Retroesternal / Desencadeada por esforço ou stress / Alivia por repouso ou nitromint									
Protocolo		Indicação			Ablação FA				
CTA		Calcium Score			AE ____ ml				
1. 80 Kv		1. Ablação FA			VPD ____				
2. 100 Kv		2. S/ exames de isquémia (<2 Anos)			VPE ____				
3. 120 Kv		3. Controlo revascularização stents / pontagens			Trombo AAE S/N				
4. 140 Kv		4. Pré-cirurgia valvular / Aórtia			2ª Passagem S/N				
5. DS XXL		5. Queixas / Exames inconclusivos							
____ DLP		6. Urgência/Suspeita SCA/Miocard.							
SAS		7. Outro _____							
Flow Rate ____		8. Triple Rule Out							
Duração Scan ____									
Dose contraste ____									
Dominância		Extra Coronários			Extra cardíacos		Qualidade CTA		
1. Direita		0. Ausente			0. Ausente		1 2 3 4		
2. Esquerda		1. Minor			1. Minor		Má Optima		
3. Balanceada		2. Major			2. Major				
Conclusão Cors		Outros		Obs.		Didático			
0. Sem lesões		Repetiu aquisição		IMT D ____ E ____					
1. Placas minor		Dessensibilização							
2. Placas major		Reacção contraste							
Placas vulneráveis		Bridging _____							
		Variantes _____				Arquivado			
SCORE CÁLCIO: 0. Não Fez 1. ≤25 2. 25-50 3. 50 4. 50-75 5. 75-90 6. ≥90									
	<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	>74
Men (25 251)	3504	4238	4940	4825	3472	2288	1209	540	235
25th Percentile	0	0	0	1	4	13	32	64	166
50th Percentile	1	1	3	15	48	113	180	310	473
75th Percentile	3	9	36	103	215	410	566	892	1071
90th Percentile	14	59	154	332	554	994	1299	1774	1982
Women (9995)	641	1024	1634	2184	1835	1334	731	438	174
25th Percentile	0	0	0	0	0	0	1	3	9
50th Percentile	0	0	0	0	1	3	24	62	75
75th Percentile	1	1	2	5	23	57	145	210	241
90th Percentile	3	4	22	65	121	193	410	631	709

Avaliação Coronária											
Segmento	<2 mm	Não Avaliável	Estenoses								
			0	<25	25-49%	50-69%	70-99%	100%	Mole	Calcif.	Mista
01-CDp	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
02-CDm	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
03-CDd	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
04-DP dta	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
05-TC	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
06-DAP	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
07-DAm	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
08-DAd	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
09-Diag1	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
10-Diag2	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
11-CXP	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
12-OM1	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
13-CXd	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
14-OM2	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
15-DP esq	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
16-PL dta	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
17-Interm	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.
18-PL esq	6.	7.	0.	1.	2.	3.	4.	5	1.	2.	3.



A				Pretest	
Variable			Choose response	Sum	
Age	Men	Women			
	<40	<50		3	
	40-54	50-64		6	
	>55	>65		9	
Estrogen Status				Positive = -3	
Women only				Negative = +3	
Angina History				Typical = 5	
Diamond Method				Atypical = 3	
				Non-anginal = 1	
Diabetes?				2	
Hyperlipidemia?				1	
Hypertension?				1	
Smoking? (Any)				1	
Family Hx CAD? 1°				1	
Obesity? BMI>27				1	
				Total Score:	

Table 4. Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms*

Age (y)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

Capítulo 2.

Fisiopatologia da doença coronária

RESUMO:

Neste capítulo é feita uma revisão da fisiopatologia da DC, com ênfase na doença não obstrutiva, não detectável pelos tradicionais exames de documentação de isquémia mas estando com frequência na origem de eventos coronários agudos. No primeiro artigo original incluído nesta tese (**artigo 1**), foi avaliado um grupo de doentes com EAM submetidos a angioplastia primária, tendo sido feita a quantificação da estenose residual após aspiração de trombos. Foi identificado um subgrupo de doentes cuja estenose residual era <50%, sugerindo que a lesão que instabilizou e esteve na origem do EAM não condicionava previamente estenose significativa e seria assim dificilmente detectável com os habituais exames que se baseiam na documentação de isquémia.

De seguida é discutida a discrepância entre a elevada prevalência de placas ateroscleróticas na árvore coronária e a baixa taxa de eventos na população geral.

Por fim, é abordada a dificuldade na estratificação de risco dos doentes com SCA, condição muito heterogénea e que constitui um exemplo do uso de scores de risco na DC. Está incluído um artigo original (**artigo 2**) em que foi feita a comparação de 3 scores de risco, ilustrando o balanço difícil entre complexidade e desempenho que é determinante para a adopção de um score na prática clínica.

ABSTRACT:

In this chapter, the pathophysiology of coronary artery disease is reviewed, with a special focus on nonobstructive disease, which is not detected by the traditional ischemia based exams but can also lead to acute coronary events. In the first original manuscript included in the present thesis (**manuscript 1**), patients with myocardial infarction undergoing primary angioplasty were evaluated and the degree of residual stenosis was quantified after thrombus aspiration. In these patients, there was a subgroup with residual stenosis <50%, suggesting that the culprit lesion leading to the myocardial infarction was not causing a significant stenosis prior to the event and in this way it would have been difficult to detect with the usual ischemia based exams.

Secondly, we discuss the discrepancy between the high prevalence of atherosclerotic plaques found in the coronary tree and the relatively low rate of events in the general population.

The last topic in this chapter is related to risk stratification of patients with acute coronary syndromes, a very heterogeneous condition that is a good example of the use of risk scores in coronary artery disease. It is also included in this chapter a manuscript (**manuscript 2**) in which a comparison of 3 risk scores was performed, illustrating the difficult balance between complexity and performance, which influences the adoption of a score in clinical practice.

ARTIGO 1/ MANUSCRIPT 1:

NONOBSTRUCTIVE CORONARY DISEASE LEADING TO STEMI: ASSESSMENT OF RESIDUAL STENOSIS AFTER THROMBUS ASPIRATION

De Araújo Gonçalves P, Brito J, Sousa PJ, Carvalho MS, Soares H, Teles RC, Raposo L, Gabriel HM, Ferreira J, Almeida M, Aleixo A, Carmo MM, Mendes M.

Coron Artery Dis. 2013 Mar;24(2):154-9.

ARTIGO 2/ MANUSCRIPT 2:

TIMI, PURSUIT, AND GRACE RISK SCORES: SUSTAINED PROGNOSTIC VALUE AND INTERACTION WITH REVASCULARIZATION IN NSTEMI-ACS.

De Araújo Gonçalves P, Aguiar C, Ferreira J, Seabra-Gomes R.

Eur Heart J 2005; 26: 865-872.

SUMÁRIO DO CAPÍTULO 2:

2.1 INTRODUÇÃO

2.2 DOENÇA CORONÁRIA NÃO OBSTRUTIVA E PLACA VULNERÁVEL

2.3 DISCREPÂNCIA ENTRE ELEVADA PREVALÊNCIA DE PLACAS ATEROSCLERÓTICAS NA ÁRVORE CORONÁRIA E A BAIXA TAXA DE EVENTOS NA POPULAÇÃO GERAL.

2.4 SÍNDROMES CORONÁRIOS AGUDOS COMO CONDIÇÃO MUITO HETEROGÊNEA E O EXEMPLO DO USO DOS SCORES DE RISCO NA SUA ESTRATIFICAÇÃO

2.5 BIBLIOGRAFIA

2.6 ARTIGOS 1 e 2

2.1 INTRODUÇÃO

Tradicionalmente, a fisiopatologia da DC tem estado centrada no processo aterosclerótico e no desenvolvimento de isquémia do miocárdio, com as consequências daí decorrentes. O termo doença cardíaca isquémica reflecte este conceito e engloba todo o espectro da DC estável aos SCA. No entanto, o processo aterosclerótico começa muito mais cedo a instalar-se, passando pela fase da doença não obstrutiva, uma vez que as placas na sua fase inicial não condicionam uma redução significativa do lúmen vascular. Mais recentemente, tem-se percebido que a DC não obstrutiva, embora não condicione isquémia do miocárdio, pode estar na origem de eventos coronários agudos. No entanto, como estas lesões não levam a uma redução significativa do lúmen vascular, não provocam sintomas nem são detectáveis pelos tradicionais exames de documentação de isquémia, e a sua detecção nesta fase só possível por exames anatómicos, como é o caso da angio TC cardíaca.

2.2 DOENÇA CORONÁRIA NÃO OBSTRUTIVA E PLACA VULNERAVEL

Vários estudos de anatomia patológica, ecografia intravascular e mais recentemente angio TC cardíaca demonstraram que o processo aterosclerótico se inicia muito cedo e que numa fase inicial ocorre uma *remodelagem* positiva da artéria para acomodar a placa aterosclerótica, não se acompanhando nesta fase de uma redução do lúmen vascular (1, 2). Estas lesões, ao não condicionarem uma redução significativa do lúmen vascular, não provocam sintomas de angina de esforço nem são detectáveis pelos exames habitualmente empregues em cardiologia para avaliação da DC, que se baseiam na documentação de isquémia do miocárdio. No entanto, apesar de não condicionarem estenoses significativas, estas placa podem ser bastante volumosas e apresentar várias características de instabilidade, estando com frequência também na origem de eventos coronários agudos. Estes resultam frequentemente da ruptura ou erosão das placas ateroscleróticas, sendo este risco directamente proporcional ao volume do núcleo lipídico, ao grau de inflamação e inversamente proporcional à espessura da cápsula fibrosa (2).

No estudo multinacional e multicêntrico PROSPECT (*Providing Regional Observations to Study Predictors of Events in the Coronary Tree*), considerado um marco na avaliação a historia natural da DC, as características das placas avaliadas por ecografia intravascular suplementada com histologia virtual (IVUS-VH) que subsequentemente estiveram na origem de eventos coronários foram a presença de um fibroateroma de cápsula fina (TCFA), uma carga de placa $\geq 70\%$ (traduzindo o *remodeling* positivo) e uma área luminal $\leq 4\text{mm}^2$ (traduzindo algum contributo do grau de estenose) (3). Apesar destas características apontarem para a presença de placas volumosas, estas lesões do ponto de vista angiográfico, não condicionavam estenoses significativas na grande maioria dos casos, sendo a média de estenose de apenas 32%, o que traduz o importante contributo do *remodeling* positivo nestas lesões potencialmente vulneráveis.

Num estudo prospectivo em que foram avaliadas as características das placas por angio TC que estariam na origem de SCA, a presença de *remodeling* positivo e de placas com baixa atenuação (<30 UH), traduzindo placas mais ricas em conteúdo lipídico, foram preditores do desenvolvimento de SCA (4). Neste trabalho que incluiu 1059 doentes avaliados por angio TC cardíaca e seguidos por um período médio de 27 meses, nos doentes que apresentavam placas com estas 2 características, a incidência de SCA foi de 22,2%, na presença de apenas 1 característica foi de 3,7% e na ausência destas características foi de apenas 0,5%. Nesta mesma população, nos doentes sem DC identificável na angio TC, não se verificaram quaisquer eventos CV no seguimento. Interessante foi também verificar que todas as lesões identificadas na angio TC cardíaca que estiveram na origem dos SCA subsequentes, tinham aquando da avaliação inicial uma estenose <75% o que tornaria difícil a sua identificação por sintomas e/ou teste de isquémia.

Recentemente foi descrito o “*Napkin-ring sign*” (NRS), como a imagem que poderá traduzir a presença de uma placa vulnerável na angio TC cardíaca. Este sinal, presente em algumas placas não calcificadas e mistas de conteúdo heterogéneo, resulta de uma diferença de atenuação (em UH) entre o núcleo central (baixa atenuação, correspondendo ao núcleo lipídico) e a periferia da placa (atenuação superior, correspondendo a tecido fibrótico) (5). Este sinal na angio TC cardíaca será o correspondente do TCFA identificado por IVUS-VH, tendo sido já demonstrada uma boa correlação entre este sinal e a presença de placas avançadas na histologia (6). Mais importante ainda, num trabalho recentemente publicado, este sinal foi associado com o desenvolvimento futuro de eventos coronários (7). Neste trabalho, foram avaliados 895 doentes e identificadas 1174 placas, das quais apenas 45 (0,4%) tinham critérios para NRS. No seguimento médio de 2,3 anos, 41% dos eventos ocorreram em placas com NRS e a presença de um NRS foi o preditor independente de eventos (morte cardíaca, EAM e AI) mais significativo, sendo os outros preditores independente a presença de *remodeling* positivo e placas de baixa atenuação.

Desde há muito tempo se sabe que as lesões coronárias não obstrutivas podem estar na origem de SCA, evidência demonstrada em doentes que sofreram um evento coronário agudo e tinham realizado uma coronariografia prévia (8-10) e de estudos angiográficos realizados após fibrinólise em doentes com EAM com supradesnivelamento do segmento ST (11).

Nos últimos anos foram desenvolvidos dispositivos de aspiração de trombos, que vieram modificar o tratamento percutâneo na angioplastia primária e fornecer uma oportunidade para estudar melhor a fisiopatologia do EAM. Num trabalho em que fomos avaliar a estenose residual da lesão *culprit* do EAM após realizada a aspiração de trombos, verificamos que em 31% dos casos a estenose residual após aspiração era inferior a 50% (quantificada por QCA), sugerindo que a lesão *culprit* que instabilizou e esteve na origem do EAM não condicionava previamente estenose significativa e não seria assim detectável com os habituais exames de documentação de isquémia (12).

Por fim, tem sido claro nos vários estudos que tem avaliado o valor prognóstico da angio TC cardíaca que a DC não obstrutiva tem impacto prognóstico, tendo uma taxa de eventos claramente diferente da dos indivíduos sem placas identificáveis, tendo isso sido já demonstrado no registo multinacional e multicêntrico CONFIRM (13), em varias meta-análises (14, 15) e mais recentemente também num estudo que avaliou o impacto prognóstico da informação fornecida pela angio TC a longo prazo (16) (aspectos detalhados no [capítulo 9](#)).

2.3 DISCREPÂNCIA ENTRE ELEVADA PREVALÊNCIA DE PLACAS ATEROSCLERÓTICAS NA ÁRVORE CORONÁRIA E A BAIXA TAXA DE EVENTOS NA POPULAÇÃO GERAL.

Apesar de a DC, mesmo na fase não obstrutiva, poder estar na origem de eventos coronários agudos, existe uma importante discrepância entre a sua elevada prevalência e a baixa taxa relativa de eventos na população geral. Embora as doenças CV sejam a principal causa de morte nos países desenvolvidos, em particular a DC (17, 18), a incidência de SCA na população geral é baixa. Nas estatísticas norte-americanas, a incidência anual de SCA na população adulta varia entre 0,2 a 1% (17), o que contrasta claramente com a elevada prevalência de indivíduos com placas ateroscleróticas na árvore coronária.

Em estudos de anatomia patológica realizados em adultos jovens que morreram de causa não natural (acidentes, suicídios, homicídios), foi possível identificar aterosclerose coronária em 83% dos casos (19). Também em estudos realizados com ecografia intracoronária foi possível detectar aterosclerose coronária em fases muito precoces e mesmo em segmentos angiograficamente normais, reflexo do processo de *remodeling* positivo (20, 21).

Do mesmo modo, a presença de placas calcificadas na árvore coronária é habitual na maioria dos homens a partir dos 40 anos e nas mulheres a partir dos 55 anos, como se pode depreender da análise dos normogramas de score de cálcio nos quais mesmo no percentil 50 já é suposto o score de cálcio ser >1 (22). Mais recentemente, com a angio TC cardíaca, tem sido também evidente a elevada prevalência de placas ateroscleróticas identificáveis nas artérias coronárias e de facto a ausência de quaisquer placas está presente em menos de metade dos indivíduos avaliados com esta técnica. No estudo multinacional e multicêntrico CONFIRM (*Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry*), só 42,5% dos indivíduos não tinham placas identificáveis na angio TC cardíaca (13).

Na nossa população, esta percentagem foi de 41,3% (23, 24), em linha com o resultado publicado por outros grupos (25).

A explicação para esta discrepância entre a elevada prevalência de placas na árvore coronária e o risco de eventos coronários poderá estar justificada pelo facto de o risco individual por placa ser de facto muito baixo e ser mais importante o número total de placas ou seja, a carga

aterosclerótica global na árvore coronária. Esta poderá também explicar porque é que uma importante percentagem de SCA ocorrem em placas não obstrutivas, uma vez que estas são muito mais prevalentes e assim em termos probabilísticos apesar de o seu risco individual poder ser inferior, existem mais probabilidade que estejam na origem de um evento (26-28). O mesmo se passa ao nível populacional, pois apesar de ser possível identificar alguns indivíduos cuja constelação de factores de risco os colocam em elevado risco de eventos CV, esta representa apenas uma minoria em número absoluto e uma vez que o número de indivíduos em patamares de risco mais baixo é exponencialmente mais elevado, os eventos CV ocorrem com frequência em indivíduos de risco não muito elevado (29).

Mais recentemente, o conceito de que determinadas características de potencial instabilidade de uma placa em particular possam ser úteis para a identificação e eventual intervenção nestas lesões foi colocado em questão pelos resultados modestos do estudo PROSPECT. Neste estudo de história natural da DC, apesar de ter sido possível identificar algumas características associadas ao risco de eventos cardíacos futuros, a grande maioria das placas com estas características não vieram a instabilizar. Mesmo a identificação de um fibroateroma de cápsula fina teve uma baixa especificidade para prever a ocorrência de eventos, uma vez que apenas 26 das 595 placas (4,3%) identificadas como de risco estiveram na origem de eventos no seguimento (média de 3,4 anos). Por outro lado, estes eventos foram na grande maioria rehospitalizações por AI e novas revascularizações e não os eventos major morte e EAM, que verdadeiramente gostaríamos de poder prevenir (3).

A identificação dos doentes em maior risco de eventos poderá passar pela identificação não das características de uma placa em particular, mas pela quantificação da carga aterosclerótica global e este foi um dos pressupostos do desenvolvimento do CT-LeSc (24), como ferramenta para quantificar esta carga aterosclerótica coronária, que se espera seja um bom preditor de eventos coronários (descrito em mais detalhe no *Capítulo 8*).

2.4 SÍNDROMES CORONÁRIOS AGUDOS COMO CONDIÇÃO MUITO HETEROGÊNEA E O EXEMPLO DO USO DOS SCORES DE RISCO NA SUA ESTRATIFICAÇÃO

Os SCA representam uma condição muito heterogênea, englobando um largo espectro de doentes em diferente risco de eventos CV, sendo essencial a sua estratificação de risco. Assim, constituem um cenário clínico exemplar para o desenvolvimento e aplicação de scores de risco, ferramentas essenciais para a tomada de decisão no manejo destes doentes, podendo tirar-se daqui varias lições úteis para o desenvolvimento e implementação de scores noutras áreas da DC.

Em 2005 o nosso grupo publicou um estudo onde foi comparado o desempenho de 3 scores de risco (GRACE, TIMI e PURSUIT) na estratificação dos doentes com SCA (30). Foi possível demonstrar que o score de risco GRACE era o que tinha um desempenho superior, fruto não só do tipo de variáveis que incluiu, mas também de algumas delas serem valorizadas de forma contínua. Este era o score que melhor previa a ocorrência de eventos cardíacos a 1 ano e permitia identificar os doentes que colhiam maior benefício da revascularização, sendo actualmente recomendado pelas *guidelines* europeias para a estratificação destes doentes (31). No entanto, o score de risco TIMI pela sua simplicidade, continua a ser usado na pratica clínica e mesmo em vários estudos, como é o caso dos recentemente publicados sobre o uso da angio TC cardíaca na avaliação dos doentes no serviço de urgência (32, 33).

Uma das lições retiradas desta experiencia, foi que um score para entrar na pratica clínica tem que ter um balanço entre complexidade e desempenho. Apesar de o desempenho ser directamente proporcional ao número de variáveis incluídas, também a sua complexidade aumenta, diminuindo assim a sua potencial aplicabilidade clínica. Da mesma forma, o modo com as variáveis são operacionalizadas (contínuas ou categóricas) também é determinante, ficando os scores tendencialmente mais simples, mas perdendo algum poder discriminativo, quando se opta por usar as variáveis como categóricas em vez de contínuas.

Este conceito esteve no racional de desenvolvimento do CT-LeSc onde tentamos procurar esse equilíbrio difícil entre complexidade e desempenho, com vista ao seu uso futuro como ferramenta para quantificação da carga aterosclerótica coronária sendo de esperar que possa traduzir a informação prognostica da angio TC cardíaca e ser adoptado na pratica clínica.

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2.6 ARTIGO 1/MANUSCRIPT 1

154 Therapy and prevention

Nonobstructive coronary disease leading to STEMI: assessment of residual stenosis after thrombus aspiration

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Aims Nonobstructive coronary atherosclerotic lesions can lead to ST-elevation myocardial infarction (STEMI). Thrombus aspiration during a primary percutaneous coronary intervention provides a setting to evaluate the degree of stenosis of culprit lesions leading to STEMI. The aim of this study was to assess the degree of culprit lesion residual stenosis after thrombus aspiration and to compare the demographic, clinical, and angiographic characteristics between patients with obstructive versus nonobstructive residual stenosis.

Methods and results From a single-center registry of 483 consecutive patients with STEMI undergoing a primary percutaneous coronary intervention, 172 patients underwent thrombus aspiration and were eligible for our study. We defined two groups according to the residual stenosis after thrombus aspiration: group A ($n=119$, 69%) with residual stenosis greater than or equal to 50%, and group B ($n=53$, 31%) with residual stenosis less than 50%. In terms of the baseline angiographic characteristics, patients with residual stenosis less than 50% had significantly lower prevalence of multivessel disease (15.1 vs. 46.2%, $P<0.001$). On multivariable analysis of the preprocedural variables, absence of vascular disease (odds ratio 4.99, 95% confidence interval 1.08–23.12,

$P=0.040$) and age less than 59 years (odds ratio 2.67, 95% confidence interval 1.25–5.73, $P=0.011$) were independent predictors of culprit residual stenosis less than 50%.

Conclusion In this population, a significant proportion of patients with STEMI had nonobstructive residual stenosis after thrombus aspiration. These patients were younger, had a lower prevalence of vascular disease in other vascular territories, and less multivessel disease, suggesting an earlier stage of atherosclerosis. *Coron Artery Dis* 24:154–159 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: acute coronary syndromes, atherosclerosis, coronary angiography, myocardial infarction, pathophysiology

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Introduction

ST-elevation myocardial infarction (STEMI) because of acute coronary artery occlusion has two main components: underlying atherosclerotic plaque and thrombus. The relative contribution of each of these factors is variable as many clinical observations suggest that myocardial infarctions are not necessarily related to previous high-grade coronary stenosis [1–3]. More often, acute events are caused by the rupture of plaques that are not associated with severe luminal narrowing, and the total coronary occlusion occurs as a result of the superimposed thrombus burden.

Evidence supporting the concept that nonobstructive atherosclerotic lesions can lead to STEMI comes mainly from serial angiographic studies retrospectively evaluating the degree of stenosis in patients with a previous coronary angiography [4–7], and from studies of patients referred

for angiography after thrombolytic therapy [8]. However, in more recent studies carried out in the setting of a primary percutaneous coronary intervention (PCI), it has been suggested that in most cases, STEMIs occurred at the site of severe obstructive stenosis [9,10].

In recent years, thrombus aspiration devices have gained an important role in primary PCI [11,12], and this provides a setting for the evaluation and better understanding of the pathophysiology of coronary artery lesions leading to STEMI.

The aim of this study was to assess the degree of residual stenosis in STEMI culprit lesions after thrombus aspiration and to compare the demographic, clinical, and angiographic characteristics between two groups of patients according to the degree of residual stenosis after thrombus aspiration.

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Methods

Study design and patient population

This was a single-center, retrospective study in which 483 consecutive patients with STEMI and no previously known history of coronary artery disease (CAD), undergoing primary PCI between January 2006 and November 2010, were eligible. Only patients ($n = 199$) undergoing thrombus aspiration (PRONTO Extraction Catheter; Vascular Solutions Inc., Minneapolis, Minnesota, USA or EXPORT Aspiration Catheter; Medtronic Inc., Santa Rosa, California, USA) were included, of whom 27 were excluded because of balloon dilatation before thrombectomy. Therefore, a total of 172 patients were included in the study (Fig. 1).

All angiograms were reviewed and analyzed by quantitative coronary analysis (edge detection techniques) of the culprit lesion and vessel after thrombus aspiration. The following parameters were measured: reference vessel diameter (RVD), lesion length, minimal luminal diameter (MLD), and diameter stenosis (DS).

Patients were divided into two groups according to the degree of culprit lesion residual DS: group A: culprit stenosis greater than or equal to 50%; and group B: culprit stenosis less than 50%.

Clinical, demographic, and angiographic data were collected at the time of the procedure and were entered in a centralized database (Cardiobase; Infortucano SI, Lisbon, Portugal).

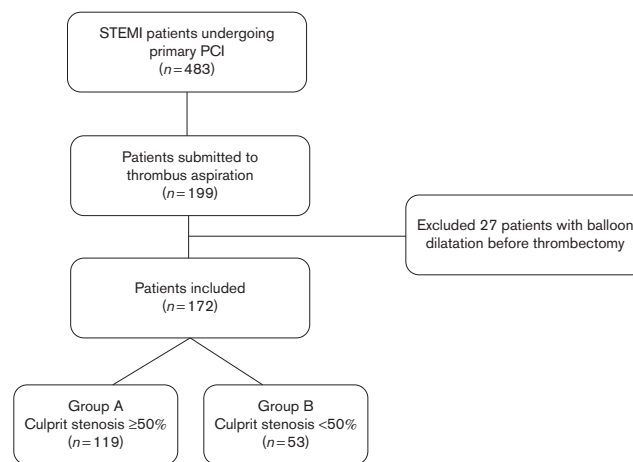
Statistical analysis

Categorical variables were expressed as percentages, and their frequencies were compared using the χ^2 test or Fisher exact test as appropriate. Continuous variables with a normal distribution were expressed as mean $\pm$ 1 SD, and were compared using a Student's unpaired t -test. Continuous variables without a normal distribution were expressed as median (first quartile; third quartile), and were compared using the Mann-Whitney test. The normality assumption for continuous variables was assessed using the Kolmogorov-Smirnov test. Receiver-operating characteristic curves were used to find the cut-off point for age. Binary logistic regression models were constructed to elucidate independent predictors of residual stenosis less than 50% after thrombus aspiration. The aim of this model was the assessment of preprocedure variables that aid the prediction of residual stenosis less than 50%. Only the traditional cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) and significant variables in univariate analysis ($P < 0.05$) were included in the multivariate model.

Two-tailed tests of significance were reported. For all comparisons, a P -value less than 0.05 was considered statistically significant. When appropriate, confidence intervals (CIs) were reported, with a 95% confidence level.

Statistical analysis was carried out using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA).

Fig. 1



Patient selection and study design. PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Results

Baseline and procedural characteristics

From a total of 172 patients included in the study, 119 (69%) had culprit residual stenosis greater than or equal to 50% after thrombus aspiration, whereas 53 patients (31%) had residual stenosis less than 50%. Patients with residual stenosis less than 50% were considerably younger (55.1 ± 14.3 vs. 62.3 ± 11.9 years, $P = 0.001$) and had a lower prevalence of vascular disease (3.8 vs. 19.3%, $P = 0.008$) in other vascular territories (cerebral or peripheral vascular disease). Although there was a trend in this group toward a lower prevalence of hypertension, diabetes, and obesity, there were no statistically significant differences (Table 1).

In terms of the baseline angiographic characteristics, patients with residual stenosis less than 50% had significantly lower prevalence of multivessel disease (15.1 vs. 46.2%, $P < 0.001$) and there were no significant differences in the location of the culprit lesion. By quantitative coronary angiography, lesions with residual stenosis less than 50% (mean DS $34.5 \pm 11.2\%$; mean MLD 1.91 ± 0.70 mm) were also shorter (12.29 ± 4.78 vs. 14.60 ± 5.74 mm, $P = 0.038$) compared with lesions with culprit residual stenosis greater than or equal to 50% (mean DS $67.6 \pm 9.9\%$; mean MLD 0.93 ± 0.34 mm). There were no significant differences in RVD (RVD 2.88 ± 0.71 vs. 2.86 ± 0.61 mm, $P = 0.912$) (Table 2).

Multivariable analysis

On multivariable analysis, which included only the demographic and clinical preprocedural variables, the

independent predictors of culprit residual stenosis less than 50% after thrombus aspiration were absence of vascular disease (odds ratio = 4.99, 95% CI 1.08–23.12, $P = 0.040$) and age less than 59 years (odds ratio = 2.67, 95% CI 1.25–5.73, $P = 0.011$) (Fig. 2).

Discussion

Nonobstructive coronary atherosclerotic lesions can often lead to STEMI as, for the total occlusion of the coronary artery, there is an important contribution of the thrombus burden superimposed on the culprit atherosclerotic plaque. This evidence comes from previous studies of patients with a previous coronary angiogram [4–7] and patients referred for angiography after thrombolytic therapy [8].

Little *et al.* [1] compiled data from four studies in which serial coronary angiograms were performed before and after an acute myocardial infarction and found that 60% of the culprit lesions contained less than 50% stenosis before the event.

Lleavador *et al.* [8], with data from the TIMI 4, 10A, 10B, and 14 trials, assessed the degree of residual stenosis in the culprit coronary artery 90 min after thrombolytic administration and found less than 50% stenosis in 8.9% of the patients. In these earlier studies, residual thrombus could have led to an overestimation of the degree of culprit artery stenosis and, in fact, some of the patients had an occluded artery at the time of the angiography. It is reasonable to assume that more aggressive antithrombotic and antiplatelet therapy, coupled with the recent aspiration devices, can lead to

Table 1 Baseline clinical and demographic characteristics according to culprit stenosis

Variable	Group A culprit $\geq 50\%$, $n=119$ (69.2%)	Group B culprit $<50\%$, $n=53$ (30.8%)	<i>P</i>
Age	62.3 ± 11.9	55.1 ± 14.3	0.001
Male sex	91 (76.5%)	46 (77.4%)	0.899
Diabetes	20 (16.8%)	6 (11.3%)	0.354
Hypertension	63 (52.9%)	23 (43.4%)	0.248
Dyslipidemia	57 (47.9%)	26 (49.1%)	0.888
Smoking	73 (61.3%)	32 (60.4%)	0.904
BMI > 30	24 (22.4%)	7 (15.6%)	0.337
Vascular disease (cerebrovascular + peripheral)	23 (19.3%)	2 (3.8%)	0.008

The bold values are statistically significant values.

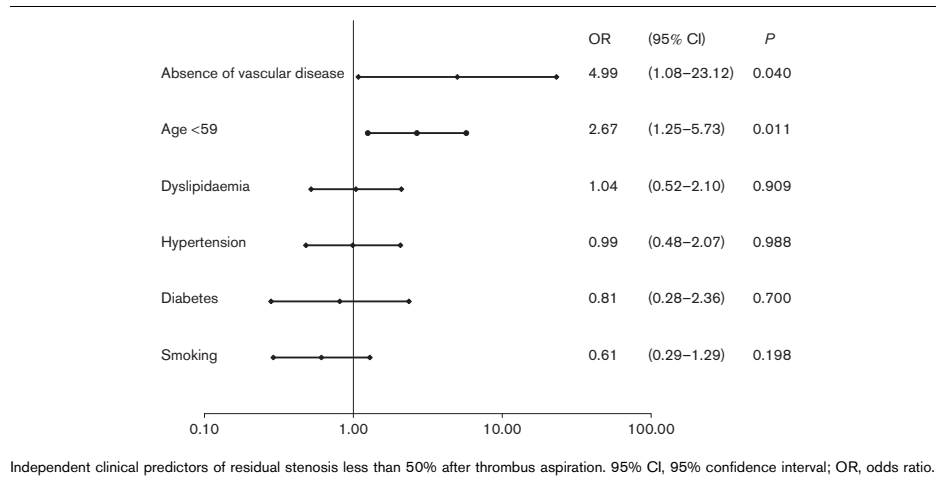
Table 2 Angiographic characteristics according to culprit stenosis

Variable	Group A culprit $\geq 50\%$, $n=119$ (69.2%)	Group B culprit $<50\%$, $n=53$ (30.8%)	<i>P</i>
Multivessel disease	55 (46.2%)	8 (15.1%)	<0.001
Culprit vessel			
Left main	1 (0.8%)	1 (1.9%)	0.554
LAD	45 (37.8%)	27 (50.9%)	0.107
LCx	14 (11.8%)	6 (11.3%)	0.933
RCA	59 (49.6%)	19 (35.8%)	0.095
QCA			
RVD (mm)	2.86 ± 0.61	2.88 ± 0.71	0.912
Lesion length (mm)	14.60 ± 5.74	12.29 ± 4.78	0.038
MLD (mm)	0.93 ± 0.34	1.91 ± 0.70	<0.001
DS (%)	67.58 ± 9.88	34.51 ± 11.18	<0.001

The bold values are statistically significant values.

DS, diameter stenosis; LAD, left anterior descending; LCx, left circumflex; MLD, minimum luminal stenosis; QCA, quantitative coronary angiography; RCA, right coronary artery; RVD, reference vessel diameter.

Fig. 2



a more effective thrombus removal and therefore to a more reliable assessment of the degree of culprit residual stenosis. More recently, Frøbert *et al.* [9] described angiographically significant stenosis in almost all patients with STEMI, referred for primary PCI, but in this study the degree of stenosis was evaluated in the angiograms obtained after wiring of the vessel. In this way, there was probably a significant contribution of residual thrombus burden to the degree of residual culprit stenosis. In the study by Manoharan *et al.* [10], the degree of stenosis was assessed only after thrombus aspiration, but this study also included patients with non-STEMI and unstable angina. In our study, only patients with STEMI undergoing a primary PCI were included.

We found thrombus aspiration during primary PCI to provide a setting to evaluate the degree of stenosis of culprit lesions leading to STEMI. In our study, 31% of the patients undergoing a primary PCI had a residual stenosis less than 50% after thrombus aspiration. Therefore, it is reasonable to assume that these culprit lesions were nonobstructive before the acute event.

It is also known that many of the nonstenotic lesions can have a high plaque burden, underestimated by luminal angiograms, as they undergo expansive or positive outward enlargement, and such remodeling is a potential surrogate marker of plaque vulnerability [13]. In the multicenter virtual histology intravascular ultrasound (VH-IVUS) PRO-SPECT study [14], 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. In this study of patients with acute coronary syndromes, lesions that led to a major adverse cardiac event had a high plaque burden by IVUS, but were mild by baseline angiography (mean DS 32%).

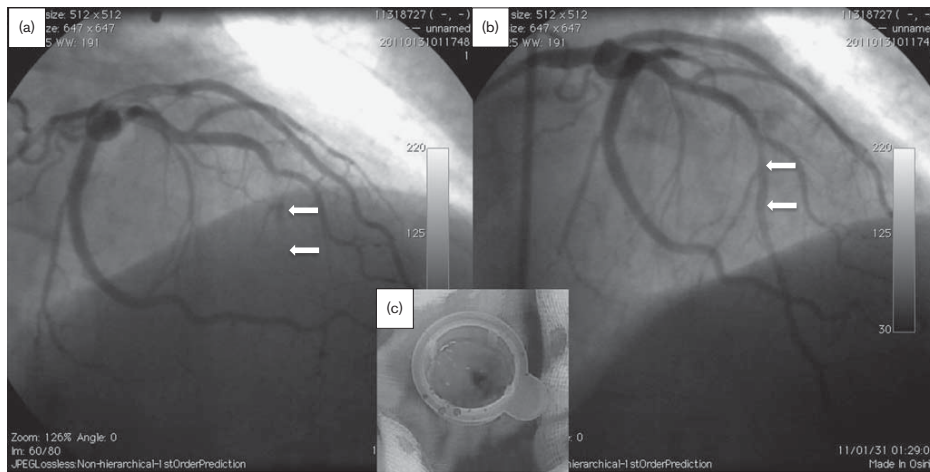
The prognostic value of nonobstructive CAD has also been reinforced recently from large cardiac CT registries [15] and meta-analysis [16].

In the large international multicenter Cardiac CT registry (CONFIRM Registry), all-cause mortality was significantly higher for patients with nonobstructive CAD compared with patients without coronary atherosclerosis. One notable finding in this registry is the superimposed survival curves of nonobstructive and one-vessel obstructive CAD, reinforcing the prognostic impact of non-obstructive coronary lesions [15].

Patients with nonobstructive culprit lesions in our study were younger and had a lower prevalence of multivessel CAD and a lower prevalence of vascular disease in other vascular territories. These findings suggest that these patients had the acute coronary event at an earlier stage of the atherosclerotic disease. Patients with nonobstructive lesions are not expected to have symptoms or to develop ischemia in noninvasive stress tests, and this could explain why it is difficult to identify patients at risk before the event and STEMI is still the first manifestation of CAD in many cases (as the case example in Fig. 3).

In the future, if we aim at preventing many of these events, the paradigm of risk stratification in primary

Fig. 3



Case example of a 51-year-old male patient, presenting with an anterior ST-elevation myocardial infarction as the first manifestation of coronary artery disease referred for urgent coronary angiography for a primary percutaneous coronary intervention. Single-vessel coronary disease with a nonobstructive (<50%) mid-left anterior descending (LAD) residual lesion after thrombus aspiration. The arrow points to the culprit location in the mid-LAD where the vessel was occluded (a) and the remaining residual angiographic stenosis of the culprit lesion after thrombus aspiration (b) and the detail of the aspirated thrombus (c).

prevention has to move from symptoms and demonstration of ischemia to the identification of atherosclerosis at an earlier stage.

Limitations

This was a single-center registry and the cohort included only patients with STEMI in whom thrombus aspiration was performed. Patients with smaller thrombus burden or with diffusely diseased and calcified vessels were less likely to have undergone thrombus aspiration. By not including these patients, we could have overestimated the relative contribution of thrombus versus plaque burden in patients with STEMI. However, with this study design, evaluating the degree of the culprit stenosis only after thrombus aspiration could have also led to some overestimation of the severity of stenosis, because it is unlikely that thrombus aspiration can remove all thrombi. Therefore, residual thrombus could have led to overestimation of the degree of residual stenosis, and some of the patients with an obstructive residual stenosis after thrombus aspiration could have been in fact patients with culprit lesions with less degree of stenosis.

IVUS was not performed, and therefore, it was not possible in the present study to evaluate the real plaque burden of the culprit lesions leading to STEMI.

Conclusion

In this population, a significant proportion of patients with STEMI had nonobstructive residual stenosis after thrombus aspiration. These patients were younger, had a lower prevalence of vascular disease in other vascular territories, and less multivessel disease, suggesting an earlier stage of atherosclerosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Clinical research

TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS

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KEYWORDS

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PURSUIT risk score;
GRACE risk score;
Coronary disease;
Myocardial infarction;
Unstable angina;
Prognosis;
Risk stratification

Aims Regarding prognosis, patients with a non-ST elevation acute coronary syndrome (ACS) are a very heterogeneous population, with varying risks of early and long-term adverse events. Early risk stratification at admission seems to be essential for a tailored therapeutic strategy. We sought to compare the prognostic value of three ACS risk scores (RSs) and their ability to predict benefit from myocardial revascularization performed during initial hospitalization.

Methods and results We studied 460 consecutive patients admitted to our coronary care unit with an ACS [age: 63 ± 11 years, 21.5% female, 55% with myocardial infarction (MI)]. For each patient, the Thrombolysis In Myocardial Infarction (TIMI), Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (PURSUIT), and Global Registry of Acute Coronary Events (GRACE) RSs were calculated using specific variables collected at admission. Their prognostic value was evaluated by the combined endpoint of death or MI at 1 year. The best cut-off value for each RS, calculated with receiver operating characteristic curves, was used to assess the impact of myocardial revascularization on the combined incidence of death or MI. Death or MI at 1 year was 15.4% (32 deaths/49 MIs). The best predictive accuracy for death or MI at 1 year was obtained by the GRACE RS (AUC [area under the curve: 0.715; confidence interval (CI): 0.672–0.756]) but the performance of the PURSUIT RS (AUC: 0.630; CI: 0.584–0.674), and TIMI RS (AUC: 0.585; CI: 0.539–0.631) was also good. We found a statistically significant interaction between the risk stratified by the best cut-off value for the GRACE and PURSUIT RSs and myocardial revascularization, with a better prognosis for the high-risk patients. The high-risk patients represented 36.7, 28.7, and 57.8% of the population, for the GRACE, PURSUIT, and TIMI RSs, respectively.

Conclusion The RSs studied demonstrated a good predictive accuracy for death or MI at 1 year and enabled the identification of high-risk subsets of patients who will benefit most from myocardial revascularization performed during initial hospital stay.

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Introduction

Patients with non-ST elevation acute coronary syndromes (NSTEMI-ACS) are a heterogeneous population with varying risks of death and recurrent cardiac events, in long-term as well as short-term follow-up.^{1,2} In these patients, early risk stratification plays a central role, as the benefit of newer and more aggressive and costly treatment strategies seems to be proportional to the risk of adverse clinical events.³⁻⁵ Different scores are now available based on initial clinical history, ECG, and laboratory tests that enable early risk stratification on admission. The thrombolysis In Myocardial Infarction (TIMI)⁶ and platelet glycoprotein IIb/IIIa in unstable angina: Receptor Suppression Using Integrilin (PURSUIT)⁷ scores were developed with the databases from large clinical trials of NSTEMI-ACS. The more recent Global Registry of Acute Coronary Events (GRACE) score was developed from the registry,⁸ with a population of patients across the entire spectrum of ACS. All these scores were developed for short-term prognosis: events in-hospital for the GRACE risk score (RS), at 14 days for the TIMI RS, and at 30 days for the PURSUIT RS. Nevertheless, a significant proportion of adverse events in NSTEMI-ACS patients occur after the first 30 days, and it is not known whether these RS can also predict their occurrence. On the other hand, it has been demonstrated that an early invasive strategy has a prognostic benefit in the long term.⁹ Recently, the GRACE risk model has also been validated as a predictor of death or myocardial infarction (MI) 6 months following hospital presentation.¹⁰

The aim of this study was to compare the performance of these TIMI, PURSUIT, and GRACE scores in risk stratification of NSTEMI-ACS patients, both at 30 days and at 1 year, and to evaluate their ability to predict benefit from myocardial revascularization performed during initial hospitalization.

Methods

Study population

This was a retrospective study of consecutive patients admitted to a coronary care unit (CCU) with NSTEMI-ACS between March 1999 and July 2001. The inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 h of admission. This could be associated with ST or T wave changes on the electrocardiogram suggestive of myocardial ischaemia or elevated levels of biomarkers of myocardial damage. The biomarkers used were cardiac troponin I (cTn I) and creatine kinase MB mass assay (CK-MB), with a threshold for positivity of 0.1 and 5 ng/mL, respectively (chemiluminescence assay—Access Immunoassay Analyser).

Risk scores

The three RSs—TIMI, PURSUIT, and GRACE—were calculated from the initial clinical history, electrocardiogram, and laboratory values collected on admission (Table 1). Although this was a retrospective study, these data were collected prospectively and

Table 1 Risk scores

PURSUIT (0–18)	Age, separate points for enrolment diagnosis	
	Decade [UA (MI)]	
	50	8 (11)
	60	9 (12)
	70	11 (13)
	80	12 (14)
	Sex	
	Male	1
	Female	0
	Worst CCS-class in previous 6 weeks	
TIMI (0–7)	No angina or CCS I/II	0
	CCS III/IV	2
	Signs of heart failure	2
	ST-depression on presenting ECG	1
	Age ≥65 years	1
	≥3 risk factors for CAD	1
	Use of ASA (last 7 days)	1
	Known CAD (stenosis ≥50%)	1
	>1 episode rest angina in <24 h	1
	ST-segment deviation	1
GRACE (0–258)	Elevated cardiac markers	1
	Age (years)	
	<40	0
	40–49	18
	50–59	36
	60–69	55
	70–79	73
	≥80	91
	Heart rate (bpm)	
	<70	0
	70–89	7
	90–109	13
	110–149	23
	150–199	36
	>200	46
	Systolic BP (mmHg)	
	<80	63
	80–99	58
	100–119	47
	120–139	37
	140–159	26
	160–199	11
	>200	0
	Creatinine (mg/dL)	
	0–0.39	2
	0.4–0.79	5
	0.8–1.19	8
	1.2–1.59	11
	1.6–1.99	14
	2–3.99	23
	>4	31
	Killip class	
	Class I	0
	Class II	21
	Class III	43
	Class IV	64
	Cardiac arrest at admission	43
	Elevated cardiac markers	15
	ST-segment deviation	30

recorded on a computer database of ACS patients admitted to our institution's CCU. Thus, no patient was excluded from the analyses performed in this study due to missing data. When calculating the TIMI RS in patients without a prior coronary angiogram, for the variable 'known coronary artery disease (stenosis $\geq 50\%$)' we attributed 1 point to a history of MI or coronary revascularization. This methodology is closer to real-world practice, and it has been validated by the authors of the TIMI RS.⁵

Regarding the TIMI and PURSUIT RSs the values are easily obtained. For the TIMI RS, as all seven variables have the same magnitude, the result for each patient is the simple arithmetic sum of the number of variables present.⁶ For the PURSUIT RS, the simple score for death and MI was used, instead of the more complex original score, and is obtained as the sum of the points given to each of the five predictive factors.⁷

For the more recently developed GRACE RS, although it was not published by the time this study was conducted, a program for PDAs (personal digital assistants) was available for download at the site of the GRACE project, and was used to calculate each patient score (GRACE ACS Risk Model 0.25, StatCoder.com) (available at <http://www.umassmed.edu/outcomes/gracel>).

Endpoint

All patients included were followed up for at least 1 year or until the occurrence of a major event. The study endpoint was the combination of all-cause mortality or non-fatal MI, according to the new ESC/ACC consensus definition.¹¹ This endpoint was analysed both at 30 days and at 1 year.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean value and standard deviation. Normality was tested with the Shapiro-Wilks test. Discrete variables were expressed as frequencies and per cent values.

Statistical comparison of baseline characteristics and outcomes was performed using the χ^2 test with Yates correction or the Fisher exact test, when appropriate, for categorical variables, and the two-tailed Student's *t*-test for continuous variables.

For each of the three RSs, receiver operating characteristic (ROC) curves were used to relate the calculated scores to the rate of adverse clinical events, both at 30 days and at 1 year. This procedure was also applied to the endpoints and time of follow-up used in the original study of each RS. The area under the curve (AUC), or C-statistic, was used as a measure of the predictive accuracy of the RS. The relative performance of each test was evaluated with the 95% confidence interval (CI) for the difference between two AUCs. The goodness of fit of the RSs was evaluated by calculating the Hosmer-Lemeshow statistic.

The cut-off points identified with the ROC curves for each score were used to separate the studied population in low- and high-risk patients. The 1-year endpoint rate for the low- and high-risk patients in each score was calculated, comparing in each subgroup patients who underwent or did not undergo a revascularization procedure during initial hospital admission.

For each score, logistic analyses were performed to test for an interaction between the score and the effect of myocardial revascularization on the 1-year outcome.

Two-tailed tests of significance are reported. For all comparisons, a *P*-value of <0.05 was considered statistically significant. When appropriate, CIs were calculated, with a 95% confidence level.

Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 6.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

A total of 460 patients were included in this study. The final diagnosis of the ACS was unstable angina in 209 patients (45.4%) and NSTEMI in the other 251 (54.6%). The baseline characteristics and in-hospital management are presented in Table 2.

Table 2 Baseline characteristics and in-hospital management

Age (years)	63.4 $\pm$ 10.8
Sex (%)	
Male	78.5
Female	21.5
Risk factors (%)	
Diabetes mellitus	23.5
Hypercholesterolemia	60.9
Systemic hypertension	61.7
Smoking	21.3
Previous history (%)	
Myocardial infarction	45.7
Myocardial revascularization	47.8
PCI	31.5
CABG	22.2
Peripheral arterial disease	11.0
TIA/stroke	8
Previous medication (%)	
Platelet inhibitors	71.5
ASA	60.2
Beta-blockers	48.3
Calcium channel antagonists	43.8
ACE inhibitors/ARBs	39.2
Statins	29.9
On admission	
Heart rate (bpm)	75.7 $\pm$ 17.5
Systolic BP (mmHg)	142.7 $\pm$ 26.1
Diastolic BP (mmHg)	80.6 $\pm$ 14.3
Signs of heart failure (%)	13.9
ST-segment depression ≥ 1 mm (%)	55.9
Tn I > 0.1 ng/mL (%)	31.5
CK-MB mass > 5 ng/mL (%)	29.1
LVEF $< 40\%$	12.3
Three vessels/left main CAD (%)	43.6
Pharmacological therapy (%)	
ASA	95.7
UFH/LMWH	78.9/41.7
GP IIb/IIIa inhibitors	38.7
Nitrates	91.1
Beta-blockers	86.3
Calcium channel blockers	15.2
ACE inhibitors	71.5
Statins	48.9
Revascularization (%)	
PCI	47.8
CABG	18.3

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; ASA, aspirin; ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; GP, glycoprotein.

By 30-day follow-up, 13 patients had died (2.8%) and 24 had had a non-fatal MI (5.2%). The 30-day endpoint rate was 7.2%.

At 1 year, there were 32 deaths (7%) and 49 patients had had an MI (10.7%), with a total 1-year endpoint rate of 15.4%.

The univariate predictors of the 30-day endpoint were age, signs of heart failure on admission, and baseline serum creatinine. Regarding the 1-year endpoint, the predictors were age, both as a continuous variable and with a cut-off of 65 years, previous history of hypertension, chronic angina CCS III or IV in the last 6 weeks, heart rate on admission, signs of heart failure on admission, ST-segment depression, and baseline serum creatinine (Table 3).

RSs: endpoint rates in the different risk groups

The mean value in this population was 13 (range: 1–19) for the PURSUIT RS, 4 (range: 1–7) for the TIMI RS, and 122 (range: 50–237) for the GRACE RS.

As shown in Figures 1–3, the distribution of the 30-day and 1-year endpoint rates in the different risk groups, for the three RS, demonstrated a consistent gradient of risk.

Predictive accuracy of the RSs

Both the PURSUIT and the GRACE scores showed a good discriminatory accuracy to predict death and recurrent MI as a combined endpoint at 30 days and at 1 year, as demonstrated by the C-statistic.

The discriminatory accuracy of the TIMI score was not as high, but this score had a good fit with both the 30-day and the 1-year endpoint, as demonstrated by a probability value of the Hosmer–Lemeshow χ^2 of 0.803 and 0.760, respectively.

For both the PURSUIT and the GRACE scores, regarding the 30-day endpoint, the probability value of the Hosmer–Lemeshow was adequate but not optimal. Nevertheless, for the 1-year endpoint, both scores had a good fit (Table 4).

The discriminatory accuracy of the three scores was also analysed to predict the standard endpoints in the original follow-up for which they were developed. The TIMI score had a C-statistic of 0.60 (95% CI: 0.56–0.65) for predicting death, MI or recurrent ischaemia with the need for urgent revascularization at 14 days. For the GRACE score, the C-statistic for predicting intra-hospital death was 0.76 (95% CI: 0.72–0.80). Regarding the PURSUIT score, the endpoints and the follow-up were the same in this study.

Table 3 Univariate predictors

	30 days			1 year		
	With events (n = 33)	Without events (n = 427)	P-value	With events (n = 71)	Without events (n = 389)	P-value
Age (years)	67.7 ± 12.1	63.0 ± 10.6	0.017	67.7 ± 10.9	62.6 ± 10.6	<0.001
≥ 65	22 (67)	204 (48)	0.056	49 (69)	177 (46)	<0.001
Male [n (%)]	28 (85)	333 (72)	0.481	60 (85)	301 (77)	0.235
Risk factors [n (%)]						
Diabetes mellitus	8 (24)	100 (23)	1.00	21 (30)	87 (22)	0.244
Hypercholesterolemia	22 (67)	258 (60)	0.60	42 (59)	238 (61)	0.850
Systemic hypertension	21 (64)	263 (62)	0.963	53 (75)	231 (59)	0.021
Smoking	7 (21)	91 (21)	1.00	13 (18)	85 (22)	0.608
≥ 3 risk factors	5 (15)	67 (16)	1.00	13 (18)	59 (15)	0.622
Previous history [n (%)]						
≥ 2 episodes rest angina <24 h	32 (97)	411 (96)	1.000	68 (96)	375 (94)	1.000
≥ 3 CCS angina last 6 weeks	23 (97)	325 (96)	0.537	46 (65)	302 (78)	0.030
Myocardial infarction	15 (45)	195 (46)	1.000	32 (45)	178 (46)	1.000
Revascularization	16 (48)	204 (48)	1.000	38 (54)	182 (47)	0.360
PCI	5 (15)	140 (33)	0.057	23 (32)	122 (31)	0.974
CABG	12 (36)	90 (21)	0.069	21 (30)	81 (21)	0.139
Known CAD	20 (61)	277 (65)	0.761	45 (63)	252 (65)	0.927
ASA in the last 7 days	17 (52)	260 (61)	0.381	38 (54)	239 (61)	0.262
On admission						
Systolic BP (mmHg)	140.5 ± 28.0	142.9 ± 25.9	0.601	143.7 ± 27.4	142.6 ± 25.8	0.739
Heart rate (bpm)	79.1 ± 20.6	75.5 ± 17.3	0.248	83.5 ± 21.9	74.3 ± 16.3	<0.001
Signs of heart failure [n (%)]	10 (30)	54 (13)	0.010	20 (28)	44 (11)	<0.001
ST depression ≥ 1 mm [n (%)]	22 (67)	235 (55)	0.265	48 (68)	209 (54)	0.265
Tn I > 0.1 ng/mL [n (%)]	12 (36)	133 (31)	0.669	26 (37)	119 (31)	0.669
Creatinine (mg/dL)	2.8 ± 1.9	1.2 ± 0.5	<0.001	2.2 ± 1.7	1.2 ± 0.5	<0.005

CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ASA, acetylsalicylic acid; BP, blood pressure.

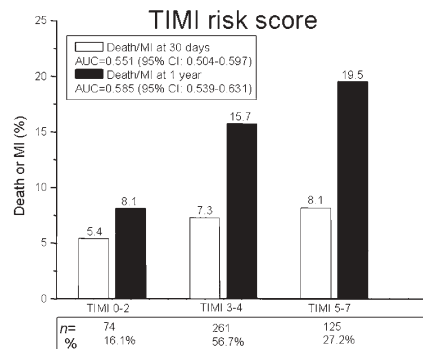


Figure 1 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the TIMI score.

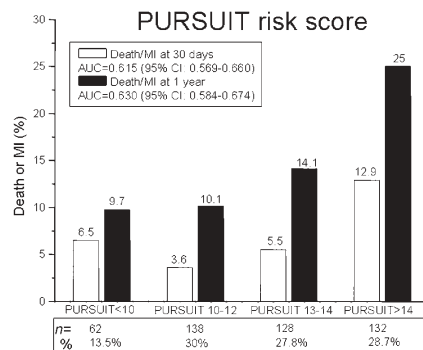


Figure 2 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the PURSUIT score.

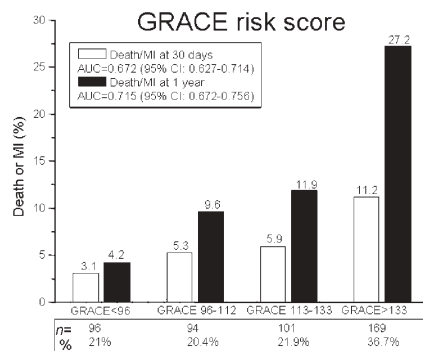


Figure 3 Distribution of the 30-day and 1-year endpoint rates in the different risk groups for the GRACE score.

There were no significant differences in the discriminatory accuracy of the three scores for the 30-day endpoint. However, for the 1-year endpoint, the discriminatory accuracy of the GRACE score was superior to that of the other two scores, this difference being statistically significant (Table 5).

Interaction between RSs and myocardial revascularization

There were no significant differences, in the study population, in the endpoint rate between patients who underwent and patients who did not undergo a revascularization procedure (either PCI or CABG). However, using the cut-off points for the three RSs identified with the ROC curves of the 1-year endpoint, there was an interaction between the admission score and the prognostic impact of myocardial revascularization performed during initial hospital stay (Figure 4). For the PURSUIT and GRACE scores, this interaction reached statistical significance.

It is worth noting that the proportion of patients who derived clear benefit from myocardial revascularization during initial hospital admission, in this model of multi-variable analysis, was only 28.7% for the PURSUIT and 36.7% for the GRACE score.

Discussion

This single-centre study, based on a consecutive NSTEMI-ACS cohort, demonstrated the superiority of the GRACE RS, compared with the PURSUIT and TIMI RSs, in the estimation of 1-year prognosis. This study validates the 1-year prognostic value of the GRACE and PURSUIT RSs, as for the TIMI score, this has already been evaluated.¹²

Short-term prognosis

All three RSs were able to discriminate patients with and without events at 30 days, which is not surprising, as they were all developed for short-term prognosis.

As expected, the performance of the TIMI and GRACE scores was superior when the original follow-up time and composite endpoints used for their development were tested.

The univariate analysis identified age, as a continuous variable, heart failure at admission and baseline serum creatinine as significant predictors of prognosis. The first two variables are generally identified as prognostic markers.^{13,14} Serum creatinine has only recently been identified as a powerful risk variable,¹⁵ as it was not generally included in ACS databases in the past.

In the present study, traditional risk markers like ST-segment depression on admission ECG or elevated cardiac biomarkers^{14,16-18} did not reach statistical significance. This may be related to the more aggressive antithrombotic and early invasive management adopted for these high-risk patients in our institution. In contrast, studies that established the prognostic value of cardiac

Table 4 Predictive accuracy and goodness of fit of the risk scores

	30 days		1 year	
	C-statistic (95% CI)	P-value (Hosmer–Lemeshow χ^2)	C-statistic (95% CI)	P-value (Hosmer–Lemeshow χ^2)
PURSUIT	0.615 (0.569–0.660)	0.137	0.630 (0.584–0.674)	0.656
TIMI	0.551 (0.504–0.597)	0.803	0.585 (0.539–0.631)	0.760
GRACE	0.672 (0.627–0.714)	0.125	0.715 (0.672–0.756)	0.884

Table 5 Comparison of the predictive accuracy of the risk scores

	30 days		1 year	
	Δ (95% CI)	P-value	Δ (95% CI)	P-value
PURSUIT vs. TIMI	0.064 (–0.054 to 0.183)	0.288	0.044 (–0.043 to 0.131)	0.319
GRACE vs. PURSUIT	0.057 (–0.058 to 0.171)	0.332	0.086 (0.004 to 0.168)	0.04
GRACE vs. TIMI	0.121 (–0.002 to 0.243)	0.054	0.130 (0.040 to 0.220)	0.004

Δ , Difference between the two AUCs.

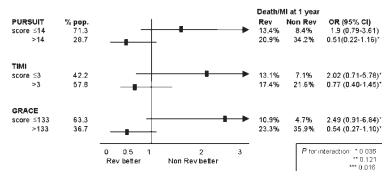


Figure 4 Interaction between the admission score and the prognostic impact of myocardial revascularization performed during initial hospital stay.

biomarkers used peak instead of baseline level, analysed for our admission RSs study.

The relative performance of the different RSs can be explained by their respective composition. Only the GRACE score, which presented the best discriminatory accuracy (AUC = 0.672 for 30 days), included all three identified prognostic variables.

The performance of the PURSUIT score, whose composition does not include serum creatinine, was somewhat inferior (AUC = 0.615). Nevertheless, its discriminatory accuracy might have been overestimated by the fact that the same follow-up time and composite endpoint—death and MI at 30 days—were used for its original development and in the present study. This apparent benefit was not observed for the other two scores.

The TIMI score presented the lowest discriminatory accuracy. Of all the risk markers identified in our univariate analysis, this score only includes age, and as a categorical variable. This is a reductive approach to the continuous prognostic value observed in the entire spectrum of age. The same is not observed in the GRACE and PURSUIT scores. Because of the low incidence of signs of heart failure on admission in the population of the TIMI

11B trial used for the development of the TIMI score, this variable was not included in the model, unlike in the other two scores. This is an important limitation, especially because the occurrence of heart failure is much more frequent in the real world than in the selected patients from clinical trials, and its prognostic value is well established.^{7,19,20}

Long-term prognosis

For the 1-year prognosis, the best performance was achieved by the GRACE score, but all three RSs presented higher discriminatory accuracies than observed for the short term. These results and the relative performance of each RS can be explained by their composition and the univariate analysis for 1-year follow-up, which identified seven variables with prognostic impact. Besides the three variables already described for the short term, a past history of hypertension, recent onset of severe angina, heart rate at admission, and ST-segment depression on admission ECG were also identified as significant prognostic markers. The long-term prognostic value of these characteristics has been described in previous studies,^{14,19} except for recent onset of severe angina and baseline serum creatinine. Although these specific variables have not been evaluated, their long-term prognostic value is established for a past history of coronary artery disease as well as for previous renal failure.^{7,21}

The number of those seven variables included in each RS is 5 for GRACE, 4 for PURSUIT and only 2 for the TIMI RS. The composition of the TIMI RS is clearly different from the other two scores. The main difference between the GRACE and PURSUIT scores is based on the inclusion of renal function in the former, which represents a significant advantage, as renal failure is an

important independent predictor of poor long-term prognosis.^{21,22} Another advantage of the GRACE score is derived from the real-world population of this clinical registry, in contrast to the more selected population of PURSUIT.

Interaction with the benefit of myocardial revascularization

We found a statistically significant interaction between the risk of death or MI at 1 year, stratified by the best cut-off value for the GRACE and PURSUIT scores, and the benefit of myocardial revascularization. For the TIMI score this interaction was not statistically significant.

The proportion of patients stratified as high risk by the best cut-off value was higher in the TIMI score (two-third vs. one-third for the other two scores), demonstrating a poorer ability to discriminate between scores 5–7 and 3–4.

Our results also demonstrated that the long-term benefit of myocardial revascularization performed during initial hospital admission was only clearly observed in high-risk patients, who accounted for about one-third of the study population. These results are in agreement with those of the FRISC II and TACTICS-TIMI 18 studies, which established the benefit of an early invasive strategy, but only for high-risk patients.^{3,16} In the former study, high risk was defined by the combined occurrence of elevated troponin T and ST-segment depression on admission ECG, and this accounted for 33.9% of the studied population. In TACTICS-TIMI 18, the benefit of an early invasive strategy on top of tirofiban was observed for patients with a TIMI RS of at least 3 or an elevated troponin level, corresponding to 75 and 59% of the study population, respectively.

Applicability

The ideal score for risk stratification on admission for a NSTEMI-ACS should have a good balance between complexity and utility. Scores that include continuous variables such as age, heart rate, and serum creatinine are more powerful, but also more complex to calculate. However, PDA applications may significantly simplify these complex calculations such that, at the present time, the complexity of a score is essentially determined by factors related to data collection, rather than the methodology involved in the calculations. In regard to this aspect, the GRACE score is more advantageous as all its variables are objective data.

Limitations

This is a small single-centre retrospective study and the analysis of the interaction between the RSs and the effect of myocardial revascularization on outcome was based on nonrandomized data.

Conclusions

The use of RSs developed from databases of clinical trials (PURSUIT and TIMI) or registries (GRACE) in the risk stratification of patients with NSTEMI-ACS revealed a fair to good discriminatory accuracy in predicting major adverse cardiac events at both 30 days and 1 year.

The GRACE RS was the best for predicting the risk of death or MI at 1 year after admission.

There was a significant interaction between the benefit of myocardial revascularization performed during initial hospitalization and the extent of risk evaluated by the GRACE and PURSUIT scores.

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Editorial do ARTIGO 2/Editorial of MANUSCRIPT 2:

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Editorial

Value of community-derived risk models for stratifying patients with non-ST elevation acute coronary syndromes

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This editorial refers to 'TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS'¹ by P. de Araújo Gonçalves *et al.*, on page 865

In their paper, de Araújo Gonçalves *et al.*¹ from Portugal compared three risk-stratification algorithms—the Thrombolysis in Myocardial Infarction (TIMI) score,² the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) score,³ and the Global Registry of Acute Coronary Events (GRACE) score⁴ in predicting 1-year outcome in 460 consecutive patients aged 63.4 ± 10.8 presenting with non-ST elevation acute coronary syndromes (NSTEMI-ACS). Predictive accuracy of each risk score was fair to good for death or myocardial infarction (MI) at 1-year, which occurred in 15.4% of patients (including 32 deaths and 49 MIs) with the C index ranging from 0.585 [95% confidence interval (CI) 0.539–0.631] with the TIMI score, to 0.630 (95% CI 0.584–0.674) with the PURSUIT score, and 0.715 (95% CI 0.672–0.756) with the GRACE score.

Of interest in this paper is the fact that the GRACE score algorithm (a score based on a community registry) performed better than the score algorithms derived for 30-day outcomes from trials (the TIMI and PURSUIT scores). Table 1 of their paper summarizes the algorithms for the calculation of these three scores. The fact that the investigators used a computer programme available from the GRACE project website to calculate the GRACE score is worthy of note.

Why should the GRACE risk score perform slightly better than the TIMI and PURSUIT risk scores? One

explanation is that the clinical trial populations from TIMI and PURSUIT were selected on the basis of restricted entry criteria, whereas the registry data from GRACE are much more likely to reflect real-life practice.^{4,5} In the TIMI trial, exclusions included planned revascularization within 24 h. It is likely that unstable patients and patients with heart failure were not recruited into TIMI-11 because of their possible need for early intervention. Also, the trial excluded patients who were thought to have a high bleeding risk from enoxaparin treatment, and this would include the many patients who had significant renal dysfunction. In the PURSUIT trial, exclusions included renal failure.

The GRACE registry is based on 94 hospitals of different sizes and with a wide range of interventional and non-interventional centres from 14 countries in Europe, North America, South America, Australia, and New Zealand. Only the GRACE score algorithm gives any weighting to renal function. Impaired renal function is commonly seen in daily practice with most patients >75 years having some renal impairment, and patients with renal impairment have high event rates. In the de Araújo Gonçalves *et al.*¹ study, those who suffered death and MI had higher creatinine levels than those who did not (2.8 ± 1.9 vs. 1.2 ± 0.5 mg/dL for 30-day events, $P < 0.001$ and 2.2 ± 1.7 vs. 1.2 ± 0.5 mg/dL for 1-year events, $P < 0.005$).

There are other major differences between the three score algorithms. The notable absence of a heart failure variable in the TIMI score is a likely consequence of the lower number of patients with heart failure in the TIMI-11 trial,⁶ and the dichotomous age cut-off may at least partly explain the slightly lower performance of the TIMI score for prognostication. Although risk prediction from the TIMI risk score could be improved by adding more factors, this would be at the expense of simplicity.

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The inherent difference in case collection between registries and trials deserves further attention. In the GRACE registry,⁷ two methods were used to identify patients—the so-called warm pursuit and cold pursuit. With the latter approach, cases were identified retrospectively after discharge or death of patients on the basis of the International Classification of Disease codes and, even with the warm pursuit, the patients may be identified some time after presentation. Thus, there may be some missing data fields when compared with prospective data collection in clinical trials, and differences in the collection of data may explain why different parameters are retained in the different algorithms. The TIMI risk score includes coronary risk factors, documented CAD, and the use of aspirin, which are not in the PURSUIT or GRACE scores.

Risk scores are clearly important for informing the patient and family about prognosis and may also be useful to target therapies. de Araújo Gonçalves *et al.*¹ found that higher risk patients as defined by the PURSUIT and GRACE scores benefited more from revascularization. This observational finding is very interesting as revascularization is often performed in low-risk patients and not in high-risk patients, who are more likely to benefit. For example, in the recent CRUSADE registry from the United States, lower risk patients (such as younger patients and those without heart failure) were more likely to undergo early revascularization.⁸ In this registry, 44.8% of patients underwent cardiac catheterization within 48 h of presentation with NSTEMI. Predictors of 'early invasive management' included cardiologist care, young age, lack of prior or current heart failure, lack of renal insufficiency, no ischaemic ECG changes, no positive cardiac markers, white race, and male gender. In addition, patients treated with the invasive strategy were also more likely to receive other therapies recommended by ACC/AHA guidelines, and they had a lower risk of in-hospital mortality after adjusting for other risk factors (2.5 vs. 3.7%; $P < 0.001$).

In the TACTICS TIMI-22 trial⁹ where revascularization was randomized, revascularizations decreased the composite of death MI, and this benefit was seen only in patients with a TIMI risk score >3 . The TIMI risk score has also been found to stratify those who may benefit more from glycoprotein IIb/IIIa inhibition with tirofiban in the PRISM-PLUS study and from enoxaparin in the TIMI IIb and ESSENCE trials.^{2,10} It is, however, important to recognize that these risk scores are relevant to predict prognosis when the patients receive the standard of care provided by the participating centres and/or specified by the trials.

Dynamic risk assessment with serial assessments can identify changing risk in patients with NSTEMI-ACS who may need more intensive therapies. For example, serial N-terminal pro-BNP levels over the first 48–72 h have

recently been found to help stratify patients.¹¹ Those with a rapidly falling BNP levels within 48–72 h after medical therapy had improved outcome, and the reverse was seen in those with rising BNP levels.

There is not much information available as to how often risk assessment is actually performed in daily clinical practice. The TIMI risk tool is the commonest used risk assessment tool. It is widely available on a palm pilot and has high user friendliness, with seven easily obtained clinical variables. Clearly, risk models will need to be defined further, perhaps with a multibiomarker approach and the addition of novel markers such as myeloperoxidase and monocyte chemoattractant protein-1. Dynamic risk assessment will also be important, but as in other areas of medicine, the major challenge is for clinicians to use the tools currently available.

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Capítulo 3.

Angio TC cardíaca – indicações clínicas

RESUMO:

Neste capítulo é feita uma revisão das actuais indicações clínicas da angio TC cardíaca, da sua acuidade diagnóstica e respectiva correlação com a coronariografia invasiva.

O capítulo é acompanhado de um artigo de revisão sobre este tema (**artigo 3**) e de vários artigos que ilustram a utilidade desta técnica noutros contextos clínicos frequentes (pontagens coronárias - **artigo 4**; miocardiopatia hipertrófica - **artigo 6**; aneurisma da aorta torácica - **artigo 9**) e em casos clínicos mais raros (divertículo do ventrículo esquerdo - **artigo 5**; origem anómala das coronárias - **artigos 7 e 8**).

Foi ainda incluído neste capítulo um artigo original sobre a rentabilidade diagnóstica de diferentes estratégias de referenciação para coronariografia invasiva (**artigo 10**), a propósito do qual se faz uma discussão acerca do posicionamento desta técnica no algoritmo de avaliação da doença coronária.

ABSTRACT:

In this chapter, the present clinical indications for cardiac CT are reviewed, as well as its diagnostic accuracy and correlation with invasive coronary angiography.

A review manuscript on this subject (**manuscript 3**) is included, as well as several manuscripts that illustrate the use of cardiac CT in frequent clinical settings (bypass grafts, **manuscript 4**; hypertrophic cardiomyopathy, **manuscript 6**; thoracic aortic aneurism, **manuscript 9**) or more unusual clinical cases (left ventricular diverticulum, **manuscript 5**; anomalous origin of coronary arteries, **manuscripts 7 and 8**).

A manuscript on the diagnostic yield of different referral strategies for invasive coronary angiography is also included (**manuscript 10**), and in line with this subject, a discussion on the role of cardiac CT in the coronary artery disease evaluation algorithm is provided.

ARTIGO 3/ MANUSCRIPT 3:

ANGIO TC CARDÍACA: O FIM DA CORONARIOGRAFIA INVASIVA COMO MODALIDADE DIAGNÓSTICA?

P. Araújo Gonçalves, H. Marques.

Rev Port Cardiol. 2009, 28 (7-8): 825-842.

ARTIGO 4/ MANUSCRIPT 4:

AVALIAÇÃO DE PONTAGENS CORONÁRIAS POR ANGIOTC DE 64 CORTES DE DUPLA AMPOLA.

R. Dourado, P. Araújo Gonçalves, H. Marques, A. Gaspar, F. Machado, J. Roquette.

Rev Port Cardiol. 2008, 27 (7-8): 995-998.

ARTIGO 5/ MANUSCRIPT 5:

DIVERTÍCULO DO VENTRÍCULO ESQUERDO: UM ACHADO POR ANGIO TC CARDÍACA

R. Dourado, P. Araújo Gonçalves, H. Marques, A. Gaspar, F. Machado, J. Roquette.

Rev Port Cardiol. 2009, 28 (3): 341-344.

ARTIGO 6/ MANUSCRIPT 6:

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P. Sousa, P. Araújo Gonçalves, M. Trabulo, H. Marques, N. Marto, J. Brito, F. Machado, J. Roquette.

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Sousa C, Gonçalves P, Ribeiro I.

Cardiol Young. 2011 Aug;21(4):454-5.

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P. Jerónimo Sousa, P. Araújo Gonçalves, S. Boshoff, H. Marques, M. S. Carvalho, J. Moradas Ferreira, J. P. Neves, M. Mendes

Rev Port Cardiol 2013; 32 (1): 59-62.

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M. B. Santos, A. Ferreira, P. Araújo Gonçalves, L. Raposo, R. Teles, M. Almeida, M. Mendes

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3.1 INTRODUÇÃO

Os avanços tecnológicos no campo da tomografia computadorizada tornaram possível a realização de uma coronariografia não invasiva, sendo esta a principal aplicação clínica da angio TC cardíaca e à qual deve a vulgar designação de “TAC das coronárias”. Esta permite excluir a presença de DC obstrutiva, sendo habitualmente empregue em doentes com probabilidade pré-teste não elevada, explorando o seu elevado valor preditivo negativo. Mais recentemente, a angio TC cardíaca tem vindo a ser empregue na avaliação da DC noutros contextos, como é o caso da avaliação de eventual DC em doentes propostos para cirurgia valvular e/ou da aorta, na avaliação etiológica da miocardiopatia dilatada, na avaliação do doente com dor torácica no serviço de urgência e na suspeita de origem anómala das artérias coronárias.

Por outro lado, a angio TC cardíaca tem igualmente sido considerada uma modalidade de eleição para avaliação extracoronária, como é o caso da avaliação prévia de doentes para ablação de fibrilhação auricular e procedimentos da implantação percutânea de válvula aórtica.

Este capítulo é acompanhado de um artigo de revisão (1) acerca das indicações clínicas da angio TC cardíaca, de vários artigos de casos clínicos que ilustram algumas destas indicações clínicas (2, 3) bem como o contributo desta técnica em contextos clínicos menos frequentes (4-7). Neste capítulo está ainda incluído um artigo que ilustra o actual processo de avaliação de doentes com suspeita de DC referenciados para cateterismo cardíaco (8), tema desenvolvido na **secção 3.3**.

Como complemento a estes artigos, e dado o crescimento exponencial da evidencia científica nesta área, faz-se de seguida uma breve revisão da acuidade diagnóstica da angio TC e correlação com a coronariografia invasiva (aspectos também desenvolvidos num capítulo de um livro de texto internacional de imagem cardiovascular que acompanha o **capítulo 9** da Tese).

3.2 ACUIDADE DIAGNÓSTICA E CORRELAÇÃO COM A CORONARIOGRAFIA INVASIVA

A acuidade diagnóstica da angio TC cardíaca foi avaliada por comparação com a coronariografia invasiva, considerada técnica “*gold-standard*” para avaliação da DC. Os estudos iniciais foram realizados com aparelhos de 4 (9-12) e de 16 cortes (13-17), com os quais já foi possível documentar alguma robustez da técnica. No entanto, com esses aparelhos de primeira e segunda geração, havia importantes limitações relacionadas com a elevada duração da aquisição e consequentemente uma necessidade de um elevado tempo de apneia e uma maior dose de contraste (aspectos revistos no **capítulo 5**). Por outro lado, era frequente a presença de artefactos impossibilitando a análise de uma importante percentagem de segmentos da árvore coronária. Numa meta-análise envolvendo 27 estudos realizados com aparelhos de pelo menos 16 cortes com comparação sistemática com a coronariografia por cateterismo cardíaco, a angio TC cardíaca teve uma elevada sensibilidade na análise por doente (96%), mas uma especificidade

mais modesta (74%), levando a um valor preditivo positivo de apenas 68% (18). Nesta meta-análise houve um predomínio de estudos realizados com aparelhos de 16 cortes e numa subanálise foi possível documentar valores superiores de sensibilidade e especificidade no conjunto dos estudos realizados com aparelhos de 64 cortes. O desenvolvimento dos aparelhos de 64 cortes acompanhou-se de significativas melhorias na qualidade dos exames, levando à rápida difusão destes exames na prática clínica diária, sendo actualmente considerados como o requisito mínimo recomendado para a realização de uma angio TC cardíaca (19, 20). Numa meta-análise mais recente incluindo apenas estudos com aparelhos de 64 cortes a sensibilidade na análise por doente foi de 99%, com uma especificidade de 89%, um valor preditivo positivo de 93% e um valor preditivo negativo de 100% (21).

No entanto, a angio TC cardíaca pode ter uma baixa especificidade quando é avaliada em contextos clínicos de maior probabilidade de doença. No estudo prospectivo multicêntrico ACCURACY (*Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography*) que avaliou doentes estáveis com suspeita de DC referenciados para coronariografia invasiva, embora a sensibilidade e o valor preditor negativos tenham sido elevados (95 e 99% respectivamente), a especificidade e o valor preditivo positivo foram mais baixos (83% e 64%) (22). Este estudo ilustra bem a não negligenciável taxa de falsos positivos que pode ocorrer numa população não seleccionada de doentes, uma vez que não foram excluídos da análise os doentes com elevado score de cálcio, índice de massa corporal ou frequência cardíaca, factores que reconhecidamente prejudicam a qualidade dos exames. Num outro estudo multicêntrico que avaliou o desempenho diagnóstico da angio TC cardíaca em doentes com suspeita de DC referenciados para coronariografia (incluindo doentes com dor torácica aguda), a especificidade foi de apenas 64% e o valor preditor positivo foi de 86% (23). Neste estudo, os segmentos com baixa qualidade de imagem resultantes de artefactos de movimento ou marcada calcificação, não foram excluídos, sendo considerados como positivos e a prevalência de DC obstrutiva (68%) foi acima do habitual para uma população avaliada por angio TC cardíaca, factores que podem explicar a sua mais baixa especificidade neste estudo.

Assim, pela análise dos vários trabalhos publicados, torna-se claro que a angio TC cardíaca é uma modalidade diagnóstica com uma elevada sensibilidade e valor preditor negativo o que a torna particularmente útil para excluir a presença de DC obstrutiva. Assim, esta técnica tem sido frequentemente usada como alternativa à coronariografia invasiva, quando a probabilidade de DC não é elevada.

A sua mais baixa especificidade e consequentes falsos positivos deve ser tida em consideração, nomeadamente na avaliação de doentes com marcada calcificação ou com insuficiente qualidade de imagem, uma vez que a angio TC neste cenários pode sobrestimar o grau de estenose.

A evolução recente em vários aspectos técnicos da angio TC incorporadas nos aparelhos de última geração, nomeadamente da resolução temporal, espacial e de cobertura craneo-caudal, tem vindo a contribuir para uma melhoria progressiva da qualidade dos exames, bem como a

uma significativa redução na dose de contraste e de radiação (ver [capítulo 5](#)), aspectos que certamente irão contribuir para a adopção em larga escala da angio TC como modalidade diagnóstico de rotina na avaliação da suspeita de DC.

3.3 ANGIO TC CARDÍACA NO ALGORITMO DE AVALIAÇÃO NA SUSPEITA DE DOENÇA CORONÁRIA

Dado a sua elevada sensibilidade e valor preditor negativo, a angio TC cardíaca é uma técnica de elevada acuidade na exclusão da presença de DC obstrutiva. Neste contexto, tem sido essencialmente empregue para obviar a necessidade de coronariografia, em doentes cuja probabilidade de DC obstrutiva não é elevada. Esta probabilidade pode ser estimada pelo uso de scores que permitem objectivar essa probabilidade partindo de dados demográficos e clínicos (aspecto melhor desenvolvido no [capítulo 6](#)).

Numa fase inicial, o seu uso estava recomendado essencialmente em doentes com exames de isquémia inconclusivos ou duvidosos e em doentes que não podiam realizar prova de esforço, por limitação funcional ou por apresentarem electrocardiogramas ininterpretáveis (24, 25).

Mais recentemente, num documento de consenso acerca dos critérios de apropriação para o uso da angio TC cardíaca, endossado por varias sociedades científicas norte-americanas e publicado em 2010 (20), foi alargado o número de indicações clínicas para o qual a angio TC é considerada apropriada, actualizando as anteriores recomendações publicadas em 2006 (24). Assim, mesmo em doentes que não apresentam limitação à realização da prova de esforço e com electrocardiogramas interpretáveis, a angio TC foi considerada apropriada como exame para avaliar a presença de DC quando a probabilidade pré-teste é intermédia. Nas mesmas recomendações, foi considerado apropriado o uso da angio TC cardíaca no contexto de exames de isquémia prévios equívocos, quando existe discordância entre o teste de imagem e a prova de esforço, na presença de prova de esforço negativa mas sintomas persistentes e mesmo na presença de teste de imagem negativo, se sintomas de novo ou com agravamento recente. Mais recentemente, nas guidelines da NICE (*National Institute for Health and Clinical Excellence*) para avaliação da dor torácica, a angio TC cardíaca foi recomendada como exame de primeira linha e não apenas após a realização de prova de esforço e/ou teste de imagem (26). Nestas recomendações, a escolha do exame deve ser feita em função da probabilidade de DC, estando indicada a angio TC cardíaca na baixa probabilidade (inferior a 30%), os testes de isquémia de imagem na probabilidade intermédia (30-60%) e a coronariografia por cateterismo cardíaco quando a probabilidade de doença é elevada (>60%). Ainda de acordo com as recomendações da NICE, a angio TC deverá ser precedida da avaliação do grau de calcificação coronária (score de cálcio), não se avançando para administração de contraste se este for zero (muito pouco

provável existir DC significativa na origem das queixas) ou superior a 400 (por compromisso da qualidade do exame com este nível de calcificação).

Num trabalho recentemente publicado pelo nosso grupo, foi avaliada a rentabilidade diagnóstica de diferentes estratégias de referenciação para coronariografia electiva por suspeita de DC (8). Numa população de 1892 doentes sem DC conhecida submetidos a coronariografia invasiva, 43% não tinha DC obstrutiva, apesar de a grande maioria ter sido referenciada com base num teste não invasivo positivo (em 82% dos casos). A angio TC cardíaca foi empregue apenas numa minoria dos doentes, mas nestes a rentabilidade da referenciação para coronariografia invasiva, avaliada pela percentagem de doença obstrutiva documentada, foi superior (81 vs 51%) ao dos exames não invasivos baseados na detecção de isquémia (prova de esforço, ecocardiograma de sobrecarga e cintigrafia de perfusão miocárdica).

A baixa rentabilidade da coronariografia invasiva com base no actual esquema de referenciação baseado essencialmente em exames de isquémia foi também ilustrada numa análise do registo multicêntrico *CathPCI* do NCDR (*National Cardiovascular Data Registry*) recentemente publicada e que envolveu quase 400.000 doentes (27). Neste registo que reflecte a prática clínica norte-americana, a taxa de DC obstrutiva identificada na coronariografia invasiva foi de apenas 38%, apesar de a grande maioria (84%) ter sido referenciada em face do resultado de um exame não invasivo. Algumas críticas foram feitas a este trabalho, porque nem sempre esse exame que motivou a referenciação para coronariografia foi um exame de isquémia uma vez que em alguns casos a referenciação foi baseada no resultado de um electrocardiograma simples o que pode ter justificado o valor preditivo modesto da positividade de um teste não invasivo prévio (OR ajustado de 1,28).

Assim, a elevada taxa de coronariografias por cateterismo cardíaco realizadas com objectivo puramente diagnóstico continua a ser bastante alto, deixando em aberto a adopção futura de modalidades alternativas de diagnóstico como é o caso da coronariografia por angio TC cardíaca que poderá obviar em muitos casos a realização do procedimento invasivo.

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3.5 ARTIGO 3/ MANUSCRIPT 3:

ARTIGOS DE REVISÃO

Angio TC cardíaca: o fim da coronariografia invasiva como modalidade diagnóstica? [67]

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RESUMO

Nos últimos anos temos assistido a uma rápida evolução na tecnologia de Tomografia computadorizada (TC) multicortes, com uma melhoria crescente da resolução temporal e espacial, fazendo desta uma robusta modalidade na avaliação das artérias coronárias. Apesar da coronariografia invasiva ser ainda considerada o exame de referência para diagnóstico de doença coronária, existem várias indicações para as quais a coronariografia por AngioTC cardíaca poderá vir a ser considerada o exame de primeira linha em detrimento da coronariografia por cateterismo cardíaco. Dado o seu elevado valor preditor negativo, esta técnica revela-se particularmente útil para excluir a presença de estenoses coronárias significativas, evitando assim procedimentos diagnósticos invasivos desnecessários, nomeadamente em doentes com probabilidade intermédia e exames de isquémia e/ou queixas inconclusivas ou na avaliação coronária que antecede a cirurgia valvular ou da aorta.

A angioTC cardíaca não se esgota na coronariografia não invasiva, e a avaliação cardíaca extra-coronária, nomeadamente da função ventricular esquerda, bem como a avaliação de achados extra-cardíacos contribuem para a rentabilidade deste exame.

Palavras-Chave

Angio TC cardíaca; Cateterismo cardíaco; Doença coronária; Diagnóstico.

ABSTRACT

Cardiac CT: the end of invasive coronary angiography as a diagnostic procedure?

In recent years, multislice computed tomographic (CT) technology has progressed rapidly, with significant improvements in spatial and temporal resolution, and has become a powerful technique for coronary artery evaluation. Although invasive angiography is still considered the gold standard for the diagnosis of coronary artery disease, there are several indications for which coronary CT angiography (CTA) may become the first-line exam, instead of invasive catheter-based coronary angiography. Because of its high negative predictive value, CTA is very useful to rule out significant coronary stenosis, thus avoiding unnecessary invasive diagnostic procedures, particularly in patients with intermediate probability and inconclusive stress tests and/or symptoms, or in routine coronary evaluation of patients scheduled for valvular or aortic surgery.

CTA is not limited to non-invasive coronary angiography; it can make important additional diagnostic contributions in both extra-coronary cardiac evaluation, such as left ventricular function, and assessment of extracardiac findings.

Key words

Cardiac CT; Cardiac catheterization; Coronary artery disease; Diagnosis.

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INTRODUÇÃO

A coronariografia invasiva por cateterismo cardíaco tem sido considerada a modalidade de eleição para identificar a presença de doença coronária. Para além de confirmar a sua presença e caracterizar a anatomia coronária e a gravidade e distribuição das lesões, a sua maior vantagem reside na possibilidade de se realizar, quando indicada, revascularização miocárdica por angioplastia. No entanto, numa elevada percentagem dos casos, apenas é realizada a coronariografia diagnóstica, não sendo o doente subsequentemente submetido a angioplastia. Existem várias justificações para esta discrepância entre o número de coronariografias diagnósticas e o número de angioplastias: em primeiro lugar, em alguns casos não se confirmam as suspeitas dos exames não invasivos e na coronariografia não se documenta a presença de estenoses significativas; em segundo lugar, uma percentagem significativa é constituída por doentes com patologia valvular ou da aorta torácica com indicação cirúrgica, nos quais está indicada a realização de uma coronariografia na avaliação de rotina pré-operatória; em terceiro lugar, em alguns casos, após a coronariografia opta-se por outra modalidade terapêutica, nomeadamente optimização da terapêutica médica ou cirurgia de revascularização. Nas estatísticas mais recentemente publicadas da Sociedade Europeia de Cardiologia, a proporção média de procedimentos de intervenção para coronariografias foi de 33% ou seja, cerca de 2 em cada 3 das coronariografias invasivas não motivaram um procedimento de intervenção⁽¹⁾. Apesar de se tratar actualmente de um procedimento bastante seguro, trata-se de um exame invasivo e assim tem um risco de complicações que, apesar de pouco frequentes, ocorrem por vezes em procedimentos puramente diagnósticos.

Com a evolução recente na tecnologia de tomografia computadorizada multicortes, tornou-se possível a realização de uma coronariografia de uma forma não invasiva. A elevada acuidade diagnóstica demonstrada nos estudos comparativos com coronariografia invasiva, justificam que, para algumas indicações, a angiografia por tomografia computadorizada (AngioTC) cardíaca seja considerada uma modalidade diagnóstica alternativa à coronariografia por cateterismo

INTRODUCTION

Invasive catheter-based coronary angiography is considered the first-line technique for detection of coronary artery disease (CAD). Besides confirming the presence of CAD and characterizing coronary anatomy and the severity and distribution of lesions, its main advantage is that it affords the possibility, when indicated, of performing myocardial revascularization by angioplasty. However, in a large percentage of cases, the procedure is merely diagnostic and the patient does not undergo angioplasty. There are various reasons for the discrepancy between the number of diagnostic exams and the number of angioplasties. Firstly, in some cases the suspicions aroused by non-invasive exams are not confirmed and coronary angiography does not detect significant stenosis; secondly, a significant proportion of patients have valvular or thoracic aortic disease with indication for surgery, coronary angiography being used in these patients for routine pre-operative evaluation; and thirdly, a different therapeutic approach may be chosen following coronary angiography, for example optimization of medical therapy or revascularization surgery. According to the latest statistics published by the European Society of Cardiology (ESC), the mean percentage of interventions during coronary angiography was 33%; in other words two out of three invasive angiograms do not result in an intervention⁽¹⁾. Although the procedure is now very safe, it is an invasive exam and as such carries a risk of complications that, while uncommon, do sometimes occur during purely diagnostic procedures.

With the recent development of multislice computed tomographic technology, non-invasive coronary angiography is now feasible. Its high diagnostic accuracy demonstrated in comparative studies with invasive coronary angiography means that for certain indications cardiac CT angiography (CTA) is considered an alternative diagnostic modality to catheter-based coronary angiography⁽²⁻⁴⁾.

The various indications for which cardiac CTA may replace catheter-based coronary angiography as the first-line exam are reviewed below.

cardíaco⁽²⁻⁴⁾.

De seguida, revêem-se varias indicações para as quais a coronariografia por AngioTC cardíaca poderá vir a ser considerada o exame de primeira linha em detrimento da coronariografia por cateterismo cardíaco.

EXCLUIR A PRESENÇA DE ESTENOSAS CORONÁRIAS SIGNIFICATIVAS EM DOENTES COM PROBABILIDADE INTERMÉDIA DE DOENÇA CORONÁRIA

Vários trabalhos publicados na literatura documentam o elevado valor preditor negativo da angioTC cardíaca, que apresenta uma consistente baixa taxa de falsos negativos quando comparada com a técnica de referência - a coronariografia por cateterismo cardíaco. Num trabalho de revisão recentemente publicado pelo grupo de estudos da Sociedade Europeia de Cardiologia, reunindo os trabalhos publicados com os aparelhos de última geração (64 cortes e 64 cortes de dupla ampola), envolvendo mais de 800 doentes, com comparação sistemática com a angiografia convencional, a sensibilidade foi de 89%, a especificidade com 96% e o valor preditor negativo foi de 98%⁽²⁾. Assim, a consistente baixa taxa de falsos negativos torna este exame muito atractivo para a exclusão da presença de doença coronária em doentes com probabilidade intermédia de doença coronária e esta é de facto a indicação mais importante e mais frequente para a realização de uma angioTC cardíaca. Num trabalho recentemente publicado por Meijboom et al⁽⁵⁾, a acuidade diagnóstica da angioTC cardíaca foi avaliada de acordo com a probabilidade pré-teste de doença coronária, tendo os autores concluído que esta é mais útil nos doentes com probabilidade baixa/intermédia, onde se pode excluir com elevado grau de certeza a presença de doença coronária significativa e evitar assim a coronariografia invasiva. Os doentes que mais se enquadram dentro desta indicação são os que tem exames de documentação de isquémia inconclusivos ou quando apesar de positivos, a probabilidade de acordo com a avaliação clínica (idade, sexo, queixas, perfil de risco) apontam para provavelmente se tratar de um falso positivo. A exclusão de estenoses coronárias com um exame com elevado valor preditor negativo como é o caso da angioTC cardíaca permite assim

EXCLUSION OF SIGNIFICANT CORONARY STENOSIS IN PATIENTS WITH INTERMEDIATE PROBABILITY OF CORONARY ARTERY DISEASE

Various studies have demonstrated the high negative predictive value of cardiac CTA, which has a consistently lower rate of false negatives than the gold standard technique of invasive catheter-based coronary angiography. A review published by the ESC working group involving over 800 patients and systematically comparing state-of-the-art equipment (64-slice and 64-slice dual source systems) with conventional angiography reported 89% sensitivity, 96% specificity and 98% negative predictive value for the former⁽²⁾. The consistently low false-negative rate makes this exam particularly attractive for excluding the presence of coronary artery disease in patients with intermediate probability for CAD and this is in fact the most common indication for performing cardiac CTA. In a recent study by Meijboom et al.⁽⁵⁾, the diagnostic accuracy of cardiac CTA was assessed according to the pretest probability of CAD, the authors concluding that it was most useful in patients with low or intermediate probability, in whom it can exclude the presence of significant CAD with a high level of certainty and thus avoid invasive coronary angiography. The patients most likely to benefit from this indication are those with inconclusive ischemia testing or those with a positive test but in whom the probability based on clinical assessment (age, gender, symptoms and risk profile) suggests that it is probably a false positive. Using an exam with a high negative predictive value such as cardiac CTA to exclude coronary stenosis avoids unnecessary cardiac catheterization in such patients (*Figs. 1 and 2*).

CORONARY EVALUATION PRIOR TO CARDIAC SURGERY

Coronary angiography prior to surgery is indicated in a wide range of patients with valvular disease, to detect the presence of significant concomitant CAD. According to the latest ESC guidelines on the management of valvular heart disease, besides being indicated in patients with a history of CAD, suspected myocardial ischemia or left ventricular systolic dysfunction, coronary

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evitar nestes doentes a realização desnecessária de cateterismo cardíaco (Fig. 1 e 2)

angiography is also recommended in those with only a single risk factor, or even none in the case of men aged over 40 or postmenopausal women⁽⁶⁾.

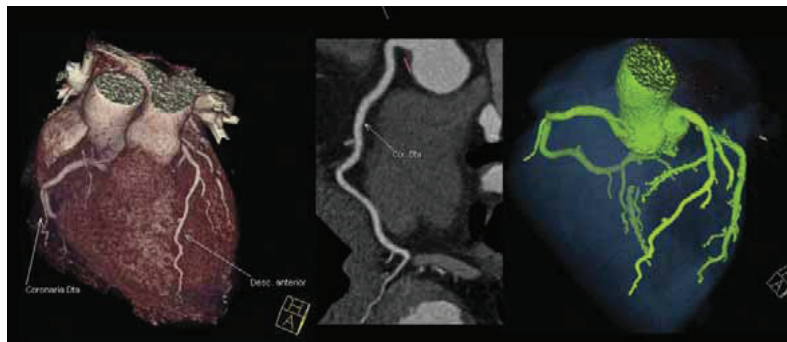


Figura 1. Reconstruções de volume (VRT), multiplanar (MPR) e coronariografia virtual, em exame com boa qualidade de imagem documentando artéria coronária direita sem placas significativas.

Figure 1. Volume-rendered reconstruction (VRT), multi-planar reconstruction (MPR) and virtual coronary angiography: good quality images showing right coronary artery without significant plaques.



Figura 2 Reconstruções de volume (VRT), multiplanar (MPR) e coronariografia virtual, em exame com boa qualidade de imagem documentando artéria descendente anterior sem placas significativas.

Figure 2 Volume-rendered reconstruction (VRT), multi-planar reconstruction (MPR) and virtual coronary angiography: good quality images showing left anterior descending artery without significant plaques.

AVALIAÇÃO CORONÁRIA PRÉ-CIRURGIA CARDÍACA

Na presença de doença valvular com indicação cirúrgica, está indicada a realização de coronariografia, para avaliar a presença concomitante de doença coronária significativa, sendo esta indicação bastante abrangente. De acordo com as últimas recomendações de manejo

It is common in such patients to find no significant CAD, and even when it is present, coronary angiography is merely diagnostic, surgical revascularization being performed at the same time as valve surgery. This means that patients are exposed to the risks inherent in an invasive exam for purely diagnostic purposes. While the risks are low, they are not negligible, particularly in patients under anticoagulant

das doenças valvulares da Sociedade Europeia de Cardiologia, para além de estar indicada em doentes com antecedentes de doença coronária, com suspeita de isquémia miocárdica ou com disfunção sistólica ventricular esquerda, a coronariografia está ainda indicada na presença de apenas um factor de risco e mesmo na ausência destes, caso se trate de um doente do sexo masculino com mais de 40 anos, ou de uma mulher pós-menopausa⁽⁶⁾.

Nestes doentes, é frequente não se encontrar doença coronária significativa e mesmo nos casos em que existe doença coronária associada à doença valvular, apenas é realizada a coronariografia diagnóstica, sendo a revascularização feita cirurgicamente aquando da cirurgia valvular. Deste modo, os doentes são expostos aos riscos inerentes a um exame invasivo, para fins puramente diagnósticos. Estes riscos, apesar de baixos, não são desprezíveis, nomeadamente em doentes anticoagulados ou na presença de insuficiência aórtica, reconhecidos preditores de complicações hemorrágicas.

Num estudo que incluiu 70 doentes com indicação para cirurgia valvular⁽⁷⁾, foi avaliada a acuidade diagnóstica da angioTC cardíaca, em comparação com a coronariografia convencional. Neste trabalho, realizado com um aparelho de 64 cortes foram excluídos doentes com fibrilhação auricular e insuficiência renal e englobou vários tipos de valvulopatia, inclusive doentes com estenose aórtica. O desempenho diagnóstico da angioTC cardíaca foi excelente, com uma sensibilidade de 100%, especificidade de 92%, valor preditor positivo de 82% e valor preditor negativo de 100%. Dos 4 falsos positivos verificados, 3 foram em doentes cuja valvulopatia era estenose aórtica. Este constitui um subgrupo de doentes valvulares onde provavelmente esta técnica se depara ainda com algumas limitações, uma vez que se tratam habitualmente de doentes mais idosos, com maior probabilidade de doença coronária concomitante e com elevada prevalência de lesões coronárias calcificadas, cujo grau de estenose é habitualmente sobrevalorizado na angioTC. Num outro trabalho que incluiu apenas doentes com estenose aórtica, o valor médio de score de cálcio foi de 609 ± 860 e foi identificado o limiar de 1000, valor a partir do qual a frequência de segmentos não interpretáveis era bastante elevada⁽⁸⁾.

Os doentes com fibrilhação auricular, frequen-

therapy and those with aortic regurgitation, which are recognized predictors of bleeding complications.

A study of 70 patients referred for cardiac valve surgery⁽⁷⁾ assessed the diagnostic accuracy of cardiac CTA compared to conventional coronary angiography. The study excluded patients with atrial fibrillation (AF) and renal failure, and covered various types of valve disease, including aortic stenosis. The diagnostic performance of cardiac CTA, using a 64-slice system, was excellent, with 100% sensitivity, 92% specificity, 82% positive predictive value and 100% negative predictive value. Three of the four false positives were in patients with aortic stenosis, and the technique probably still has certain limitations in this patient subgroup, since they are usually older and thus more likely to have concomitant CAD with a high prevalence of calcified lesions, in which the degree of stenosis is generally overestimated by CTA. In another study that included only patients with aortic stenosis, the mean calcium score was 609 ± 860 ; a threshold of 1000 was identified, beyond which the proportion of non-interpretable segments was too high⁽⁸⁾.

Patients with AF, which is common in the context of mitral disease, are another subgroup in whom coronary CTA has lower diagnostic accuracy. This arises from the need to synchronize the images acquired with the ECG, which is particularly difficult in the presence of considerable RR variability. The better temporal resolution of the latest 64-slice dual source CT systems may overcome this limitation and initial studies have been promising^(9,10) (Fig. 3). Moreover, new 320-slice systems that provide sufficient craniocaudal coverage to acquire the entire heart in a single rotation, thus eliminating stair-step artifacts, also have great potential in these patients. For now, AF remains a significant obstacle to obtaining a good diagnostic quality CT coronary angiogram in most AF patients using standard 64-slice equipment.

Non-invasive coronary angiography is thus a good alternative for pre-operative evaluation of CAD in the context of valve disease. In fact, while not as yet a recommendation, the use of cardiac CTA by experienced centers is mentioned in the latest ESC guidelines on valvular heart disease as a way to exclude CAD in patients with low probability⁽⁶⁾.

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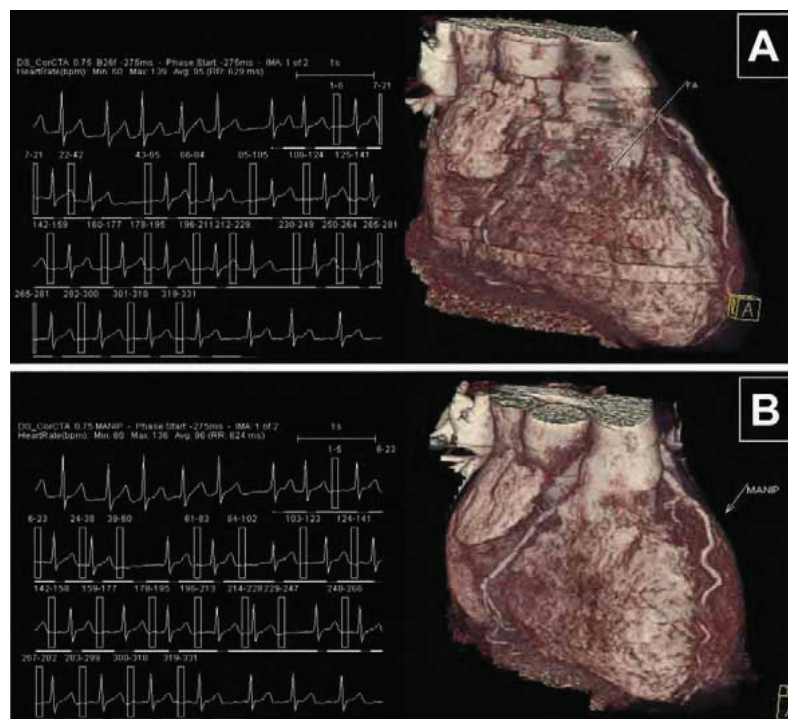


Figura 3 Reconstruções de volume (VRT) do mesmo doente em fibrilhação auricular com resposta ventricular média de 95/min durante a aquisição, com grande variabilidade RR (60-139). A – reconstrução automática em -275 ms; B- reconstrução após edição manual do ECG.

Figure 3 Volume-rendered reconstruction (VRT) of the same patient in atrial fibrillation with mean ventricular rate of 95bpm and considerable RR variability (60-139). A: automatic reconstruction at -275 ms; B: reconstruction after manual editing of the ECG.

te no contexto de doença mitral, constituem um outro subgrupo em que a coronariografia por TC tem uma menor acuidade diagnóstica. Este facto resulta da necessidade de sincronizar com o ECG as imagens adquiridas, o que se torna particularmente difícil quando existe grande variabilidade RR. A elevada resolução temporal dos aparelhos de angioTC de última geração de 64 cortes de dupla ampola, poderá vir a ultrapassar esta limitação, sendo a experiência inicial bastante promissora^(9,10) (Fig. 3). Por outro lado, os novos aparelhos de 320 cortes, ao permitir uma cobertura crâneo-caudal suficiente para a aquisição cardíaca total numa só rotação,

ASSESSMENT OF PATIENTS WITH PREVIOUS MYOCARDIAL REVASCULARIZATION

Monitoring of patients with previous surgical or percutaneous myocardial revascularization is by clinical assessment and ischemia testing, and control coronary angiography is not routinely indicated. However, it can be scheduled during follow-up in certain cases, generally following complex interventions, such as angioplasty of the left main coronary artery, or in patients enrolled in clinical trials evaluating new stents. Assessment of stent patency is hindered by

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eliminando assim os artefactos de escada, terão um elevado potencial de aplicação nestes doentes. De qualquer modo, a fibrilhação auricular é ainda uma importante limitação à realização de uma coronariografia por TC de boa qualidade diagnóstica, na grande maioria dos doentes, com os aparelhos *standard* de 64 cortes.

A realização da coronariografia não invasiva poderá ser assim uma boa alternativa para estudo pré-operatório de doença coronária no contexto de doença valvular. De facto, apesar de não constituir ainda uma recomendação, nas mais recentes *guidelines* de doenças valvulares da ESC, vem já referida a hipótese de, em doentes com baixa probabilidade, ser realizada a exclusão de doença coronária por angioTC cardíaca, em centros com experiência nesta técnica⁽⁶⁾.

artifacts arising from the alloys used in stents, as well as by stent diameter, because of CTA's limited spatial resolution compared to conventional angiography. However, most modern stents of a reasonable caliber (>3 mm) can be assessed. In a recent review by the ESC Working Group of the results of various studies comparing 64-slice and 64-slice dual source systems with conventional angiography, 88% of the 684 stents included in these studies were correctly assessed⁽³⁾. Thus, for cases in which control angiography is indicated during follow-up and particularly when there is a low likelihood of need for further percutaneous intervention, CTA may be a good alternative (*Fig. 4*).

In patients with previous coronary bypass surgery, the usefulness of cardiac CTA depends mainly on the clinical reason for the exam. If the objective is to assess bypass graft patency, CTA is highly accurate, not only because of its sensitivity but also due to its high specificity in



Figura 4 Reconstrução multiplanar (MPR) e coronariografia virtual, documentando ausência de restenose de um *stent* Xience 3,5x8mm no tronco comum.

Figure 4 Multi-planar reconstruction (MPR) and virtual coronary angiography showing absence of restenosis in a 3.5x8.0mm Xience stent in the left main coronary artery.

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AValiação DE DOENTES COM ANTECEDENTES DE REVASCULARIZAÇÃO MIOcÁRDICA

O seguimento dos doentes com antecedentes de revascularização miocárdica cirúrgica ou percutânea é feito clinicamente e com exames de documentação de isquémia, não estando indicada a realização, por rotina, de uma nova coronariografia de controlo. No entanto, em determinados casos, fica planeada a realização de nova coronariografia no seguimento. Habitualmente tratam-se de casos de intervenções complexas, como é o caso da angioplastia do tronco comum ou então de doentes incluídos em ensaios clínicos para avaliação de novos *stents*. A avaliação da patência dos *stents* é prejudicada pelos artefactos resultantes das ligas metálicas dos *stents*. Esta depende não só do tipo de liga metálica, mas sobretudo do diâmetro do *stent*, dadas as limitações de resolução espacial desta técnica, em comparação com a angiografia convencional. De qualquer modo, a grande maioria dos *stents* de nova geração, desde que tenham um calibre razoável (>3mm), são passíveis de avaliação. Numa revisão recente do grupo de estudos da Sociedade Europeia de Cardiologia, englobando os resultados de vários trabalhos publicados com aparelhos de 64 cortes e 64 cortes de dupla ampola, com comparação sistemática com angiografia convencional, 88% dos 684 *stents* incluídos nestes estudos, foram correctamente avaliados⁽⁴⁾. Assim, para os casos em que esteja indicada uma nova coronariografia no seguimento e sobretudo quando se antecipa uma baixa probabilidade de nova intervenção percutânea, a coronariografia por TC poderá constituir uma boa alternativa. (*Fig. 4*)

No caso dos doentes com antecedentes de cirurgia coronária, a utilidade da angioTC cardíaca depende sobretudo da questão clínica. Se o objectivo for documentar a patência das pontagens, a acuidade da angioTC é elevada, não só pela habitual sensibilidade, mas também por uma elevada especificidade, dado tratar-se de vasos de maior calibre, com menor movimento e cujas lesões habitualmente não são calcificadas (*Fig. 5*). No caso das pontagens arteriais, apesar da presença de artefactos resultantes dos *clips* metálicos (*Fig. 6*), a sua avaliação é igualmente possível na grande maioria dos casos e é ainda possível avaliar a sua relação com a parede

assessing large caliber vessels that are liable to move less and in which the lesions are generally not calcified (*Fig. 5*). Arterial grafts can also be assessed in most cases, despite the presence of surgical clip artifacts (*Fig. 6*), as can their relationship to the thoracic wall, which is useful information when repeat sternotomy is necessary. A recent study assessing 418 bypass grafts in 138 patients with a standard 64-slice system reported 97% specificity, with no significant differences between venous and arterial grafts⁽¹¹⁾.

However, assessment of native circulation in such patients is more difficult due to the presence of advanced coronary atherosclerosis, frequently with widespread disease, multiple calcified plaques and small caliber arteries, all significant limitations given the current spatial resolution of CTA, even using the latest systems⁽¹²⁾.

INDICATIONS IN THE EMERGENCY DEPARTMENT

Exclusion of acute coronary syndrome (ACS) in patients in the emergency department is sometimes difficult, particularly when initial assessment detects no significant ECG abnormalities and biomarkers of myocardial damage are negative. Patients often remain under observation, serial assessments being performed until the likelihood of ACS is considered low. In cases of an apparently normal ECG and negative biomarkers, using CTA to exclude significant coronary disease would enable rapid risk stratification and earlier discharge. Conversely, it could also identify patients who do in fact have significant coronary disease despite being considered at low risk on the basis of conventional assessment by ECG and biomarkers. Initial studies have demonstrated the high diagnostic accuracy of CTA in this context^(13,14), as well as its cost-effectiveness, compared to stratification using standard algorithms⁽¹⁵⁾. A study following patients discharged early after exclusion of significant CAD by CTA reported no significant coronary events⁽¹⁶⁾. Further studies will help to validate the prognostic impact of this strategy.

Besides ACS, differential diagnosis of patients admitted to the emergency department with acute chest pain includes aortic dissection and pulmonary embolism. Protocols have been developed that enable assessment of these three

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Figura 5 Reconstruções de volume (VRT) e multiplanar (MPR) documentando lesão significativa do segmento médio de uma safena para obtusa marginal; imagem correspondente da coronariografia invasiva.

Figure 5 Volume-rendered reconstruction (VRT) and multi-planar reconstruction (MPR) showing significant lesion of the mid segment of a saphenous vein to obtuse marginal graft. Corresponding image from invasive coronary angiography.

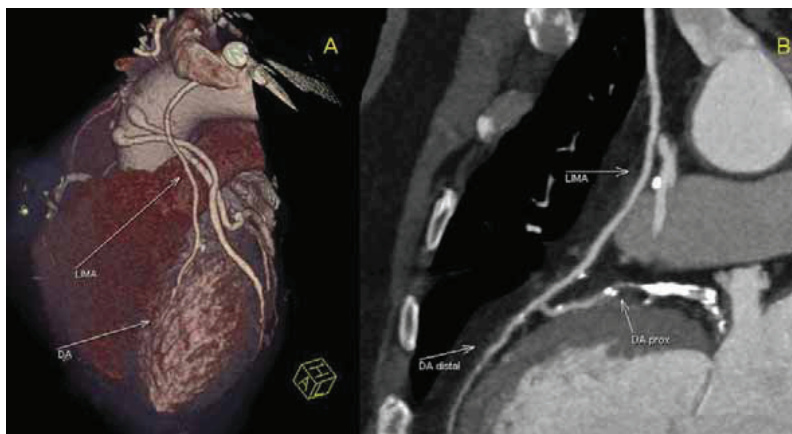


Figura 6 Reconstruções de volume (VRT) e multiplanar (MPR) documentando patência da pontagem de mamária interna esquerda para a descendente anterior, bem como doença significativa calcificada suboclusiva na descendente anterior a montante da anastomose.

Figure 6 Volume-rendered reconstruction (VRT) and multi-planar reconstruction (MPR) showing patent internal mammary to left anterior descending graft (LAD), as well as significant calcified subocclusive disease in the LAD upstream of the anastomosis.

torácica, informação útil nos casos em que é necessário nova esternotomia. De facto, num trabalho recentemente publicado que envolveu a avaliação de 418 pontagens em 138 doentes com um aparelho de 64 cortes convencional, a especificidade chegou aos 97% e não houve diferenças significativas entre pontagens venosas ou arteriais⁽¹¹⁾.

important pathologies in a single CT scan, known as “triple rule-out”^(17,18).

Finally, for some patients admitted to the emergency department with chest pain, the diagnosis is myocarditis or myopericarditis. Such cases often present repolarization abnormalities on the ECG and positive biomarkers of myocardial damage, so differential diagnosis must be made

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No entanto, nestes doentes, a avaliação da circulação nativa torna-se mais difícil, dada a presença de aterosclerose coronária avançada, sendo frequente a presença de doença difusa, múltiplas placas calcificadas e artérias de pequeno calibre, limitações importantes perante a actual resolução espacial destes exames, mesmo com os aparelhos de última geração⁽¹²⁾.

INDICAÇÕES NO SERVIÇO DE URGÊNCIA

A avaliação de doentes no serviço de urgência para exclusão da hipótese de síndrome coronário agudo (SCA) é por vezes difícil, sobretudo nos casos em que na avaliação inicial não se detectam alterações significativas no ECG e os biomarcadores de lesão miocárdica são negativos. Estes doentes ficam por vezes em observação, fazendo avaliações seriadas até ser considerada baixa a probabilidade de se tratar de um SCA. Nestes casos em que o ECG é “inocente” e os biomarcadores negativos, a exclusão de doença coronária significativa por angio TC poderá permitir uma rápida estratificação de risco, conduzindo a uma alta precoce. Por outro lado poderá também identificar alguns doentes que com base na avaliação convencional com ECG e biomarcadores seriam considerados de baixo risco e que apresentam de facto doença coronária significativa. Alguns estudos iniciais documentaram a elevada acuidade diagnóstica da angioTC neste contexto^(13,14), bem como o custo-eficácia desta estratégia, quando comparada com a estratificação pelos algoritmos convencionais⁽¹⁵⁾. Num estudo em que foi feito o seguimento dos doentes a quem foi dada alta precoce, após exclusão de doença coronária significativa pela angio TC, foi documentada a ausência de eventos coronários significativos nesta população⁽¹⁶⁾. Mais trabalhos contribuirão certamente para validar o impacto prognóstico desta estratégia.

No diagnóstico diferencial do doente admitido no serviço de urgência com dor torácica aguda, para além dos síndromes coronários agudos fazem igualmente parte a dissecação da aorta e a embolia pulmonar. Foram já desenvolvidos protocolos que permitem avaliar estas 3 patologias importantes na mesma aquisição – protocolo *triple rule out*^(17,18).

Finalmente, alguns doentes admitidos no

with ACS, for which they are generally referred for invasive coronary angiography to exclude CAD. Since many of these patients – usually young individuals with no history of cardiovascular disease and a low risk profile – have a low probability of CAD, this situation would be a good indication for non-invasive angiography using CTA. Studies have yet to be performed to validate this strategy.

CARDIAC CT ANGIOGRAPHY BEYOND NON-INVASIVE CORONARY ANGIOGRAPHY: EXTRA-CORONARY CARDIAC EVALUATION AND ASSESSMENT OF EXTRACARDIAC FINDINGS

Another advantage of CTA compared to conventional coronary angiography is that it can provide extra-coronary cardiac information and assess extracardiac findings in the same exam, without the need to increase radiation or contrast doses. Although extra-coronary cardiac evaluation is not usually the reason for the exam and most patients will already have undergone echocardiography, findings may be identified that went undetected in previous exams, particularly in patients with poor acoustic windows⁽¹⁹⁻²¹⁾ (Fig. 7).

The technique also scans the thoracic segments included in cardiac acquisition, and extracardiac findings are common in the lung and mediastinal fields⁽²²⁾.

CARDIAC CT ANGIOGRAPHY BEYOND DOCUMENTING SIGNIFICANT STENOSIS: PLANNING REVASCULARIZATION STRATEGIES

Although exclusion of CAD is the main indication for cardiac CTA, when significant coronary stenosis is detected the information provided by this exam can be useful in planning revascularization strategies.

Recent studies have demonstrated the value of cardiac CTA to predict the outcome of recanalization of chronic occlusions^(23,24) and to assess distribution patterns of coronary bifurcation lesions^(25,26), which is useful in decisions regarding revascularization (Fig. 8).

Cardiac CTA can also characterize plaques,

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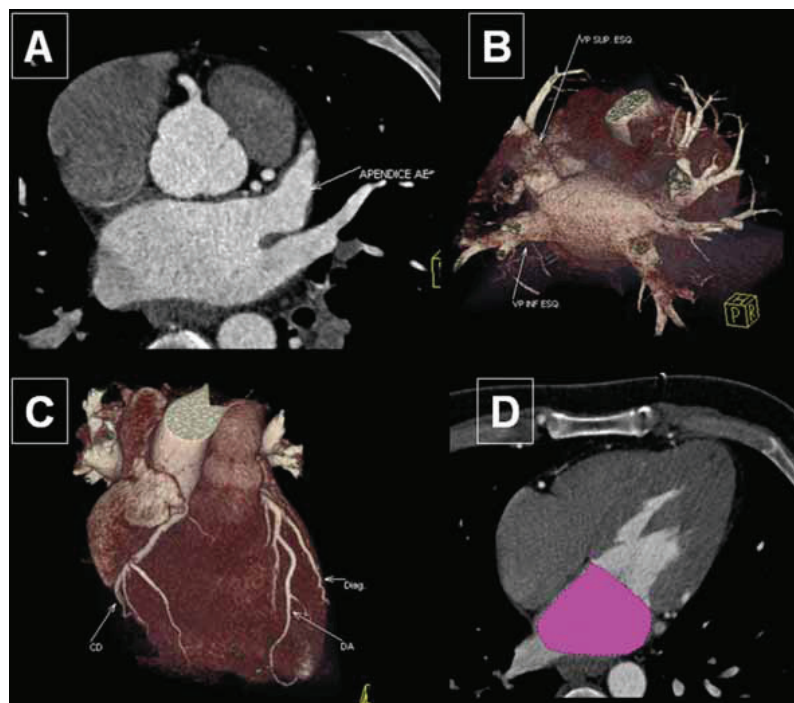


Figura 7. Reconstruções de volume (VRT) e multiplanares (MPR) num doente que realizou angioTC cardíaca para avaliação pré-ablação de fibrilhação auricular. Para além da exclusão de trombo no apêndice auricular esquerdo (A), avaliação do padrão de distribuição das veias pulmonares (B), avaliação coronária (C) e medição do volume da aurícula esquerda (D), foi ainda diagnosticada uma miocardiopatia hipertrófica apical.

Figure 7. Volume-rendered reconstruction (VRT) and multi-planar reconstruction (MPR) of a patient undergoing cardiac CT angiography for pre-ablation assessment of atrial fibrillation. As well as excluding thrombus in the atrial appendage (A), assessing the distribution of the pulmonary veins (B), coronary evaluation (C), and measurement of left atrial volume (D), apical hypertrophic cardiomyopathy was also diagnosed.

serviço de urgência por precordialgia, o diagnóstico é de miocardite ou miopericardite. Como é frequente estes casos se acompanharem de alterações da repolarização no ECG e de positividade dos biomarcadores de lesão miocárdica, torna-se necessário fazer o diagnóstico diferencial com síndrome coronário agudo, pelo que geralmente são propostos para a realização de coronariografia invasiva para exclusão de doença coronária. Como em muitos destes casos a probabilidade de doença coronária é baixa – tratam-se geralmente de indivíduos jovens, sem antecedentes cardiovasculares e com baixo perfil de risco - esta seria uma boa

particularmente the presence of calcification, which is also important for coronary interventions, since angioplasty of calcified coronary lesions is generally more difficult and sometimes requires special devices.

OTHER INDICATIONS

There are other clinical situations for which cardiac CT could be considered the first-line exam instead of conventional coronary angiography, one of which is suspected anomalous origin of the coronary arteries, a known cause of sudden

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indicação para coronariografia não invasiva por angioTC. Aguardam-se ainda estudos que validem esta estratégia.

A ANGIO TC CARDÍACA PARA ALÉM DA CORONARIOGRAFIA NÃO INVASIVA: AVALIAÇÃO CARDÍACA EXTRA-CORONÁRIA E ACHADOS EXTRA-CARDÍACOS

Outra vantagem da angioTC em relação à coronariografia convencional reside na possibilidade de se obter no mesmo exame, informação cardíaca extra-coronária e avaliar achados extra-cardíacos, sem que para isso seja necessário aumentar a dose de radiação ou de contraste. No que diz respeito à avaliação cardíaca extra-coronária, embora este não seja habitualmente o motivo do exame e geralmente os doentes já tenham feito anteriormente um ecocardiograma, por vezes são documentados achados que passaram despercebidos nos exames anteriores, nomeadamente em doentes com deficiente janela acústica⁽¹⁹⁻²¹⁾, (*Fig. 7*)

Nestes exames é ainda feita uma leitura dos segmentos torácicos incluídos na aquisição cardíaca, sendo igualmente frequentes os achados extracardíacos nos campos pulmonares ou mediastínicos⁽²²⁾.

A ANGIO TC CARDÍACA PARA ALÉM DA DOCUMENTAÇÃO DE ESTENOSES SIGNIFICATIVAS: PLANEAMENTO DA ESTRATÉGIA DE REVASCULARIZAÇÃO

Embora a exclusão da presença de CAD seja a principal indicação para a realização de uma angioTC cardíaca, nos casos em que se identificam estenoses coronárias significativas a informação recolhida neste exame poderá ser útil no planeamento da estratégia de revascularização.

Trabalhos publicados recentemente demonstram a utilidade da angio-TC cardíaca para identificar preditores de sucesso de recanalização de oclusões crónicas^(23,24) e para avaliar padrões de distribuição das lesões coronárias em bifurcação^(25,26), informação útil para o planeamento da estratégia de revascularização (*Fig. 8*).

death in young athletes⁽²⁷⁾. Cardiac CTA can determine not only the origin but the trajectory of anatomical variants, identifying malignant forms that course between the aorta and the pulmonary artery, which are difficult to characterize with conventional coronary angiography (*Fig. 9*).

Another indication is in patients with dilated cardiomyopathy (DCM), in whom a coronary etiology must generally be excluded. In a study involving 61 patients with DCM of undetermined cause that compared the performance of cardiac CTA with invasive angiography for detection of CAD⁽²⁸⁾, sensitivity and specificity of CTA were 99% and 96.2% respectively, even with a 16-slice system. The study also assessed the safety of the two diagnostic modalities; no complications were observed with cardiac CTA, while the rate of complications in patients undergoing invasive angiography was 16%, 9.8% due to acute heart failure and 6.5% related to vascular access.

Besides excluding the presence of significant coronary disease in patients with DCM, cardiac CTA also accurately measures volumes and ejection fraction in the same scan, thus avoiding the need to increase contrast or radiation doses. Since acquisition is synchronized with the ECG, reconstructions at different phases of the cardiac cycle can be compared in order to select the best systolic and diastolic phases. This, together with the technique's excellent endocardial definition and the fact that the 17 segments can be represented in multiplane reconstructions, leads to highly accurate and reproducible determination of volumes and ejection fraction. Given the prognostic and therapeutic implications of ejection fraction in patients with left ventricular dysfunction⁽²⁹⁾, this capability is an important additional advantage of non-invasive angiography, and further enhances the value of cardiac CTA in such patients (*Fig. 10*).

LIMITATIONS OF CARDIAC CT ANGIOGRAPHY

The limitations of cardiac CTA are related to spatial and temporal resolution, the lack of functional information and radiation doses.

The spatial resolution of CTA is inferior to that of invasive coronary angiography, making assessment of small caliber distal segments more

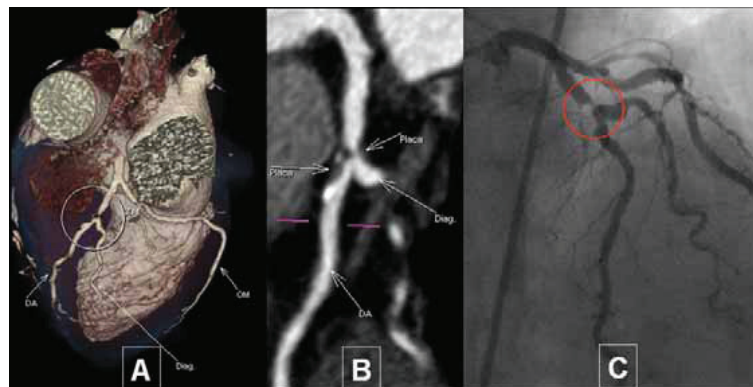


Figura 8 Reconstruções de volume (VRT) documentando estenose significativa na descendente anterior, em bifurcação com a 1ª diagonal (A). Na reconstrução multiplanar (MPR) é possível avaliar que se trata de placa predominantemente não calcificada e permite ainda apreciar o envolvimento do colateral pela placa (B), que não é perceptível na angiografia convencional (C).

Figure 8 Volume-rendered reconstruction (VRT) showing significant stenosis of the left anterior descending artery at the bifurcation with the first diagonal (A). In multi-planar reconstruction (MPR) it can be seen that this is a mainly non-calcified plaque, which also involves the collateral (B); this is not visible on conventional angiography (C).

A angio TC cardíaca permite ainda avaliar o tipo de placa, nomeadamente a presença de calcificação, informação igualmente importante para a intervenção coronária, uma vez que a angioplastia de estenoses coronárias calcificadas é habitualmente mais difícil, exigindo por vezes a utilização de dispositivos específicos.

OUTRAS INDICAÇÕES

Existem ainda outras indicações clínicas, para as quais a angioTC cardíaca poderá ser considerada o exame de primeira linha, em vez da coronariografia invasiva convencional. Um destes exemplos é a suspeita de origem anómala das artérias, reconhecida causa de morte súbita em jovens⁽²⁷⁾. A angioTC cardíaca permite delinear não só a origem mas sobretudo o trajecto das variantes anatómicas, permitindo assim identificar as variantes malignas, nas quais o trajecto se faz entre a aorta e a artéria pulmonar, aspectos difíceis de caracterizar na coronariografia convencional.

Outro exemplo é o dos doentes com Miocardiopatia Dilatada nos quais se tem habitualmen-

te dificuldade, which is why most studies limit their analysis to segments of ≥ 1.5 mm. Evaluation of calcified lesions is also difficult, the degree of stenosis generally being overestimated by CTA. Special filters are usually employed in reconstructions aimed at assessing stent patency, and these should also be used in patients with calcified lesions to minimize the effect of blooming artifacts⁽⁶⁾.

Temporal resolution is also inferior to conventional angiography, which hinders assessment of patients with high heart rates or arrhythmias. However, this limitation has been overcome by the latest 64-slice dual source systems, which can assess patients with high heart rates and even those in atrial fibrillation^(9,10).

The lack of functional information is another limitation of the technique. The ability to provide data on the functional impact of plaques or stenosis as well as anatomical information would make cardiac CTA the most complete non-invasive method of assessing CAD. There are two lines of research in this area: one seeks to assess perfusion on the basis of myocardial density, which is linearly correlated with perfusion following administration of iodinated contrast; the

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Figura 9 Reconstruções de volume (VRT) e multiplanar (MPR) documentando origem anómala da coronária direita no seio de valsalva esquerdo, com trajecto interarterial, tratando-se por isso de uma variante maligna.

Figure 9 Volume-rendered reconstruction (VRT) and multi-planar reconstruction (MPR) showing anomalous origin of the right coronary artery in the left sinus of Valsalva, which has an interarterial course, and is therefore a malignant variant.

te que excluir etiologia coronária. Num estudo que envolveu 61 doentes com miocardiopatia dilatada de etiologia indeterminada, foi avaliado o desempenho da angioTC cardíaca por comparação com a angiografia invasiva na detecção de doença coronária⁽²⁰⁾. Nesta série, a sensibilidade e a especificidade foram de 99% e 96,2%, respectivamente, e tendo os exames sido realizados com um aparelho de apenas 16 cortes. Neste trabalho foi ainda avaliada a segurança das duas modalidades diagnósticas, não se tendo verificado complicações relacionadas com a angioTC cardíaca. Nos doentes submetidos a angiografia invasiva a taxa de complicações chegou aos 16%, sendo 9,8% por insuficiência cardíaca aguda e 6,5% por complicações relacionadas com o acesso vascular.

Nos doentes com miocardiopatia dilatada, para além de ser possível excluir a presença de doença coronária significativa, a angioTC cardíaca permite ainda calcular correctamente os volumes e a fracção de ejeção, na mesma aquisição, não sendo assim necessário aumentar a dose de contraste ou de radiação. Como a aquisição é sincronizada com o ECG, é possível comparar as reconstruções nas várias fases do ciclo cardíaco, para selecção da melhor fase sistólica e diastólica. Este facto, associado a uma óptima definição endocárdica e à possibilidade de se ter a representação dos 17 segmentos nas reconstruções multiplanares, torna assim possível uma avaliação bastante correcta e reprodutível dos volumes e fracção de ejeção.

other exploits the ability of dual energy methods to quantify iodine concentration in tissue. Both methods are still at the initial development stage in a few centers and there are various obstacles to be overcome, particularly the need to avoid a significant increase in radiation dose and the ability to perform exams under pharmacological stress.

Finally, the radiation dose in cardiac CTA, around 11 mSv even in studies with ECG-dependent dose modulation, is higher than in conventional coronary angiography, which is estimated at 7 mSv⁽³⁰⁾. As well as ECG-dependent dose modulation, which is now routine in such exams, new protocols have recently been developed aimed at reducing the dose even further. One consists of reducing the voltage from 120 kV to 100 kV, which is feasible in most patients except the obese. In a study comparing the radiation doses of different protocols in 1035 patients, a mean dose of 5.4 mSv was obtained with 64-slice systems using a combination of ECG-dependent dose modulation and the 100 kV protocol, which corresponds to a 64% reduction compared to standard protocols⁽³¹⁾. Another recently developed protocol that has considerable potential to reduce the radiation dose even further consists of acquisition with prospective, rather than the usual retrospective, ECG triggering, known as step-and-shoot mode. Initial studies using this protocol have reported doses of 1.2 to 2.6 mSv⁽³²⁾.

The recently introduced 320-slice systems,

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Dadas as reconhecidas implicações prognósticas e terapêuticas da fracção de ejeção nos doentes com disfunção ventricular esquerda⁽²⁹⁾, esta avaliação torna-se assim um complemento importante à coronariografia não invasiva, e contribui para a rentabilidade da angioTC cardíaca nestes doentes (*Fig. 10*).

which enable acquisition of the entire heart volume in a single RR interval, should also lead to significant reductions in radiation and contrast doses.

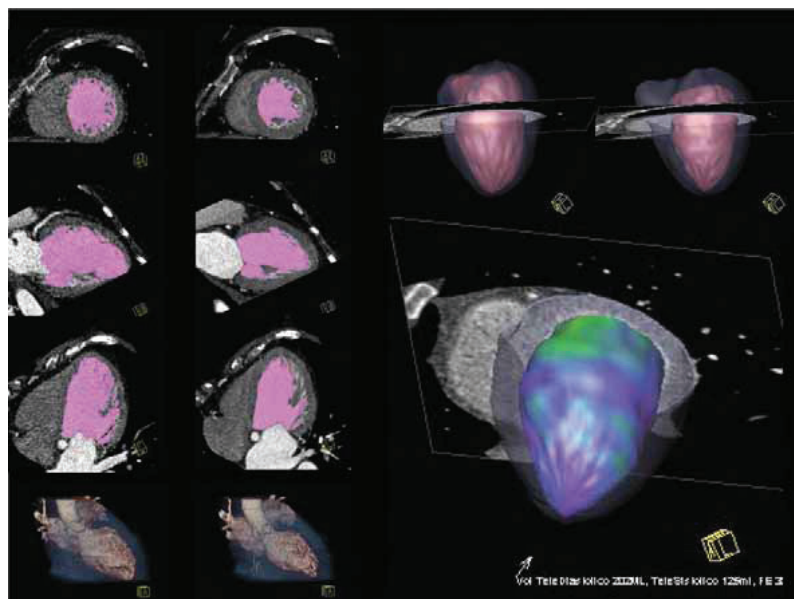


Figura 10 Cálculo de volumes e fracção de ejeção em doente com miocardiopatia dilatada, a partir da delimitação do contorno endocárdico nas várias reconstruções multiplanares, com representação dos 17 segmentos miocárdicos.

Figure 10 Determination of volumes and ejection fraction in a patient with dilated cardiomyopathy by delimiting the endocardial outline in various multiplanar reconstructions, representing the 17 myocardial segments.

LIMITAÇÕES DA ANGIOTC CARDÍACA

As limitações da AngioTC cardíaca estão relacionadas com resolução espacial, resolução temporal, ausência de informação funcional e dose de radiação.

A resolução espacial da angioTC cardíaca é inferior à da coronariografia invasiva o que dificulta a avaliação de segmentos distais de pequeno calibre, razão pela qual na maior parte dos estudos, a análise foi limitada aos segmentos com $\geq 1,5\text{mm}$. A avaliação de lesões

CONCLUSION

Ongoing research and technological advances in the area of multislice computed tomography have progressively improved the spatial and temporal resolution of cardiac CTA exams. In addition to the current indications for use of the technique, notably exclusion of coronary artery disease in patients with intermediate probability, this diagnostic modality is also proving useful in other areas, and may become a first-line technique.

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calcificadas é igualmente difícil, sendo o grau de estenose habitualmente sobrevalorizado na angioTC. Existem filtros dedicados, que são habitualmente empregues na reconstrução de exames para avaliação da patência de *stents*, que devem igualmente ser empregues na presença de lesões calcificadas, para minimizar o efeito de *blooming*.

A resolução temporal é igualmente inferior à da coronariografia convencional, o que torna difícil a avaliação de doentes com frequências cardíacas altas e arritmias. Esta limitação tem vindo a ser ultrapassada com os aparelhos de angioTC cardíaca de última geração com 64 cortes e dupla ampola, sendo possível com estes aparelhos realizar exames em doentes com frequências cardíacas altas e mesmo em fibrilhação auricular^(9,10).

A ausência de informação funcional tem sido apontada como uma das limitações desta técnica. A possibilidade de se adicionar à informação anatómica a informação do impacto funcional das placas/estenoses, tornaria a angioTC cardíaca o método não invasivo mais completo na avaliação da doença coronária. Existem nesta área duas linhas de investigação divergentes: uma que procura avaliar a perfusão através da densidade do miocárdio (uma vez que existe uma correlação linear entre a densidade do miocárdio e a sua perfusão após injeção de contraste iodado); a outra explorando as capacidades da codificação do iodo nos tecidos pelo método da dupla energia. Actualmente ainda em fase de desenvolvimento inicial em poucos centros, estes métodos têm várias barreiras a superar, nomeadamente a necessidade de não haver um aumento relevante de dose de radiação e a capacidade de ser realizado em condições de *stress* farmacológico.

Por fim, a dose de radiação atribuída à angio TC cardíaca, de cerca de 11 mSv em trabalhos com modulação da dose de acordo com o ECG, é mesmo assim superior à dose da coronariografia convencional, que está estimada em 7 mSv⁽³⁰⁾. Para além da modulação da dose de radiação pelo ECG, utilizado actualmente por rotina nestes exames, foram recentemente desenvolvidos novos protocolos que visam reduzir ainda mais a dose de radiação destes exames. Um destes protocolos consiste na redução da kilovoltagem da ampola de 120 para 100Kv, possível na grande maioria dos doentes, à excepção dos obesos. Num trabalho em que foram comparadas

When significant coronary stenosis is detected, the information provided by cardiac CTA can be useful in planning revascularization strategies. However, the exam is not limited to assessment of the coronary tree, and the same acquisition protocol can be used for extra-coronary cardiac evaluation, particularly multiplane reconstructions to determine ejection fraction and for assessment of extracardiac findings in the thoracic segments included in the scan.

It is hoped that some of the technique's current limitations will be overcome in the future, particularly with regard to radiation doses and assessment of calcified lesions, and that cardiac CT angiography will be able to combine both anatomical and functional information in the same non-invasive exam. Initial results have been extremely promising and we shall see what the future will bring.

as doses de radiação com diferentes protocolos em 1035 doentes, foi possível obter uma dose média de 5,4mSv em aparelhos de 64 cortes, com o uso combinado de modulação da dose de acordo com o ECG e utilização de protocolo de 100Kv, o que corresponde a uma redução de 64% em relação aos protocolos convencionais⁽³¹⁾. Um outro protocolo recentemente desenvolvido e com elevado potencial para reduzir ainda mais a dose de radiação consiste na aquisição sincronizada com o ECG de forma prospectiva em vez da habitual retrospectiva, o chamado protocolo *step and shot*. Estão descritas doses de 1,2 a 2,6 mSv nos trabalhos iniciais com este protocolo⁽³²⁾.

Finalmente, os aparelhos de 320 cortes recentemente introduzidos, que permitem realizar a aquisição de todo o volume cardíaco em apenas um intervalo RR, deverão igualmente conduzir a uma redução significativa da dose de radiação e de contraste.

CONCLUSÃO

A constante investigação e evolução tecnológica na área da TC multicortes tem vindo a permitir uma melhoria progressiva na resolução espacial e temporal dos exames de angioTC cardíaca. Para além das indicações actualmente aceites para esta técnica, nomeadamente a exclusão da presença de doença coronária em doentes com probabilidade intermédia, esta modalidade diagnóstica tem-se revelado útil também noutras áreas, podendo de futuro constituir-se como uma modalidade de primeira escolha.

Nos casos em que se documentam estenoses coronárias significativas, a informação recolhida pela angioTC cardíaca poderá ser útil no planeamento da estratégia de revascularização. Por outro lado, um exame de angioTC cardíaca não se limita à avaliação da árvore coronária, sendo possível com o mesmo protocolo de aquisição fazer ainda uma avaliação cardíaca extracoronária, nomeadamente com cálculo multiplanar da fracção de ejeção e fazer ainda uma apreciação de eventuais achados extracardíacos nos segmentos torácicos incluídos na aquisição.

De futuro, espera-se que seja possível ultrapassar algumas das presentes limitações desta técnica, nomeadamente no que diz respeito à dose de radiação, à avaliação de lesões calcificadas e à possibilidade da angioTC cardíaca poder vir a conciliar no mesmo método não invasivo a informação anatómica e funcional – os resultados iniciais têm sido muito promissores, veremos o que o futuro nos reserva.

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ARTIGO 4/ MANUSCRIPT 4:

Avaliação de Pontagens Coronárias por Angio TC de 64 Cortes de Dupla Ampola [74]

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Palavras-Chave

Angio TC de 64 cortes de dupla ampola; Pontagens Coronárias

Assessment of Coronary Artery Bypass Grafts by 64-slice Computed Tomographic Angiography

Key words

64-slice computed tomographic angiography; Coronary artery bypass grafts

Os doentes com antecedentes de cirurgia de revascularização miocárdica, pela sua história natural, apresentam 25% das pontagens venosas ocluídas, ao fim de 5 anos^[1].

O aperfeiçoamento de técnicas de imagem nomeadamente da tomografia computadorizada cardíaca por multidetectores (Angio TC cardíaca), permite a avaliação não invasiva das pontagens coronárias com elevada acuidade^[2].

Os autores apresentam o caso clínico de um doente do sexo masculino, de 72 anos de idade, com hipertensão arterial e dislipidemia como factores de risco para doença coronária e com antecedentes de cirurgia de revascularização miocárdica em 1999.

Em Outubro de 2007 realizou prova de esforço que foi positiva para isquémia silenciosa, razão pela qual foi solicitado Angio TC cardíaca para avaliação da patência das pontagens coronárias.

A angio TC foi realizada num aparelho de 64 cortes e dupla ampola (Dual source CT - Somatom Definition®, Siemens-medical). A aquisição do *scan* demorou 12 segundos, foram administrados 108 ml de contraste isoosmolar (Iodixanol 320 mgI/ml- Visipaque®). A frequência cardíaca média na aquisição foi de 68 bpm e a dose de radiação foi de 1244 DLP.

The natural history of coronary artery bypass surgery is such that 25% of venous grafts are occluded after 5 years^[1].

Improvements in imaging techniques, particularly multislice cardiac computed tomographic (CT) angiography, mean that coronary artery grafts can now be visualized noninvasively and in great detail^[2].

We present the case of a 72-year-old man with risk factors for coronary disease (hypertension and dyslipidemia) and history of coronary artery bypass surgery in 1999.

In October 2007 he underwent exercise testing which was positive for silent ischemia, and so he was referred for CT angiography to assess the patency of the coronary artery grafts.

The scan was performed on a 64-slice dual source Somatom Definition® system (Siemens Medical Solutions), and took 12 seconds with 108 ml of iso-osmolar contrast (iodixanol 320 mgI/ml - Visipaque®) being administered. Mean heart rate during acquisition was 68 bpm and the radiation dose was 1244 DLP.

The image quality was sufficiently good to assess all the grafts: left internal mammary artery (LIMA) to left anterior descending (LAD), sequential graft with the saphenous vein to the intermediate and first obtuse marginal (OM1), and saphenous vein to posterior descending

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A qualidade de imagem permitiu a avaliação de todas as pontagens: artéria mamária interna esquerda (LIMA) para a descendente anterior (DA), pontagem sequencial com safena para a intermediária e primeira obtusa marginal (OM 1) e safena para descendente posterior (DP) (*Fig. 1*).

A pontagem MIE para a DA estava patente e não apresentava estenoses (*Fig. 2*).

A pontagem sequencial veia safena para intermediária e OM1 não apresentava estenoses (*Fig. 3*).

A pontagem da safena para a descendente posterior apresentava placa calcificada não significativa (*Fig. 4*).

A circulação nativa abaixo das anastomoses era de pequeno calibre mas estava patente.

Uma das vantagens da tecnologia de dupla ampola é o facto de apresentar o dobro da resolução temporal, de um aparelho de 64 cortes convencional. Assim, torna-se possível a obtenção de imagens com menos artefactos em doentes com frequências cardíacas mais elevadas, extrasístoles frequentes e até mesmo em fibrilhação auricular^[3].

Para além da reconhecida elevada sensibilidade da angio TC cardíaca para excluir a presença de estenoses coronárias significativas^[4], a especificidade no caso da avaliação de estenoses nas pontagens é igualmente elevada, chegando a 97% em alguns trabalhos^[2].

artery (PDA).

The LIMA to LAD graft was patent and without stenosis

The sequential saphenous vein graft to the intermediate and OM1 were without stenosis (*Fig. 3*).

The saphenous vein to PDA graft presented non-significant calcification (*Fig. 4*).

The native circulation below the anastomoses was small but the artery was patent.

One of the advantages of dual source technology is that its temporal resolution is twice that of a conventional 64-slice system. This means it can obtain images with fewer artifacts in patients with high heart rates, frequent extrasystoles or even atrial fibrillation^[3].

Besides the known high sensitivity of cardiac CT angiography in excluding significant coronary stenosis^[4], the technique is also highly specific (up to 97% in some studies) in evaluating graft stenosis^[2].

Evaluation of native circulation becomes more difficult when there is advanced coronary atherosclerosis, often with diffuse disease, multiple calcified plaques and arteries of small caliber. Despite these limitations, in some cases 64-slice dual source cardiac CT angiography can evaluate not only coronary artery grafts but also the extent of disease in the native circulation, as shown in the case presented.



Figura 1. Reconstrução 3D “volume-rendered” das pontagens coronárias

Figure 1. 3D volume-rendered image of the coronary artery grafts



Figura 2. Visualização da pontagem mamária interna esquerda (LIMA) para descendente anterior (DA). A - Reconstrução 3D "volume-rendered" B - Reconstrução curva multiplanar

Figure 2. LIMA to LAD graft. A: 3D volume-rendered image; B: curved multiplanar reconstruction

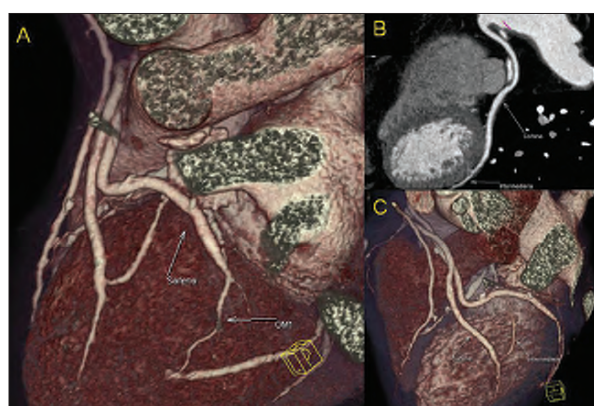


Figura 3. Visualização da pontagem safena para intermediária e obtusa marginal. A e C - Reconstrução 3D "volume-rendered". B - Reconstrução curva multiplanar

Figure 3. Saphenous vein graft to the intermediate and OM1. A and C: 3D volume-rendered image; B: curved multiplanar reconstruction

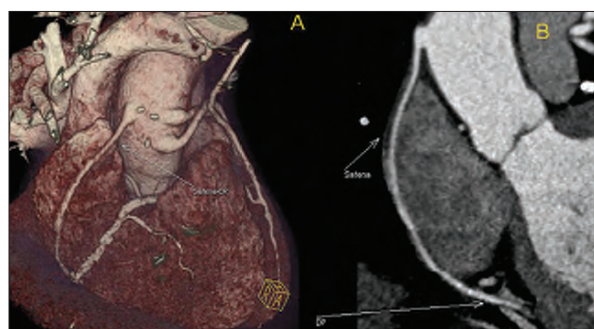


Figura 4. Pontagem veia safena para a descendente posterior. A - Reconstrução 3D "volume-rendered" B - Reconstrução curva multiplanar

Figure 4. Saphenous vein to PDA graft. A: 3D volume-rendered image; B: curved multiplanar reconstruction

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A avaliação da circulação nativa torna-se mais difícil, dada a presença de aterosclerose coronária avançada, sendo frequente a presença de doença difusa, múltiplas placas calcificadas e artérias de pequeno calibre. Apesar destas limitações, este caso é ilustrativo de como é possível em alguns casos, com a angio TC cardíaca de 64 cortes de dupla ampola, avaliar não só as pontagens coronárias, mas também a extensão da doença na circulação nativa.

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ARTIGO 5/ MANUSCRIPT 5:

IMAGEM EM CARDIOLOGIA

Divertículo do ventrículo esquerdo: um achado por Angio TC cardíaca [32]

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Rev Port Cardiol 2009; 28 (3): 341-344

Palavras-Chave

Divertículo do ventrículo esquerdo; Angio TC de 64 cortes de dupla ampola; Achados em angio TC.

Left ventricular diverticulum: a finding by cardiac CT angiography

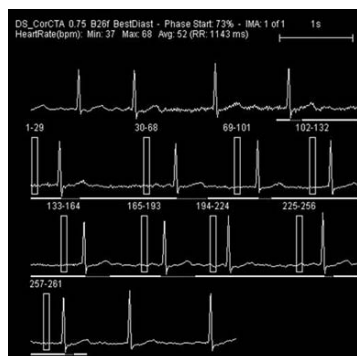
Key words

Left ventricular diverticulum;
64-slice dual source computed tomographic angiography;
Incidental findings by CT.

INTRODUÇÃO

Os autores apresentam o caso clínico de uma doente de 72 anos, com estenose mitral moderada, submetida a angio Tomografia Computorizada (TC) cardíaca, para avaliação pré-operatória de doença coronária.

A angio TC foi realizada num aparelho de 64 cortes de dupla ampola, (Dual source CT - Somatom Definition®, Siemens-medical). A aquisição do scan demorou 10 segundos, foram administrados 96 ml de contraste isoosmolar (Iodixanol 320 mgI/ml- Visipaque®) e a dose de radiação foi 12 mSv.



INTRODUCTION

We present the case of a 72-year-old woman with moderate mitral stenosis who underwent cardiac computed tomographic (CT) angiography for preoperative assessment of coronary artery disease.

The scan was performed on a 64-slice dual source system (Somatom Definition®, Siemens Medical Solutions) and took 10 seconds. Iodixanol (Visipaque®) 320 mgI/ml iso-osmolar contrast (96 ml) was administered and the radiation dose was 12 mSv.

During the scan the patient developed atrial fibrillation, with a ventricular response of between 37 and 68 bpm (Figure 1).

Figura 1. ECG durante a aquisição da Angio TC cardíaca. Frequência cardíaca média 52 bpm (37- 68bpm).

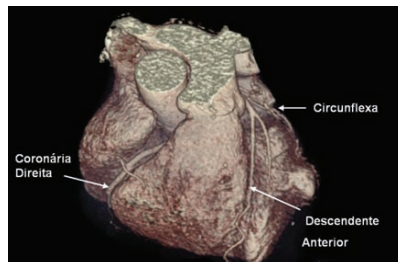
Figure 1. ECG during cardiac CT angiography. Mean heart rate 52 bpm (37- 68bpm).

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Durante a aquisição a doente apresentava fibrilhação auricular, com uma resposta ventricular entre 37 e 68 bpm (*Figura 1*).

A qualidade de imagem permitiu a avaliação de todos os segmentos, excluindo-se doença coronária significativa (*Figuras 2 e 3*).



The image quality was sufficiently good to assess all segments and significant coronary disease was excluded (*Figures 2 and 3*).

Figura 2. Reconstrução 3D “volume-rendered”.

Figure 2. 3D volume-rendered reconstruction.

Coronária Direita: right coronary artery; Circunflexa: circumflex artery; Descendente Anterior: anterior descending artery.

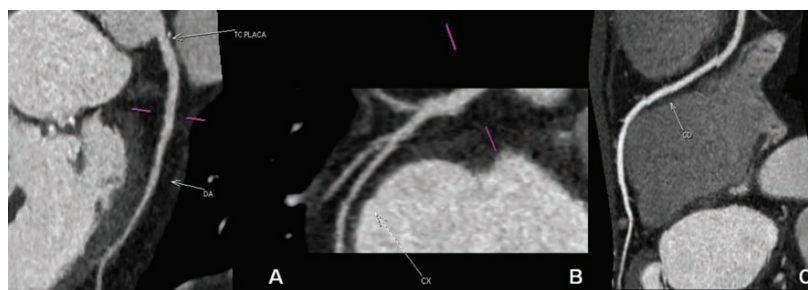


Figura 3. Reconstrução curva multiplanar. A – Visualização do tronco comum (TC) com placa calcificada não significativa e descendente anterior (DA) sem placas significativas. B e C - Circunflexa (CX) e Coronária direita (CD) respectivamente sem placas significativas.

Figure 3. Curved multiplanar reconstruction. A: Left main artery (TC) showing an insignificant calcified plaque and the anterior descending artery (DA) with no significant plaques. B and C: Circumflex (CX) and right coronary (CD) arteries, respectively, with no significant plaques.

Na avaliação cardíaca, para além da ausência de doença coronária significativa, documentou-se aurícula esquerda dilatada, válvula mitral de folhetos espessados e calcificados, com restrição da sua abertura e normal função sistólica ventricular esquerda (*Figura 4 B*).

No ventrículo esquerdo visualizou-se uma imagem de contornos bem definidos, de pequenas dimensões, fazendo protusão da parede lateral, através de uma conexão estreita. Esta imagem era compatível com a presença de um divertículo do ventrículo esquerdo (*Figuras 4 e 5*).

Besides the absence of significant coronary disease, cardiac assessment revealed a dilated left atrium, thickened and calcified mitral valve leaflets with restricted opening, and normal left ventricular systolic function (*Figure 4B*).

A small, well-defined image was observed in the left ventricle protruding from the lateral wall with a narrow connection, compatible with a left ventricular diverticulum (*Figures 4 and 5*).

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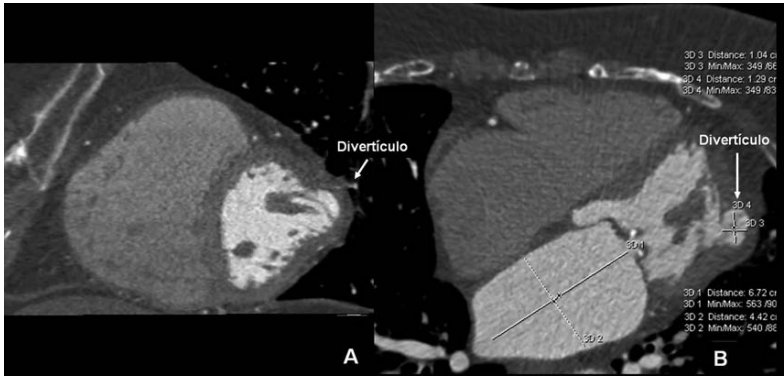


Figura 4. Visualização do divertículo do ventrículo esquerdo (A) em curto eixo e (B) em longo eixo. B - aurícula esquerda dilatada, válvula mitral com folhetos espessados e calcificados.

Figure 4. Left ventricle in short-axis (A) and long-axis (B) view showing diverticulum. B: dilated left atrium and mitral valve with thickened and calcified leaflets.

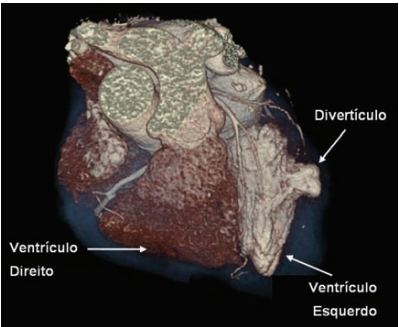


Figura 5. Reconstrução 3D “volume-rendered” do divertículo do ventrículo esquerdo.

Figure 5. 3D volume-rendered reconstruction of the left ventricular diverticulum.

Ventrículo Direito: right ventricle; Divertículo: diverticulum;
Ventrículo Esquerdo: left ventricle

O divertículo apresenta contractilidade síncrona com o ventrículo esquerdo, esvaziando quase na totalidade em sístole (Figura 6).

The diverticulum contracted in synchrony with the left ventricle, almost completely emptying in systole (Figure 6).

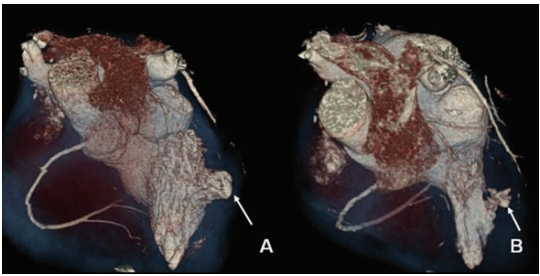


Figura 6. Reconstrução 3D “volume-rendered” do divertículo do ventrículo esquerdo (seta) em diástole (A) e em sístole (B).

Figure 6. 3D volume-rendered reconstruction of the left ventricular diverticulum (arrow) in diastole (A) and in systole (B).

Os divertículos ventriculares congénitos são raros, particularmente os diagnosticados em adultos⁽¹⁻³⁾.

Os divertículos podem cursar com fenómenos embólicos, insuficiência cardíaca, regurgitação valvular, rotura da parede ventricular, taquicardia ventricular ou morte súbita. Na maioria dos casos os divertículos são assintomáticos e constituem achados incidentais nos métodos de imagem^(1,4). O diagnóstico faz-se pela visualização por eco-cardiograma, ventriculografia, tomografia computadorizada ou ressonância magnética cardíaca de uma protusão da parede ventricular, com conexão estreita e contractilidade síncrona com a cavidade ventricular^(1,5). Os divertículos são constituídos pelas 3 camadas cardíacas. O diagnóstico diferencial faz-se com aneurismas, sendo que estes habitualmente são formações saculares, de tecido fibroso, com conexão larga e movimento paradoxal⁽⁵⁾.

O tratamento dos divertículos varia de acordo com a forma de apresentação, das anomalias associadas e possíveis complicações. Nos doentes sintomáticos com fenómenos embólicos o tratamento é cirúrgico associado a anticoagulação oral. Embora seja controverso alguns autores preconizam a ressecção cirúrgica nos doentes assintomáticos, atendendo ao elevado risco de morte por rotura da parede ou eventos arritmicos graves⁽⁵⁾.

Congenital left ventricular diverticula are rare, especially when diagnosed in adulthood⁽¹⁻³⁾. They can be associated with embolism, heart failure, valve regurgitation, ventricular wall rupture, ventricular tachycardia and sudden death. In most cases they are asymptomatic and are incidental findings on imaging studies^(1,4). Diagnosis is obtained by echocardiography, ventriculography, CT scan or magnetic resonance imaging of a protrusion from the ventricular wall, with a narrow connection and contracting in synchrony with the ventricular chamber^(1,5). Diverticula are composed of all three cardiac layers. Differential diagnosis is with aneurysms, which are usually saccular in form and consist of fibrous tissue, with a wide connection and paradoxical motion⁽⁵⁾.

Treatment varies according to the form of presentation, associated anomalies and possible complications. In symptomatic patients with embolic phenomena, treatment is surgical associated with oral anticoagulation therapy. Although controversial, surgical resection is recommended by some authors even in asymptomatic patients, given the high risk of death due to wall rupture or severe arrhythmias⁽⁵⁾.

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Miocardiolpatia Hipertrofica – Dois Padrões Atípicos Diagnosticados por AngioTC Cardíaca [70]

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RESUMO

A miocardiopatia hipertrofica é uma doença genética relativamente comum (prevalência de 0,2%), com um espectro clínico que pode ir desde a ausência de manifestações até à apresentação como morte súbita. As formas atípicas constituem um desafio diagnóstico, podendo novas técnicas de imagiologia cardíaca, como a AngioTC e a RMN cardíaca dar um contributo importante. A propósito de dois casos de miocardiopatia hipertrofica diagnosticados por AngioTC cardíaca, apresentamos uma revisão desta entidade.

Palavras-Chave

Angio TC cardíaca; TC de 64 cortes de dupla ampola;
Miocardiopatia hipertrofica.

ABSTRACT

Hypertrophic cardiomyopathy – two atypical forms diagnosed by cardiac CT

Hypertrophic cardiomyopathy is a relatively common genetic disease (prevalence of 0.2%), with a clinical spectrum that ranges from absence of symptoms to presentation as sudden cardiac death. Atypical forms are a diagnostic challenge and recent cardiac imaging techniques, such as cardiac CT and magnetic resonance imaging, can make an important contribution. We present a review of this disease based on two case reports.

Key words

Cardiac CT; 64-slice dual source CT;
Hypertrophic cardiomyopathy

INTRODUÇÃO

A miocardiopatia hipertrofica (MCH) é uma perturbação genética complexa relativamente comum, afectando um em cada 500 adultos jovens. Define-se pela presença de hipertrofia ventricular esquerda sem cavidade dilatada, sendo o diagnóstico habitualmente ecográfico, pela demonstração de uma espessura parietal do ventrículo esquerdo, uni ou multissegmentar, de pelo menos 15 mm.⁽¹⁻³⁾ Apesar de o padrão mais típico ser a hipertrofia da porção anterior

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a relatively common complex genetic disease that affects one in 500 young adults. It is characterized by left ventricular (LV) hypertrophy without dilatation and is usually diagnosed by echocardiographic evidence of LV wall thickness of at least 15 mm in one or more segments⁽¹⁻³⁾. While the most typical pattern is hypertrophy of the anterior portion of the ventricular septum⁽⁴⁾, HCM can present any pattern. In patients with

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do septo interventricular,⁽⁴⁾ a MCH pode assumir qualquer padrão. Em doentes com janela acústica insuficiente, ou quando a hipertrofia ventricular esquerda está limitada a segmentos de difícil avaliação ecográfica, a Ressonância Magnética e a Angiografia por Tomografia Computorizada (AngioTC) cardíaca podem dar um contributo diagnóstico adicional.^(1,3-6)

A propósito desta entidade, apresentamos dois casos clínicos.

CASO CLÍNICO 1

Doente de 31 anos, sexo masculino, raça caucasiana. Não tinha antecedentes relevantes nem factores de risco cardiovasculares (nomeadamente hipertensão arterial, tabagismo, dislipidemia, diabetes *mellitus* ou história familiar de doença coronária precoce). Por apresentar episódios sincopais recorrentes, foi internado para esclarecimento de eventual etiologia cardíaca. O electrocardiograma mostrou a presença de padrão de hipertrofia ventricular esquerda com sobrecarga (*Fig. 1*) e na monitorização cardíaca observaram-se sístoles prematuras ventriculares frequentes. O ecocardiograma transtorácico sugeriu tratar-se de variante médio-ventricular de

poor acoustic windows, or when hypertrophy is limited to segments that are difficult to evaluate echographically, magnetic resonance imaging and cardiac computed tomography angiography (CTA) can help with diagnosis^(1,3-6).

We present two cases of this entity.

CASE REPORT 1

A 31-year-old man, white, with no relevant history or cardiovascular risk factors (hypertension, smoking, dyslipidemia, diabetes or family history of premature coronary artery disease [CAD]), was admitted for investigation of a possible cardiac etiology of recurrent episodes of syncope. The electrocardiogram showed a pattern of LV overload hypertrophy (*Fig. 1*) and frequent premature ventricular systoles. Transthoracic echocardiography suggested mid-ventricular HCM. To confirm the diagnosis and exclude the presence of significant CAD, cardiac CTA was performed using a 64-slice dual source system (SOMATOM Definition®, Siemens Medical Solutions). Mean heart rate during acquisition (8 seconds) was 96 bpm, with several ventricular extrasystoles (*Fig. 2*).

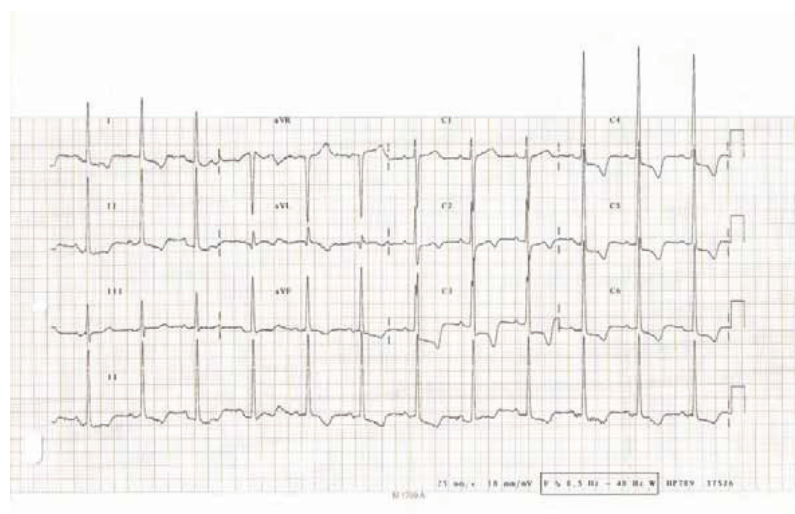


Figura 1. ECG demonstrando padrão de hipertrofia ventricular esquerda com sobrecarga.

Figure 1. ECG showing pattern of left ventricular overload hypertrophy.

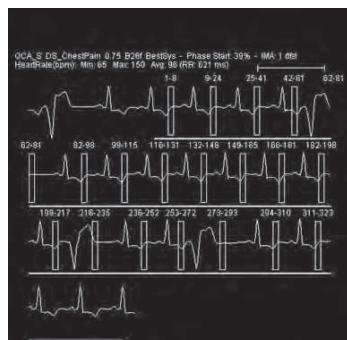


Figura 2 Traçado electrocardiográfico durante a aquisição do AngioTC cardíaco mostrando ritmo sinusal com sístoles prematuras ventriculares.

Figure 2 ECG trace during cardiac CT acquisition showing sinus rhythm with premature ventricular systoles.

MCH. Para confirmação do diagnóstico e excluir a presença de doença coronária significativa, realizou Angio TC cardíaco (aparelho de 64 cortes e dupla ampola - *Dual source CT - Somatom Definition®*, Siemens-medical). Durante a aquisição (8 segundos), a FC média foi de 96/bpm e apresentou várias extrassístoles ventriculares (Fig. 2).

Foi demonstrada a presença de hipertrofia ventricular esquerda limitada aos segmentos médios, ausência de doença coronária significativa (Fig. 3) e normal função sistólica global. Este doente foi posteriormente submetido a implantação de CDI.

CASO CLÍNICO 2

Doente de 42 anos, sexo masculino, sem fatores de risco para doença coronária. Diagnóstico de fibrilhação auricular paroxística desde há 10 anos, não havendo cardiopatia estrutural no ecocardiograma transtorácico. Foi proposto para realização de uma angioTC cardíaca para estudo prévio a ablação de fibrilhação auricular (aparelho de 64 cortes e dupla ampola - *Dual source CT - Somatom Definition®*, Siemens-medical). Durante a aquisição (8 segundos), a FC média foi de 77/bpm (Fig. 4). A angioTC cardíaca demonstrou ausência de doença coronária significativa, normal função sistólica, pequeno

LV hypertrophy was observed in the middle segments, with no significant CAD (Fig. 3) and normal global systolic function. The patient subsequently received an implantable cardioverter-defibrillator (ICD).

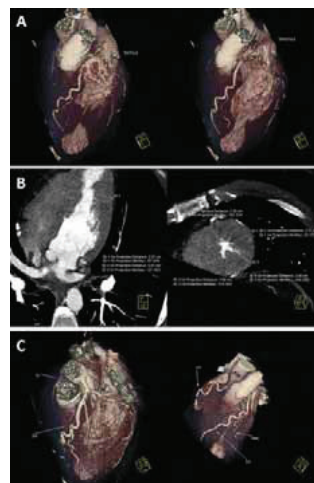


Figura 3 A - Reconstrução 3D VRT *volume-rendered* cardíaca demonstrando colapso sistólico meso-ventricular; B - Reconstrução multiplanar (MPR): visualização em longo eixo e curto eixo do ventrículo esquerdo em diástole, e quantificação do aumento da espessura parietal (≈20mm); C - Reconstrução 3D VRT *volume-rendered* cardíaca demonstrando artérias coronárias sem estenoses.

Figur3 3 A: 3D VRT (volume rendering technique) reconstruction showing midventricular systolic collapse; B: multi-planar reconstruction (MPR): long and short axis views of left ventricle in diastole and quantification of increased wall thickness (≈20 mm); C: 3D VRT reconstruction showing coronary arteries with no stenosis.

CASE REPORT 2

A 42-year-old man, with no risk factors for CAD, had been diagnosed with paroxysmal atrial fibrillation (AF) ten years previously, transthoracic echocardiography showing no structural heart disease. He was referred for cardiac CTA (64-slice dual source system, SOMATOM Definition®, Siemens Medical Solutions) for evaluation prior to AF ablation. Mean heart rate during acquisition (8 seconds) was 77 bpm (Fig. 4). Cardiac CTA showed no

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aneurisma apical e presença de padrão apical de miocardiopatia hipertrófica (Fig. 5).

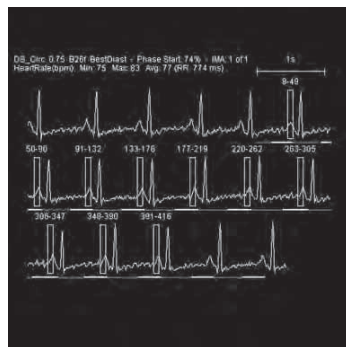


Figura 4 Traçado electrocardiográfico durante a aquisição do AngioTC cardíaco mostrando ritmo sinusal.

Figura 4 ECG trace during cardiac CT acquisition showing sinus rhythm.

Tratando-se de um doente que iria realizar ablação de fibrilhação auricular, o AngioTC cardíaco também excluiu a presença de trombo no apêndice auricular esquerdo, determinou o volume da aurícula esquerda, e definiu o padrão anatómico das veias pulmonares (Fig. 6).

DISCUSSÃO

Tal como mencionado, a MCH é uma perturbação genética complexa relativamente comum, afectando 1 em cada 500 adultos jovens.⁽²⁾ A primeira referência da forma moderna desta doença foi efectuada em 1958 por Teare, que descreveu a “hipertrofia cardíaca assimétrica” como responsável por morte súbita cardíaca em jovens.⁽⁷⁾

A transmissão da MCH é autossómica dominante, tendo sido identificados 13 genes potencialmente responsáveis, 11 dos quais codificando proteínas do sarcómero.^(3,8) As mutações predominantes envolvem genes codificadores da cadeia pesada beta da miosina, da proteína C de ligação à miosina e da troponina T cardíaca, estando presentes em mais de 50% dos doentes genotipados.⁽¹⁾

significant CAD, normal systolic function, a small apical aneurysm and apical HCM (Fig. 5).

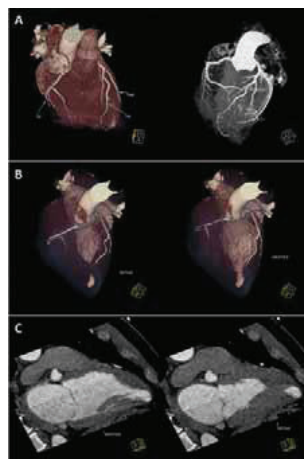


Figura 5 A - Reconstrução 3D VRT “volume-rendered” cardíaca (à esquerda) e coronariografia não invasiva (à direita) demonstrando artérias coronárias sem estenoses; B - Reconstrução 3D VRT “volume-rendered” cardíaca demonstrando colapso sistólico meso-ventricular e pequeno aneurisma apical; C - Reconstrução multiplanar (MPR): visualização em longo eixo do ventrículo esquerdo em diástole e sístole, demonstrando aumento da espessura parietal e pequeno aneurisma apical.

Figure 5 A: 3D VRT reconstruction (left) and non-invasive coronary angiography (right) showing coronary arteries with no stenosis; B: 3D VRT reconstruction showing midventricular systolic collapse and a small apical aneurysm; C: MPR: long axis view of left ventricle in diastole and systole, showing increased wall thickness and small apical aneurysm.

As the patient was to undergo AF ablation, cardiac CTA was also used to exclude the presence of thrombi in the left atrial appendage, to measure left atrial volume and to determine pulmonary vein anatomy (Fig. 6).

DISCUSSION

Hypertrophic cardiomyopathy is a relatively common complex genetic disease, affecting one in 500 young adults⁽²⁾. The first modern description of the disease was published in 1958 by Teare,

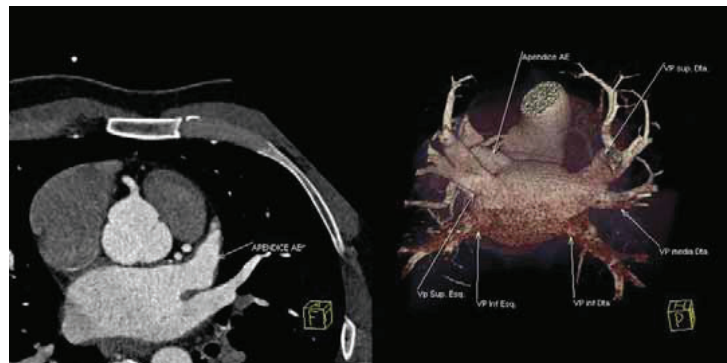


Figura 6. Esq.: Reconstrução multiplanar (MPR): visualização do apêndice auricular esquerdo preenchido por contraste, excluindo trombos no seu interior. Dta.: Reconstrução 3D VRT “volume-rendered” cardíaca demonstrando a anatomia das veias pulmonares.

Figure 6. Left: MPR: left atrial appendage filled with contrast, excluding thrombi; right: 3D VRT reconstruction showing pulmonary vein anatomy.

A expressão fenotípica da MCH é produto não só da mutação original, mas também da expressão de genes reguladores e de factores ambientais^(1,9). A genética da MCH foi alvo de uma revisão publicada recentemente.⁽¹⁰⁾

A MCH caracteriza-se e define-se pela presença de um ventrículo esquerdo hipertrofiado e não dilatado (habitualmente com colapso sistólico da sua cavidade), na ausência de causas sistémicas ou cardíacas que o justifiquem (Ex: hipertensão arterial, estenose valvular aórtica). A hipertrofia, habitualmente assimétrica, pode assumir qualquer padrão, desde atingir apenas um segmento (um terço dos doentes)⁽³⁾ a ser difusa, obstrutiva ou não obstrutiva.^(1-3,9, 11,12) A área mais frequentemente afectada pela hipertrofia é a porção anterior do septo interventricular.⁽⁴⁾

Apesar de a hipertrofia ventricular esquerda ser a expressão fenotípica da doença, não é necessária espessura mínima para se considerar que estamos na presença de MCH. De facto, é frequente crianças com menos de 13 anos serem portadoras silenciosas da doença, sendo a remodelagem com hipertrofia ventricular esquerda manifestada na adolescência, associada à fase de crescimento acelerada e maturação física, completando-se com o atingir da idade adulta, aos 17-18 anos.^(1,3) Após esta idade a progressão da hipertrofia é pouco frequente⁽¹³⁾, mas pode, contudo, surgir em idades mais avan-

who reported “asymmetrical hypertrophy of the heart” as the cause of sudden death in young adults⁽⁷⁾.

Transmission of HCM is autosomal dominant, and 13 genes have been identified as potentially responsible, 11 of which code for sarcomeric proteins^(3,8). The predominant mutations, involving genes encoding the beta-myosin heavy chain, myosin-binding protein C and cardiac troponin T, are found in over 50% of genotyped patients⁽¹⁾.

The phenotypic expression of HCM is the result not only of the original mutation, but also of the expression of regulatory genes and of environmental factors^(1,9). The genetic aspects of HCM have been the subject of a recent review⁽¹⁰⁾.

HCM is characterized by a hypertrophied, non-dilated left ventricle, usually with systolic chamber collapse, that is not due to any systemic or cardiac cause such as hypertension or aortic valve stenosis. The hypertrophy, which is usually asymmetrical, can take any form, involving a single segment (in a third of patients)⁽³⁾ or diffuse, and can be obstructive or non-obstructive^(1-3,9,11, 12). The most commonly affected area is the anterior portion of the ventricular septum⁽⁴⁾.

Although LV hypertrophy is the phenotypic expression of the disease, there is no minimum

çadas, havendo formas de doença com baixa penetrância até à quinta década de vida. Esta forma “tardia” de MCH é mais frequentemente causada por mutações no gene da proteína C de ligação à miosina^(8,14,15), da troponina T⁽¹⁶⁾ e da cadeia pesada alfa da miosina.⁽¹⁷⁾

Por ser de acesso fácil e não invasiva, a ecocardiografia é considerada o exame inicial de eleição, sendo o diagnóstico estabelecido pela demonstração de uma espessura parietal do ventrículo esquerdo, uni ou multissegmentar, de pelo menos 15 mm.^(1,2) Contudo, a ecocardiografia apresenta algumas limitações técnicas, por estar dependente de uma janela acústica adequada e por as imagens serem obtidas com obliquidade.⁽⁴⁾ Assim, em doentes com janela acústica insuficiente, ou quando a hipertrofia ventricular esquerda é segmentar e se limita a localizações pouco habituais dificultando a sua visualização por ecocardiograma (particularmente na parede antero-lateral ou ápex), a ressonância magnética pode representar uma modalidade diagnóstica adicional.^(1,3-5)

Nos últimos anos, a evolução da AngioTC cardíaca conduziu a melhorias na resolução espacial, temporal e de contraste, o que permite aquisição não invasiva de imagens tridimensionais com informação anatómica e funcional das artérias coronárias, câmaras cardíacas, miocárdio e pericárdio.⁽⁶⁾ Nos casos apresentados, mesmo tendo sido efectuados estudos ecocardiográficos prévios, o diagnóstico de MCH foi estabelecido por angioTC cardíaca, exame que permitiu quantificar a espessura parietal do ventrículo esquerdo correctamente.

No segundo caso apresentado, o doente era portador não diagnosticado de MCH apical. Nesta, a hipertrofia limita-se ao ápex do ventrículo esquerdo, sendo uma forma relativamente rara da doença^(12,18). Foi descrita pela primeira vez em 1976 no Japão, por Sakamoto.⁽¹⁹⁾ e é neste país que é mais frequente, representando 15-25% dos doentes com MCH.^(5,18-20)

A MCH apical está associada a algumas deficiências genéticas específicas (Ex: actina cardíaca Glu101Lys)⁽¹²⁾, não havendo associação com mutações da proteína C de ligação à miosina, uma das mais frequentes na MCH.⁽¹²⁾ Este fenotipo de MCH associa-se a uma deformação do ventrículo esquerdo classicamente referida como “em ás de espadas” e o electrocardiograma mostra ondas T marcadamente negativas nas

wall thickness required for a diagnosis of HCM. Children aged under 13 are often silent carriers, LV remodeling with hypertrophy not being manifested until adolescence, associated with accelerated growth and physical maturation, the process continuing until adulthood at age 17-18 years^(1,3). It is rare for hypertrophy to progress after this age⁽¹³⁾, but low penetrance forms of the disease can appear at older ages, up to the fifth decade of life. Late-onset HCM is mainly caused by myosin-binding protein C^(8,14,15), troponin T⁽¹⁶⁾ or alpha-myosin heavy chain gene mutations⁽¹⁷⁾.

Echocardiography, which is readily available and non-invasive, is considered the first-choice initial exam, diagnosis being based on LV wall thickness of at least 15 mm in one or more segments^(1,2). However, echocardiography has certain technical limitations since it is dependent on an adequate acoustic window and images are often obtained with obliquity⁽⁴⁾. In patients with poor acoustic windows, or when the hypertrophy is segmental or in an uncommon location that makes echographic visualization difficult (particularly the anterolateral wall or the apex), magnetic resonance imaging can be used as a complementary diagnostic technique^(1,3-5).

Developments in cardiac CTA technology in recent years have led to improved spatial and temporal resolution and contrast, which enables non-invasive acquisition of three-dimensional images with anatomical and functional information on the coronary arteries, cardiac chambers, myocardium and pericardium⁽⁶⁾. In the cases presented, even though previous echocardiographic studies had been performed, a definitive diagnosis of HCM was established by cardiac CTA, which accurately assessed LV wall thickness.

In the second case, the patient had undiagnosed apical HCM, in which hypertrophy is limited to the LV apex. This is a relatively rare form of the disease^(12,18), and was first described in 1976 by Sakamoto in Japan⁽¹⁹⁾, the country where it is most common, accounting for 15-25% of HCM patients^(5,18-20).

Apical HCM is associated with specific genetic defects, such as the cardiac actin Glu101Lys missense mutation⁽¹²⁾, and is not linked to mutations in the myosin-binding protein C gene, one of the commonest involved in HCM⁽¹²⁾. The apical HCM phenotype is associated with LV deformation traditionally

derivações precordiais.⁽¹¹⁾ Estas podem ser lábeis e mesmo desaparecer a longo termo.^(12,21,22)

Em países ocidentais a MCH apical é menos frequente (1-7% dos doentes com MCH) mas menos benigna.^(5,18-20) Pode originar manifestações (clínicas, electrocardiográficas, arritmogénicas, isquémicas e progressão morfológica) semelhantes à generalidade das MCH, sendo mais frequentes com a progressão da idade.^(18,22) Para além disso, esta forma apresenta risco adicional de enfarte e aneurisma apical.⁽⁶⁵⁾ O segundo caso apresentado corresponde a um doente com MCH apical e aneurisma do ápex, provavelmente consequente a necrose silenciosa prévia.

A isquémia miocárdica como manifestação da MCH, pode ser consequência de vários factores, além da aterosclerose coronária concomitante. Por um lado, a presença de microvasculatura anormal, consistindo em arteríolas coronárias intramurais com parede espessada (por hipertrofia da média), conduz a diminuição do lúmen coronário e capacidade vasodilatadora reduzida. Por outro lado, há desequilíbrio entre a massa ventricular esquerda aumentada e o fluxo coronário, com diminuição do fluxo de reserva e aumento da resistência vascular coronária devido a aumento da tensão parietal diastólica, secundária a perturbação do relaxamento e enchimento ventricular.^(1,18,23)

O “*bridging*” miocárdico, presente quando um segmento de uma coronária epicárdica *major* tem um percurso intramural, pode também ser responsável por isquémia na MCH. A frequência na população geral não está definitivamente estabelecida (1,5 a 16% por coronariografia)⁽²⁴⁾ mas é mais frequente em doentes com MCH (até 30%, também por coronariografia).⁽²⁵⁾ O diagnóstico é tradicionalmente estabelecido quando a compressão sistólica do segmento intramiocárdico é visualizado na coronariografia ou ultrassonografia intravascular.⁽²⁶⁾ A angioTC cardíaca oferece vantagens no diagnóstico pois, além de não ser invasiva, permite avaliação do segmento intramiocárdico tanto na sístole como na diástole (mesmo na ausência de compressão e diminuição do calibre do lúmen no momento da aquisição das imagens) e pode demonstrar a sua profundidade e comprimento.⁽²⁷⁾

A MCH tem um espectro clínico variável, desde formas assintomáticas até casos que evoluem com insuficiência cardíaca grave. No

referred to as an “ace of spades” configuration, and the electrocardiogram shows giant negative T waves in the precordial leads⁽¹¹⁾. These can be labile and may even disappear over time^(12,21,22).

Apical HCM is less common in western countries (1-7% of HCM patients) but is less benign^(5,18-20). Its manifestations (clinical, electrocardiographic, arrhythmogenic, ischemic and morphological) can be similar to most HCM cases, and are more frequent with advancing age^(18,22). Moreover, this form has an increased risk of infarction and apical aneurysm⁽⁶⁵⁾. The second case presented is of a patient with apical HCM and apical aneurysm, probably the result of previous silent necrosis.

Myocardial ischemia as a manifestation of HCM can be due to various factors, besides concomitant coronary atherosclerosis. The presence of abnormal microvasculature, with intramural coronary arterioles having thickened walls due to medial hypertrophy, leads to reduced lumen diameter and hence a decline in vasodilator capacity. At the same time, there is an imbalance between increased LV mass and coronary flow, with impaired flow reserve and raised coronary vascular resistance due to increased diastolic wall tension secondary to impaired ventricular relaxation and filling.^(1,18,23)

Myocardial bridging, in which a segment of a major epicardial coronary artery has an intramural course, can also be the cause of ischemia in HCM. Its prevalence in the general population has not been definitively established (1.5 to 16% by coronary angiography)⁽²⁴⁾, but it is more common in patients with HCM (up to 30% by angiography)⁽²⁵⁾. Diagnosis is traditionally made when systolic compression of the intramyocardial segment is detected on coronary angiography or intravascular ultrasound⁽²⁶⁾. Cardiac CTA has advantages for diagnosis since, besides being non-invasive, it can assess the intramyocardial segment in both systole and diastole (even in the absence of compression and reduction in lumen diameter at the time of image acquisition) and can determine its depth and length⁽²⁷⁾.

The clinical spectrum of HCM ranges from absence of symptoms to cases that evolve to severe heart failure. However, the most devastating aspect of its natural history is its association with sudden cardiac death in young adults, including trained athletes, with an annual mortality rate of 1-1.4%^(1,3,18).

entanto, o componente mais devastador da sua história natural é a possibilidade de originar morte súbita e inesperada em indivíduos jovens, incluindo atletas treinados, tendo uma taxa de mortalidade anual de 1-1.4%.^(1,3,18)

A implantação de CDI como prevenção de arritmias malignas em doentes com MCH deve ser considerada quando está presente pelo menos um dos seguintes factores de risco: paragem cardíaca prévia, TV espontânea (mantida ou não mantida), história familiar de morte súbita, síncope inexplicada, espessura da parede ventricular esquerda ≥ 30 mm e evolução anormal da pressão arterial na prova de esforço (indicação classe IIa, nível de evidência C). Esta é uma população de alto risco, onde a mortalidade anual pode chegar aos 6%⁽²⁸⁾. No primeiro caso apresentado, a demonstração da presença de MCH em doente com história de síncope que colocou a indicação para a implantação de um CDI.

CONCLUSÃO

Nos casos apresentados a AngioTC cardíaca permitiu uma delineação adequada da espessura miocárdica em todos os segmentos do ventrículo esquerdo, bem como avaliação das cavidades cardíacas. Isto permitiu estabelecer o diagnóstico de MCH, num doente como achado e noutro confirmando a suspeita estabelecida por ecocardiograma. Para além disso, por ter permitido uma coronariografia não invasiva, pôde-se excluir doença coronária significativa, principal indicação para este exame.⁽²⁹⁾

Assim, a AngioTC pode ter um papel determinante no diagnóstico de MCH em casos de localizações atípicas da hipertrofia, como localizações apicais. Permite uma avaliação coronária não invasiva, útil como diagnóstico diferencial e na avaliação pré-operatória nos doentes com indicação cirúrgica. Finalmente, a miocardiopatia hipertrófica pode ser um achado em doentes que efectuem AngioTC cardíaca por outros motivos, podendo determinar alterações de terapêuticas e / ou de seguimento.

Implantation of an ICD as a preventive measure against malignant arrhythmias should be considered in HCM patients with any of the following risk factors: previous cardiac arrest, spontaneous ventricular tachycardia (sustained or non-sustained), family history of sudden death, unexplained syncope, LV wall thickness ≥ 30 mm, or abnormal blood pressure changes during exercise testing (class IIa recommendation, level of evidence C). Annual mortality in this high-risk population can reach 6%⁽²⁸⁾. In the first case presented, evidence of HCM in a patient with a history of syncope constituted an indication for ICD implantation.

CONCLUSION

In the cases presented, cardiac CTA was able to determine myocardial thickness in all LV segments, as well as assessing the cardiac chambers. This led to detection of HCM in one patient and confirmation of suspected HCM based on echocardiography in the other. In addition, as a form of non-invasive coronary angiography, it also excluded the presence of significant CAD, the main indication for this type of exam⁽²⁹⁾.

Computed tomography angiography can thus make an important contribution in the diagnosis of atypical forms of HCM, such as apical hypertrophy. It enables non-invasive assessment of the coronary arteries, which is useful for differential diagnosis and pre-operative evaluation in patients with indication for surgery. Finally, cardiac CTA performed for other reasons may detect hypertrophic cardiomyopathy, and thus lead to modification of therapy and/or follow-up.

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Images in Congenital Cardiac Disease

Anomalous origin of the right coronary artery from the pulmonary artery

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Keywords: Cardiac imaging; congenital cardiac disease; right coronary artery

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Case report

A 57-YEAR-OLD WOMAN PRESENTED WITH ATYPICAL complaints of fatigue. Her past medical history and physical examination were unremarkable. Electrocardiogram and echocardiogram were normal.

Treadmill exercise testing was positive for ischaemia and myocardial perfusion scan was suggestive of mild anterior wall ischaemia, more pronounced in the apical segment. Cardiac catheterisation revealed a preserved ejection fraction (70%), no abnormal wall kinetics and no significant lesions in the left main, left descendant, and circumflex arteries. The right coronary artery was not catheterised, but contrast medium injection in the left main artery filled the right coronary artery retrogradely into (apparently) the left coronary sinus.

Computed tomographic coronary angiography was performed with a 64-slice scanner and the intravenous contrast medium injection showed the right coronary artery arising from the pulmonary trunk and being filled retrogradely from the left coronary circulation – no significant atherosclerotic lesions were identified (Fig 1). With a heart rate of 83 beats per minute and the use of electrocardiographic pulsing and 100 kilovolts, it was possible to perform low-radiation dose cardiac computed tomography at 4,1 milisievert.

A stress echocardiogram with dobutamine and atropine was negative for ischaemia.

The patient has been asymptomatic and is under beta-blocker; the decision not to intervene surgically was taken as no ischaemia from the right coronary artery territory is demonstrable.

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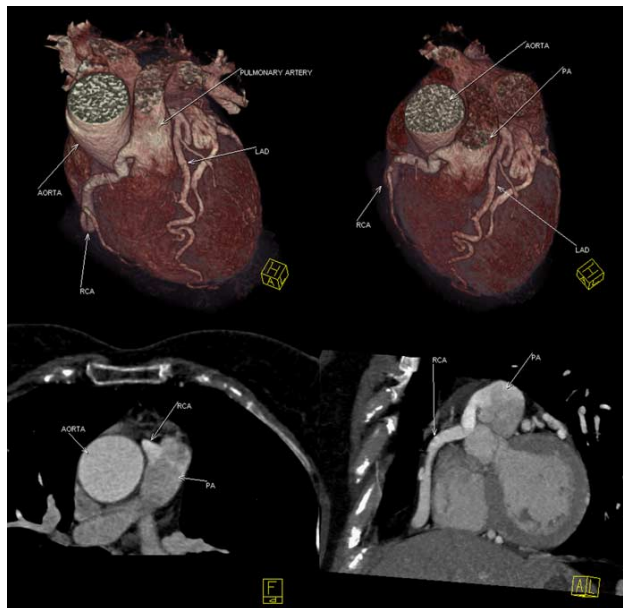


Figure 1.

The top two images represent volume-rendering technique reconstructions and the bottom two images are maximum intensity projection – the right coronary artery can be seen arising from the pulmonary trunk.

ARTIGO 8/ MANUSCRIPT 8:

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CASE REPORT

Anomalous origin of left coronary artery: A malignant interarterial variant with a benign clinical course[☆]

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KEYWORDS

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PALAVRAS-CHAVE

Origem anómala das
coronárias;
AngioTC cardíaca;
Morte súbita

Abstract Anomalous origin of coronary arteries represents a clinical challenge because of the anatomical variability and possible functional consequences, the pathophysiological mechanisms involved, and the lack of large published series that would provide evidence to guide the clinical and therapeutic approach. The authors describe the case of a 55-year-old male patient with a long history of atypical chest pain who was considered to have a low to intermediate likelihood of coronary artery disease. Therefore, and also bearing in mind his physical limitations (congenital left leg atrophy), he was referred for cardiac CT to rule out coronary artery disease. The exam showed a left coronary artery arising from the right coronary cusp and with an interarterial course, between the aorta and pulmonary trunk. Although this is a potentially malignant anatomical variant with surgical indication, a conservative approach was chosen, considering the late diagnosis and particular risk-benefit profile.

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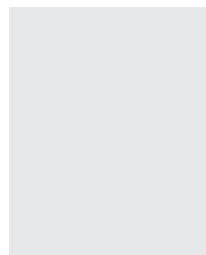
Origem anómala da coronária esquerda: variante interarterial maligna com evolução clínica benigna

Resumo A origem anómala das artérias coronárias constitui um importante desafio clínico pela variabilidade anatómica, possíveis repercussões funcionais, mecanismos fisiopatológicos implicados e também pela ausência de grandes séries na literatura que forneçam sólida evidência científica para a sua orientação clínica e terapêutica.

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Os autores descrevem o caso de um doente de 55 anos, com antecedentes de hipertensão, dislipidemia e atrofia congénita da perna esquerda, que se apresentou com quadro de dor retroesternal atípica com um ano de evolução. Tendo em conta os fatores de risco cardiovasculares e exames complementares de diagnóstico previamente realizados, considerou-se ser um doente com probabilidade baixa a intermédia de doença coronária. Assim, e pela sua limitação funcional, realizou angioTC cardíaca que revelou uma origem anómala da coronária esquerda na cúspide coronária direita e com trajeto entre a aorta e a artéria pulmonar. Embora esta seja uma variante anatómica com potencial evolução maligna, optou-se por uma atitude conservadora após ponderação do risco-benefício no contexto clínico deste doente.

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Introduction

Coronary artery anomalies are the third leading cause of sudden death in young athletes¹; their incidence in healthy individuals is estimated at 0.3–1%.²

Various different anomalies have been described, and classifications have been proposed based on anatomy (anomalies of origin, course and termination) and on prognosis (with or without clinical significance).² With regard to the latter, most anomalies have no clinical significance and thus require no specific treatment.³

However, congenital coronary artery fistulas, myocardial bridging and anomalous origin in the pulmonary artery can be associated with malignant evolution.

Another potentially serious anomaly is origin of a coronary artery from the contralateral coronary sinus, which can lead to myocardial ischemia and sudden death when it courses between the aorta and pulmonary artery (interarterial course). Other courses—retroaortic, prepulmonary and subpulmonary, and septal—are considered benign.^{4,5}

Origin of the left coronary artery in the right sinus of Valsalva is rare, with an estimated incidence of 0.09–0.11% in patients undergoing coronary angiography,⁶ but it is frequently associated with sudden cardiac death during intense physical activity and in adolescents and young adults, half of whom were previously asymptomatic.^{7,8} An interarterial course is seen in most of these patients⁹; their poor prognosis may be due to the acute angle of the artery from the ostium, stretching of the intramural segment, or compression between the commissure of the right and left coronary cusps.⁵

Cardiac CT angiography is a recent and valuable complementary exam that has high spatial resolution and provides three-dimensional views of the coronary arteries, with better definition of their origin and proximal portion, course, and relations with other cardiac structures than conventional angiography.¹⁰ The increasing popularity of this technique has greatly improved detection of coronary artery anomalies, which has made clinical decision-making more difficult, since there is, and is unlikely to be, sufficient evidence on which to base therapeutic strategies in doubtful cases as the one presented.

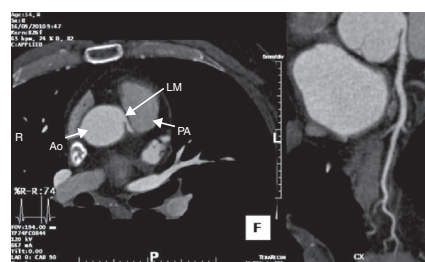


Figure 1 Multiplanar reconstruction. Ao: aorta; PA: pulmonary artery; LM: left main.

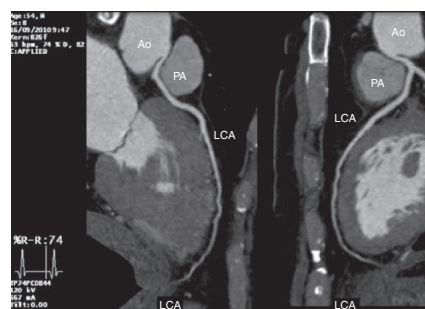


Figure 2 Multiplanar reconstruction. Ao: aorta; PA: pulmonary artery; LCA: left coronary artery.

Case report

A 54-year-old male patient was assessed in the cardiology outpatient clinic for atypical chest pain of about one year's evolution. He reported no other relevant cardiovascular symptoms, including fatigue, dyspnea, palpitations or syncope.

His cardiovascular risk factors included hypertension and dyslipidemia; he also had congenital left leg atrophy. He was

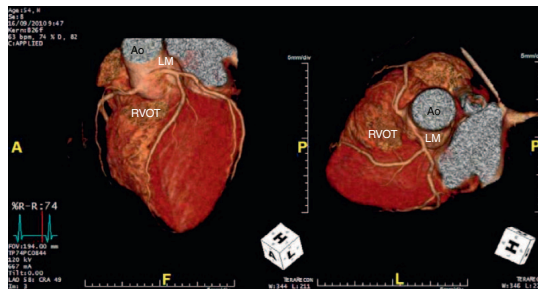


Figure 3 Volume-rendering technique. Ao: aorta; RVOT: right ventricular outflow tract; LM: left main.

medicated with simvastatin, propranolol, candesartan and aspirin.

The electrocardiogram showed sinus rhythm with incomplete right bundle branch block but no other significant alterations. He had undergone myocardial perfusion scintigraphy with adenosine a year before, which was negative for ischemia.

To clarify the clinical picture and since he was considered to have a low to intermediate likelihood of coronary artery disease, and also bearing in mind his physical limitations, he was referred for cardiac CT to rule out coronary artery disease. The exam showed a left coronary artery arising from the right coronary cusp and with an interarterial course, between the aorta and pulmonary trunk (Figures 1–3). No coronary plaque was detected and his calcium score was 0.

Given the clinical context of his age (54 years) and absence of typical angina or syncope, it was decided to perform ischemia testing. Although imaging exams such as dobutamine stress echocardiography, myocardial perfusion scintigraphy and magnetic resonance imaging have higher sensitivity and specificity for ischemia testing, treadmill exercise testing was chosen in order to determine the patient's actual maximum functional capacity. Beta-blocker therapy was suspended for the test.

The patient achieved maximal exercise (3 min 12 s with the Bruce protocol), reaching the maximum predicted heart rate with no angina or ST-segment alterations suggestive of ischemia, and with no arrhythmias. In the light of this result, it was decided to keep the patient under clinical surveillance with no referral for cardiac surgery.

However, this case had some unusual aspects: the patient was older than the age-group most affected; he had no symptoms that were unequivocally associated with anomalous origin of the coronary arteries, particularly typical exertional angina or history of syncope; and no ischemia was documented on exercise testing, in which the patient achieved the limit of his functional capacity (maximum predicted heart rate) without the effect of beta-blockers. The patient's congenital left leg atrophy may paradoxically have had a protective effect by preventing him from performing strenuous exercise, which can trigger malignant arrhythmias in this situation.

Therefore, considering all factors, it was decided that the risk-benefit ratio favored a conservative approach.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Discussion

Although there is still disagreement on the subject, some guidelines recommend surgical coronary revascularization in patients with anomalous left coronary artery arising from the right sinus of Valsalva and coursing between the aorta and pulmonary artery (class I recommendation, level of evidence B in the ACC/AHA guidelines for the management of adults with congenital heart disease).¹¹ When the right coronary has an anomalous origin, ischemia testing is recommended before referral for surgical correction (class I recommendation, level of evidence B).

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CASE REPORT

**Marfan syndrome with ascending aortic aneurysm:
Value of cardiac computed tomography**

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KEYWORDS

Cardiac CT;
Marfan syndrome;
Aortic aneurysm

Abstract We report the case of a 40-year-old man with known Marfan syndrome who presented with severe aortic valve regurgitation secondary to significant aortic root dilatation. To rule out coronary artery disease and to evaluate the rest of the thoracic aorta before surgery, cardiac computed tomography (CT) was performed. A brief review of the literature shows how cardiac CT can, in selected cases, rule out coronary artery disease before non-coronary cardiothoracic surgery.

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PALAVRAS-CHAVE

AngioTC cardíaca;
Síndrome de Marfan;
Aneurisma da aorta

Síndrome de Marfan com aneurisma da aorta ascendente – importância da angioTC cardíaca

Resumo Descrevemos o caso de um doente de 40 anos de idade com Síndrome de Marfan, que apresenta regurgitação valvular aórtica grave, secundária a dilatação severa da raiz aórtica. Para excluir a presença de doença coronária e estudar os restantes segmentos aórticos antes da cirurgia, foi realizada uma angioTC cardíaca. Uma breve revisão da literatura demonstra como, em determinados contextos, a angioTC cardíaca pode ter vantagens na exclusão de doença coronária antes de cirurgia cardio-torácica não coronária.

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Case report

We report the case of a 40-year-old man with no known cardiovascular risk factors who was diagnosed with Marfan syndrome at the age of 32. His medical history included gastroesophageal reflux syndrome and previous ophthalmic surgery for lens dislocation and orthopedic surgery on the tibial-tarsal joints. He was being medicated with bisoprolol and pantoprazole.

For the previous six months he had presented worsening exercise dyspnea and had marked limitation in activity due to symptoms (NYHA class II–III).

The echocardiogram showed severe aortic valve regurgitation secondary to significant aortic root dilatation (64 mm diameter at the Valsalva sinus) and left ventricular dilatation, but with normal systolic function.

To exclude coronary artery disease and simultaneously to evaluate the rest of the thoracic aorta, cardiac computed tomography (CT) was performed (including the thoracic aorta). This exam ruled out coronary artery disease (Figure 1) and confirmed the presence of significant aortic root dilatation (70 mm), the rest of the aorta being normal (Figure 2).

The patient was referred for surgery, with no need for invasive catheterization. He underwent a Bentall procedure with implantation of an aortic conduit and a prosthetic aortic valve (29 mm St. Jude). There were no complications after surgery, the echocardiogram showing the prosthetic aortic valve with normal motion and the conduit functioning correctly. The patient was discharged six days later and warfarin was added to his medication.

At 6-month follow-up the patient was asymptomatic and free from cardiovascular events.

Discussion

Marfan syndrome is the most common inherited multi-systemic disorder of connective tissue, with a reported incidence of 2-3 per 10 000 population, without gender, racial, or ethnic predilection.¹ Its cardiovascular features were first outlined by McKusick in 1955²; according to the current diagnostic criteria major cardiovascular manifestations include dilatation of the ascending aorta, with or without dissection.³

In the presence of ascending aorta dilatation, prophylactic surgery is recommended when the diameter of the ascending aorta at the aortic sinuses reaches 4.5 cm, or in some cases even less (when there is a family history of aortic dissection, in the presence of rapid aortic dilatation or severe aortic valve regurgitation, or when a valve-sparing operation is possible).^{1,4}

In the case reported, the presence of severe aortic root dilatation (>60 mm) with associated aortic valve regurgitation was a clear indication for surgery.

Although the patient had no angina, obstructive coronary artery disease was ruled out prior to aortic surgery. This evaluation should be performed in asymptomatic male patients over the age of 40 or postmenopausal women, and is also indicated for patients with previous coronary artery disease, symptoms of left ventricular dysfunction, presumed ischemic mitral regurgitation or one or more cardiovascular risk factor.⁴

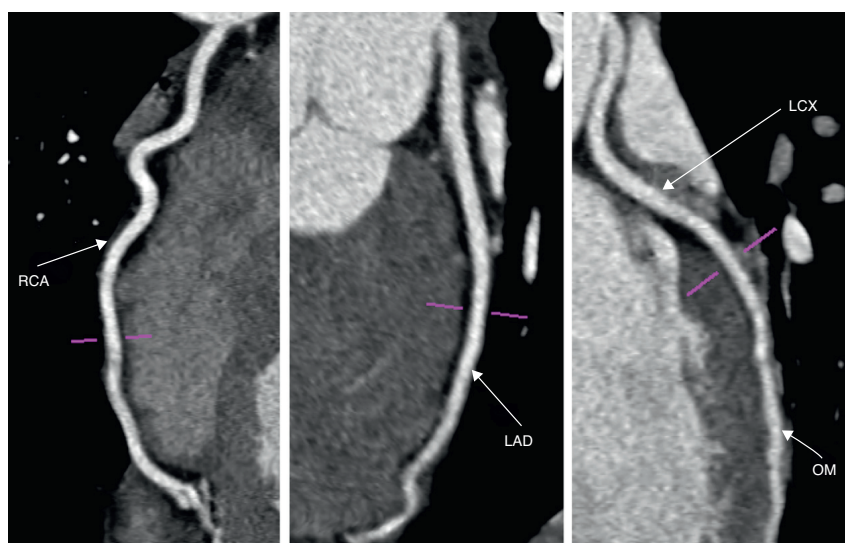


Figure 1 Cardiac computed tomography: multiplanar reconstructions ruling out significant coronary artery disease. LAD: left anterior descending artery; LCX: left circumflex artery; OM: obtuse marginal artery; RCA: right coronary artery.

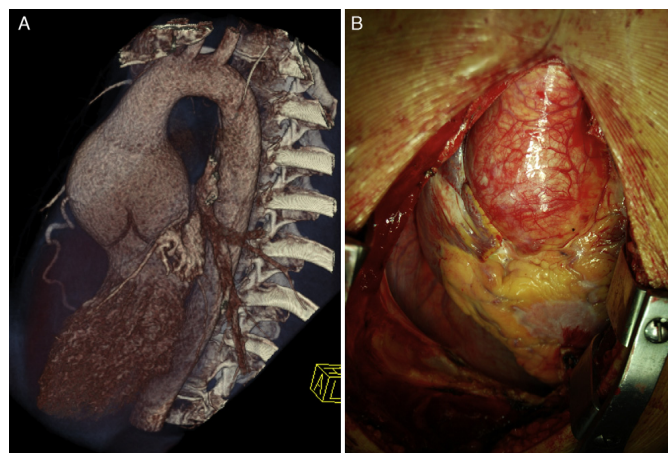


Figure 2 Aortic root dilatation seen in cardiac computed tomography volume-rendered image (A) and in intraoperative photograph (B).

Traditionally, the study of coronary artery anatomy is performed through invasive angiography. However, this can also be safely done with cardiac CT^{5,6} taking advantage of the high negative predictive value of this exam⁶; this is one indication for which cardiac CT can replace invasive angiography.⁷

This approach can be applied to a high percentage of patients when study of coronary artery anatomy is indicated prior to valvular or aortic surgery, as it is more convenient and less invasive than invasive coronary angiography. Furthermore, some patient subsets may derive greater benefit from this approach, when there is higher iatrogenic potential (such as in the presence of aortic dissection or aortic valve thrombus/vegetations) or when coronary catheterization would be difficult (such as in the presence of aortic root dilatation or anomalous coronary artery origin). In these cases, cardiac CT, avoiding the need for potential prolonged invasive cardiac catheterization, reduces not only radiation and contrast doses, but also the risk of complications. Among the latter, aortic dissection has been described as a rare (0.04%) but serious complication of cardiac catheterization and was found to be associated with the use of non-conventional catheters.⁸

The risk of contrast-induced nephropathy should be weighed when coronary angiography is considered. Since there are no differences in the contrast dose used in coronary angiography performed invasively or by cardiac CT,⁹ this risk should be similar with both techniques.

In the case reported, there were two risk factors for complications with invasive coronary angiography: the presence of aortic root dilatation and severe aortic valve regurgitation. This favored the choice of cardiac CT to study the cardiac anatomy, which was safe, ruled out coronary artery disease and simultaneously provided detailed anatomy of the thoracic aorta.

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 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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ORIGINAL ARTICLE

Diagnostic yield of current referral strategies for elective coronary angiography in suspected coronary artery disease—An analysis of the ACROSS registry

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KEYWORDS

Coronary angiography;
Chest pain/diagnosis;
Stable angina;
Myocardial ischemia

Abstract

Introduction and Objectives: The purpose of this study was to assess the diagnostic yield of current referral strategies for elective invasive coronary angiography (ICA).

Methods: We performed a cross-sectional observational study of consecutive patients without known coronary artery disease (CAD) undergoing elective ICA due to chest pain symptoms. The proportion of patients with obstructive CAD (defined as the presence of at least one $\geq 50\%$ stenosis on ICA) was determined according to the use of noninvasive testing.

Results: The study population consisted of 1892 individuals (60% male, mean age 64 ± 11 years), of whom 1548 (82%) had a positive noninvasive test: exercise stress test (41%), stress myocardial perfusion imaging (36%), stress echocardiogram (3%) or coronary computed tomography angiography (3%). Referral without testing occurred in 18% of patients. The overall prevalence of obstructive CAD was 57%, higher among those with previous testing (58% vs. 51% without previous testing, $p=0.026$) and when anatomic rather than functional tests were used (81.3% vs. 57.1%, $p=0.001$). A positive test and conventional risk factors were all independent predictors of obstructive CAD, with adjusted odds ratios (95% confidence interval) of 1.34 (1.03–1.74) for non-invasive testing, 1.05 (1.04–1.06) for age, 3.48 (2.81–4.29) for male gender, 1.86 (1.32–2.62) for current smoking, 1.74 (1.38–2.20) for diabetes, 1.30 (1.04–1.62) for hypercholesterolemia, and 1.39 (1.08–1.80) for hypertension.

Conclusions: More than 40% of patients without known CAD undergoing elective ICA did not have obstructive lesions, even though four out of five had a positive noninvasive test. These exams were relatively weak gatekeepers; functional tests were more often used but appeared to be outperformed by the anatomic test.

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PALAVRAS-CHAVE

Angiografia coronária;
Dor
torácica/diagnóstico;
Angina estável;
Isquemia miocárdica

Rendimento das atuais estratégias de referência para coronariografia eletiva por suspeita de doença coronária—análise do registo ACROSS

Resumo

Introdução e objetivos: O objetivo do estudo foi avaliar o rendimento das atuais estratégias de referência eletiva para coronariografia invasiva.

Métodos: Estudo transversal de indivíduos consecutivos sem doença coronária conhecida submetidos a coronariografia por dor torácica. Determinação da prevalência de doença coronária obstrutiva (definida pela presença de pelo menos uma estenose $\geq 50\%$) de acordo com a utilização de testes não-invasivos para despiste de cardiopatia isquêmica.

Resultados: Foram avaliados 1892 indivíduos (60% homens, idade média 64 ± 11 anos), dos quais 1548 (82%) tinham um teste não-invasivo positivo: prova de esforço (41%), cintigrafia de perfusão miocárdica (36%), ecocardiograma de stress (3%) e angiografia coronária por tomografia computadorizada (3%). Ocorreu referência sem teste prévio em 18% dos doentes. A prevalência global de doença obstrutiva foi 57%, sendo mais elevada nos doentes submetidos a testes não-invasivos (58% versus 51% nos doentes sem testes prévios, $p = 0,026$) e naqueles em que o teste era anatómico versus funcional (81,3% versus 57,1%, $p = 0,001$). Um teste não-invasivo positivo e fatores de risco convencionais foram preditores independentes de doença obstrutiva, com *odds-ratio* ajustado (intervalo confiança 95%) de: teste não-invasivo 1,34 (1,03-1,74), idade 1,05 (1,04-1,06), sexo masculino 3,48 (2,81-4,29), tabagismo ativo 1,86 (1,32-2,62), diabetes 1,74 (1,38-2,20), hipercolesterolemia 1,30 (1,04-1,62) e hipertensão 1,39 (1,08-1,80).

Conclusões: Mais de 40% dos doentes sem doença coronária conhecida que realizam coronariografia eletiva não têm doença obstrutiva, apesar de quatro em cada cinco ter um teste não-invasivo positivo. Estes testes são *gatekeepers* relativamente fracos; os funcionais foram utilizados mais frequentemente mas o anatómico pareceu ter melhor desempenho.

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List of abbreviations

CAD	coronary artery disease
CCTA	coronary computed tomography angiography
ECG	electrocardiogram
ICA	invasive coronary angiography
SPECT	single-photon emission computed tomography

Methods

Population

This was an observational, cross-sectional study performed at a single hospital center serving an urban population of 900 000 inhabitants in Lisbon, Portugal. The study population consisted of all patients referred for elective ICA for evaluation of chest pain symptoms between January 2006 and November 2010. Patients' referral for ICA and the decision to perform previous noninvasive testing, including the testing modality, were left to the discretion of attending physicians. Noninvasive testing was performed mostly at private practice facilities.

The modalities of noninvasive testing were exercise electrocardiogram (ECG) stress testing, stress myocardial single-photon emission computed tomography (SPECT), stress echocardiography and coronary computed tomography angiography (CCTA). 'Ischemic changes' on the resting ECG were not considered noninvasive testing. The following exclusion criteria were applied sequentially: non-elective setting (acute coronary syndrome), previously known CAD (defined as previous acute coronary syndrome, revascularization procedure or documented coronary stenosis $\geq 50\%$ on previous ICA), preoperative evaluation, presenting symptom other than chest pain, negative noninvasive test result and incomplete information on patients' clinical characteristics or ICA result.

Introduction

The evaluation of patients with suspected coronary artery disease (CAD) is based on clinical assessment, often supplemented by noninvasive tests which serve as gatekeepers for invasive coronary angiography (ICA).¹⁻³ ICA is the diagnostic gold standard for CAD but is costly, has limited availability and carries a risk of complications related to its invasive nature.⁴ The aims of performing noninvasive testing in this setting include minimizing unnecessary risks and costs, and identifying patients who will benefit from revascularization. However, despite the frequent use of noninvasive testing, a significant proportion of patients undergoing ICA do not have obstructive CAD or are not eligible for revascularization.^{5,6} The purpose of this study was to assess current patterns of noninvasive testing and to appraise their diagnostic yield among symptomatic patients undergoing ICA for suspected CAD.

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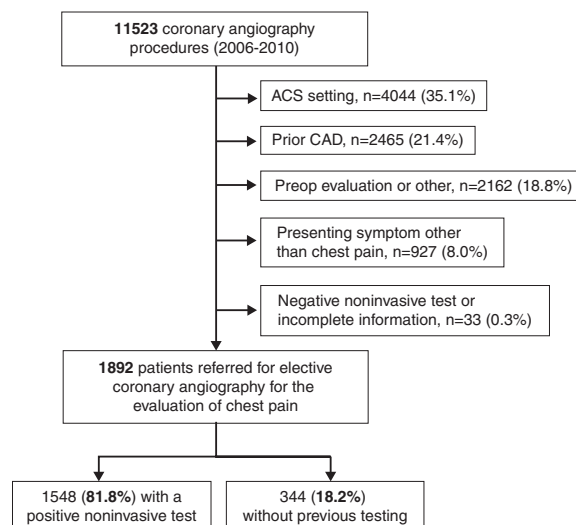


Figure 1 Selection of the study population. ACS: acute coronary syndrome; CAD: coronary artery disease; preop: preoperative.

Patient evaluation

Data on demographic characteristics, cardiovascular risk factors, type of noninvasive testing and results of coronary angiography were prospectively collected in the ongoing ACROSS (Angiography and Coronary Revascularization On Santa cruz hoSpital) registry, approved by the local ethics committee. The diagnoses of hypertension, hypercholesterolemia and diabetes (regardless of type, duration or current treatment) were assigned if indicated in the patients' referral letter or if the patient was being treated with anti-hypertensive or lipid-lowering drugs, oral antidiabetics or insulin. To avoid underdiagnosis, obstructive coronary was defined as a $\geq 50\%$ reduction in vessel diameter as compared to a nondiseased proximal segment. This broad definition of obstructive CAD was not used as a criterion for revascularization.

Statistical analysis

Data are presented as counts (%), medians (interquartile range) or means $\pm$ standard deviation. Categorical variables were compared using Fisher's exact test. Continuous variables were compared by means of the t test. Patients with and without obstructive CAD were compared for differences in age, gender, body mass index, prevalence of cardiovascular risk factors and use of noninvasive testing. Variables that showed significant association with obstructive CAD ($p < 0.10$) in univariate analysis were included in a binary logistic regression model to identify independent predictors. Temporal differences during the study period in the prevalence of obstructive CAD and the use of noninvasive

testing were assessed using the chi-square test for trend. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using the statistical package SPSS® version 17.0 (SPSS, Inc., Chicago, IL).

Results

During the study period, 11 523 patients underwent ICA at our hospital. After the exclusion criteria were applied (Figure 1), 1892 patients were included in the analysis.

Most patients (81.8%, $n=1548$) were referred after a positive noninvasive test. On ICA, the overall prevalence of obstructive CAD was 56.7% (1072/1892). One-vessel, two-vessel or three-vessel/left main disease were identified in 21.1% ($n=398$), 17.1% ($n=323$) and 18.6% ($n=351$) of patients, respectively. The prevalence of obstructive CAD was lower in patients referred without previous noninvasive testing than in those with a positive test (51.2% vs. 57.9%, $p=0.026$). Myocardial revascularization (percutaneous coronary intervention or referral for coronary artery bypass grafting) was performed in 46.7% ($n=883$) of patients.

Increasing age, male gender, traditional cardiovascular risk factors and positive noninvasive testing were predictors of obstructive CAD in univariate and multivariate analysis (Table 1).

There were no significant temporal differences in the prevalence of obstructive CAD during the study period, despite a significant increase in the proportion of patients undergoing noninvasive testing (Figure 2). Exercise stress testing and stress SPECT were the most used tests,

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Table 1 Population characteristics.

	Total	Univariate analysis			Multivariate analysis		
		Obstructive CAD (n=1072)	No obstructive CAD (n=820)	p	Adjusted odds ratio	95% CI	p
Age, years	64±11	65.7±10.4	61.7±11.0	<0.001	1.05	1.04–1.06	<0.001
Male, n (%)	1141 (60.3%)	769 (71.7%)	372 (45.4%)	<0.001	3.48	2.81–4.29	<0.001
Body mass index, kg/m ²	28.0±3.9	27.6±3.9	28.0±4.5	0.030	0.98	0.96–1.01	0.240
Cardiovascular risk factors, %							
Hypertension	78.4%	81.3%	74.6%	<0.001	1.39	1.08–1.80	0.011
Diabetes	27.5%	32.5%	21.1%	<0.001	1.74	1.38–2.20	<0.001
Smoking	11.4%	13.2%	8.9%	0.003	1.86	1.32–2.62	<0.001
Hypercholesterolemia	69.2%	71.9%	65.7%	0.004	1.30	1.04–1.62	0.019
Previous positive noninvasive testing	81.8%	83.6%	79.5%	0.026	1.34	1.03–1.74	0.028

CAD: coronary artery disease; CI: confidence interval.

accounting for more than 90% of noninvasive testing. CCTA use increased significantly from 2006 to 2010.

The rates of obstructive coronary artery disease and myocardial revascularization according to type of noninvasive testing are presented in Figure 3. Comparing functional and anatomic tests, the prevalence of obstructive CAD (57.1% vs. 81.3%, $p=0.001$) was higher in the latter group.

Discussion

Diagnostic yield of the current referral strategy

In our European, urban clinical setting, less than 57% of patients referred for elective ICA for evaluation of chest pain symptoms had obstructive lesions (defined by a broad criterion of $\geq 50\%$ luminal stenosis), despite the fact that four out of five patients had undergone previous testing. Noninvasive testing was frequently used but was only a weak independent predictor of obstructive CAD (OR 1.34, $p=0.028$). This apparently low performance of noninvasive

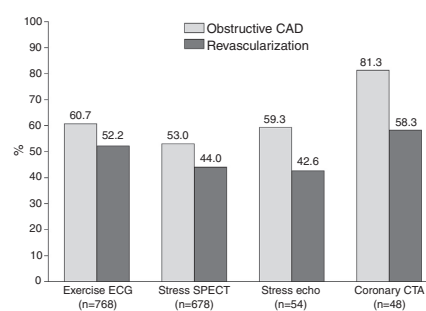


Figure 3 Rate of obstructive coronary artery disease and myocardial revascularization according to type of noninvasive testing. CAD: coronary artery disease; CTA: computed tomography angiography; ECG: electrocardiogram; Echo: echocardiogram; SPECT: single-photon emission computed tomography.

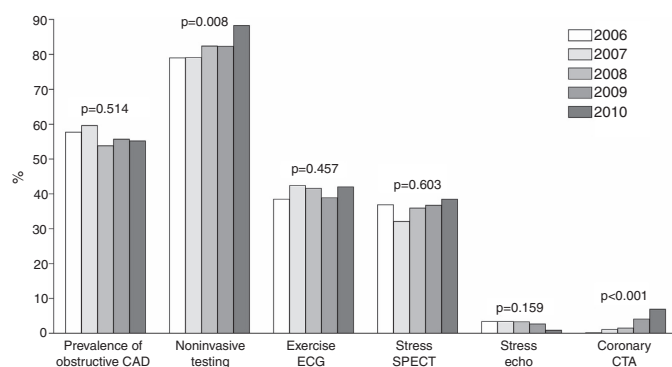


Figure 2 Trends of noninvasive testing between 2006 and 2010. CAD: coronary artery disease; CTA: computed tomography angiography; ECG: electrocardiogram; Echo: echocardiogram; SPECT: single-photon emission computed tomography.

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tests as gatekeepers for ICA has several possible explanations. One is that the performance of these tests in the “real world” is worse than that reported in the literature from large experienced centers. Another explanation would be a low pretest probability of obstructive CAD in this population, resulting in a relatively large absolute number of patients without obstructive disease undergoing ICA.⁷ A third hypothesis, supported by increasing evidence,^{6,8} is that the pretest likelihood of angiographically significant CAD may be overestimated when calculated on the basis of age, gender and chest pain characteristics in accordance with the seminal work of Diamond, Forrester and Pryor.^{9,10}

The yield of any diagnostic test depends on the pretest likelihood of the patients in whom it is used and on the way the test modifies that probability. Ideally, a positive noninvasive test should increase the probability of obstructive disease to a level that justifies performing ICA, and a negative test should reduce that likelihood to a level at which obstructive CAD can be safely ruled out. While ICA will always be performed on some patients without coronary lesions, the 2011 standards for catheterization laboratory accreditation from the Accreditation for Cardiovascular Excellence organization suggest that the incidence of non-obstructive disease in elective patients should be <40%. In the interests of individual patients and of overall healthcare cost-effectiveness, extreme rates are undesirable. Recently, Genders et al.⁶ reported a rate of obstructive CAD of 58% (ranging from 39.4% to 75.5%) in a multicenter study involving 11 European hospitals. In the USA, Patel et al.⁵ reported an overall rate of 41% of patients with obstructive CAD in the National Cardiovascular Data Registry, although this varied significantly between different centers, from 23 to 100%.¹¹ Taken together, these studies suggest that better gatekeepers are needed. Our findings are in line with both these studies, underlining the relatively low prevalence of obstructive CAD on ICA in a population with a high frequency of noninvasive testing.

We were also able to assess differences between non-invasive tests. It should be noted that our findings are mainly the result of using functional tests, particularly exercise ECG and stress SPECT, which accounted for more than 90% of testing, as gatekeepers for ICA. Although the proportion of obstructive CAD was higher in the CCTA group than for functional tests, it is uncertain whether the overall results would have been different if anatomic tests had been used more frequently. There is some evidence that CCTA may be a useful and cost-effective gatekeeper for ICA (particularly in patients with intermediate to low pretest probability), reducing the number of patients without obstructive CAD referred for invasive testing.^{12–19} Recent guidelines for the management of patients with chest pain from the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) recommend choosing tests according to the pretest probability of CAD. Functional imaging tests are preferred for patients with 30–60% pretest probability of disease, whereas CCTA (preceded by calcium score) is the preferred method for patients with 10–29% pretest probability.²⁰ According to these guidelines, ICA should be offered as the first test to patients with pretest probabilities over 60%. Currently, there is disagreement over which type of test should be used as first line.²¹ Results from the US

National Institutes of Health-sponsored PROMISE study (a clinical endpoint-driven randomized study comparing functional studies with CCTA for the evaluation of patients with suspected CAD) will hopefully shed more light on this matter.^{22,23}

Study limitations

Several limitations of this study should be acknowledged. Since the characteristics of chest pain were not systematically assessed and recorded for each patient, it was not possible to calculate the pretest probability of CAD. Although the median age and prevalence of risk factors are compatible with a typical CAD risk population, it is not possible to ascertain whether the weak predictive power of noninvasive testing is related to its application to a population with low pretest probability. Another pitfall is related to the dichotomized classification of noninvasive tests as positive or negative for obstructive CAD. In most tests there is a continuum of ‘positivity’ which is difficult to address with this study design. It should also be emphasized that this was not a randomized trial of noninvasive testing and, as such, direct comparisons of testing vs. no testing and comparisons between noninvasive modalities should be interpreted with caution. The diagnostic performance of noninvasive testing is dependent on the pretest probability of disease, and the decision to perform noninvasive testing and the choice of the test itself depend on the physician’s perception of pretest probability, which may have differed between the different diagnostic modalities applied.

Conclusions

Nearly half of patients without known CAD undergoing elective ICA due to chest pain did not have obstructive lesions, even though four out of five had a positive noninvasive test. Functional tests were by far the most commonly used gatekeepers but were relatively weak predictors of obstructive CAD and appear to be outperformed by CCTA. There is considerable room for improving the current referral strategy for ICA.

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 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 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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Capítulo 4.

Doença coronária não obstrutiva – identificação por angio TC cardíaca

RESUMO:

Neste capítulo é descrita a capacidade da angio TC cardíaca identificar a presença da doença coronária não obstrutiva, característica impar entre os vários exames de diagnóstico não invasivos em cardiologia. O desempenho da angio TC na identificação da placa aterosclerótica é comparado com o dos métodos de imagem intracoronária.

Neste capítulo é feita ainda uma revisão dos diferentes marcadores de aterosclerose subclínica e das actuais limitações ao uso da angio TC com este objectivo.

Foram incluídos neste capítulo dois artigos: O **artigo 11** discute, a propósito de um caso clínico, o contraste entre a carga aterosclerótica documentada por angio TC e o risco cardiovascular; o **artigo 12** é um artigo original em que foi avaliada a prevalência e os preditores de doença coronária na ausência de calcificação coronária.

ABSTRACT:

In this chapter, the evaluation of nonobstructive coronary artery disease by cardiac CT is described, a unique feature among noninvasive diagnostic tests in cardiology. The performance of cardiac CT is compared to other invasive imaging modalities used for the identification of the atherosclerotic plaque. It is also provided in this chapter a review on the subclinical atherosclerosis markers and the present limitation on the use of cardiac CT for this indication.

Included in this chapter are two manuscripts: **Manuscript 11** is a case report related to which the contrast between cardiovascular risk and coronary atherosclerotic burden is discussed; **manuscript 12** is an original paper describing the prevalence and predictors of coronary artery disease in patients with a calcium score of zero.

ARTIGO 11/ MANUSCRIPT 11:

DOENÇA CORONÁRIA NAO OBSTRUTIVA DOCUMENTADA POR ANGIOTC CARDÍACA: CONTRASTE ENTRE A CARGA ATEROSCLERÓTICA E O RISCO CARDIOVASCULAR.

H. Dores, P. Araújo Gonçalves, M.S. Carvalho, P. Jeronimo Sousa, H. Marques, N. Cardim, A. Aleixo, M. Mota Carmo, F. P. Machado, J. Roquette.

Rev Port Cardiol. 2013 Jun 28. doi: 10.1016/j.repc.2012.10.013. [Epub ahead of print]

ARTIGO 12/ MANUSCRIPT 12:

PREVALENCE AND PREDICTORS OF CORONARY ARTERY DISEASE IN PATIENTS WITH A CALCIUM SCORE OF ZERO.

Carvalho MS, de Araújo Gonçalves P, Garcia-Garcia HM, Jerónimo Sousa P, Dores H, Ferreira A, Cardim N, Mota Carmo M, Aleixo A, Mendes M, Pereira Machado F, Roquette J, Marques H.

Int J Cardiovasc Imaging. 2013; *submetido para publicação*

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4.1 INTRODUÇÃO

Existem importantes limitações à capacidade de identificar clinicamente os indivíduos em risco de eventos cardíacos e, em números absolutos, a grande maioria dos indivíduos que sofrem um EAM seriam considerados previamente de baixo risco (1, 2). Este dado epidemiológico espelha a discrepância entre o risco relativo (ou seja, indivíduos com scores de risco mais altos tem taxas de eventos mais altas) e os números em absoluto (na população geral existem muito mais indivíduos em patamares de risco mais baixos) justificando assim que a grande maioria dos eventos ocorram em indivíduos que não se qualificariam previamente para medidas de prevenção mais agressivas (3). Esta discrepância entre o risco individual e o risco populacional, por um lado, e a ausência prévia de sintomas e a dramática forma de apresentação clínica inaugural da DC - EAM e morte súbita numa larga fatia de doentes - por outro, fornecem o racional para o uso de marcadores de aterosclerose subclínica.

Por outro lado, muitas das lesões que estão na origem de eventos coronários agudos não condicionam estenoses significativas (4-9), tornando difícil a sua identificação com os habituais métodos de diagnóstico baseados na detecção de isquémia. O facto de lesões não obstrutivas estarem frequentemente na origem de SCA resulta do facto de estas serem muito mais prevalentes, apesar de se reconhecer que o risco individual por placa ser superior para as lesões obstrutivas (4, 10) . Assim, as modalidades de imagem não invasivas que forneçam informação acerca da totalidade da carga aterosclerótica (obstrutiva e não obstrutiva) têm um elevado potencial na estratificação do risco de eventos cardíacos.

4.2 MARCADORES DE ATEROSCLEROSE SUBCLÍNICA.

Os marcadores de aterosclerose subclínica ao permitirem identificar a presença de doença numa fase precoce, poderão categorizar um indivíduo em particular num patamar de risco mais elevado. Os dois principais marcadores de aterosclerose subclínica são a espessura intima-média carotídea e o score de cálcio das coronárias, apresentando este último uma clara superioridade em nível de evidencia científica gerada nos últimos anos (11-13), que é mais modesta para a espessura intima-média carotídea (14-16).

Uma vez que a calcificação coronária ocorre quase em exclusividade em placas ateroscleróticas, a quantificação do cálcio nas artérias coronárias fornece uma estimativa da carga aterosclerótica global (17, 18) tendo sido já demonstrado em vários estudos clínicos que o score de cálcio é um bom preditor de eventos CV (19). Por outro lado, a ausência de cálcio nas coronárias, embora não exclua totalmente a presença de DC (podem existir placas ateroscleróticas não calcificadas), associa-se a um excelente prognóstico CV a longo prazo e tem uma elevada sensibilidade e especificidade para excluir a presença de DC obstrutiva (20, 21). Numa análise de 3012 doentes

que realizaram score de cálcio seguido de angioTC cardíaca, a ausência de cálcio nas artérias coronárias (n=864 doentes) associou-se a uma taxa de placas na árvore coronária na angioTC de apenas 12,4%, das quais apenas uma minoria condicionava estenose significativa (estenoses $\geq 50\%$ em 1,6% dos doentes com CaSc=0) (21).

Recentemente, foi comparado o poder discriminativo do score de cálcio com o de outros marcadores de aterosclerose subclínica numa larga população de doentes incluídos no estudo MESA (*Multi-Ethnic Study of Atherosclerosis*)(13) . Quando comparado com outros marcadores de risco (como a proteína C-reativa ou o índice calcanhar-braço) e mesmo com a espessura íntima-média carótídea, o score de cálcio demonstrou ter o maior poder discriminativo um desempenho superior na reclassificação do risco CV de indivíduos que estariam à partida num grupo de risco intermediário.

Um aspecto importante nos marcadores de aterosclerose é o facto de eles não serem apenas bons preditores para a ocorrência do evento CV do seu território mais específico, tendo sido já demonstrado que a espessura íntima-media carótídea é um bom preditor do risco de EAM (22), assim como o score de cálcio é um bom preditor do risco de acidente vascular cerebral (23). Isto não é de estranhar uma vez que o processo arteriosclerótico é sistémico, partilha os mesmo factores de risco e com frequência coexistem no mesmo indivíduos manifestações em vários territórios vasculares, como aliás ficou elegantemente documentado pelo estudo REACH (*Reduction of Atherothrombosis for Continued Health*) (24).

No entanto o score de cálcio apresenta também algumas limitações, nomeadamente a ausência de informação relativamente ao grau de estenose e assim acerca do potencial impacto funcional das placas e não detectar a presença de placas não calcificadas, subvalorizando assim a real extensão da aterosclerose coronária.

Assim, no futuro, outros marcadores de aterosclerose subclínica poderão vir a entrar na prática clínica, um dos quais é a angio TC cardíaca, técnica que tem vindo a ganhar uma robustez na avaliação da DC, com a evolução técnica na tecnologia multidetectores, conduzindo a melhorias da resolução espacial, temporal, bem como uma progressiva redução da dose de radiação.

Uma das vantagens da angio TC neste campo reside na sua capacidade de identificar não só as lesões calcificadas mas também as placas não calcificadas, dando assim uma informação mais completa da carga aterosclerótica coronária total pela informação acerca do tipo de placa (calcificada, mista ou não calcificada), localização precisa na árvore vascular e grau de estenose (obstrutiva e não obstrutiva), informação esta que pode ser reunida e quantificada em scores de carga aterosclerótica (ver [Capítulo 8](#)).

Tem-se tornado evidente que a DC não obstrutiva identificada pela angio TC cardíaca tem um impacto prognóstico adverso e claramente diferente da ausência de placas na árvore coronária. Esta evidência tem sido consolidada com o resultado de estudos multicêntricos (25, 26) e também em estudos do valor prognóstico da angio TC cardíaca a longo prazo (27) (ver [Capítulo 9](#)).

Num estudo realizado em doentes com EAM sem supradesnivelamento do segmento ST, foi avaliado o valor prognóstico das lesões não obstrutivas, avaliada por angioTC cardíaca (28). Neste trabalho, a carga de placa não calcificada correlacionou-se com a taxa de eventos CV no seguimento, não se tendo verificado o mesmo para a carga de placa calcificada. Este facto demonstra que mesmo num contexto que não o da DC estável, a identificação da DC não obstrutiva poderá fornecer informação prognóstica adicional na estratificação de risco deste grupo heterogéneo de doentes (29). Numa meta-análise englobando vários estudos que avaliaram o valor prognóstico da angio TC cardíaca, a presença de DC (independente de condicionar ou não estenose significativa) aumentava o risco de eventos CV em 4,5 vezes. Nesse trabalho, foi ainda feita a estimativa de risco de eventos CV por cada segmento da árvore coronária com placa, sendo o HR estimado em 1,23 por cada segmento com doença, o que significa um aumento de risco de 23% por cada segmento envolvido. Esta avaliação foi independente da presença de calcificação coronária e o risco relativo até foi ligeiramente superior (HR 1,29) para os segmentos com placa não calcificada (30).

4.3 IDENTIFICAÇÃO DA PLACA ATEROSCLERÓTICA POR ANGIO TC E CORRELAÇÃO COM MÉTODOS DE IMAGEM INTRAVASCULAR

A identificação e caracterização da placa aterosclerótica têm sido o alvo de extensa investigação de diferentes modalidades de imagem coronária invasiva, nomeadamente da ecografia intravascular (intravascular ultrasound - IVUS), da histologia virtual (IVUS-VH) e da tomografia de coerência óptica (optical coherence tomography - OCT). Estas modalidades têm uma elevada resolução espacial, possibilitando a avaliação detalhada das placas ateroscleróticas, permitindo assim identificar características associadas à sua potencial vulnerabilidade.

No entanto, embora sejam úteis para estudar a fisiopatologia da DC, a sua aplicabilidade está limitada por se tratarem de modalidades diagnósticas invasivas. Por outro lado, dado serem realizadas em doentes referenciados para coronariografia por suspeita de DC e frequentemente após um SCA, muitos destes doentes já se qualificam para medidas de prevenção secundária que alteram a história natural da doença e reduzem o risco de eventos CV no seguimento (31, 32). No estudo multicêntrico PROSPECT, foi feita a avaliação por IVUS complementada por histologia virtual, com o objectivo de estudar a história natural das lesões não intervencionadas (não *culprit*). Neste estudo, uma elevada carga de placa ($\geq 70\%$), uma baixa área luminal mínima ($\leq 4\text{mm}^2$) e a presença de um fibroateroma com cápsula fibrosa fina (Thin-cap fibroatheroma - TCFA) foram preditores independentes de eventos cardíacos adversos no seguimento. Por outro lado, as lesões que estiveram na origem de eventos no seguimento, tinham uma estenose angiograficamente não significativa (estenose média de 32%) na coronariografia basal (32).

O estudo PROSPECT foi um marco na investigação da história natural da DC, mas a sua aplicabilidade fica limitada pelo tipo de população estudada, que foi incluída na sequência de um SCA e assim já se qualificaria (independentemente do resultado na avaliação por imagem intravascular) para medidas de prevenção secundária. Este facto poderá explicar a baixa taxa de eventos maior (morte e EAM) verificados no seguimento e o baixo poder preditivo destas variáveis mesmo quando associadas, uma vez que mesmo na presença dos 3 preditores independentes, a probabilidade de um evento foi de apenas 18,2%, sendo na sua grande maioria novas revascularizações e reinternamentos por angina instável.

A possibilidade de identificar e caracterizar placas ateroscleróticas na árvore coronária por angio TC cardíaca foi já avaliada em vários estudos, por comparação com modalidades de imagem intravascular (IVUS, IVUS-VH e OCT). Existem habitualmente pequenas diferenças na avaliação da área e volume da placa entre a angio TC e a IVUS, bem como do grau de estenose, com uma tendência para sobrevalorização da área lúmenal por angio TC. Numa meta-análise recente, foi demonstrada uma boa acuidade diagnóstica da angio TC cardíaca para a detecção da presença de placas, por comparação com a IVUS, com uma área abaixo da curva ROC de 0,94, uma sensibilidade de 90% e uma especificidade de 92%. (33).

Mais importante ainda é o potencial que a angio TC tem de poder identificar características nas placas ateroscleróticas associadas à sua vulnerabilidade. Num estudo de Hoffman e col, as lesões *culprit* de doentes com SCA tinham mais frequentemente *remodeling* positivo e uma área de placa superior, por comparação com indivíduos com DC estável (34).

Num trabalho de Motoyama e col, as lesões *culprit* de doentes com SCA tinham com maior frequência *remodeling* positivo, placas com baixa atenuação (<30 HU) e calcificação *spotty* (35). Posteriormente, estes mesmos autores, foram avaliar prospectivamente a associação destas características identificadas na angio TC, com o desenvolvimento futuro de SCA num estudo que envolveu 1059 doentes com um seguimento médio de 27 meses. Foi possível demonstrar que o *remodeling* positivo e a presença de placas com baixa atenuação se associavam ao desenvolvimento subsequente de SCA, que ocorreram em 22,2% dos doentes que apresentavam simultaneamente estas 2 características. Em contrapartida, nos doentes em que apenas se documentou uma destas características, a taxa de SCA foi de 3,7% e nos doentes sem *remodeling* positivo nem placas com baixa atenuação a incidência de SCA foi de apenas 0,5%, validando assim prospectivamente o conceito de placa vulnerável por angio TC.

A angio TC foi também validada por comparação com a tomografia de coerência óptica (OCT) (36) e a histologia virtual (IVUS-VH) (37), sendo consistente nos vários trabalhos que as características que marcam as placas potencialmente vulneráveis na angio TC são o *remodeling* positivo e a baixa atenuação.

Mais recentemente foi descrito um sinal de atenuação em anel da porção não calcificada das placas, tendo sido designado como “*napkin ring sign*”, tendo esta característica por angio TC sido associada a placas de maior risco de instabilidade (36, 38, 39).

No entanto, apesar do elevado potencial da angio TC na caracterização das placas ateroscleróticas existem presentemente importantes limitações à capacidade da angio TC identificar as placas potencialmente vulneráveis, nomeadamente por limitações de resolução espacial dos actuais aparelhos, pela influência de diferentes protocolos de aquisição na valorização dos valores medidos de atenuação nas placas (40, 41) (tornando assim difícil padronizar um valor para definição de placa de baixa densidade, como marcador de vulnerabilidade) e por fim pela baixa reprodutibilidade inter-observador desta avaliação (42, 43).

No futuro, melhorias na resolução espacial, maior padronização dos protocolos de aquisição e adopção de softwares de quantificação da carga aterosclerótica poderão contribuir para melhorar o desempenho da angio TC cardíaca na identificação das placas potencialmente vulneráveis.

4.4 LIMITAÇÕES DA ANGIO TC CARDÍACA NA AVALIAÇÃO DA ATEROSCLEROSE SUBCLÍNICA

Existem actualmente importantes limitações à utilização da angio TC cardíaca em indivíduos assintomáticos com o objectivo de identificar a aterosclerose subclínica, nomeadamente:

1. Trata-se de uma exame actualmente ainda pouco disponível. Apesar de se ter assistido nos últimos anos a uma adopção crescente da angio TC cardíaca na prática clínica, esta tem sido essencialmente empregue para exclusão de DC obstrutiva. A avaliação e quantificação das placas não obstrutivas requer uma elevada qualidade de imagem, que é mais consistente nos aparelhos de última geração, com melhor resolução espacial, temporal e de cobertura volumétrica, não estando estes aparelhos ainda amplamente difundidos.
2. Emprega radiação ionizante, com os associados potenciais riscos estocásticos. Nos últimos anos tem-se assistido a uma impressionante redução na dose de radiação, mas esta permanece ainda como uma importante limitação, sobretudo ao se considerar a sua utilização em indivíduos mais jovens.
3. Em face da elevada prevalência da DC não obstrutiva na população em geral, torna-se necessário desenvolver métodos para quantificar a carga aterosclerótica coronária global (scores – um dos objectivos desta tese e desenvolvido no *Capítulo 8*)
4. Ausência de normogramas que permitam enquadrar a carga aterosclerótica documentada pela angio TC cardíaca de acordo com o esperado para a idade e o sexo (à semelhança do que já foi

feito para outros marcadores de aterosclerose subclínica como é o caso do score de cálcio) e assim sejam identificados os indivíduos cuja carga aterosclerótica seja acima do esperado e possa beneficiar de medidas mais intensivas de prevenção primária.

5. Ainda não existe evidência de que a utilização da angio TC com este objectivo possa modificar favoravelmente o manejo dos doentes e em última análise conduzir a uma redução dos eventos CV.

Assim, até à presente data, ao contrário do score de cálcio, a angio TC cardíaca não está indicada para a detecção de DC subclínica como método para estimar o risco CV (44, 45). No entanto, a capacidade que a angio TC cardíaca tem de documentar a presença de DC não obstrutiva, mesmo na ausência de calcificação, a par da impressionante redução da dose de radiação já possível com os aparelhos de última geração (46-48), fazem dela um método de elevado potencial para avaliação da carga aterosclerótica coronária global, podendo vir a ter um papel no futuro como método de avaliação da aterosclerose subclínica.

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4.6 ARTIGO 11/ MANUSCRIPT 11:

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CASO CLÍNICO

Doença coronária não obstrutiva documentada por tomografia computadorizada 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 computadorizada 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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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.

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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 computadorizada (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 publicados¹, 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/m²; 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.

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Artery	Number of Lesions (1)	Volume [mm ³] (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

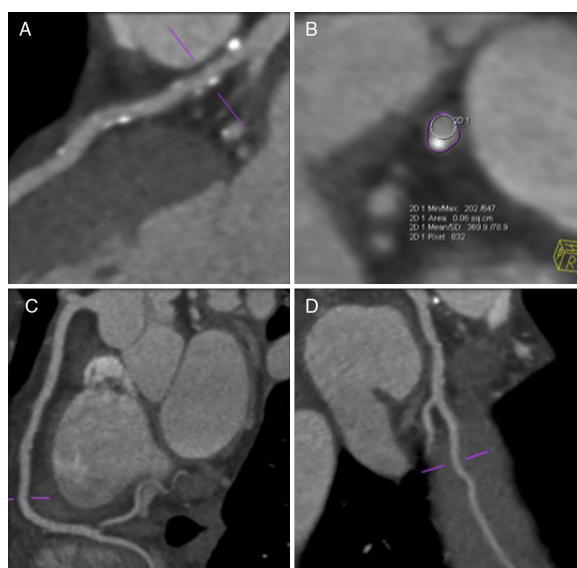


Figura 2 AngioTC cardíaca: A – placas predominantemente calcificadas dispersas no segmento proximal da artéria descendente anterior, sem condicionar estenose significativa; B – placa mista, excêntrica, com remodelagem positiva; C e D – artérias circunflexa e coronária direita (vaso dominante) com placas mistas *minor*, sem estenoses significativas.

Como citar este artigo: Soares H, et al. Doença coronária não obstrutiva documentada por tomografia computadorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. <http://dx.doi.org/10.1016/j.repc.2012.10.013>

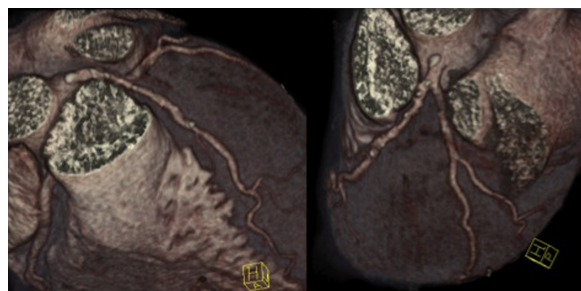


Figura 3 Imagens de reconstrução volumétrica da árvore coronária demonstrando placas ateroscleróticas dispersas na coronária esquerda, não condicionando estenoses significativas.

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 realizados². 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 prazo³. Por outro lado, além do pior prognóstico comprovado pela presença de doença coronária obstrutiva determinada

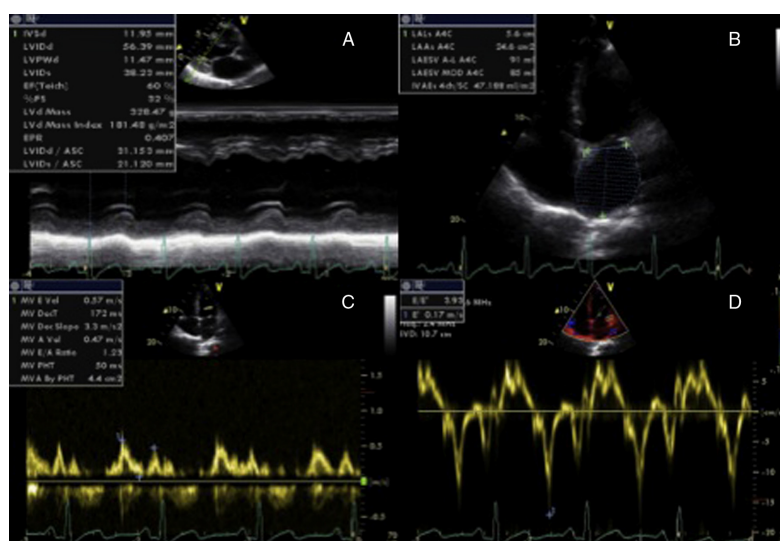


Figura 4 Ecocardiograma transtorácico revelando hipertrofia ventricular esquerda excêntrica (A), dilatação auricular esquerda (B), fluxo Doppler transmitral e padrão de enchimento normais (C e D).

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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 doentes⁴. 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 alterações⁵. 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 estatina⁸. 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%)⁹. 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 estática⁹. 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 100⁹. 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 Helsinquia.

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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Prevalence and predictors of coronary artery disease in patients with a calcium score of zero
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Order of Authors Secondary Information:	
Abstract:	Aims: 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. Methods and Results: Prospective registry of 3012 consecutive patients that performed 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

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	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 [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%. Conclusions: 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.
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ABSTRACT

Aims:

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.

Methods and Results:

Prospective registry of 3012 consecutive patients that performed 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 [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%.

Conclusions:

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.

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 [4,5].

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 [6] 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 [7]. Nevertheless, in previous studies, a high variation was reported in the incidence of obstructive CAD in patients with a CaSc of zero, ranging from 3.5 to 32% [8,9,10,11]. For instance, in the recent CONFIRM registry, it was shown that in patients with a CaSc of zero, obstructive CAD is possible and is associated with increased cardiovascular events [12]. 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 3012 consecutive patients undergoing Dual Source Cardiac 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 (Figure 1).

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 ≥ 126 mg/dL or the need for insulin or oral hypoglycemic agents) [13]; 2) Dyslipidemia (defined as a total cholesterol level ≥ 200 mg/dL or treatment with lipid-lowering drugs) [14]; 3) Hypertension

(defined as blood pressure $\geq 140/90$ mmHg or the use of antihypertensive medication) [15]; 4) Obesity (body mass index ≥ 30 kg/m²); 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) [16]; 6) smoking (defined as previous [less<1year] or current smoker.

Pre-test probability of CAD was determined using both the modified Diamond and Forrester [17] and the Morise score [18]. The cardiovascular risk was assessed with the HeartScore [19]. 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 HeartScore, the cut-off of $\geq 5\%$ (high-risk) was used.

Scan protocol and image reconstruction

All scans were performed with a first generation 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 gating technique with ECG triggering at 70% of the R-R interval if the heart rate was below 80bpm 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 120kV and 128mAs/rot tube current, with CAREdose 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 (CaScoring- Siemens), where every area at least with 3mm^2 within a coronary vessel with a density above 130HU (Hounsfield Units) was selected. For CCTA, sublingual nitroglycerin was administered to all patients, except when contraindicated, and intravenous metoprolol (5mg, with a titration dose up to 20 mg) was administered in patients with heart rate >70 beats/min. 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) x 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 in the same session by both a cardiologist and a radiologist with Level III- equivalent experience. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures $>1\text{ mm}^2$ 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 [20]. 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 $\geq 50\%$ stenosis.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean $\pm$ one 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 . 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 HeartScore (only 11.9% had a Heart Score $\geq 5\%$) - 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 – figure 2. Considering the degree of stenosis of the obstructive CAD group, 64% (n=9) had a 50 to 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%).

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 to 4 times higher probability of being of a high CAD probability group. Cardiovascular risk, estimated by the HeartScore, 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 2.

Multivariate analysis

By multivariate analysis, the independent predictors of CAD in patients with a calcium score of zero were age $\geq$ 55 (odds ratio=1.631, confidence interval 95% 1.054-2.524, p=0.028), hypertension (odds ratio=1.641, confidence interval 95% 1.051-2.560, p=0.029) and dyslipidemia (odds ratio=1.538, confidence interval 95% 1.002-2.361, p=0.049) (table 3 and figure 3). In the presence of these 3 variables (n=176 patients, 20.4% of the population), the probability of having coronary plaques was 21% (versus 12.4% in the total studied population).

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 calcium score of zero has been evaluated in several cohorts, but with conflicting results, depending on the population included. Data from the CONFIRM registry [12], Rubinshtein et al [11] and Akram et al [9], are in line with our results, with a low prevalence of obstructive CAD (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 [8] and Gottlieb et al [10], 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.

Calcium scoring enables a noninvasive quantification of the total coronary atherosclerotic burden, although it underestimates the burden of disease, by not measuring noncalcified plaque [21]. 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 [Error!

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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, when the pretest CAD probability is low. This is in line with the excellent prognosis that has been demonstrated for patients with a calcium score of zero [6].

In our population, older age (≥ 55 years), hypertension and dyslipidemia were independent predictors of CAD in 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 [Error! **Bookmark not defined.**]. 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

(figure 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.

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 ($\geq 50\%$) 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.

All the authors declare that they have no conflict of interest.

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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	
HeartScore ≥5%	103 (11.9)
CCTA	
Normal / no plaque	737 (87.3)
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

Table 2: 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

Table 3: Multivariate analysis.

Independent predictors of CAD			
	OR	CI (95%)	p
Age ≥55	1.631	1.054-2.524	0.028
Hypertension	1.641	1.051-2.560	0.029
Dyslipidemia	1.538	1.002-2.361	0.049

OR – odds ratio; CI – confidence interval

FIGURE LEGENDS

Figure 1: Patient selection and study design

Figure 2: Distribution of CT angiographic findings

Figure 3: Independent predictors of CAD in patients with a CaSc of zero

Figure 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.

Figure 1

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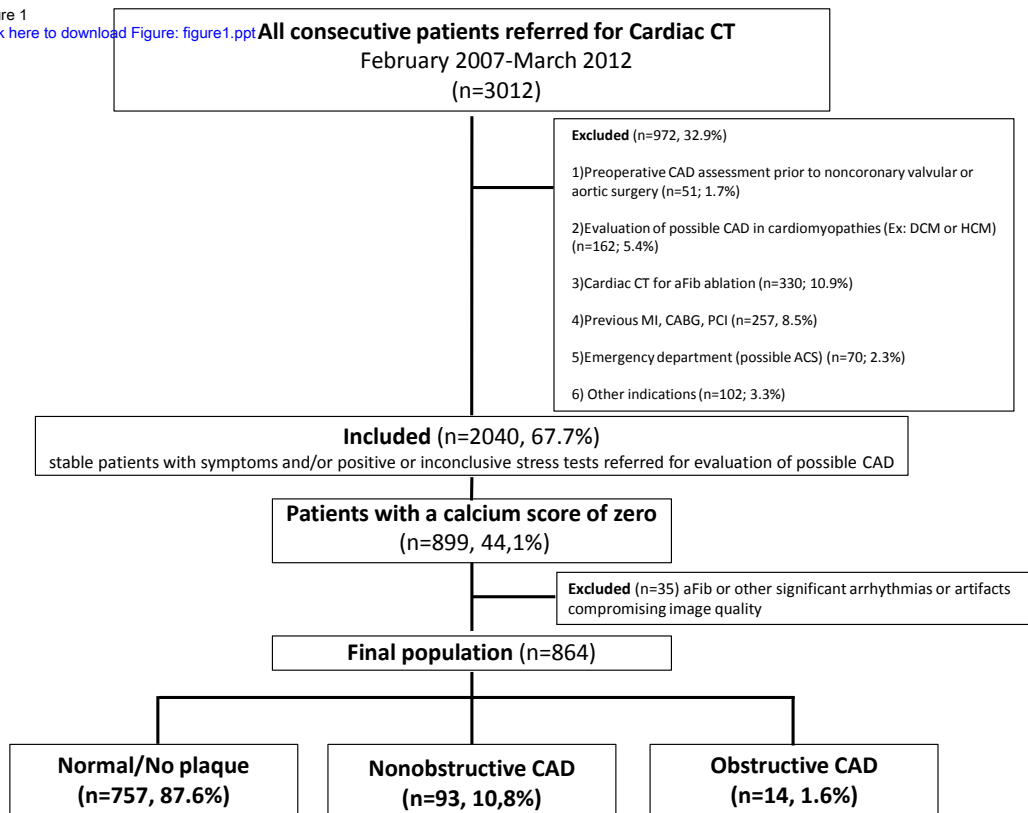


Figure 2
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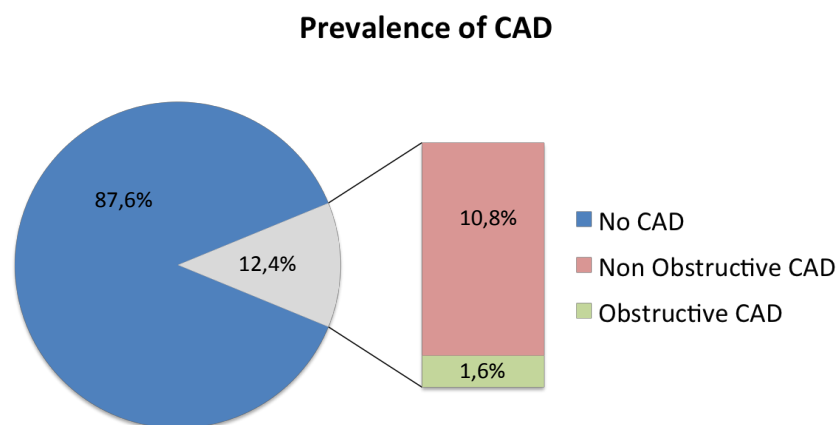
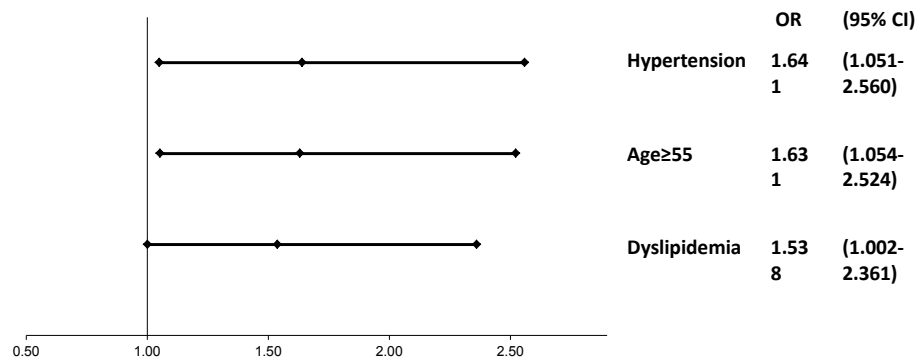
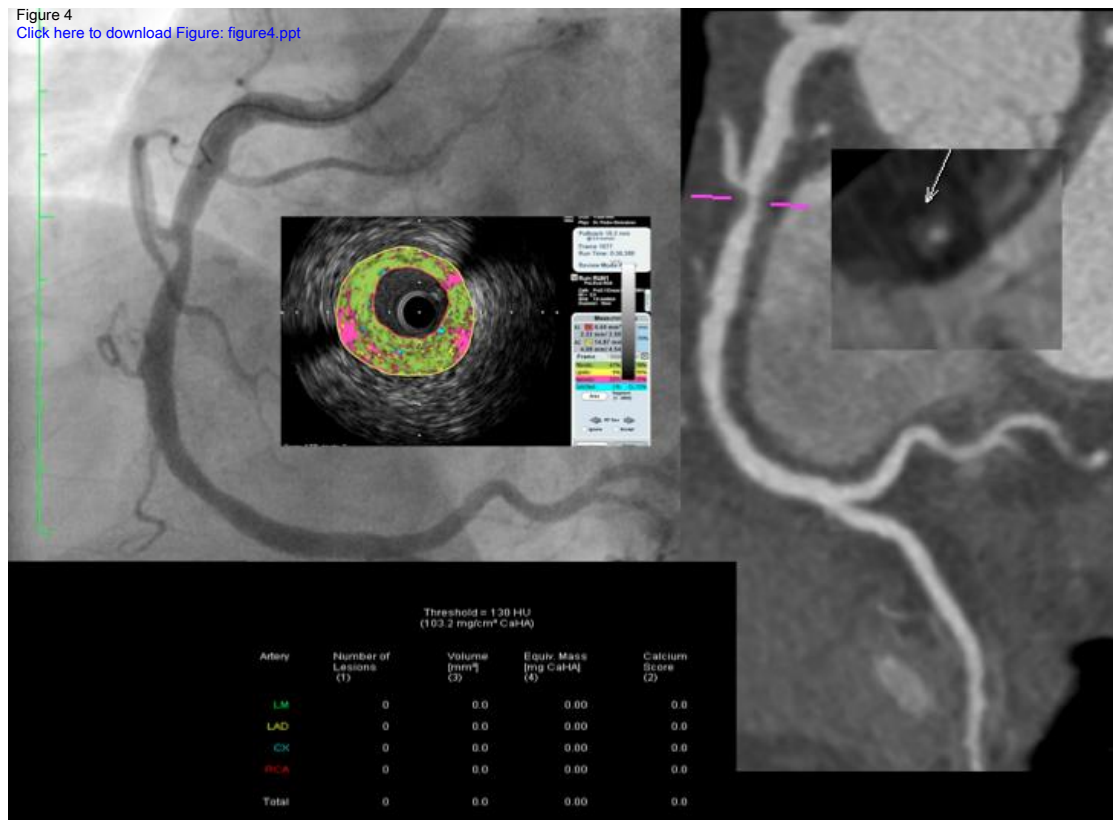


Figure 3
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Capítulo 5.

Angio TC cardíaca – aspectos técnicos

RESUMO:

Neste capítulo é feita uma revisão de alguns aspectos técnicos da angio TC, nomeadamente da resolução espacial e temporal, da cobertura cráneo-caudal e da dose de radiação, cuja evolução nos últimos anos tem contribuído para uma melhoria significativa da qualidade dos exames. É dado particular destaque à dose de radiação empregue e às diferentes estratégias e protocolos desenvolvidos para a reduzir, aspecto essencial para a sua adopção na prática clínica e influenciando o seu posicionamento no algoritmo de avaliação da doença coronária.

Estão incluídos neste capítulo dois artigos que abordam a questão da radiação em angio TC. No **artigo 13** é feita uma avaliação dos preditores de maior dose utilizada e a sua progressiva redução ao longo do tempo, dependente em larga medida da implementação de novos protocolos de aquisição. No **artigo 14**, a dose de radiação da angio TC é comparada com a dos outros exames usados para estudo da doença coronária que usam radiação ionizante. Neste estudo que incluiu mais de 6000 exames, a angio TC cardíaca foi o exame com a dose média mais baixa, seguida da coronariografia invasiva, que por sua vez foi mais baixa que a da cintigrafia de perfusão miocárdica.

ABSTRACT:

In this chapter, some technical issues related to cardiac CT are described, like spatial and temporal resolution, volume coverage and radiation dose, whose recent advancements have lead to significant improvements in image quality. The issue of radiation dose and the different available strategies to reduce it are discussed in more detail, since this influences its clinical use and the positioning of cardiac CT in the coronary artery disease evaluation algorithm.

Two manuscripts are included in this chapter, both related to the issue of cardiac CT radiation dose. In **manuscript 13**, the predictors of higher dose are described, as well as its reduction over time, largely dependent of the adoption of new acquisition protocols. In **manuscript 14**, a comparison of the radiation dose of three diagnostic tests is provided. In this study, including more than 6000 exams, cardiac CT was associated with a mean lower dose than invasive coronary angiography, which, in turn, was lower than that of single-photon emission computed tomography.

ARTIGO 13/ MANUSCRIPT 13:

RADIAÇÃO NA ANGIOTC CARDÍACA: PREDITORES DE MAIOR DOSE UTILIZADA E SUA REDUÇÃO AO LONGO DO TEMPO.

P. Sousa, P. Araújo Gonçalves, H. Marques, L. Raposo, R. Cale, J. Brito, A. Gaspar, F. Machado, J. Roquette.

Rev Port Cardiol. 2010, 29 (11): 1655-65.

ARTIGO 14/ MANUSCRIPT 14:

RADIATION DOSE OF 3 DIAGNOSTIC TESTS: SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY, INVASIVE CORONARY ANGIOGRAPHY AND CARDIAC COMPUTED TOMOGRAPHY

Araújo Gonçalves P, Jerónimo Sousa P, Cale R, Marques H, Santos MB, Dias A, Dolores H, Carvalho MS, Ventosa A, Martins T, Teles R, Almeida M, Mendes M.

Rev Port Cardiol 2013; aceite para publicação (REPC-D-13-00036).

SUMÁRIO DO CAPÍTULO 5:

5.1 INTRODUÇÃO

5.2 RESOLUÇÃO ESPACIAL, RESOLUÇÃO TEMPORAL E COBERTURA CRANEO-CAUDAL

5.3 DOSE DE RADIAÇÃO E ESTRATÉGIAS PARA SUA REDUÇÃO

5.4 BIBLIOGRAFIA

5.5 ARTIGOS 13 e 14

5.1 Introdução

Nos últimos anos, tem-se assistido a impressionante evolução na tecnologia da TC multidetectores com progressivas melhorias na resolução espacial, temporal e de cobertura craneo-caudal que vieram permitir a avaliação não invasiva das artérias coronárias e tornar a angio TC cardíaca uma ferramenta importante na prática clínica diária.

De seguida são revistos alguns aspectos técnicos da angio TC cardíaca, com especial ênfase na dose de radiação e nas estratégias desenvolvidas para a sua redução.

5.2 Resolução espacial, temporal e cobertura craneo-caudal

A primeira geração de aparelhos de TC multidetectores que possibilitava a avaliação das artérias coronárias foi introduzida no ano 2000 e eram aparelhos de 4-cortes (1). Estes aparelhos, apesar de inaugurarem uma nova era de avaliação coronária não invasiva, apresentavam ainda marcadas limitações de resolução temporal e espacial, que vieram a ser posteriormente minimizadas com o desenvolvimento de aparelhos de 16 e 64 cortes, sendo estes últimos considerados actualmente como o requisito ideal mínimo para a realização de exames de angio TC cardíaca (2).

A **resolução espacial** dos primeiros aparelhos, intimamente relacionada com a colimação dos cortes, variava entre 1 a 4mm, tendo melhorado para 0.5 a 0.75mm com a introdução dos aparelhos de 16 e 64 detectores. Desde essa altura, não tem havido melhoria significativa neste parâmetro, sendo uma das importantes limitações desta técnica, dificultando a avaliação de segmentos de pequeno calibre, bem como a avaliação na presença de importante calcificação e de artefactos metálicos, como os provocados na presença de stents.

A resolução actualmente possível impõe igualmente limitações à avaliação detalhada das placas ateroscleróticas, nomeadamente quando comparada com a resolução das modalidades de imagem intracoronária – 200 a 250 μm para a IVUS e 10-15 μm para a OCT (3). Este é um aspecto técnico a ter em consideração no que diz respeito à possibilidade de avaliação das características de potencial instabilidade das placas por TC, em face das limitações já apresentadas pelas técnicas intracoronárias de muito mais elevada resolução espacial (4).

A **resolução temporal** é igualmente um aspecto técnico importante na TC multidetectores quando aplicada a estruturas em movimento como é o caso do coração. Esta é função do tempo que demora a adquirir uma imagem, que por sua vez é função da velocidade de rotação da gantry. Para formação de uma imagem de TC, torna-se necessária a aquisição de raios-X em 180 graus, ou seja, em meia rotação da gantry. Assim, nos aparelhos de 1ª geração com 4 cortes, como a

gantry demorava 500 ms a dar uma volta completa, a resolução temporal era de 250 ms (meia volta para aquisição de 1 imagem). O desenvolvimento dos aparelhos de 16 e mais tarde de 64 cortes acompanhou-se de uma redução do tempo de rotação e assim uma melhoria da resolução temporal. Para um aparelho de 64 cortes com um tempo de rotação de 330 ms, a resolução temporal correspondente é de 165ms.

A resolução temporal tem importantes implicações na qualidade dos exames, uma vez que quanto mais rápida for a aquisição menor é o tempo necessário de apneia e assim minimiza o risco de artefactos relacionados com a respiração. Por outro lado, a melhoria da resolução temporal permitiu aumentar o ritmo de administração do contraste sem aumentar muito a dose total (a aquisição dura menos ciclos cardíacos) e assim melhorar a qualidade do exame (melhor contraste entre o lúmen e a parede do vaso e restantes tecidos).

A resolução temporal tem ainda importantes implicações na dependência de uma frequência cardíaca baixa durante a aquisição e assim da necessidade de administração de beta-bloqueantes previa à realização do exame. Nos actuais aparelhos de 64 cortes, o número de batimentos cardíacos necessário para completar a aquisição cardíaca baixou dos iniciais 20 a 30m batimentos (com os aparelhos de 4 cortes) para 4 a 8 batimentos. Com o desenvolvimento mais recente de **aparelhos de dupla ampola**, associados a uma rotação da *gantry* de 330 ms foi possível reduzir a resolução temporal para 82,5ms, uma vez que as imagens são obtidas por integração da informação obtida das 2 ampola (separadas 90°) bastando assim apenas $\frac{1}{4}$ de rotação para se obter uma imagem ($330\text{ms}/4$) elevando a uma menor dependência da frequência cardíaca na qualidade dos exames e permitindo inclusive a avaliação de doentes com arritmias (5).

Mais recentemente, os aparelhos de dupla ampola que na 1ª geração tinham 2 conjuntos de 64 detectores (2x 64) evoluíram na 2ª geração para 2x128 cortes e com ainda menor tempo de rotação da *gantry* (280ms) melhorando a resolução temporal para 75 ms ($280\text{ms}/4$). Com estes aparelhos de ultima geração foi possível desenvolver protocolos de aquisição de *pitch* elevado e assim aquisição simultânea de todo o exame num único ciclo cardíaco e com uma impressionante redução na dose de radiação (6-8).

Outro aspecto técnico importante na angio TC prende-se com a **cobertura craneo-caudal**, que depende directamente do número de detectores. A largura de um detector varia entre 0,5 a 0,6mm e assim os aparelhos de 64 cortes adquirem em cada rotação 3,2cm do volume total. Com o desenvolvimento de aparelhos de 320 cortes, foi possível uma cobertura craneo-caudal de 16cm ($0,5\text{mm} \times 320 = 160\text{mm}$) e assim possibilitar a aquisição cardíaca total numa única rotação da ampola e num único ciclo cardíaco. Estes aparelhos eliminaram os artefactos de escada e levaram a importantes reduções na dose de contraste, pelo menor tempo de aquisição, e de radiação, uma vez que deixa de haver sobreposição de detectores (9, 10). Mais importante ainda, uma vez que a distribuição do contraste é uniforme na totalidade do volume cardíaco adquirido,

estes aparelhos vieram abrir um novo campo de possibilidades na avaliação da perfusão do miocárdio e na realização de protocolos de isquémia (11).

5.3 Dose de radiação e estratégias para sua redução

Uma das limitações da angio TC cardíaca está relacionada com o uso de radiação ionizante e o seu risco para a saúde resultante dos seus efeitos determinísticos e estocásticos. Os efeitos determinísticos resultam da exposição a doses elevadas e num curto período de tempo, originando lesão celular directa, sendo incomuns verificar-se no contexto de imagem médica. Os efeitos estocásticos são neste contexto mais importantes, pelo potencial de indução de mutações no DNA e consequentemente do desenvolvimento posterior de neoplasias. A relação entre a radiação ionizante e o risco de desenvolvimento de neoplasias foi bem documentada nos acidentes nucleares, tendo sido depois feita uma extrapolação linear das doses elevadas registadas nesses acidentes para as doses habitualmente empregues nos exames médicos. A proporção estimada é de que o risco de morte por neoplasia aumenta 0,5% por uma exposição a 100mSv (12). Não havendo dados observacionais com doses inferiores a 100mSv tem sido assumida a teoria “*linear no threshold*”, que é deliberadamente conservadora e defende que não havendo prova em contrario, qualquer exposição a radiação ionizante aumenta o risco de desenvolvimento de uma neoplasia mantendo a mesma proporção nas doses baixas. Este é o modelo sobre o qual é defendido o princípio de ALARA – “*As low as reasonably achievable*” que deve orientar o uso de radiação ionizante em medicina (13, 14).

A melhoria na qualidade dos exames com o desenvolvimento dos aparelho de 16 e 64 cortes foi acompanhada de uma aumento significativo na dose de radiação empregue pela angio TC cardíaca que chegou a 20 mSv. Varias estratégias foram desenvolvidas para redução da dose de radiação na angio TC cardíaca, nomeadamente a correcta limitação da janela de aquisição, a modulação da dose pelo ECG e o uso de uma reduzida kilovoltagem (100Kv) em indivíduos não obesos, aspectos que levaram a uma redução significativa da dose empregue neste exames (15).

Em 2009 foram publicados os resultados do registo multinacional e multicêntrico PROTECTION I (*Prospective Multicenter Study On Radiation Dose Estimates Of Cardiac CT Angiography in Daily Practice*) no qual a dose média de radiação foi de 12 mSv, reflexo já da implementação de algumas destas estratégias de redução da dose (16).

Em 2010 publicamos um trabalho em que foi avaliada a evolução temporal da dose de radiação, tendo sido possível demonstrar uma redução significativa da dose ao longo do tempo com a progressiva implementação de novos protocolos, nomeadamente com o uso de uma reduzida kilovoltagem da ampola (17). Nesta trabalho, a dose média foi de 6,6 mSv e foi possível identificar os preditores associados a uma elevada dose de radiação que foram: um IMC>32 kg/m², o uso de 120 Kv (pela impossibilidade de se adquirir o exame com 100 Kv nos indivíduos obesos); antecedentes de cirurgia cardíaca (pela necessidade de irradiar todo o tórax para

inclusão das pontagens); presença de ritmo de fibrilhação auricular (uma vez que impossibilita o correcto *gating* cardíaco).

Mais recentemente foram desenvolvidas estratégias adicionais que contribuíram para reduzir ainda mais a dose de radiação, sendo um exemplo disto a aquisição prospectiva ou adaptativa, conduzindo a doses médias de 2-3 mSv (18) e a aquisição com *high-pitch* nos aparelhos topo de gama de dupla ampola (128x2) com doses inferiores a 1mSv (6), sem que estas redução da dose leve a uma compromisso da qualidade da imagem.

Actualmente, as doses médias empregues pela angio TC cardíaca são inferiores às dos outros exames em cardiologia que empregam radiação ionizante, nomeadamente a cintigrafia de perfusão miocárdica (dose 10-15 mSv) e a coronariografia por cateterismo cardíaco (dose 7 mSv) (12, 19, 20).

Num outro trabalho em que comparamos a dose de radiação deste 3 exames numa população de 6196 doentes consecutivos avaliados durante 2 anos, a dose mais baixa foi a da angio TC cardíaca (5,4 mSv), seguida da coronariografia por cateterismo cardíaco (8,1 mSv), que por sua vez foi mais baixa do que a da cintigrafia de perfusão miocárdio (10,7 mSv) (21). Neste trabalho, foi ainda possível verificar uma redução na dose de radiação ao longo do tempo (resultado da adopção de novos protocolos) e uma subida da dose da coronariografia (resultante sobretudo do uso crescente do acesso radial), não havendo modificação significativa nos exames de cintigrafia ao longo do tempo. Em todos os exames, a obesidade associou-se a uma dose de radiação significativamente mais alta em todos os exames, sendo a subida mais evidente na angio TC cardíaca.

Por fim, os softwares de reconstrução iterativa recentemente desenvolvidos poderão ainda levar a uma redução adicional da dose, tendo muito recentemente sido descritos protocolos com doses mesmo inferiores a 0,1mSv (22). Caso se venha a confirmar ser possível a aplicação clínica destes protocolos com doses que se aproximam das usadas num simples RX de tórax, sem compromisso da qualidade dos exames, poderá ter implicações no posicionamento da angio TC cardíaca na avaliação da DC, nomeadamente na estratificação do risco CV em doentes assintomáticos.

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5.5 ARTIGO 13/ MANUSCRIPT 13:

ARTIGOS ORIGINAIS

Radiação na AngioTC cardíaca: preditores de maior dose utilizada e sua redução ao longo do tempo [115]

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RESUMO

A tomografia computadorizada cardíaca é um método não invasivo de obter informação da anatomia cardíaca, permitindo avaliar a doença coronária. No entanto, uma das limitações que tem vindo a ser apontada a este exame é a utilização de radiação. O objectivo deste trabalho foi avaliar a variação da dose de radiação ao longo do tempo e identificar variáveis que se associassem ao seu aumento.

Foi analisado um registo prospectivo de 643 doentes submetidos a TC cardíaca com 64 cortes e dupla ampola (Dual source CT - Somaton Definition®, Siemens-medical) durante os anos de 2007 e 2008.

A amostra foi dividida em quartis, segundo a ordem cronológica de realização dos exames. Verificou-se uma redução progressiva da mediana da dose de radiação ao longo dos quartis analisados [Q1: 8,9 (5,9-14,1), Q2: 6,6 (5,5-10,7), Q3: 6,4 (5,3-8,7), Q4: 6,1 (5,2-7,9)], significativa quando o primeiro quartil foi comparado com os restantes ($p < 0,05$). Paralelamente a este decréscimo, verificou-se uma utilização progressivamente maior de uma voltagem da ampola de 100Kv ($p < 0,001$). Os preditores

Radiation in cardiac CT: predictors of higher dose and its reduction over time

ABSTRACT

Introduction: Cardiac CT provides noninvasive information on cardiac anatomy, particularly in coronary artery disease. However, exposure to radiation has been identified as a limitation of this exam. The aim of this study was to evaluate variations in radiation dose over time and to identify variables associated with use of higher radiation doses.

Methods: A prospective registry of 643 patients who underwent 64-slice dual source cardiac CT scan (Dual source CT - Somaton Definition®, Siemens-Medical) during 2007 and 2008 was analyzed.

Results: The sample was divided into quartiles according to the chronological order of the exams. There was a progressive reduction in median radiation dose in the quartiles analyzed (Q1: 8.9 [5.9-14.1], Q2: 6.6 [5.5-10.7], Q3: 6.4 [5.3-8.7], Q4: 6.1 [5.2-7.9] mSv), significant when the first quartile was compared with the others

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de uma dose de radiação alta foram: IMC>32, cirurgia cardíaca prévia, presença de fibrilhação auricular na aquisição, maior tempo de aquisição e o uso 120 kV como voltagem da ampola. Quando pelo menos uma destas características estava presente (um terço da população), a dose de radiação foi significativamente superior [12,1 (9,5-14,8) versus 5,7 (5,0-6,7) mSv, $p<0,001$].

Palavras Chave:
AngioTC Cardíaco; Radiação

($p<0,05$). Along with this reduction, there was a progressive increase in the use of a tube voltage of 100 kV ($p<0,001$). Predictors of a higher radiation dose were higher body mass index, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV. When one or more of these variables were present (one third of the population), the radiation dose was significantly higher [12.1 [9.5-14.8] vs. 5.7 [5.0-6.7] mSv, $p<0,001$].

Key words
Cardiac CT; Radiation

INTRODUÇÃO

A coronariografia invasiva é considerada o *gold standard* para o diagnóstico de doença coronária. Contudo, exames não invasivos, tais como a prova de esforço, a cintigrafia de perfusão miocárdica, o ecocardiograma de sobrecarga, a tomografia computadorizada e a ressonância magnética nuclear cardíaca são uma alternativa na avaliação da anatomia e fisiologia cardíacas.

Nas três últimas décadas, a tomografia computadorizada (TC) tem demonstrado um papel importante na avaliação diagnóstica. A era moderna da angiotomografia computadorizada cardíaca (AngioTC cardíaca) iniciou-se aproximadamente em 1997, com a introdução na prática clínica dos sistemas helicoidais de corte único⁽¹⁾. Com as gerações sucessivas de aparelhos de TC, até aos sistemas de 64 cortes, verificou-se uma melhoria progressiva da resolução espacial e temporal, bem como uma diminuição importante do tempo de aquisição. Assim, desde 2004, com a introdução da TC de 64 cortes na prática clínica, a coronariografia não invasiva por TC cardíaca tem despertado interesse particular, nomeadamente pela sua utilidade na exclusão da presença de doença coronária, fruto do seu elevado valor preditivo negativo⁽²⁾ (*Figura 1*).

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INTRODUCTION

Invasive coronary angiography is considered the gold standard for diagnosis of coronary artery disease. However, noninvasive exams such as exercise testing, myocardial perfusion scintigraphy, stress echocardiography, computed tomography (CT) and cardiac magnetic resonance imaging are alternative methods of assessing cardiac anatomy and physiology.

Over the last thirty years, CT has come to play an important role in diagnostic evaluation. The modern era of CT angiography began around 1997 with the introduction into clinical practice of single-slice spiral systems⁽¹⁾. The development of new generations of CT scanners led to progressive improvements in spatial and temporal resolution and significant reductions in acquisition time. Since the introduction of 64-slice systems in 2004, non-invasive coronary CT angiography has aroused particular interest for its ability to exclude the presence of coronary artery disease due to its high negative predictive value⁽²⁾ (*Figure 1*).

In parallel with these technological advances, the radiation doses used to acquire CT images has increased in the most recent systems, with exposure rising from 5-8 mSv (four-slice) to 15-20 mSv (64-slice)⁽³⁾. However, it is hoped that the better image quality of the



Figura 1. Coronariografia virtual (A) e reconstrução multiplanar (B) em exame com boa qualidade de imagem documentando coronárias sem placas significativas

Figure 1. Virtual coronary angiography (A) and multiplane reconstruction (B) in good-quality cardiac CT images showing coronaries without significant plaques

Paralelamente a esta evolução tecnológica, a dose de radiação utilizada na aquisição de imagens de TC tem vindo a aumentar com os aparelhos mais recentes. A exposição estimada aumentou de 5-8 mSv (TC de quatro cortes) para 15-20 mSv (TC de 64 cortes)⁽³⁾. Com os sistemas de última geração, em particular com os aparelhos de dupla ampola e os de 320 cortes, espera-se que a melhoria da qualidade de imagem seja acompanhada por uma redução da dose de radiação.

Existe igualmente uma grande variabilidade nesta dose entre os vários centros e os vários aparelhos, com medianas de doses de radiação que variam entre 4,9 e 29,1 mSv⁽⁴⁾.

No entanto, esta dose de radiação elevada, apontada como uma limitação para esta técnica, pode ser eficazmente reduzida tanto pela optimização dos protocolos de aquisição existentes, como pelo desenvolvimento de novos *softwares* e protocolos.

O objectivo deste trabalho foi avaliar a evolução temporal da dose de radiação na TC cardíaca e identificar variáveis associadas a doses mais elevadas de radiação.

MÉTODOS

Todos os doentes submetidos a TC cardíaca

latest generation scanners, particularly dual-source and 320-slice machines, will be accompanied by a reduction in radiation dose.

There are also considerable variations between different centers and systems, with median radiation doses ranging between 4.9 and 29.1 mSv⁽⁴⁾.

This high radiation dose has been identified as a limitation of the technique, but it can be significantly reduced by optimization of existing acquisition protocols and by the development of new software and protocols.

The aim of this study was to evaluate variations in radiation dose in cardiac CT over time and to identify variables associated with use of higher radiation doses.

METHODS

All patients who underwent cardiac CT with a dual-source 64-slice scanner (Somatom Definition® - Siemens Medical Systems) during 2007 and 2008 were enrolled in a prospective single-center registry. This population of 643 patients was divided into quartiles (Q1-Q4) according to the chronological order of the exams, in order to analyze radiation dose over time.

Demographic (age and gender) and clinical

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de 64 cortes de dupla ampola (*Somaton Definition® - Siemens Medical*) de 2007 e 2008 foram incluídos num registo prospectivo de centro único. Esta população (643 doentes) foi dividida em quartis, de acordo com a ordem cronológica dos exames, para estudar a dose de radiação ao longo do tempo.

Variáveis demográficas (idade, sexo), clínicas [presença de factores de risco cardiovascular, índice de massa corporal (IMC), cirurgia cardíaca prévia, enfarte de miocárdio prévio e presença de fibrilhação auricular] e de protocolo (tempo de aquisição, dose de contraste, frequência cardíaca e uso de voltagem da ampola de 120 kVs) foram avaliadas de modo a identificar os preditores de uma dose de radiação mais elevada (definida como presente quando superior à mediana da população). As variáveis identificadas como preditores por análise univariada foram combinadas num modelo de regressão logística para apurar os preditores independentes da utilização de elevada dose de radiação.

Protocolo de aquisição e reconstrução de imagens

Todas as TC cardíacas foram efectuadas com um aparelho de 64 cortes com dupla ampola (*Somatom Definition, Siemens Medical®, Forchheim, Germany*), com o doente em decúbito dorsal e em apneia após inspiração profunda. Foi administrada nitroglicerina sublingual em todos os doentes (salvo contra-indicações). Não foi administrado beta-bloqueante especificamente para a realização do exame.

A voltagem da ampola foi definida para 100 ou 120 kVs, de acordo com o IMC. Utilizou-se modulação por ECG da corrente da ampola, reduzindo-a a 20% nas fases do ciclo cardíaco não utilizadas para avaliação das coronárias. Esta modulação não foi utilizada nos doentes em fibrilhação auricular. O *pitch* – velocidade de movimento da mesa – foi variável com a frequência cardíaca, aspecto regulado automaticamente pelo equipamento dependendo da frequência cardíaca, sendo este ajuste feito automaticamente. Foram reconstruídas imagens transaxiais, sendo a resolução

variables (cardiovascular risk factors, body mass index [BMI], previous cardiac surgery, previous myocardial infarction [MI] and atrial fibrillation) and protocol parameters (acquisition time, contrast dose, heart rate and use of 120-kV tube voltage), were analyzed in order to identify predictors of a higher radiation dose (defined as higher than the median in the population). Variables identified as predictors on univariate analysis were combined in a logistic regression model to determine independent predictors of use of higher radiation doses.

Acquisition protocol and image reconstruction

All scans were performed with a dual-source 64-slice scanner (*Somatom Definition, Siemens Medical Systems, Forchheim, Germany*), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated. No beta-blockers were administered specifically for the exam.

Tube voltage was 100 or 120 kV, depending on BMI. ECG-gated tube current, which reduces current by 20% in phases of the cardiac cycle that are not used for assessment of the coronary arteries, was used except for patients in atrial fibrillation. Pitch was varied according to heart rate, this adjustment being carried out automatically by the equipment. 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 multiplane reconstructions, maximum intensity projection and volume rendering technique.

The contrast medium used was intravenous iodixanol (320 mg/ml – *Visipaque®*) in a 6 ml/s infusion. The quantity of contrast was calculated according to the following formula: (acquisition time + 6 s delay) x flow (6 ml/s).

Contrast administration was followed by flushing with 50 ml saline (6 ml/s).

Statistical analysis

SPSS version 17.0 was used for the statistical analysis. Continuous variables are pre-

temporal de 83ms, a espessura dos cortes de 0,75mm, com incrementos de 0,4mm. Foi feito o pós-processamento numa consola com o software *Circulation*, sendo utilizadas reconstruções multiplanares (MPR), de projecção de intensidade máxima (MIP) e de volume (VRT).

Foi utilizado meio de contraste (Iodixanol 320 mg/mL – Visipaque®) endovenoso, a uma infusão de 6 mL/seg. A quantidade de contraste dependeu da duração da aquisição e foi calculada pela seguinte fórmula: (duração da aquisição + delay 6 seg) x fluxo (6mL/seg) .

A injeção de contraste foi seguida de um *flush* de 50 mL de soro fisiológico (6 mL/seg).

ANÁLISE ESTATÍSTICA

A análise estatística foi efectuada utilizando a aplicação SPSS Statistics 17,0 para Windows. As variáveis contínuas apresentam-se como mediana (intervalo interquartil) e as categóricas como número (n) ou frequência (%).

Para comparar diferenças entre variáveis contínuas, utilizaram-se os testes não paramétricos de Mann-Whitney ou Kruskal-Wallis e o Chi quadrado foi aplicado para testar diferenças em frequências. A análise multivariada foi efectuada através de um modelo de regressão logística.

Aceitou-se existir diferença significativa quando $p < 0,05$ (duas caudas).

RESULTADOS

Os resultados apresentam-se na Tabela I.

A mediana da idade foi de 59 (52-66) anos, 60% dos indivíduos eram do sexo masculino e o IMC foi de 26 (24-29) kg/m². O tempo de aquisição foi de 8 (7-10) segundos, foi administrado 84 (78-96) mL de contraste e a dose de radiação foi de 6,6 (5,4-10,7) mSv. A frequência cardíaca durante a aquisição foi 65 (56-75) bpm, não tendo sido efectuada redução adicional da frequência cardíaca para a aquisição. Não se verificaram diferenças entre os quartis analisados relativamente a estas variáveis.

A mediana da dose de radiação foi de 6,6

sented as medians (interquartile range) and categorical variables as frequencies (n) or percentages (%).

The non-parametric Mann-Whitney or Kruskal-Wallis tests were used to compare continuous variables, and the chi-square test to test differences in frequencies. Multivariate analysis was performed using a logistic regression model.

Differences were taken to be significant when $p < 0.05$ (two-tailed).

RESULTS

The results are presented in Table I.

The patients' median age was 59 (52-66) years, 60% were male and BMI was 26 (24-29) kg/m². Acquisition time was 8 (7-10) s, 84 (78-96) mL of contrast was administered and the radiation dose was 6.6 (5.4-10.7) mSv. Heart rate during acquisition was 65 (56-75) bpm, with no additional heart rate lowering being carried out. No differences were observed between quartiles in terms of these variables.

There was a progressive reduction in the median radiation dose over time (Q1: 8.9 [5.9-14.1], Q2: 6.6 [5.5-10.7], Q3: 6.4 [5.3-8.7], Q4: 6.1 [5.2-7.9] mSv). This difference was significant when the first quartile was compared with the others (Figure 2).

A tube voltage of 100 kV was used in 78% of the exams. There was a progressive increase in the use of this voltage over time (Q1: 54%, Q2: 79%, Q3: 87%, Q4: 91%; $p < 0.001$) (Figure 2).

On univariate analysis, predictors of a higher radiation dose (above the median) were male gender, higher BMI, previous cardiac surgery, previous MI, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV (Table II).

On multivariate analysis, predictors of a higher radiation dose were higher BMI, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV (Table III).

Patients with one or more of the following:

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Tabela I. Resultados da população total e após divisão em quartis das variáveis estudadas

	Total	Q1	Q2	Q3	Q4	p
n	643	161	161	161	160	NS
Idade (anos)	59 (52-66)	58 (52-64)	59 (51-68)	61 (51-67)	59 (52-67)	NS
% sexo masculino	60	69	53	63	56	NS
IMC (kg/m ²)	26 (24-29)	27 (24-29)	26 (24-29)	26 (24-28)	27 (24-29)	NS
FRCV (n)	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	2 (1-3)	0,01
Dose de contraste (mL)	84 (78-96)	84 (78-96)	84 (78-90)	84 (78-96)	84,0 (72-90)	NS
Duração aquisição (seg)	8 (7-10)	8 (7-10)	8 (7-9)	8 (7-10)	8 (6-10)	NS
FC média (bpm)	65 (56-75)	65 (56-75)	64 (54-72)	65 (57-76)	66 (57-76)	NS
Dose de radiação (mSv)	6,6 (5,4-10,7)	8,9 (5,9-14,1)	6,6 (5,5-10,7)	6,4 (5,3-8,7)	6,1 (5,2-7,9)	<0,05
% 100 Kv	78	54	79	87	91	<0,01

FC: frequência cardíaca; FRCV: índice de RFCV; IMC: Índice de massa corporal

Table I. Variables studied for the total study population and divided into quartiles

	Total	Q1	Q2	Q3	Q4	p
n	643	161	161	161	160	NS
Age (years)	59 (52-66)	58 (52-64)	59 (51-68)	61 (51-67)	59 (52-67)	NS
% male	60	69	53	63	56	NS
BMI (kg/m ²)	26 (24-29)	27 (24-29)	26 (24-29)	26 (24-28)	27 (24-29)	NS
CVRF (n)	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	2 (1-3)	0,01
Contrast dose (ml)	84 (78-96)	84 (78-96)	84 (78-90)	84 (78-96)	84,0 (72-90)	NS
Acquisition time (s)	8 (7-10)	8 (7-10)	8 (7-9)	8 (7-10)	8 (6-10)	NS
Mean HR (bpm)	65 (56-75)	65 (56-75)	64 (54-72)	65 (57-76)	66 (57-76)	NS
Radiation dose (mSv)	6.6 (5.4-10.7)	8.9 (5.9-14.1)	6.6 (5.5-10.7)	6.4 (5.3-8.7)	6.1 (5.2-7.9)	<0.05
% 100 kV tube voltage	78	54	79	87	91	<0.01

BMI: body mass index; CVRF: cardiovascular risk factors; HR: heart rate

(5,4-10,7) mSv e verificou-se uma redução progressiva ao longo do tempo [Q1: 8,9 (5,9-14,1), Q2: 6,6 (5,5-10,7), Q3: 6,4 (5,3-8,7), Q4: 6,1 (5,2-7,9)]. Esta diferença foi significativa quando o primeiro quartil foi comparado com os restantes (*Figura 2*).

Em 78% dos exames utilizou-se uma voltagem da ampola de 100 kVs. Houve um aumento progressivo da selecção desta voltagem com o tempo (Q1: 54%, Q2: 79%, Q3: 87%, Q4: 91%; p<0,001 – *Figura 2*).

Por análise univariada, os preditores de uma dose de radiação alta (acima da mediana) foram: sexo masculino, maior IMC, cirurgia cardíaca prévia, enfarte de miocárdio prévio, ritmo de fibrilhação auricular na aquisição, maior tempo de aquisição ou dose de contraste administrada, menor frequência cardíaca e utilização de uma voltagem da ampola de 120 kV (*Tabela II*).

Por análise multivariada, os preditores de uma dose de radiação alta foram: maior IMC, cirurgia cardíaca prévia, presença de fibrilhação auricular na aquisição, maior tempo de

BMI >32,4 kg/m² (the best cutoff to predict high radiation dose), previous cardiac surgery, atrial fibrillation during acquisition or acquisition time >10 s (the best cutoff to predict high radiation dose) made up 38% of the population. Radiation dose was higher in this subgroup than in patients without any of these characteristics (12.1 [9.5-14.8] vs. 5.7 [5.0-6.7] mSv, p<0.001).

DISCUSSION

In this study we set out to identify the factors associated with a higher radiation dose in cardiac CT angiography. The use of a 120-kV tube voltage was a predictor of a higher radiation dose, as was higher BMI, since this meant the voltage could not be reduced. Longer acquisition time and higher contrast dose (which, as it depends on the former, lost its predictive value on multivariate analysis) were also associated with higher radiation dose.

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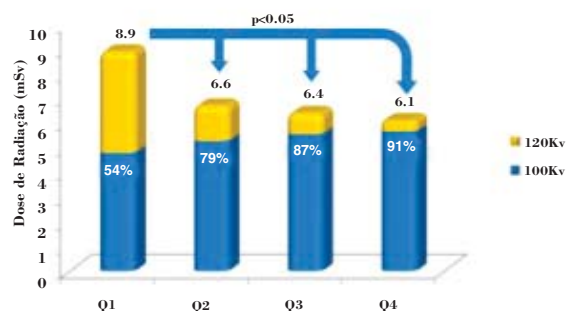


Figura 2. Representação gráfica da evolução da dose de radiação de acordo com os quartis de tempo. A percentagem incluída nas colunas representa a proporção de utilização de 100 kV como voltagem da ampola (*versus* 120 kV)

Figure 2. Chart showing changes in radiation dose by quartiles of time. The percentages in the columns represent the proportion of use 100 kV tube voltage (vs. 120 kV)

Tabela II. Variáveis testadas para preditores de dose de radiação elevada por análise univariada

Dose de radiação			
	Abaixo da mediana (6,6mSv)	Acima da mediana (6,6mSv)	p
Variáveis demográficas			
Idade (anos)	58 (52-65)	60 (51-68)	0,202
Sexo masculino (%)	50	68	<0,001
Variáveis clínicas			
≥ 1 FRCV (%)	83%	87%	0,
IMC (kg/m²)	26 (24-28)	27 (25-30)	<0,001
Cirurgia cardíaca prévia (%)	1%	11%	<0,001
Enfarte de miocárdio prévio (%)	5%	10%	0,010
FA (%)	0%	11%	<0,001
Variáveis do protocolo			
Tempo de aquisição (seg)	7 (6-8)	9 (7-11)	<0,001
Dose de contraste	78 (72-84)	90 78-102)	<0,001
Frequência cardíaca	68 (60-77)	63 (54-73)	<0,001
Voltagem da ampola120 kV	2%	41%	<0,001

FA: Fibrilhação auricular; FRCV: Factores de Risco Cardiovasculares; IMC: Índice de Massa Corporal;

Table II. Variables tested to identify predictors of higher radiation dose on univariate analysis.

	Radiation dose		
	Below median (6.6mSv)	Above median (6.6mSv)	p
Demographic variables			
Age (years)	58 (52-65)	60 (51-68)	0.202
% male	50	68	<0.001
Clinical variables			
≥ 1 CVRF (%)	83%	87%	0.170
BMI (kg/m ²)	26 (24-28)	27 (25-30)	<0.001
Previous cardiac surgery (%)	1%	11%	<0.001
Previous MI (%)	5%	10%	0.010
AF (%)	0%	11%	<0.001
Protocol parameters			
Acquisition time (s)	7 (6-8)	9 (7-11)	<0.001
Contrast dose	78 (72-84)	90 78-102)	<0.001
Heart rate	68 (60-77)	63 (54-73)	<0.001
120 kV tube voltage	2%	41%	<0.001

AF: atrial fibrillation; BMI: body mass index; CVRF: cardiovascular risk factor; MI: myocardial infarction

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aquisição e o uso 120 kV como voltagem da ampola (*Tabela III*).

Doentes com pelo menos uma das seguintes variáveis de: IMC $>32,4$ kg/m² (melhor limiar para discriminar radiação alta), cirurgia cardíaca prévia, aquisição em fibrilhação auricular ou duração da aquisição >10 s (melhor limiar para discriminar radiação alta) constituíram 38% da população. Neste subgrupo, a dose de radiação foi superior, quando comparados com a ausência de todas estas características [12,1 (9,5-14,8) versus 5,7 (5,0-6,7), $p<0,001$].

DISCUSSÃO

Neste trabalho procurámos identificar os factores associados a uma dose de radiação superior, na AngioTC cardíaca. A utilização de uma voltagem da ampola de 120 kV foi um preditor de maior dose de radiação. Em concordância com este achado, um elevado IMC, pela impossibilidade de se reduzir a voltagem da ampola, associou-se a uma maior dose de radiação. Um maior tempo de aquisição e maior dose de contraste (que, dependendo da anterior, perdeu o valor preditor por análise multivariada) associaram-se igualmente a uma dose de radiação superior.

O tempo de aquisição maior aumenta a dose de radiação, por traduzir uma maior área corporal adquirida ou por estarmos na presença de frequências cardíacas mais lentas, aumentando o tempo de diástole e a duração da aquisição nesta fase do ciclo cardíaco. A frequência cardíaca baixa, quando analisada isoladamente, também foi um preditor de maior dose de radiação. Igualmente, a presença de cirurgia cardíaca prévia, associou-se a uma maior dose de radiação. Isto resulta de uma maior prevalência de doentes com revascularização miocárdica cirúrgica, o que aumenta a janela de aquisição, para incluir as pontagens. Já a presença de enfarte de miocárdio prévio, que também foi preditor de maior dose de radiação, perdeu este valor na análise multivariada, possivelmente pelo efeito de incluir neste grupo doentes com

Longer acquisition time increases radiation dose and may reflect a larger body surface area scanned or lower heart rate causing prolonged diastole and hence acquisition time. Low heart rate, when analyzed in isolation, also predicted higher radiation dose, as did previous cardiac surgery (due to the high proportion of patients with previous CABG who required a longer acquisition window in order to include the grafts). Previous MI, which was a predictor of higher radiation dose on univariate analysis, lost its predictive value on multivariate analysis, possibly because this group included patients with previous CABG. Finally, atrial fibrillation during acquisition was associated with higher radiation dose, since it prevented ECG pulsing (see below).

Other studies have likewise found that greater body weight and absence of a stable sinus rhythm are associated with higher radiation doses⁽⁴⁾.

After excluding the main predictors of higher radiation dose (BMI $>32,4$ kg/m², previous cardiac surgery, atrial fibrillation during acquisition, and acquisition time >10 s), a subgroup of two-thirds of the population was identified in whom the radiation dose was significantly lower (5.7 mSv), a reduction of 53%.

As well as identifying the variables associated with higher radiation dose, we found that there was a progressive reduction in radiation dose over time, due to the increasing availability of low-radiation protocols, such as limiting tube voltage to 100 kV, which did not exist when our center began operating. There has also been progressive optimization of acquisition protocols to individual patient characteristics, which also helps reduce radiation dose.

There have been few studies analyzing changes in radiation dose over time. A study by Hausleiter et al. showed that a 12-month increase in experience in cardiac CT angiography was associated with a reduction of 1% in radiation dose⁽⁴⁾. Another, presented by Bettencourt de Sousa et al. at the 2008 Congress of the European Society of Cardiac Radiology, demonstrated an inverse relation-

Tabela III. Preditores independentes de dose de radiação elevada por análise multivariada

Variável	HR	IC (95%)	p
IMC	1,129	1,038-1,229	0,045
Cirurgia cardíaca prévia	5,776	1,042-32,28	0,003
FA	30,874	3,247-293,617	<0,001
Duração da aquisição	1,975	1,672-2,334	<0,001
120 kV	71,394	23,363-218,170	<0,001

FA: Fibrilhação Auricular; HR: Hazard Ratio; IC: Intervalos de Confiança; K: Índice de Massa Corporal

Table III. Independent predictors of higher radiation dose on multivariate analysis.

Variable	HR	CI (95%)	p
BMI	1.129	1.038-1.229	0.045
Previous cardiac surgery	5.776	1.042-32.28	0.003
AF	30.874	3.247-293.617	<0.001
Acquisition time	1.975	1.672-2.334	<0.001
120 kV tube voltage	71.394	23.363-218.170	<0.001

AF: atrial fibrillation; BMI: body mass index; CI: confidence interval; HR: hazard ratio

revascularização miocárdica cirúrgica prévia. Finalmente, a presença de fibrilhação auricular na aquisição associou-se a maior dose de radiação administrada por prejudicar a aquisição com “ECG gating” (descrito abaixo).

Em concordância com o encontrado, outros estudos verificaram que maior peso e a ausência de um ritmo sinusal estável, se associava a uma maior dose de radiação utilizada⁽⁴⁾.

Após exclusão dos principais preditores de elevada dose de radiação (IMC>32,4 kg/m², cirurgia cardíaca prévia, aquisição em fibrilhação auricular, duração da aquisição >10seg), foi identificado um subgrupo, correspondente a 2/3 da população, em que a dose de radiação foi significativamente menor (5,7 mSv, redução de 53%).

Além de apurarmos as variáveis que se associaram a uma dose superior de radiação, verificámos que esta foi sendo progressivamente menor ao longo do tempo. Contribuiu para este efeito o facto de terem surgido uma maior disponibilidade de protocolos de baixa radiação, como a limitação da voltagem da ampola a 100 kV, que não estava presente no início do funcionamento deste centro. Por outro lado, houve uma progressiva optimização dos protocolos de aquisição às características dos doentes, com consequente redução da dose de radiação.

A informação disponível no que respeita à

ship between a center’s experience and radiation dose, with a 22% reduction after 1000 exams⁽⁵⁾.

Reductions can be achieved by tailoring the acquisition protocol to individual patient characteristics⁽⁶⁾. Firstly, instead of rigidly scanning from carina to diaphragm, the scan range can be adjusted to the patient’s anatomy, according to a prior low-dose scan for calcium scoring⁽⁴⁾. This is a simple way to reduce the radiation used, since each 1 cm increase in scan range is associated with an increase of 5% in radiation dose⁽⁴⁾. Secondly, the tube voltage should be reduced to the lowest value that will allow image quality to be maintained for a given patient’s anatomic shape and for the equipment used⁽⁴⁾. Reducing tube voltage from 120 to 100 kV considerably reduces radiation dose, since this varies with the square of the tube voltage⁽⁷⁾. In suitable patients (nonobese), this measure can lead to a reduction of 40-46% in radiation dose without compromising image quality^(4, 8). Finally, since cardiac motion is least during diastole, diastolic image reconstructions are most likely to be free of motion artifacts, and so restricting maximum tube current to a predefined time window during diastole and decreasing it during the rest of the cycle (ECG pulsing) can reduce total radiation while maintaining image quality^(4, 9, 10). In the extreme form of this

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análise da variação da dose de radiação com a evolução temporal é escassa. Um trabalho de Hausleiter demonstrou que um aumento de 12 meses de experiência na realização de AngioTC cardíaca se associou a uma diminuição da dose de radiação de 1%⁽⁴⁾. Um outro trabalho, apresentado por Bettencourt de Sousa no Congresso da Sociedade Europeia de Radiologia Cardíaca 2008, demonstrou a presença de uma relação inversa entre a experiência do centro e a dose de radiação utilizada (redução de 22% após 1000 exames)⁽⁵⁾.

Esta redução na dose de radiação pode conseguir-se ajustando os parâmetros do protocolo de aquisição às características individuais dos doentes⁽⁶⁾. Em primeiro lugar, em vez da aquisição de imagens se estender sistematicamente da carina ao diafragma, esta deve ser ajustada de acordo com a anatomia de cada doente, de acordo com uma primeira passagem com baixa dose de radiação para *score* de cálcio⁽⁴⁾. Esta é uma técnica fácil para reduzir a radiação utilizada, já que por cada centímetro a mais na extensão de aquisição de imagens há um aumento de 5% na dose de radiação⁽⁴⁾. Em segundo lugar, a corrente da ampola deve ser reduzida para o valor mais baixo que se espere manter uma boa qualidade de imagem para determinado biótipo de doente e aparelho de AngioTC. Uma redução da voltagem da ampola de 120 kV para 100 kV diminui consideravelmente a dose de radiação, já que esta varia com o quadrado da voltagem⁽⁷⁾. Em doentes apropriados (IMC não elevado) esta medida pode levar a uma redução de 40-46% da dose de radiação sem comprometer a qualidade da imagem^(4,8). Finalmente, tendo em conta que o movimento cardíaco é menor durante a diástole, as reconstruções de imagem efectuadas nesta fase serão, com maior probabilidade, livres de artefactos de movimento. Assim, limitando a corrente máxima da ampola a uma porção pré-definida da diástole e diminuindo-a no restante ciclo cardíaco, pode diminuir-se a radiação total utilizada, mantendo a possibilidade de obter imagens de qualidade (técnica denominada “ECG *pulsing*”)^(4, 9, 10). Levando este protocolo ao extremo, pode ligar-se ape-

protocol, prospective gating, the X-ray tube is only switched on during part of diastole and is switched off for the rest of the cardiac cycle, resulting in sequential rather than spiral scanning. This protocol requires a stable heart rate below 65 bpm and hence intravenous beta-blockers are often needed⁽⁸⁾. Although it results in a substantial reduction in radiation dose, this technique does not provide functional information such as ventricular or valve function^(8, 9). A combination of 100 kV tube voltage and prospective gating can achieve an impressive reduction of 90%⁽⁸⁾.

Although the debate on the use of radiation in imaging studies has focused on cardiac CT angiography, it should be remembered that other common techniques use radiation. In 2006, cardiac CT angiography accounted for only 3% of the collective radiation exposure resulting from medical exams in the US⁽¹¹⁾. Considering only cardiological exams, the mean radiation dose in coronary angiography is 7 mSv, while for myocardial perfusion scintigraphy it is 15.7 mSv. The latter exam accounted for 22.1% of radiation exposure resulting from diagnostic exams (cardiac or non-cardiac) in the US⁽¹²⁾.

CONCLUSION

In this study of consecutive patients undergoing cardiac CT angiography, independent predictors of higher radiation dose were higher body mass index, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV. In two-thirds of the study population, none of these characteristics was present and radiation dose was significantly lower (5.7 mSv). Over time, it has been possible to reduce the radiation dose used in these exams, as a result of the development of new protocols and progressive optimization of existing protocols and by adapting them to individual patient characteristics.

nas a ampola durante parte da diástole e desligá-la no restante ciclo cardíaco com aquisição não helicoidal (“gating prospectivo”). Este protocolo requer uma frequência cardíaca estável e inferior a 65 batimentos por minuto, com necessidade frequente da utilização de betabloqueantes endovenosos⁽⁸⁾. Apesar de diminuir bastante a dose de radiação utilizada, não permite obter informação funcional (ex: função ventricular ou valvular)^(8, 9). A combinação da utilização de uma voltagem da ampola de 100 kV e a aquisição prospectiva podem conseguir uma impressionante redução de 90%⁽⁸⁾.

Embora o debate sobre o uso de radiação em exames de imagem se tenha centrado na AngioTC cardíaca, deve referir-se que outras técnicas frequentemente utilizadas usam radiação. Em 2006, a AngioTC cardíaca correspondeu apenas a cerca de 3% da dose colectiva de radiação recebida em consequência de exames médicos⁽¹¹⁾. Considerando apenas os exames na área da cardiologia, referimos que a dose de radiação usada numa coronariografia 7 mSv e de uma cintigrafia de perfusão miocárdica é de 15,6 mSv. Este último exame foi responsável por 22,1% da exposição de radiação em consequência da realização de exames complementares de diagnóstico (cardíacos ou não cardíacos)⁽¹²⁾.

CONCLUSÃO

Nesta análise de doentes consecutivos submetidos a AngioTC cardíaco, foram preditores independentes de maior dose de radiação um elevado índice de massa corporal, antecedentes de cirurgia cardíaca, presença de fibrilhação auricular na aquisição, maior tempo de aquisição e o uso 120 kV como voltagem da ampola. Em 2/3 da nossa população, nenhuma destas características está presente e a dose de radiação é significativamente mais baixa (5,7mSv). Ao longo do tempo tem sido possível diminuir a dose de radiação utilizada nestes exames, resultante do aparecimento de novos protocolos e por uma progressiva optimização dos já disponíveis, adaptando-os às características individuais de cada doente.

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Ionizing radiation, Single Photon Emission Computerized Tomography, Invasive Coronary Angiography, and Cardiac Computed Tomography; Obesity

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Abstract: 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 objectivos deste estudo foram: 1) Comparar a dose de radiação de três exames: Cintigrafia de perfusão miocárdica (SPECT), coronariografia invasiva (CAT) e tomografia computadorizada 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 prospectivos (SPECT, CAT e AngioTC) durante 2 anos. A dose de radiação foi convertida a mSv e comparada entre os três registos. A evolução temporal foi avaliada por comparação do primeiro e quarto 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 3 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.

Background

Diagnostic tests that use ionizing radiation play a central role in cardiology and their use has grown in the last years, leading to an increasing concern because of their potential stochastic effects.

The aims of this study were: 1) 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 time trends. 2) To evaluate the impact of body mass index in the radiation dose.

Methods

Consecutive patients included in three prospective registries (SPECT, ICA and Cardiac CT) during 2 years.

Radiation dose was converted to mSv and compared between the 3 registries.

Differences over time were evaluated by comparing the first with the forth semesters.

Results

6196 exams were evaluated: 35% were 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; 5.4 ± 3.8 mSv for Cardiac CT ($p < 0.001$ for all).

Radiation dose over time: Very small reduction in SPECT's (10.7 to 10.5 mSv, $p = 0.004$); significant increase (25%) in ICA (7.0 to 8.8 mSv; $p < 0.001$); significant reduction (29%) in Cardiac CT (6.5 to 4.6 mSv, $p < 0.001$). Obesity was associated with a significantly higher radiation dose, across the different exams.

Conclusions

Cardiac CT had a mean radiation effective dose lower than Invasive Coronary Angiography, which, in turn, had a mean radiation effective dose lower than SPECT.

There was a significantly increase in the ICA registry and a significantly decrease in Cardiac CT registry radiation dose over time.

*Documento com corpo do artigo

TITLE: Radiation effective dose of three diagnostic tests in Cardiology: Single-Photon Emission Computed Tomography, Invasive Coronary Angiography and Cardiac Computed Tomography Angiography

TITULO: Dose efectiva de radiação de três exames de diagnóstico em Cardiologia: Cintigrafia de perfusão miocárdica, Coronariografia invasiva e Tomografia computadorizada cardíaca

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Palavras chave: Radiação, Cintigrafia de Perfusão Miocárdica, Coronariografia invasiva; Tomografia Computorizada Cardíaca, Obesidade.

Key words: Ionizing radiation, Single Photon Emission Computerized Tomography, Invasive Coronary Angiography, and Cardiac Computed Tomography; Obesity

RESUMO

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

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Doentes consecutivos incluídos em três registos prospectivos (SPECT, CAT e AngioTC) durante 2 anos. A dose de radiação foi convertida a mSv e comparada entre os três registos. A evolução temporal foi avaliada por comparação do 1º e 4º 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 3 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.

ABBREVIATIONS

Cardiac CT: Cardiac Computed Tomography

ICA: Invasive Coronary Angiography

SPECT: Single-Photon Emission Computed Tomography

BMI: Body mass index

INTRODUCTION

In recent years, the development of imaging techniques using ionizing radiation has resulted in considerable progress in the diagnosis and treatment of heart diseases. For the evaluation of patients with possible coronary artery disease, three commonly used diagnostic modalities use ionizing radiation: Single Photon Emission Computerized Tomography (SPECT), Cardiac Computed Tomography (Cardiac CT) and Invasive Coronary Angiography (ICA), the later being considered the gold standard for coronary artery disease diagnosis. (1)

Different dosages of radiation 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 the more frequent use of these exams, there have been growing concerns about radiation's potential secondary effects, especially the stochastic effects related to the high cumulative doses over time (6, 7).

We have previously reported on the radiation effective dose associated with cardiac CT in a single center registry, documented a significantly decrease in dose over time, and were able to identify the predictors of higher dose. (8)

Recently, new scanners and acquisition protocols were developed which lead to significant reductions in radiation dose associated with cardiac CT (9, 10).

The aims of this study were: 1) To evaluate and compare the radiation effective dose used in three diagnostic tests: SPECT, ICA and Cardiac CT, as well as their time trends. 2) To evaluate the impact of body mass index (BMI) in the radiation dose.

METHODS

From three prospective registries of SPECT, ICA and Cardiac CT, we selected for this analysis the exams performed during two consecutive years (01/October/2008 to 30/September/2010) and in which the indication was the evaluation of possible coronary artery disease.

The exams were performed with: Gamma-camera SMV DST-SX using ^{99m}Tc -tetrofosmin with stress / rest protocol (SPECT registry); Siemens Coroscop top / ARTIS dFC (ICA registry) and Siemens Dual Source Somatom definition CT (Cardiac CT registry). Radiation effective dose was converted to mSv (according with current literature references and manufacturer information) and compared between the registries. Briefly, for the conversion of cardiac CT dose length product (DLP) a conversion factor of $0.014 \text{ mSv Gy}^{-1} \text{ cm}^{-1}$ was used (9, 11); for the conversion of the ICA dose area product (DAP), a conversion factor of $0.183 \text{ mSv Gy}^{-1} \text{ cm}^{-1}$ was used (12, 13) ; for the conversion of the SPECT injected activity the conversion factors of $0.0060 \text{ mSv MBq}^{-1}$ (after exercise) and $0.0071 \text{ mSv MBq}^{-1}$ (at rest) were used (14-16).

To evaluate the time trend in radiation doses, the population was divided in 4 semesters according to the date of the exam and radiation effective dose was compared between the first and the last semester 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 $\pm$ standard deviation (otherwise specified),

and categorical variables as number (n) or frequency of patients (%).

Continuous variables were analyzed using Mann-Whitney or the Kruskal-Wallis nonparametric tests. Chi squared was used to test for differences in the frequencies.

Statistical significance was accepted for 2-sided P values <0.05.

Statistical analysis was performed using SPSS Statistics 17.0 for Windows.

RESULTS

During the 2 years included in this analysis, 6196 exams were performed: 3267 (52.7%) were ICAs, 1585 (25.6%) were SPECTs and 1344 (21.7%) were Cardiac CTs. Population demographic and clinical characteristics are presented in Table 1.

Mean radiation effective dose was 8.2 ± 5.6 mSv for the whole population. Mean radiation effective 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 comparisons, Figure 1).

After the population was divided in semesters, the temporal analysis showed that there was a very small but significant reduction in SPECT's mean radiation effective dose (10.7 to 10.5 mSv; $p < 0.01$). In Cardiac CT there was a significant 29% decrease (6.5 to 4.6 mSv, $p < 0.001$) and in the ICA registry a significant 25% increase in mean radiation effective dose with time (7.0 to 8.8 mSv; $p < 0.001$) (table 2 and figure 2).

Considering the 25% increase in ICA's mean radiation effective dose from the first to the forth semester, the variables associated with this increase were: higher proportion of positive exams, of radial vascular access and of exams performed by fellows in training

(Table 3). In the first semester 39% of the ICAs 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 the ICAs were performed by radial access, while in the fourth semester this proportion increased to 46%. In our population, the use of a radial vascular access was associated with a mean increase in 15% of the radiation effective dose (from 7.8 mSv with femoral to 9.0 with radial access, $p<0.001$). Finally, the proportion of exams performed by fellows in training increased from 26% in the first semester to 52% in the fourth. In this registry, when the exam was performed by a fellow in training there was a mean increase in 29% of the radiation effective dose (from 7.3 mSv with a senior operator to 9.4 mSv with a fellow operator, $p<0.001$).

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

The influence of body mass index in mean radiation effective doses was also evaluated. There was a significantly higher dose in obese patients ($BMI \geq 30 \text{ kg/m}^2$) as compared to overweight patients which in turn was higher than that of patients with normal weight ($BMI < 25 \text{ kg/m}^2$) – figure 3.

DISCUSSION

In this analysis, we found significantly different radiation effective doses associated with common diagnostic tests used in Cardiology. The dose was higher for SPECT, followed by ICA and lower for Cardiac CT. Furthermore, in the present registry we found some time trends in the mean radiation effective dose associated with ICA and Cardiac CT, related to different clinical and procedural methodologies.

The biologic effects of ionizing radiation are related with the cumulative effective doses, and doses above 100 mSv have been linked to stochastic effects like the development of cancer, while the effects of lower levels of radiation, common in diagnostic X-ray imaging, are much less clear (4, 17). Although some theoretical models like the dose threshold and the hormetic models have been proposed, the more conservative linear no-threshold model is widely accepted and in this regard it is assumed that no level of radiation is without risk (4, 17).

This is the reason that procedures that use ionizing radiation should be performed in accordance with the As Low As Reasonably Achievable (ALARA) philosophy and physicians ordering and performing cardiac imaging should be very familiar with the dosage of radiation from cardiac diagnostic tests and ways in which dose can be minimized.

The mean radiation effective dose we found for each exam is in line with previously published data (3, 4, 6, 18). Furthermore, we confirmed that there are variables that influence the radiation effective dose delivered by these exams. For ICA, the radiation

effective dose increased with the use of radial access and when operators had less experience, which is in line with data previously published (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 radiation effective dose difference between positive and negative ICAs, we could assume that positive tests needed more cine angiograms of the coronary arteries with a consequent increase in radiation effective dose used.

For Cardiac CT, the introduction and progressively more frequent use of the prospective protocol during the study period was associated in our experience with a significant decrease in the radiation effective dose in this exam, as was demonstrated by other authors (20-22). Finally, for SPECT, the dose change over time was very small, and this was expected since there were no protocol changes during the study period.

Mean radiation effective doses were significantly higher for obese patients in all the evaluated exams. This was especially true for cardiac CT and ICA, with an almost two fold difference in radiation dose between them and 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, special consideration should be taken regarding cardiac CT dose, since patients in our registry undergoing cardiac CT were significantly younger than patients in the ICA or the SPECT registries.

Although the present manuscript is focused on the comparison of the radiation dose between 3 different diagnostic exams, other features should be regarded when

1
2
3
4 comparing different imaging modalities. As cardiac CT and ICA require the
5
6 administration of iodinated contrast, some attention should be directed to the
7
8 presence of an impaired renal function and history of allergies; likewise, the
9
10 probability of coronary artery disease is considered to be also an important factor,
11
12 as SPECT and ICA are more adequate for patients at higher CAD probability (24, 25).
13
14 This way, all these features (dose of radiation, need for iodinated contrast and CAD
15
16 probability) should be taken into consideration when selecting the most
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18 appropriate exam for each patient.
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31 **CONCLUSIONS**

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37 In these registries of diagnostic tests commonly used in cardiology, the radiation
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39 effective dose used in Cardiac CT was lower than the one used in Invasive Coronary
40
41 Angiography, which, in turn, was lower than the effective dose used in SPECT. There was
42
43 a significant increase over time in the mean radiation effective dose associated with
44
45 Invasive Coronary Angiography, mainly related to the increase use of radial access, and a
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47 decrease in Cardiac CT effective dose as a consequence of the implementation of the
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49 prospective protocol. Obesity was associated with a significantly higher radiation dose,
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51 across the different exams.
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FIGURE LEGENDS:

Figure 1. Mean radiation effective dose used in each exam studied.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography

Figure 2. Time trends in mean radiation effective dose used in each exam.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography

Figure 3: Mean radiation effective doses for each exam across different BMI classes.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography; Body mass index

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Tabelas 1-3

Table 1. Population demographic and clinical characteristics

	Cardiac CT (n=1344)	ICA (n=3267)	SPECT (n=1585)
Age (years, mean± SD)	59 ± 12	66 ± 12	64 ± 9
Male gender (%)	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 Habits (%)	27%	31%	N/A
Previous MI (%)	3%	17%	N/A
Previous PCI (%)	7%	18%	N/A
Previous CABG (%)	3%	7%	N/A

Values are mean SD or percentages.
N/A: Not available

Table 2. Mean radiation effective dose for each exam across the 4 semesters.

	1 st semester	2 nd semester	3 rd semester	4 th semester	p (1 st vs 4 th)
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

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography;

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

		Δ mSv	1st Semester	4th Semester
ICA	Proportion of patients that performed PCI	N.D.	39%	42%
	Exams performed by fellows in training	↑29%	26%	52%
	Proportion of radial vascular access	↑15%	1%	46%
Cardiac CT	Prospective acquisition	↓60%	0%	45%

Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography;

Figura 1
[Click here to download high resolution image](#)

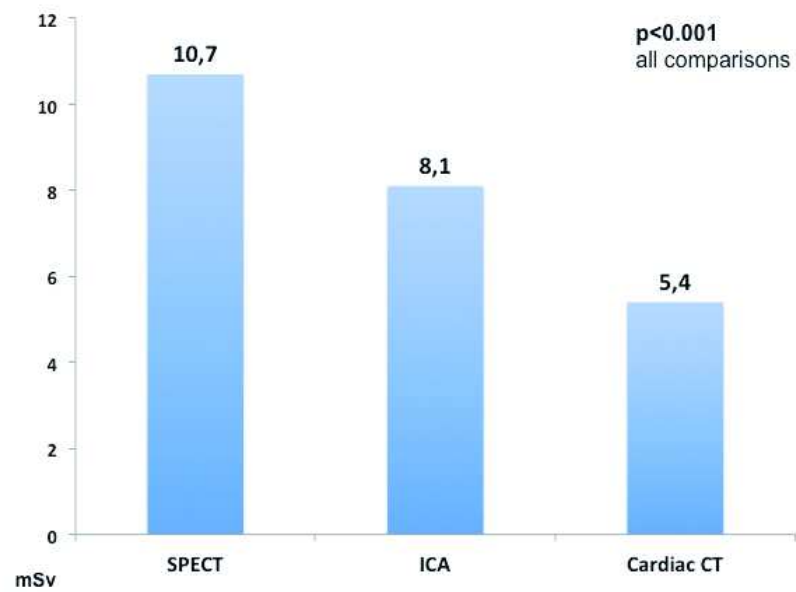


Figura 2
[Click here to download high resolution image](#)

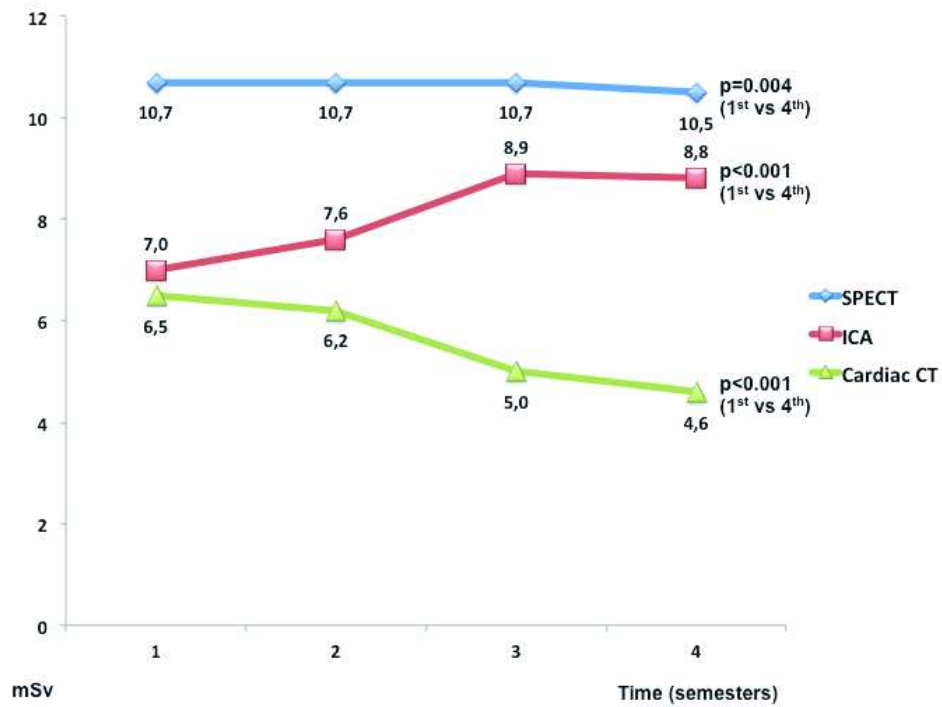
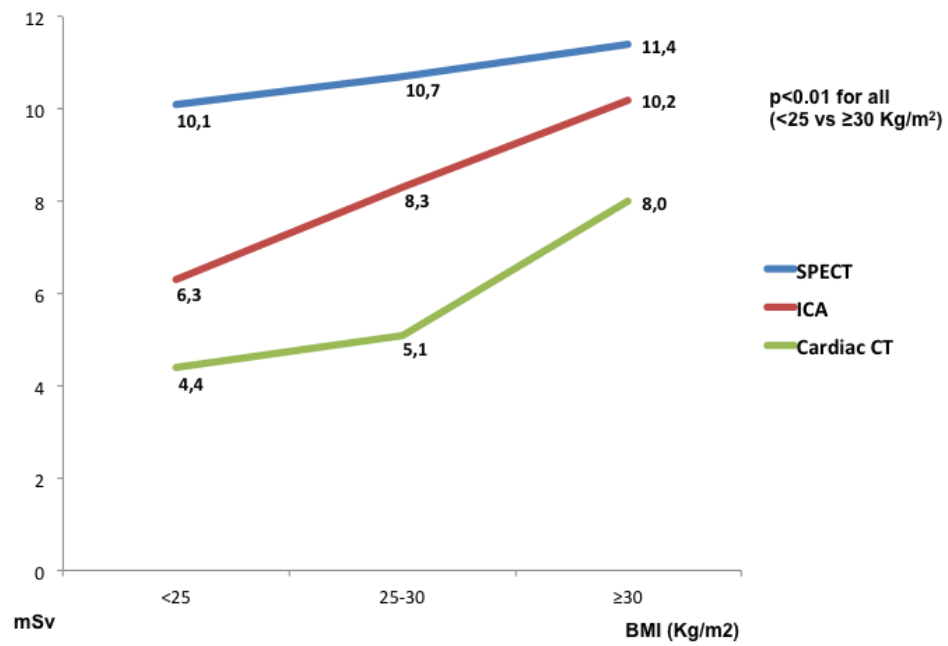


Figura 3
[Click here to download high resolution image](#)



Capítulo 6.

Desempenho dos scores de risco clínicos

RESUMO:

Este capítulo aborda um dos objectivos desta tese: a avaliação do desempenho dos scores de risco clínicos na identificação da presença e da gravidade da doença coronária documentada por angio TC cardíaca. São descritos os scores de probabilidade de DC (Diamond-Forrester e Morise) e de risco CV (HeartScore) usados e os resultados modestos na identificação dos doentes com elevada carga aterosclerótica. Uma importante percentagem dos doentes estudados considerados de baixa probabilidade de DC ou de baixo risco CV apresentavam doença, com predomínio de DC não obstrutiva. Por outro lado, um subgrupo de doentes considerados pelos scores clínicos como de elevada probabilidade e/ou risco CV, não tinha qualquer placa identificável na sua árvore coronária.

Foi incluído neste capítulo um artigo original (**artigo 15**) que aborda a questão do paradoxo da obesidade revisitado pela angio TC cardíaca e ilustra as limitações da estimativa clínica da carga aterosclerótica coronária.

ABSTRACT:

This chapter describes one of the objectives of the present thesis: to evaluate the performance of clinical scores to identify the presence and severity of coronary artery disease documented by cardiac CT. The pre-test coronary disease probability (Diamond-Forrester and Morise) and the CV risk (HeartScore) scores are described, as well as their modest results in the identification of patients with a high disease burden. A significant percentage of the studied population considered as low probability or CV risk had coronary disease, predominantly nonobstructive. On the other hand, a subset of patients considered by the risk scores as high probability or CV risk had no atherosclerotic plaques in the coronary tree.

Included in this chapter is an original manuscript (**manuscript 15**) on the obesity paradox revisited by cardiac CT, as it illustrates well the limitations to clinically estimate the coronary atherosclerotic burden.

ARTIGO 15/ MANUSCRIPT 15:

BODY MASS INDEX AS A PREDICTOR OF THE PRESENCE BUT NOT THE SEVERITY OF CORONARY ARTERY DISEASE EVALUATED BY CARDIAC-CT

Dores H, de Araújo Gonçalves P, Carvalho MS, Jerónimo Sousa P, Ferreira A, Cardim N, Mota Carmo M, Aleixo A, Mendes M, Pereira Machado F, Roquette J, Marques H.

Eur J Prev Cardiol. 2013 Jun 17. [Epub ahead of print] DOI:10.1177/2047487313494291.

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6.1. INTRODUÇÃO

6.2 SCORES DE RISCO CARDIOVASCULAR

6.3 SCORES DE PROBABILIDADE PRÉ-TESTE DE DOENÇA CORONÁRIA

6.4 DESEMPENHO DOS SCORES CLÍNICOS NA IDENTIFICAÇÃO DE PRESENÇA E GRAVIDADE DA DOENÇA CORONÁRIA DOCUMENTADA POR ANGIO TC CARDÍACA.

6.5 OBESIDADE E DOENÇA CORONÁRIA – IMPLICAÇÕES PARA OS SCORES

6.6 BIBLIOGRAFIA

6.7 ARTIGO 15

6.1. INTRODUÇÃO

Os doentes que já sofreram uma manifestação clínica do processo aterosclerótico, qualificam-se automaticamente para um patamar de risco mais elevado e, após esta etapa, existem linhas claras acerca da sua orientação e seguimento, na chamada prevenção *secundária*. O desafio mais importante, tanto na Cardiologia como em outras áreas da Medicina, consiste na correcta identificação dos indivíduos que estão em risco de eventos CV, identificando assim a doença numa fase precoce e iniciando medidas de prevenção *primária* com o objectivo de alterar a sua história natural.

Os factores de risco modificáveis (tabagismo, diabetes, dislipidémia, hipertensão arterial, obesidade) e não modificáveis (idade, sexo e história familiar) permitem estimar o risco CV e o seu desempenho melhora quando agrupados em scores. O uso dos scores de risco CV é recomendado nas varias *guidelines* uma vez que permitem através da conjugação dos diferentes factores de risco, fornecer uma estimativa do risco de eventos CV, sendo assim útil para decidir o nível de agressividade nas medidas de prevenção primária.

Para além dos scores de risco CV, existem scores que permitem estimar a probabilidade de DC, os chamados scores de probabilidade pré-teste, úteis sobretudo na selecção do melhor exame a usar na investigação da DC.

6.2 SCORES DE RISCO CARDIOVASCULAR

Um dos exemplos de score de risco CV é o **score de Framingham** (1), amplamente divulgado na recomendações do “*National Cholesterol Educational Program-Adult Treatment Panel III*” (NCEP-ATPIII) para decisão no manejo do doente com dislipidémia (2). As variáveis incluídas no score de Framingham são a idade, o sexo, tabagismo, diabetes, colesterol total, colesterol HDL e a tensão arterial sistólica. De acordo com o resultado, os doentes são classificados em baixo risco de eventos coronários (EAM e morte) a 10 anos se <10%; em risco intermédio se entre 10 e 20%; em risco elevado se >20%. O score de Framingham tem sido usado em varias recomendações de prevenção primária (3, 4), sendo também referido como ferramenta para selecção dos doentes para angio TC cardíaca (5).

Mais recentemente, foi desenvolvido o **HeartScore** (ou SCORE), que acompanhou as *guidelines* de prevenção primária da sociedade europeia de cardiologia em 2003(6), actualizadas em 2012 (7) e que foi construído a partir dos dados epidemiológicos de vários países da Europa. Na sua constituição, e à semelhança do score de Framingham, entram as variáveis idade, sexo, colesterol total, tabagismo e tensão arterial sistólica – **figura 1**. Os intervalos de risco do HeartScore são inferiores aos do score de Framingham porque este foi desenvolvido para prever apenas morte

CV. Os seus patamares para morte CV a 10 anos são os seguintes: Baixo risco de <1%; risco moderado de 1-5%; ≥5% risco elevado; ≥10% risco muito elevado.

Assim, quer o score de Framingham quer o HeartScore são ferramentas úteis para estimar o risco CV, etapa fundamental para adequar as medidas de prevenção primária. No entanto, apesar de esta estimativa resultar em termos populacionais, torna-se difícil por vezes perante um indivíduo em particular estimar o seu risco, que frequentemente vem subvalorizado, nomeadamente nos indivíduos mais novos ou com história familiar de doença CV prematura. Por outro lado, apesar de em *termos relativos* os indivíduos de patamares de risco superiores terem maior probabilidade de virem a sofrer um evento CV, em *termos absolutos*, como a maior parte da população está em patamares de risco mais baixos, a grande maioria dos indivíduos que vem a sofrer um acidente CV estaria previamente classificados em patamares de risco não elevados (8).

6.3 SCORES DE PROBABILIDADE PRÉ-TESTE DE DOENÇA CORONÁRIA

A selecção de determinado tipo de exame, bem como a valorização do seu resultado está na dependência não só da acuidade diagnóstica do exame mas também da probabilidade pré-teste de doença, de acordo com o teorema de *Bayes*. No caso concreto da DC, existem varias ferramentas que permitem, a partir da dados demográficos e clínicos, fazer esta estimativa.

Um destes exemplo é o **score de Diamond-Forrester**, desenvolvido como um método para estimar a probabilidade de DC obstrutiva a partir de 3 variáveis facilmente colhidas: idade, sexo e características da dor torácica (9) – **figura 2**. Apesar das suas limitações, nomeadamente por não entrar em linha de conta com os habituais factores de risco CV e a larga dependência nas características da dor torácica, este score tem resistido à passagem do tempo e o seu uso ainda é actualmente recomendado em varias guidelines (10, 11). O score de Diamond e Forrester espelha algo que é transversal a todos os scores: o balanço entre a sua complexidade (para ter poder discriminativo) e simplicidade (influenciada pelo número e operacionalização das variáveis) é crucial para a adopção na prática clínica (12) – aspecto discutido no **capítulo 2**.

Recentemente, foi feita uma actualização deste score a partir de dados de coortes mais recentes de doentes incluídos em bases de dados de coronariografia convencional, tendo sido demonstrado que o score original sobrestimava a probabilidade real de DC nesta população mais recente (13). Esta calibração, publicada pelo **CAD consortium**, entra com as mesmas variáveis embora usando a idade como variável continua. As categorias de probabilidade são as seguintes:

- <30%, baixa probabilidade
- ≥30-70%, probabilidade intermédia
- ≥70% - probabilidade alta

Esta disponível *online* uma calculadora para este efeito (14) – **figura 3**.

Um outro score validado para estimar a probabilidade de DC obstrutiva é o **score de Morise**, que entra em linha de conta com os mesmas 3 variáveis do score de Diamond-Forrester e adicionalmente com factores de risco CV, nomeadamente a diabetes, dislipidémia, hipertensão arterial, obesidade, status estrogénico e tabagismo (15) – **figura 4**.

Este score demonstrou ser útil não só para prever a presença de DC, mas também a sua gravidade e posteriormente foi também avaliado o seu desempenho como score prognóstico (16). Neste score, as categorias de probabilidade são as seguintes:

- scores de 0 a 8, probabilidade baixa
- scores de 9 a 15, probabilidade intermédia
- scores ≥ 16 , probabilidade alta.

FIGURA 1: Tabela do HeartScore para países de baixo risco cardiovascular

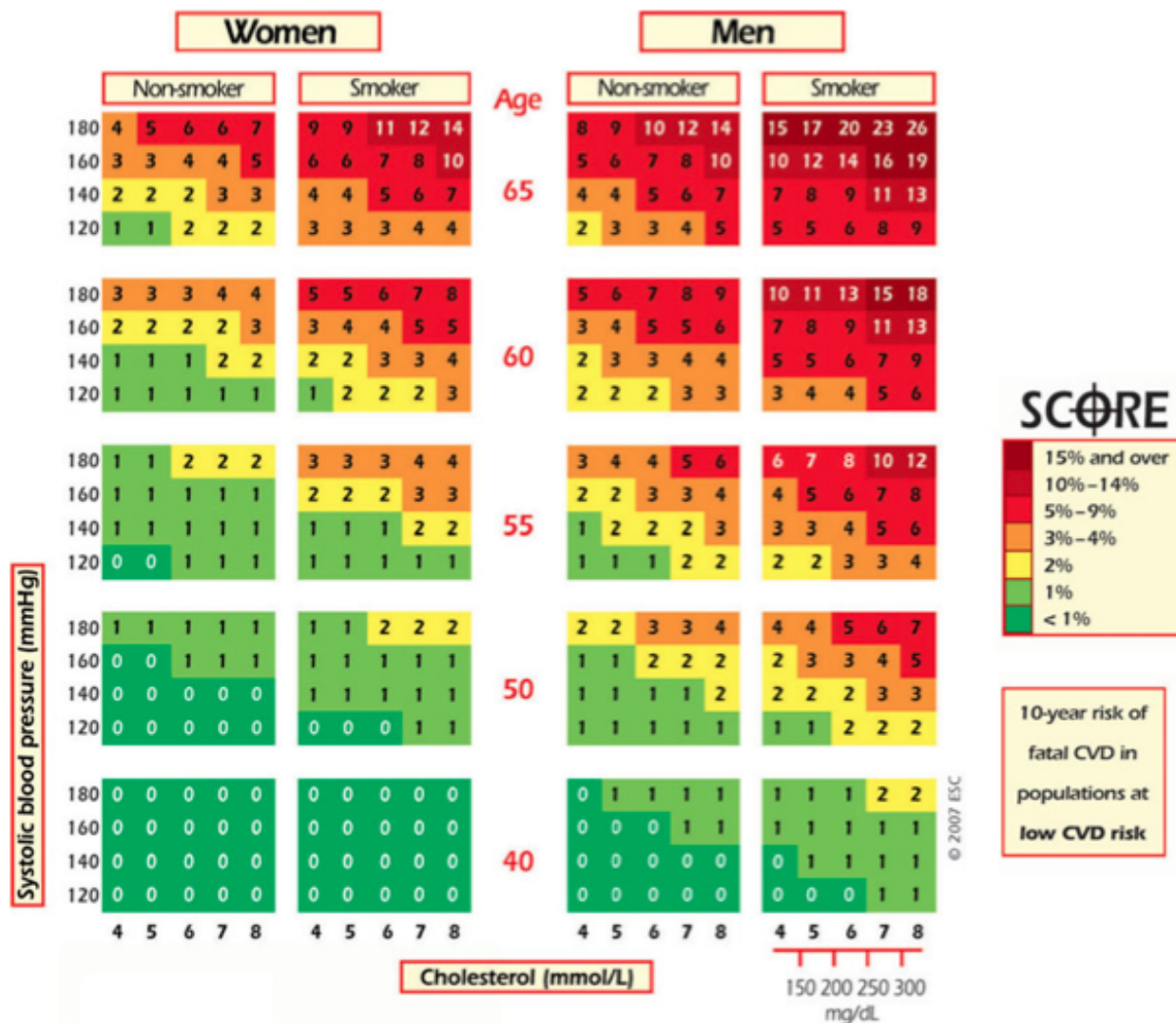


FIGURA 2: Score de Diamond-Forrester

(*adaptação das Guidelines "Exercise testing ACC/AHA 2002"*)

Table 4. Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms*

Age (y)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

FIGURA 3: Score de Diamond-Forrester – CAD consortium

(calculadora disponível no site:

<http://rcc.simpal.com/RCEval.cgi?Owner=tgenders&RCName=CAD%20consortium>)



CAD consortium 1

Age		?
Sex	Male v	?
Symptoms	Typical v	?

Probability of CAD (≥ 1 vessel with $\geq 50\%$ lumen diameter reduction on conventional angiography)

¹ [Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011.](#)



Risk Calculator hosted by The Cleveland Clinic

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CAD consortium coordinator <t.genders@erasmusmc.nl>

FIGURA 4: Score de Morise

A Pretest

<i>Variable</i>			<i>Choose response</i>	<i>Sum</i>
Age	Men	Women		
	<40	<50	3	
	40-54	50-64	6	
	≥55	≥65	9	
Estrogen Status			Positive = -3	
Women only			Negative = +3	
Angina History			Typical = 5	
Diamond Method			Atypical = 3	
			Non-anginal = 1	
Diabetes?			2	
Hyperlipidemia?			1	
Hypertension?			1	
Smoking? (Any)			1	
Family Hx CAD? 1°			1	
Obesity? BMI>27			1	
			Total Score:	

6.4 DESEMPENHO DOS SCORES CLÍNICOS NA IDENTIFICAÇÃO DE PRESENÇA E GRAVIDADE DA DOENÇA CORONÁRIA DOCUMENTADA POR ANGIO TC CARDÍACA.

Um dos objectivos da tese foi avaliar o desempenho dos scores clínicos na identificação da presença e da gravidade da DC (obstrutiva e não obstrutiva) documentada por angio TC cardíaca.

Para esta análise, foi feita a distribuição da população previamente descrita (*capítulo 1*) pelos diferentes scores clínicos: HeartScore, Morise e Diamond-Forrester.

Foi possível documentar um razoável desempenho dos scores clínicos, mas uma importante percentagem dos doentes estudados considerados de baixa probabilidade de DC ou de baixo risco CV apresentavam doença, com predomínio de DC não obstrutiva. Por outro lado, um subgrupo de doentes considerados pelos scores clínicos como de elevada probabilidade e/ou risco CV, não tinha qualquer placa identificável na sua árvore coronária (*Figuras 5, 6 e 7 e tabela 1*).

Na *Figuras 5* é apresentada a distribuição da presença e gravidade de DC de acordo com o risco CV classificado pelo **HeartScore**. A percentagem de doentes com DC (obstrutiva e não obstrutiva) foi significativamente mais alta na população de elevado risco CV (HeartScore $\geq 5\%$). No entanto, em quase metade (48,7%) da população considerada como de baixo risco CV, foram documentadas placas na árvore coronária e em 8,5% dos casos a doença era obstrutiva.

Foi interessante verificar que o HeartScore, ferramenta útil para estimar o risco CV, foi também um bom preditor da presença de DC, tendo inclusive sido o score com melhor desempenho a este nível. Na nossa população, os doentes com um HeartScore ≥ 5 tinham uma probabilidade cerca de 4 vezes superior de ter DC (qualquer placa na árvore coronária) e quase 3 vezes superior de ter DC obstrutiva (*Tabela 1*).

Nas *Figuras 6 e 7* está representada a análise da distribuição da população em função da presença e gravidade da DC nos vários patamares de probabilidade pré-teste de DC, estimada pelo score de **Diamond-Forrester** e de **Morise** respectivamente. À semelhança da distribuição encontrada para o score de risco CV, apesar da percentagem de DC (quer obstrutiva quer não obstrutiva) acompanhar o aumento da probabilidade de DC, uma percentagem significativa dos doentes com baixa probabilidade (45,2% com o Diamond-Forrester e 25% com o Morise) tinham placas ateroscleróticas na árvore coronária.

Os scores de probabilidade pré-teste de DC estão muito na dependência da presença de sintomas. Estes, sobretudo no caso da angina típica, dão um contributo muito importante para a probabilidade de DC, uma vez que estes scores foram desenvolvidos para prever a presença de DC obstrutiva identificada na coronariografia invasiva. Isto é sobretudo verdade para o score de Diamond-Forrester, uma vez que para além dos sintomas entra apenas em linha de conta com a idade e o sexo. No caso do score de Morise, para além dos sintomas, sexo e idade, estão incluídos os habituais factores de risco CV, sendo inclusive dado um valor ponderal superior à diabetes em relação aos restantes factores de risco. Esta maior robustez do score faria prever um melhor desempenho em relação ao score de Diamond-Forrester, mas na nossa análise o desempenho para prever a presença de DC, quer obstrutiva quer não obstrutiva foi muito semelhante para estes dois scores. Isto pode ter sido o resultado de nesta análise se ter usado a nova calibração do Diamond-Forrester (CAD consortium), que foi validada recentemente com bases de dados contemporâneas, tendo-se percebido que o score original sobrestimava a probabilidade, sobretudo nas mulheres (13).

FIGURA 5: Desempenho do HeartScore na identificação da presença e gravidade da doença coronária

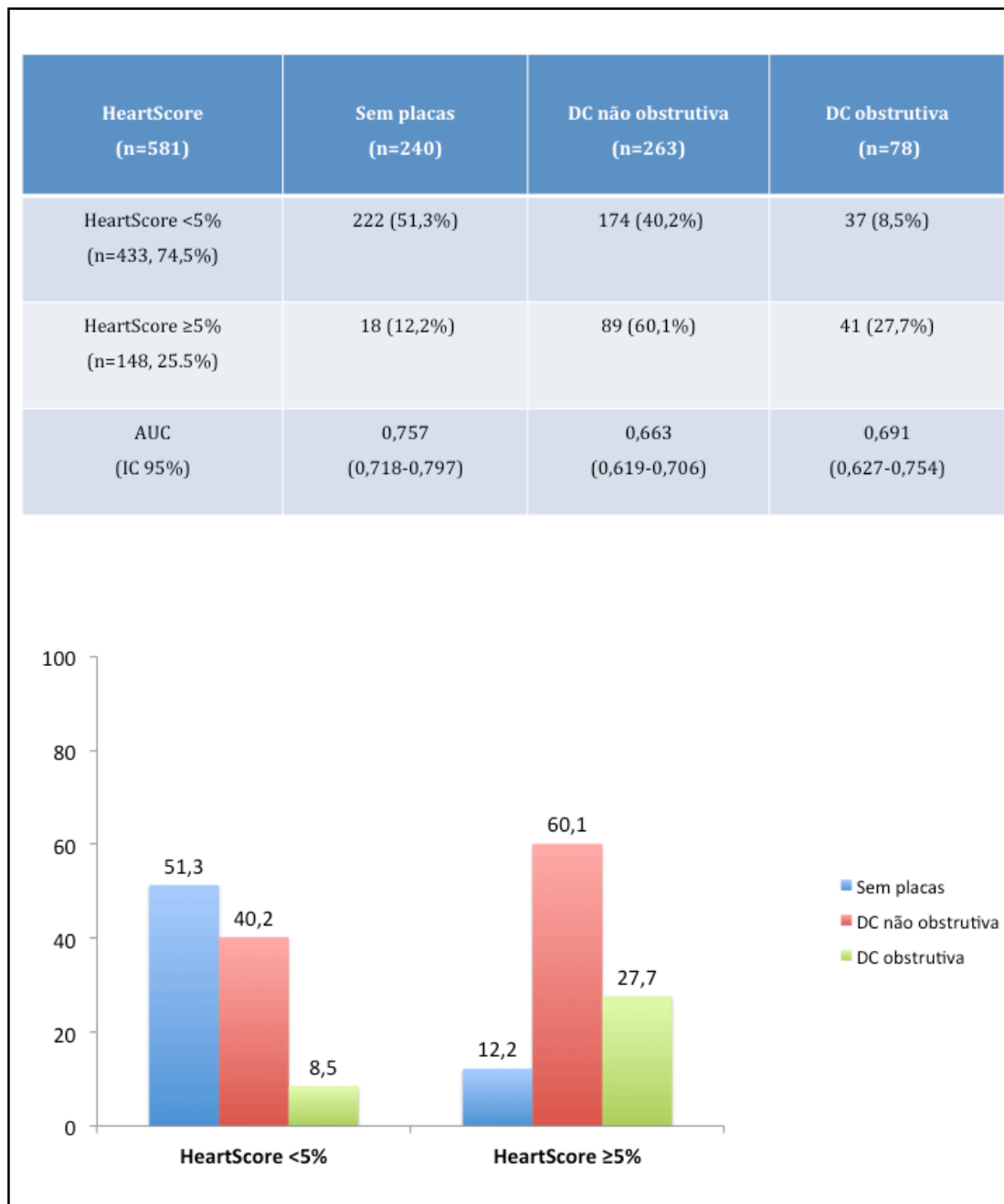


FIGURA 6: Desempenho do score de Diamond-Forrester (calibração CAD consortium) na identificação da presença e gravidade da doença coronária.

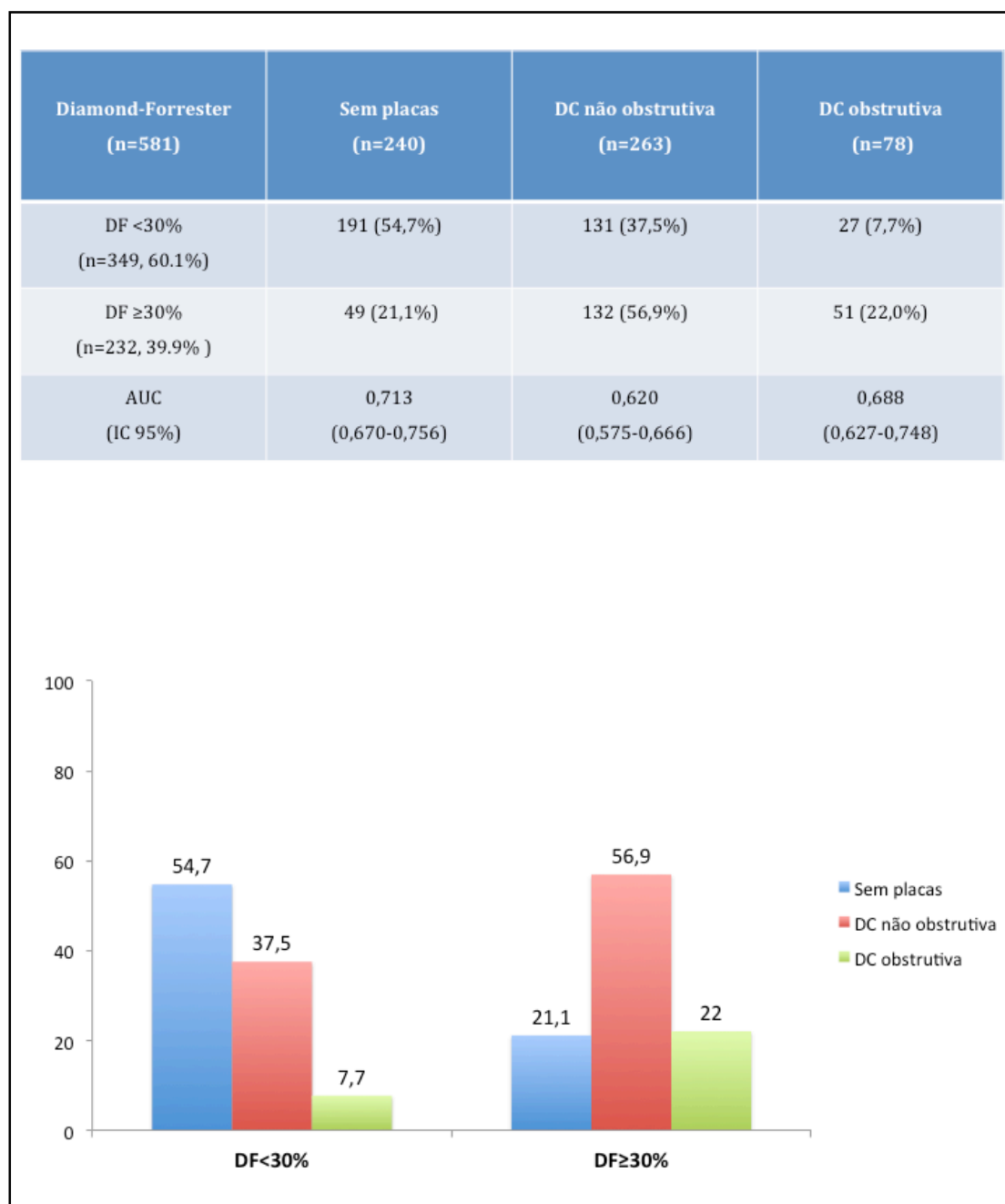


FIGURA 7: Desempenho do score de Morise na identificação da presença e gravidade da doença coronária.

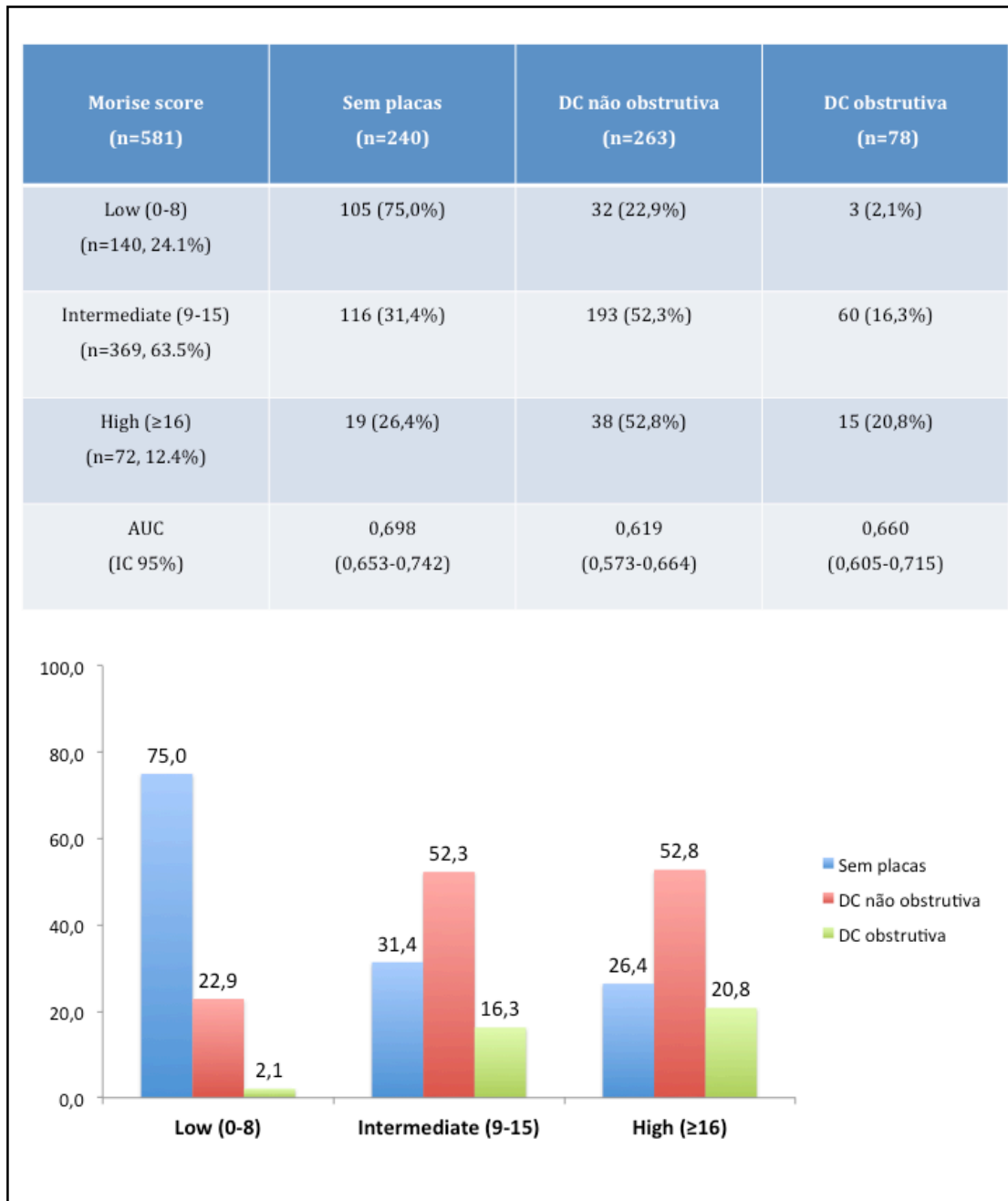


TABELA 1: Análise multivariável dos scores clínicos como preditores independentes da presença e gravidade da doença coronária.

Presença de doença coronária (qualquer placa)

	OR	(IC 95%)	p
HeartScore $\geq$ 5	3,896	2,189-6,935	<0,001
DF-CAD consortium $\geq$ 30%	2,623	1,697-4,052	<0,001
Morise $\geq$ 16	2,549	1,568-4,144	<0,001

Doença coronária obstrutiva (estenose $\geq$ 50%)

	OR	(95% CI)	p
HeartScore $\geq$ 5	2,709	1,503-4,880	0,001
DF-CAD consortium $\geq$ 30%	1,884	1,036-3,424	0,038
Morise $\geq$ 16	1,838	1,057-3,197	0,031

6.5 OBESIDADE E DOENÇA CORONÁRIA – IMPLICAÇÕES PARA OS SCORES

Nos últimos anos tem-se assistido a um aumento da prevalência da obesidade, sendo considerado um importante factor de risco CV, sobretudo pela sua associação com a síndrome metabólica e o desenvolvimento de diabetes tipo 2 (17, 18).

No entanto, a sua associação com a DC tem sido controversa, tendo sido descrito por alguns autores um paradoxo, com menor carga aterosclerótica e prevalência mais baixa de uma anatomia coronária de elevado risco nos doentes obesos, quando corrigido para os restantes factores de risco (19-21).

Um dos scores de probabilidade pré-teste usados, o score de Morise, inclui a obesidade (com o limiar discriminativo $>27 \text{ kg/m}^2$) como um dos factores que aumenta a probabilidade de DC, com o mesmo valor que os restantes factores de risco (tabagismo, hipertensão arterial, dislipidémia) à excepção da diabetes ao qual é atribuído um valor ponderal superior (15). Na nossa análise o score de Morise, apesar de incluir estas variáveis adicionais, não demonstrou ter uma acuidade diagnóstica superior ao score de Diamond-Forrester, podendo em certa medida ter sido influenciado também pelo paradoxo da obesidade.

A avaliação detalhada da carga aterosclerótica coronária possível com a angio TC cardíaca, com identificação não só de DC obstrutiva mas também de placas não obstrutivas, poderá contribuir para esclarecer melhor este paradoxo.

Com o objectivo de esclarecer a relação entre o índice de massa corporal e a presença e extensão da DC, fizemos uma análise envolvendo um elevado número de doentes ($n=1706$), estáveis e sem antecedentes de DC conhecida, referenciados para avaliação de eventual DC por angio TC (22). Neste trabalho, foi possível identificar que a obesidade ($\text{BMI} \geq 30 \text{ Kg/m}^2$; presente em 21,9% dos doentes) na análise multivariável, era um preditor independente da presença de DC (qualquer placa na árvore coronária), embora com um *OR* muito modesto. No entanto, o IMC não foi significativamente diferente quando comparados os doentes com ou sem DC obstrutiva (IMC médio $27.7 \text{ vs } 27.2 \text{ kg/m}^2$) e na distribuição dos doentes com DC obstrutiva pela diferentes classes de IMC não houve diferenças estatisticamente significativas.

Por outro lado, na avaliação detalhada da carga aterosclerótica, a percentagem de doentes com pelo menos 5 segmentos da árvore coronária com placa ($\text{SIS} > 5$) também não foi diferentes entre os grupos de doentes com peso normal, excesso de peso e obesidade. Assim, na nossa população de doentes estáveis, sem antecedentes de DC conhecida, a obesidade não foi um preditor da gravidade da DC, avaliada quer pela prevalência de DC obstrutiva, quer pelo número de segmentos da árvore coronária com placas, marcadores da carga aterosclerótica com reconhecido impacto prognóstico.

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6.7 ARTIGO 15

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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/m², $p < 0.001$); 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/m², $p = 0.120$). 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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(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

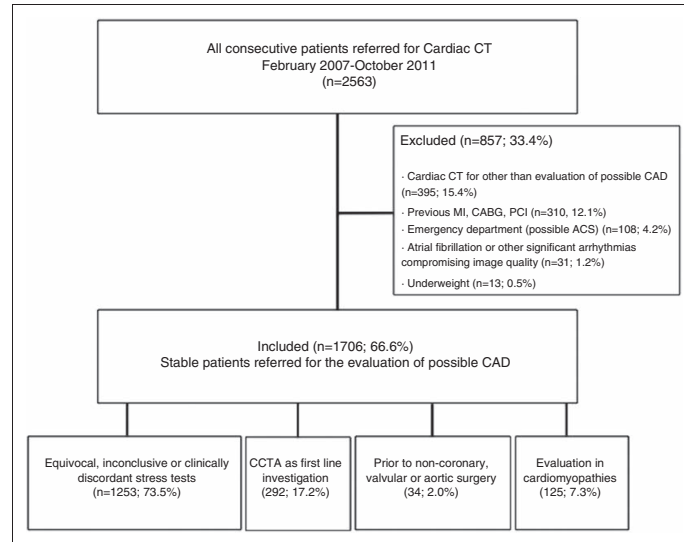
lipid-lowering drugs); (c) hypertension (defined as blood pressure $\geq 140/90$ mm Hg or the use of antihypertensive medication); (d) Positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years old); (e) smoking (defined 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/m²), normal (18.5 – 24.9 kg/m²), overweight (25.0 – 29.9 kg/m²) and obesity ($IMC \geq 30.0$ kg/m²). 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 classification¹² was used regarding segmentation (16 segments), stenosis severity ($<25\%$; 25–49%; 50–69%; 70–99%;



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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 $> 1 \text{ mm}^2$ 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- SiemensTM), 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

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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/m² 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/m², *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/m², *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

Table 1. Demographic and clinical characteristics

Variables	All patients (<i>n</i> = 1706)
Demographic	
Age, median (IQR) years	59.0 (51.0–66.0)
Male gender, <i>n</i> (%)	976 (57.2)
Cardiovascular risk factors, <i>n</i> (%)	
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%, <i>n</i> (%)	293 (17.2)
Chest pain, <i>n</i> (%)	
Asymptomatic	836 (49.0)
Non-cardiac	369 (21.6)
Atypical	363 (21.3)
Typical	138 (8.1)
BMI (kg/m²)	
Median (IQR)	26.7 (24.4–29.4)
Normal, <i>n</i> (%)	530 (31.1)
Overweight, <i>n</i> (%)	802 (47.0)
Obesity, <i>n</i> (%)	374 (21.9)

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

versus all other patients: 0.241, 0.450 and 0.663 respectively).

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 in 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

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.

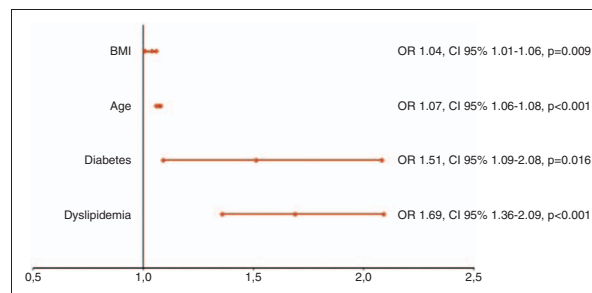


Figure 2. Independent predictors of coronary artery disease (CAD) presence (multivariate analysis). BMI: body mass index; CI: confidence interval; OR: odds ratio.

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 survival⁴ 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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Capítulo 7.

Diabetes mellitus - subgrupo modelo de elevada carga aterosclerótica

RESUMO:

Este capítulo é dedicado à diabetes mellitus, como modelo de DC mais avançada, tendo sido o preditor clínico mais importante da presença e da gravidade da DC. Deste modo a diabetes mereceu uma análise detalhada, servindo como subgrupo modelo para a avaliação do desempenho de diferentes scores de carga aterosclerótica.

Foi incluído neste capítulo o **artigo 16**, que resulta da análise dos diferentes índices de carga aterosclerótica na população incluída na tese e no qual é discutida a questão da diabetes como equivalente de risco de DC.

O padrão de DC na diabetes, mais extensa e difusa, justifica as dificuldades impostas à revascularização, tema ilustrado pelo **artigo 17** e discutido numa secção específica deste capítulo.

ABSTRACT:

This chapter is dedicated to diabetes mellitus, as a model for more advanced coronary disease, since it was identified as the single most important predictor of the presence and severity of coronary disease. In this regard, the subgroup of diabetic patients was the subject of an individual detailed analysis, useful as a model to evaluate the performance of different atherosclerotic burden scores.

Manuscript 16 was included in this chapter, since it was the result of the analysis of the different atherosclerotic burden scores and includes a discussion on the issue of diabetes as a coronary artery disease equivalent.

The coronary disease pattern in diabetes, more diffuse and severe, explains the difficulties posed to revascularization, and this issue is illustrated by **manuscript 17** and also discussed in a specific section in this chapter.

ARTIGO 16/ MANUSCRIPT 16:

DIABETES AS AN INDEPENDENT PREDICTOR OF HIGH ATHEROSCLEROTIC BURDEN ASSESSED BY CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: THE CORONARY ARTERY DISEASE EQUIVALENT REVISITED.

De Araújo Gonçalves P, Garcia-Garcia HM, Carvalho MS, Dorés H, Jerónimo Sousa P, Marques H, Ferreira A, Cardim N, Teles R, Raposo L, Mesquita-Gabriel H, Almeida M, Aleixo A, Mota Carmo M, Pereira Machado F, Mendes M.

Int J Cardiovasc Imaging. 2013; 29:1105–1114

ARTIGO 17/ MANUSCRIPT 17:

COMPLEMENTARY EFFECTS OF SIROLIMUS-ELUTING STENTS AND GLYCOPROTEIN IIB/IIIA INHIBITORS FOR PERCUTANEOUS CORONARY INTERVENTION IN DIABETIC PATIENTS: 1-YEAR FOLLOW-UP OF A SINGLE CENTER REGISTRY.

De Araújo Gonçalves P, Seabra-Gomes R, Teles R, Almeida M, Aguiar C, Raposo L, Ferreira J, Pereira Machado F.

Heart 2006, 92; 1155-56.

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7.1 INTRODUÇÃO

A diabetes mellitus é um distúrbio metabólico complexo, caracterizado por um estado de hiperglicémia crónico, resultante da interacção de diferentes factores genéticos e ambientais e culminando na lesão de vários órgãos alvo. É um importante factor de risco CV, não só pela sua estreita associação fisiopatológica, mas também pela elevada prevalência, o que a torna um importante problema de saúde pública (1).

No estudo PREVDIAB, a prevalência de diabetes tipo 2 em 2009, na população portuguesa (amostra de 5167 indivíduos entre os 20 e os 79 anos) era de 11,7%, dos quais 43,6% não tinham sido previamente diagnosticados. Esta prevalência era mais elevada nos homens e na faixa etária entre os 60 e os 79 anos, onde atingia cerca de 1 em cada 4 indivíduos (26,3%) (2).

De acordo com os últimos números do relatório anual do observatório nacional da diabetes, em 2011 esta prevalência aumentou para 12,7%, correspondendo em números absolutos a cerca de 1 milhão de doentes com diabetes em Portugal (3).

Os doentes com diabetes representam um subgrupo com elevado risco de eventos CV, estando recomendado, de acordo com as várias linhas de orientação, um manejo mais agressivo destes doentes (4-6).

No entanto este trata-se também de um subgrupo muito heterogéneo de doentes e para o qual não está actualmente indicada antiagregação em prevenção primária, reforçando o potencial papel de métodos de estratificação de risco que possam identificar os doentes antes das manifestações clínicas da aterosclerose.

7.2 DIABETES COMO EQUIVALENTE DE RISCO DE DOENÇA CORONÁRIA

Num estudo clássico publicado em 1998 no *New England Journal of Medicine*, que ficou conhecido como o estudo *Haffner*, foi avaliada a taxa de EAM numa população com e sem diabetes, para responder à questão se os doentes com diabetes deveriam ser alvo de uma terapêutica agressiva semelhante à que se fazia para os doentes com antecedentes de EAM. Neste trabalho, a taxa de enfarte verificada ao longo dos 7 anos de seguimento nos doentes com diabetes, foi sobreponível à dos doentes já com antecedentes de EAM (7). Este foi um dos trabalhos que levou ao conceito da diabetes como equivalente de risco de doença coronária, justificado por se antecipar uma taxa de eventos semelhante ao de uma população de prevenção secundária pós-enfarte.

Nas recomendações do NCEP-ATP3 publicadas em 2001 a diabetes vem considerada no patamar de risco mais elevado, a par de outros equivalentes como a doença vascular periférica, o aneurisma da aorta abdominal, a doença carotídea sintomática ou uma conjugação de diferentes factores de risco que confirmem um risco de morte ou EAM superior a 20% aos 10 anos (6).

Nas recomendações europeias é feita a mesma equivalência, sendo um doente com diabetes considerado pelo menos de elevado risco CV, com risco $\geq 5\%$ de morte CV a 10 anos ou até de muito alto risco ($\geq 10\%$ morte CV a 10 anos) se tiver associado outros factores de risco e/ou lesões de órgão alvo como microalbuminúria (5).

No entanto, a diabetes representa um grupo bastante heterogéneo de doentes e trabalhos mais recentes colocaram em questão se o risco desta população estaria ao nível de um patamar de prevenção secundária.

Num estudo que desafiou o conceito de diabetes como equivalente de doença coronária, foi feita a comparação da taxa de eventos vasculares de acordo com a presença de diabetes ou de doença coronária (estenose $\geq 50\%$ na coronariografia invasiva), tendo sido concluído que a diabetes por si só não deveria ser considerado como equivalente de risco de doença coronária, uma vez que a taxa de eventos verificada aos 4 anos de seguimento nos doentes com diabetes mas sem doença coronária era significativamente inferior à dos doentes com antecedentes de doença coronária e sem diabetes (8).

Num outro trabalho recentemente publicado que envolveu 1,2 milhões de doentes da base de dados do “*Alberta Kidney Disease Network (AKDN)*” e o “*National Health and Nutrition Examination Survey (NHANES)*”, seguidos durante 4 anos, a taxa de EAM no subgrupo de doentes com diabetes (5,4 EAM por 1000 doentes/ano) foi claramente inferior à dos doentes com EAM prévio. (18,5 EAM por 1000 doentes/ano) (9). Neste registo de larga dimensão, esta taxa de EAM verificada nos doentes com diabetes foi ainda inferior à verificada nos doentes com insuficiência renal crónica (6,9 EAM por 1000 doentes/ano), definida neste estudo como uma taxa de filtração glomerular estimada $< 60 \text{ ml/min/1.73m}^2$.

Por outro lado, embora o benefício dos antiagregantes plaquetares seja indiscutível nos doentes com diabetes e doença CV estabelecida (10), a sua indicação em prevenção primária é mais duvidosa e actualmente não recomendada na ausência de manifestações clínicas de aterosclerose (5).

Numa meta-análise de 6 estudos randomizados de aspirina vs placebo, envolvendo mais de 10.000 indivíduos em prevenção primária, não foi possível documentar redução significativa da taxa de eventos CV na população global, embora tenha ocorrido uma redução significativa na taxa de EAM no sexo masculino (11).

Este achado é aparentemente paradoxal, uma vez que nos doentes com diabetes existe um estado de maior activação plaquetar e endotelial que contribuem para a criação de um meio pró-trombótico (12). No entanto, a ausência de um benefício claro da antiagregação em prevenção primária poderá ser reflexo de uma maior taxa de resistência ao ácido acetilsalicílico nestes doentes (13). Por outro lado, esta ausência de benefício do uso indiscriminado de antiagregação nos doentes com diabetes pode colocar em evidência a heterogeneidade desta população, sendo que em vários casos a baixa taxa de eventos CV pode não ser suficiente para contrabalançar o

aumento das complicações hemorrágicas associadas ao uso destes fármacos. Torna-se assim necessário em prevenção primária estratificar o risco destes doentes, para melhor decidir quais beneficiam destas medidas farmacológicas mais agressivas.

7.3 A DIABETES MELLITUS COMO SUBGRUPO MODELO DE ELEVADA CARGA ATEROSCLERÓTICA CORONÁRIA

A doença coronária é a causa de morte mais comum nos doentes com diabetes (14) e em termos epidemiológicos, o risco de EAM destes doentes é cerca de 2 vezes superior ao da população não diabética, de acordo com os resultados do estudo INTERHEART (15).

Independentemente de se considerar ou não a diabetes como equivalente de risco de doença coronária e assim alvo de prevenção secundária, nos doentes que têm doença coronária estabelecida existem alguns aspectos particulares, nomeadamente em relação à extensão e distribuição da doença, que a tornam um **subgrupo modelo** de elevada carga aterosclerótica coronária. Na presença de diabetes, a doença coronária é frequentemente mais extensa, com maior número de lesões e vasos envolvidos. Por outro lado, a distribuição anatómica das placas na árvore coronária pode ser diferente, favorecendo uma localização mais distal nos doentes com diabetes. De acordo com a análise da distribuição dos diferentes índices de carga aterosclerótica dos doentes incluídos na tese, todos os índices estudados eram significativamente mais prevalentes nos doentes com diabetes, que tinham um número superior de placas em todos os vasos – **artigo 16** (16). Neste trabalho foi feita a análise detalhada por segmento da árvore coronária (mais de 8000 segmentos avaliados), incluindo as lesões não obstrutivas, o que permitiu estudar a distribuição anatómica na árvore coronária, tendo-se verificado uma distribuição preferencial das lesões pelos segmentos mais distais (rácio proximal/distal 0,75), por comparação com os doentes sem diabetes (rácio proximal/distal 1,04). Esta mais elevada carga aterosclerótica e diferente distribuição na árvore coronária poderá ter implicações para a eficácia das estratégias de revascularização miocárdica nestes doentes.

Por outro lado, a inflamação desempenha um papel central na aterosclerose e pode ser um factor unificador da fisiopatologia da diabetes e da doença coronária, de acordo com a hipótese “*common soil*” que sugere que um estado de inflamação de baixo grau poderia ser o meio propício ao desenvolvimento da resistência à insulina e à formação e desenvolvimento das placas ateroscleróticas na árvore vascular (17). Esta hipótese vem reforçada não só pela associação epidemiológica, mas sobretudo por trabalhos que demonstraram o papel da inflamação no

desenvolvimento do processo aterosclerótico (18) e a associação entre níveis elevados de factores inflamatórios e pró-tromboticos e o desenvolvimento subsequente de diabetes (19).

De qualquer modo, em última análise, o aparecimento dos eventos CV nestes doentes é o resultado de complexas interações entre as lesões ateroscleróticas vulneráveis, do meio pró-trombótico ou sangue vulnerável e também da vulnerabilidade do miocárdio, no conceito actual que ultrapassa a visão mais simplificada da placa, passando para o conceito do doente vulnerável (20, 21).

7.4 IMPLICAÇÕES PARA A DECISÃO DA ESTRATÉGIA DE REVASCULARIZAÇÃO.

A escolha da estratégia de revascularização, deve ter em conta estes aspectos particulares da DC na diabetes. Vários estudos demonstraram que quanto mais extensa e complexa é a doença coronária maior é o benefício da revascularização cirúrgica em relação à angioplastia, motivo pelo qual na doença do tronco comum, na doença de 3 vasos e na doença de 2 vasos com envolvimento da descendente anterior proximal a recomendação é mais forte para a cirurgia vs angioplastia (22), sobretudo em scores de Syntax elevados (23, 24).

Por outro lado, os doentes com diabetes representam um subgrupo com maior mortalidade e morbilidade após revascularização, seja ela cirurgia ou percutânea (4, 22). Após a angioplastia em particular, os doentes com diabetes tem maior risco de reestenose e de trombose, sendo justificado o uso de stents “*drug-eluting*” e medidas farmacológicas mais agressivas (25-27).

No estudo BARI-2D, doentes com diabetes e doença coronária estável foram randomizados para terapêutica medica otimizada isolada ou em associação à revascularização, tendo havido um benefício desta ultima, mas apenas no subgrupo cirúrgico (28).

No recentemente publicado ensaio randomizado FREEDOM, ficou demonstrada mais uma vez a superioridade da revascularização cirúrgica em relação à angioplastia com stents “*drug-eluting*” nos doentes com diabetes e envolvimento multivaso, com menor taxa de morte e EAM, embora à custa e uma maior incidência de acidentes vasculares cerebrais (29).

Na análise dos doentes com diabetes ou síndrome metabólico incluídos no estudo SYNTAX, foi igualmente demonstrada superioridade da revascularização cirúrgica, embora apenas nos doentes com anatomia coronária mais complexa, no último tercil de score de Syntax (30).

No registo multicêntrico PORTO, que avaliou a eficácia da angioplastia com stents “*drug-eluting*” em vasos de pequeno calibre, a taxa de eventos cardíacos foi significativamente superior no subgrupo de doentes com diabetes (que representaram 44% dos doentes incluídos, nomeadamente a taxa de reestenose. No entanto, a grande maioria das novas revascularizações verificadas no seguimento a 1 ano deste registo resultaram de progressão da doença noutros

segmentos da árvore coronária, com revascularizações do mesmo vaso não resultantes de restenose e bem como de outros vasos (31).

O principal motivo para a consistente superioridade da cirurgia em relação à angioplastia nos doentes com diabetes está relacionado com a necessidade de novos procedimentos de revascularização no seguimento, por progressão de lesões anteriormente não obstrutivas. Esta variável é mais importante para um tratamento mais focal, como é o caso da angioplastia, embora também possa interferir com o resultado da cirurgia, se houver progressão de doença nos segmentos da árvore coronária distais às anastomoses. Deste modo, a carga aterosclerótica coronária parece ser determinante para a manutenção a longo prazo de um bom resultado do procedimento de revascularização, pelo que a sua avaliação poderá ser útil no manejo destes doentes.

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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

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 $\geq 140/90$ mm Hg or the use of antihypertensive medication) [8]; (4) Obesity (body mass index ≥ 30 kg/m²); (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 than 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.

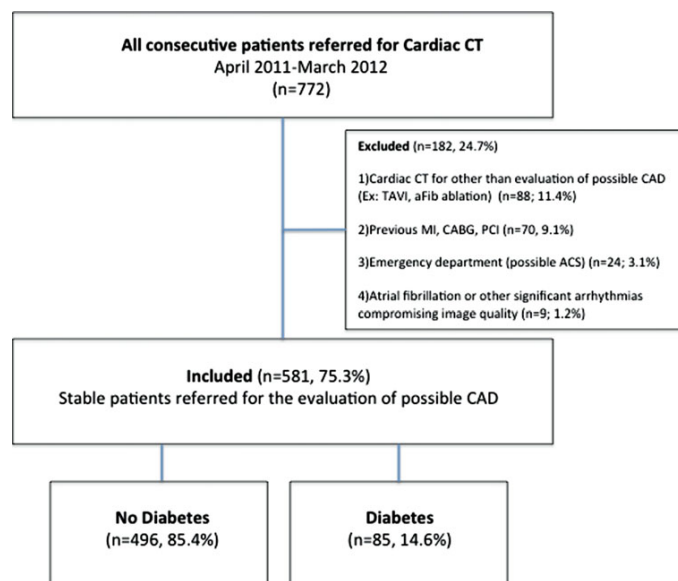
Scan protocol and image reconstruction

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) $\times$ 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

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 $>1 \text{ mm}^2$ 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

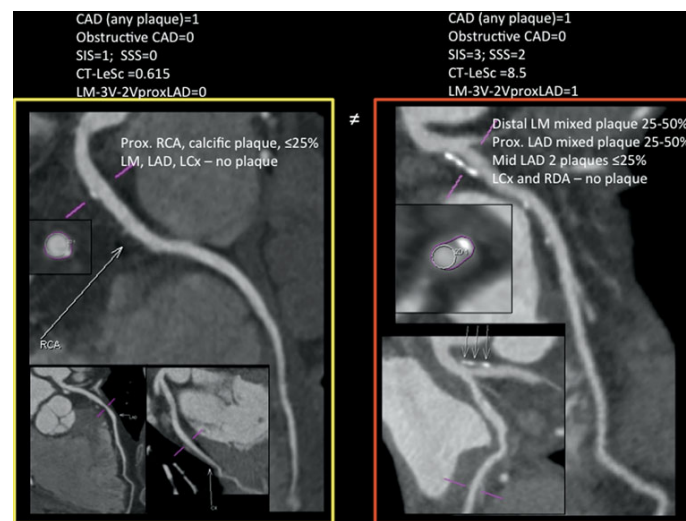


Fig. 2 Two case examples of diabetic patients with nonobstructive CAD. The different plaque burden indexes are shown. CAD coronary artery disease, SIS segment involvement score, SSS segment stenosis score, CT-LeSc CT Leaman score, LM left main, LAD left anterior

descending, LCx left circumflex, 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 $\geq 50\%$ 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 ≥ 75 th 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 $\pm$ 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.

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 $\pm$ 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 ≥ 75 th 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 $\pm$ 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 millisievert

Fig. 3 Diabetes and indexes of coronary atherosclerotic burden. CAD coronary artery disease, LM left main, LAD left anterior descending, LCx left circumflex, 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

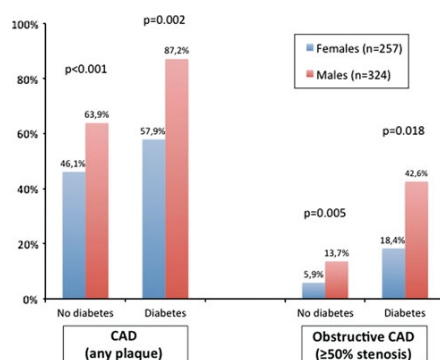
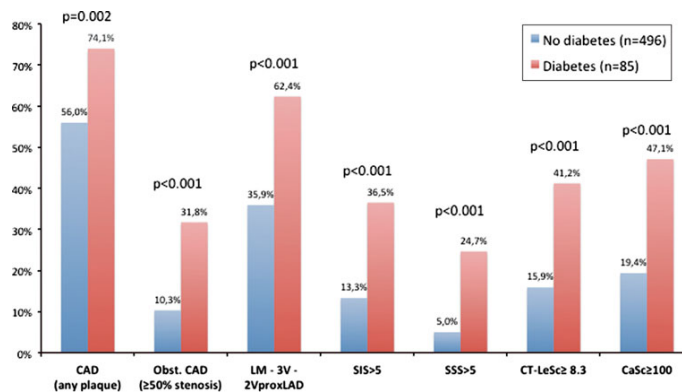


Fig. 4 Prevalence of coronary artery disease (any plaque and obstructive) across the different diabetes and sex subgroups. CAD coronary artery disease

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.

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 circumflex, 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

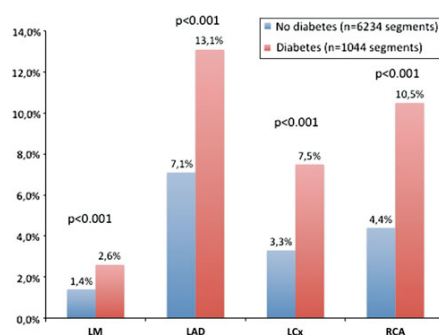


Fig. 5 Prevalence and localization of plaques (any plaque) on a *per segment* analysis. LM left main, LAD left anterior descending, LCx left circumflex, RCA right coronary artery

- Several different coronary atherosclerotic burden indexes were more prevalent in diabetics, indicating more diffuse and severe CAD, and this was especially true for males.
- 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 circumflex, 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

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 ≥ 75 th 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;

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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SCIENTIFIC LETTER

Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow up of a single-centre registry

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Patients with diabetes mellitus have an increased risk of cardiac events after percutaneous coronary intervention (PCI). As drug-eluting stents (DES) reduce restenosis and glycoprotein (Gp) IIb/IIIa inhibitors reduce the risk of death and myocardial infarction, the use of both treatments may be complementary and be a powerful tool for reducing cardiac events after PCI in diabetic patients. On the other hand, there are some concerns about the rate of stent thrombosis with DES, and some recent reports have pointed to diabetes as one of the risk factors.¹

We therefore tested the hypothesis that Gp IIb/IIIa inhibitors may reduce the rate of major cardiac events after PCI with sirolimus-eluting stents (SES) in patients with diabetes mellitus.

METHODS

This was a prospective non-randomised single-centre registry, including all consecutive patients with diabetes undergoing PCI with at least one SES at our institution from April 2002 to April 2003.

One-year clinical follow up was assessed in all patients. Patients were divided into two subgroups according to the periprocedural use of Gp IIb/IIIa inhibitors (99 patients in the group with Gp IIb/IIIa inhibitors and 104 in the group without).

The intervention strategy was entirely dependent on the operator and was performed according to standard guidelines. Patients were given a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter, for at least three months.

We evaluated a clinical end point defined as the combined incidence of the major adverse cardiac events (MACE) death, non-fatal myocardial infarction and target vessel revascularisation (TVR) at the one-year follow up.

Data were statistically analysed with SPSS V.11.0 software (SPSS Inc, Chicago, Illinois, USA) by χ^2 test, Student's unpaired t test, log rank test and Cox proportional hazards models as appropriate.

RESULTS

Of 1310 patients undergoing PCI at our institution from April 2002 to April 2003, 203 (15.5%) had diabetes and were treated with at least one SES. The Gp IIb/IIIa inhibitor used most often was abciximab (83%). Patients with acute coronary syndromes were given eptifibatide (13%) and tirofiban (4%) upstream before going to the cath lab.

The two groups of patients did not differ significantly in the baseline characteristics. However, more of the patients treated with Gp IIb/IIIa inhibitors were current smokers

(20.4% v 12.1%, $p = 0.16$) and had PCI in the setting of an acute coronary syndrome (40.8% v 28.3%, $p = 0.08$), and fewer of them had peripheral arterial disease (9.7% v 18.2%, $p = 0.12$) or a previous stroke (2.9% v 10.1%, $p = 0.07$).

Regarding the angiographic characteristics, patients treated with Gp IIb/IIIa inhibitors had a higher rate of PCI on a total occlusion (16.3% v 4.0%, $p = 0.008$), a higher mean total stent length (42.6 v 29.3 mm, $p = 0.002$) and more stents ≥ 33 mm implanted (41.3% v 24.2%, $p = 0.015$). Other important differences between the two groups of patients were the higher numbers of implanted stents (2.5 v 1.9, $p = 0.021$) and SES (2.1 v 1.6, $p = 0.028$) per patient in the group treated with Gp IIb/IIIa inhibitors.

Complete one-year follow-up information was available for all patients. The cumulative incidence of MACE at one year was significantly lower in the patients treated with Gp IIb/IIIa inhibitors (8.7% v 23.2%; hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.16 to 0.74, $p = 0.006$). There was a trend for a lower combined incidence of death and non-fatal myocardial infarction (4.8% v 12.1%; HR 0.38, 95% CI 0.14 to 1.09, $p = 0.072$) and for a lower target lesion revascularisation rate (1.9% v 7.1%; HR 0.26, 95% CI 0.05 to 1.23, $p = 0.089$) in the Gp IIb/IIIa inhibitor treated group. The rate of TVR, which includes lower target lesion revascularisation, was significantly lower in the Gp IIb/IIIa inhibitor group (4.8% v 13.1%; HR 0.34, 95% CI 0.12 to 0.95, $p = 0.040$). Two insulin-requiring patients in the group not treated with Gp IIb/IIIa inhibitors presented with subacute stent thrombosis (2.02%), on day 6 and day 8 after the procedure. Both patients had a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter. No further thrombotic stent occlusion or unexplained sudden cardiac deaths were observed in the late follow up.

Multivariable Cox proportional hazards analysis identified Gp IIb/IIIa inhibitor use to be independently associated with a reduced risk of MACE (adjusted HR 0.30, 95% CI 0.13 to 0.67, $p = 0.003$) (fig 1) and of death and myocardial infarction (adjusted HR 0.34, 95% CI 0.12 to 0.99, $p = 0.048$).

The incidence of death, non-fatal myocardial infarction and TVR was consistently lower in patients treated with Gp

Abbreviations: CARDia, Coronary Artery Revascularization in Diabetes; DES, drug-eluting stents; Gp, glycoprotein; HR, hazard ratio; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; SES, sirolimus-eluting stents; TVR, target vessel revascularisation

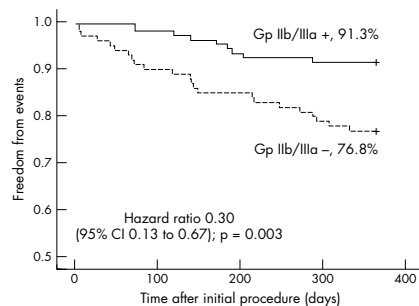


Figure 1 Major adverse cardiac event-free survival at one year. CI, confidence interval; Gp, glycoprotein.

IIb/IIIa inhibitors across the different subgroups analysed. The benefit was higher in insulin-treated patients.

DISCUSSION

This was a clinical study with consecutive patients in routine daily practice that evaluated the benefit of Gp IIb/IIIa inhibition in the context of SES in patients with diabetes mellitus. The use of Gp IIb/IIIa inhibitors was associated with a reduction in the combined incidence of death and myocardial infarction and the overall combined MACE. To the best of our knowledge, no other data have been published on this issue.

Although DES are a powerful tool against restenosis, they are not expected to have a significant impact on the rate of death and myocardial infarction after PCI.² Gp IIb/IIIa inhibitors, by having a favourable effect on these major events, can therefore exert an important complementary effect, especially in high-risk patients with diabetes. In the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry, there was a 16% rate of Gp IIb/IIIa inhibitor administration. Diabetes mellitus was an independent predictor of both MACE and TVR, and patients with diabetes were one of the subgroups in which the benefit of SES did not reach significance.³ In the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) study, which found no benefit of abciximab in low- to intermediate-risk patients undergoing elective PCI after pretreatment with 600 mg of clopidogrel, patients with diabetes under medical treatment were excluded from enrolment.⁴

Insulin-treated patients with diabetes have been one of the most difficult groups of patients to treat with DES. In our registry, the benefit of the Gp IIb/IIIa inhibitor was higher in the insulin-treated patients and in other high-risk subgroups such as patients with multivessel disease or acute coronary syndromes and patients receiving 33 mm or longer stents. Insulin-requiring patients mainly have type 2 diabetes who became insulin dependent in a later stage of disease progression. This is a particularly diseased subgroup of patients, with a more extensive burden of atherothrombotic disease. In these patients, the high incidence of death, myocardial infarction and repeat PCI at different sites may offset the benefit of local interventions, even with very effective DES that, at best, reduce restenosis.

Although in randomised clinical trials the reported rate of DES thrombosis has been within the expected range, a substantially higher incidence was recently reported in registries of real-world patients, and diabetes was identified as one of the independent predictors.¹ In our registry, the two cases of stent thrombosis were observed in the group undergoing PCI without a Gp IIb/IIIa inhibitor, and the patients were treated with insulin. Although this study is underpowered to look for differences in this infrequent event, the lack of a single case of SES thrombosis in the high-risk group of patients with diabetes taking Gp IIb/IIIa inhibitors underscores the potential benefit of these agents in this context.

In the CARDia (Coronary Artery Revascularization in Diabetes) trial, up-to-date coronary artery bypass grafting is being compared with optimal PCI, in which the use of abciximab was recommended.⁵ This is one of the ongoing randomised trials designed to evaluate the best revascularisation strategy in patients diabetes that are expected to consider these issues in a more definite manner.

This was a single-centre registry and not a randomised study with a 2 × 2 factorial design, which would have been better suited for evaluating the complementary effects of two different interventions. The baseline characteristics of the two groups were well matched but there were some differences in the angiographic and procedural characteristics. Nevertheless, these differences were in favour of the group not receiving a Gp IIb/IIIa inhibitor, and this could have underestimated the benefit of these agents.

The use of Gp IIb/IIIa inhibitors in the context of SES in patients with diabetes gave superior clinical results, due to a significant reduction in the combined incidence of death, myocardial infarction and TVR. This benefit was greater in insulin-treated patients with diabetes. This, and the lack of a single case of SES thrombosis in this high-risk group of patients who were given a Gp IIb/IIIa inhibitor during stenting, seems to warrant a randomised controlled trial to examine this issue.

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EDITORIAL

Darwin and the survival of the fittest in modern interventional cardiology

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The diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome

The use and disuse of new drugs, devices and treatments follows a frantic pace in interventional cardiology. A taste for innovation is probably a necessary inborn trait that may “naturally select” individuals who successfully pursue a career in interventional cardiology. In a healthcare environment with limited resources the competition between new and old treatments resembles the Darwinian “struggle for survival”. However, the dark side of this Darwinian marker of success is the attitude of the interventionalist to forget too hastily the proven benefits of established treatments when their attention is distracted by newly emerging therapies.

DIABETES CONFERS HIGHER RISK FOR PCI

Diabetes mellitus portends a worse prognosis in patients with coronary artery disease who undergo either percutaneous coronary intervention (PCI) or surgical revascularisation.^{1,2} The pathophysiology for the higher complication rate found in diabetic patients may involve an enhanced platelet activation state³ and proliferative response⁴ resulting in an elevated risk of thrombosis, embolisation and re-stenosis.^{2,5}

Platelet glycoprotein (Gp) IIb/IIIa inhibitors are potent antiplatelet agents and pooled analysis of earlier studies have shown they confer sustained mortality benefit in diabetic patients undergoing plain balloon angioplasty or percutaneous bare metal stent implantation (PCI).⁶

The recent trials of drug eluting stents (DES) have shown a significant fall in target vessel revascularisation rates, but they have failed thus far to show any clear mortality benefit in diabetic patients.^{7,8} One may argue that the characteristics of the population treated in these initial trials, including mainly patients with single vessel disease and a good ejection fraction, may have undermined the potential benefit of DES. Restenosis may conceivably have deadly consequences in patients with multivessel or left main stem disease who have silent ischaemia and accelerated disease progression in untreated segments.

BENEFITS OF GLYCOPROTEIN IIb/IIIa INHIBITORS IN DIABETIC PATIENTS RECEIVING DES

In this issue of Heart, Gonçalves *et al*⁹ remind us of an obvious truth: the benefit conferred by a new treatment does not cancel the effectiveness of a pre-existing proven therapy if the two treatments have completely different operative mechanisms. In a relatively large cohort of 203 patients receiving sirolimus eluting stents, the use of Gp IIb/IIIa inhibitors led to a reduction of death and non-fatal myocardial infarction (MI) (from 12.1 to 4.8 at one year) that was greater than that observed with Gp IIb/IIIa inhibitors in the seminal trials of plain balloon angioplasty and bare metal stents.⁶ In a real world population with complex coronary disease (average stent length of 42.6 mm in the treated group) it may be hypothesised that prompt inhibition of platelet function reduces platelet plugging at the ostia of multiple side branches covered by stents and prevents distal embolisation, these being the main causes of periprocedural damage during stent implantation. As the use of longer stents is a consequence of the strategy of full plaque coverage adopted with DES, one may postulate that the advantages of Gp IIb/IIIa inhibitors are likely to be greater now than before.

LIMITATIONS OF THE STUDY

It is more difficult to explain another striking result from this study—the finding that at one year the curves of the two randomisation arms for major adverse cardiac events (MACE)-free and death or MI-free survival continue to separate. Although one can foresee a reduced late mortality rate from the initial fall of non-Q wave infarction, it would be difficult to understand why the effect on MI would continue long term. Since this is a non-randomised study, any difference in the observed outcome can be significantly influenced by differences in the baseline clinical, angiographic and procedural characteristics driven by the selection process of candidates for Gp IIb/IIIa inhibitors. Although not reaching statistical significance, there was a noticeable trend of greater unfavourable variables stacked against the group not receiving the Gp IIb/IIIa inhibitors (for example, greater percentage of patients with previous MI, coronary artery bypass surgery and peripheral arterial disease).

Abbreviations: DES, drug eluting stents; Gp, glycoprotein; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation

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Various mechanism(s) have been proposed to explain the reduced target lesion revascularisation (TLR) rates observed with Gp IIb/IIIa inhibitors in some of the aforementioned studies. These include cross-reaction with the leucocyte integrin Mac-1¹⁰ and also blocking vitronectin ($\alpha_v\beta_3$) receptors on platelets and smooth muscle cells,¹¹ thereby limiting neointimal hyperplasia.¹² However, no randomised comparisons have confirmed these observations, and the results of this study suggest that such effects of Gp IIb/IIIa inhibitors persist and cause an additional positive response even in the presence of high local concentrations of an antiproliferative agent (sirolimus) in the stent.

Another limitation of the study by Gonçalves *et al*⁹ involved the timing and dose of clopidogrel in relation to the procedure. Recent studies have demonstrated that an aggressive pre-PCI regimen of aspirin and 600 mg clopidogrel leads to no significant additional benefit of Gp IIb/IIIa inhibitor on risk of death or MI in diabetic patients receiving mainly bare metal stents.^{13–14} This issue becomes all the more pertinent when it was subsequently disclosed that the two insulin-requiring diabetics who suffered thrombotic complications had an insufficient loading regimen of 300 mg clopidogrel apparently given immediately after the procedure.

FUTURE DIRECTIONS

Clopidogrel with a high loading dose of 600 mg is now being tested by the Munich group in a new randomised trial of unstable patients, but this drug, unlike Gp IIb/IIIa inhibitors, induces no more than 80% inhibition of platelet aggregation with a slow onset of action and a large variability in response. As developments in peri-PCI adjuvant drug treatment evolve, newer safer agents may threaten to supersede the use of Gp IIb/IIIa inhibitors. Another drug which may reduce the need for Gp IIb/IIIa inhibitors is the direct anti-thrombin bivalirudin which, unlike heparin, does not induce platelet activation. In a recent study with stable or mildly unstable patients undergoing PCI, bivalirudin was as effective as heparin and Gp IIb/IIIa inhibitors with lower bleeding, vascular complication rates and shorter intensive therapy unit stay.¹⁵ Bivalirudin is now under evaluation in a trial of highly unstable patients with a complex randomisation scheme.¹⁶

While awaiting the results of such trials, this study reminds us all that the diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome.

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Capítulo 8.

Desenvolvimento do CT-LeSc

RESUMO:

Neste capítulo é descrito o CT-LeSc,, uma ferramenta para quantificação da carga aterosclerótica coronária, cujo desenvolvimento foi um dos objectivos centrais desta tese. O CT-LeSc engloba informação acerca da localização, grau de estenose e tipo de placa, traduzindo assim a carga aterosclerótica coronária global (obstrutiva e não obstrutiva) obtida de modo não invasivo pela angio TC cardíaca.

O **artigo 18** incluído neste capítulo descreve a sua metodologia e os seus preditores clínicos.

ABSTRACT:

The development of the CT-LeSc, as a tool to quantify coronary atherosclerotic burden, was one of the main objectives of the Thesis, and is described in this chapter. The CT-LeSc reflects the comprehensive information about localization, degree of stenosis and type of plaque, reflecting total (obstructive and nonobstructive) coronary atherosclerotic burden, noninvasively provided by cardiac CT.

The methodology is described in **manuscript 18**, as well as the analysis on its clinical predictors.

ARTIGO 18/ MANUSCRIPT 18:

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY-ADAPTED LEAMAN SCORE AS A TOOL TO NONINVASIVELY QUANTIFY TOTAL CORONARY ATHEROSCLEROTIC BURDEN.

Araújo Gonçalves P, Garcia-Garcia HM, Dorés H, Carvalho MS, Jeronimo Sousa P, Marques H, Ferreira A, Cardim N, Teles R, Raposo L, Mesquita-Gabriel H, Almeida M, Aleixo A, Mota Carmo M, Pereira Machado F, Mendes M.

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8.5 ARTIGO 18

8.1 - INTRODUÇÃO

O desenvolvimento e implementação da coronariografia por cateterismo cardíaco veio permitir documentar a presença e extensão da DC, tendo sido desenvolvidos desde cedo vários **scores angiográficos** para quantificação da carga aterosclerótica coronária. Estes scores, usaram diferentes combinações e ponderações acerca da localização e do grau de estenose, tendo sido possível demonstrar que a carga aterosclerótica coronária tinha um forte valor prognóstico (1-4). Um dos scores angiográficos mais recentemente desenvolvidos foi o score de Syntax, reunindo informação detalhada acerca da localização, grau de estenose, presença e tipo de bifurcação, presença e tipo de oclusão, tortuosidade, calcificação, presença de trombo e comprimento das lesões (5). Este score foi desenvolvido para permitir quantificar a extensão e a gravidade da DC num estudo que comparou a revascularização percutânea com stents “*drug-eluting*” com a revascularização cirúrgica. Grande parte das variáveis incluídas neste score estão relacionadas com a complexidade da DC e a dificuldade imposta ao tratamento por angioplastia, que foi menos eficaz nos doentes com scores de Syntax mais elevados (6, 7). No entanto, foi interessante verificar que este score, apesar de ter apenas variáveis angiográficas na sua composição, leva consigo importante informação prognóstica, o que demonstra o importante valor da carga aterosclerótica coronária global para prever a ocorrência de eventos coronários adversos (8, 9).

Mais recentemente, com o desenvolvimento tecnológico que permitiu o uso de **técnicas de imagem intracoronária**, foi possível quantificar a carga aterosclerótica coronária de um modo mais preciso, tirando proveito da sua elevada resolução espacial (10-12). No entanto, estas técnicas tem a sua aplicação inerentemente limitada pelo facto de serem invasivas e assim só empregues em populações seleccionadas referenciadas para coronariografia invasiva. Esta população geralmente já está em prevenção secundária e assim sob o efeito de múltiplos fármacos que provaram alterar a historia natural da DC e diminuir a taxa de eventos CV (13-16).

Nos últimos anos, assistimos a uma crescente adopção da **angioTC cardíaca** na prática clínica, resultante essencialmente do seu elevado valor preditor negativo, o que a torna uma técnica ideal para exclusão de DC e assim um bom *gatekeeper* para a coronariografia invasiva (17) (ver [Capítulo 3](#)).

A angio TC permite também a identificação de lesões coronárias não obstrutivas e assim poderá ser uma ferramenta útil na quantificação da carga aterosclerótica coronária global. No entanto, dada a elevada prevalência de placas na árvore coronária (18-21), torna-se necessário desenvolver ferramentas que permitam quantificar a carga aterosclerótica e assim o risco de eventos coronários. A angio TC cardíaca permite avaliar não só a presença, mas também a localização das lesões, o grau de estenose e o tipo de placa, fornecendo assim uma avaliação detalhada da carga aterosclerótica coronária global.

Alguns scores foram já desenvolvidos, reflectindo algumas destas características e demonstraram ter valor prognóstico (22-24).

8.2 - DESENVOLVIMENTO DE UM SCORE DE CARGA ATEROSCLERÓTICA QUANTIFICADA POR ANGIO TC CARDÍACA – CT-LeSc

O CT-LeSc foi desenvolvido com o objectivo de permitir quantificar a carga aterosclerótica coronária, englobando três aspectos avaliáveis por angio TC, nomeadamente acerca da localização das lesões na árvore coronária, do grau de estenose e do tipo de placa aterosclerótica. Neste score foi feita a adaptação do score angiografico de Leaman, desenvolvido para quantificar a gravidade da DC obstrutiva, de acordo com a sua localização documentada na coronariografia invasiva (1).

No CT-LeSc foi feita a ponderação para 3 variáveis identificadas na angio TC (*tabela 1*):

1. Localização das lesões: Foram atribuídos pesos diferentes às lesões de acordo com a sua localização mais proximal na árvore coronária, reflectindo a massa de miocárdio em risco dependente dessa lesão. Na adaptação do score de Leaman angiográfico original, fizemos uma modificação na ponderação por segmento compatível com anatomia balanceada, usando valores intermédios entre e dominância direita e esquerda, de acordo com metodologia já empregue em numa tese de doutoramento prévia realizada na nossa instituição (25). Esta adaptação teve implicações nos valores atribuídos aos segmentos da CD (proximal, médio, distal) à descendente posterior, ao TC e à CX (segmentos proximal e distal),

1. Tipo de placa: No CT-LeSc foi introduzida uma ponderação para o tipo de placa, explorando a acuidade diagnostica da angio TC na identificação e classificação dos diferentes tipo de placas (26). Para efeito do CT-LeSc as placas não calcificadas e mistas foram agrupadas na mesma categoria, à qual foi atribuído o valor ponderal de 1,5. O valor ponderal atribuído às placas calcificadas foi deliberadamente inferior (1,0), tentando reflectir o maior potencial de instabilização das placas mistas e não calcificadas (12, 23, 27, 28).

3. Grau de estenose: Foi ainda feita uma última ponderação para o grau de estenose, sendo que na presença de uma lesão obstrutiva (estenose $\geq 50\%$) o valor era multiplicado por 1; no caso das lesões não obstrutiva, o score dessa placa era multiplicado por 0,615. Este factor foi obtido a partir da proporção dos *hazard ratios* para mortalidade associados à DC obstrutiva e não obstrutiva (2,6 e 1,6 respectivamente) obtidos no largo registo CONFIRM (24). Assim, tentou-se que esta proporção reflectisse o menor risco por placa das lesões não obstrutiva vs obstrutivas,

mas mantendo uma contribuição destas para o score global, explorando assim a mais valia do angio TC em identificar lesões mesmo na ausência de estenoses significativas.

Por fim, o valor do CT-LeSc para cada doente é obtido pelo somatório dos valores parciais de cada lesão identificada na árvore coronária.

TABELA 1: CT-LeSc: Factores de ponderação para localização, grau de estenose e tipo de placa

Localização			
Segmento	Dominância direita	Dominância esquerda	Dominância balanceada
CD proximal	1	0	0.5
CD média	1	0	0.5
CD distal	1	0	0.5
Descendente Posterior	1	na	0.5
Tronco comum	5	6	5.5
DA proximal	3.5	3.5	3.5
DA media	2.5	2.5	2.5
DA distal	1	1	1
1ª Diagonal	1	1	1
2ª Diagonal	0.5	0.5	0.5
Cx proximal	1.5	2.5	2.0
1ª Obtusa marginal	1	1	1
Cx distal	0.5	1.5	1
2ª Obtusa marginal	1	1	1
DP esquerda	na	1	na
Postero-lateral esquerda	na	0.5	0.5
Postero-lateral direita	0.5	na	na
Ramo intermediário	1	1	1
Grau de estenose			
DC obstrutiva (≥50%)	1		
DC não obstrutiva	0.615		
Tipo de placa			
Não calcificada ou mista	1.5		
Calcificada	1		

8.3 – RESULTADOS DO CT-LeSc NA POPULAÇÃO DA TESE

Na população total estudada (n=581), a mediana do CT-LeSc foi de 2.2 (IQR 0-6.8). Na população com DC (n=341), a mediana do CT-LeSc foi de 5.8 (IQR 3.2-9.6), sendo de 4.6 (IQR 2.9-7.7) na DC não obstrutiva (n=263) e 11.7 (IQR 8.7-14.4) nos doentes com DC obstrutiva (n=78).

A população com DC foi dividida em tercís de acordo com o valor do CT-LeSc e o valor do 3º tercil foi considerado o limiar discriminativo para identificar um subgrupo de elevada carga aterosclerótica.

Os tercís do CT-LeSc foram: T1 ≤ 3.7 (0.3-3.7); T2 (3.8-8.3); T3 ≥ 8.3 (8.3-24.1).

O CT-LeSc foi significativamente mais elevado nos homens, nos doentes com diabetes, com HTA bem como nos doentes considerados como de elevado risco CV (HeartScore $\geq 5\%$) (*figura 1*).

Na **análise univariada**, um CT-LeSc elevado associou-se a uma idade mais avançada (≥ 60 anos), à presença de diabetes e de HTA. O sexo masculino e a dislipidémia também foram percentualmente mais frequentes nos doentes com elevado CT-LeSc, embora esta diferença não tenha atingido significado estatístico. Os doentes com elevado CT-LeSc eram com maior frequência doentes com probabilidade de pré-teste mais elevada (com um Diamond-Forrester-CAD consortium $\geq 30\%$ e um score de Morise ≥ 16) e com maior risco cardiovascular (reflectida na maior percentagem de doentes com um HeartScore $\geq 5\%$). Alguns dos tradicionais factores de risco CV como a obesidade e o tabagismo, não tiveram uma distribuição preferencial pelo grupo de elevado CT-LeSc, o que foi igualmente verificado com a presença de dor torácica (*tabela 2*).

Na **análise multivariada**, os preditores independentes de um CT-LeSc elevado (≥ 8.3) foram: sexo masculino, diabetes, HTA, score Morise ≥ 16 e HeartScore ≥ 5 (*figura 2*). No que diz respeito aos factores de risco modificáveis, a diabetes associou-se a um risco 3x superior e a HTA a um risco 2,5x superior de um elevado CT-LeSc. Um HeartScore $\geq 5\%$ (elevado risco CV) e um score de Morise ≥ 16 (elevada probabilidade de DAC) associaram-se a um risco 2,5x e 2x superior de ter uma elevada carga aterosclerótica, avaliada pelo CT-LeSc (*tabela 3*).

FIGURA 1: Mediana do CT-LeSc em diferentes subgrupos de doentes.

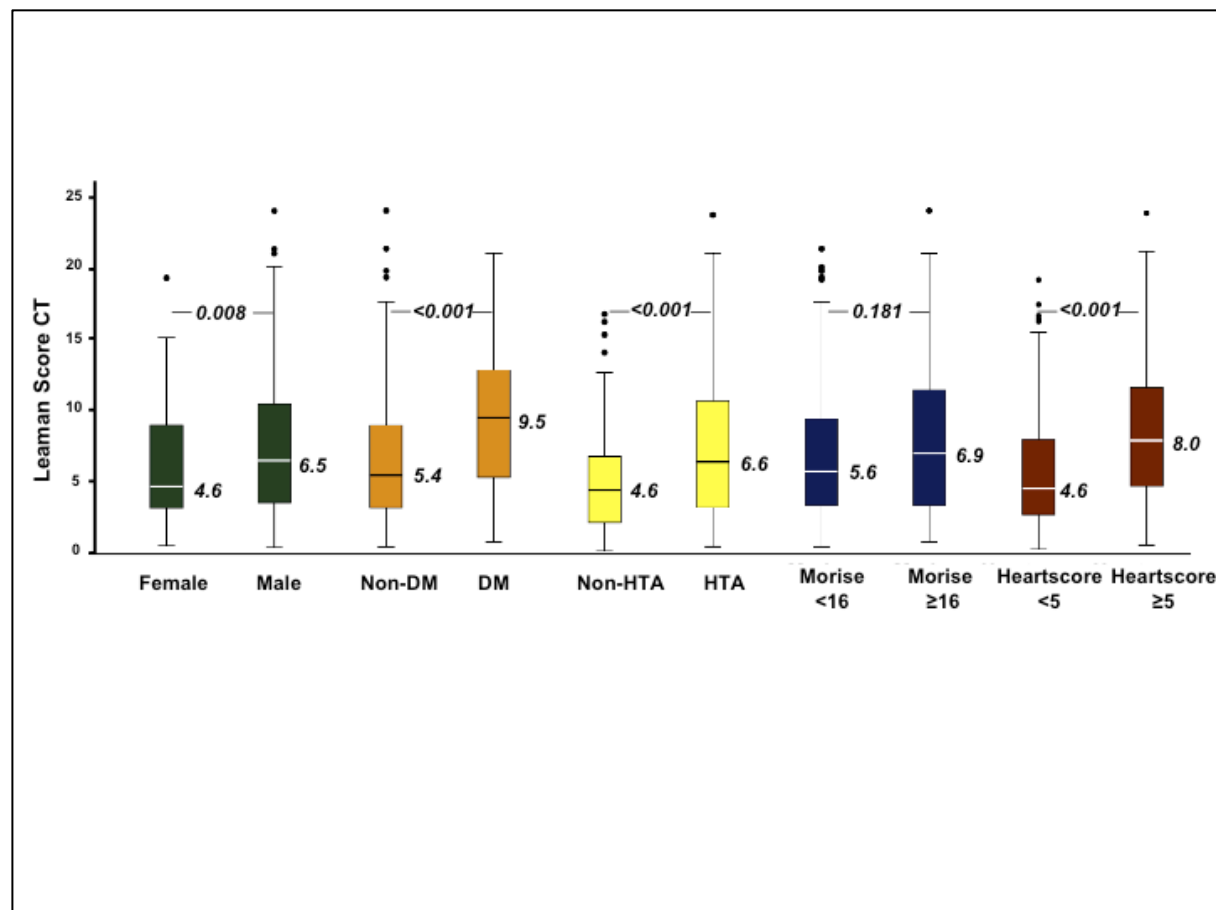


TABELA 2: Preditores de um CT-LeSc elevado ($\geq T3$) - Análise univariada.

	CT LeSc T1+2 (<8.3)	CT LeSc $\geq T3$ (≥ 8.3)	p
Idade ≥ 60 anos	126 (56.0)	79 (68.1)	0.031
Sexo masculino	138 (61.3)	81 (69.8)	0.121
IMC ≥ 30 kg/m ²	41 (18.3)	25 (22.1)	0.404
Diabetes	26 (11.6)	36 (31.0)	<0.001
Hipertensão arterial	144 (64.0)	98 (84.5)	<0.001
Dislipidemia	146 (64.9)	87 (75.0)	0.057
Tabagismo	53 (23.6)	31 (26.7)	0.520
História familiar de DC prematura	77 (34.2)	37 (31.9)	0.666
Dor torácica	106 (47.3)	59 (51.3)	0.487
DF-CAD consortium $\geq 30\%$	66 (29.3)	64 (55.2)	<0.001
Score de Morise ≥ 16	105 (46.7)	78 (67.2)	<0.001
HeartScore ≥ 5	29 (12.9)	24 (20.7)	0.060

Valores apresentados em média $\pm$ desvio padrão

TABELA 3: Preditores independentes de um CT-LeSc elevado ($\geq T3$) - Análise multivariada.

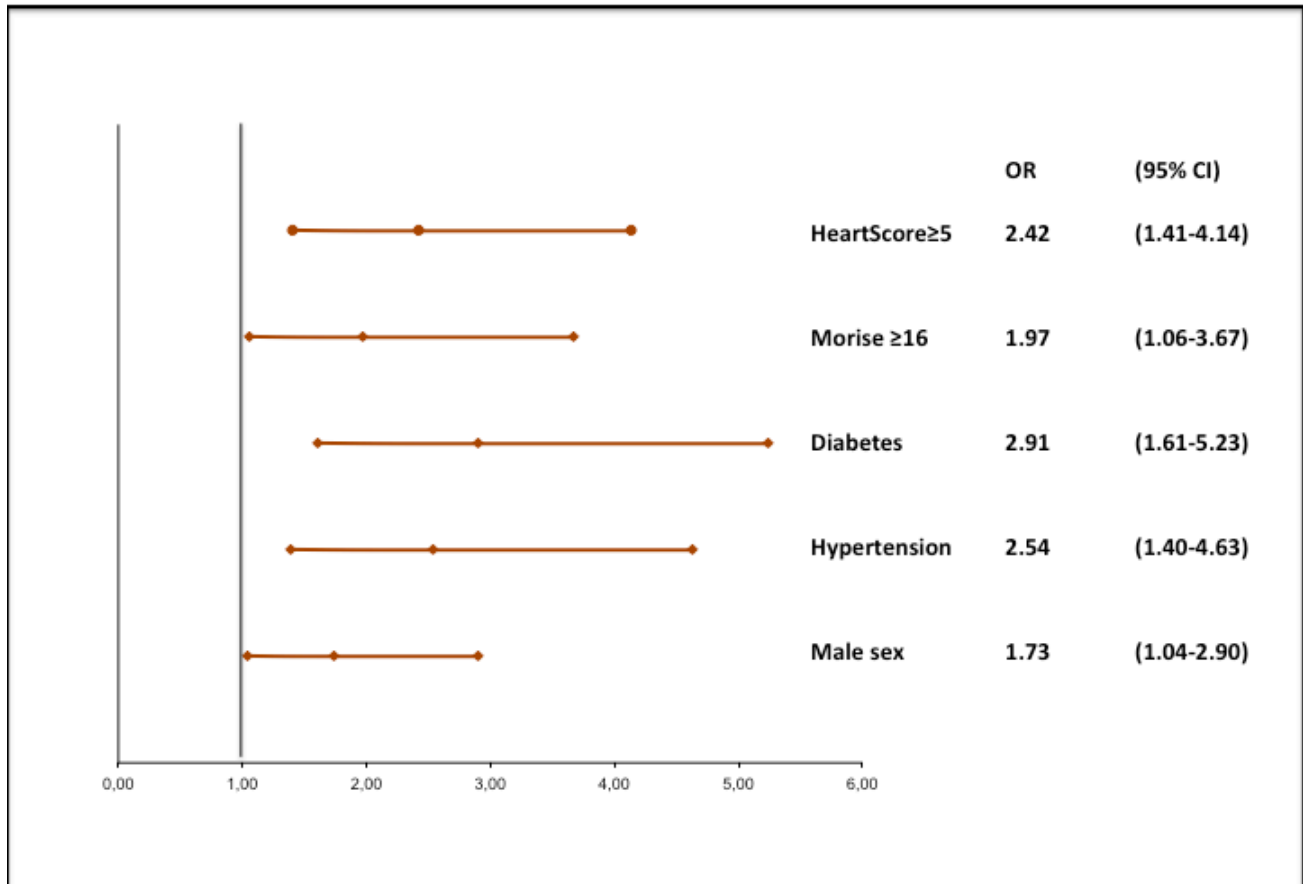
VARIÁVEIS DEMOGRÁFICAS E CLÍNICAS

	OR	(IC 95%)	p
Idade $\geq$ 60 anos	1.370	0.819-2.291	0.230
Sexo masculino	1.732	1.035-2.901	0.037
Diabetes	2.905	1.612-5.234	<0.001
Hipertensão arterial	2.543	1.395-4.634	0.002
Dislipidemia	1.563	0.919-2.660	0.099

SCORES CLÍNICOS

	OR	(IC 95%)	p
HeartScore$\geq$5	2.416	1.411-4.135	0.001
DF-CAD consortium $\geq$ 30%	1.590	0.918-2.754	0.098
Morise $\geq$16	1.971	1.060-3.666	0.032

FIGURA 2: Preditores independentes de um elevado CT-LeSc (>8,3).



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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 ≥ 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 ± 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 ≥ 16 (OR 1.97; 95 % CI 1.06–3.67) and HeartScore ≥ 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 ≥ 5 and a Morise score ≥ 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.

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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 $\geq 140/90$ mm Hg or the use of antihypertensive medication) [10]; (4) Obesity (body mass index ≥ 30 kg/m²); (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.

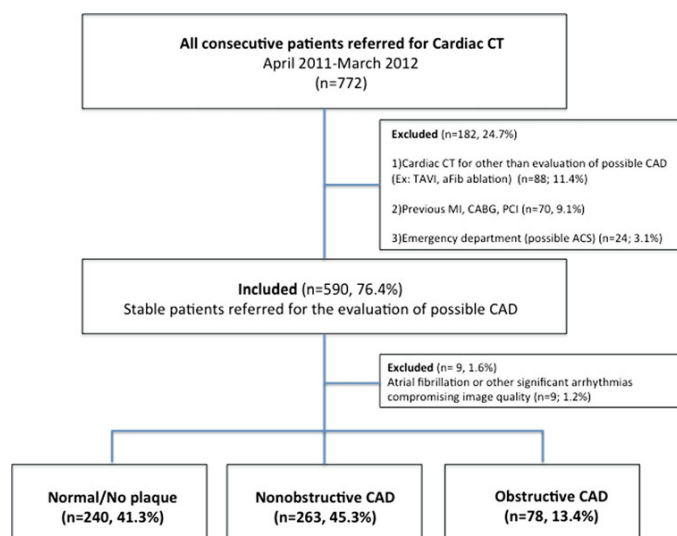
For the Morise, the population was divided in terciles, and for the HeartScore the established high risk cut-off of ≥ 5 % was used.

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

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) $\times$ 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 mm² 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

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 or 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* ($<50 \geq 50\%$ stenosis). In the presence of obstructive CAD ($\geq 50\%$ 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 $\pm$ 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 ≥ 75 th 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

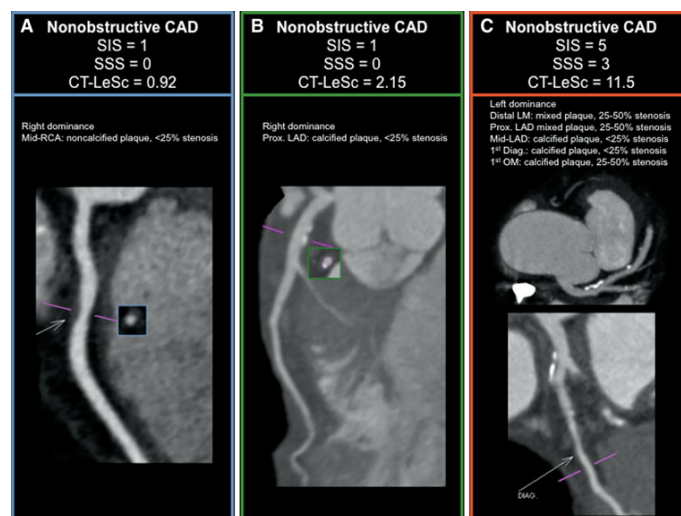


Fig. 2 Three cases examples of patients with nonobstructive CAD stratified by different coronary atherosclerotic burden scores. In panel A, a patient with a single lesion in the mid-RCA (weighting for localization $\times$ type of plaque $\times$ stenosis severity = $1 \times 1.5 \times 0.615 = 0.92$); In panel B, a patient with a single proximal LAD lesion (CT-LeSc = $3.5 \times 1 \times 0.615 = 2.15$). In panel C, a patient with left dominance and 5 nonobstructive lesions with a total

CT-LeSc = LM ($6 \times 1.5 \times 0.615$) + prox. LAD ($3.5 \times 1.5 \times 0.615$) + mid-LAD ($2.5 \times 1 \times 0.615$) + 1st Diag. ($1 \times 1 \times 0.615$) + 1st OM ($1 \times 1 \times 0.615$) = 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 circumflex, 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 ≥ 75 th 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

Table 2 Demographic, clinical and CCTA characteristics of the study population

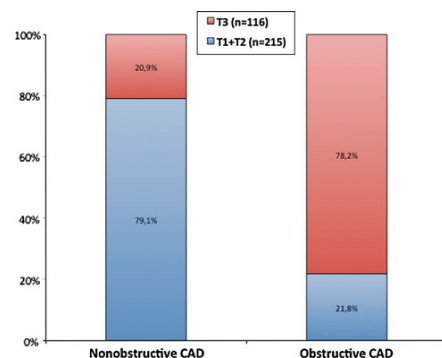
	All patients (n = 581)
Demographic	
Age	57.6 ± 11.1
Male sex	324 (55.8)
Risk factors	
Obesity (BMI ≥30)	109 (18.8)
Diabetes	85 (14.6)
Hypertension	364 (62.7)
Dyslipidemia	360 (62.0)
Smoking	138 (23.8)
Family history of premature CAD	194 (33.4)
Chest pain	
Asymptomatic	270 (46.5)
Noncardiac	169 (29.1)
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 millisievert

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

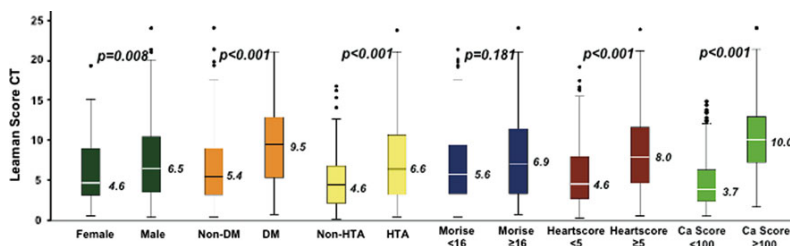


Fig. 4 Median CT-LeSc in different patient subgroups. *DM* diabetes mellitus, *HTA* hypertension, *Ca score* calcium score, *CT-LeSc* CT Leaman score

Table 3 Univariate analysis

	CT LeSc T1 + 2 (<8.3)	CT LeSc ≥ T3 (≥8.3)	<i>p</i>
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

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 non-obstructive 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

Table 4 Multivariate analysis—independent predictors of a high CT-LeSc (3rd tertile, score ≥8.3)

	OR	(95 % CI)	<i>p</i>
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

most important information collected by CT and finally to homogenize the reporting of CT findings.

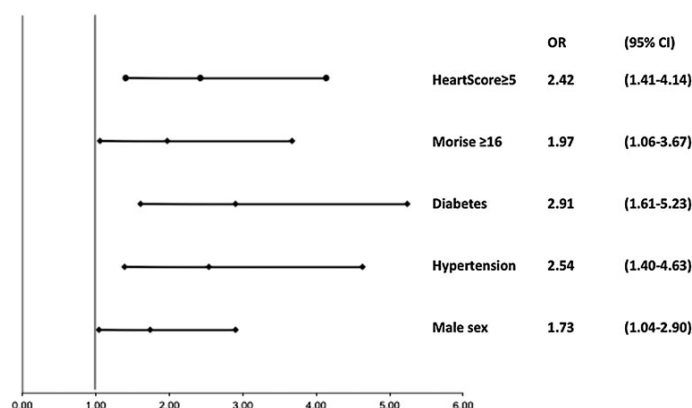
There are already some CT scores developed and prognostically validated namely the segment involvement score (SIS) and the segment stenosis score (SSS), but they only reflect some aspects of the coronary atherosclerotic burden, the former only takes into account the number of segments with plaque and 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.

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

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 developed 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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CAPÍTULO 9.

VALOR PROGNÓSTICO DA ANGIOTC CARDÍACA

RESUMO:

Neste capítulo é revisto o valor prognóstico da angio TC cardíaca nas suas várias etapas, desde os pequenos estudos iniciais, passando pelas meta-análises e até aos grandes registos multicêntricos e à validação a longo prazo.

O **artigo 19** incluído neste capítulo é uma carta ao editor, comentando alguns aspectos de um trabalho publicado acerca do valor prognóstico da angio TC cardíaca a longo prazo..

Foi ainda incluído um **capítulo de um livro de texto** onde são revistos alguns aspectos da angio TC cardíaca, com particular ênfase na sua validação prognóstica.

ABSTRACT:

The prognostic value of cardiac CT is reviewed in this chapter, from the initial small studies and the subsequent meta-analysis, leading to the large multicenter registries and long-term validation.

Included in the chapter is manuscript 19, a letter to the editor commenting on a work addressing the long-term prognostic value of cardiac CT.

It was also included a textbook chapter in which several aspects of cardiac CT are reviewed, with a particular emphasis of the prognostic validation.

ARTIGO 19/ MANUSCRIPT 19:

PROGNOSTIC VALUE OF CORONARY CT ANGIOGRAPHY

Araújo Gonçalves P, Garcia-Garcia HM.

JACC Cardiovasc Imaging. 2013; 6(1):127-128.

CAPÍTULO EM LIVRO DE TEXTO/ TEXTBOOK CHAPTER:

ANGIO TC CARDÍACA II. CARACTERIZACIÓN DE PLACA POR TC. CORRELACIÓN CON LA CINECORONARIOGRAFÍA Y EL ULTRASONIDO INTRAVASCULAR. VALOR PRONÓSTICO.

de Araújo Gonçalves P, Garcia-Garcia HM

Em: Rodriguez-Granillo G, Gómez E, Bastarrika G, Cademartiri F, editores. TC y RM Cardiovascular: Fundamentos Clínicos. Editora Ediciones Journal 2013.

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9.1 INTRODUÇÃO

Uma importante limitação apontada à angioTC cardíaca era, até muito recentemente, a ausência de validação prognóstica, o que não seria de estranhar dado tratar-se da técnica mais recente no campo da avaliação não invasiva da DC. No entanto, nos últimos anos, assistiu-se a uma adopção crescente da angio TC cardíaca na prática clínica, nomeadamente na sua indicação mais comum de exclusão de DC em doentes de probabilidade e risco CV intermédio a baixo (1). À melhoria da qualidade e do número de exames realizados, seguiu-se a evidência científica que permitiu validar o valor prognóstico da angio TC cardíaca na avaliação de doentes com suspeita de DC (2-7).

9.2 ESTUDOS INICIAIS DE VALIDAÇÃO PROGNÓSTICA

Um dos primeiros estudos que avaliou esta temática foi publicado por Pundziute e col (2) num pequeno grupo de doentes (n=100) referenciados para a realização de angio TC cardíaca por suspeita DC ou para avaliação de DC prévia. No seguimento médio de 16 meses, não ocorreram eventos cardíacos major nos indivíduos em que a angio TC excluiu a presença de doença, em claro contraste com uma taxa de eventos de 30% nos doentes em que foi identificada DC. Um dos aspectos mais interessantes deste estudo pioneiro, foi ter sido possível demonstrar que a taxa de eventos cumulativa no subgrupo com DC não obstrutiva era significativamente mais elevada do que a dos indivíduos sem placas identificadas na angio TC cardíaca, cujo prognóstico foi excelente. Este estudo inicial teve algumas limitações, nomeadamente a reduzida dimensão da amostra e a inclusão das revascularizações no seguimento e os internamentos por AI como eventos. Este último aspecto é importante, uma vez que estes eventos “não-major” podem ser influenciados pelo resultado da angio TC cardíaca, o que pode ter exagerado o impacto prognóstico desta técnica nesta pequena coorte de doentes.

Num outro trabalho inicial em que foi avaliado o valor prognóstico da angio TC, Min e col (3) avaliaram 1127 doentes sintomáticos com suspeita de DC. Neste estudo foi demonstrado o excelente prognóstico dos indivíduos com uma angio TC negativa (sem quaisquer placas ateroscleróticas na árvore coronária) com uma taxa de mortalidade de 0.3% nos 15 meses subsequentes. O aspecto mais importante deste estudo foi o desenvolvimento e validação prognóstica de vários índices de carga aterosclerótica. Para alguns destes índices o resultado não foi surpreendente, uma vez que já tinham sido avaliados com a coronariografia invasiva e reflectem apenas o que já era sabido sobre a fisiopatologia da DC, nomeadamente que o prognóstico se agrava com a extensão da doença (nº de vasos envolvidos), grau de estenose e localização mais proximal da árvore coronária (nomeadamente no TC e DA proximal). No

entanto, alguns índices foram especificamente desenvolvidos com a informação obtida pela angio TC e entrando em linha de conta com a presença de placas não obstrutivas (<50% de estenose), como foi o caso dos índices “segment involvement score” e “segment stenosis score” (estes índices são descritos em mais detalhe nos [capítulos 1 e 8](#)).

9.3 META-ANÁLISES E ESTUDOS MULTICÊNTRICOS

Mais recentemente, em 2011, foram publicadas 2 meta-análises que avaliaram o impacto prognóstico da DC documentada por angioTC (4, 5) chegando a conclusões semelhantes:

- 1) A presença e extensão da DC avaliada na angio TC cardíaca são importantes preditores de eventos CV futuros.
- 2) A ausência de DC na angio TC associa-se a um excelente prognóstico CV.

É de realçar o facto de em ambas as meta-análises ter sido possível isolar o impacto prognóstico da DC não obstrutiva, com um comportamento nas curvas de sobrevivência para eventos CV claramente diferente do dos indivíduos sem placas identificadas na angio TC cardíaca.

Mais recentemente foram publicados os dados do registo CONFIRM (*Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry*) (6) onde também foi avaliado o impacto prognóstico da DC avaliada por angio TC. Neste registo multinacional e multicêntrico que incluiu nesta análise dados de mais de 20.000 doentes que realizaram uma angio TC cardíaca, a ausência de DC associou-se a um prognóstico excelente (taxa de morte anual de 0,28%). Neste registo, aos 2,3 anos de seguimento, o risco de mortalidade conferido pela DC foi 2,6 vezes superior para a DC obstrutiva e 1,6 vezes superior para a DC não obstrutiva (valor dos HR, por comparação com a ausência de doença). Numa outra análise do registo CONFIRM, Chow e col (7) demonstraram que o valor prognóstico das variáveis relacionadas com a presença e gravidade da DC era independente e incremental ao fornecido pela fracção de ejeção ventricular esquerda e pelos habituais factores de risco, mesmo agrupados no scores clínicos. Neste trabalho, a mortalidade total foi de 0,65% nos indivíduos sem DC, de 1,99% na presença de DC não obstrutiva, de 2,9% na DC obstrutiva e de 4,95% na DC obstrutiva com critérios de gravidade (definida neste estudo como doença do TC com estenose $\geq 50\%$ ou doença de 3 vasos com estenoses $\geq 70\%$ ou doença de 2 vasos com envolvimento da DA proximal).

9.4 VALIDAÇÃO PROGNÓSTICA A LONGO PRAZO

Sendo uma técnica de implementação relativamente recente na prática clínica, são ainda poucos os estudos que evidenciem o valor prognóstico da angio TC cardíaca a longo prazo. Recentemente, foi publicado um trabalho por Andreini e col (8) no qual foi avaliada a taxa de

eventos CV a 4 anos de seguimento numa coorte de 1304 doentes referenciados para angio TC cardíaca por suspeita de DC. Neste estudo, embora os autores tenham excluídos doentes com DC prévia, a probabilidade pré-teste da população incluída foi bastante elevada (42,5%), sendo que $\frac{1}{4}$ dos doentes era de elevada probabilidade e foram igualmente incluídos doentes com SCA. A taxa de eventos registada (54% de eventos major no subgrupo com DC obstrutiva) foi muito acima do esperado para uma população de DC estável e assim o desenho deste estudo poderá ter exagerado o valor prognóstico da angio TC cardíaca (9).

9.5 VALOR INCREMENTAL E COMPARAÇÃO COM OUTRAS TÉCNICAS DE IMAGEM

No que diz respeito ao valor prognóstico incremental da angio TC cardíaca ao de outras técnicas de imagem, van Werkhoven e col (10) demonstraram o potencial efeito sinérgico da angio TC cardíaca, como exame anatómico, com o de um exame funcional, neste caso a cintigrafia de perfusão miocárdica.

No entanto, esta combinação de diferentes técnicas de imagem, apesar de ser apelativa e interessante do ponto de vista investigacional, quer para efeitos de diagnóstico quer prognóstico, esse conceito pode ser difícil de implementar na prática clínica, sendo necessário avaliar também qual o seu incremento numa abordagem de custo-eficácia. Mais importante ainda é a posição relativa das diferentes técnicas de imagem disponíveis num algoritmo de avaliação dos doentes com suspeita de DC. Uma das abordagens recomendadas consiste na selecção do tipo de exame em função da probabilidade pré-teste de doença, estratégia que favorece a escolha de exames funcionais nos doentes de probabilidade intermédia e da angio TC cardíaca nos doentes de baixa probabilidade, explorando assim o seu elevado valor preditor negativo (11) (aspectos discutidos no [capítulo 3](#)).

A validação prognóstica da informação obtida na angio TC cardíaca está em larga medida na dependência do risco basal na população incluída, como é aliás verdade para as várias modalidades de imagem disponíveis para estratificação da DC. Assim, estudos que incluam uma elevada percentagem de doentes com probabilidade pré-teste e/ou risco CV intermédio a elevado ou até mesmo com DC já conhecida podem mais facilmente atestar o valor prognóstico da angio TC. Do mesmo modo, estudos que incluam eventos CV não major, como é o caso das hospitalizações e das revascularizações subsequentes, mais facilmente demonstram o desempenho prognóstico, uma vez que o resultado da angio TC poderá influenciar a taxa de revascularizações subsequente, como já foi demonstrado em vários estudos (12). Por este motivo, vários estudos mais recentes que avaliaram esta temática excluíram as revascularizações realizadas após a angioTC (geralmente nos 3 a 6 meses subsequentes) da análise de impacto prognóstico (4, 8).

Por fim, é importante enquadrar a informação prognóstica da angio TC cardíaca com a que é fornecida pelas outras modalidades de imagem não invasiva como é o caso da cintigrafia de perfusão miocárdica e o ecocardiograma de sobrecarga, já avaliadas em estudos prévios (13, 14). Nesta comparação, é de destacar que o prognóstico de uma angioTC cardíaca normal (ausência de placas identificáveis na árvore coronária) – taxa de eventos anual de 0,17% numa meta-análise (4) é ainda melhor que o previamente demonstrado nas respectivas meta-análises para um ecocardiograma de sobrecarga normal (sem alterações segmentares; taxa de eventos anual de 1%) e até mesmo que o de uma cintigrafia normal (perfusão normal; taxa de eventos anual de 0,6%) (15).

Esta diferença poderá ser explicada pelo facto de a angio TC cardíaca identificar a doença coronária não obstrutiva, que geralmente é negativa nos exames de imagem baseados na detecção de isquémia, e deste modo pode fornecer uma informação mais completa da carga aterosclerótica coronária total, que parece ser o factor de prognóstico mais forte para prever a ocorrência de eventos CV.

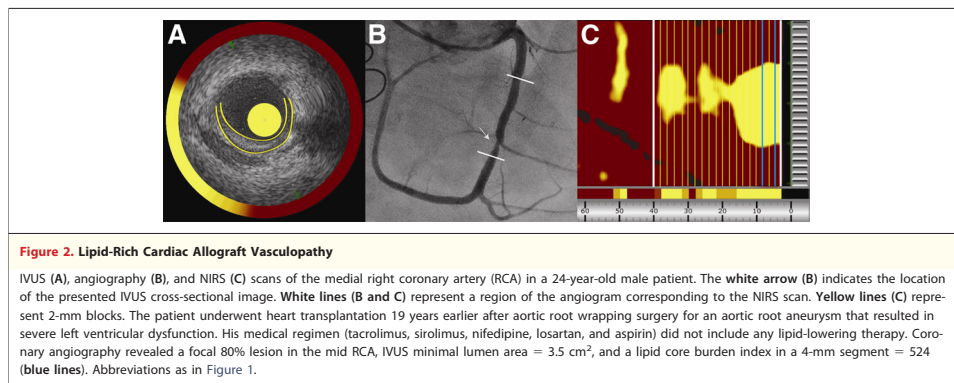
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9.7 ARTIGO 19/ MANUSCRIPT 19:

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yellow). Chemogram analysis enables one to divide the scan into 2-mm blocks and quantify the amount of lipid on a scale of 0 to 1,000, termed the lipid core burden index (LCBI).

Similar to Hou et al., we captured 2 distinct patterns of CAV by NIRS during the routine hemodynamic and angiographic assessment in long-term survivors after heart transplantation. Simultaneous gray-scale IVUS and NIRS scans in the 2 allograft recipients 11 and 19 years after the transplantation demonstrated fibrotic (Fig. 1) and lipid-rich plaques (Fig. 2), respectively. Interestingly, the NIRS chemogram showed lipid-rich regions, even for the angiographically normal-appearing vessel in the latter patient who did not receive statin therapy.

The 2 different NIRS scans of CAV in transplant recipients may correspond to the difference in elapsed survival time from transplantation and use of medical therapy. Autopsy studies have confirmed that in the first 5 years after transplantation, CAV plaques are mostly composed of fibrotic tissue, whereas lipid accumulation is seen later. Gray-scale IVUS studies have provided some insight into the etiology of CAV in survivors 1 to 9 years post-transplantation (4). They have revealed diffuse and circumferential lesions in mid and distal coronary segments, suggestive of the fibrotic tissue. Focal and noncircumferential lesions observed in the proximal segment of the vessel early after transplantation indicated pre-existing atherosclerotic lesions. Radiofrequency (RF) analysis by IVUS (virtual histology) suggested that lipid-rich regions in neointima increased and fibrosis decreased with time over 1 to 20 years after the heart transplantation (5). However, the accuracy of RF-IVUS in lipid-rich plaque determination has been questioned, and characterization of the IH by other imaging modalities should be confirmatory. Interestingly, the accelerated lipid-rich atherosclerotic process in CAV seems to be slower compared with vein coronary graft plaques and in-stent restenosis development. This insidious process is often a result of younger vasculature of the allografts, which is likely to be devoid of pre-existing disease. The immunosuppressive therapy could also contribute to the delay in the process; statin supplementation further enhances the immunosuppressive efficacy of calcineurin inhibitors.

New intravascular imaging modalities may improve CAV screening in allograft recipients. They would contribute to the

understanding of the disease process and help to better define management strategies. Allograft vasculopathy is not unique to heart transplantation and may occur similarly in all transplanted organs, and the knowledge gained from coronary screening may have wider implications.

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Please note: Drs. Sharma and Roleder contributed equally to this paper.

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Prognostic Value of Coronary CT Angiography

We read with interest the paper from Andreini et al. (1) that provided more evidence on the prognostic value of cardiac computed tomography angiography (CTA) in patients referred for evaluation of possible coronary

artery disease (CAD), an area of research in need of long term follow up studies like this one (mean follow-up >4 years).

However, we noticed that the mean pre-test probability of CAD in the study population was 42.5%, with one-quarter of the patients having a high CAD probability, which is not in line with the most favored low-to-intermediate probability population referred for CTA for the exclusion of possible CAD (2), and that could explain the higher-than-expected hard event rate for a stable CAD population (almost 1 out of 2 patients with obstructive CAD dying or having a nonfatal myocardial infarction [MI]) in the follow-up (3). This could have been the result of having included patients admitted to the hospital because of new-onset chest pain (43%), a subset that could be considered as possible acute coronary syndrome (ACS) unstable angina/non-ST-segment elevation MI and can explain the higher than expected rate of major (death/MI) events in the follow-up (event-free survival of 54%). In how many cases was an ACS diagnosis confirmed? If any, the authors should have excluded these patients from the study. We fully agree that CTA can provide useful prognostic information beyond the exclusion of obstructive CAD, but the inclusion of patients with possible ACS and high CAD probability could have lead to an overestimation of the prognostic power of CTA.

Another striking point was the fact that 45% of patients had hypercholesterolemia but only 26% were treated with statins. Further, statins turned out in multivariable analysis to be independent predictors for hard events. Likewise, 26% of the population (with suspected CAD) was taking aspirin, which is not generally recommended as primary prevention. Use of aspirin was also an independent predictor of all cardiac events. It would have been interesting to know if the use of these drug groups is allocated to a more severe subset of patients (more frequently used in obstructive vs. nonobstructive vs. normal patients) and in this way are just a surrogate marker of higher disease burden. Likewise, it would be of interest to know if patients were already taking these drugs before the CTA or if they were just started after significant disease was identified and, in this way, they could not have had enough time to come out with its protective effects in a more severe CAD subgroup of patients.

The Framingham risk score (FRS) was used to estimate the cardiovascular risk of this Italian cohort of patients; it could have been more accurately estimated with the European-based HeartScore (4). This could have also influenced the results, as the multivariable analysis models were adjusted for the FRS.

It is not mentioned that the events were independently adjudicated and that the adjudication event committee is an experienced one with acceptable intra-committee reproducibility for the adjudication of events. This point is of utmost relevance in a report of this nature. In addition, regarding *revascularizations*, we agree that early revascularizations should be excluded to avoid the influence of CTA results in patient management but most of the previous studies considered early as 30 days (5) and not 6 months like in the paper from Andreini et al. (1). This could have also influenced the results, as revascularizations in obstructive CAD group are likely to have happened sooner after the CTA and in this regard could have underestimated the prognostic value of obstructive versus nonobstructive CAD. Further, it is not mentioned whether the revascu-

larizations were ischemia-driven (i.e., only for obstructive lesions) or not.

Despite the fact that authors have scored hierarchically the plaque type per segment (i.e., in case of presence of 2 plaques, calcified and noncalcified, only one was scored and labeled as calcified) which underestimates the frequency of noncalcified plaques, in the univariate analysis, these were found to be independent predictors of hard events. This methodology seems to us to be counterintuitive, since it has been reported many times that high-risk plaques (i.e., plaques prone to rupture and associated with an event) are those noncalcified or mixed, which could have come out as strong predictors also in the multivariate analysis if the authors had not underscored them.

Undoubtedly, this is a report with an important message, but we feel that the above-mentioned points should be further explained to strengthen the conclusions.

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REPLY

The comments of Garcia-Garcia and Goncalves are relevant and allow us to expand on some results of our study (1). First, we found

a relatively high cumulative event rate at follow-up in multidetector computed tomography coronary angiographic (MDCT-CA) obstructive coronary artery disease compared with other studies, which may be due to characteristics of patients who had chest pain and positive stress tests in 43% and 29% of cases, respectively. However, the CONFIRM registry demonstrated that MDCT-CA has the best prognostic value in this patient subset, whereas its value in asymptomatic patients is quite limited (2). We agree that including patients with acute coronary syndromes (ACS) may lead to an overestimation of MDCT-CA prognostic capability. Accordingly, we excluded patients in whom ACS was confirmed by cardiac enzyme or electrocardiographic changes. The discrepancy between hypercholesterolemia rate and statin use in our patients is in agreement with the suboptimal therapy adherence reported in a substantial proportion of European patients (3). Medical therapy reported in our patients was administered before MDCT-CA. Indeed, 26% of them were taking aspirin, not for CAD but for other indications. We agree that the European Heart Score would have been more appropriate than Framingham cardiovascular risk estimation. However, the former has been challenged because it is not mathematically consistent and unfit to estimate cardiovascular mortality (4). In the first version of our paper, revascularizations were defined “early” if performed within 2 months after MDCT-CA. However, a reviewer criticized this definition. Indeed, using a 2-month cutoff, only 6 patients were excluded despite 295 patients having MDCT-CA stenosis $\geq 70\%$. This indicates that many revascularizations occurring later than 60 days were probably driven by MDCT-CA. We agree that the 6-month cutoff may have led to an underestimation of obstructive CAD prognostic value. However, this limitation did not affect hard cardiac events survival analysis. Finally, we believe that assigning 1 coronary plaque per coronary segment and classifying a plaque as calcific in cases in which a coronary segment contained calcific and noncalcific plaques was correct, as previously reported (5). Indeed, in the presence of small plaques, those calcific plaques are the easiest to detect with MDCT-CA, and most prognostic data are based on simple coronary plaque scores, regardless of plaque composition (3).

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Ultrasonographic Measure of Carotid Plaque Burden

In their excellent paper, Sillesen et al. (1) omitted mention of the original work on measurement of carotid plaque burden. Spence et al. (2) first measured carotid total plaque area (TPA) in 1990, and developed it for patient management and genetic research, and 3-dimensional methods for evaluation of new therapies. They showed that TPA and progression of TPA strongly predicted the 5-year risk of stroke, death, or myocardial infarction after adjusting for coronary risk factors.

Sillesen et al. (1) stated that the prevalence of plaque they observed (78%) was 2-fold higher than previously reported. However, in the NOMAS (Northern Manhattan Study) study, a population-based study of individuals free of stroke at similar ages, plaque prevalence was 58% on 2-dimensional ultrasound imaging and it was greater by age and among certain race-ethnic groups (3). Prevalence of plaque depends on age and how it is defined. If defined as a focal thickening >1 mm, in vascular patients it increases from 75% of patients at age 35 to 45 years to 99% by age 65 to 75 years, and 100% over age 75 years (2).

Besides plaque burden, other ultrasonographic characteristics of plaque morphology such as plaque surface irregularity, ulceration, texture, and plaque density may be even more important predictors of stroke and cardiovascular disease.

The Tromsø study showed that TPA was a stronger predictor of myocardial infarction and stroke (4) than intima-media thickness, and this was confirmed in a meta-analysis (5). Three-dimensional plaque volume is highly correlated with TPA, and is much more sensitive to change with therapy than intima-media thickness or TPA, so it is the best way to assess effects of new therapies (2). There is little doubt that carotid plaque burden will be a stronger predictor of cardiovascular events in the High Risk Plaque Bioimaging Study than any of the other imaging modalities measured, with the possible exception of coronary calcium.

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9.8 CAPÍTULO EM LIVRO DE TEXTO / TEXTBOOK CHAPTER:

Libro: TC y RM Cardiovascular: Fundamentos Clínicos

Capítulo número 9

TÍTULO:

ANGIO TC CARDÍACA II. CARACTERIZACIÓN DE PLACA POR TC.
CORRELACIÓN CON LA CINECORONARIOGRAFÍA Y EL ULTRASONIDO
INTRAVASCULAR. VALOR PRONÓSTICO

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diagnostic accuracy*

9.3 PLAQUE CHARACTERIZATION AND CORRELATION WITH INTRAVASCULAR
ULTRASOUND – *pushing the limits of spatial resolution*

9.4 PROGNOSTIC VALUE – *Cardiac CT reaching adulthood*

9.1 INTRODUCTION

Advances in the field of Computed Tomography (CT) have made possible to noninvasively evaluate the presence of coronary artery disease (CAD) and in recent years Coronary CT angiography (CCTA) has become a widely adopted technique. This was due not only to its high diagnostic accuracy, but also to the fact that CCTA provides a comprehensive evaluation of both obstructive and nonobstructive CAD and, more recently, its prognostic information has been validated.

The initial studies of CCTA addressed mainly its diagnostic accuracy. This was done both by comparison with the gold standard invasive coronary angiography (ICA) and with intravascular ultrasound (IVUS) (both described in more detail in sections 9.2 and 9.3 of this chapter).

From the beginning it was also evident that this technique allowed not only the exclusion of obstructive CAD but also provided information regarding the presence of nonobstructive lesions, and this was a unique feature in the field of noninvasive CAD evaluation.

As the technique became more robust and widely adopted in clinical practice, data was gathered regarding cardiovascular outcomes and this opened a 2nd phase of studies addressing its prognostic value (described in more detail in section 9.4 of this chapter).

The latest technological advances have significantly improved CCTA temporal resolution and volume coverage, leading to a decrease in radiation and contrast dose, and improvements in image quality, that will further reinforce the role of CCTA for the evaluation of patients with possible CAD.

9.2 CORRELATION WITH INVASIVE CORONARY ANGIOGRAPHY – *Cardiac CT diagnostic accuracy*

Many studies have been published evaluating the diagnostic accuracy of CCTA, by comparing with the gold standard invasive coronary angiography. These were initially done with 4-slices (1-4), followed by 16-slices scanners (5-9), but by that time significant limitations existed related to the dose of contrast, long breath-hold times and high percentage of segments excluded from analysis due to insufficient image quality. In a meta-analysis of 27 studies comparing CCTA (with scanners of at least 16 slices) with invasive coronary angiography, the per-patient sensitivity was very high (96%) but the specificity was only modest (74%), leading to a positive predictive value of 68% (10).

With the development of 64-slices scanners, now considered to be the minimum requirement for CCTA (11), significant technological advances were incorporated, which have been translated to improvements in diagnostic performance and lead to the widely adoption of CCTA in clinical practice. In a more recent meta-analysis, including only studies with 64 slices scanners, the reported per-patient sensitivity was 99%, specificity 89%, positive predictive value (PPV) was 93% and negative predictive value (NPV) was 100% (12).

Nevertheless, even with 64 scanner slices, some multicenter trials, have reported low specificity when evaluating consecutive nonselected patients. In the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial, a prospective multicenter evaluating stable patients without known CAD who underwent CCTA before clinically indicated ICA, CCTA had a diagnostic sensitivity, specificity, PPV, and NPV of 94%, 83%, 48%, and 99%, respectively. (13). The low specificity reported in this trial could be related to the fact that patients were consecutively included irrespective of baseline coronary calcium score, body mass index or heart rate, variables that are well known to influence image quality.

In another multicenter study, Meijboom and coll (14) evaluated the diagnostic performance of CCTA in a population including both stable and acute chest pain patients without known CAD referred for invasive coronary angiography. No

patients or segments were excluded because of impaired image quality attributable to either coronary motion or calcifications and the prevalence of obstructive CAD was 68%, factors that could explain the low per-patient specificity of 64% for CCTA found in this study, leading to a positive predictive value of 86%. Once again, the per-patient sensitivity was 99% and the negative predictive value was 97%.

Improvements in spatial and temporal resolution and volume coverage with the newest generation scanners lead to further improvements in image quality, and significant reductions on radiation and contrast dose, all factors expected to further reinforce the role of CCTA in the evaluation of patients with suspected CAD.

With the development of dual source scanners, there was a significant increase in temporal resolution, leading to a less dependence on heart rate control (15) and a significant reduction in radiation dose with high-pitch spiral acquisitions, without compromising diagnostic accuracy (16, 17) – **figure 1**.

Likewise, 320-rows scanners also lead to significant improvements, reducing the radiation dose and amount of contrast while maintaining high diagnostic accuracy (18, 19)

Summing up the different multicenter trials and meta-analysis addressing this issue, it has become clear now that this noninvasive imaging technique has a very high sensitivity for detecting patients with significant CAD, leading to a very high (virtually 100%) negative predictive value, which makes CCTA a perfect gatekeeper for invasive angiography.

Regarding the still limited specificity, this has to be taken in consideration, especially when evaluating patients with severe calcification, since CCTA often overestimates the degree of coronary stenosis in this setting (blooming effect).

In conclusion, when evaluating the diagnostic accuracy of CCTA, some factors have to be considered, that could influence the performance of the exam, and could explain the differences between different studies:

- type of scanner technology (64 slices is now considered to be the typical minimum standard)
- population studied, regarding expected prevalence of obstructive CAD (can be calculated with pre-test CAD probability scores – CCTA is indicated in low to intermediate CAD probability)
- inclusion of nonevaluable segments in the analysis (considering nonevaluable segments as positive improves sensitivity but reduces specificity)
- inclusion of patients with high body mass index, high calcium score or high heart rates, factors known to negatively affect image quality.

9.3 PLAQUE CHARACTERIZATION AND CORRELATION WITH INTRAVASCULAR ULTRASOUND – *pushing the limits of spatial resolution*

Relevance of plaque characterization and limitations of the presently available imaging modalities (both invasive and ischemia based)

Since many myocardial infarctions present in previously asymptomatic patients and not infrequently the first manifestation of CAD is sudden cardiac death, the main challenge that we face today is to identify patients at risk before those events occur. In this regard, clinical evaluation alone might be insufficient, as many patients don't have previous symptoms and it has also been demonstrated that only a minority of patients experiencing an acute myocardial infarction would have been identified as high risk by the available risk-factors based scores, prior to the event (20).

Coronary plaque characterization, namely the identifications of features of vulnerability, has been the focus of extensive research by different coronary imaging modalities like intravascular ultrasound (IVUS), IVUS-virtual histology (IVUS-VH) and optical coherence tomography (OCT). These imaging modalities, although providing the highest possible spatial resolution, have their applicability limited by their invasive nature, and are usually employed in patients already referred for invasive angiography because of suspected CAD or with acute coronary syndromes (ACS). Many of these patients will be (independent of the result of the imaging modality) under secondary prevention of CAD, which changes natural history and reduces the risk of subsequent cardiovascular events (21, 22).

In the multicenter PROSPECT study (22), a large plaque burden, a small lumen area and the presence of a thin cap fibroatheroma assessed by IVUS-VH in nonculprit lesions, were independent predictors of future major adverse cardiac events. In this study, lesions that led to major adverse cardiac event had a high plaque burden by IVUS, but were mild by baseline angiography, with a mean diameter stenosis of only 32%. Although the Prospect trial was a landmark study of CAD natural-history, its applicability is limited by the fact that patients were evaluated in the setting of an acute coronary syndrome, for whom aggressive

secondary prevention is, in any case, recommended, independent of the imaging evaluation. This is important since medication changes natural history and can explain why the prediction power of the identified variables is rather weak. In fact, even in the presence of these 3 features, only 18,2% of the patients really experienced an event in the subsequent 3.4 years of follow-up, and many of those events were rehospitalization for unstable or progressive angina, a rather soft event.

On the other hand, *ischemia based imaging modalities* have also some limitation in this regard, especially related to the fact that nonobstructive lesions are not associated with ischemia, but can also be the culprit of coronary events (22-25) – (figure 2).

This is of utmost importance since it has been demonstrated that nonobstructive lesions can lead to myocardial infarctions (25-27). On the other hand, it is now recognized that although obstructive plaques can be more prone to rupture than their nonobstructive counterparts, these nonobstructive lesions are much more prevalent with makes them, on absolute numbers, frequently the culprit of acute coronary syndromes (28). Therefore, the importance of nonobstructive disease should not be underestimated and imaging techniques that convey information about the whole (obstructive + nonobstructive) coronary atherosclerotic burden have a great potential for risk stratification (29) (figure 3)

In this regard, *CCTA* might qualify as a possible useful tool, in face of its noninvasive nature, widespread adoptance in clinical practice and the impressive reductions in radiation dose made possible with the new generation scanners (figure 4).

Correlation with invasive imaging modalities

Several studies have reported on the correlation between CCTA plaque features with invasive coronary imaging modalities like IVUS, IVUS-VH and OCT. In a recent meta-analysis, CCTA had a good diagnostic accuracy to detect coronary plaques compared with the gold standard IVUS, with an area under the curve for the receiver operating characteristics analysis of 0.94, a sensitivity of 90%, and a

specificity of 92%, with small differences in the assessment of plaque area and volume, percent area stenosis, and a slight overestimation of lumen area (30).

Several CCTA plaque characteristics have now been shown to be more prevalent in culprit lesions in the setting of acute coronary syndromes. In a study done by Hoffman and coll, a significantly larger plaque area and positive remodelling were found in culprit lesions of ACS patients, compared with patients with stable CAD (31). Positive remodelling has been considered for many years a surrogate marker of plaque vulnerability, and many of these lesions have a high plaque burden that is underestimated by luminal angiograms because they undergo expansive or positive outward enlargement and are frequently nonstenotic (24).

Figure 6.

In another small study, Motoyama and coll found that culprit lesions of patients with ACS had more frequently positive remodelling, low-density plaque [<30 Hounsfield units (HU)] and spotty calcifications (32).

Extending on these results, the same authors conducted a large prospective trial including 1059 patients who underwent CCTA, and demonstrated that positive remodelling and low attenuation plaques were associated with the subsequent development of acute coronary syndromes (23). In this study, the percentage of patients with these 2 features that subsequently developed ACS was 22,2%, compared with only 3,7% for patients with only one feature and 0,5% for patients with neither positive remodelling or low-attenuation plaques.

In a study by Kashiwagi and col, evaluating 105 patients with coronary artery disease, CCTA findings have been also validated against OCT (33). In this study, thin cap fibroatheromas (TCFAs) had higher remodelling indexes, lower CT attenuation values and more often “ring-like” enhancement by CCTA (44% in the TCFA group vs 4% for the non-TCFA group).

In a recent study, Papadopoulou and coll evaluated the distribution and composition of coronary plaques at bifurcations with both CCTA and IVUS-VH (34). They found that plaques with high-risk phenotype as assessed by IVUS-VH were more commonly found in segments proximal to the bifurcation, rather than in the bifurcation or distal to the bifurcation. Interestingly, by evaluating the

geometry of the bifurcation, a feature easily assessed with CCTA, they found that a wide angle was more often associated with high-risk plaques.

As a group, these studies provide evidence on how CCTA can noninvasively provide information on several plaque characteristics - like plaque volume, remodelling, plaque composition, distribution and geometry of the coronary tree - that can be associated with the development of future coronary events (Figure 6).

Limitations of CCTA for plaque characterization:

In recent years, several technical developments were possible in the field of cardiac CT, leading to significant improvements in temporal resolution (with increased gantry rotation speed and dual source scanners) and high volume coverage (with scanners up to 320 rows). It has become possible to scan patients in one heart cycle leading to very low breath-hold times, impressive reductions in contrast and radiation doses and significant improvements in image quality.

Nevertheless, spatial resolution has not seen significant improvements and remains presently one of the major technical limitations of CCTA. In what concerns plaque characterization, the spatial resolution of current available scanners (in the range of 400-600 μm) prevent the detailed assessment of several features associated with vulnerable plaques, as is the case of the evaluation of a thin fibrous cap. This spatial resolution is significantly lower than that of IVUS (200-250 μm) or OCT (10-15 μm) (35) and this has to be taken in consideration and should temper our expectations regarding the potential of CCTA for plaque assessment in face of the limitations already faced by other invasive imaging modalities regarding the identification of the vulnerable plaque.

Another limitation faced by CCTA plaque characterization is related to the fact that coronary plaque attenuation values are significantly modified by differences in lumen contrast densities, as has been demonstrated both ex vivo and in vivo

(36, 37). This is important because lumen attenuation can be influenced by different contrast and scanning protocols and therefore makes it difficult to establish thresholds for the definition low attenuation plaque as a surrogate of vulnerable plaque, that can be widely adopted.

One last important limitation in this regard is related to the reproducibility of CCTA plaque measurements, as many previous studies have reported significant interobserver variability in the assessment of several CCTA plaque characteristics (38, 39). This is dependent on image quality, vessel size and degree of calcification, features that are dependent again on spatial resolution. In the future, improvements in spatial resolution and the development of robust dedicated automated quantification software could contribute to overcome these difficulties.

9.4 PROGNOSTIC VALUE – *Cardiac CT reaching adulthood*

The lack of prognostic validation was, until recently, one of the major limitations of cardiac CT. This was expected as cardiac CT was the new player in the field of noninvasive imaging of coronary artery disease. Nevertheless, this “new player” has now become widely adopted in clinical practice, being commonly used in low-to intermediate risk patients to exclude the presence of obstructive CAD (11). As the technique became more robust and more data become available, cardiac CT proved also to be a strong prognostic tool for the evaluation of patients with suspected CAD (40-45).

One of the first studies addressing this issue was done by Pundziute and col (40) in a small subset of 100 patients with known or suspected CAD. During a mean follow-up of 16 months, there were no major cardiac events on the subset of patients without CAD, contrasting with the 30% event rate of patients with CCTA documented CAD. More importantly, the cumulative event rate of patients with nonobstructive CAD was higher and different from the excellent prognosis of patients without plaques on CCTA. This earlier study had some limitations, both related to the small sample size and the fact that some of the included cardiovascular events (revascularization and unstable angina requiring hospitalization) are not “hard” endpoints and could be influenced by the CCTA result.

In another important work addressing this issue, Min and coll (41) evaluated the prognostic value of identifying CAD with CCTA in a single-center cohort of 1127 patients with stable chest symptoms. In this initial study, a negative CCTA was associated with an excellent prognosis and some CCTA derived CAD indexes were developed and prognostically validated. Some of those indexes were expected to convey prognostic information, as these observations extend on what was previously documented for invasive coronary angiography, as was the case of number of diseased vessels, degree of stenosis and more proximal location. More importantly was the fact that they were able to demonstrate the prognostic value of more CCTA specific indexes derived from the comprehensive

information of both obstructive and nonobstructive plaque. The authors developed 2 indexes that reflect some aspects of the coronary atherosclerotic burden and could be used as CCTA prognostic tools: The Segment involvement score (SIS), obtained as the total number of segments with plaque (1 point for each segment with plaque, irrespective of the degree of luminal stenosis) and the Segment stenosis score (SSS), obtained by grading the stenosis severity of each segment with plaque (segments graded from 0 to 3 according to the degree of stenosis). For both SIS and SSS, a value of 5 was identified as the best cut-off to predict all cause mortality.

In 2011, 2 meta-analysis were published (42, 43) evaluating the prognostic value of CCTA and (not surprisingly) had the same 2 main conclusions: 1) that the presence and extent of coronary artery disease on CCTA are strong and independent predictors of future cardiovascular events; 2) the absence of CAD on CCTA is associated with an excellent prognosis.

Of note, in both meta-analysis, it was possible to distinguish between the excellent prognosis of patients in the absence of CAD from that of patients with nonobstructive CAD, as documented by CCTA.

More recently, data from the CCTA registry CONFIRM (Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (44) was published and examined once again the prognostic power of CCTA. In this large (>20.000 patients) multicenter and multinational registry of patients evaluated by CCTA, absence of CAD was associated with an excellent prognosis (annualized death rate of 0.28%). At 2.3 years follow-up, both obstructive and nonobstructive CAD conferred an increased mortality risk with hazard ratios of 2.6 and 1.6 respectively.

In another report of the CONFIRM database, it was demonstrated that CCTA measures of CAD severity yield independent and incremental prognostic value to that of left ventricle ejection fraction (LVEF) and routine clinical predictors (45). In this report, all-cause mortality occurred in 0.65% of patients without CAD, in 1.99% of patients with nonobstructive CAD, 2.90% of patients with non-high-risk CAD, and 4.95% with high-risk CAD.

In what concerns the incremental prognostic value of CCTA over other CAD imaging modalities, Werkhoven JM and coll (46) have evaluated the potential

synergistic effect of a functional test (single-positron emission CT – SPECT) and CCTA (as an anatomical test). They found CCTA to be an independent predictor of cardiovascular events and its prognostic information was incremental to that of SPECT. Nevertheless, although the potential synergistic role of both anatomical and functional imaging modalities can be appealing, for both diagnostic and prognostic purposes, this concept might be difficult to prove as a cost effective strategy and probably not desirable to perform both exams in the same patient. This way, more research is needed to further evaluate the role and relative position of the different imaging modalities in the algorithm for the evaluation of patients presenting with possible CAD. One proposed approach is to select the type of exam according to the patient CAD probability, favoring functional exams in the intermediate probability and CCTA for the lower probability patient, as recommended by the National Institutes of Clinical Excellence – NICE - clinical guidelines on “Chest pain of recent onset” (47).

The prognostic evaluation of CCTA data (as is the case for other CAD imaging modalities) is dependent on the baseline risk of the population included and the outcomes evaluated. Studies including higher percentage of patients with intermediate to high CAD probability and/or risk, or even with known CAD, can more easily document the prognostic power of CCTA. This is also the case for studies evaluating the impact on total cardiovascular events (instead of only “hard” CV events). This is especially true regarding the inclusion of revascularizations after CCTA, as the result of this anatomical test could influence and increase subsequent procedures. For this reason, many study’s addressing this issue have now excluded earlier revascularizations from the outcome analyses (42, 48).

In another recently published study, Andreini and coll evaluated the long term (>4 years follow-up) prognostic value of CCTA in a cohort of 1304 patients with suspected CAD (48). Although the authors excluded patients with known CAD, the mean pre-test probability of CAD in the study population was high (42.5%, with one-quarter of the patients having a high CAD probability) and they also included patients with possible acute coronary syndromes. This led to a higher-than-expected hard event rate for a stable CAD population (event-free survival of

54% for patients with obstructive CAD). Therefore, the design of studies to address the prognostic value of CCTA can be influenced by these 2 important aspects: inclusion of many high risk/high CAD probability patients and of revascularization as a cardiovascular event can lead to an overestimation of the prognostic power of CTA.

When comparing the prognostic prognostic information conveyed by CCTA with that of other noninvasive imaging modalities like SPECT or stress echo, it is remarkable that the excellent prognosis of a normal CCTA – no plaque – (0.17.% annual event rate in a CCTA meta-analysis (43) is even lower than what was previously demonstrated for patients with normal perfusion on SPECT (0.6% annual event rate) or normal wall motion on stress echo (1.0% annual event rate) in previous meta-analysis (49, 50).

This difference could be explained by the fact that CCTA identifies nonobstructive CAD (usually negative of stress based exams) and in this way provides a more comprehensive evaluation of the total coronary atherosclerotic burden that has a stronger prognostic meaning.

Figure 1: CCTA performed on a dual-source scanner (B) and corresponding invasive coronary angiography (A) at a low radiation dose of 3mSv (212 DLP, conversion factor of 0.014) depicting a noncalciﬁed plaque (C) with 50-70% stenosis in the mid-segment of the right coronary artery.

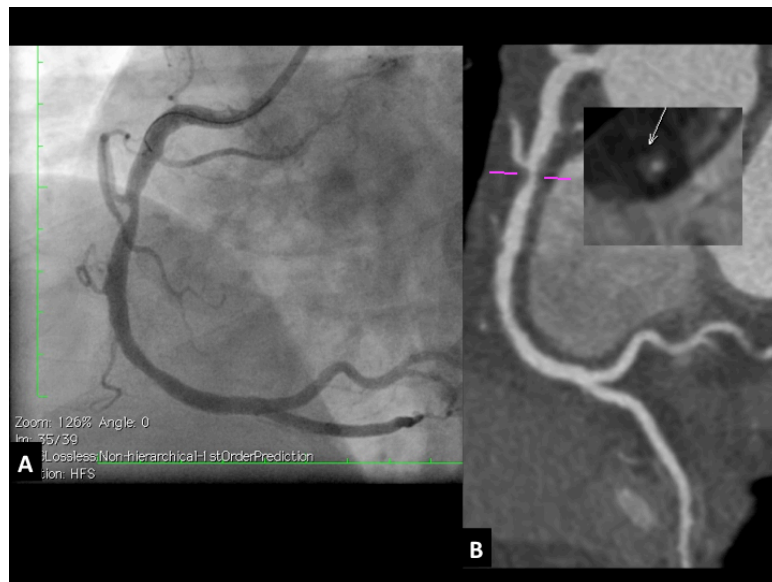


Figure 2: Identification of nonobstructive CAD as a unique feature of CCTA as a noninvasive CAD imaging modality.

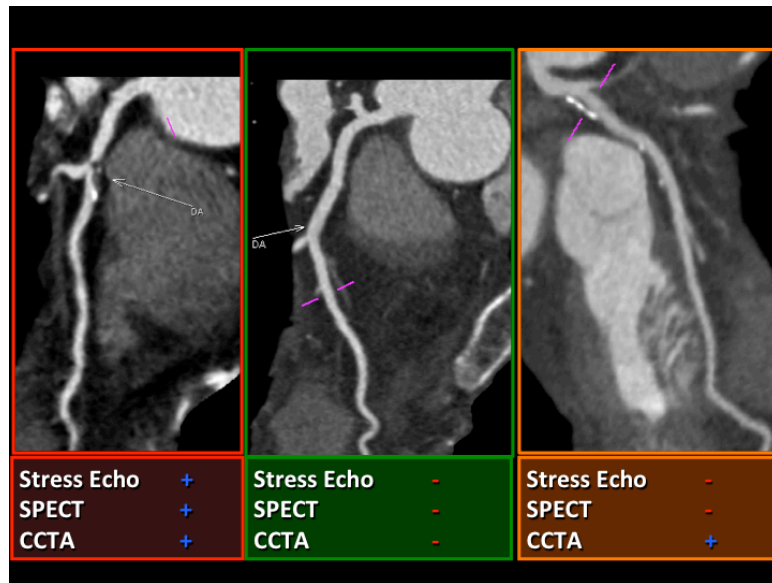


Figure 3: Contrast between CV risk, as assessed by the HeartScore, and the presence of nonobstructive (but probably not innocent!) mixed plaque in the left main in a 51 years-old male with hypertension, dyslipidemia and an HeartScore <5%.

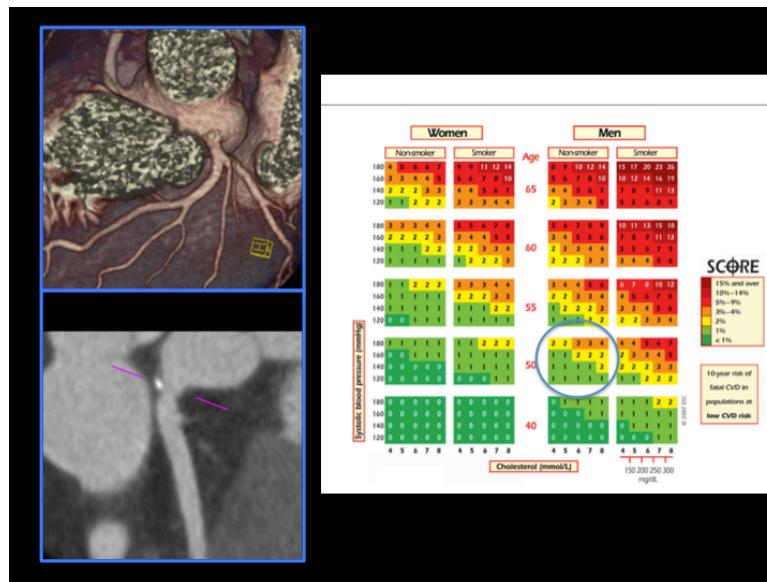


Figure 4: CCTA with prospective triggering with an estimated radiation dose of 1.1mSv (79DLP, conversion factor of 0.014), in a patient with normal coronary arteries.

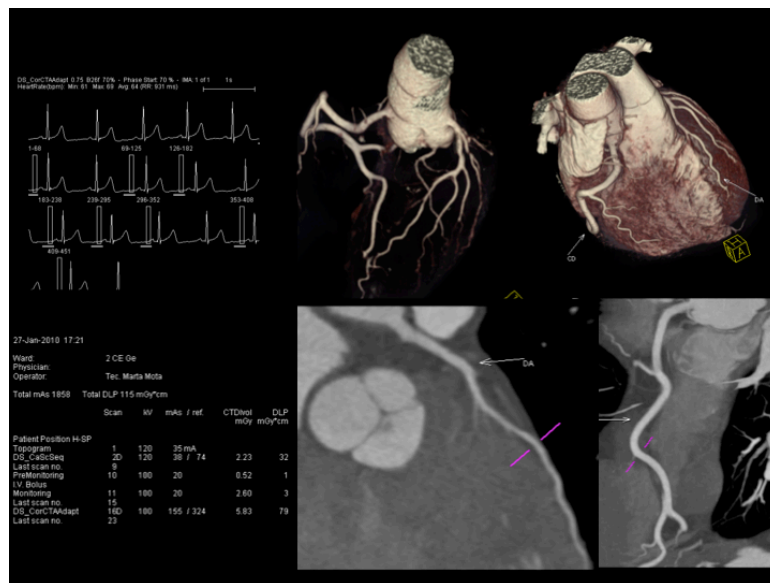


Figure 5: CCTA depicting a noncalcified plaque in the proximal left anterior descending artery without significant stenosis (A). In invasive angiography (B) this lesion was not apparent but was confirmed with IVUS (C).



Figure 6: Mixed plaque in the proximal left anterior descending artery with positive remodeling and without significant stenosis (<25% by visual estimation). This was a 31 year old male patient with a family history of premature coronary artery disease.



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Capítulo 10.

Discussão, conclusões e direcções para trabalhos futuros

SUMÁRIO DO CAPÍTULO 10:

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10.2 CONCLUSÕES

10.3 DIRECÇÕES PARA TRABALHOS FUTUROS

10.3 BIBLIOGRAFIA

10.1 DISCUSSÃO GLOBAL

O trabalho que foi desenvolvido no âmbito desta tese esteve assente em vários pressupostos de **epidemiologia e fisiopatologia da DC** e do relativo contributo e respectivas limitações das **diferentes modalidades de diagnóstico por imagem** no estudo da DC, nomeadamente na identificações dos doentes em risco de eventos coronários:

1) Apesar de toda a evolução farmacológica e de meios complementares de diagnóstico possível nos últimos anos, ***o EAM e a morte súbita continuam a ser a primeira manifestação da aterosclerose coronária*** para muitos doentes. Muitos destes doentes não tinham sintomas previamente ao evento e o seu risco CV era baixo, sendo difíceis de identificar clinicamente (1-3). A justificação para esta discrepância entre o risco por doente e o risco populacional resulta do facto de a população de risco CV moderado ou baixo ser muito superior à de risco elevado e assim uma importante fatia dos eventos CV ocorre em indivíduos de menor risco relativo (4).

2) Os exames complementares de diagnóstico tradicionalmente usados para avaliar a DC, baseiam-se na ***documentação de isquémia***, sendo esta a sua maior limitação, uma vez que a sua positividade exige a presença de lesões coronárias obstrutivas. Assim, estes exames não permitem a avaliação da carga aterosclerótica coronária global e a detecção de lesões coronária não obstrutivas, que se sabe estarem também implicadas na etiologia de eventos coronários (5-7).

3) Estudos de placa vulnerável com ***imagiologia intracoronária*** avançada, de elevada resolução espacial e suplementada por caracterização tecidular - IVUS-VH - forneceram resultados desapontadores acerca da possibilidade de identificação das placas vulneráveis. No estudo PROSPECT (8), com esta avaliação invasiva e numa população que já tinha sofrido um SCA, foi possível identificar 3 características de risco nas placas associadas ao desenvolvimento subsequente de eventos coronários. No entanto, mesmo pela conjugação dessas 3 variáveis, a probabilidade de um evento coronário no seguimento médio de 3,4 anos foi de apenas 18,2%, ou seja, cerca de 4 em cada 5 doentes que tem placas que reúnem simultaneamente estas 3 características de risco não vieram a sofrer qualquer evento. Neste trabalho considerado um marco no estudo da história natural da DC, mesmo a identificação de um TCFA teve uma baixa especificidade para prever a ocorrência de eventos, uma vez que apenas 26 das 595 placas identificadas como de risco estiveram na origem de eventos. Por outro lado, a grande maioria dos eventos verificados foram rehospitalizações por AI e novas revascularizações e não os eventos major que verdadeiramente gostaríamos de poder prevenir, a morte e o EAM. Este último aspecto pode ter sido igualmente influenciado pelo facto de estes doentes estarem já em prevenção secundária, com medicação que reconhecidamente reduz o seu risco (nomeadamente antiagregação plaquetar e estatina) e com a habitual vigilância apertada dos ensaios clínicos, o

que pode ter contribuído para reduzir a taxa de eventos. De qualquer modo, este trabalho está em linha com o conceito de que apesar de o risco por placa poder ser superior para determinadas lesões que reúnem estas características de instabilidade, o risco final para o doente resulta da probabilidade somada de todas as suas lesões, sendo que quanto maior for a carga aterosclerótica maior será o risco, conceito bem alicerçado por toda a evidência reunida ao longo de vários anos sobre o valor prognóstico do score de cálcio (9-11).

4) Existe um **contraste entre o risco absoluto por placa e a prevalência dos diferentes tipos de placas**. Apesar de o risco absoluto de instabilização por placa ser superior para placas mais volumosas e obstrutivas (assumindo o mesmo nível das restantes características de risco, nomeadamente o grau de inflamação e a espessura da cápsula fibrosa), estas são menos prevalentes do que as placas não obstrutivas e assim, por questões probabilísticas, os eventos coronários resultam com frequência de instabilização destas lesões não obstrutivas (12, 13).

A **angio TC cardíaca** é a mais recente técnica não invasiva para o estudo da DC, tendo surgido nos últimos anos fruto de importantes avanços tecnológicos na tecnologia de TC multidetectores. Desde o seu aparecimento, tem-se assistido a uma progressiva melhoria da resolução espacial e temporal, contribuindo para uma evolução favorável da qualidade dos exames, bem como uma significativa redução da dose de radiação (14-16). A par desta **evolução tecnológica**, foi aumentando a experiência e gerada mais evidência clínica, tornando a angio TC cardíaca numa técnica cada vez mais robusta na avaliação da DC, sendo já considerada o exame de eleição em várias indicações e tendo vindo a aumentar progressivamente a sua **aplicabilidade clínica** e o número de indicações para a qual é considerada como apropriada (17, 18).

Para além de permitir excluir a presença de DC e de identificar a presença de estenoses significativas, a angio TC cardíaca permite identificar ainda um 3º grupo de doentes com **lesões coronárias não obstrutivas**, característica impar desta técnica como modalidade de imagem não invasiva. Ao permitir identificar a totalidade das lesões ateroscleróticas (obstrutivas e não obstrutivas), a angio TC cardíaca poderá fornecer uma quantificação da carga aterosclerótica coronária total, podendo essa identificação ser útil na estratificação dos indivíduos em risco de eventos coronários. No entanto, dada a elevada prevalência de placas ateroscleróticas identificáveis na árvore coronária por angio TC, que na maioria dos estudos corresponde a mais de metade dos doentes (19, 20), torna-se importante desenvolver ferramentas que permitam quantificar a carga aterosclerótica coronária e assim identificar os indivíduos com maior carga aterosclerótica que poderão eventualmente beneficiar de medidas de prevenção mais agressivas (21).

A angio TC cardíaca, como modalidade não invasiva, tem ainda importantes limitações de resolução espacial para a avaliação detalhada das características de potencial instabilidade de uma placa em particular, nomeadamente não permitindo avaliar a espessura da cápsula fibrosa nem o grau de inflamação, mas permite avaliar de modo não invasivo a carga aterosclerótica coronária global, incluindo as lesões não obstrutivas. Esta identificação e quantificação da **carga aterosclerótica** poderá ser mais importante para o desenvolvimento futuro de eventos do que as potenciais características de instabilidade de uma placa em particular.

A angio TC cardíaca, ao fornecer uma avaliação detalhada da árvore coronária, no que diz respeito à presença, localização, grau de estenose e tipo de placa, poderá dar informação acerca do risco não apenas resultante de uma placa em particular, mas da totalidade da carga aterosclerótica da árvore coronária.

Assim, torna-se fundamental desenvolver e validar prospectivamente scores que integrem toda esta informação e permitam quantificar a carga aterosclerótica coronária global que terão provavelmente uma boa correlação com o risco de eventos coronários futuros. Este foi o objectivo do desenvolvimento do **CT-LeSc** (22).

Por fim, o conceito de **árvore coronária vulnerável** poderá ser mais importante do que o da placa vulnerável e a sua identificação pela angio TC cardíaca poderá ser importante numa estratégia de prevenção mais avançada. Esta poderá permitir **personalizar as medidas de prevenção primária**, doseando melhor a sua intensidade em função da carga aterosclerótica, podendo esta vir a constituir uma das mais importantes indicações da angio TC cardíaca no futuro.

10.2 CONCLUSÕES

1. Foram identificados preditores demográficos e clínicos para uma elevada carga aterosclerótica, avaliada pela angio TC cardíaca. A diabetes mellitus em particular foi um dos preditores clínicos mais importantes, funcionando como modelo de DC mais avançada, útil para avaliar o desempenho dos diferentes índices de carga aterosclerótica ([artigo 16](#)).
2. O desempenho destas variáveis demográficas e clínicas, mesmo quando agrupadas em scores clínicos para prever a presença e da gravidade da DC (obstrutiva e não obstrutiva) documentada por angioTC cardíaca foi modesta. Entre os vários scores, o desempenho foi um pouco melhor para o score de risco cardiovascular HeartScore. Estas limitações espelham a dificuldade de prever apenas com base em variáveis clínicas, mesmo quando agrupadas em scores, a presença e extensão da DC. Um dos factores de risco clássicos, a obesidade, parece ter uma relação paradoxal com a carga aterosclerótica, o que pode justificar algumas limitações da estimativa com base em scores clínicos ([artigo 15](#)).
3. Foi desenvolvido um índice de carga aterosclerótica que reúne a informação global acerca da localização, do grau de estenose e do tipo de placa, obtida não invasivamente pela angio TC cardíaca ([artigo 18](#)). Este score poderá vir a ser uma ferramenta útil para quantificação da carga aterosclerótica coronária sendo de esperar que possa traduzir a informação prognóstica da angio TC cardíaca, uma vez que a DC pode manifestar-se clinicamente mesmo na ausência de lesões obstrutivas ([artigo 1](#)), numa fase em que não é expectável que cause sintomas e em que é silenciosa nos habituais exames de documentação de isquémia.

10.3 DIRECÇÕES PARA TRABALHOS FUTUROS

1. Um dos objectivos centrais desta tese foi o desenvolvimento de um score que reflecte a carga aterosclerótica coronária global, o CT-LeSc. Na nossa população foi possível demonstrar uma associação significativa entre o CT-LeSc e reconhecidos factores de risco cardiovasculares como a diabetes, cuja presença de associou a uma probabilidade quase 3 vezes superior de um elevado CT-LeSc. Por outro lado, também um elevado risco cardiovascular (estimado pelo Heartscore) associou-se a uma probabilidade 2,5 vezes superior de se encontrar uma elevada carga aterosclerótica traduzida por este índice.

No entanto, o CT-LeSc carece ainda de validação prognóstica, antes da sua adopção na prática clínica. A sua validação como ferramenta para identificar os doentes em maior risco de eventos, mesmo no subgrupo sem doença coronária obstrutiva, deverá idealmente ser feito numa população com um tempo de seguimento não muito curto e/ou com maior risco cardiovascular, dada a baixa taxa de eventos observada nas populações de risco intermédio a baixo, tipicamente referenciadas para angio TC cardíaca para exclusão de doença coronária. Este será o próximo passo, tendo já sido desenvolvido algum trabalho nesta área por ligação a grupos internacionais que fazem investigação nesta área .

2. Por fim, a identificação por angio TC cardíaca dos doentes com elevada carga aterosclerótica em maior risco de eventos coronários e que assim poderão beneficiar de uma prevenção primária mais agressiva, irá levar ao desafio de se desenvolver estratégias de prevenção mais avançadas.

Estas poderão no futuro passar pela adopção de medidas já empregues em prevenção secundária, nomeadamente pelo uso de dupla antiagregação plaquetar ou dos novos antiagregantes mais potentes, já validados no contexto de síndromes coronários agudos (23, 24), embora estas medidas tenham sempre de ser contrabalançadas pelo esperado aumento do risco de complicações hemorrágicas. Um abordagem alternativa e possivelmente mais segura poderá passar por uma terapêutica mais direccionada aos mecanismos do desenvolvimento da aterosclerose. À medida que se conhece cada vez melhor a fisiopatologia da aterosclerose e o papel central da inflamação (5, 6, 25, 26), não só na progressão destas lesões mas sobretudo no seu risco de instabilização, novas estratégias direccionadas para estes mecanismos poderão vir a ser empregues, estando já alguns fármacos em fase de ensaios clínicos (27) .

Por outro lado, o paradigma de intervenção na doença coronária poderá vir a mudar. Actualmente a angioplastia no contexto de doença coronária estável está sobretudo indicada para melhoria dos sintomas, podendo ter impacto prognóstico favorável quando realizada em lesões obstrutivas responsáveis por extensas áreas de isquémia (28). A intervenção percutânea em lesões não obstrutivas mas que apresentam outras características de potencial instabilidade é para já uma hipótese teórica, tendo duas limitações importantes: Em primeiro lugar, está limitada pela actual baixa especificidade na identificação não invasiva (29) e mesmo invasiva (8),

das placas vulneráveis. Em segundo lugar, a intervenção nestas lesões tem que partir do pressuposto de que a historia natural destas placas vulneráveis se associa a um risco de eventos superior ao risco relacionados com a própria intervenção, estando assim intimamente ligada à eficácia e segurança da própria angioplastia. Nos últimos anos tem-se assistido a avanços tecnológicos impressionantes na área da cardiologia de intervenção, com reduções muito significativas da taxa de restenose e mais recentemente também da taxa de trombose. O desenvolvimento recente de stents absorvíveis veio abrir um novo campo de possibilidades à intervenção percutânea e os impressionantes resultados experimentais e clínicos obtidos poderão levar a reequacionar as indicações clínicas e contribuir para esta mudança de paradigma.

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All truth passes through three stages.

First, it is ridiculed.

Second, it is violently opposed.

Third, it is accepted as being self-evident.

Arthur Schopenhauer