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EDITORIAL COMMENT

Diagnostic questions in hypertrophic cardiomyopathy: What is the significance of late gadolinium enhancement on cardiac magnetic resonance?☆

Enigmas diagnósticos na miocardiopatia hipertrófica – qual o significado do realce tardio obtido por ressonância magnética?

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Echocardiography remains the first-line imaging modality for the diagnosis of hypertrophic cardiomyopathy (HCM), but cardiac magnetic resonance (CMR) is increasingly used to assess phenotypic manifestations of the disease due to its high spatial resolution, absence of acoustic window limitations and ability to characterize tissue, in what has been termed a form of in-vivo histological assessment.[1] It is particularly valuable in HCM, giving reliable information on parameters that have prognostic significance for which echocardiography can be inadequate, such as thickness of ventricular wall segments and the presence of apical aneurysms, as well as the degree of mitral regurgitation and abnormalities of the subvalvular apparatus.

One CMR technique that has aroused great interest is late gadolinium enhancement (LGE). This has been validated for the detection and quantification of myocardial necrosis,[2] but also provides important information for the characterization of diseases of the myocardium, particularly in terms of patterns and distribution.[3]

The value of LGE in HCM has been the subject of intense debate. The myocardial fibrosis that is the hallmark of HCM is histopathologically diffuse in both replacement and interstitial forms, and is assumed to be a substrate for tachyarrhythmias and sudden death. While the latter is uncommon in the general HCM population, the subgroups most at risk have yet to be fully identified[4]; the currently proposed risk markers have low accuracy in predicting which patients are at risk.[4,5]

LGE on CMR, which essentially shows the focal distribution of fibrosis, and can present in a wide variety of patterns, is common in HCM patients (56–67% in large series[6–8]), and is also found in some asymptomatic mutation carriers. LGE is not currently considered a risk marker for sudden death, but might be considered a potential risk modifier, particularly when seen in extensive areas of the myocardium.[4] What evidence is available on the clinical significance of LGE in HCM?

Firstly, it is known to be a valid indicator of fibrosis. LGE was initially validated in a post-mortem study of a patient with end-stage HCM, in which histopathological study revealed extensive fibrosis; the contrast agent was distributed in areas of fibrosis and increased collagen and there was a clear correlation between CMR and histological findings. However, this case – with severe ventricular dysfunction – is not representative of most HCM patients in clinical practice.[9] Characterization of the histological mechanisms underlying LGE in patients with preserved ventricular

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function was hampered by the lack of an animal model of HCM. Recently, Moravsky et al.,[10] analyzing myectomy specimens from patients with obstructive HCM, showed that LGE reliably reflects total myocardial fibrosis when appropriate analytical techniques are used, but they were unable to distinguish replacement from interstitial fibrosis, in which there is expansion of the extracellular matrix, which some studies suggest has different implications for the genesis of arrhythmias. Characterization of myocardial fibrosis in HCM by LGE is thus not easy, not only because of the difficulty in differentiating the two types of fibrosis, as described above, but also because areas of focal contrast deposition can be found adjacent to areas of diffuse distribution, which are beyond the spatial resolution of CMR.

Secondly, in terms of clinical significance, early studies showed that LGE is linked to the electrophysiological substrate, and is associated with ventricular arrhythmias on Holter ECG monitoring.[11] However, its relationship to prognosis is still a controversial subject. The presence of LGE was associated with greater risk of death in two large studies of asymptomatic or mildly symptomatic patients: Bruder et al. found an independent risk of sudden death that was higher in patients with LGE than with traditional risk factors,[6] while according to O'Hanlon et al., LGE was related only to a composite endpoint of adverse cardiac outcomes, but the risk was independent and increased with the extent of LGE.[7] The high prevalence of LGE in HCM, in contrast to the relative rarity of sudden death in the general HCM population, has intensified the debate, and some argue that it is an insufficiently accurate marker to indicate the need for prophylactic implantation of a cardioverter-defibrillator.

In a study of 1300 HCM patients, Chan et al.[12] found no association between the presence of LGE and risk of progressive heart failure symptoms/cardiovascular death and sudden death. However, a significant linear relation was evident between the extent of LGE and these endpoints, and it was independently associated with an increased risk of sudden death, even after controlling for traditional sudden death risk factors. LGE in $\geq$15% of the myocardium conferred a more than three-fold higher risk of sudden death. These findings imply that arrhythmic risk in HCM could be reclassified according to the extent of myocardial fibrosis.

It should be noted that other studies suggest that the extent of LGE is not related directly to the degree of ventricular dysfunction, and that patients with low-normal ejection fraction may have a similar degree of LGE to those with end-stage HCM and severe dysfunction.[13]

Despite the limitations of the study by Caetano et al. in this issue of the *Journal*,[14] including the small population size, the fact that it was a convenience sample and hence subject to bias arising from referral for CMR, the older age of the patients compared to other series (and therefore greater likelihood of comorbidities), and their relative heterogeneity, the presence of LGE was associated with hemodynamically and morphologically more severe or advanced forms of the disease, as well as with traditional risk factors. This is in agreement with current thinking, based on large populations, that focal fibrosis identified by LGE on CMR has clinical significance.

New CMR techniques that enable mapping and quantification of diffuse fibrosis[15] may add prognostic information, as well as widening understanding of the underlying mechanisms and improving individual clinical decisions.

Such a prospect suggests new research pathways for this poorly understood entity. It is to be hoped that innovative answers will be found to the challenging question of the relation between clinical phenotype and outcome in HCM, in areas ranging from genetics to cell biology and environmental interactions

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Friedrich M. Tissue characterization of acute myocardial infarction and myocarditis by cardiac magnetic resonance. J Am Coll Cardiol Img. 2008;1:652–62.
2. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100:1992–2002.
3. Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005;26:1461–74.
4. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58:e212–60.
5. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–12.
6. Bruder O, Wagner A, Jensen CJ, et al. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:875–87.
7. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:867–74.
8. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:51–8.
9. Moon JC, Reed E, Sheppard M, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43:2260–4.
10. Moravsky G, Ofek E, Rakowski H, et al. Myocardial fibrosis in hypertrophic cardiomyopathy: accurate reflection of histopathological findings by CMR. JACC Cardiovasc Imaging. 2013;6:587–96.
11. Adabag AS, Maron BJ, Appelbaum E, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369–74.
12. Chan R, Maron BJ, Olivotto I, et al. Prognostic utility of contrast-enhanced cardiovascular magnetic resonance in hypertrophic cardiomyopathy: an international multicenter study. J Am Coll Cardiol. 2012;59:E1570.

13. Olivotto I, Maron BJ, Appelbaum E, et al. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:261–7.
14. Caetano F, Botelho A, Trigo J, et al. Expressão fenotípica da miocardiopatia hipertrófica e realce tardio na ressonância magnética cardíaca. Rev Port Cardiol. 2014;33: 261–7.
15. Puntmann VO, Voigt T, Chen Z, et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. JACC Cardiovasc Imaging. 2013:475–84.