



EDITORIAL COMMENT

Uncovering hypertrophic cardiomyopathy pathophysiology – the unsolved role of microvascular dysfunction



Fisiopatologia da miocardiopatia hipertrófica: o papel da disfunção microvascular

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Hypertrophic cardiomyopathy (HCM) is considered the most common genetic heart disease, with an estimated prevalence in the general population ranging from 1:500 to 1:200.^{1,2} HCM diagnosis is based on otherwise unexplained left ventricular hypertrophy (LVH) observed using imaging techniques,³ mostly transthoracic echocardiography, which is the initial imaging modality, and establishes the diagnosis in the majority of cases. However, increased left ventricular (LV) wall thickness in one or more myocardial segments, detected by echo and corresponding to LVH, reflects only one of the several pathophysiologic features of this complex disease, which also involves myocyte disarray, interstitial and replacement fibrosis, microvascular remodeling and microcirculatory dysfunction.

Myocardial ischemia in the absence of epicardial coronary artery disease is common in HCM patients,⁴ whether chest pain is present or not. A study performed in asymptomatic HCM patients demonstrated reversible perfusion defects indicative of ischemia in 50% of patients.⁵ In fact, myocar-

dial ischemia in HCM is an established pathophysiologic feature and may be associated with important disease-related complications, including adverse left ventricular remodeling and systolic dysfunction. Moreover, microvascular ischemia has been associated with outcomes such as all cause mortality, cardiovascular death, heart transplant, heart failure, sustained ventricular tachycardia and atrial fibrillation.^{6,7} However, its routine assessment is difficult and its management remains controversial.

Myocardial ischemia in HCM patients results from an imbalance between oxygen demand, increased by LVH, left ventricular outflow tract obstruction (LVOTO), diastolic dysfunction, and supply, decreased by small vessel disease, abnormal vascular response, increased resistance, and myocardial bridging. The latter, in most cases, it is considered a benign condition and curiously myocardial bridging is much more frequent in HCM patients than in the general population, with an autopsy study suggesting prevalence is as high as 41% in HCM patients.⁸

Among these mechanisms, the major cause of myocardial ischemia in HCM is microvascular dysfunction, which is multifactorial, resulting from vascular remodeling with arteriolar medial hypertrophy and intimal hyperplasia, fibro-

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sis, myocyte disarray, extravascular compression due to LVH, diastolic dysfunction and LVOTO.⁶ It may be present even in non-hypertrophied LV segments,⁹ suggesting an important role in the pathophysiology of HCM, perhaps in pre-hypertrophic stages.

Interestingly, HCM patients with identified sarcomere mutations have more severe microvascular dysfunction compared with genotype-negative patients.¹⁰ Similarly, recent HCM registries^{11,12} separate these two subgroups of patients: sarcomere positive HCM patients tend to be younger age at diagnosis, more often present reverse septal morphology, more myocardial fibrosis and a worse prognosis when compared to nonfamilial HCM patients. The more severe microvascular dysfunction reported in sarcomere positive HCM may in fact contribute to this different evolution profile.

In this issue of Portuguese Journal of Cardiology, Brás et al.¹³ studied the association between microvascular dysfunction, tissue characterization and myocardial deformation in 75 HCM patients using cardiac magnetic resonance segmental analysis. In such a heterogeneous disease, many cases present focal, non-diffuse disease. By performing segment-by-segment analysis, this study enabled direct comparisons between segments and the establishment of novel associations, not apparent in other.¹⁴

The main findings of this study are:

1. Perfusion defects occurred across all LV wall thickness (WT) segments, although more frequent in more hypertrophied segments (19% in non-hypertrophied segments, 43% in LVWT 12-14 mm and 64% in LVWT 15 mm). This finding supports the hypothesis of myocardial ischemia, driven by microvascular dysfunction, is present in early stages of the disease, in particular in the non-hypertrophic stage, perhaps contributing to myocyte death, replacement fibrosis and LV remodeling. Increasing grades of LVH, with a corresponding increase in oxygen demand, and with a more distorted cardiomyocyte architecture, with more fibrosis and disarray, will further aggravate microvascular function and culminate with more perfusion defects, which may explain the higher prevalence of perfusion defects in the thickest segments.
2. Perfusion defects were associated with higher T1 and extracellular volume (ECV), higher T2 and had late gadolinium enhancement (LGE) more frequently, independently of WT. Even in segments with normal WT, tissue characterization revealed abnormalities, in particular increased ECV and LGE, which may correspond to interstitial and replacement fibrosis respectively, in an early stage of HCM. Cause or consequence, microvascular dysfunction and ischemia seem to be associated with interstitial and replacement fibrosis and may become important risk markers as well a target for therapy in these patients.

Increased native T1 levels and higher T2 values also correlated with ischemia in this study, independently of WT, reflecting tissue abnormalities which may precede LV remodeling in HCM.

3. Lower deformation assessed by circumferential and radial strain (but not longitudinal strain) was associated with perfusion defects and LGE. Indeed, hypoperfused segments and segments with focal fibrosis are expected to present worse deformation parameters. The reason why longitudinal strain was not associated with perfusion defects remains unclear. Further and larger studies addressing this issue are needed.

Microvascular dysfunction plays a crucial role in HCM pathophysiology, although interactions with other involved pathways still remain unclear. The cascade of events, beginning with morphologic and functional alterations in coronary microvasculature leading to ischemia, followed by myocyte necrosis, replacement fibrosis and LV remodeling with systolic dysfunction, ventricular arrhythmias and sudden cardiac death is conceptually attractive, explaining the natural history of some HCM patients. Ischemia assessment in HCM may help to understand the pathophysiology of this complex disease, adding an incremental value to the clarification of symptoms and possibly to risk stratification and redefinition of prognosis. Intensive research in this area is warranted to explore new specific treatment targets in order to minimize ischemia and modify the natural history of these patients.

Conflicts of interest

The author has no conflicts of interest to declare.

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