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Noninvasive Cardiac Imaging in Patients With Hypertrophic Cardiomyopathy

Sherif F. Nagueh, MD, FACC, John J. Mahmarian, MD, FACC
Houston, Texas

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy and the most common cause of cardiac death in young athletes in the U.S. Noninvasive imaging plays an important role in detecting the disease, understanding its pathophysiology, and selecting as well as guiding appropriate therapy. In this review, we discuss the existing methodology with emphasis on current and emerging clinical applications in patients with HCM. (J Am Coll Cardiol 2006; 48:2410–22) © 2006 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, with an estimated prevalence of 0.2% (1). It is caused by >100 mutations in 11 genes coding for sarcomeric proteins (2) and is a common cause of death among athletes (1). Noninvasive cardiac imaging techniques play a pivotal role in detecting the disease, understanding its pathophysiology and selecting and guiding appropriate therapy. In this review, we discuss the existing methodology with emphasis on current and emerging applications in HCM patients.

ECHOCARDIOGRAPHY

Echocardiography has been used since its early days to gain insight into this complex disease, because it provides a practical and comprehensive assessment of cardiac structure and function (Table 1). In addition to left ventricular (LV) dimensions and volumes, the pattern and extent of left ventricular hypertrophy (LVH) can be determined. Asymmetric LVH (Fig. 1) is most commonly observed (95%), particularly with upper septal hypertrophy (3). However, mid ventricular, apical, or posterolateral hypertrophy also occur. In addition, up to 5% of patients have concentric LVH. During acquisition and analysis, one has to exercise caution to avoid oblique transection of the septum by the ultrasound beam and to exclude myocardium on the right ventricular (RV) side of the septum when measuring septal thickness. The identification of the apical variant can be challenging but is significantly enhanced by high frequency transducers and intravenous contrast agents.

Quantification of LV mass poses problems with conventional methods, given the variable wall thickness and dimensions throughout the LV. Reasonable alternatives include semiquantitative scores such as the Wigle (3) and the Maron and Spirito score (4). The latter reports the sum of maximal wall thickness taken from septal, posterior, lateral, and anterior myocardial areas in the short axis views at mitral and papillary muscle levels.

From the Department of Cardiology, The Methodist DeBakey Heart Center, The Methodist Hospital, Houston, Texas.

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More recently, real time 3-dimensional echocardiography has been applied to determine LV mass, but there is a paucity of data about its accuracy in HCM. Maximal wall thickness is a simple and important measurement that should be reported, because it can predict sudden cardiac death in this population (5).

Differential diagnosis. Before establishing the diagnosis of HCM, other reasons for LVH such as hypertension and aortic stenosis should be excluded, although at times they coexist with HCM. The patients for whom the diagnosis of HCM is easiest to establish are those who have positive family history or harbor a known mutation with advanced asymmetric LVH, despite a mild degree of aortic stenosis or well controlled hypertension. By contrast, the diagnosis of HCM is difficult to ascertain in patients with mild concentric LVH and hypertension or aortic stenosis. Recently, more severely reduced systolic compression (by strain Doppler echocardiography) along with asymmetric LVH readily identified biopsy-proven HCM patients from those with hypertension (6).

Up to 30% of HCM patients have systolic anterior motion (SAM) of the mitral valve, leading to left ventricular outflow tract (LVOT) obstruction. However, SAM is not pathognomonic of HCM. Systolic anterior motion has been observed in elderly women with hypertension, sigmoid septum, and a hyperdynamic state due to anemia and/or hypovolemia (7). It is also noted after mitral valve repair with an annular ring and anterior displacement of the anterior mitral valve leaflet (8). Other causes of dynamic obstruction are listed in Table 2.

The differential diagnosis includes cardiac amyloidosis, tumors, adherent thrombi, and Fabry disease. The latter is an X-linked recessive metabolic defect that frequently results in cardiac hypertrophy and should be considered in men with unexplained LVH. The diagnosis can be reliably made in men by measuring the serum level of the lysosomal enzyme alpha-galactosidase and noting the binary appearance of LV endocardial border by echocardiography (9). This diagnosis should be entertained, given the presence of specific enzyme replacement therapy that results in regression of LVH and improvement of cardiac function. Table 2 lists other metabolic defects.

Abbreviations and Acronyms

Aa	= late diastolic velocity
AV	= atrioventricular
Ea	= early diastolic velocity
EF	= ejection fraction
HCM	= hypertrophic cardiomyopathy
LA	= left atrium/atrial
LV	= left ventricle/ventricular
LVH	= left ventricular hypertrophy
LVOT	= left ventricular outflow tract
MR	= mitral regurgitation
RV	= right ventricle/ventricular
SAM	= systolic anterior motion
SPECT	= single-photon emission computed tomography
TD	= tissue Doppler

Detection of HCM in athletes. Diagnosis of HCM in athletes is important, given the high propensity to sudden cardiac death in HCM patients engaging in competitive sports. The diagnosis can be particularly challenging in athletes with an advanced degree of physiologic LVH. Helpful clues include the presence of wall thickness >12 mm (>11 mm in women) in the presence of a non-dilated LV (10) in HCM, because HCM patients usually have normal or reduced LV dimensions and no cavity dilatation (>55 mm is common in athletes), except with disease progression and systolic dysfunction. Hypertrophic cardiomyopathy patients have abnormal myocardial function as detected by tissue Doppler (TD) imaging, including mitral annulus velocities and myocardial early diastolic velocity (Ea) gradient or strain rate (11). In equivocal cases, it is reasonable to recommend stopping exercise with repeat imaging later, when one would expect regression of physiologic but not pathologic LVH.

Assessment of systolic function. This is performed with shortening fraction and/or ejection fraction (EF). Most HCM patients have hyperdynamic EF, whereas a small subset might develop LV enlargement along with depressed EF (1). The presence of LV enlargement and depressed EF versus normal EF is important for proper selection of medical therapy, because patients with depressed EF should receive angiotensin-converting enzyme inhibitors and cardiac glycosides, which are avoided in patients with LVOT obstruction.

In HCM a normal EF does not exclude contractile dysfunction, which can be detected by more sensitive techniques such as myocardial systolic velocities, strain rate,

Table 1. Echocardiographic Evaluation of Cardiac Structure and Function in Patients With Hypertrophic Cardiomyopathy

LV dimensions and volumes
Pattern of LV hypertrophy (asymmetric, concentric, or apical)
Septal, posterior, and maximum wall thickness
LVEF
LV relaxation and filling pressures (using Ea by TD and E/Ea ratio)
Pulmonary artery systolic pressure (using tricuspid regurgitation jet)
LA maximum volume
RV size, function, and whether RV hypertrophy is noted
Presence and location of dynamic obstruction and whether chordal or valvular SAM is noted
Magnitude of outflow tract gradient at rest and Valsalva
Presence and magnitude of dynamic obstruction in the RV outflow tract
Presence and severity of mitral regurgitation
The presence of co-existing pathology, such as aortic, pericardial disease, and so on

E = mitral E; Ea = early diastolic velocity; EF = ejection fraction; LA = left atrial; LV = left ventricular; RV = right ventricular; SAM = systolic anterior motion; TD = tissue Doppler.

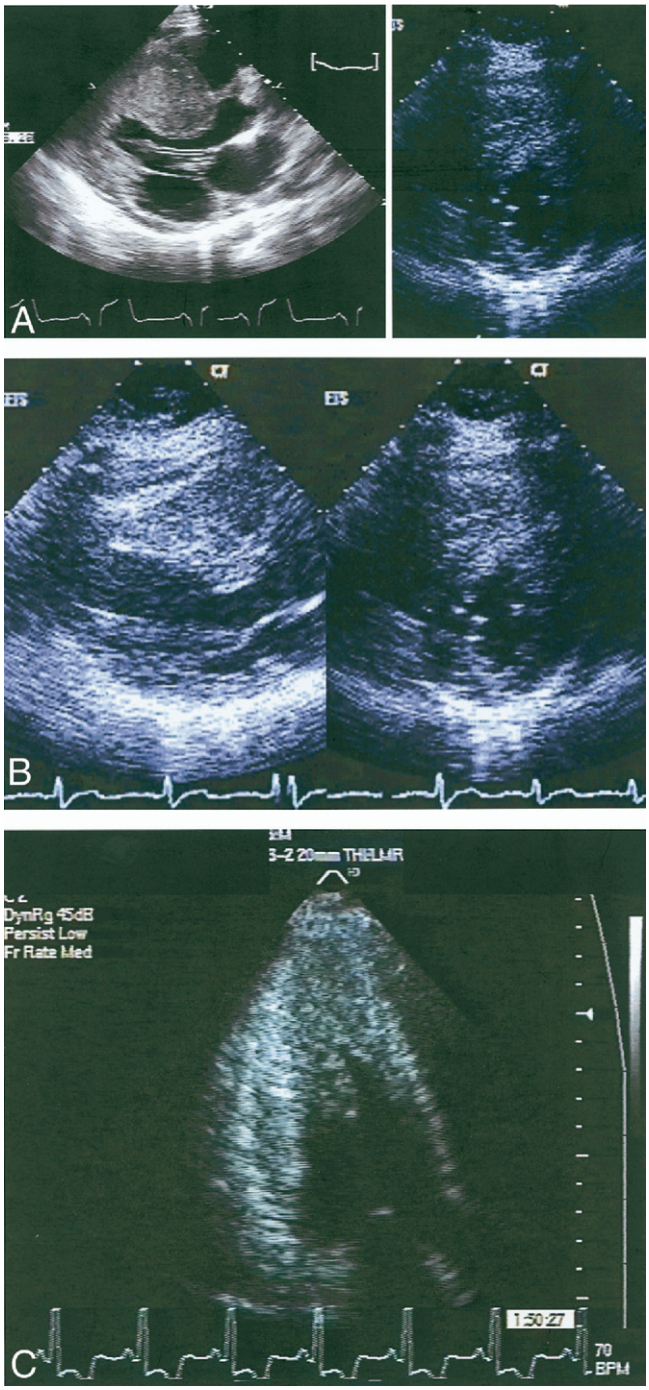

Figure 1. **(A)** Asymmetric septal hypertrophy; **(B)** concentric hypertrophy; **(C)** apical hypertrophy.

JACC Vol. 48, No. 12, 2006
December 19, 2006:2410–22

Table 2. Differential Diagnosis of Hypertrophic Cardiomyopathy

Differential Diagnosis of LVH
Athlete's heart
Hypertension
Valvular aortic stenosis
Sub-valvular fixed obstruction
Fabry disease
Glycogen storage disorders
Friedrich ataxia
Mitochondrial myopathy
Cardiac amyloidosis
Septal tumors
Adherent thrombi
Differential Diagnosis of Dynamic Outflow Tract Obstruction
Elderly women with hypertension, sigmoid septum, and hyperdynamic EF
After mitral valve repair
After acute MI with apical dysfunction and hyperdynamic basal function
Massive posterior mitral annulus calcification
Anomalous papillary muscle
After aortic valve replacement with LVH and hyperdynamic EF

LVH = left ventricular hypertrophy; MI = myocardial infarction; other abbreviations as in Table 1.

and strain (6,11). Notwithstanding, at this time, it is reasonable to report LVEF until the incremental and prognostic value of the new methods are determined.

Assessment of diastolic function. The accuracy of mitral and pulmonary venous flow in evaluating LV diastolic function was explored in a number of cross sectional studies. Both LV and left atrial (LA) filling abnormalities have been noted, but no close correlation was observed between Doppler filling patterns, extent of LVH, and invasive indexes of diastolic function (12), with the exception of the atrial flow signal recorded from the pulmonary veins, which has a significant correlation with LV end diastolic pressure (13). In contrast, TD imaging in combination with transmitral inflow can provide reasonably accurate predictions of filling pressures (13). Tissue Doppler recording of the mitral annulus motion is obtained by placing a 5-mm sample volume at the septal and lateral sites of the annulus, with adjustment of scale, gains, and filters to allow for a clear signal with minimal background noise. It is possible to measure the absolute value of the early (Ea) and late (Aa) diastolic velocities as well as Ea/Aa and mitral E to annular Ea ratios (Fig. 2). Importantly, E/Ea ratio detects changes in filling pressures after alcohol-induced septal ablation (14,15) and cardiac surgery (15) and predicts exercise tolerance in adults (16) and children (17) with HCM. In addition, septal Ea is an independent predictor of death and ventricular dysrhythmia in children with HCM (17).

Left atrial volume reflects the LA hemodynamic burden from LV diastolic dysfunction, mitral regurgitation (MR),

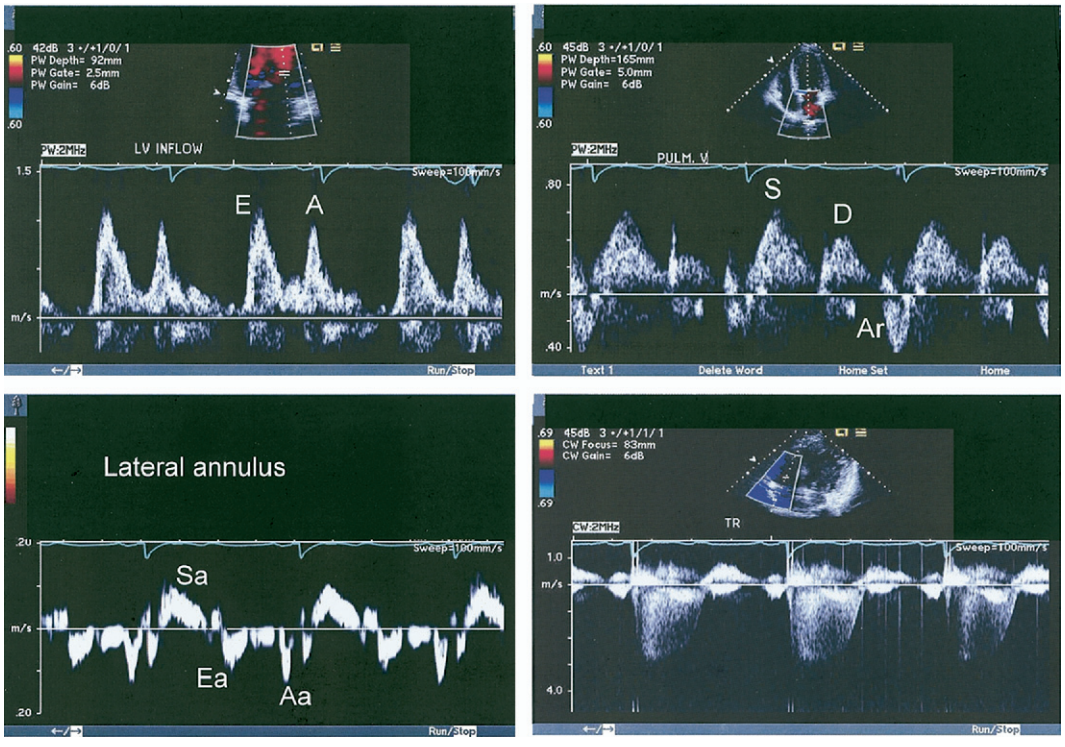

Figure 2. **(Upper left)** Mitral left ventricular (LV) inflow; **(upper right)** pulmonary venous flow; **(lower left)** tissue Doppler velocities at lateral side of mitral annulus; **(lower right)** tricuspid regurgitation (TR) jet by continuous wave (CW) Doppler. Mitral inflow is pseudonormal (E/A ratio of 1), and systolic/diastolic (S/D) velocity (and time velocity integral) ratio >1 in the pulmonary veins. However, atrial reversal (Ar) velocity in pulmonary venous flow is increased both in amplitude and duration, indicating increased LV end diastolic pressure. The early diastolic (Ea) velocity is reduced and Ea/ late diastolic (Aa) velocity ratio is <1, indicating abnormal LV relaxation. The E/Ea ratio is increased to 12.5, indicating increased LV pre-A pressure. Peak TR velocity = 2.8 m/s, indicating an RV and pulmonary artery (PA) systolic pressure of at least 31 mm Hg.

and atrial myopathy. A number of studies have now reported a significant association between LA dimensions and subsequent development of atrial fibrillation as well as adverse outcomes after myectomy (18).

Dynamic obstruction. This dynamic abnormality has captured the attention of cardiologists and surgeons over the years and remains so at this time. Obstruction can occur at multiple levels in the same patient and is variable with time (1), being dependent on intravascular blood volume, afterload, and cardiac contractility. It is important to perform careful mapping by pulse wave Doppler to determine the site of obstruction. Continuous wave (CW) Doppler is used to determine peak LVOT gradient with caution exercised to exclude the MR jet.

A number of theories have been examined to understand the mechanisms of LVOT obstruction, and the 2 most viable are the Venturi (3) and drag forces. The Venturi theory proposes that the earliest event is an increased ejection velocity, leading to an increase in kinetic energy. Given the principle of conservation of energy, the increase in kinetic energy is accompanied by a decrease in potential energy and local pressure leading to the anterior motion of the mitral valve. This in turn leads to a gap between the anterior and posterior mitral leaflets through which MR occurs (i.e., "eject, obstruct, leak" sequence) (3). In contrast, the theory implicating drag forces (19) looks at anterior movement of the mitral valve because of drag forces, which act on the posterior surface of the valve and are proportional to the surface area of the leaflets exposed to these forces and systolic flow velocity. This mechanism is supported by the presence of SAM at a time when the LVOT velocity is not increased (20). Irrespective of the underlying mechanism(s), LVOT obstruction is associated with worse clinical outcomes, including death and heart failure (21).

It is also important to look for dynamic obstruction in the RV outflow tract, which can occur in younger subjects.

Provocable obstruction. A number of methods can provoke obstruction in the echocardiography laboratory, including Valsalva maneuver, amyl nitrite, exercise, and dobutamine. It is relatively easy to acquire data during the strain phase of Valsalva in most patients, but when the gradient is <30 mm Hg, particularly in highly symptomatic patients, it is reasonable to proceed to other methods of provoking obstruction.

For those able to exercise, exercise Doppler should be used (1), because exercise is the modality that most closely simulates physiologic stress. Additional data such as exercise duration, blood pressure with exercise, and peak oxygen consumption may be obtained during the same test. Although supine bike exercise is more conducive to acquiring multiple hemodynamic data sets, this position increases venous return and might decrease the likelihood and extent of LVOT obstruction. Accordingly, upright exercise, which has the greatest resemblance to daily physiologic activities, should be used.

For patients unable or unwilling to exercise, medical provocation is a viable alternative. Isoproternol, because of its positive inotropic properties, has been used for decades in the catheterization laboratory, providing the rationale and precedent for dobutamine injection in the echocardiography laboratory. The use of dobutamine is not advocated for subjects with LVH due to hypertension and not HCM; nor is it advocated for HCM patients who are asymptomatic with mild symptoms or able and willing to exercise. The infusion protocol starts with a drip rate of 5 μg/kg/min up to 20 μg/kg/min. Importantly, treating provocable obstruction has resulted in significant clinical, exercise, and hemodynamic improvement (22).

MR. Mitral regurgitation can occur in HCM patients because of rheumatic heart disease or myxomatous degeneration. In patients with dynamic obstruction, MR jet is directed posterolaterally. The direction of the MR jet is an important clue for the underlying mechanism (23), because an anteriorly/medially directed jet is not related to dynamic obstruction but is due to a primary leaflet pathology (Fig. 3). Echocardiographic studies (24) have drawn attention to the reduced mobility and length of the posterior mitral leaflet leading to a shorter coaptation length and therefore a longer free segment of the anterior leaflet that is amenable to drag forces. Mitral regurgitation related to dynamic obstruction is improved by septal reduction therapy (25,26).

Echocardiography to guide treatment in HCM. Symptomatic patients with LVOT obstruction are treated with negative inotropic drugs (beta-blockers, verapamil, diltiazem, and disopyramide) as the first line of therapy. These drugs decrease LVOT gradient by reducing acceleration rate of LV systolic flow and prolonging acceleration time relative to ejection time, thereby reducing the time available for the build up of the dynamic gradient (27). A successful response to medical therapy results in an improvement of cardiac symptoms and a reduction in LVOT gradient that can be assessed by Doppler echocardiography. In addition, beta-blockers, verapamil, and diltiazem prolong the diastolic filling time and reduce the likelihood of developing ischemia through their favorable effect on ischemia/demand balance.

Pacemaker therapy. When medical therapy fails or cannot be tolerated, other options are considered, including pacing. There is seldom a need for transthoracic imaging during implantation of a pacemaker. However, if there are doubts about whether the RV lead is positioned in the apex or there are concerns about cardiac perforation, transthoracic imaging should be performed.

As for hemodynamic effects, initial observational studies were encouraging, but randomized controlled studies showed a highly variable and modest benefit from pacing (1). Unlike patients with congestive heart failure and depressed EF where an improvement of LV dyssynchrony is sought with biventricular pacing, RV pacing in patients with obstructive HCM is used to induce further dyssynchrony to decrease LVOT gradient (28), as recently demonstrated by TD. Because HCM patients have normal atrioventricular (AV) conduction, a short AV delay is needed for ventricular pacing. However, this approach can result in abbreviated

JACC Vol. 48, No. 12, 2006
December 19, 2006:2410–22

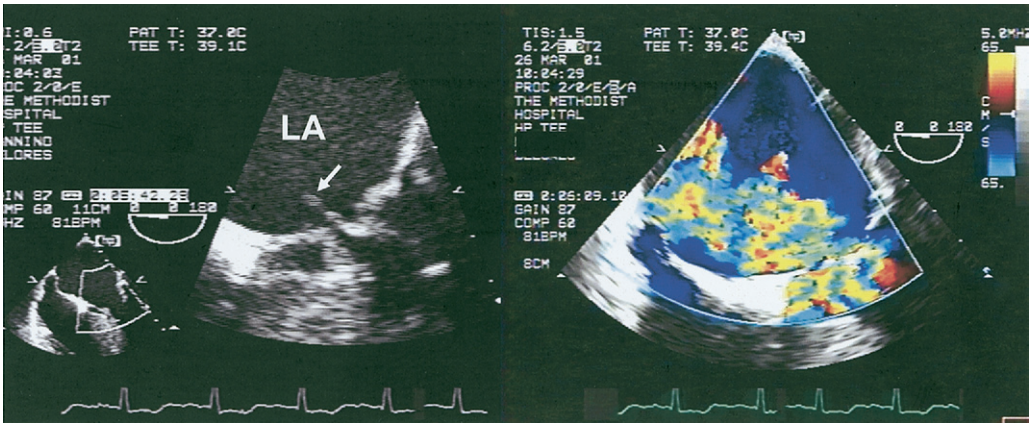

Figure 3. **(Left)** Flail segment of posterior mitral leaflet. **(Right)** Color Doppler with eccentric mitral regurgitation jet directed antero-medially. LA = left atrium.

LV diastolic filling, reduction in stroke volume, and increase in filling pressures. It is therefore imperative to identify the longest AV delay that leads to adequate filling yet results in complete ventricular pre-excitation. To achieve this objective, Doppler echocardiography is applied to determine the effects of different AV delays on LV diastolic filling time. Echocardiography can monitor the effects of pacing on LVOT gradient and filling pressures.

Echocardiographic evaluation for septal reduction therapy. Septal reduction therapy is feasible with intracoronary ethanol and surgical myectomy. For both procedures, dynamic obstruction at rest (30 to 50 mm Hg) or provocation (≥60 mm Hg) should be present as well as a septal thickness of ≥1.6 cm.

Before septal reduction, it is important to identify the site of obstruction (i.e., SAM vs. mid or distal obstruction). This distinction is essential, because reduction of septal base thickness will not result in an improvement of distal obstruction. It is also important to identify co-existing valvular disease that warrants surgery, for example subvalvular fixed stenosis (Fig. 4), anomalous insertion of papillary muscle, or a flail valve. It can be challenging to assess the severity of aortic stenosis in patients with obstructive HCM, and it is reasonable to proceed, if needed, to transesophageal echocardiography to measure the aortic valve area by planimetry in short axis views.

When septal reduction therapy cannot be performed because of inadequate septal thickness, plication of anterior mitral leaflet or mitral valve replacement can be considered.

Alcohol septal reduction. During alcohol septal reduction therapy, procedural guidance with myocardial contrast echocardiography is important (Fig. 5) (29). This results in a significantly shorter procedure time and lower likelihood of heart block (30). In addition, it is possible to identify the myocardial territory of septal perforator branches that arise from vessels other than the left anterior descending coronary artery. Contrast opacification of other LV/RV segments or papillary muscle precludes the injection of ethanol, which would result in infarction outside the culprit septal segments but not septal reduction. The risk area by myocardial

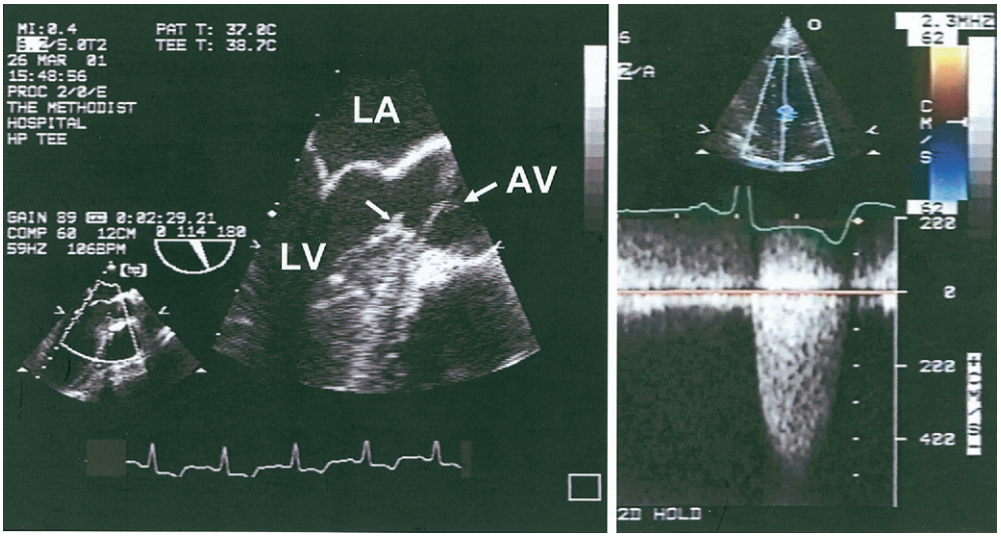

Figure 4. **(Left)** Transesophageal echocardiography of left ventricular outflow tract showing sub-valvular membrane **(arrow)**. **(Right)** Continuous wave signal of abnormal flow. Note the early peaking with a gradient of almost 100 mm Hg and the presence of aortic regurgitation. Both are unexpected with dynamic obstruction. AV = aortic valve; LA = left atrium; LV = left ventricle.

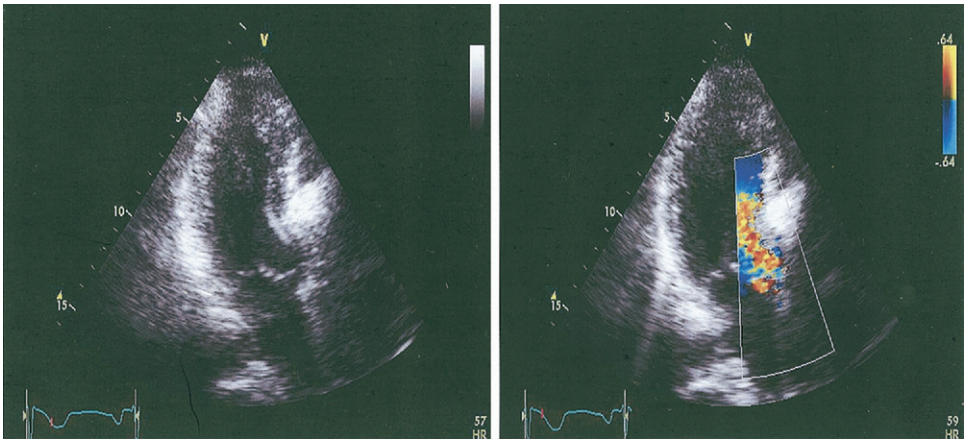

Figure 5. **(Left)** Apical long-axis view after opacification of septal base with radiographic contrast in the course of alcohol septal ablation. **(Right)** Color Doppler showing the site of flow acceleration in relation to the opacified septal base.

contrast echocardiography relates significantly to the perfusion defect size by single-photon emission computed tomography (SPECT), peak creatine kinase leak (29), and development of heart block and ventricular dysrhythmia (31).

The reduction of LVOT gradient in the acute phase is related to the decrease in systolic thickening and excursion of septal base due to necrosis/ischemia-stunning (Fig. 6) as well as global decrease in LV systolic function, which can be detected by invasive measurements and peak acceleration rate of LV ejection (25). An acute improvement is usually noted in the severity of MR without significant change in leaflet mobility (25). Later on, LVOT widening, reduction in drag forces, and decrease in peak LV ejection acceleration rate account for the reduction in LVOT obstruction (25).

After alcohol septal reduction therapy, LV end-diastolic volume increases and septal and maximal wall thickness decrease as well as EF, albeit still in the normal range (32). As for LV diastolic function, the time constant of LV relaxation shortens (14) and filling pressures are reduced (14,15,30). Interestingly, despite septal infarction, LV dyssynchrony improves and contributes to the acute improvement in LV relaxation (33). Left ventricular stiffness improves as well (14,34) and is related to the decrease in LV mass/volume ratio (32), total collagen and collagen I isoform (34), and improvement in LV relaxation. The improvement in LV diastolic function and the severity of MR lead to a decrease in LA volumes, ejection force, and stroke work, which nevertheless remain significantly increased when compared with a normal group (35).

Surgery. During surgery, transesophageal echocardiography is needed (36) to determine the adequacy of septal resection, because inadequate septal resection is an important cause of residual obstruction. Additional reasons for repeat surgery include mid-ventricular obstruction and anomalous papillary muscle insertion (37). Both can be identified by echocardiography and surgical inspection of the LVOT. In contrast to alcohol septal reduction therapy, most of the reduction in LVOT gradient after surgery

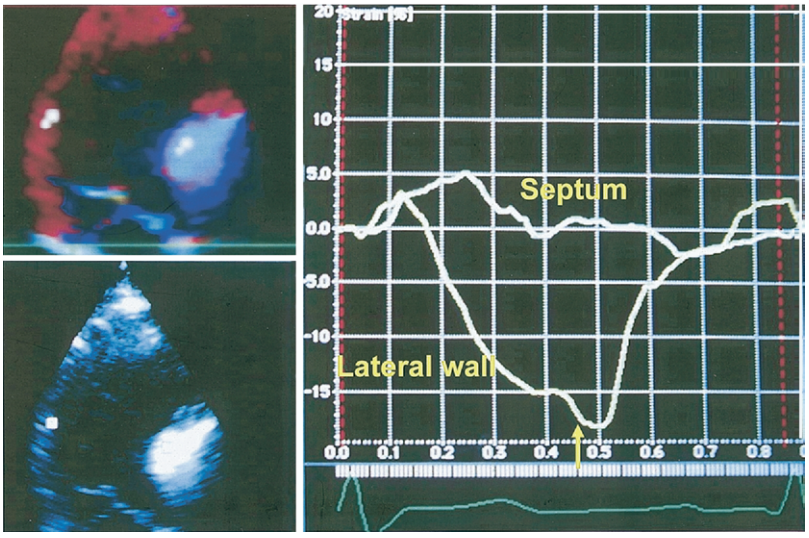

Figure 6. Septal and lateral base function by Doppler strain–time curves, after alcohol injection. Systolic compression is present in the lateral wall, but the base of the septum is dysfunctional. The **arrow** points to post-systolic compression, which is not uncommon in hypertrophic cardiomyopathy and seems related to abnormal loading conditions and possibly ischemia.

JACC Vol. 48, No. 12, 2006
December 19, 2006:2410–22

occurs acutely owing to widening of the LVOT, which is maintained at follow-up. Transesophageal echocardiography is also important in determining the adequacy of mitral valve repair in cases with MR due to primary leaflet pathology or with additional surgical procedures, such as valve plication/extension. In most patients, postoperative complications (when suspected), such as pericardial effusion, aortic regurgitation, and septal rupture, can be readily diagnosed by transthoracic imaging.

Surgical myectomy results in increase in LV volumes, decrease in LV systolic function (26), and reduction in LV mass and filling pressures (15).

Screening and pre-clinical diagnosis of HCM. Echocardiography is the most practical technique at the present time for HCM screening. It is considered in first degree relatives and potentially in other family members of the index cases. Given the adolescent growth spurt, repeat imaging at yearly intervals is reasonable during this time period (38). Repeat imaging is also considered for adults at longer time intervals of 5 years (38) because of the possibility of later development of LVH (39). All myocardial segments—and not only the interventricular septum—should be carefully examined for screening purposes. In a recent study where genotyping was the gold standard, the Spirito-Maron hypertrophy score was highly specific with a better sensitivity than maximal wall thickness (40).

Studies from transgenic animal models have noted the presence of abnormal myocardial function (41) at a time preceding the development of LVH. These observations have led to the investigation of TD imaging in the preclinical diagnosis of HCM in individuals carrying sarcomeric protein mutations encoding HCM. Four reports have provided encouraging results (42–45), with an additional study (39) showing subsequent LVH in such subjects (Fig. 7). In addition, this methodology proved accurate in the identification of patients with Fabry disease without LVH (46).

However, additional data from a larger number of subjects is needed to determine TD velocity values that provide the highest diagnostic accuracy with narrow confidence intervals. Additional limitations to this approach include the lower specificity in older individuals or those with coexisting disease, such as hypertension and coronary artery disease, which can result in abnormal myocardial function. Furthermore, it is difficult to interpret Doppler data and provide counsel to subjects who carry the mutation but who still have normal velocity values. Given the variable penetrance, these subjects might never develop HCM including abnormal myocardial function. Alternatively, it is possible that the abnormality in cardiac function is present but at a mild degree that is not amenable to diagnosis by TD (role of strain imaging as more sensitive marker of myocardial disease remains to be established). Therefore, repeat imaging is reasonable, possibly at yearly intervals, in an attempt to detect myocardial dysfunction and/or LVH if and when they develop.

NUCLEAR IMAGING

In the past 2 decades, gated blood pool radionuclide angiography has provided helpful insights into the measurement of LV volumes, EF, and filling rates in HCM patients. Verapamil has been shown to increase the peak filling rate and to shorten the time to peak filling rate in HCM patients (47). Because LV filling rates and time intervals are affected not only by LV relaxation but also

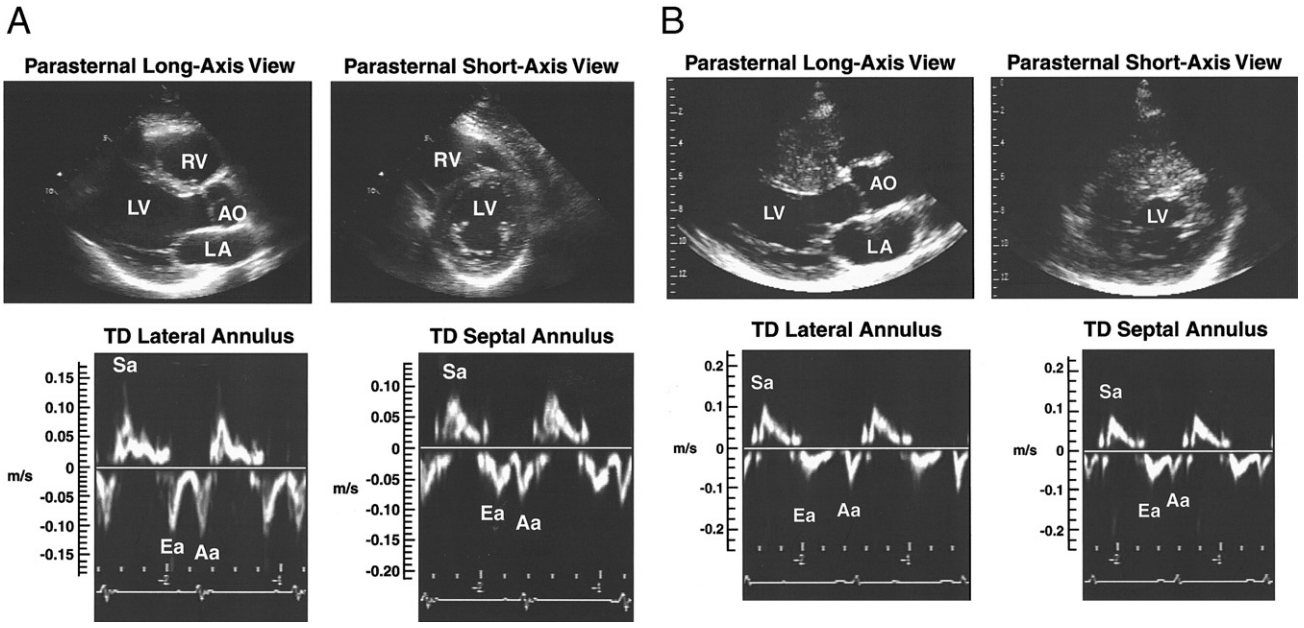

Figure 7. **(A)** Parasternal long- and short-axis views and tissue Doppler (TD) velocities at lateral and septal side of mitral annulus, from a 20-year-old subject carrying a known mutation for hypertrophic cardiomyopathy. Left ventricular hypertrophy is absent, but systolic (Sa) and early diastolic (Ea) velocities are reduced for age. **(B)** After 2 years, asymmetric septal hypertrophy developed and TD annular velocities remain reduced. AO = aorta; Aa = late diastolic velocity; LA = left atrium; LV = left ventricle; RV = right ventricle.

filling pressures, it is possible to observe pseudonormal filling rates when filling pressures are increased. At the present time, echocardiography is applied to assess diastolic function because it allows beat to beat measurement of filling patterns and the acquisition of less load-dependent indexes of LV relaxation.

SPECT myocardial perfusion imaging. Patients with HCM might have epicardial coronary artery disease, and many HCM patients with chest pain undergo stress perfusion imaging to detect ischemia. Treadmill, bicycle exercise, atrial pacing, dipyridamole, and adenosine were examined in this population. Defects, both reversible and fixed, were noted from 10% to 100% of the patients imaged (see Table 3 from Keng et al. [48] for a summary). Most defects involve the septum but can occur in other walls. Although the general principles of SPECT interpretation apply to HCM patients, cardiologists should be cautious of "hot spots." These have increased count activity and are most frequently noted in the septum in patients with asymmetric LVH. The increased count activity might be related to LVH and/or increased regional blood flow. Irrespective of the etiology of "hot spots," if the tomographic slices are normalized to this area of increased count activity, regions adjacent to and distinct from the "hot spot" will appear relatively less intense, thereby creating spurious perfusion defects (Fig. 8). Inaccurate image interpretation can be avoided by paying attention to the location and type of perfusion defects. The lateral wall is most frequently involved, and perfusion defects are usually fixed. Furthermore, on gated SPECT images, normal regional function will be noted despite the apparently reduced perfusion.

Abnormal myocardial perfusion in HCM patients, despite normal coronary angiography, has been linked to sudden cardiac death (49). More recently, worse prognosis was noted with microvascular dysfunction as determined by myocardial blood flow and coronary flow reserve measured by ^{13}N labeled ammonia (50). Aside from perfusion defects, additional abnormalities have been reported, including increased washout rates of Tc-99m tetrofosmin, which is positively correlated with New York Heart Association functional class and wall thickness (51).

SPECT monitoring of results of non-medical therapy. Overall the published literature reports on few HCM patients who had nuclear imaging studies after non-medical therapy. In 20 patients who underwent surgical myectomy or mitral valve replacement, an improvement of myocardial perfusion was noted in most patients (52). However, 4 developed new fixed defects after surgery along with a large decrement in EF ($-26 \pm 15\%$) that was statistically significant when compared with the remaining patients ($-3 \pm 14\%$, $p < 0.01$).

In the largest report with gated SPECT after alcohol septal reduction therapy in 30 patients, only fixed septal perfusion defects were present after alcohol injection involving basal (100% of patients) and mid septum (38% of patients). In addition, significant reductions in lung to heart and in septal to lateral wall count ratios were noted (48). These observations

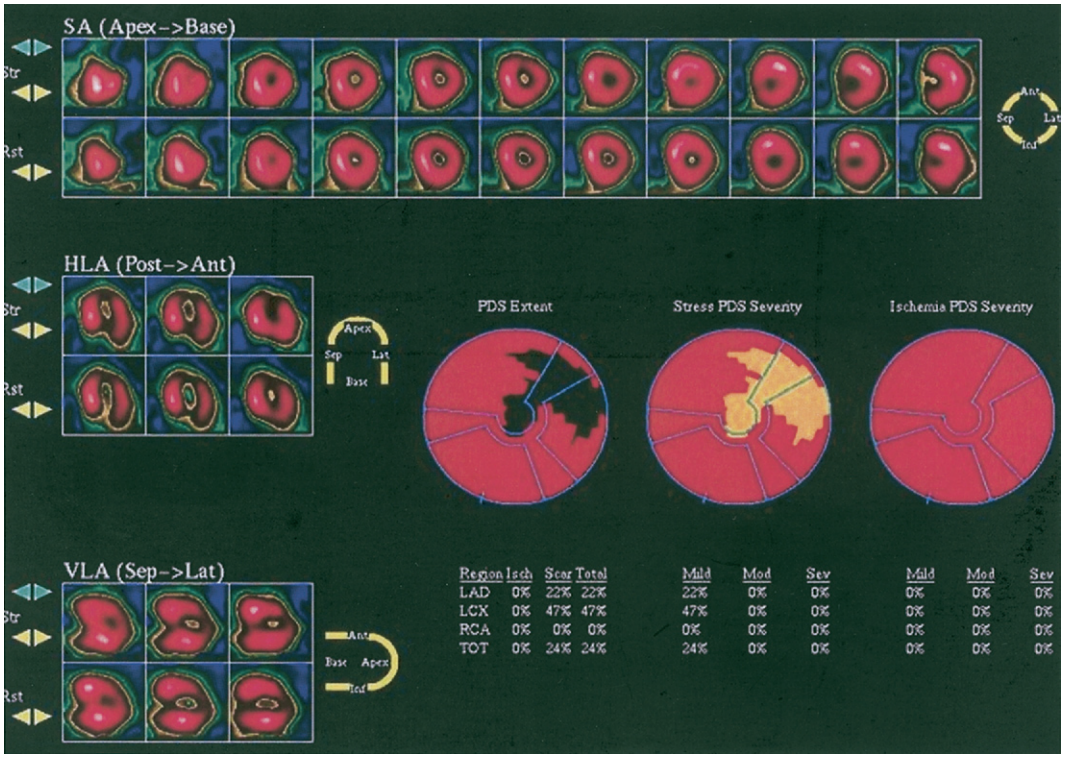

Figure 8. Single-photon emission computed tomography perfusion imaging from a hypertrophic cardiomyopathy patient. Septal thickness is increased as is the count activity (hot spot) in the septum relative to lateral wall. The computer analysis software registered a fixed perfusion defect (scar) in the lateral and apical regions upon normalization to the septum. HLA = horizontal long axis; PDS = perfusion defect size; SA = short axis; VLA = vertical long axis.

JACC Vol. 48, No. 12, 2006
December 19, 2006:2410–22

are due to the reduction of LV filling pressures and septal thickness after alcohol-induced infarction.

Imaging of metabolism and myocardial receptors in HCM. A number of interesting observations were made with cardiac metabolic and neurotransmission imaging. BMIPP (iodine-123-beta-methyl-iodophenylpentadecanoic acid, a marker of fatty acid metabolism) imaging was investigated in Japanese patients with HCM. BMIPP uptake was decreased, whereas its washout was increased in HCM (53), with regional BMIPP dynamics related to regional function and perfusion.

Intriguing observations were noted with iodine-123 labeled MIBG (metaiodobenzylguanidine), which tracks the presynaptic uptake and storage of neurotransmitters. In one study, HCM patients with ventricular tachycardia had a significantly higher MIBG global washout rate, which was the most powerful predictor of ventricular tachycardia on multiple regression analysis (54). Interestingly, a progressive decrease in MIBG uptake and increase in its washout rate are noted in HCM patients, as LV size increases and EF decreases (55).

Other studies (56,57) have explored changes in beta-adrenergic receptor density, with the radioactive tracers HED (^{11}C-hydroxyephedrine) and ^{11}C-CGP-12177 (potent hydrophilic beta-blocker, with little cellular uptake). These studies demonstrated the presence of reduced beta-adrenergic receptor density with reduced norepinephrine reuptake by presynaptic terminals. The reduction in beta-adrenergic receptor density seems to be particularly prominent in patients with heart failure (58).

Collectively, the aforementioned findings suggest that autonomic dysfunction might play a role in sudden death, disease progression, and the development of heart failure in HCM. However, additional studies are needed in a larger number of patients to corroborate these observations.

MAGNETIC RESONANCE IMAGING (MRI)

Cardiac morphology. Recent studies have shown that MRI can be applied to measure LV dimensions, volumes, and EF with high reproducibility (59), including in patients with LVH. In HCM, MRI plays a major role in identifying the pattern and extent of hypertrophy (Fig. 9), which can be more extensive than appreciated by echocardiography, particularly in the anterolateral free wall (60). This is also true with apical LVH (61). Furthermore, it is possible to identify early disease when hypertrophy is limited to the apical region of the lateral wall (62). Follow-up by MRI has shown that these cases progress to circumferential hypertrophy (62) and the "spade"-like configuration. Therefore, MRI or contrast echocardiography is essential when evaluating patients with anterolateral T-wave abnormalities and no obvious underlying etiology. In addition, given its accuracy, this technique is useful for familial screening and genetic linkage studies. In summary, cardiac MRI is considered a class I indication for patients with apical HCM and a class II indication for other phenotypic variants of HCM (59).

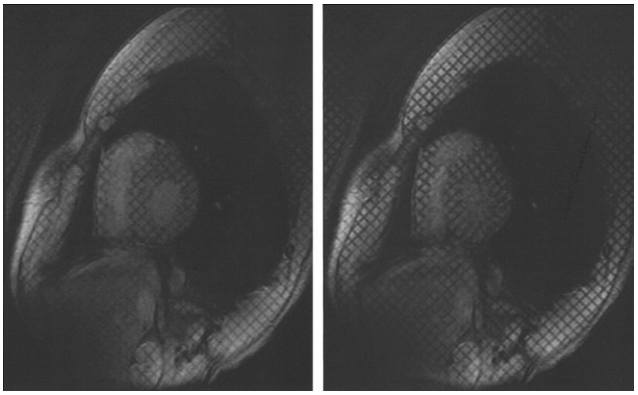

Figure 9. End-diastolic **(left)** and end-systolic **(right)** frames with the grid laid across the image. Notice the increased anteroseptal thickness and the reduced stripe deformation in that area.

Regional function. Systolic wall thickening and circumferential strain can be measured with the tagging sequence where a grid of dark lines is laid across the image (Fig. 9). With contraction, the grid is deformed and can be used to derive myocardial strain. It can also detect LV dyssynchrony by measuring the time interval to maximal wall thickening in different regions (63).

Magnetic resonance imaging studies have shown reduced circumferential shortening in hypertrophied segments with an inverse relation to local thickness and with most shortening occurring in early systole (64,65). Longitudinal shortening is likewise reduced in the basal septum (65). On a global basis, the number of hypokinetic segments is a strong independent predictor of LV mass, confirming the association of LVH with myocardial dysfunction (66).

LV hemodynamic condition. Cine MRI is useful for identifying the presence of MR and its severity (59) as well as SAM (67,68) (see online Appendix for supplemental videos). It is possible to quantify MR volume as the difference between LV and RV stroke volumes or by subtracting aortic flow (by velocity mapping) from LV stroke volume. In patients with SAM, a signal void area is present in the LVOT during systole. This signal reaches its maximal intensity in early systole in patients with severe obstruction (68).

The LV diastolic function can be examined with phase-contrast magnetic resonance to determine mitral E and septal Ea velocities. The E/Ea ratio by magnetic resonance seems to have a good correlation with invasively measured mean wedge pressure (69). Although these initial results are promising, additional studies are needed, including those in patients with HCM. There are also concerns with the MRI technique in unstable patients or those with contraindications to MRI and the long time needed for offline analysis. For the aforementioned reasons, Doppler echocardiography is the method of choice for hemodynamic assessment in HCM patients.

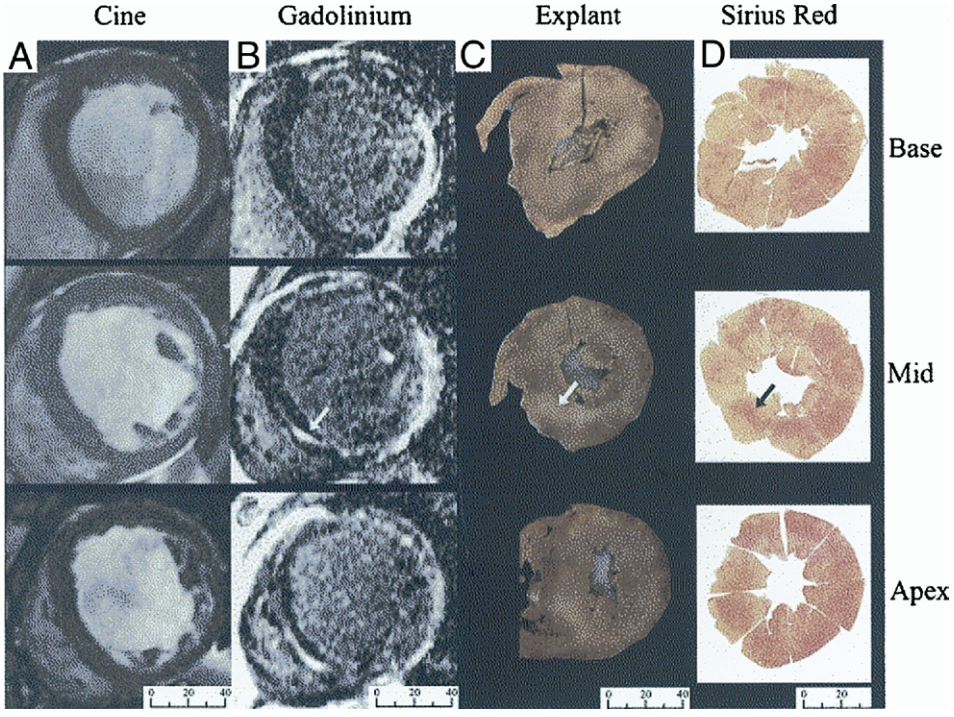

Figure 10. **(A)** In vivo end diastolic images, **(B)** in vivo gadolinium-enhanced images, **(C)** corresponding sections from explanted heart, and **(D)** staining with sirius red for collagen. Areas of gadolinium enhancement correspond to unstained pale myocardium and red-stained collagen. A representative area is marked by the **arrow**. Reproduced with permission from Moon et al. (72).

Tissue characterization. Abnormal areas of hyperenhancement by gadolinium can be noted in some HCM patients. There are different patterns for these areas. In the benign pattern, hyperenhancing areas are present at the junction between the RV and LV. Another pattern is characterized by a patchy distribution in other regions, the extent of which is positively correlated with regional wall thickness and inversely with systolic thickening (70). Furthermore, its overall extent is inversely related to EF and is higher in patients with LV dilation and ≥2 risk factors of sudden cardiac death (71). On histopathology (Fig. 10), these areas correspond to regions of increased collagen but not disarray (72). This is an important area for future research, because MRI might play a critical role in identifying HCM patients who should be considered for primary prevention by automatic implantable defibrillators (AICD) devices. Abnormal gadolinium hyperenhancement has also been noted in the basal infero-lateral wall in patients with Fabry disease (73).

Assessment of results of septal reduction therapy. There are few MRI studies that examined the changes in cardiac structure and function after septal reduction procedures. In 1 series with 37 patients, cine MRI was successfully used before surgical myectomy to grade the severity of SAM and LVOT obstruction with the aorta/LVOT signal ratio. In the 4 patients who were studied after surgery, SAM grade and the aorta/LVOT signal ratio decreased significantly (67).

More recently, MRI was used to study patients who underwent ethanol septal reduction therapy. These carefully performed sequential studies identified several changes. With gradient echo sequences in 10 patients, a continuous and non-linear improvement of the outflow tract area was noted during a 12-month period of follow-up, which correlated well with symptomatic improvement (74). The size of septal infarct averaged 20 ± 9 g (10 ± 5% of the LV). Infarct size by MRI related well with peak creatine kinase leak (75), similar to myocardial contrast echocardiography (29). The LV remodeling was observed early and

Table 3. Comparison of Existing and Potential Roles of Echocardiography, Nuclear Imaging, and MRI in the Evaluation of Patients With HCM

	Echocardiography	Nuclear Imaging	Cardiac MRI
LV dimensions and volumes	+++	+/−	+++
LV wall thickness, mass	+++	+/−	+++
LV EF	+++	+++	+++
Regional function	+++	+	+++
LV filling pressures	+++	+	+
PA pressure: rest and exercise	+++	−	−
LA volume and function	+++	−	+
Dynamic obstruction	+++	−	++
Mitral regurgitation	+++	+	++
Ischemia/CFR	+	+++	+
Cardiac metabolism	−	+++	+
Neurotransmission	−	+++	−
Monitoring of therapy	+++	+	+
Tissue characterization	++	?	++
Pre-clinical diagnosis	++	?	+

CFR = coronary flow reserve; HCM = hypertrophic cardiomyopathy; PA = pulmonary artery; other abbreviations as in Tables 1 and 2.

JACC Vol. 48, No. 12, 2006
December 19, 2006:2410–22

Table 4. Application of Cardiac Imaging for the Risk Stratification of Sudden Cardiac Death in Patients With HCM

Echocardiography
LV maximal wall thickness (≥30 mm)
LV dilatation and depressed EF
Reduced septal Ea in children
LVOT gradient at rest ≥30 mm Hg (better predictor for overall mortality)
Nuclear imaging
Perfusion defects
Reduced coronary flow reserve
Increased MIBG washout rate
Cardiac MRI
LV maximal wall thickness (≥30 mm)
LV dilatation and depressed EF
Late enhancing areas with late gadolinium-enhanced images

LVOT = left ventricular outflow tract; MIBG = metaiodobenzylguanidine; other abbreviations as in Tables 1 and 2.

progressed at 6 months of follow-up. Similar to that observed in echocardiographic studies (32), regression of LVH was observed at remote sites not involved with infarction and the change in LV mass was significantly related to infarct location and the reduction of LVOT gradient (76).

Preclinical diagnosis. A number of studies using ^{31}P nuclear magnetic resonance spectroscopy reported on the presence of abnormal myocardial metabolism in HCM patients (77). In an attempt to identify patients at a preclinical stage, Crilley et al. (78) used this methodology to determine the cardiac phosphocreatine (PCr)/adenosine triphosphate (ATP) ratio in 31 patients. The PCr/ATP ratio was reduced in the HCM group by 30% relative to the control group, including 7 subjects without LVH, suggesting that abnormal cardiac energetics might play a role in development of the disease.

However, with respect to pre-clinical diagnosis, the overlap of values with the control group is an important limitation. It remains to be seen whether this strategy can be used for predicting disease progression, because PCr/ATP ratio might decrease further with the development of hypertrophy and heart failure.

CONCLUSIONS

In summary, imaging can provide important information that is needed for the appropriate evaluation of HCM patients. Each of the imaging modalities discussed in the previous text has its advantages and drawbacks and, depending on the clinical situation, one might need information from 1 or more of these techniques (Table 3). In addition to clinical risk factors, imaging studies can play a critical role in risk stratification for sudden cardiac death (Table 4). However, their full potential remains to be realized.

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Reprint requests and correspondence: Dr. Sherif F. Nagueh, Department of Cardiology, The Methodist DeBakey Heart Center, 6550 Fannin, Suite 677, Houston, Texas 77030. E-mail: snagueh@tmh.tmc.edu.

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APPENDIX

To view videos referenced in the text, please see the online version of this article.