Is there a role for cardiac positron emission tomography in hypertrophic cardiomyopathy?

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Coronary microvascular dysfunction and, its functional consequence, myocardial ischemia are common pathologic features in patients with hypertrophic cardiomyopathy (HCM). Both have been commonly invoked as potential triggers of and/or contributors to the underlying pathophysiological processes leading to heart failure, and malignant ventricular arrhythmias. Positron emission tomography (PET) with myocardial blood flow quantification provides a unique opportunity to evaluate the integrity and function of the coronary microcirculation in HCM. The purpose of the present review is to summarize all the pertinent literature and future perspectives of the role of PET in the evaluation and risk stratification of patients with HCM. (J Nucl Cardiol 2019;26:1125–34.)

Key Words: Basic science • Diseases/processes • Modalities • Tests

Abbreviations

HCM	Hypertrophic cardiomyopathy	MFR	Myocardial flow reserve
MBF	Myocardial blood flow	CMD	Coronary microvascular dysfunction
SCD	Sudden cardiac death	CAD	Coronary artery disease
LGE	Late gadolinium enhancement	VT	Ventricular tachycardia
MPI	Myocardial perfusion imaging		

See related editorial, pp. 1135–1137

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is considered the most common inherited cardiovascular disorder with a prevalence of approximately 0.2% in the general population.[1] HCM affects people of all ages and is characterized by a heterogeneous clinical expression, and diverse clinical course, in which most individuals remain asymptomatic throughout life, whereas others develop angina, heart failure, stroke, or sustained tachyarrhythmias, which could ultimately result in sudden cardiac death (SCD), the most dreaded complication of HCM.

Myocardial ischemia has been traditionally considered a key actor in the pathophysiology of HCM, including the transition to symptomatic disease. Earlier evidence suggested the clinical importance of myocardial

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ischemia, in particular for possible risk stratification in HCM. Yet, with the advent of cardiac magnetic resonance (CMR) imaging, investigation of myocardial fibrosis with late gadolinium enhancement (LGE) became the norm, and with that, the clinical and investigational interest in myocardial ischemia in HCM decreased substantially. On the other hand, cardiac positron emission tomography (PET) has become the gold standard technique for quantification of myocardial blood flow (MBF), a method that appears to be superior to myocardial perfusion scintigraphy, especially for the evaluation of microvascular ischemia. Consequently, a renewed interest exists in the added contribution of MBF quantification, to the clinical information provided by echocardiography and LGE-CMR. The aim of the present review is to summarize the most relevant literature related to current and potentially future applications of cardiac PET in the evaluation and management of patients with HCM.

GENESIS AND PREVALENCE OF MYOCARDIAL ISCHEMIA IN HCM

The etiology of myocardial ischemia is not fully understood, but based on our current understanding, it appears to result from a combination of structural and functional alterations. Firstly, marked arterial wall thickening and luminal narrowing of the intramural coronary microvascular network,[2,3] and reduced capillary density (reduced number of capillaries per cross-sectional myocardial area),[4,5] lead to coronary microvascular dysfunction (CMD), whereas increased left ventricular (LV) intracavity pressures[6] and metabolic demand of the hypertrophied myocardium[7] are factors that may further contribute to impaired myocardial flow reserve (MFR; the ratio of stress MBF to rest MBF) and the development of subendocardial myocardial ischemia in HCM.

The prevalence of clinical or subclinical myocardial ischemia varies significantly in HCM ranging between 22 and 80% (mean roughly $\sim$ 45%) depending on the case series, and diagnostic method employed (Table 1). Elliot et al.[8] found that 27% of examined patients had transient electrocardiographic episodes of ischemia ($\geq$ 1 mm ST-segment depression from baseline) on ambulatory 48-hour Holter monitoring, whereas abnormal myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) suggestive of ischemia is present in 22%-52% of unselected HCM patients. Inducible ischemia by means of invasive investigation has been elicited in up to 62% of selected patients.[9] Moreover, post-mortem data suggest that changes consistent with CMD can be seen in up to 83% of necropsies of individuals with HCM, and that the prevalence of CMD is equally high in patients with (79%) and without (85%) clinical history of chest pain prior to death.[2] This data clearly underscores the high prevalence of clinical and subclinical myocardial ischemia in HCM.

IMPAIRED MYOCARDIAL FLOW RESERVE AS A MARKER OF MICROVASCULAR DYSFUNCTION

Cardiac PET offers several advantages from an instrumentation perspective over SPECT, including higher spatial resolution of the reconstructed axial image (3.9-5.8 mm vs. $\sim$ 10 mm at 10 cm), superior detection sensitivity for identification of tissue radiotracer concentration, better temporal resolution, and improved correction methods for photon scatter and photon attenuation (Figure 1).[10] PET tracers such as ^{13}N-ammonia ($^{13}NH_3$) and ^{15}O-water also have superior pharmacokinetic properties due to a greater myocardial net uptake rate at higher coronary flows compared to their SPECT counterpart.[11] But perhaps, one of the most important properties that distinguishes PET is its capability for data acquisition in dynamic sequences to delineate tracer kinetics, which ultimately allows for MBF quantification, usually provided in milliliter per minute per gram of tissue ($ml \cdot minute^{-1} \cdot g^{-1}$).

PET has been extensively validated for the non-invasive quantification of MBF at baseline and during pharmacologic stress in pre-clinical and clinical studies.[12-17] Myocardial flow reserve is the ratio of stress MBF to rest MBF, in other words, the maximum MBF achieved during exercise or pharmacologic stress above the resting or baseline MBF. Normal values for MFR continue to be a matter of debate, but in general MFR > 2.5 is considered within the limits of normal, and < 2.0 is regarded as abnormal. Values between 2.0 and 2.5 are in the low-normal range, and usually occurs in subjects with one or more cardiovascular risk factors.[18,19] Importantly, MFR is influenced by any factors affecting the resting and/or stress MBF. For example, factors augmenting myocardial oxygen consumption and metabolic demand, such as tachycardia, hypertension, aging, and chronic kidney disease, may increase MBF at rest, and potentially exacerbate the impact of impaired MFR.[17] In contrast, stress MBF is less affected by such factors, but is usually impaired by the presence of flow-limiting coronary artery disease (CAD), and/or CMD. Accordingly, in the absence of obstructive CAD, impaired stress MBF, and thereby MFR, is considered a surrogate marker of CMD (Figure 2).

PREDICTORS OF ABNORMAL MYOCARDIAL FLOW RESERVE IN HCM

PET studies have demonstrated that patients with HCM have a wide range of MFR at diagnosis, with many patients showing normal values, and others

Table 1. Prevalence of chest pain and ischemia in HCM

Author (journal and year)	N	Chest pain N (%)	Diagnostic modality	Ischemia definition	Ischemia N (%)
Maron (JACC 1986)	48	19 (40)	Necropsy	Small vessel disease	40 (83)*
O'Gara (Circulation 1987)	72	36 (50)	^{201}Tl-SPECT	Reversible defects	24 (33)
Udelson (Circulation 1989)	29	5 (17)	^{201}Tl-SPECT	Reversible defects	14 (48)
Cannon III (Circulation 1991)	50	40 (80)	Atrial pacing	Cardiac lactate extraction	31 (62)
Elliott (EHJ 1996)	94	56 (60)	48-hr Holter	$\geq$1 mm ST depression	25 (27)
Sorajja (AHJ 2006)	158	75 (47)	^{201}Tl-SPECT	SDS $\geq$ 1	83 (52)
Yamada (EHJ 2008)	216	77 (36)	^{201}Tl-SPECT	SDS $>$ 1	48 (22)
Bravo (Circ Imaging 2013)	47	38 (60)	$^{13}NH_3$ PET	MFR $<$ 2.0	18 (38)
Total	714	346 (48)			317 (44)

SDS, Summed difference score; *MFR*, myocardial flow reserve
*Pathologic findings consistent with coronary small vessel disease are used as a surrogate for subclinical or clinical ischemia

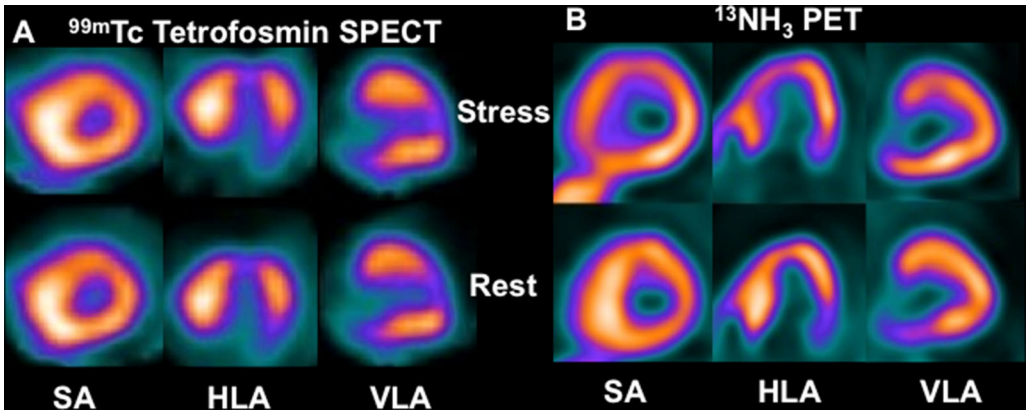

Figure 1. Cardiac SPECT (**A**) and PET (**B**) images (8 months apart) of a 24-year-old woman with hypertrophic cardiomyopathy and intractable chest pain. SPECT depicts similar regional myocardial perfusion at stress and rest images. Whereas $^{13}NH_3$ PET showed moderate-to-severely decreased perfusion preferentially in the subendocardium of the septum and anterior wall during vasodilator stress compared to rest images, consistent with myocardial ischemia. This highlights the superior diagnostic capability of PET compared to SPECT. *SA*, Short axis; *HLA*, horizontal long axis; *VLA*, vertical long axis.

exhibiting severely reduced MFR.[20] The reasons for this MFR heterogeneity in HCM are not completely understood but there appears to be a pre-determined or inherited component. This was suggested by Olivotto et al.[21] in a study where the investigators observed significantly lower stress MBF (1.7 ± 0.6 ml·minute^{-1}·g^{-1} vs. 2.4 ± 1.2 ml·minute^{-1}·g^{-1}; $P < .02$) by PET as well as higher prevalence of LGE (96% vs. 67%, $P = .038$) by CMR in patients testing positive for myofilament-encoding genes compared to genotype-negative HCM patients despite similar baseline characteristics, including maximal LV wall thickness, between groups.[21] This study suggested that certain genetic mutations causing HCM may represent a major determinant of microvascular remodeling in HCM and set the ground to future studies exploring the effect of HCM-causing mutations (e.g., in phenotype-negative cohorts) on the development of CMD.

An inverse correlation between stress MBF (and thus MFR), measured by PET or CMR, and maximal LV wall thickness has been consistently observed in HCM.[20,22,23] Ex vivo studies have provided important morphologic and histopathologic correlations in this respect.[5,24,25] Tanaka et al. observed that the percentage of luminal narrowing of intramural coronary vessels was inversely correlated with heart weight and myocyte size

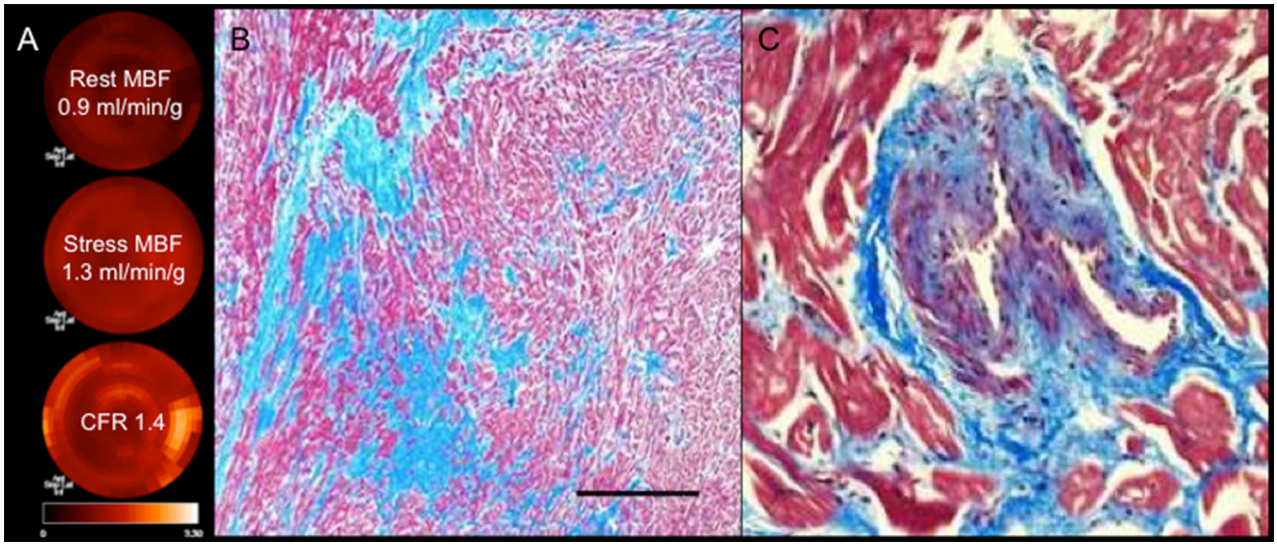

Figure 2. In vivo and ex vivo evidence of severe coronary microvascular dysfunction in HCM (same patient from Figure 1). (**A**) Quantitative flow polar maps derived from $^{13}NH_3$ PET revealed nearly blunted CFR. Patient eventually underwent orthotropic heart transplantation due to intractable angina. (**B**) Histopathology of the explanted heart showed areas of patchy fibrosis (blue) replacing clusters of myocytes in the anteroseptal wall (Masson trichrome stain, scale bar = 1 mm). (**C**) A dysplastic intramural coronary vessel (10×) with significant luminal narrowing associated with medial smooth muscle hyperplasia, irregular medial thickening, and fibrosis within the wall (blue). Courtesy of Charles Steenbergen, MD, PhD, Johns Hopkins Hospital.

in the LV septum and free wall during necropsies of individuals with HCM.[24] Similarly, Krams et al. described an inverse relationship between normalized coronary arteriolar lumen and degree of LV hypertrophy in myectomy specimens of HCM patients.[5] Impaired MFR and myocardial ischemia are also significantly more prevalent in the presence of myocardial fibrosis (Figures 2, 3).[23,26,27] In the absence of LGE, for example, patients with HCM usually exhibit normal (or close to normal) global MFR without regional flow heterogeneity; however, when LGE is present, global MFR is impaired in approximately half of symptomatic HCM patients, with LGE-positive (fibrotic) myocardial segments exhibiting significantly lower peak-MBF than remote LGE-negative (non-fibrotic) myocardial segments.[27] Post-mortem series have yielded similar findings.[2,24] Baron et al. evaluated 48 necropsies of patients with HCM and observed a significantly higher frequency of CMD in myocardium tissue sections that exhibited moderate or severe fibrosis (74%) compared to sections with mild or no fibrosis (30%).[2] Given the strong association that exists between myocardial ischemia and fibrosis in HCM, it has been postulated that fibrosis may be the result of repetitive episodes of myocardial ischemia. However, the causal relation between ischemia and fibrosis is not definitive, since both ex-vivo[28] and in-vivo[27] studies have shown that myocardial fibrosis can occur in approximately 8% of the cases in the absence of clinically relevant CMD (Figure 3), indicating that myocardial ischemia, while important, is likely not the sole cause for the development of myocardial fibrosis in HCM.

Taking together, these data highlight the interrelation that seems to exist between impaired MFR (or CMD), genetic-predisposition, hypertrophy, and fibrosis in HCM.

CLINICAL IMPLICATIONS OF IMPAIRED MYOCARDIAL FLOW RESERVE IN HCM

The clinical manifestations that have been associated with impaired MFR are likely mediated by the induction of myocardial ischemia and are quite diverse in HCM, ranging from asymptomatic,[29,30] to chest pain,[6,8] dyspnea, heart failure progression,[9,31] and even potentially triggering malignant ventricular arrhythmias (VA).[32,33]

Chest pain is likely the most common clinical expression of impaired MFR with a prevalence of approximately 50% based on multiple HCM series (Table 1). The character of chest pain can be indistinguishable from that of typical angina pectoris, or can be quite atypical, occurring at rest and for long periods of time.[8] Importantly, CAD is not uncommon among HCM patients and its recognition is particularly relevant. This was evidenced by a study from the Mayo Clinic, which

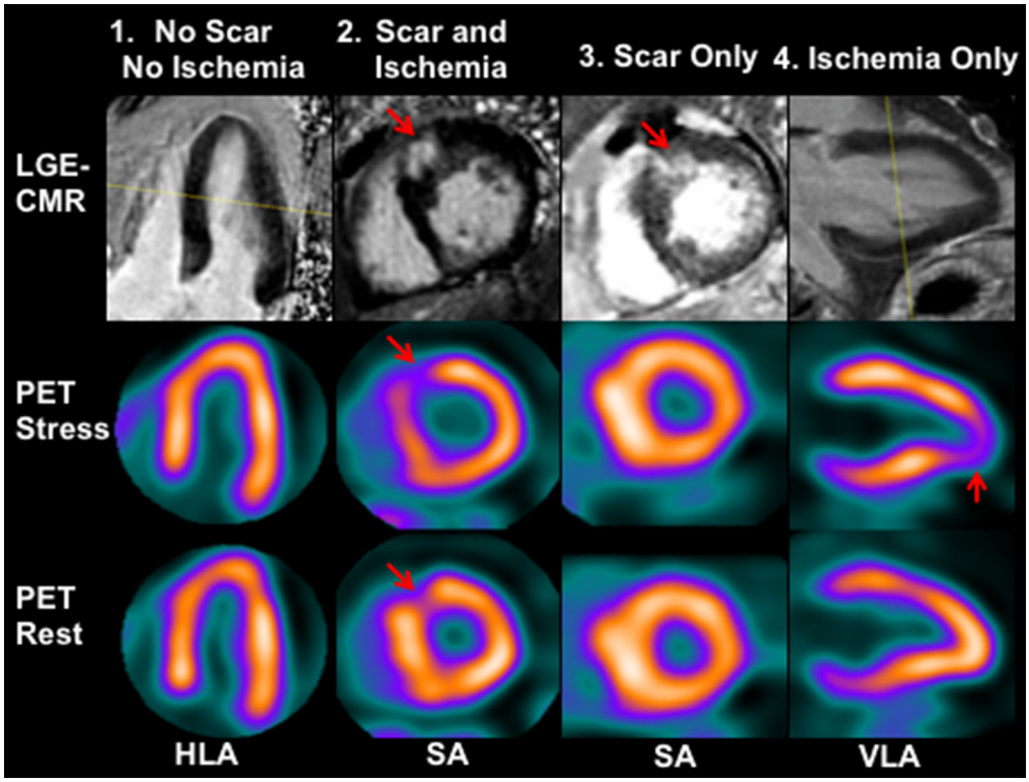

Figure 3. Patients with HCM can be segregated into four groups based on LGE status on CMR and myocardial perfusion PET findings: (**1**) negative LGE and normal myocardial perfusion, (**2**) matched LGE and myocardial ischemia on PET (red arrows), (**3**) LGE on CMR (red arrow) with normal myocardial perfusion on PET, and (**4**) evidence of myocardial ischemia on PET (red arrow) but negative LGE on CMR. *HLA*, Horizontal long axis; *SA*, short axis; *VLA*, vertical long axis.

evaluated 433 HCM patients who underwent invasive coronary angiography between 1972 and 2000.[34] The incidence of severe CAD was 26% (n = 114), and the 10-year overall survival was significantly lower in patients with severe CAD (46.1%), compared to those with mild-to-moderate CAD (70.5%), or no CAD (77.1%; adjusted $P = .0006$).[34] Given the significant symptom overlap between HCM and CAD, and the clinical implications of this latter diagnosis, it is imperative that obstructive epicardial CAD be excluded in older patients and/or those with risk factors for CAD. In this regard, normal MPI along with preserved quantitative MFR by PET may be enough to exclude hemodynamically significant CAD, whereas the presence of abnormal MPI, especially coupled with depressed MFR, will require further definition of the coronary anatomy in those with atherosclerotic risk factors by means of invasive or computed tomography coronary arteriography to assure that PET findings are indeed the result of CMD and not obstructive CAD (Figure 4).[35]

On the other hand, not all HCM patients who complain of chest pain have evidence of inducible ischemia on PET, in the same way as there are patients with impaired MFR on PET whose main clinical feature is dyspnea and not chest pain; moreover, there is evidence that HCM patients with clinical findings of heart failure usually have impaired MFR by PET. A previous study found an inverse relationship between MFR and New York Heart Association (NYHA) functional class in HCM.[31] NYHA class I patients (n = 53) had the highest MFR (1.93 ± 0.64), while NYHA class III individuals (n = 7) showed the lowest MFR (1.40 ± 0.43; $P \leq .05$). Furthermore, the potential role of impaired MFR in the genesis of heart failure was suggested in a study by Olivotto et al.[36] In this observational prospective study, 51 HCM patients had ammonia PET at baseline and were then followed for 8.1 ± 2 years. The investigators found that patients who developed LV systolic dysfunction on follow-up (n = 11) had a significantly lower stress MBF at baseline (1.04 ± 0.38 vs. 1.63 ± 0.71 ml·minute^{-1}·g^{-1}; $P = .001$) than those individuals who remained with preserved LV systolic function (n = 40).[36] Additional data also suggest that patients with reduced MFR may have a higher prevalence of atrial fibrillation,[37] as stress

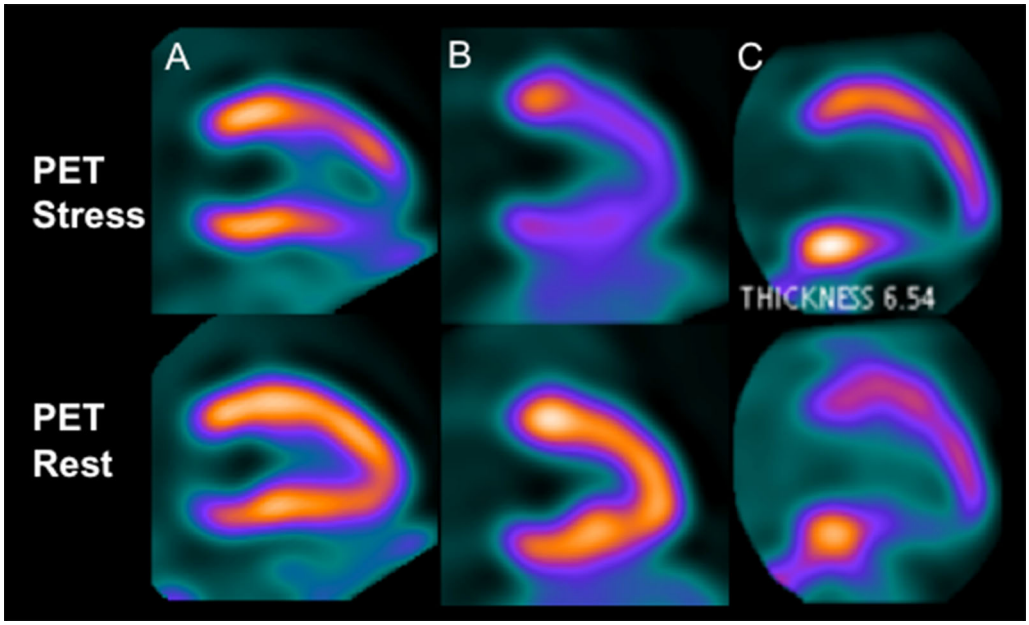

Figure 4. Vertical long axis $^{13}NH_3$ cardiac PET images of three different patients with HCM. **A** demonstrates severe ischemia in the distal inferior wall and apex, and mild ischemia in the mid-anterior wall. **B** has a large area of severe ischemia involving the entire inferior wall and apex and most of the anterior wall. **C** exhibits a severe fixed defect of the apical half of the inferior wall suggestive of transmural scar. All three patients subsequently had angiographically normal epicardial coronaries on invasive catheterization.

MBF is typically lower in patients with history of paroxysmal or chronic atrial fibrillation.

Together, these findings suggest a significant association between abnormal MFR, as measured by PET, and the onset and/or perpetuation of angina, heart failure, and related complications in HCM. Determining whether an actual cause-and-effect relationship exists will require further investigation.

CAN CARDIAC PET BE USED FOR RISK STRATIFICATION IN HCM?

Risk stratification for primary prevention of SCD is of utmost importance in HCM. Current accepted risk factors include a family history of SCD in a first-degree relative, recent (within 6 months) unexplained syncope, and maximal LV thickness $\geq$ 30 mm.[35] Less accepted risk markers are non-sustained ventricular tachycardia (especially in individuals under 30 years) and abnormal blood pressure response with exercise.[35] Most recently the extent of myocardial LGE ($\geq$ 15% of LV mass) on CMR has gained significant interest as a risk modifier, especially in those situations where risk stratification remains inconclusive after review of conventional risk factors.[35,38]

Myocardial ischemia has been long speculated as a potential trigger or predisposing phenomenon to the genesis of malignant VA in HCM. In one post-mortem series of 19 young HCM individuals ($\leq$ 35 years of age) who died of sudden cause, histological changes consistent with acute/subacute myocardial ischemia (coagulative necrosis, neutrophilic infiltrate, myocytolisis, and granulation tissue healing) were seen in 14 subjects (74%), including 1 individual with evidence of acute myocardial infarction in the setting of normal epicardial coronaries, suggesting that myocardial ischemia may play a significant role in the pathogenesis of SCD.[32] In another study, 23 young HCM patients with previous SCD (n = 8), syncope (n = 7) or family history of SCD (n = 8) underwent exercise Tallium-201 (^{201}Tl) SPECT and electrophysiologic studies to induce ventricular tachycardia (VT).[33] Inducible VT was not seen in patients with family history of SCD but was present in 4 of 15 subjects with history of SCD or syncope, whereas SPECT evidence of myocardial ischemia was seen in 3 out of 8 patients with family history of SCD, but in all 15 patients with previous SCD or syncope history,[33] implying an important association between SCD, syncope, and myocardial ischemia. However, the predictive value of SPECT was less obvious in a subsequent work, where abnormal MPI on ^{201}Tl SPECT was not an independent predictor of cardiovascular death (n = 13) among 216 young HCM patients, after 41 ± 21 months of follow-up, despite a significant

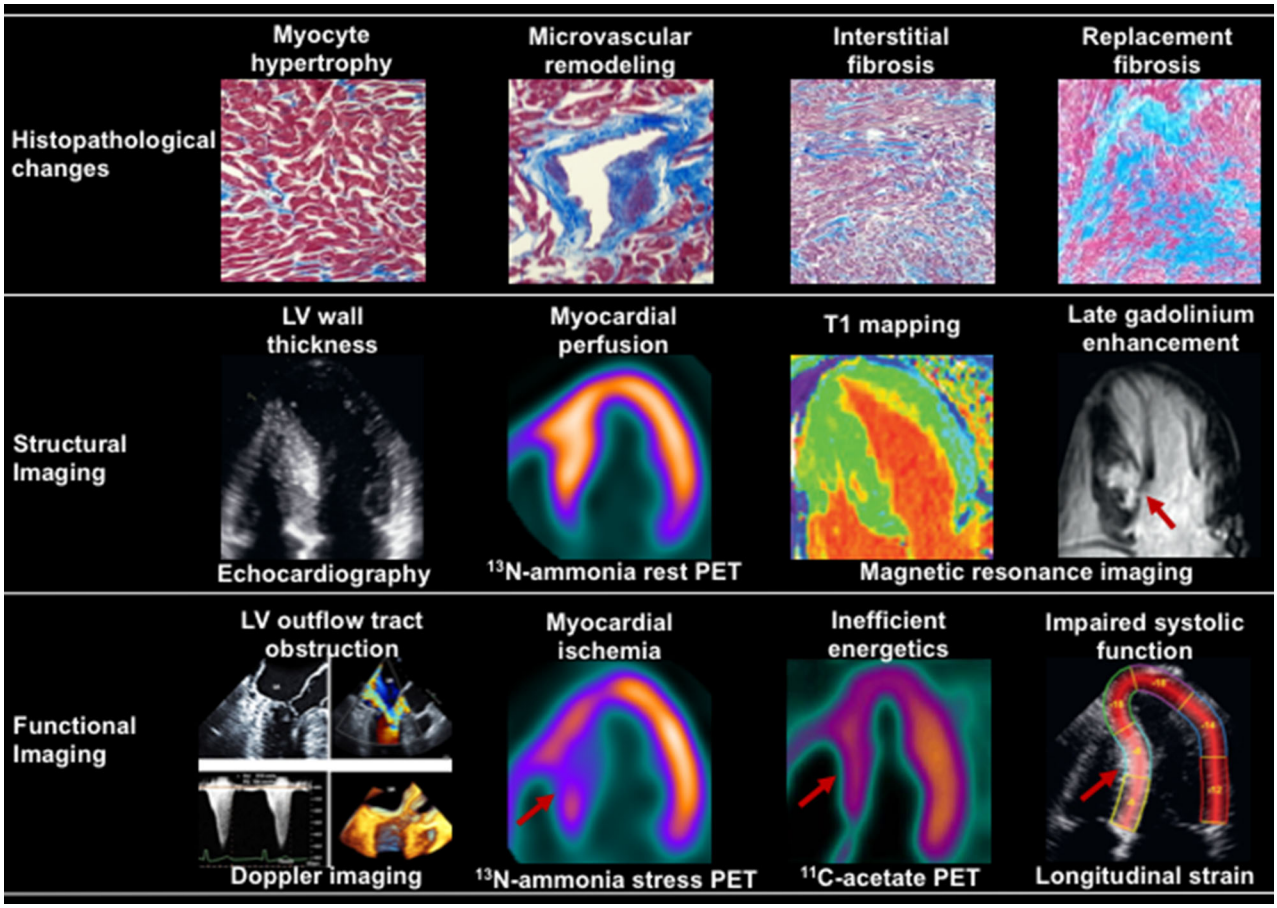

Fig. 5. Multimodality imaging of the structural and functional consequences resulting from the histopathological features of HCM. Echocardiography is important for evaluation of left ventricular (LV) hypertrophy, outflow tract obstruction, and myocardial mechanics. PET is key for investigation of the microvascular function with quantitative myocardial perfusion imaging but can also aid in our understanding of myocardial energetics with metabolic imaging, including ^{11}C-acetate a marker of oxygen consumption and overall myocardial efficiency. Contrast-enhanced cardiac MRI is the modality of choice for myocardial fibrosis assessment using late gadolinium enhancement (LGE) for detection of focal fibrosis and quantitative T1-mapping techniques for uncovering more diffuse fibrosis not seen on LGE imaging. In addition, MRI is an excellent alternative for morphologic and functional assessment of the LV in HCM. In the present example, myocardial fibrosis (LGE), microvascular dysfunction (ischemia on stress PET), oxygen consumption (^{11}C-acetate), and systolic function (longitudinal strain) are generally worse in the myocardial segments exhibiting the most hypertrophy (red arrow), which is typically the septum in HCM. Images were modified and adapted to fit current format from Güçlü et al,[53] Kellman et al,[54] Collier et al,[55] and Hindieh et al,[56] with permission of the publishers.

correlation between abnormal MPI with syncope, LV cavity size, and reduced exercise capacity.[39]

On the other hand, the literature, while still limited, offers important insights of the enhanced predictive value of PET with MBF quantification. Cecchi et al. investigated prospectively the potential prognostic role of quantitative stress MBF by PET in HCM at two medical centers in Italy over a decade ago.[30] In this work, 51 HCM patients were divided into tertile groups according to stress-MBF results. After a follow-up of 8.1 ± 2 years, patients in the lowest stress-MBF group (n = 12/18) had significantly higher incidence of unfavorable outcomes (NYHA progression, sustained VT, and cardiovascular-related death) compared to the middle (n = 1/16) and highest (n = 3/17) stress-MBF groups. However, most of this outcome difference was driven by NYHA progression (n = 4/18) and heart failure- or stroke-related deaths (n = 4/18). Fatal SCD (n = 5), on the other hand, was reported in 3 patients in the lowest, and 2 patients in the upper stress-MBF group, while non-fatal VT was only seen in one patient and occurred in the lowest stress-MBF group. In a

multivariate analysis, the authors found that reduced stress MBF measured by PET was the only independent predictor of death and unfavorable outcomes.[30] In agreement with these findings, a more recent work in 100 HCM patients in Italy found that stress MBF, particularly at the lateral wall, was an important predictor of non-sudden cardiac death and other unfavorable outcomes (NYHA progression and stroke), yet, no episodes of SCD or appropriate implantable cardioverter defibrillator discharge were identified during 4.0 ± 2.2 years of follow-up, thus, the role of quantitative flow to predict SCD could not be assessed.[40] In contrast, a group from Johns Hopkins recently found that the presence of significant flow heterogeneity (defined as the ratio of the highest to lowest regional stress MBF per patient), and not the global or regional LV stress-MBF results, is perhaps a better biomarker for risk-prediction of VA.[41] In this work, the authors followed 133 HCM patients for 3.3 ± 1.6 years after PET, and identified 23 individuals who eventually experienced VA, including sustained VT (n = 9) and non-sustained VT (n = 14). No fatal cases of SCD were reported. They found that the LV septum had the lowest and the lateral wall the highest stress MBF in the study cohort, and none of these parameters in isolation were independent predictors of VA. In contrast, the index for stress-MBF heterogeneity (using a cutoff of $\geq$ 1.85) was a potent independent predictor for VA after adjusting for age, LV outflow tract obstruction status, and personal history of VA. Similar to prior studies, stress MBF was also predictive of a composite of NYHA progression, stroke, and non-sudden cardiac death.

FUTURE PERSPECTIVES

Prior ex vivo and in vivo observations have shown the strong interrelation between myocardial fibrosis and CMD in HCM.[2,23,24,26,27] This is further substantiated after comparing the high prevalence of both LGE on CMR ($\sim$ 60%)[42] and myocardial ischemia by non-invasive means ($\sim$ 45%) in HCM (Table 1). Interestingly, HCM patients can be segregated into 4 different groups according to LGE-CMR and PET findings as following: (1) negative fibrosis and ischemia, (2) fibrosis plus ischemia, (3) fibrosis only, and (4) ischemia only (Figure 3).[27] The importance of this concept revolves around the fact that despite the high prevalence of LGE in HCM, only a small fraction of patients will eventually experience cardiovascular events.[43-46] This highlights the inconsistency with which LGE predicts clinical events and generates the hypothesis of whether further risk stratification could be accomplished by demonstration of concomitant myocardial ischemia or MBF heterogeneity by PET. For example, it is conceivable that patients with LGE but preserved MFR on PET may still be at low risk for future events, whereas those with coexistent LGE (especially in large amounts) and severe CMD by PET may be at higher risk. Alternatively, it is also possible that CMD is simply closely associated with fibrosis or represent an epiphenomenon, rather than a key marker of risk. Obviously, this is speculative at this point, and remains to be prospectively explored in future studies.

Investigation on the treatment and monitoring of myocardial ischemia in HCM is also lacking. Although, CMD in HCM shares some similar anatomic and functional features with hypertrophy resulting from LV pressure-overload states (e.g., systemic hypertension, aortic stenosis),[24,47,48] there is no evidence that proven therapies associated with LVH regression (e.g., renin-angiotensin system inhibition)[49,50] will have similar results in HCM.[51] Future studies investigating not only these but other novel therapeutic approaches, including the anti-anginal medication Ranolazine, are urged.[52]

Finally, further multimodality imaging studies enrolling genotype-positive/phenotype-negative and phenotype-positive HCM patients will be key to improving our understanding of the natural history of disease progression and the complex interplay between the structural and functional consequences of the underlying histopathological abnormalities seen in patients with HCM (Figure 5).[53-56]

CONCLUSION

In summary, the existing data support the clinical and investigational role of quantitative myocardial perfusion PET imaging to (1) detect myocardial ischemia, (2) establish the diagnosis and grade the severity of microvascular dysfunction, and (3) become an important biological marker associated with a number of adverse cardiovascular outcomes in HCM. However, its role for risk stratification of ventricular arrhythmic events, including SCD, remains less certain, in part due to the sample size and limited number of hard events in PET studies. Thus, the current evidence precludes our ability to provide meaningful evidence-based recommendations in favor of or against PET for risk stratification in SCD. Further studies, investigating the potential risk-stratification role of MBF quantification, but especially in combination with myocardial fibrosis assessment, are required.

Disclosures

Dr. Bravo declares no disclosures or conflict of interest.

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