The Case for Myocardial Ischemia in Hypertrophic Cardiomyopathy
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J. Am. Coll. Cardiol. 2009;54;866-875

This information is current as of August 18, 2009

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Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with a prevalence in the general population of 1:500, and characterized by extreme heterogeneity with regard to phenotypic expression, pathophysiology, and clinical course (1–5). HCM is the most common cause of sudden cardiac death in the young, but also a major cause of heart failure disability at any age (6–9). Myocardial ischemia is an established pathophysiologic feature in HCM and may be associated with important disease-related complications that impact clinical outcome, including adverse left ventricular (LV) remodeling and systolic dysfunction (10–20). Nevertheless, for much of the past 50 years, ischemia has been an underappreciated (or unrecognized) component of the HCM disease process, particularly compared with the better-known pathophysiologic mechanisms of LV outflow obstruction (21–23) and diastolic dysfunction (24–26).

Although perfusion defects on thallium-201 single-photon emission computed tomography (SPECT) were convincingly shown in HCM patients more than 25 years ago (27,28), assessment of myocardial ischemia is currently not part of routine clinical diagnostic or management strategies in this disease (4). This limitation almost certainly impacts our capability for providing a more comprehensive evaluation of individual HCM patients.

More recently, a number of studies using contemporary cardiovascular imaging modalities such as positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) imaging have led to an enhanced understanding of the role that myocardial ischemia plays in this complex and heterogeneous genetic disease (12,29–34). Therefore, we believe it is particularly timely to focus attention on the current understanding of myocardial ischemia in HCM and its importance as a potential prognostic marker and to revisit the contribution of contemporary imaging strategies for assessment, as well as possible treatment approaches.
Pathophysiology, Substrate, and Biomarker Evidence for Myocardial Ischemia

Pathologic and hemodynamic evidence. The initial evidence for myocardial ischemia in HCM was derived from post-mortem studies of patients who had died suddenly and in whom extensive areas of myocardial damage were evident. A spectrum of ischemic injury was observed, from an acute phase with coagulative necrosis and neutrophilic infiltrate to a chronic post-necrotic replacement-type fibrosis, always in the absence of atherosclerotic epicardial coronary artery disease (35).

In addition to gross pathologic evidence of myocardial scarring, autopsy studies in HCM patients have shown structural abnormalities of intramural coronary arterioles, characterized by thickening of the intima and/or medial layers of the vessel wall associated with decreased luminal cross-sectional area (Fig. 1) (35–40). Indeed, these morphologic abnormalities of the intramural coronary arterioles (i.e., small vessel disease) most likely represent the primary morphologic substrate for microvascular dysfunction (i.e., impaired vasodilatory capacity) and its functional consequence, that is, blunted myocardial blood flow (MBF) during stress (i.e., hypoperfusion) (41–43).

Periods of abnormal MBF occur in patients with HCM because of the increased myocardial oxygen demand of the hypertrophied ventricular myocardium, and in patients with LV outflow tract obstruction metabolic demand is further increased because of the greater workload induced by substantially elevated intraventricular pressures. Although not all episodes of abnormal MBF lead to ischemia, such circumstances arise frequently enough during the clinical course of an HCM patient that absolute MBF can be regarded as a surrogate for myocardial ischemia. Other structural abnormalities, including myocyte disarray, increased interstitial (matrix) fibrosis, and reduced capillary density, may also contribute to impairment of MBF in HCM (44–48).

Biomarker evidence. During the mid-1980s, elegant invasive cardiac catheterization studies provided the most compelling and direct evidence for the presence of myocardial ischemia in HCM (11,49–51). In the absence of epicardial coronary artery disease, patients showed decreased lactate consumption (sampled from the great cardiac vein via the coronary sinus) during rapid atrial pacing in association with decreased venous flow and elevated LV end-diastolic pressures (52).

Because the great cardiac vein is responsible for venous drainage from the vascular territory supplying the anterior septum (the most common location for LV hypertrophy in HCM), these findings were regarded as evidence of myocardial ischemia (11). Furthermore, elevations in serum biomarkers of cardiac injury (i.e., troponin) have also been documented in this disease (53). Because increases in troponin show high specificity for myocyte cell death, this observation provides further evidence for a process of subclinical myocardial ischemia.

Therefore, it was more than 25 years after the contemporary description of HCM in 1958 that evidence from post-mortem and invasive hemodynamic studies convinc-
ingly showed that myocardial ischemia occurs in this disease. Indeed, the consequences of repetitive bouts of ischemia include myocyte death and associated myocardial replacement fibrosis leading to adverse LV remodeling in the form of regional replacement fibrosis and loss of myocyte function. This will result in altered diastolic function, and in some patients, progression to systolic dysfunction (i.e., the end-stage phase of HCM) (Fig. 2).

**Noninvasive Assessment of Microvascular Function and Myocardial Ischemia**

Currently, no technique allows the direct visualization of the coronary microcirculation in vivo in humans. Therefore, the assessment of myocardial ischemia relies on the measurement of parameters such as MBF that reflect microvascular dysfunction. Over the past 3 decades, several noninvasive tests have assessed coronary microvascular function and myocardial ischemia in patients with HCM (Table 1).

**PET.** The most reliable noninvasive method for assessing myocardial ischemia in HCM by quantitative measurement of its surrogate MBF (29,54) is PET with either 13N-labeled ammonia or 15O-labeled water. The measurement of MBF under basal conditions and in conditions of near-maximal vasodilatation (after intravenous adenosine or dipyridamole) permits calculation of coronary flow reserve, that is, the ratio of maximum to basal MBF. In the absence of obstructive epicardial coronary disease, flow resistance is primarily determined by the microvasculature (>90% of coronary resistance resides in arterioles <300 μm in diameter), and therefore a reduced coronary flow reserve (and MBF) are markers of coronary microvascular dysfunction (17).

In patients with HCM, PET studies have shown that although resting MBF is similar to that of normal control subjects, the increase of blood flow after dipyridamole infusion is significantly blunted, reflecting an inability to increase myocardial perfusion to match increased demand (10,30,55,56). For example, maximum MBF after dipyridamole stress in HCM patients is often <2 ml/min/g, compared with an average of 4 ml/min/g in healthy control subjects. Furthermore, flow abnormalities are most profound in the subendocardium, including reduced flow in areas of myocardium contiguous to segments in which perfusion is preserved (10). Therefore, although MBF is often markedly impaired in the hypertrophied ventricular septum, it may also be reduced in the nonhypertrophied portions of the LV wall (10). These observations suggest a primary and diffuse impairment of coronary microvascular function in HCM, a finding that is supported by postmortem studies showing evidence of abnormal intramural coronary arterioles distributed throughout the LV myocardium (35,38,40). In addition, abnormalities of MBF during dipyridamole stress are more pronounced in the subendocardial layer compared with the subepicardium (Figs. 3A and 3B), consistent with the SPECT finding of transient ischemic dilatation (10,17,30).

**CMR.** CMR provides 3-dimensional tomographic imaging of the heart with high spatial and temporal resolution, in any plane and without ionizing radiation (33,57,58). After
the first pass of intravenous gadolinium administration, CMR perfusion sequences permit both qualitative and quantitative assessment of MBF at rest and during pharmacologic stress (typically adenosine) with superior spatial resolution compared with PET or SPECT (33,34,58). Furthermore, after a delay of approximately 10 to 15 min after the acquisition of the first-pass perfusion images, late gadolinium enhancement (LGE-CMR) sequences can identify the presence (and quantitatively measure the extent) of myocardial fibrosis in HCM patients (32,59–61). Evidence that areas of LGE represent myocardial fibrosis in HCM can be found in a small number of case reports of

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CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; LAD = left anterior descending coronary artery; LV = left ventricular; MBF = myocardial blood flow; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

(A and B) A 23-year-old patient with HCM and massive asymmetric ventricular septal hypertrophy (wall thickness 39 mm). At baseline (A), an area of reduced 13-N-ammonia uptake by PET can be seen at the base of the anterior papillary muscle (11 o’clock position; arrow). (B) PET after dipyridamole stress, in which myocardial blood flow increases more substantially in the subepicardial than in the subendocardial ventricular septum (VS) as well as the contiguous anterior LV wall (Ant. FW). (C and D) Relationship of abnormal myocardial blood flow by PET and areas of myocardial fibrosis by contrast-enhanced CMR. (C) A PET short-axis slice at the basal LV level in a patient with HCM, with color scale showing highest myocardial blood flow in red and lowest in green. (D) In the same patient, after intravenous infusion of gadolinium, a corresponding short-axis contrast-enhanced CMR image showing areas of late gadolinium enhancement (bright) that match closely to the identical areas of abnormal myocardial blood flow by PET. Reprinted, with permission, from Sotgia et al. (65). CMR = cardiovascular magnetic resonance; PET = positron emission tomography; other abbreviations as in Figure 1.
end-stage patients in which concordance has been shown between in vivo LGE-CMR images and gross and histopathological findings of fibrosis in native hearts after transplantation (62,63). Therefore, CMR affords an opportunity to provide insights into the pathophysiology of myocardial ischemia in HCM by matching areas of abnormal perfusion with other important morphologic findings such as segmental LV hypertrophy and fibrosis.

Similar to PET, a recent stress CMR study in HCM showed blunted MBF in response to stress. In addition, MBF was reduced to a greater degree in the subendocardial compared with the subepicardial layer, and also the degree of abnormal perfusion related to magnitude of wall thickness (34). Importantly, areas of myocardium in which fibrosis was present (as determined by LGE) were most often associated with reduced MBF (34). Furthermore, hyperemic flow was substantially reduced in LV segments occupied by LGE as well as severely blunted in areas situated adjacent to myocardial fibrosis (Figs. 3C and 3D) (64,65). Taken together, these CMR observations show an association between ischemia, myocardial fibrosis, and LV remodeling, providing further support for the principle that abnormal MBF caused by microvascular dysfunction is responsible for myocardial ischemia–mediated myocyte death, and ultimately repair in the form of replacement fibrosis.

Finally, abnormalities of MBF assessed with PET and detection of myocardial fibrosis with contrast-enhanced CMR have also been shown previously in patients with LV hypertrophy caused by longstanding pressure overload from systemic hypertension or aortic stenosis, as well as other cardiomyopathies (e.g., Anderson–Fabry disease) (29). Based on these studies, we conclude that diffuse impairment in the coronary microvasculature leading to ischemia and ultimately myocardial scarring is not a process unique to HCM and occurs in a similar fashion in other forms of primary and secondary LV hypertrophy.

Radionuclide myocardial perfusion imaging. Using the potassium analogue thallium-201 or the $^{99m}$Tc labeled compounds as perfusion tracers (11,16,27,28,66,67), SPECT myocardial perfusion imaging has shown both fixed and reversible myocardial perfusion defects in HCM patients. Fixed defects are more often associated with reduced systolic function, lower peak oxygen consumption, and increased LV cavity dimensions, and consequently have been regarded as areas of myocardial scarring (16). Reversible defects induced by exercise have been considered markers of myocardial ischemia based on high concordance with metabolic evidence of ischemia induced by pacing or infusion of sympathomimetic drugs (11). That reversible defects reflect a dynamic abnormality of coronary microvascular function is also suggested by the reduction of such defects reported with verapamil therapy (66). In HCM, SPECT imaging has also shown stress-induced transient cavity dilatation, suggestive of diffuse subendocardial ischemia. Although SPECT imaging is widely available, this technique is limited by allowing only the assessment of relative changes in regional perfusion and by an inability to quantify absolute MBF.

Electrocardiographic monitoring. Traditional, noninvasive methods for detecting myocardial ischemia clinically, including ST-segment changes on 12-lead and ambulatory Holter electrocardiographic monitoring or exercise testing, have proved to be insufficiently sensitive or specific for detecting ischemia in HCM (17). ST–segment depression during Holter monitoring occurs commonly in HCM patients both during exertion and while sedentary, but has not been consistently linked with either chest pain or perfusion abnormalities on SPECT imaging (68).

Clinical Evidence for Ischemia

Chest pain symptoms are a frequent complaint among 25% to 50% of HCM patients (3,4,68). Episodes of chest pain in patients with HCM can be prolonged and atypical in character, occurring frequently under resting conditions (69), but also may be consistent with classic angina pectoris provoked with exertion and after meals (68). However, the relationship among the various types of chest pain encountered in HCM and active myocardial ischemia is at present unresolved. In those HCM patients with typical angina in whom suspicion of underlying epicardial coronary artery disease is increased based on more advanced age, assessment of traditional coronary risk factors and pertinent noninvasive testing, coronary angiography (or alternatively cardiac computed tomographic angiography) should be considered to exclude obstructive atherosclerotic coronary artery disease (70) as well as other causes of chest pain (e.g., myocardial bridging or congenital coronary artery anomalies).

Electrocardiographic changes consistent with ischemia such as ST–segment depression may occur frequently during exercise testing and Holter monitoring, but are most often not associated with chest pain (27,68). Consequently, a clear association between chest pain and microvascular ischemia has not been established in HCM, suggesting that ischemia often occurs silently (11). In one study of young asymptomatic HCM patients, reversible thallium perfusion defects were present in about 50% of patients, supporting the concept of clinically silent ischemia (66). In addition, no consistent relationship has been established between chest pain and LV wall thickness, outflow obstruction, or other HCM disease features (3).

Verapamil and beta-blockers may improve symptoms of chest pain and exertional dyspnea in HCM. This probably occurs via reduction in heart rate and oxygen consumption (beta-blockers), and possibly because of direct effects on the microvasculature and diastolic filling (verapamil), leading to redistribution of transmural MBF and improved subendocardial perfusion (56). In this regard, verapamil has been shown to decrease or eliminate reversible myocardial perfusion abnormalities on SPECT imaging, and therefore is
generally the preferred initial therapy for treating predominant chest pain symptoms in HCM patients (4). Also, in recognition of the known clinical benefit of septal reduction therapies in reducing subendocardial ischemia, consideration should be given to these procedures to relieve outflow obstruction in HCM patients with advanced symptoms of severe debilitating chest pain refractory to drug therapy (49). In this regard, there is now evidence showing an improvement in myocardial perfusion after septal reduction therapy (71).

Clinical Significance of Myocardial Ischemia

Observations with PET. Although a number of observations had been made defining the presence of myocardial ischemia in HCM over the last 25 years (16,19,20,27,49,52,67), it was the study by Cecchi et al. in 2003 (12) that provided the initial evidence that ischemia does in fact have important prognostic disease consequences. In a cohort of 51 HCM patients followed prospectively for more than 8 years after identification of ischemia by PET, a dipyridamole MBF in the lowest tertile proved to be a powerful independent predictor of cardiovascular mortality (Fig. 4) (12). Specifically, increased risk was associated with MBF <1.1 ml/g/min with a relative risk of 9.6 for cardiovascular death and 20.0 for unfavorable outcome. Although at the time of the initial PET studies none of the patients had severe limiting symptoms and few were regarded as high-risk for disease progression, impaired MBF after dipyridamole nevertheless predicted subsequent major cardiovascular events.

Furthermore, patients with the greatest impairment of MBF were more likely to experience long-term LV remodeling with end-diastolic LV chamber enlargement and wall thinning, and decline in systolic function (i.e., to the end-stage) (Fig. 4) (72). Specifically, all patients in this cohort who subsequently progressed to the end stage, and in whom severe heart failure symptoms developed were in the...
lowest tertile of dipyridamole MBF flow at study entry. Therefore, severe abnormalities in MBF caused by microvascular dysfunction seemed to be a powerful determinant of impaired systolic function, whereas preserved MBF identified the low-risk subgroup (72). Finally, the proportion of patients who received potential anti-ischemic pharmacologic agents (such as beta-blockers or calcium-channel blockers) was statistically similar within each tertile of MBF both at the time of PET and during follow-up.

This study was not designed to determine the primary benefit of these anti-ischemic agents on clinical outcome. On the other hand, in another study, verapamil reversed or eliminated stress-induced perfusion abnormalities (presumably from small vessel disease) on SPECT imaging (66). Although this study did not address whether the benefit in reducing perfusion defects with verapamil improved outcome. Nevertheless, it would be reasonable to consider such therapy in HCM patients with evidence of myocardial ischemia. Given the paucity of data presently available with regard to the benefit of medical intervention on improving microvascular function, it would seem premature to offer a strong recommendation for repeat imaging to assess potential changes in the presence or magnitude of ischemia after treatment.

Consequently, the assessment of myocardial ischemia in select patients with HCM (with preserved LV function) may represent a prognostic tool for identifying those patients at risk for profound disease progression. This has important clinical implications because HCM patients in the end stage experience a high rate of unfavorable disease consequences, including progressive heart failure (often requiring heart transplantation) and sudden unexpected death (prompting consideration for prophylactic defibrillator implantation). Therefore, it would seem prudent for HCM patients with severely blunted MBF to undergo regular clinical surveillance (with echocardiography) for prospective detection of changes in heart failure symptoms and LV remodeling (Fig. 5). However, currently, we cannot strongly advocate for all HCM patients to undergo routine imaging for ischemia given that relevant data are confined to a single-center study (12). Therefore, until additional prospective studies assessing ischemia in HCM are undertaken, the decision concerning which patients should undergo routine imaging remains unresolved. Nevertheless, at the present time, consideration could be given to assessing myocardial ischemia in select HCM patients, in whom concern persists regarding prognosis after conventional risk assessment.

**Observations with CMR.** Several recent studies in HCM provide potential insights into the clinical implications of LGE and ischemic myocardial damage (15,59–61,73). The presence of LGE has been associated with the development of heart failure symptoms and an inverse relationship is evident between the extent of LGE and ejection fraction (59–61); patients who showed the most marked reduction in ejection fraction ≤50% (i.e., end-stage phase) had the most extensive LGE compared with HCM patients with preserved systolic function (61). Furthermore, the presence of LGE (but not extent) has been associated with ventricular tachyarrhythmias (including rapid ventricular tachycardia) present on ambulatory 24-h Holter electrocardiogram, suggesting that contrast-enhanced CMR may define the unstable arrhythmogenic substrate in HCM, and that LGE could ultimately serve as a risk marker for sudden death (73).

However, at present, sufficient follow-up data are not available to clarify whether LGE is an independent risk factor for sudden death in HCM. Therefore, it is probably premature to make any firm assumptions regarding the role of LGE in risk stratification for sudden death. We would not advocate implantable cardioverter-defibrillator (ICD) therapy solely on the presence of LGE (i.e., in the absence of any conventional high-risk features). Nevertheless, al-
though definitive data are not yet available, it is likely that some weight can be given to extensive areas of LGE as an arbitrator in reaching recommendations for prophylactic ICDs in selected patients, particularly when ambiguity remains concerning individual patient sudden death risk after an assessment of the conventional risk markers (73,74). Therefore, the use of contrast-enhanced CMR to detect LGE may be relevant to clinical decision making and considerations for prophylactic ICD therapy in individual patients (Fig. 5).

Future Research Considerations

Identification (by imaging) and potential therapeutic strategies for microvascular ischemia in HCM are at an early stage and requires additional investigative effort, given that most of our understanding regarding the clinical significance of myocardial ischemia in HCM is derived from a limited number of single-center studies. Consequently, there is a need for future research considerations to be directed toward forming larger prospective and well-designed multicenter studies to determine: 1) when active myocardial ischemia begins with respect to the development of the HCM phenotype, that is, does ischemia precede the development of LV hypertrophy and, therefore, could be considered an early therapeutic target; 2) the pathophysiologic relationship between ischemia and the development of myocardial fibrosis (i.e., LGE); 3) the relationship of clinical symptoms, such as chest pain, to ischemia and whether biomarkers can identify patients with active, ongoing myocardial ischemia; and 4) more precisely the contribution of both ischemia and fibrosis to stratification of risk in HCM. Such well-designed studies will also help provide further insights into which HCM patients will derive the greatest benefit from implantation of primary prevention defibrillators, and limit excessive and unnecessary testing.

There is also a great need to identify pharmacologic therapies aimed at mitigating ischemia. In this regard, there is currently interest in drugs such as spironolactone, which inhibit the renin-angiotensin-aldosterone system and could improve coronary microvascular function. Although no formal clinical studies have been completed using such drugs in HCM, evidence derived from patients with hypertensive heart disease (in which there are structural abnormalities of the intramural arterioles and resultant replacement fibrosis similar to HCM) (75), and from transgenic mouse models of HCM, has shown that drugs which inhibit the renin-angiotensin-aldosterone system can reduce both coronary microvascular remodeling and fibrosis and improve diastolic function (76,77). As a result, future clinical investigations directed at assessing the efficacy of such drugs and their role in decreasing myocardial ischemia and fibrosis (using PET and CMR) may well prove informative and clinically relevant.

Clinical Implications for Management and Conclusions

It is now evident that myocardial ischemia caused by microvascular dysfunction occurs in the HCM population (reported largely from tertiary centers) and is an important pathophysiologic component of this complex disease process, promoting LV remodeling and impacting on clinical course and outcome (12,15,20,29,35,59–61,72). Recently there has been substantial progress in identifying the presence and quantifying the magnitude of myocardial ischemia and its sequelae (i.e., myocyte death and replacement fibrosis) with contemporary imaging modalities having broad applications in cardiovascular medicine. The pathophysiologic cascade of events, beginning with the morphologic and functional abnormalities of the intramural coronary arterioles promoting blunted MBF during stress, and leading to myocardial ischemia and eventually replacement fibrosis, is a likely therapeutic target for favorably altering the disease phenotype. Future investigative efforts will focus on creating diagnostic methods for detecting myocardial ischemia before adverse LV remodeling begins so that targeted treatment strategies can be developed to mitigate ischemia and alter the natural history of HCM.

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Key Words: hypertrophic cardiomyopathy • myocardial ischemia • fibrosis • MRI • PET.
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