Characterization of Hypertrophic Cardiomyopathy Using Magnetic Resonance “Fibrosis” Imaging

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Abstract

Hypertrophic Cardiomyopathy (HCM) affects one in five hundred people in the United States. It is historically recognized by abnormal patterns of hypertrophy in at risk populations. However, from its first description fibrosis of the myocardium has been integrally linked to the disease, its clinical manifestations and its progress. Magnetic Resonance Imaging allows non-invasive realization of this fibrosis and may improve early diagnosis, improve our understanding of the true prevalence of disease as well as risk assessment while offering the opportunity for recognition and perhaps treatment of pre-clinical disease.

ABBREVIATIONS

HCM: Hypertrophic Cardiomyopathy; MR: Magnetic Resonance Imaging; LGE: Late Gadolinium Enhancement; LV: Left Ventricle

INTRODUCTION

The first description of hypertrophic cardiomyopathy [HCM] focused upon clinical observations that included, “marked cardiac hypertrophy; symptoms of cardiac insufficiency; occurrence of various types of arrhythmia”, and the natural history, “rapidly progressive course after the onset of symptoms; and death from gradual cardiac failure or in sudden fashion”. A crucial but long overlooked observation came from autopsy, “all show hypertrophy of the muscle fibers. In some cases, this is the only lesion. In others there is also fibrosis, which, in different instances, may be slight or extensive. There may be areas of necrosis, both old and recent”[1].

The most common and prominent finding in patients with symptoms of HCM is the harsh murmur of obstruction to ventricular ejection. Therefore, with bedside, and echocardiographic recognition driven by the dynamic outflow obstruction due to septal hypertrophy, discussions of HCM centered upon this aspect of the disease. Controversies in disease understanding claimed that artifact of measurement falsely suggested obstruction or that obstruction was not a principle driver of symptoms eventually gave way to recognition of substantial relief of symptoms after relief of obstruction. Ventricular deformity and the physical effect upon ejection phase and ventricular mechanics is established as a major determinant of functional limitation and disease progression [2]. At the same time, there is increasing recognition of the complex nature of this disease, the extent to which disease may exist outside of the anatomic descriptions from echocardiographic observations and that, in addition to the myocyte, abnormal connective tissue metabolism may alter physical and electrical behavior of the ventricles. HCM actually reduces systolic myocyte efficiency, impairs diastolic function and distorts electrical conduction and recovery. Indeed, the accompaniment to myocyte misbehavior is interstitial myocardial fibrosis, whose cause and impact is increasingly recognized as an important influence upon symptoms, clinical disease progression and the most feared outcome, sudden death [3-5].

MYOCARDIAL FIBROSIS AND HCM

Normal ventricular function requires the coordinated function of cellular contractile elements, proteins anchoring contractile elements to the sarcolemma and elastic connective tissue in parallel and in series with the myocyte. With age, collagen rich tissue begins to replace elastic and influence cardiac function but this effect is relatively modest in the absence of pathology. Abnormal fibrotic tissue found within left ventricular myocardium has long been observed after specific injury such as myocardial infarction replacement fibrosis and with chronic pressure overload (interstitial fibrosis) (Figure 1). Both forms of fibrosis are observed in HCM though the interstitial form appears to be the more important [6].
Echocardiography is currently the gold standard method for diagnostic screening, physiological assessment and follow up of patients with HCM. Its use has somewhat skewed understanding of the anatomic variants of HCM, toward variants producing dynamic obstruction to left ventricular outflow. At the same time, refinements in image processing have allowed description of regional myocardial dysfunction that is not immediately apparent on standard imaging [20, 21]. These methods have predictive value in screening for electrical risk in HCM and may provide complimentary information to magnetic resonance imaging (MR) [22].

**MAGNETIC RESONANCE IMAGING**

Late Gadolinium Enhancement

Freedom from imaging "windows" and geometric assumptions led to the suggestion of MR for HCM evaluation in 1985 [23]. Later development of the gadolinium enhanced inversion recovery sequence provided striking images of fibrotic myocardium referred to as regions of Late Gadolinium Enhancement (LGE) [24]. The LGE technique is widely used for the assessment of myocardial viability in patients with ischemic heart disease, as well as the detection of infiltration or irreversible damage in non-ischemic cardiomyopathy, HCM, sarcoidosis, myocarditis and amyloidosis [25-36] (Figure 2).

Gadolinium-chelates (Gd) do not cross intact myocardial cell membranes, maintaining residence in the extracellular space [37]. LGE methods take advantage of this fact by obtaining images at approximately 10 – 15 minutes after intravenous administration of 0.1-0.2 mmol/kg Gd, using an inversion recovery (IR), T1-weighted gradient echo sequence [38]. Iterative adjustment of the inversion time is made to best coincide with the time of magnetization recovery of the normal myocardial tissue when crossing zero. Simplified, images are repeated until minimum signal, "nulled", is apparent in at least some parts of the myocardium with maximum contrast compared to non-nulled segments [38]. In areas with expanded extracellular space, the presence of gadolinium shortens T1 relaxation time thus maximizing signal, showing up as bright white on the image, termed "hyberenhancement" [37].

**ELECTROCARDIOGRAM**

An adage among senior clinicians that HCM is rarely present when the ECG is normal reflects the importance of electrical behavior in diagnosis. In addition, the ECG may reflect aspects of disease severity, in particular complicating fibrosis and its predominant location. Pathological Q waves are considered by many to be the sine qua non of focal, replacement fibrosis of the myocardium. In the setting of HCM, replacement fibrosis may be present but Q waves may also result from vector shifts accompanying focal hypertrophy [16]. Rather than the Q wave, prolongation of the QRS, and fractionation or distortion of the QRS is more reliable in detecting both the presence and severity of myocardial fibrosis [17]. Right Bundle Branch Block is highly specific for the presence of imaging evidence of fibrosis in the ventricular septum, with sensitivity 21% and specificity 94% [18]. In fact, multifocal distribution of apparent fibrosis or that confined to the interventricular septum is closely associated with increased QRS duration. Meanwhile, apparent fibrosis in the apex of the heart is associated with negative T-wave, particularly deep negative T-wave inversion [19].
The ability to easily visualize fibrosis in such a fashion influenced diagnosis and provided a means of quantifying the impact of interstitial fibrosis upon symptoms and prognosis. With the capacity for non-invasive assessment in asymptomatic as well as symptomatic individuals, the patterns and associations of fibrosis have been more completely elucidated without ascertainment bias that is the limitation of autopsy studies. In addition, the combination of excellent anatomic definition with fibrosis location has substantially improved understanding of diffuse and apical variants of the disease as well as the description of a new, spiral variant. This new type of HCM is probably only recognizable using MR with mid-cavity obliteration that would likely be the sole observation from echocardiography [39].

Generally, LGE is present in roughly one half of patients with HCM representing less than 10% of myocardial mass in the majority [40,41] (Figure 3). The presence of LGE identifies a more than threefold increased risk of major clinical events, principally new onset heart failure. That risk is proportional to the amount of apparent fibrosis present [42]. Similarly, the presence of LGE is associated with observation of complex ventricular arrhythmia; appropriate defibrillator discharge and an increased risk of all cause mortality, in particular sudden death [41,43-45]. The correlation between LGE and sudden death event is independent of known other risk factors [40].

The IR sequence used to visualize LGE is not completely standardized with wide variation in the threshold used for identifying abnormal myocardium [30,46,47]. Furthermore, this technique represents an essentially binary method that is dependent upon regional heterogeneity. Therefore, it is limited in the detection and measurement of diffuse extracellular expansion that is commonly associated with various non-ischemic cardiomyopathies. In these instances, the "iterative" technique may produce uniform appearance with little apparent contrast despite the presence of histological evidence that diffuse fibrosis is present [48,49].

Thus, some variation will exist between investigator’s measurement of the extent of fibrosis present and its correlation with clinical events. Nonetheless, patients with known clinical risk factors for sudden death have a greater burden of visible LGE than patients without risk factors, (14% versus 3%, p = 0.001) as do patients with inducible ventricular tachycardia during electrophysiological study, (22% versus 10%, p = 0.03) [50]. Therefore, accepting that LGE measurement is semi-quantitative and almost certainly varying with variation in test conditions, LGE evidence of fibrosis extent correlates with the frequency of ventricular arrhythmia.

Inter-exam variance in LGE extent has been studied in attempts to identify a reliable threshold difference reflecting an actual change in fibrous tissue volume [51]. While no method has histologically proven accuracy, patients examined roughly two years apart, with an incremental growth in LGE volume by more than about 5 cm³ experienced worsening symptoms of heart failure. Patients with the apical variant of HCM generally have less LGE than other variants perhaps explaining their more benign prognosis [52]. However, those with an interval increase in LGE volume are more likely to report symptoms of heart failure [53]. One explanation for the association between heart failure symptoms, electrical events and MR evidence of fibrosis, particularly its progression, is ischemia. Pathological hypertrophy in HCM is associated with aberrancy in the regulation of nutrient flow. Abnormal myocyte efficiency and energy requirements combined with impaired nutrient flow may result in secondary interstitial fibrosis.

Hyperemic flow is reduced in regions of LGE and adjacent, apparently normal myocardium. The association between ischemia and myocardial fibrosis supports the contention that abnormal microvascular dysfunction is responsible for myocardial ischemia–mediated myocyte death and replacement fibrosis [3,54,55]. The fact that hypoperfused regions exceed regions with LGE argues that hypoperfusion may precede fibrosis and may be a more sensitive marker of diseased myocardium in HCM [56]. However LGE may lead to an overestimation of the total ischemic burden on non-corrected perfusion maps by as much as 28% [57].

Specific patterns of LGE, focal, mottled, diffuse and replacement patterns similar to ischemic infarction may associate with specific hemodynamic and clinical behaviors and prognosis. These patterns argue that there may be more than ischemia driving this behavior. Hypertrophy and replacement fibrosis influence the LV systolic mechanics while extent of replacement fibrosis and interstitial fibrosis influence the LV diastolic mechanics [58]. Roughly 10% of patients with LGE are affected only in the anterior and/or inferior areas of right ventricular insertion and have a low risk of adverse events [59]. Meanwhile, LGE outside interventricular insertion points is associated with an increased risk of sudden cardiac death or its equivalent as well as overall mortality [60]. In patients with apical left ventricular hypertrophy, LGE is apparent at the junction between left and right ventricles in 30% [61].

**T1 Mapping**

Imaging LGE is not the only mechanism of screening for or quantifying pathological fibrosis. Imaging sequences that make fibrous tissue visible, such as Diffusion Weighted imaging, and T1-Rho sequence have been used in myocardial infarction and HCM [62-64]. However, a different and perhaps more useful approach is examination of extracellular tissue volume (ECV).
using the native and gadolinium enhanced T1 relaxation time (Figure 4) [65].

T1 relaxation time is a measure of how susceptible the protons in a region of tissue are to the influence of the scanner’s magnetic field after a radiofrequency excitation [66]. T1 values and will vary between tissue types, MR scanner field strengths and the presence or absence of gadolinium contrast. In addition, specific disease processes may influence the T1 time of native myocardium e.g., shortening with hemochromatosis and Fabry-Anderson disease or prolonged in ischemic heart disease, myocarditis, sarcoidosis and amyloidosis [65].

There are multiple MRI sequences that provide quantitative assessment of myocardial T1 [65,67-69]. The basic principle involves exciting the protons of a given region with a radiofrequency pulse and measuring the signal that can be achieved from those regions at different time periods. T1 values are obtained for blood and myocardium before Gd administration (native T1) and at 15-20 minutes afterward [65]. If the T1 value is encoded in each imaging pixel, the term T1 mapping is used. Myocardial ECV can be obtained by the following equation [68,70,71].

\[
\text{ECV}_{\text{MYO}} = \frac{\Delta R1_{\text{MYO}}}{\Delta R1_{\text{BLOOD}}} \times (1 - \text{hematocrit})
\]

\[
\text{ECV}_{\text{MYO}} = \text{myocardial extracellular volume; } R1 = \text{tissue relaxation rate (i.e } 1/T1)\text{; and } \Delta R1\text{is } R1 \text{ of post contrast} - R1 \text{ of pre-contrast of the specific tissue; } 1- \text{ hematocrit is the volume distribution of blood.}
\]

There are a number of factors that may influence T1 measurements including heart rate, scanner field strength, renal function, hematocrit, imaging protocol. The computation of myocardial ECV can potentially avoid some of these confounding variables. The ability in the detection of diffuse fibrosis that can otherwise maybe missed by LGE makes T1 mapping an attractive imaging option for HCM as well as most other forms of cardiomyopathy [65,68] [67,72-82].

T1 values before and after contrast differs between normal and HCM patients but the overlap is substantial making the value of limited use in diagnosis [74,78,83,84]. However, ECV differs in gene mutation carriers with and without hypertrophy compared to control patients (0.36 ± 0.01 vs 0.33 ± 0 vs 0.27 ± 0.01 respectively, P=0.001 for intergroup comparison) and may be the best method for screening for diffuse fibrosis [76]. T1 quantification methods may allow earlier diagnosis in at risk patient populations as well as separately evaluating the principle source of symptoms and guiding treatment [85-90].

Patients and controls undergoing MR compared with respect to regional myocardial fibrosis measured using late gadolinium enhancement (LGE) and post-contrast T1 mapping differ in MR and histologic measures of fibrous tissue deposition. In a subgroup of HCM patients undergoing myectomy, collagen content and post-contrast myocardial T1 time correlate rather closely. HCM patients have more LGE as well as more evidence of interstitial fibrosis by T1 mapping. LGE is focally distributed, correlates with incident ventricular tachyarrhythmia and inversely with left-ventricular systolic function. Abnormal T1 time is distributed diffusely and associated with LV diastolic impairment and dyspnea [61,86,91].

Myocardial signal on T2-weighted short-tau inversion recovery (STIR) (HyT2) images is considered a sign of acute damage. In sixty-five patients with HCM, HyT2 was detected in 42% associating with LV mass, LGE, and complex ventricular arrhythmia and inversely with EF [92].

Lastly, perhaps one of the most important arenas of MR imaging, is in patients and kindreds with genetic abnormalities without clinical evidence of disease. Earlier recognition of disease, designed medical therapy and the capacity to measure the impact of that therapy represent a major step in the evaluation and management of kindreds with HCM. Losartan is and angiotensin receptor antagonist with recognized influence upon myocardial interstitial fibrosis [93]. In HCM patients treated with losartan, increase in LV mass over serial assessments was slowed and the extent of LGE was diminished over a period of one year [94]. This observation suggests a need for assessment of asymptomatic individual at increased risk of developing HCM by virtue of family history or measured genetic defect. Further, trial evidence is needed to assess the clinical utility of these observations, perhaps changing practice substantially.

CONCLUSION

HCM is a genetic disease leading to functional limitation,
cardiac rhythm disturbance and an increased risk of sudden death. Its clinically apparent manifestations are a function of ventricular dysmorphology, reduced myocyte systolic function, impaired myocyte and organ diastolic function and the complex impact of altered ion homeostasis and cardiac conduction that accompany individual mutations, resultant hypertrophy and fibrosis. It is a disease more complex than dynamic left ventricular outflow tract obstruction that often occupies center stage. While echocardiography remains the gold standard method for rapid anatomic and functional assessment of HCM, MR represents a significant advance in anatomic definition, diagnostic assessment and perhaps prognosis estimate. New imaging and measurement techniques such as the inversion recovery sequence and T1 mapping allow for the crucial assessment of myocardial fibrosis whose presence, pattern and extent characterize the disease more completely and accurately. Most importantly, MR assessment methods that identify abnormalities prior to symptom onset as well as providing useful serial evaluations represent an opportunity to study and apply anticipatory medical therapy that may modify the natural history of the disease. 

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