How to Image Hypertrophic Cardiomyopathy

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A 48-year-old man, with only a history of mild systemic hypertension, was initially evaluated after presenting with symptoms of exertional dyspnea occurring predominantly with inclines. At that time, an abnormal 12-lead ECG was obtained demonstrating left ventricular hypertrophy by conventional voltage criteria, prompting additional testing with a 2-dimensional echocardiogram that showed normal systolic function (ejection fraction=65%), with 14-mm ventricular septal thickness and 12 mm in the posterolateral wall, and mild systolic anterior motion (SAM) of the mitral valve (bend of anterior leaflet into outflow tract without septal contact). A stress nuclear stress test showed no myocardial ischemia at rest or at peak exercise with a normal blood pressure response and no arrhythmias or ST-T changes during exercise or in recovery. The patient was prescribed a β-blocker for treatment of systemic hypertension.

During the next 2 years, the patient developed more limiting exertional symptoms with routine activities. β-Blocker dosage was increased, and a repeat echocardiogram demonstrated similar findings to the initial study, borderline left ventricular (LV) wall thickness despite well-controlled blood pressure. The abnormal ECG, and mild SAM at rest, raised consideration for a diagnosis of hypertrophic cardiomyopathy (HCM) and management for limiting heart failure symptoms.

Diagnosis and Phenotypic Characterization

HCM is often suspected in a patient based on the presence of cardiovascular symptoms, detection of abnormal ECG, systolic ejection murmur on routine examination, or as part of pedigree screening.[1,2] Abnormalities on ECG are present in >90% of patients with HCM, although no specific ECG pattern is pathognomonic.[1] Clinical diagnosis of HCM can reliably be made in the majority of patients with 2-dimensional transthoracic echocardiography by imaging increased LV wall thickness (≥15 mm) with a nondilated cavity in the absence of any disease known to cause LV hypertrophy of that magnitude (ie, systemic hypertension or aortic stenosis).[1–5] In certain situations, mild increases in LV wall thickness can be considered diagnostic (13–14 mm), including in relatives of patients with HCM.[1,2] Increased RV wall thickness is present in over one third of HCM patients (ie, ≥8 mm), although its prognostic significance is uncertain.[6] The superior spatial resolution of cardiovascular magnetic resonance (CMR) can provide reliable determination of RV hypertrophy, although particular care should be taken to exclude epicardial fat, pericardium, and trabeculations.

Maximal LV wall thickness measurements should be assessed perpendicular to the ventricular septum in either the parasternal long-axis or short-axis imaging planes, and the measurement derived from the LV segment with greatest thickness within the chamber.[3,4] Overestimation of LV wall thickness can occur if the crista supraventricularis, a prominent right ventricular (RV) muscle structure that originates in the RV apex and transects the cavity to insert on the ventricular septum, is not recognized and included in the transdimensional measurement of basal ventricular septal thickness.[6] The crista is often identified with echocardiography (and particularly with CMR) on the basal short-axis images and observed to separate from the septum in systole allowing the endocardial borders of the ventricular septum to be clearly delineated, thereby providing accurate assessment of septal wall thickness.[6]

Occasionally, a diagnosis of HCM is suspected based on a patient's clinical profile but imaging with echocardiography is technically suboptimal or LV wall thickness measurements are borderline. CMR should be performed in these situations to clarify diagnosis by providing the opportunity for precise and reliable wall thickness measurements by virtue of sharp contrast between bright blood and dark myocardium with high spatial resolution imaging (Figure 1).[5,7,8] Particularly in those HCM patients with increased wall thickness confined to the anterolateral wall, apex, and posterior septum.[5,7,8] In patients in whom distal LV chamber is not well visualized or there is concern for increased apical wall thickness, and CMR is not available, contrast echocardiography should be performed (Figure 2).[3,4]

HCM Versus Hypertensive Cardiomyopathy

Differentiation of phenotypes corresponding to HCM or alternatively to pressure overload conditions (eg, systemic hypertension) can be challenging solely from an imaging standpoint with echocardiography and CMR, given the considerable morphological overlap between the 2 conditions.[9] However, LV wall–thickening patterns that are clearly asymmetrical, in which all or most LV segments do not demonstrate the same or similar thicknesses, is most consistent with HCM, particularly when noncontiguous areas of focal hypertrophy are evident with CMR.[8]

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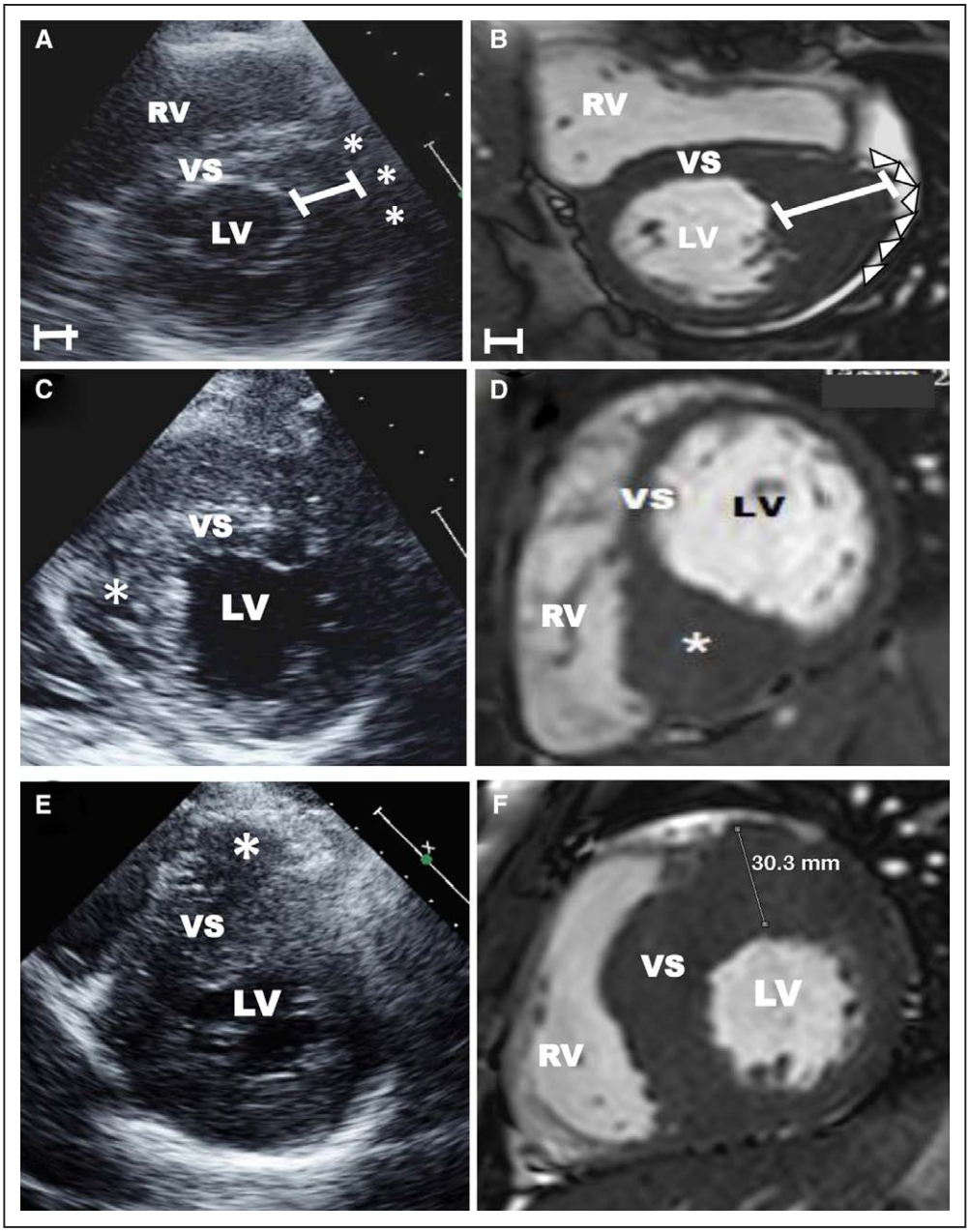

Figure 1. Advantage of cardiovascular magnetic resonance (CMR) compared with 2-dimensional echocardiography (2DE). **A**, 2DE. Anterolateral left ventricular (LV) free wall is 18 mm; epicardial border and adjacent extracardiac structures are not well defined (asterisks). **B**, CMR in the same patient shows well-delineated border of anterolateral LV wall (arrowheads), which is massively thickened (35 mm), creating a SD risk factor. **C**, 2DE. Posterior ventricular septal (VS) thickness is 21 mm (asterisk). **D**, CMR in same patient; massive hypertrophy (41 mm; asterisk) creating a SD risk marker. **E**, 2DE. Maximal LV wall thickness measurement is ambiguous as anterior LV wall border not well defined. **F**, CMR in same patient clearly delineates LV border providing reliable measurement of massive hypertrophy (30 mm) of anterior wall. Reprinted from Maron[8] with permission of the publisher. Copyright © 2012. SD indicates sudden death; RV, right ventricle; and VS, ventricular septum.

On the contrary, pressure overload most often produces more symmetrical (or concentric) patterns of LV wall thickness in which all segments of the wall seem to have identical or similar thicknesses. A limitation for reliably making this diagnostic distinction of asymmetrical versus symmetrical hypertrophy is the lack of consensus criteria for this morphological differentiation.[9] Nevertheless, useful features that can favor the HCM phenotype versus systemic hypertension are LV wall thickness >18 mm and mitral valve systolic anterior motion with septal contact.[8,9] Also, treatment with antihypertensive drugs producing regression of LV hypertrophy would favor a diagnosis of hypertensive heart disease.

- CMR can be used to clarify HCM diagnosis or the extent of wall thickness in those patients in whom LV hypertrophy measurements remain uncertain or borderline with 2-dimensional echocardiography, whereas contrast echocardiography considered in patients in whom there is concern for apical hypertrophy and CMR is not available.
- Overestimation of LV wall thickness can occur if RV muscle structures are included in ventricular septal

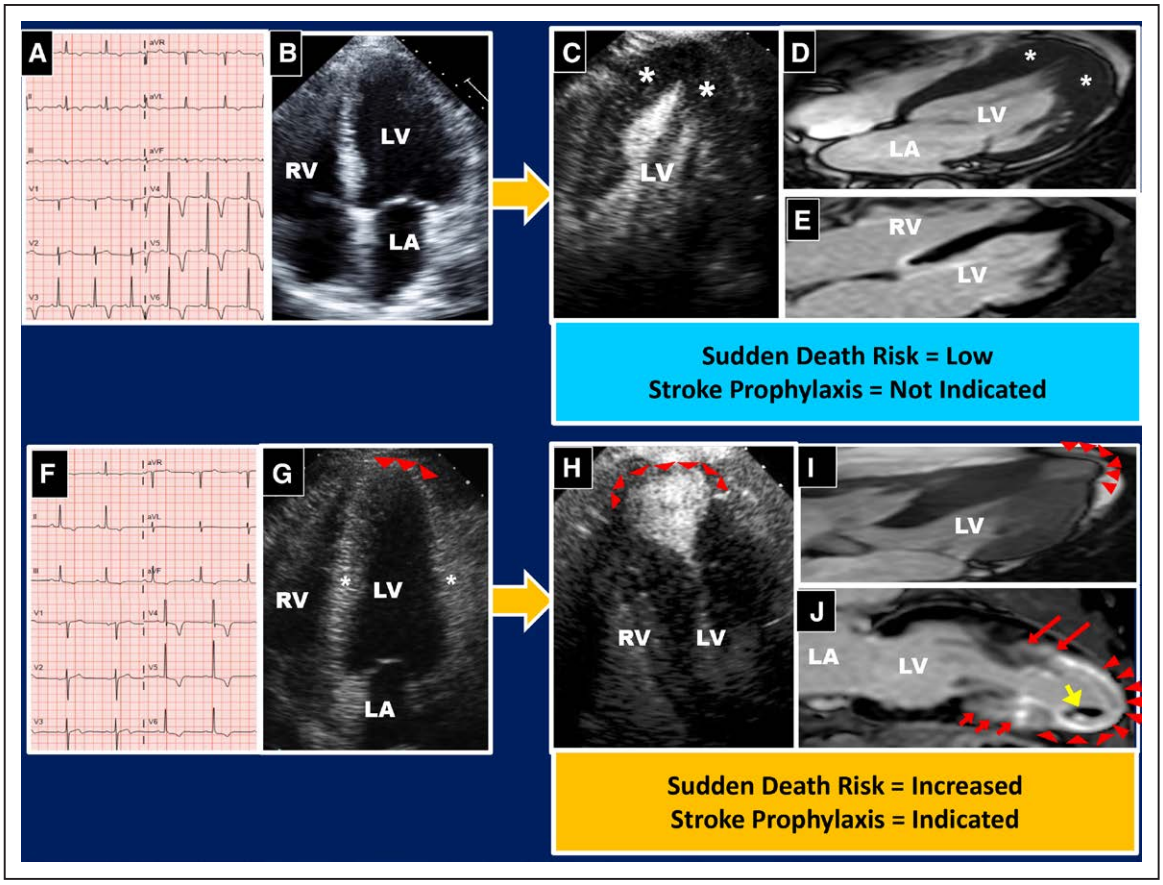

Figure 2. Morphological abnormalities of the left ventricular (LV) apex more reliably identified by contrast echocardiography and cardiovascular magnetic resonance (CMR) in patients with hypertrophic cardiomyopathy (HCM), implications for management. **A–E**, Lower risk apical hypertrophy. **A**, Abnormal 12-lead ECG pattern. **B**, Four-chamber echocardiogram shows normal LV wall thickness. **C**, In the same patient, opacification of LV chamber with echocardiographic contrast demonstrates regional area of increased wall thickness at apex of 16 mm (asterisks). **D**, High-resolution CMR imaging confirms apical hypertrophy (asterisks). **E**, Contrast CMR images show no late gadolinium enhancement (LGE), consistent with the absence of myocardial scarring, associated with lower risk for sudden death events. **F–J**, Higher risk LV apical aneurysm. **F**, Abnormal 12-lead ECG pattern; **G**, Four-chamber echocardiogram shows increased LV wall thickness at mid-LV level but no apical aneurysm (arrow heads). **H**, In same patient, opacification of LV chamber with echocardiographic contrast demonstrates medium-sized thin-wall apical aneurysm (arrowheads) with associated hour-glass–shaped LV chamber with regional area of increased wall thickness at mid-LV level of 16 mm (asterisks). **I**, High-resolution CMR imaging confirms apical aneurysm (arrowheads). **J**, Contrast CMR images show transmural LGE of aneurysm rim (arrowheads) with contiguous extension into the inferior (short arrow) and anterior LV walls (long arrow), a potential nidus of monomorphic VT. In addition, marked signal intensity contrast between the bright aneurysm rim and hypointense mass (yellow arrow) confirms presence of a thrombus in the apical aneurysm that was not seen on echocardiography, raising consideration for stroke prophylaxis with anticoagulation. LA indicates left atrium; RV, right ventricle.

measurement, while high spatial resolution imaging with CMR can reliably aid in differentiating these structures and provide accurate LV wall thickness measurements.

Sudden Death

After confirmatory diagnosis, assessment of sudden death risk is a critical component of the routine evaluation of all HCM patients (Figure 3). Currently, 2011 ACC/AHA expert consensus guidelines recommend identification of high-risk patients based on the presence of noninvasive conventional risk factors.[1] With particular relevance for the cardiovascular imager is the requirement to provide reliable wall thickness measurements because massive LV hypertrophy (≥30 mm) is a risk factor that can itself be sufficient, even in the absence of other conventional risk markers, to consider a patient to be at unacceptably high risk and offer primary prevention implantable cardioverter defibrillator therapy (Figure 3).[1–4,10] In addition, the linear relationship between wall thickness and sudden death risk in HCM[10] also suggests that less extensive wall thickness measurements, which approach 30 mm, can inform sudden death risk.[1] In this regard, consideration should be given to incorporating CMR into the initial evaluation of HCM patients to ensure accurate wall thickness measurements, particularly because in some patients extent and magnitude of hypertrophy can be underestimated by echocardiography, particularly when present in the anterolateral wall or apex (Figures 1 and 2).[1,2,5,7,8] Calculated LV mass has not emerged as an independent predictor of sudden death events.[11]

More recently, the European Society of Cardiology has promoted a novel score for risk stratification,[2] which takes into account many clinical variables some of which are not considered in the ACC/AHA guidelines, including assessment of outflow tract obstruction. However, the US/Canadian guidelines have emphasized the difficulty in using obstruction as an independent risk marker in HCM, given the highly

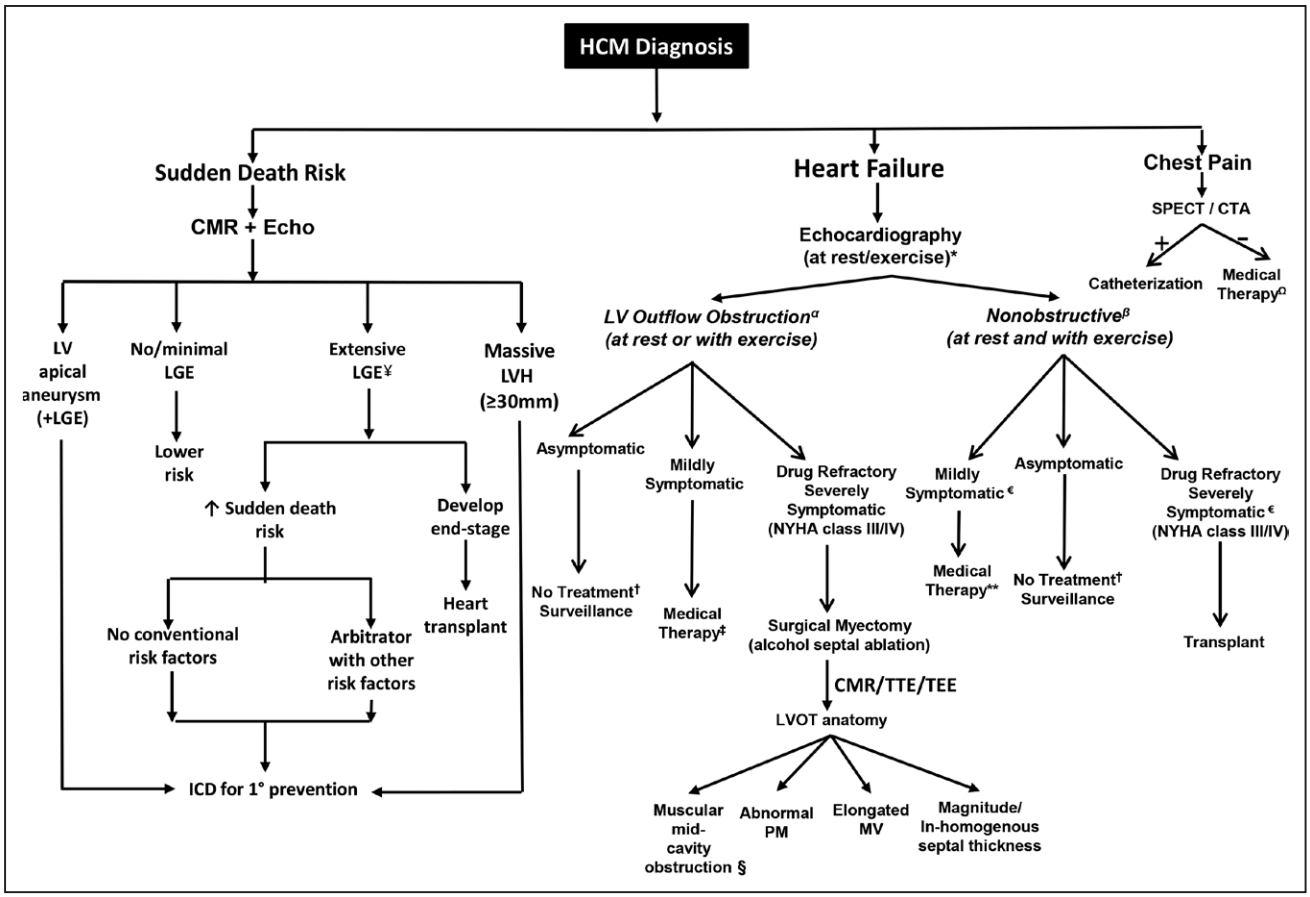

Figure 3. Flow diagram outlining the role of imaging in hypertrophic cardiomyopathy (HCM) management strategies. *Patients without LV outflow tract gradient (<30 mm Hg) at rest should undergo stress (exercise) echocardiography. †No data on benefit of pharmacological therapy, although β-blockers are often administered prophylactically in clinical practice. **β-Blockers, calcium channel antagonists, and possibly diuretics administered judiciously. ‡Usually, β-blockers or calcium channel antagonists (verapamil), or disopyramide. ΩCalcium channel antagonists or alternatively β-blockers. αGenerally regarded as ≥30 mm Hg outflow gradient, but ≥50 mm Hg when septal reduction intervention is considered (ie, septal myectomy and alcohol ablation). βNo or trivial (<30 mm Hg) outflow gradient at rest and with exercise. ¥≥15% of total LV mass. €Assessment of LV filling pressures should take into account transmitral Doppler flow velocities, pulmonary venous flow velocity, mitral deceleration time, estimated pulmonary artery pressures, left atrial size, and myocardial strain imaging. §Includes anomalous papillary muscle insertion directly into anterior mitral leaflet and aberrant LV muscle bundles. ASA indicates alcohol septal ablation; LGE, late gadolinium enhancement; LVOT, left ventricular outflow tract; and MV, mitral valve. Reprinted from Maron and Maron[5] with permission of the publisher. Copyright © 2015.

dynamic nature of gradients and the fact they can be mitigated or eliminated with drug therapy or invasive treatment.[1] Left atrial size assessed with transdimensional measurement is also included in the ESC risk score, although the independent relationship between left atrial size and sudden death risk in HCM is unresolved and therefore itself is not a measurement used to dictate management decisions for sudden death prevention.[1]

A relatively uncommon but important phenotypic subgroup, which falls outside the traditional risk stratification algorithm, are HCM patients with LV apical aneurysm formation (sometimes associated with midcavity hypertrophy and outflow obstruction).[12] Aneurysms are considered a high-risk phenotype based on increased likelihood of adverse disease-related consequences, including sudden death and thromboembolism (Figure 2). Because imaging the distal portion of the LV chamber may be limited with echocardiography in some patients, a high index of suspicion is required for detection of the aneurysm and potential apical thrombus, requiring CMR, or if not available, contrast echocardiography(Figure 2).[12]

More recently, there has been increasing interest in identifying patients at risk for sudden death by imaging the underlying abnormal myocardial substrate of fibrosis with contrast-enhanced CMR.[13–17] After intravenous injection, gadolinium will accumulate in areas of expanded extracellular space within the myocardium (Figure 4), likely representing myocardial fibrosis,[18] imaged as late gadolinium enhancement (LGE), and expressed as percent of LV mass. Cross-sectional studies have demonstrated a strong association between LGE and increased risk for ambulatory nonsustained ventricular tachyarrhythmia,[13] suggesting that LGE may represent a structural nidus for ventricular tachyarrhythmias in HCM (Figure 4). Many longitudinal studies assessing LGE in HCM cohorts have been analyzed in a pooled manner, demonstrating a strong relationship between the amount of LGE and risk of a sudden death event (Figure 4).[14] On the basis of these observations, extensive LGE occupying ≥15% of LV mass may identify HCM patients at increased risk for sudden death (even without conventional risk factors) and who may benefit from primary prevention therapy

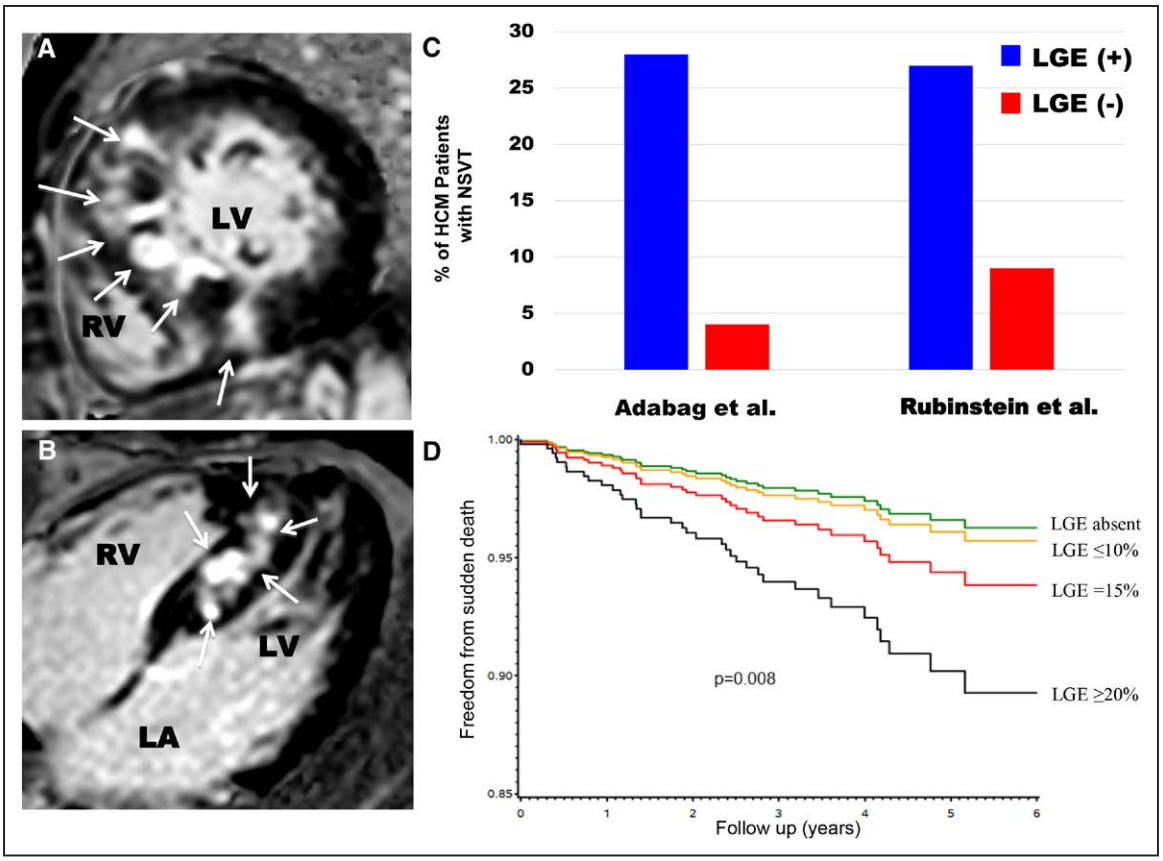

Figure 4. Relationship between late gadolinium enhancement and sudden death risk in hypertrophic cardiomyopathy (HCM). **A** and **B**, Contrast-enhanced cardiovascular magnetic resonance (CMR) images in 2 different HCM patients, each with extensive late gadolinium enhancement (LGE) throughout the ventricular septum (arrows). **C**, NSVT on 24-h Holter ECG is 7-fold more common in HCM patients with LGE as compared with those without LGE. **D**, Relation between extent of LGE and sudden death events in 1293 patients with HCM. Reprinted from Chan et al[15] with permission of the publisher. Copyright © 2014. LA indicates left atrium; LV, left ventricle; and RV, right ventricle.

(Figure 3); absent or focal LGE associated with low risk.[5,14,15] In addition, extensive LGE can act as an arbitrator to resolve decision making on ICDs in patients who reside in a gray area of ambiguity in which future risk is difficult to define precisely, with extensive LGE swaying toward a decision of ICD and no or minimal LGE potentially away from device therapy (Figure 3).[5,15]

Of note, the pattern of LGE in HCM is diverse, and therefore, it is not possible to predict outcome based on LGE distribution. LGE confined to areas of confluence between RV and septum is limited in size and is associated with lower risk for sudden death, similar to patients with no LGE. This observation is likely because of the fact that LGE localized to this area does not represent myocardial scarring but rather an expanded extracellular matrix because of confluence of intersecting LV and RV myofibrils.[17].

T1 mapping is a novel, emerging CMR technique, which provides a noninvasive assessment of expanded extracellular space within the myocardium.[19] Extracellular volume fraction has emerged as a promising measure of the extracellular matrix and is calculated by measuring longitudinal relaxation (T1) of the myocardium before (native T1) and after injection of gadolinium. Currently, many small-scale studies have found significant correlations between extracellular volume fraction values and collagen volume fraction quantified from histopathology obtained from LV tissue obtained from patients with HCM.[19]

The early clinical experience with T1 mapping in HCM has largely been confined to differentiating HCM from other cardiovascular disease. Extracellular volume fraction values have been found to be significantly higher in HCM patients compared with patients with LV hypertrophy secondary to cardiac amyloidosis or Fabry disease.[20,21] However, in the absence of clinical outcome studies, there is currently no role for T1 mapping in risk assessment. Further clarification of many of these CMR-based issues in HCM will emerge from the international multicenter HCMR study (Hypertrophic Cardiomyopathy Registry).[22]

- Massive LV wall hypertrophy is an important marker of increased risk for sudden death in HCM, and consideration should be given to CMR to provide reliable measurements of wall thickness.
- HCM patients with LV apical aneurysm represent a high-risk subgroup, and CMR, or alternatively contrast echocardiography, should be performed for reliable identification.
- Extent of LGE by contrast-enhanced CMR may help identify high-risk patients who have none of the traditional risk markers and help resolve complex ICD

decision making in patients whose high-risk status remains uncertain after assessment with the traditional risk markers.

Special Considerations: CMR in HCM

The last decade has seen enormous penetration of CMR into routine clinical cardiovascular practice, although some challenges still persist with regard to image analysis and interpretation when applying CMR to a complex, heterogeneous genetic heart disease such as HCM. There is currently no expert consensus on standardization in 2 key areas: (1) protocol for CMR image acquisition in HCM and (2) analysis and interpretation of clinically relevant morphology, the most visible of which is LGE. Specific examples include

- Determination of wall thickness in all regions of the LV chamber can be impacted by interobserver reader interpretation, which may involve differentiating morphological structures such as crista supraventricularis and LV papillary muscles/trabeculations from the LV wall.
- Considerations related to quantification of LGE can be more complex. The study by Chan et al[15] established the management principle for LGE in HCM and sudden death risk stratification—that is, that it is not the presence of LGE that is important, but rather the extent and distribution of LGE in the LV as expressed by the percent of LV mass. Quantification of LGE was formulated using a standardized core laboratory study design to establish reproducible measurements.
- Nevertheless, the persistent challenge lies with translating the core laboratory experience to the many CMR laboratories outside of the academic realm because of the current lack of standardization involving (1) differences in magnetic resonance imaging scanner hardware and software; (2) diverse LGE protocols with lack of agreement on the most appropriate technique to quantify LGE; (3) use of different types and dosage protocols for gadolinium contrast; and (4) inconsistent optimization of inversion times and properly nulled LV myocardium.
- On the basis of the data given by Chan et al,[15] we use a grayscale threshold 6 SD above the mean signal intensity of nulled myocardium to quantify LGE (Data Supplement), although other methods including full-width at half maximum (ie, pixels that are ≥50% the signal intensity of a hyperenhanced area) have also been shown to have high reproducibility.[23] However, qualitative estimation of %LGE by visual interpretation can be useful in many cases when routine quantification seems unnecessary.

Identification of HCM Patients at Risk for Heart Failure Symptoms

LV Outflow Tract Obstruction

Subaortic obstruction in HCM is the most common pathophysiologic mechanism leading to limiting heart failure symptoms in this disease (Figure 5).[1,2,24–26] Therefore, once HCM diagnosis is confirmed, determining whether a patient has obstruction is fundamental to clarifying natural history and determining appropriate management strategies because patients with obstruction (at rest or with provocation) are candidates for therapies not available to patients without obstruction (Figure 3). β-Blockers or calcium channel blockers are first-line therapies in symptomatic patients with obstruction, and occasionally, disopyramide can be considered.[1,2]

With echocardiographic imaging, the typical mechanism of subaortic obstruction in HCM can be reliably defined, with SAM of the mitral valve and septal contact (Figure 6).[3,4,24] During SAM–septal contact, incomplete coaptation between the anterior and posterior leaflet of the mitral valve can lead to posteriorly directed mitral regurgitation, which is usually mild to moderate in severity (Figure 6).[27]

Continuous-wave Doppler techniques are conventionally used to reliably estimate maximal instantaneous gradient using the peak LV outflow tract velocity (Figure 5).[3,4] Because contamination of the outflow tract Doppler profile by the mitral regurgitation jet will result in overestimation of the outflow tract gradient,[24,28] particular care should be taken to differentiating these 2 distinct Doppler profiles. Doppler systolic flow patterns representative of LV outflow gradients characteristically demonstrate gradual increase in velocity in early systole with acceleration and peaking in midsystole (dagger-shaped).[28] In contrast, the mitral regurgitation signal begins abruptly at the onset of systole and rapidly establishes markedly increased velocity (usually >6 m/s), which persists throughout systole (bell-shaped).[28] Occasionally, HCM patients with typical subaortic obstruction will also have coexistant aortic stenosis, making assessment of aortic valve disease challenging because of altered outflow tract flow dynamics. Planimetry of aortic valve area by TEE can be considered in such situations to clarify severity of aortic stenosis.[3]

In patients with resting outflow tract gradients ≥50 mm Hg, provocative maneuvers appears unnecessary for the purpose of making management decisions and probably contraindicated because the association between substantial gradients and limiting symptoms is already been established.[1] For those patients without obstruction under resting conditions, exercise (stress) echocardiography is generally the preferred method for provoking physiological gradients with a symptom-limited Bruce treadmill protocol (Figures 3 and 5).[1,2,24] Outflow gradients are assessed in the recovery period while supine, although there seems to be little difference in the magnitude of outflow gradients obtained upright at peak exercise compared with immediately after exercise in the supine position.[25] Consideration should be given to holding cardiovascular drugs before assessment of outflow tract gradients to provide a pure assessment of an individual HCM patient's propensity to generate obstruction. However, in many patients, withdrawal of medication may not be a practical strategy in the clinical arena for a variety of reasons.

Pharmacological agents (eg, amyl nitrite, dobutamine, or isoproterenol), administered during the echocardiographic study, or in the catheterization laboratory, to provoke subaortic gradients, are nonphysiological and may not reliably represent gradients incurred by patients during daily physical activities or may well under- or overestimate magnitude of the outflow gradient compared with physiological exercise.[29]

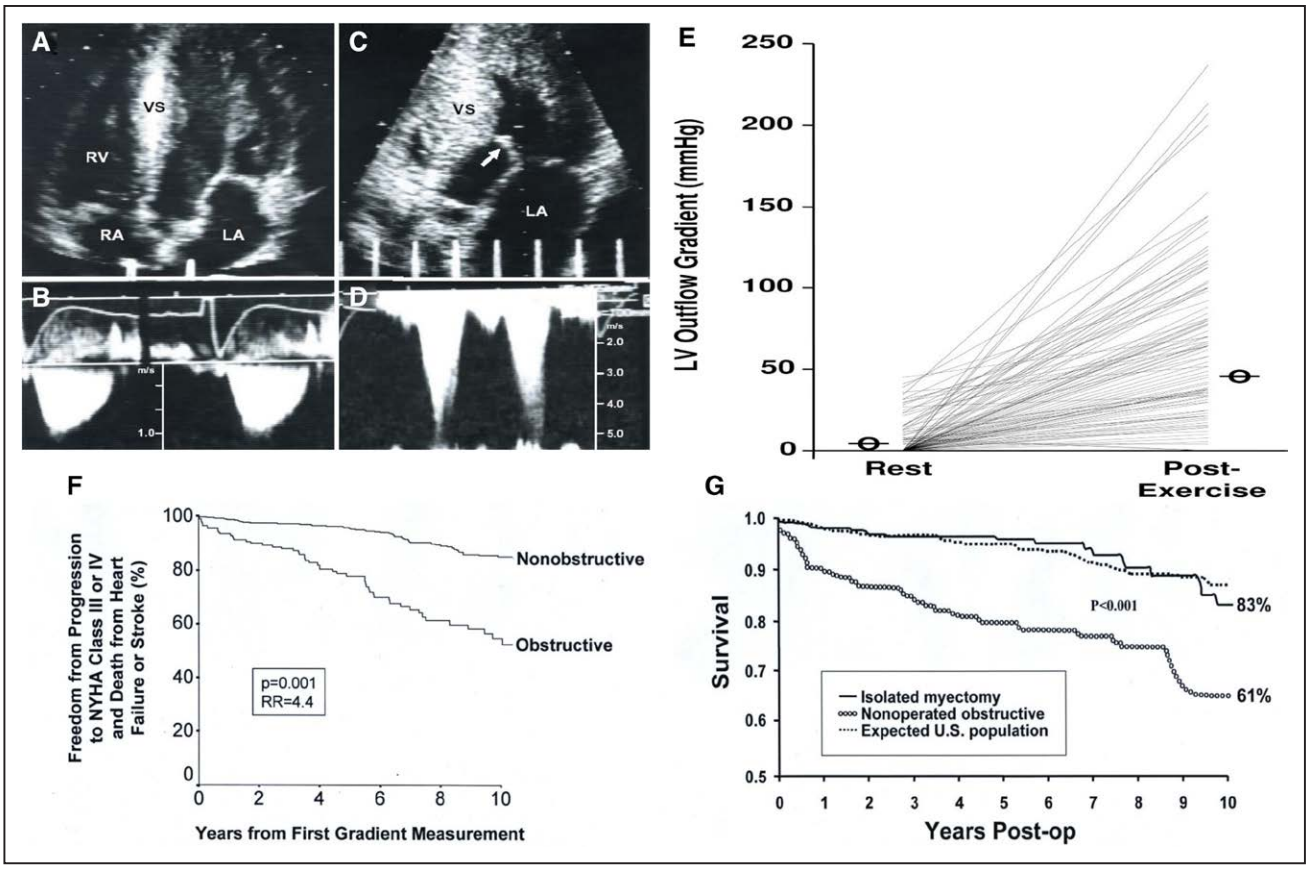

Figure 5. Clinical significance and implications of left ventricle (LV) outflow tract obstruction. **A** and **B**, Apical 2-dimensional echocardiography (2DE) and CW Doppler showing absence of systolic anterior motion (SAM) and obstruction at rest. **C** and **D**, Intense exercise provokes SAM–septal contact (arrow) and outflow velocity of 5 m/s (100 mm Hg gradient). **E**, Changes in LV outflow gradient from rest to postexercise showing physiologically provoked gradients in large consecutive cohort (by mechanism in (**C**) and (**D**)). **F**, Patients with outflow gradients ≥30 mm Hg at rest are at greater risk for HCM-related progressive heart failure or heart failure or stroke death. **G**, Abolition of LV outflow gradient by surgical septal myectomy is associated with long-term survival (with respect to all-cause mortality) similar to that expected in age- and sex-matched general US population and exceeding that in a comparison group of symptomatic nonoperated patients with obstruction. Reprinted from Maron et al[26] with permission of the publisher. Copyright © 2014. CW indicates continuous wave; NYHA, New York Heart Association; and RR, relative risk.

With respect to Valsalva, the one nonphysiological maneuver performed routinely with echocardiography, normal velocities observed with this method do exclude outflow obstruction because ≈50% of such patients will generate gradients with physiological exercise.[24] Alternatively, increased Valsalva velocities consistently predict outflow gradients generated with exercise, although the magnitude of gradients are significantly underestimated by Valsalva compared with exercise (by 25–65 mm Hg).[24] Therefore, in patients who can exercise, Valsalva does not seem to provide additional management information. However, in selected candidates for septal reduction who cannot perform exercise echocardiography because of comorbidities, a positive Valsalva maneuver can be considered sufficient evidence of the capability to generate outflow tract obstruction.[24] With Valsalva maneuver, LV outflow gradients should be acquired ≈5 to 10 seconds after forced expiration, when venous return is significantly reduced and stroke volume is lowest.

The presence of an exercise-induced outflow gradient creates treatment options in symptomatic patients aimed at mitigating or eliminating obstruction, including invasive septal reduction therapies, underscoring the importance of performing this test as part of the routine evaluation of HCM patients without rest obstruction (Figure 3).[1–3,24,29] This principle can also be extended to asymptomatic HCM patients because an outflow gradient identifies patients who are at greater likelihood of developing limiting symptoms and should be followed longitudinally to anticipate changes in clinical state that could justify therapeutic intervention.[24,29] In addition, β-blockers have been demonstrated to mitigate provocable gradients and could be considered for this purpose in asymptomatic obstructive HCM patients with the potential to decrease (or possibly delay onset) future functional disability. Serial assessment of outflow tract gradients should be performed as part of annual evaluations or if there is a change in clinical status that suggests a potential and clinically relevant change in the magnitude of the outflow gradient.[1,2]

Patient Selection and Planning for Septal Reduction

HCM patients with outflow tract gradients of ≥50 mm Hg at rest, or with provocation, and drug-refractory advanced heart failure symptoms become candidates for relief of obstruction with surgical myectomy or alcohol

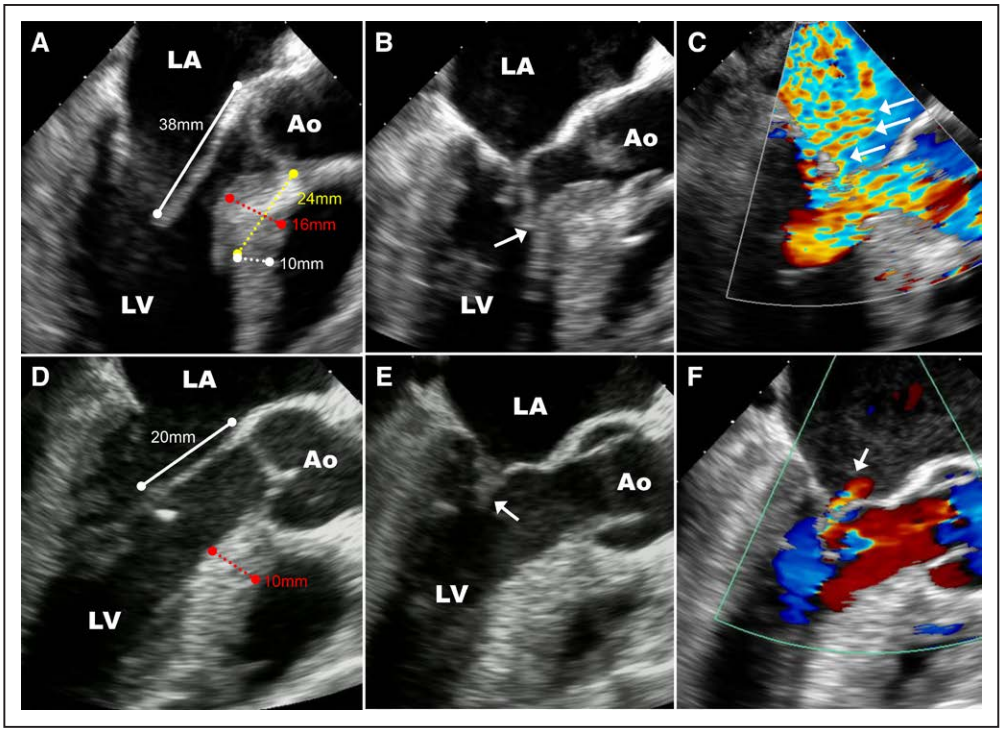

Figure 6. Transesophageal echocardiography (TEE) to guide surgical myectomy operative strategy. **A**–**C**, Preoperative TEE. **A**, End-diastolic image demonstrating measurements of ventricular septum to plan depth and extent of muscular resection necessary to achieve optimal relief of outflow obstruction including maximal thickness at point of systolic anterior motion (SAM)–septal contact (red dotted line), length from aortic valve plane to point of septal thinning (yellow dotted line), and wall thickness measurement at point of septal thinning (white dotted line). In addition, mitral valve leaflet is substantially elongated (white line), resulting in SAM–septal contact (arrow) more distal in ventricular septum than typical (**B**). **C**, Color Doppler in same view as in (**B**) demonstrating moderate to severe posterior directed mitral regurgitation (arrows) because of SAM and gap between anterior and posterior mitral valve leaflets. **D–F**, Postoperative TEE. **D**, End-diastolic image demonstrating extended septal myectomy trough with basal septal thickness reduced (red dotted-lines) and shortening (ie, plication) of elongated anterior mitral leaflet (white line). **E**, In midsystole, systolic anterior motion of the mitral valve is absent (arrow). **F**, In same view as (**E**), color Doppler imaging demonstrates trace mitral regurgitation (arrow).

septal ablation.[1,2] Multimodality imaging has emerged as an important strategy to identify morphological anomalies of the LV chamber, which contribute to subaortic obstruction and which may impact proper selection of patients for surgical myectomy (or alcohol septal ablation), as well as inform preprocedural planning for each of these invasive options (Figure 3).[3,27,30]

Surgical Myectomy

Contemporary surgical strategy has evolved beyond limited resection of the basal septum (Morrow procedure) to an intervention that can directly address all important structural abnormalities contributing to the mechanism of outflow obstruction through extended myectomy and extensive reconstruction of the entire LV outflow tract area.[27,31] Presurgical planning should routinely include echocardiography and CMR imaging, with particular focus on 3 aspects of the LV chamber: (1) pattern and extent of ventricular septal hypertrophy; (2) mitral valve structure; and (3) submitral valve morphology including papillary muscles, accessory muscle bundles, and chordal connections (Figure 3).

Clarifying preoperatively the distribution and extent of ventricular septal thickening can provide the surgeon with an accurate road map to plan the depth and extent of muscular resection necessary to achieve optimal relief of outflow obstruction (Figure 6). In addition, with the limited field of view created by the transaortic approach, it is also advantageous to perform certain measurements with intraoperative TEE to further guide the septal resection, including maximal thickness at the point of SAM–septal contact and length from aortic valve plane to the point at which septal thickness becomes substantially less than at the point of mitral–septal contact (Figure 6).

Mitral valve leaflets can be greatly increased in length in many HCM patients, particularly evident when the anterior leaflet extends in systole beyond the coaptation point and moves unrestricted into the outflow tract area to contact the septum distal to the usual site of subaortic obstruction.[27,30–32] Echocardiography and CMR can reliably measure mitral valve leaflet length, typically in the 3-chamber orientation with leaflets fully extended parallel to the septum and free wall (Figures 6 and 7).[3,27] For HCM patients undergoing myectomy, preoperative identification of elongated mitral valve (or with intraoperative TEE) may alter surgical strategy by promoting adjunctive mitral valve repair to correct excess leaflet length or slack (Figure 6). Some investigators have proposed performing an adjunctive mitral valve repair in HCM patients with an anterior leaflet length >30 mm, irrespective of the maximal thickness of the basal septum, or only when anterior leaflet is elongated and septal thickness is modest

(<18 mm).[27] Mitral regurgitation jet because of obstruction is typically directed posteriorly (Figure 6); conversely, anterior or centrally directed jets suggest intrinsic mitral valve disease (Figure 7) and should prompt preoperative TEE to define morphology and consideration for mitral valve repair, or rarely, mitral valve replacement.[3,27]

A diverse spectrum of structural abnormalities of the papillary muscles are relevant to planning for myectomy.[27,30,33] Insertion of an anomalous, hypertrophied anterolateral papillary muscle directly into the anterior mitral leaflet (in the absence of chordae tendineae) represents important mechanism of muscular midcavitary obstruction (Figure 7). It is critical to identify this anomaly because it dictates a specific surgical approach with deep, extended muscular resection well beyond the contact point of the mitral valve and ventricular septum, as well as reduction of papillary muscle thickness.[27,31,33] Reliable identification of this anomaly can be made with CMR by using a comprehensive tomographic stack of long-axis images acquired throughout the LV outflow tract, whereas with echocardiography, unconventional off-axis imaging is often required for identification.[33]

Similarly, apically displaced accessory anterolateral, double bifid papillary muscles, and accessory LV muscle bundles can displace the plane of the mitral valve more anteriorly toward the ventricular septum contributing to the mechanism of outflow obstruction (Figure 7).[30,34] The location and position of these accessory papillary muscle, including proximity to other LV structures such as the ventricular septum and LV free wall, can be visualized on short- and long-axis imaging planes using either echocardiography and CMR.[27,30,31] Under direct visual assessment, the surgeon can address these abnormalities by thinning the papillary muscle heads and releasing abnormal connections of the muscles to allow a more normal orientation of the mitral valve plane.[31]

Alcohol Septal Ablation

For HCM patients undergoing percutaneous approach to relief of obstruction with alcohol septal ablation, contrast echocardiography during the procedure is essential for producing optimal results and decreasing risk of complications including complete heart block requiring permanent pacemaker implantation (Figure 8).[1–3,35] After access of the septal perforator branch, contrast is injected into the septal artery to identify whether the vascular distribution supplied by that branch is appropriate by involving that portion of the basal septum where mitral–septal contact occurs, while not extending into other myocardial structures involving the RV wall or moderator band (Figure 8).[35]

– For obstructive HCM patients who are candidates for invasive septal reduction therapy, a multimodality imaging approach can identify important morphological anomalies of the LV chamber, which contribute to obstruction

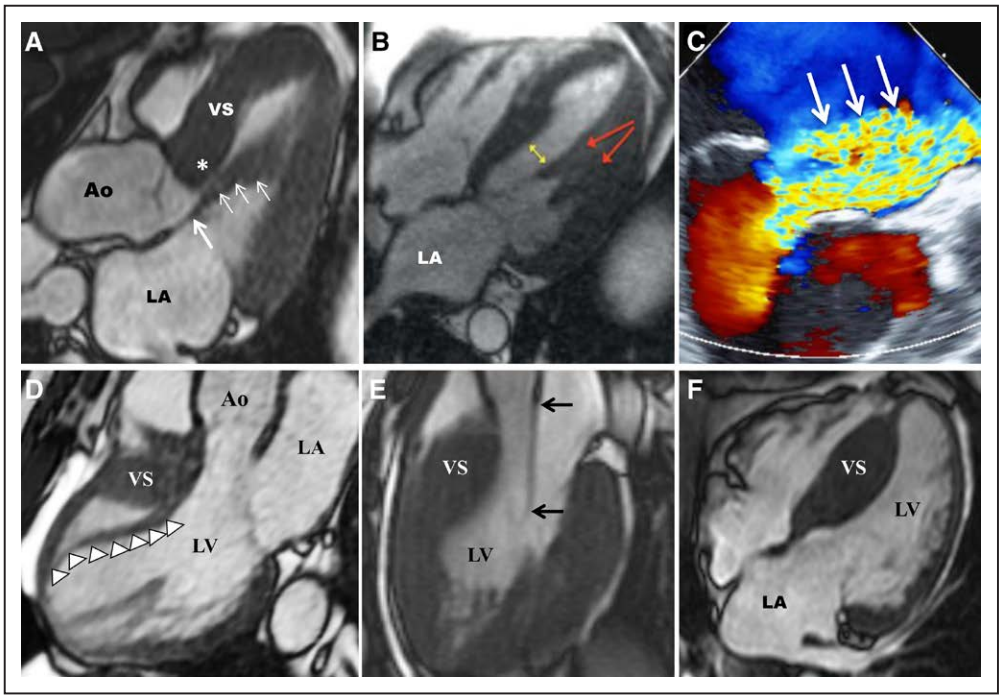

Figure 7. Morphological abnormalities of the left ventricular (LV) chamber contributing to outflow tract obstruction in hypertrophic cardiomyopathy (HCM) patients and which may impact management decision for invasive septal reduction therapies. **A**, Anomalous insertion of papillary muscle (thin arrows) directly into the anterior leaflet of the mitral valve (thick arrow; in the absence of chordae tendineae) producing obstruction to blood flow from the apposition of the papillary muscle and basal ventricular septum (asterisk). Reprinted from Maron[8] with permission of the publisher. Copyright © 2012. **B**, Hypertrophied and apically displaced anterolateral papillary muscle (red arrows) with superior head in close proximity to the septum, positioning mitral valve plane closer to the ventricular septum (yellow arrow). Reproduced from Sherrid et al[27] with permission of the publisher. Copyright © 2016. **C**, TEE shows anteriorly directed mitral regurgitation jets (arrows) because of intrinsic mitral valve disease. **D**, Prominent LV apical–basal muscle bundle (arrowheads). Reprinted from Gruner et al[34] with permission of the publisher. Copyright © 2014. **E**, Extraordinarily long anterior mitral valve leaflet measuring 33 mm (arrows); PML is of normal length (although not well visualized in this frame). Reproduced from Maron et al[32] with permission of the publisher. Copyright © 2011. **F**, Massive hypertrophy of the ventricular septum (31 mm). PML indicates posterior mitral leaflet.

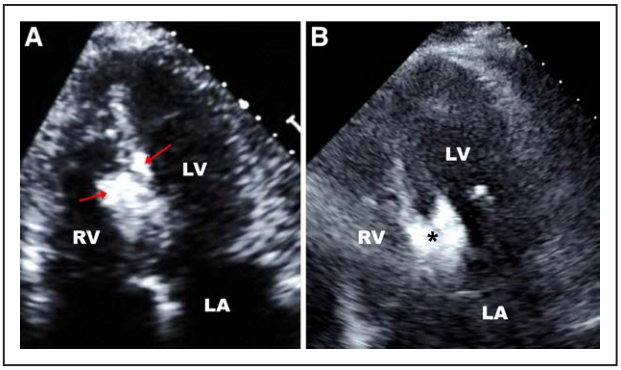

Figure 8. Contrast echocardiography to guide alcohol septal ablation. **A**, Five-chamber view after echocardiographic contrast injection into first septal artery demonstrating enhancement (red arrows) of the ventricular septum at the mid-left ventricular (LV) level (distal to the point of mitral–septal contact). **B**, After repositioning of catheter into a more basal branch of first septal perforator, echocardiographic contrast injection shows enhancement isolated to basal septum (asterisk).

and therefore which procedure may provide optimal relief of obstruction for individual patients.

– For patients undergoing surgical myectomy or alcohol septal ablation, a complimentary imaging strategy may also inform procedural planning to ensure that optimal relief of outflow tract obstruction.

Nonobstructive HCM and Diastolic Dysfunction

Exercise echocardiography can also be used to reliably determine the absence of outflow tract obstruction, categorizing HCM patient as truly nonobstructed.[27] Future risk for developing progressive limiting heart failure symptoms in asymptomatic nonobstructed patients is low,[29] underscoring the importance of this imaging test in clarifying natural history by virtue of excluding outflow tract obstruction. Indeed, the vast majority of nonobstructive HCM patients never require medical therapy, while drug treatment in those that develop symptoms is limited to AV nodal blocking agents (and possibly low-dose diuretics), which may be beneficial by improving myocardial blood flow and LV filling time.[1]

A small subgroup of nonobstructive patients will develop refractory symptoms related to diastolic dysfunction for which advanced heart failure therapies, such as transplant may be the only definitive option.[29] Over the past 2 decades, much attention has been directed at noninvasive assessment of diastolic function as a surrogate measure for intracardiac filling pressures, to inform management decisions. However, currently, no single echocardiographic variable has emerged as a reliable measure of filling pressures, which likely reflects the principle that diastolic function in HCM is complex, resulting from the interaction of numerous mechanisms including LV hypertrophy, abnormal myocardial blood flow at the microvascular level, myocardial fibrosis, and abnormal calcium handling. Indeed, only a modest relationship has been demonstrated between the transmitral Doppler-derived measures of mitral inflow (E/A ratio) or tissue Doppler imaging-derived mitral annular velocities with simultaneous direct measurement of LA pressure by catheterization.[36] In addition, echocardiographic Doppler measures of diastolic function at rest have not been shown to correlate well with exercise duration or predict future risk of progressive heart failure symptoms.[37] One exception are HCM patients with restrictive mitral inflow patterns, a subgroup at increased risk for adverse disease-related events.[38] For this reason, we advocate taking into consideration numerous noninvasive echocardiographic measures to assess filling pressures, including traditional parameters such as transmitral velocities, pulmonary venous flow, mitral deceleration time, estimated pulmonary artery pressures, left atrial size, and tissue Doppler (Figures 3 and 9).[3,4,36]

– The cause of limiting symptoms in nonobstructive HCM patients is complex and multifactorial, with increase in filling pressures because of diastolic dysfunction a prominent mechanism.

– Noninvasive assessment of filling pressures in HCM is predicated on assessing many echocardiographic measures, along with a patient's clinical profile.

Systolic Dysfunction (End-Stage HCM)

In the majority of HCM patients, systolic function is normal (or supernormal) with respect to ejection fraction.[1,2,4] Given the substantial heterogeneity of LV morphology in HCM, fractional shortening, sampling a limited portion of the septum and posterior wall, may over or underestimate systolic function in HCM and, therefore, is not a reliable method to assess contractile performance in this disease. However, the application of newer ultrasound techniques such as speckle tracking has expanded our understanding of regional myocardial mechanics and function in HCM. Global longitudinal strain has emerged recently as the most promising parameter for measuring systolic function and has been used to demonstrate subclinical LV dysfunction in patients with HCM, suggesting impaired myocardial contractile function despite preserved ejection fraction.[3,4] However, the prognostic significance of abnormal global longitudinal strain in HCM is uncertain.

An increasingly important subgroup of ≈10% of patients with nonobstructive HCM in tertiary center cohorts will develop the end-stage phase of HCM, defined by ejection fraction <50% assessed with echocardiography or CMR.[29,39] Patients evolve to this phase by a process of adverse LV remodeling with myocardial scarring resulting in systolic dysfunction and demonstrable extensive, diffuse, and transmural LGE.[15,16,39] The only clinical markers associated with increased risk of developing systolic dysfunction are a family history of end-stage HCM and extensive LGE ≥20% (Figure 3).[15,16,39] Timely recognition of systolic dysfunction in HCM patients can impact management by considering the addition of traditional heart failure drug therapies (eg, angiotensin-converting enzyme inhibitors or aldosterone inhibitors) and primary prevention ICD therapy because end-stage HCM is associated with increased risk for life-threatening ventricular tachycardia/ventricular fibrillation and advanced heart failure symptoms.[1,2]

– Although ejection fraction is normal in the majority of HCM patients, echocardiographic measures of strain suggest that regional LV myocardial performance is abnormal in some patients, although the impact of this on clinical management strategies is uncertain.

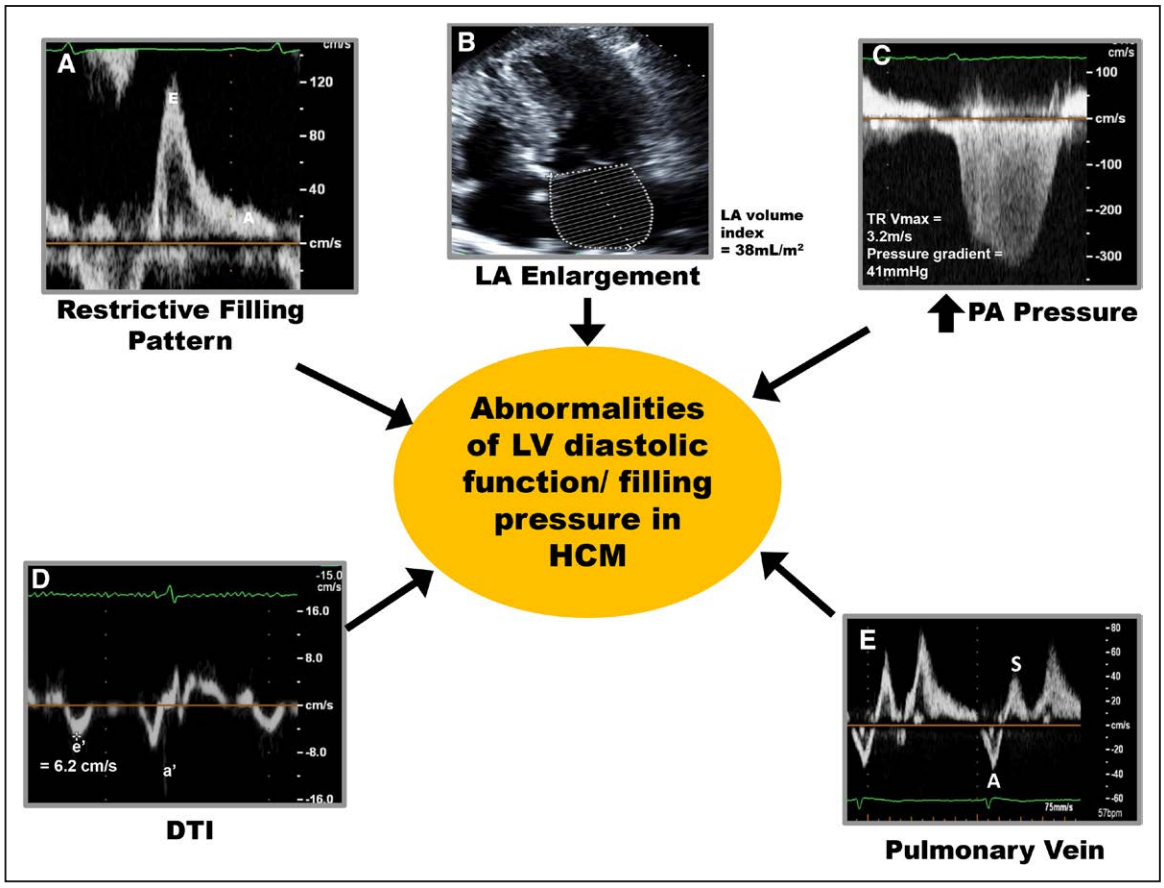

Figure 9. Abnormalities of left ventricular (LV) filling pressures and diastolic dysfunction evaluated by transthoracic echocardiography in hypertrophic cardiomyopathy (HCM). **A**, Mitral inflow pattern shows restrictive inflow pattern with elevated E/A ratio of 3.1. **B**, Four-chamber view demonstrating severe left atrial enlargement. **C**, Tricuspid regurgitant jet velocity used in combination with right atrial pressure to estimate peak pulmonary artery systolic pressure. **D**, Lateral annular tissue Doppler (TD) velocities in which e′ is markedly reduced (6.2 cm/s) consistent with impaired LV relaxation. **E**, Pulmonary venous flow velocity demonstrating blunted systolic atrial flow (S) and increased atrial velocity (A), consistent with elevated left atrial pressures.

- Evolution to end-stage HCM (ejection fraction <50%) is associated with increased risk of sudden death and advanced heart failure.
- Extensive LGE by CMR and family history of the end-stage HCM are the 2 clinical markers associated with increased risk of developing end-stage HCM.

Left Atrium and Risk

Many retrospective and observational echocardiographic studies have demonstrated increased LA size to be associated with adverse disease-related events, with marked LA enlargement >48 mm (transverse linear dimension) or ≥118 mL (chamber volume), associated with increased risk for heart failure death or atrial fibrillation.[40,41] HCM patients with increased LA size should have close longitudinal surveillance to detect changes in symptoms or development of atrial fibrillation that may allow for targeted treatment options, including importantly anticoagulation for stroke prophylaxis.

Currently, consensus is lacking on which metric for measuring LA chamber size is preferable, with some studies using linear transverse diameter from the parasternal long axis (2-dimensional echocardiography) or biplane volumetric assessment (echocardiography or CMR) in which endocardial border of the LA is manually traced in vertical and horizontal long-axis imaging planes.

Chest Pain

Atypical chest pain is a common limiting symptom in patients with HCM due to impaired coronary microvascular function (ie, small-vessel ischemia) resulting from inappropriate vasodilation of structurally abnormal intramural vessels.[42] However, this form of small vessel–mediated chest pain can be challenging to differentiate based on clinical history from obstructive atherosclerotic coronary disease based on clinical history. In HCM patients with high-pretest probability of coronary artery disease, single photon emission computed tomographic myocardial perfusion imaging can be performed initially to evaluate chest pain symptoms and if normal strongly suggest low likelihood of epicardial coronary disease. However, single photon emission computed tomographic imaging has relatively low specificity for detecting epicardial coronary artery disease in a HCM population, because of false-positive results attributable to small-vessel ischemia, a limitation also associated with exercise echocardiography and stress CMR.[42] Computed tomographic angiography or coronary angiography are more reliable tests for detection of epicardial coronary artery disease in HCM patients (Figure 3).[1–3]

– Chest pain is common in HCM and in the majority of patients caused by small-vessel ischemia.
– Because of low specificity of single photon emission computed tomographic and stress echocardiography for identification of epicardial coronary artery disease in HCM, computed tomographic angiography or coronary catheterization can be considered.

Family Screening

Imaging with echocardiography is recommended in at-risk family members starting at the beginning of puberty and continued at 12- to 18-month intervals until reaching full physical maturity.[1,2] If testing is normal at the end of adolescence, imaging can be extended every 3 to 5 years through midlife because it is possible for patients to demonstrate delayed phenotypic conversion with LV hypertrophy developing in the fourth or fifth decade of life.[1] Screening in the preadolescent period can also be considered, particularly if symptoms emerge, or when a child is engaged in intense systematic physical activity at an early age. It is reasonable to consider CMR as part of the screening evaluation of family members because the HCM phenotype may demonstrate segmental areas of LV hypertrophy more reliably identifiable with CMR.[43]

Family members with a disease-causing sarcomere mutation but without LV hypertrophy (ie, genotype positive–phenotype negative) may have demonstrable structural myocardial abnormalities, including myocardial crypts (ie, narrow deep blood-filled invaginations within LV myocardium), expanded extracellular space (with T1 mapping), LGE, elongated mitral leaflets, and diastolic dysfunction on tissue Doppler imaging (Figure 10).[32,44–49] The presence of one or more of these abnormalities is associated with an increased likelihood that a family member may be carrying a disease-causing sarcomere mutation and should prompt close surveillance with serial imaging for the development of LV hypertrophy and potentially genetic testing to aid in confirming HCM diagnosis.

– Screening family members with imaging is an important component to the evaluation of most HCM patients.
– CMR should be considered as part of the initial screening assessment because limited, focal LV hypertrophy can be missed with echocardiography.
– Many myocardial structural abnormalities can be identified with imaging in family members who carry a disease-causing sarcomere mutation without LV hypertrophy and should prompt consideration to performing genetic testing for confirmatory diagnosis or close longitudinal follow-up to detect possible conversion to clinical diagnosis.

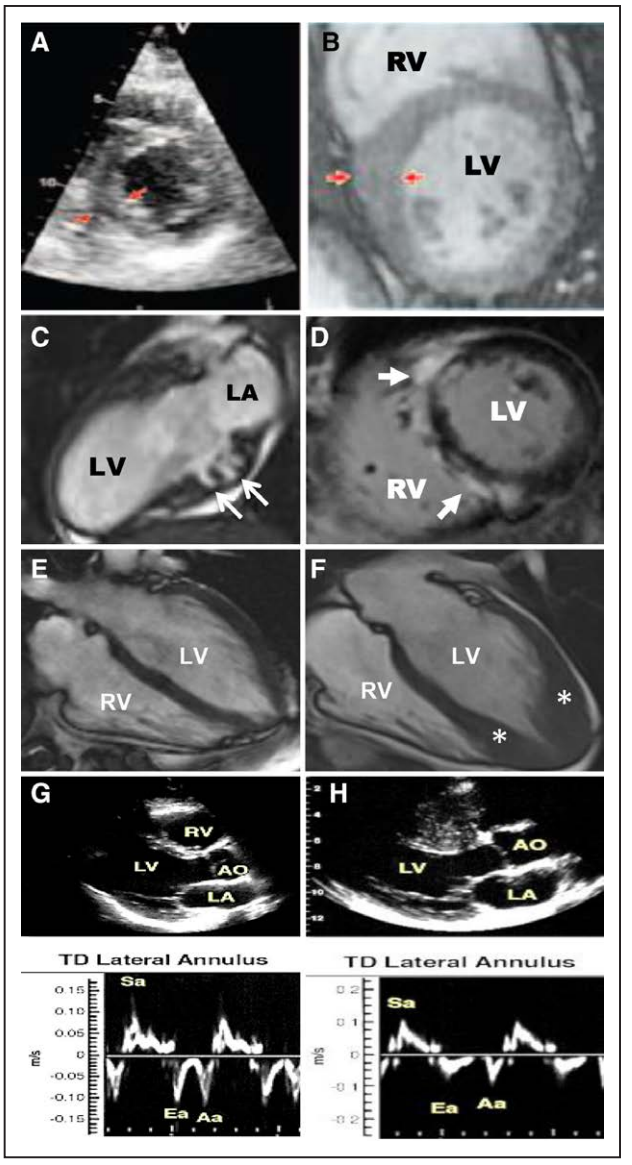

Figure 10. Imaging hypertrophic cardiomyopathy (HCM) family members. **A** and **B**, Advantage of cardiovascular magnetic resonance (CMR) compared with 2-dimensional echocardiography (2DE). **A**, Basal left ventricular (LV) short-axis echocardiographic image demonstrating normal LV wall thickness in genotype positive HCM family member. **B**, CMR in the same patient shows focal region of increased LV wall thickness of 14 mm (arrows), confirming clinical diagnosis of HCM. Regions of ununiform increased LV wall thickness are indicated by the arrows. Reprinted from Valente et al[43] with permission of the publisher. Copyright © 2013. **C** and **D**, Morphological abnormalities in the absence of LV hypertrophy. **C**, Multiple LV myocardial crypts (arrows). **D**, Late gadolinium enhancement indicative of replacement myocardial fibrosis (arrows). **E** and **F**, De novo phenotypic conversion at advanced age. **E**, LVH absent at age 46 y. **F**, Apical HCM (*) present at age 51 y. Reprinted from Maron et al[48] with permission of the publisher. Copyright © 2012. **G** and **H**, Diastolic dysfunction precedes LV hypertrophy. **G**, Parasternal long-axis echocardiographic image in genotype positive HCM family member showing normal LV wall thickness but systolic (Sa) and early diastolic (Ea) tissue Doppler velocities are reduced. **H**, In same patient imaged 2 y later, LV wall thickness in ventricular septum has increased and tissue Doppler velocities remain reduced. Reprinted from Nagueh et al[49] with permission of the publisher. Copyright © 2006. Ao indicates aorta; LA, left atrium; LVH, left ventricular hypertrophy; and RV, right ventricle.

Approach to the Illustrative Patient

Prevention of Sudden Death

The application of CMR imaging to this patient confirmed diagnosis by providing a more precise assessment of LV wall thickness, in 2 regions of the wall: basal ventricular septum (21 mm) and posterolateral wall (14 mm). After confirmation of an HCM diagnosis, the patient underwent 48-hour ambulatory Holter monitoring that demonstrated 2 short 5-beat bursts of asymptomatic nonsustained ventricular tachycardia, at 130 bpm. In the absence of other conventional risk markers, this

finding placed the patient in an ambiguous gray zone of HCM risk stratification. However, contrast CMR images demonstrated extensive LGE (fibrosis) occupying 20% of LV mass that conveyed an 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. Two years later, the ICD spontaneously delivered a life-saving defibrillation shock terminating ventricular fibrillation (235 bpm) and restoring sinus rhythm.

Heart Failure Management

The patient exercised on a standard Bruce protocol stress (exercise) echocardiogram for 12 minutes, demonstrating mitral–septal contact producing a 4.5 m/s velocity (90 mm Hg gradient) in the LV outflow tract with associated moderate posteriorly directed mitral regurgitation. Recognition of a high provocable outflow tract gradient altered management by opening up additional treatment options, including invasive septal reduction therapy. Despite higher doses of β-blocker and disopyramide, the patient continued to experience limiting symptoms on a daily basis.

In addition to impacting sudden death risk assessment with LGE, acquisition of tomographic CMR images through the LV chamber identified an anomalous anterolateral papillary muscle inserting directly into anterior mitral valve leaflet producing midcavity muscular obstruction. Given this anatomy, it was our judgment that the patient's gradient could not be relieved effectively and safely by percutaneous alcohol septal ablation. Instead, surgical septal myectomy was performed with a deep and extended muscular resection (ie, beyond the contact point of the papillary muscle and ventricular septum), as well as partial resection of papillary muscle obstruction. At the 6-month postoperative follow-up visit, echocardiography demonstrated absence of outflow obstruction at rest and with provocation; the patient reports complete resolution of heart failure symptoms.

The HCM diagnosis in the proband prompted family screening. The asymptomatic 16-year-old son had an abnormal ECG with voltage criteria for LV hypertrophy but normal LV wall thickness by echocardiography and CMR. However, multiple, deep myocardial crypts were observed in the basal inferior wall, supporting further the decision for the father to undergo genetic testing that identified a disease-causing (pathogenic) sarcomere mutation. The son was then tested and found to have the same sarcomere mutation, converting his clinical status to genotype positive/phenotype negative. In the absence of a clinical HCM diagnosis, annual surveillance with imaging was recommended to assess potential phenotypic conversion to LV hypertrophy.

This case highlights the important role and clinical impact of multimodality cardiovascular imaging techniques in the contemporary evaluation of patients with (or suspected of) HCM. This includes consideration to CMR as part of the initial evaluation for all HCM patients, given the substantial data demonstrating its impact on many clinical management issues including diagnosis, prognosis, preprocedural planning for invasive septal reduction therapy, and assessment of family members.

Disclosures

None.

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