EDITORIAL

What Is Late Gadolinium Enhancement in Hypertrophic Cardiomyopathy?

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Hypertrophic cardiomyopathy (HCM) is a condition that can be defined in three ways: genetically, as caused by sarcomeric protein mutations; phenotypically by the presence of unexplained hypertrophy in the absence of afterload; and histologically by myocardial fibrosis, disarray, and small vessel disease. All these definitions have problems: only around half of HCM cases have an identifiable mutation, HCM phenocopies are common, and histological diagnosis requires whole heart sampling to be definitive. Late gadolinium enhancement (LGE) promises clarity. By apparently directly visualising myocardial fibrosis in vivo, the presence of “myopathy” may be confirmed, whilst the pattern and extent of such fibrosis may predict adverse events – heart failure, and, potentially, sudden death. But does the technique live up to the hype?

In this issue, 2 papers use the late enhancement technique to explore HCM.1,2 In the paper by Pujadas et al,1 43 consecutive, mainly low risk patients were found to have a wide range of patterns and distributions of LGE, correlating with regional wall thickness, and more weakly with the presence of conventional risk factors, and familial disease. Similar findings occurred in the Dumont paper,2 where LGE additionally correlated with the presence of non-sustained ventricular tachycardia, and inversely with the heart’s ability to generate a stress outflow tract gradient.

How Does LGE Work?

To understand the technique more clearly, it is best to explore from first principles the LGE technique. Contrast magnetic resonance imaging (MRI) has been used since 1982, initially in myocardial infarction, when the earliest tracers were manganese based.3 Similarly, interstitial imaging ex vivo has been performed since the 1960s using radiolabelled tracers such as 51Chromium-ethylenediaminetetraacetic acid (51Cr-EDTA).4 These techniques converged with current MRI techniques where gadolinium chelated to diethylenetriaminopentacetic acid (DTPA) is used.5 The gadolinium (Gd) makes the contrast visible by MRI, the DTPA defines the in vivo behaviour of the whole. Gd-DTPA diffuses rapidly out of capillaries (unlike echocardiographic microbubbles), into tissue but cannot cross intact cell membranes. So after an intravenous bolus, both normal and abnormal myocardium passively accumulate Gd-DTPA, but with time, because of slower kinetics, and a larger volume of distribution, abnormal myocardium possesses a slightly larger amount per unit volume of Gd-DTPA.6,7 Although this technique was known since the early 1980s, little progress was made in the field until 1991 when an MRI sequence called inversion-recovery was developed and optimized for cardiac work.8 This technique is highly sensitive to subtle regional differences in gadolinium concentration, and is an “image intensification” technique. The operator visually selects a parameter (TI —Time to Inversion, the time to the null point—) so background myocardium is nulled, returning no signal, appearing black. Regions with different magnetic properties (T1), and in the myocardium this means different concentration of gadolinium, appear bright white, late gadolinium enhancement. The consequence is an “all-or-none” technique with very high sensitivity to regional interstitial expansion, and heterogeneity, but with little information about the actual extent of the interstitial compartment in either the nulled (dark), or enhancing (bright) myocardium. All that is known is that they are on different sides of a threshold.

LGE in Myocardial Infarction

In myocardial infarction, because of the wavefront of myocardial necrosis due to trans-myocardial perfusion gradients, within any one voxel, myocytes tend to die in an all-or-none way.9 So “dark” myocardium is alive; hence the mantra “bright is dead.” The technique can be used in combination with regional wall motion assessment, to determine whether myocardial dysfunction is potentially reversible.10 As dark myocardium consists of living myocytes excluding Gd-DTPA, if dark

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myocardium is dysfunctional, then potentially, intervention can restore function – be it revascularisation for hibernation, the passage of time for stunning, resynchronisation for dysynchrony, or medical intervention for heart failure.

Fibrosis in HCM

The pathological processes occurring in HCM are very different from myocardial infarction. Our knowledge of the histology of HCM is derived principally from post mortem studies in patients who have died of their disease. The events that lead from sarcomeric protein mutation to fibrosis are not well understood. The morphology of this fibrosis is complex and a number of different patterns have been observed. There may be a generalised increase in the normal interstitium with pericellular, intercellular, and fascicular connective tissue. In extreme cases, individual myocytes may become encaised in collagen. Disarray, another key component of the myocardial abnormality in HCM, and one that may be linked to outcome, is also but not ubiquitously associated with fibrosis, called plexiform fibrosis, particularly at the right ventricle (RV) insertion points. Other types of fibrosis in HCM are perivascular fibrosis and microscopic replacement scars. In advanced disease with heart failure, extensive areas of replacement scarring may be present and macroscopic. Some of these areas may be indistinguishable from myocardial infarction.

LGE in HCM

It follows from the above, that late enhancement is different in cardiomyopathy to myocardial infarction. Firstly, late enhancement may represent something other than interstitial expansion related to fibrosis or acute myocardial damage. Only one example of this is known, that of cardiac amyloid, where global subendocardial LGE may occur. Secondly, any diffuse interstitial expansion will not be visualised at all. Late enhancement will represent only focal regions of increased fibrosis, not all fibrosis. Thirdly, regions of late enhancement are not necessarily complete replacement fibrosis. For example, in one published histology/late enhancement correlation, when a myocardial segment had more than 20% fibrosis (not 100%), the segment was perceived visually as enhancing, but the range of fibrosis in enhancing segments was from 20%-90%, all appearing broadly similar.

So bearing in mind the above, what does LGE in HCM mean?

LGE in HCM Is Not Specific

Firstly, LGE is not a specific finding to HCM. Because myocytes do not divide substantially, LGE may potentially reflect focal myocardial fibrosis in any condition that causes myocyte death and consequent fibrosis, and the extent of such LGE may be clinically and prognostically important because fibrosis is the substrate for heart failure and arrhythmia. In HCM phenocopies, specific patterns of fibrosis have been described, ranging from the basal infero-lateral wall in Anderson Fabry disease, global subendocardial in amyloid (although the interstitial water may be associated with amyloid fibrils rather than fibrosis in this case), very limited in afterload hypertrophy (aortic stenosis), occurring once wall thickness exceeds 18 mm, and its presence has been described but not systematically studied in others (Noonans, glycogen storage disease). In such heart muscle diseases with hypertrophy, in early disease, the LGE pattern may suggest the diagnosis, but in advanced disease, particularly when progressing towards systolic heart failure, early impressions are that they all begin to appear similar with extensive LGE suggesting fibrosis as a final common pathway.

LGE in HCM Misses Diffuse Interstitial Expansion

Secondly, because LGE reflects only focal fibrosis, diffuse global interstitial expansion will be missed. LGE may correlate with markers of collagen turnover, but the contribution from diffuse hypertrophy will be missed – in the paper by Sipola et al, 46% of the variability in collagen turnover could be explained by LGE. As an endpoint for, say, a medical therapy to reduce diffuse fibrosis, LGE may be sub-optimal. Any correlation with diastolic dysfunction will also be missing the role of diffuse interstitial expansion and impairment of active calcium driven relaxation (cellular dysfunction as well as interstitial dysfunction).

LGE in HCM – Not Only Replacement Fibrosis

Thirdly, regions of LGE will have heterogenous interstitial expansion. Operators performing this technique are aware that some LGE is easier to visualize than others, being “brighter,” or more “well defined,” and different patterns of LGE have been described. These are likely to represent different types of fibrosis, and different extents of interstitial expansion. The RV insertion point LGE may represent plexiform fibrosis related to the RV fibres crossing left ventricle (LV) fibres to form the septum, whereas other types of confluent LGE, sometimes with a perfusion defect, may represent replacement fibrosis. This heterogeneity may help explain a confusing phenomenon where regional wall thickening is apparently undiminished in some areas of LGE — suggesting that interstitial expansion in these cases is modest and insufficient to reduce radial thickening.
The clinical significance of LGE in HCM

What do we know about the clinical significance of LGE in HCM? When HCM is systematically studied using the LGE technique, the most striking impression is of great heterogeneity of extent and pattern of LGE. What on morphological criteria alone appears a single disease, after LGE appears more like a collection of related diseases. LGE correlates with wall thickness, family history, inversely to ejection fraction, inversely to exercise induced outflow tract obstruction, and to exercise test evidence of ischemia. This is promising. Strong evidence is beginning to suggest that LGE is necessary for progressive disease and heart failure, as in the two papers in this issue. Few if any cases of systolic dysfunction in HCM with less than 20% LGE have been reported. Whether LGE can predict heart failure remains unknown. For presence of ventricular tachycardia (VT) or established clinical risk factors for sudden death, the unknown. For presence of ventricular tachycardia (VT) reported. Whether LGE can predict heart failure remains unknown. For presence of ventricular tachycardia (VT) or established clinical risk factors for sudden death, the unknown. For presence of ventricular tachycardia (VT) reported. Whether LGE can predict heart failure remains unknown. For presence of ventricular tachycardia (VT) or established clinical risk factors for sudden death, the unknown. For presence of ventricular tachycardia (VT) reported. Whether LGE can predict heart failure remains unknown. For presence of ventricular tachycardia (VT) or established clinical risk factors for sudden death, the unknown. For presence of ventricular tachycardia (VT) reported. Whether LGE can predict heart failure remains unknown. For presence of ventricular tachycardia (VT) or established clinical risk factors for sudden death, the unknown. For presence of ventricular tachycardia (VT) reported. Whether LGE can predict heart failure remains unknown.

LGE appears to correlate with all the expected parameters of greater disease expression, supported by the two papers in this issue, and promises to bring the histological criteria for HCM into the clinical arena for the first time. But the cohort studies so far leave major questions unanswered. It is key for the future to know whether the presence of LGE, particularly when extensive and in the young is a strong risk factor for sudden death. The converse question also requires an answer – whether little or no LGE (particularly if confined to a limited area of the RV insertion points) is reassuring about future risk. Similarly, an understanding of serial changes in myocardial LGE and its interaction with conventional risk factors is need. Answers to these questions will take time and collaboration between centres with highly characterised populations of HCM patients, but are vital to fully understand the clinical significance of LGE. In the meantime, LGE remains a highly promising technique in the clinical evaluation of HCM, and one with enormous potential for the future.

REFERENCES


