Clinical Impact of Contemporary Cardiovascular Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy

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Case Presentation
An asymptomatic athletic 42-year-old man has an abnormal 12-lead ECG obtained during his initial employment examination at a new job (Figure 1). He had no family history of hypertrophic cardiomyopathy (HCM) or unexplained sudden deaths. Echocardiogram demonstrated a 13-mm ventricular septal thickness without systolic anterior motion of the mitral valve. The patient exercised on a standard Bruce protocol stress (exercise) echocardiogram for 12 minutes, without symptoms or arrhythmias, and with appropriate blood pressure augmentation. In the immediate recovery period, systolic anterior motion was absent and outflow tract velocities were normal. A 24-hour ambulatory (Holter) ECG demonstrated normal sinus rhythm without ventricular ectopy. This clinical evaluation left a number of unanswered questions for the patient regarding the diagnosis of HCM, prognosis, and whether a genetic heart disease was present in his family.

Since the early 1970s, cardiovascular imaging has played a critical role in describing the structure and function of the heart in HCM. Indeed, HCM is a disorder uniquely suited to noninvasive imaging, given HCM’s characteristic heterogeneous morphology and hemodynamics, including dynamic left ventricular (LV) outflow obstruction. For much of 40 years, echocardiography has been the dominant imaging technique, first with rudimentary M-mode and then ultimately 2-dimensional imaging and Doppler, now widely available and accessible.

The past decade has witnessed the introduction of cardiac magnetic resonance (CMR) into clinical HCM practice. This contemporary technique provides images with high spatial and temporal resolution and sharp contrast between the myocardial border and blood pool, allowing precise measurements of LV wall thickness and complete tomographic reconstruction of the entire cardiac chamber (without obliquity), unencumbered by a limited acoustic window or interference from thoracic and pulmonary parenchyma. In addition, contrast-enhanced CMR with late gadolinium enhancement (LGE) has the capability of identifying areas of myocardium damaged by fibrosis/scarring, information not obtainable with echocardiography. These unique attributes of CMR are particularly well-suited for characterizing the diverse phenotypic expressions of HCM, providing both diagnosis and risk prediction, thereby introducing into cardiovascular practice a new era of imaging for this disease. For these reasons, it is timely to update the important and growing impact of CMR in HCM. We will discuss specific areas in which CMR has contributed to the routine clinical evaluation of patients with this complex genetic heart disease.

Diagnosis
The clinical noninvasive diagnosis of HCM is highly dependent on accurate quantification of LV wall thickness. Although HCM may be suspected based on the initial presentation (eg, cardiac symptoms, abnormal 12-lead ECG, or family history of inherited heart disease), echocardiographic examination may nevertheless provide nondiagnostic LV wall thickness measurements that
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appear to fall within normal or borderline range. In such clinical situations, CMR has the distinct advantage, by virtue of high spatial resolution imaging, to provide a more precise assessment of LV wall thickness and hypertrophy (Figures 2 and 3).\textsuperscript{3,5,6} For example, tomographic CMR has identified focal and segmental areas of hypertrophy within the LV chamber not reliably detected by 2-dimensional echocardiography. These potentially echo-blind areas can be in the anterolateral free wall, apex, or posterior (inferior) septum (Figure 2).\textsuperscript{1,3,5,6} This is an important consideration, given that 20% of HCM patients have relatively small areas of hypertrophy confined to 1 or 2 LV segments.\textsuperscript{3}

Even when identified by echocardiography, areas of LV hypertrophy may be importantly underestimated, with resolution only by CMR.\textsuperscript{6} This principle can have important management implications for individual patients, particularly when an extreme degree of LV hypertrophy, an independent risk factor for sudden death, can only be recognized by CMR (Figure 2).\textsuperscript{6} In addition, although LV noncompaction is a cardiomyopathy distinct from HCM, characterized by highly trabeculated myocardium (noncompacted) residing on myocardium with normal LV wall thickness (compacted), it occasionally may be difficult with echocardiography to distinguish between this entity and apical HCM. This diagnostic dilemma can be clarified with high-resolution CMR by reliably distinguishing prominent trabeculations from compact myocardium in the distal LV (Figure 3).\textsuperscript{1}

**Assessment of HCM Family Members**

**Application to Screening**

Clinical screening of relatives for transmission of the HCM disease phenotype (i.e., LV hypertrophy) is a standard recommendation.\textsuperscript{1,11,12} Although echocardiography has been the primary screening test in this setting, recognition that CMR provides a more precise delineation of wall thickness throughout the LV chamber creates an important role for CMR in determining whether relatives have clinical evidence of HCM.\textsuperscript{12} This principle integrates CMR into the routine screening of family members and also provides a baseline assessment for future serial studies to define the progression of LV wall thickening.\textsuperscript{1,12}

**In Lieu of Genotyping**

Actionable genetic testing results are present in only 35% of HCM family probands.\textsuperscript{11} When genotyping is negative or ambiguous, or when it is not pursued, CMR can define a number of structural abnormalities in nonhypertrophied LV myocardium, potentially serving as presumptive surrogate markers for positive genetic status: (1) slit-like blood-filled crypts in the LV wall, (2) elongated mitral valve leaflets, and...
These findings in family members, for whom genetic testing has not yet occurred, underscore the value of future formal genotyping to achieve definitive HCM diagnosis (Figure 3), or alternatively, serial CMR imaging to identify possible phenotypic conversion to clinical disease (ie, development of LV hypertrophy).

Prognosis
Sudden Death Risk

Several clinical risk markers have proven highly effective in identifying many HCM patients at increased risk for sudden death who will benefit from primary prevention implantable cardioverter-defibrillators (ICDs; Figure 4). Nevertheless, the HCM risk algorithm is incomplete, and a minority of high-risk patients without conventional markers remains unrecognized, underscoring the need for additional strategies to improve the prediction of sudden death risk. In this regard, interest has focused on contrast-enhanced CMR sequences with LGE to image in vivo the potentially arrhythmogenic substrate of myocardial fibrosis common in HCM hearts. Indeed, early cross-sectional CMR studies reported a strong (7-fold) association between the presence of LGE and risk for nonsustained ventricular tachyarrhythmias on ambulatory (Holter) ECG monitoring, providing evidence that LGE could represent the structural basis for life-threatening rhythms.

These observations led to several contrast-CMR outcome studies, each in relatively small patient cohorts with short follow-up periods, in which HCM patients with LGE were at increased...
risk for composite end points of cardiovascular or all-cause mortality. These studies focused on the presence per se of LGE, particularly common in 50% to 70% of HCM patients, a prevalence too high to be considered a practical risk marker, because it would lead to an excess of primary-prevention ICD implants.

More recently, in a large international, multicenter and prospective study of almost 1300 HCM patients, quantitative contrast-CMR provided evidence that the extent of LGE is a determinant of arrhythmogenicity, capable of identifying patients at increased sudden death risk, now representing a novel risk marker. Extensive LGE emerged as an independent predictor of sudden death, with ≥15% of LV mass conveying a 2-fold increase in risk for those relatively young asymptomatic patients without conventional sudden death markers and who would otherwise not be considered at risk, but now may benefit from primary prevention ICDs (Figures 2 and 3). Substantial LGE also has the potential to resolve complex ICD decision making, acting as an arbiter in selected patients for whom sudden death risk remains ambiguous even after standard risk stratification (Figures 3 and 4). Alternatively, the absence of LGE is associated with lower risk for adverse events, providing a measure of reassurance to patients and to their healthcare providers.

In addition, a unique subgroup of arrhythmogenic high-risk HCM patients, not previously recognized with echocardiography, has been identified with contrast-CMR by high-signal-intensity LGE in the distal LV wall thickness associated with apical aneurysm formation. Apical scarring represents a border zone of fibrosis with normal hypertrophied myocardium and is the nidus for monomorphic tachycardia and ventricular fibrillation in these patients (Figures 2 and 3).

### Advanced Heart Failure
Extensive LGE can also be predictive of a second adverse disease pathway in HCM, ie, the end-stage phase characterized by LV remodeling with ventricular cavity enlargement, wall thinning attributable to scarring, and systolic dysfunction (ejection fraction...
Systolic dysfunction (Figure 2).7

CMR, by virtue of its tomographic high-resolution imaging capability, is uniquely positioned to define LV outflow tract anatomy relevant to strategic planning for septal reduction procedures (Figure 3).1,19,20 with the goal of optimal reduction of outflow gradient. Owing solely to their specific anatomic features of the LV outflow tract, some patients will be more suitable for septal myectomy than percutaneous alcohol ablation.

Preprocedural planning for septal reduction with CMR takes into account several critical issues. First, LV outflow obstruction is attributable to systolic anterior motion and septal contact in the vast majority of HCM patients.3 However, subaortic gradients can occasionally result from muscular apposition in the mid-LV cavity, when an anomalous anterolateral papillary muscle inserts directly into the anterior mitral leaflet (in the absence of chordae tendinae).19 Identification of this uncommon but important anomaly, which requires stacked contiguous tomographic images acquired throughout the LV outflow tract, will alter surgical strategy, requiring extended myectomy, and papillary muscle debulking (Figure 2).19 Other aberrant muscle bundles, now recognized as particularly common with the increased use of CMR in clinical HCM practice, can contribute to LV outflow obstruction and may require resection to achieve optimal hemodynamic results.

Second, elongated mitral valve leaflets, identifiable by CMR in many young HCM patients, often displace the point of obstruction more distally than usual, requiring a myectomy that takes such morphology into consideration, and possible valve repair (eg, plication).20 Also, septal thickness can be inhomogeneous in the preferred area of the myectomy, requiring the muscular resection to be shifted anteriorly or posteriorly from its usual position to avoid the possibility of an iatrogenic ventricular septal defect. Such LV outflow tract abnormalities, recognized as part of HCM, make it less likely that the myocardial infarction induced by percutaneous alcohol septal ablation (fixed in its location by distribution of the first septal perforator coronary artery) will achieve the desired hemodynamic result in certain individual patients.

Conclusions: Who Should Get a CMR?
CMR has emerged as powerful imaging strategy uniquely suited to the diverse HCM phenotype and disease spectrum, creating a paradigm shift in the noninvasive clinical evaluation of HCM patients.3 CMR provides relevant diagnostic and prognostic information largely not obtainable with traditional echocardiographic imaging. CMR impacts a variety of clinical issues in this complex disease, from diagnosis and family screening to preprocedural planning for septal reduction, and notably prediction of sudden death and advanced heart failure progression. Indeed, based on the evidence summarized here, CMR should now be regarded as an obligatory part of the initial (and probably serial) contemporary assessment of all patients with a confirmed (or suspected) HCM diagnosis. We propose an expanded
role for CMR in clinical cardiovascular practice well beyond the specific indications in the 2011 American College of Cardiology Foundation/American Heart Association consensus practice guidelines for HCM.  

Case Presentation: Outcome
The application of CMR to our patient created a cascade of HCM-related observations that affect him and his family. Borderline LV wall thickness by echocardiography and a distinctly abnormal ECG triggered a CMR, which demonstrated a focal area of hypertrophy (19 mm) in the posterior (inferior) portion of ventricular septum (Figure 2), a location in the chamber often imaged unreliably with echocardiography.

This patient had been considered low risk for sudden death given the absence of conventional risk markers. However, contrast-CMR images demonstrated extensive LGE (fibrosis) occupying 20% of LV mass (Figure 2), which conveyed a substantial >2-fold increase in sudden death risk. After a shared decision-making discussion, taking into account the wishes of the fully informed patient, a primary prevention ICD was implanted. Eighteen months later, the ICD spontaneously delivered a life-saving defibrillation shock, terminating ventricular fibrillation (250 beats/min) and restoring sinus rhythm during sleep.

The HCM diagnosis in the proband also prompted clinical screening of first-degree relatives. The asymptomatic 19-year-old son, a competitive ice hockey player, had an abnormal ECG with precordial T-wave inversions, although the echocardiogram was normal. CMR identified a focal area of hypertrophy in the distal LV of 16 mm, consistent with apical HCM, but without LGE. This patient was considered at low risk for sudden death because of the absence of all conventional risk markers, although he was restricted from organized competitive sports, including collegiate ice hockey, based on consensus recommendations.  

Normal CMR studies in 2 adolescent daughters (14 and 16 years of age) ruled out clinical disease, but genetic testing identified the same disease-causing sarcomere mutation (MYBPC3 Arg502Trp) in the 14-year-old daughter that is present in the father, converting her clinical status to genotype positive/phenotype negative. As a result, regular annual surveillance with imaging was recommended during adolescence to exclude potential development of clinical disease, but did not require restriction from competitive sports, also in accord with consensus recommendations. The 16-year-old daughter is free of the family mutation, essentially eliminating her from any future risk of developing HCM and the burden of longitudinal screening with imaging.

This case highlights the essential role for CMR in the multigenerational assessment of HCM. By introducing CMR into the evaluation of the index patient (proband), a number of important clinical milestones were achieved, including a definitive HCM diagnosis, risk stratification leading to a prophylactic ICD with life-saving therapy, and the diagnosis and management of other family members based on genetic testing, as well. Taken together, the evaluation of a family with HCM underscores the power of CMR imaging for providing novel and clinically relevant information beyond that of echocardiography.

Disclosures
Dr B. Maron is a consultant with GeneDx. Dr M. Maron reports no conflicts.

References


