What is the Value of Perfusion Scintigraphy and Cardiac PET in Hypertrophic Cardiomyopathy?

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Abstract

Hypertrophic cardiomyopathy is the most common hereditary heart disease and affects about 1:500 individuals in the general population. Diagnosis is not always simple due to phenotypic variation and concomitance with other pathologies. It is initially based on electrocardiographic and echocardiographic criteria and on the absence of other diseases occurring with ventricular hypertrophy. Having myofibrillar derangement and fibrosis as a cellular base resulting in hemodynamic abnormalities, hypertrophic cardiomyopathy may reveal myocardial ischemia (not related to atherosclerosis) and sudden death. Therefore, evaluation of functional repercussion with myocardial perfusion scintigraphy using the Single Photon Emission Computed Tomography (SPECT) has gained space, since 25% of patients with hypertrophic cardiomyopathy have fixed or ischemic perfusion defects. In this context, some perfusion disorders are not necessarily associated with the type of hypertrophic cardiomyopathy, but are able to predict morbidity and mortality in these individuals. Another recent scintigraphy technique is the positron emission tomography (PET), which stands out in the evaluation of microcirculation, coronary flow reserve and myocardial metabolism. In patients with hypertrophic cardiomyopathy, studies have shown unfavorable results when myocardial blood flow and coronary flow reserve are lower. Metabolic myocardial evaluation using PET seems to be useful in the pathophysiological understanding of this disease and in the prognostic evaluation of alcohol ablation, a procedure performed in severe obstructive forms. This review addresses the role of nuclear cardiology using SPECT and myocardial PET in the diagnostic, prognostic and therapeutic evaluation of hypertrophic cardiomyopathy.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited genetic heart disease and affects about 1:500 individuals in the general population.1-3 However, a higher prevalence (1:200) can be observed when clinical and genetic aspects are considered, in addition to family history.4

Diagnosis is initially based on electrocardiographic and echocardiographic criteria, such as ventricular wall thickening greater than 15 mm, in the absence of other diseases that include ventricular hypertrophy, such as valvular or subvalvular aortic stenosis, infiltrative cardiomyopathies (e.g.: amyloidosis), and hypertension.1 However, diagnosis is not always simple for two main reasons: firstly, due to the large phenotypic variation and, secondly, the concomitance of other variables associated with ventricular hypertrophy, such as systemic arterial hypertension,4 which may be present in almost half of the patients with HCM. This difficulty in diagnosis may lead to greater morbidity and mortality, as some of the individuals affected may evolve with sudden death (SD) and heart failure (HF).5

Besides, properly distinguishing it from other entities is of extreme importance because when HCM is confirmed, lifestyle modifications proportional to the type and severity of hypertrophy should be implemented. A classic example is distinguishing this cardiomyopathy from athletic heart syndrome. In the athletic heart syndrome, interruption of exercise ceases the cardiac disorders until the pre-training conditions are restored without any major risks. In HCM, there is a contraindication to the practice of moderate to high-intensity exercising, especially in a competitive environment.1

Cellular bases and pathophysiological mechanisms

The cellular base in HCM consists of myocardial hypertrophy with myofibrillar disarray and fibrosis, initially resulting in diastolic dysfunction in virtually all cases, which is secondary to hemodynamic disorders, including prolonged and non-uniform ventricular relaxation, loss of ventricular “suction,” reduced chamber compliance and abnormal intracellular calcium uptake.6

Another important point is the presence of left ventricular outflow tract obstruction (LVOT), defined by a gradient of more than 30 mmHg, which is determinant in the therapeutic approach of these individuals, because it is associated with high morbidity and mortality.

Interestingly, about 70% of the individuals with HCM have obstruction either at rest or in provocative tests,5 and the absence of obstruction produces an excellent prognosis, with survival similar to that of the population of the same sex, ethnicity and age.5

Most individuals are asymptomatic, but may present dyspnea, chest pain or atrial fibrillation (AF).5 HCM may also be found incidentally in individuals with myocardial infarction, embolic events, ventricular fibrillation and HF.7 In these cases,
Evaluation of hypertrophic cardiomyopathy using myocardial perfusion scintigraphy (myocardial SPECT)

Diagnostic evaluation of HCM is based on electrocardiographic, echocardiographic and cardiac magnetic resonance imaging (CMRI) findings, such as: deep “T” waves (>10 mm, especially in apical forms) and symmetric inversion or strain pattern in precordial leads on electrocardiography; presence of myocardial hypertrophy (>15 mm thickness) with a description of its location and degree on echocardiography – myocardial thickness above 30 mm is considered massive and results in a higher risk of cardiac SD;1 confirmation or identification of myocardial hypertrophy (especially in forms with apical predominance), differential diagnosis with other pathologies, such as amyloidosis, hemochromatosis, apical cardiac tumors, noncompacted myocardium in isolated ventricular form, endomyocardial fibrosis and athletic heart syndrome. CMRI also allows the evaluation of fibrosis using the late enhancement technique. The presence of major late enhancement is associated with worse prognosis and correlates with increased ventricular wall thickness, ischemia, reduced left ventricular ejection fraction (LVEF), non-sustained ventricular tachycardia and mortality.1

However, in addition to anatomical evaluation using the methods described, evaluation of myocardial ischemia in patients with HCM is of prognostic importance. Myocardial ischemia in these patients is a well-recognized phenomenon, whose mechanisms, besides those described in the previous section, involve arteriolar architecture distortion, small vessel disease, reduced coronary flow reserve and inherent imbalance between oxygen supply and consumption because of hypertrophied segments and ventricular overload conditions.8-11

Functional evaluation and assessment of the extent of ischemia using myocardial perfusion scintigraphy (MPS) have gained space, since a quarter of the patients with HCM have fixed or ischemic perfusion defects on scintigraphy images and are associated with abnormal metabolism (e.g.: reduced pH in the coronary sinus) and abnormal hemodynamics (e.g.: increased end-diastolic pressure), as well as ventricular arrhythmias, cardiac arrest and syncope.12 However, the literature on this subject is scarce, especially including many forms of HCM, besides the specific scope of the apical form.13 In general, the pattern described is an increase in myocardial thickness, involving the septal region, which may result in increased myocardial uptake of the radiopharmaceutical drug in this region, on resting and post-stress images, and relatively reduced uptake in the other walls due to the normalization of the take degree by the pixel of higher intensity (Figure 1).14

In a study with 158 adult patients, Sorajja et al.12 observed myocardial perfusion disorders in about 62% of the cases with 56% presenting ischemia. Multiple perfusion defects were observed in 52% of the patients, but these are unrelated to the type of hypertrophy identified on echocardiography or CMRI. Only 22.5% of the patients with abnormal test results were symptomatic. During follow-up, there were 19 deaths of cardiac origin, but only five patients had Coronary Artery Disease (CAD) diagnosed. In patients with normal tests, survival at 5 and 10 years was, respectively, 98% and 89% significantly higher than that found in patients with abnormal test results, and annual cardiovascular mortality was about 1.0%, similar to the normal population. Nevertheless, univariate analysis showed that the degree of ischemia or any perfusion disorder was a predictive factor of lower cardiovascular survival, with the incidence of cardiovascular death being 3.6% per year in patients with ischemic test results and 3.3%, considering any perfusion disorders under stress, that is, close to those individuals considered to be at high cardiovascular risk in the population (Figure 2).12

It should be noted that the presence of ischemia occurs quite often in this population, predominantly not associated with atherosclerosis, but probably with the histopathological finding of myocyte disarray with known pathophysiological consequences, such as CMRI. The evaluation of myocardial perfusion is suggested to play a fundamental role in HCM.15

Regarding the apical form of HCM, a rarer condition compared to the septal form, a greater number of cases is found in Japan, with a prevalence estimated at 25% of individuals with HCM. In other populations, this form presents prevalence of about 1 to 2% of patients with HCM. This HCM presentation is associated with better prognosis and lower risk of SD.16 However, the electrocardiographic abnormalities associated with chest pain present in apical HCM can mimic atherosclerotic CAD, emphasizing the importance of its correct identification, preferably using non-invasive methods available.15,17

Although echocardiography is fundamental in the diagnosis of HCM, some cases with apical involvement may not be identified by this method due to the inappropriate acoustic window and echocardiographer’s low clinical suspicion. Irwin et al.18 reported three cases of patients referred for perfusion scintigraphy to evaluate chest pain, with electrocardiography revealing diffuse T wave inversion or T wave in the precordial leads, which presented normal initial echocardiography. In perfusion scintigraphy, two cases presented increased concentration of the radiopharmaceutical drug at the apex, sometimes accompanied by hypokinesia. When the possibility of HCM in scintigraphy was discussed, the patients had a new contrast echocardiography done, which confirmed the diagnosis. These findings were also described in other case series, in which the patients were referred for MPS to assess precordial pain and electrocardiographic abnormalities suggestive of ischemia, conducting investigations with contrast echocardiography after observing apical hyperuptake on scintigraphy. Final diagnosis was apical HCM.14,18
Diagnosis of apical HCM should be considered in patients referred for thoracic pain associated with electrocardiographic abnormalities that present hyperconcentration of the radiopharmaceutical drug in the apical region in the MPS (Figures 3 and 4), as well as fixed and/or transitory defects in this area, or “solar polar map” pattern and ventricular chamber with “ace of spades” deformity and pattern, with sensitivity and specificity of those last findings of 75% and 100%, respectively. This solar polar map pattern consists of a significant increase of radiotracer concentration in the apical region, surrounded by a ring of areas of lower concentration.

Some recommendations of suspicion criteria for the diagnosis of HCM (apical and other forms), based on scintigraphic findings, are described in Table 1 (Figures 1 and 3 to 6). It is worth noting that this test is often the first one to be considered by the clinicians and this is mainly due to complaints of chest pain and electrocardiograms with abnormalities.

**Positron emission tomography (PET) in hypertrophic cardiomyopathy**

In the past, HCM was described as a disease with high mortality rates (up to 6% per year), reflecting the limited treatment choices of the time. However, this scenario has improved over the past few years. Survival rates reach levels similar to those of the general population if patients are correctly assessed and followed up. This progress has also occurred due to the evolution of diagnostic methods, especially in identifying the intermediate phenotypes among the great variety that is known. PET evaluation plays a role in this context. Better levels of PET sensitivity and specificity compared to the perfusion images of MPS using Single Photon Emission Computed Tomography (SPECT) to detect myocardial ischemia are known. Another advantage of PET is the possibility of evaluating microcirculation and coronary flow reserve. Microcirculatory disease is an important predictor of clinical deterioration and death in HCM, especially in individuals with low coronary flow reserve at the maximum peak effect of dipyridamole.

To assess the importance of myocardial perfusion evaluation in HCM, Castagnoli et al. developed a study with one hundred patients undergoing PET with N-ammonia, with complaints of dyspnea and/or angina, no epicardial CAD, in order to determine the prognosis of these individuals based on the level of microvascular perfusion.

To do this, they divided the group into myocardial blood flow (MBF) terciles based on previous studies that found that MBF < 1.1 mL/min/g would have a worse impact on outcomes in patients with HCM, namely:

- Lower tercile: 0.73 to 1.53 mL/minute/g.
- Intermediate tercile: 1.54 to 2.13 mL/minute/g.
- Upper tercile: 2.14 to 5.89 mL/minute/g.

This study found an inverse relationship between MBF level and clinical outcomes (cardiovascular death, defined as death due to HCM-related causes such as HF, SD and Ischemic Stroke – IS); and unfavorable combined outcomes, including cardiovascular death, progression of HF with severe...
functional limitation – New York Heart Association (NYHA) III/IV, sustained ventricular arrhythmias requiring implantable cardioverter defibrillator (ICD), or nonfatal IS with significant increase of the risk associated with the lower terciles, especially the lower one, which included seven of the 12 patients with an unfavorable outcome, including three of the four patients who died (Figure 7).11

An analysis performed on this lower tercile showed MBF < 1.35 mL/minute/g as the best cut-off point for predicting unfavorable outcomes by the Receiver Operating Characteristic (ROC) curve (Figure 8).23

Another approach was performed, this time separating the segments from the lateral and septal regions. Specific MBF terciles were identified for these regions, corresponding, on average, to 2.29 ± 1.1 mL/minute/g (lateral region) and 1.67 ± 0.75 mL/minute/g (septal region) then also separating them into terciles. The lower MBF terciles were in the septal region, expressing the preferred hypertrophy and fibrosis site for this region, consisting of a weak predictor of outcomes. Interestingly, patients in the upper tercile of the septal region had greater event-free survival. The lateral region, on the other hand, was relatively preserved from fibrosis and, when affected, reflected a powerful predictor of outcomes, involving ventricular dysfunction, since the four deaths reported in the study occurred in patients in the lower tercile group of this region. A possible explanation is that involvement of the lateral wall reflects the diffuse involvement of cardiomyopathy, extending to areas other than those initially affected, predicting ventricular dysfunction. Therefore, when the lateral wall is preserved, it suggests that the disease is more localized and gives greater survival.

Thus, this study was relevant to conclude that: MBF after the test with dipyridamole was valuable in the prognosis of the patient with HCM; the cutoff value for the prediction of adverse events and death was MBF < 1.53 mL/minute/g (lower tercile); the location of hypertrophy/fibrosis was preferably in the septal region; involvement of the lateral region is the best prognostic predictor of outcomes associated with ventricular dysfunction, since it probably reflects diffuse ventricular involvement of the disease.

Figure 2 – On the left, bar histogram charts showing patterns of perfusion abnormalities on myocardial perfusion scintigraphy (SPECT) in patients with asymmetric (chart at the top), apical (chart in the middle) and concentric (chart at the bottom) septal hypertrophic cardiomyopathy. The horizontal axis of the charts shows the type of perfusion defect. In black, the reversible abnormalities and, on the diagonal lines, the fixed abnormalities. On the right, survival curves in years, according to the presence of perfusion defects. Patients with perfusion defects had lower survival rates. In this study, the lower the stress score (SSS), the greater the perfusion defect. SRS means score plus reversibility of the defect, therefore ≥ 1 means ischemia. Patients with ischemia presented lower survival. Source: adapted with permission. Sorajja P et al.,2005. 

Table 2 - Follow-up, survival and MBF results for different territories and combinations of territories in patients with HCM. SSS = Stress score; SRS = Score plus reversibility of the defect. MBF < 1.35 mL/minute/g is the best cut-off point for predicting unfavorable outcomes by the Receiver Operating Characteristic (ROC) curve (Figure 8).
In addition to this analysis, it is possible to see the degree of functional repercussion induced by microcirculation ischemia, as demonstrated by Sciagra et al., who analyzed the difference in subepicardial and subendocardial blood flow before and after pharmacological testing with dipyridamole in patients undergoing PET perfusion study. In this study, the objective of which was to evaluate the variables associated with inadequate response of ejection fraction in patients with HCM, it was found that not only ventricular wall thickness is a poor predictor, but also subendocardial ischemia in these hypertrophic patients.

Regarding metabolic evaluation via PET, it is known that the main source of normal myocardial energy is fatty acids (>90%). In some pathologies, when inflammation or ischemia occurs, the source can be modified to glucose. Situations such as increased energy demand due to
myocardial hypertrophy, inflammatory response due to infiltration of inflammatory cells involved in the pathogenesis and myocardial ischemia by microangiopathy, may lead to the up-regulation of hypoxia-inducible factors that trigger a change in metabolism in favor of glycolysis, by inducing the transcription of glucose membrane transporters.

Katagiri et al., observing an abnormal $^{18}$F-FDG concentration at the cardiac apex in a series of $^{18}$F-FDG PET cases, found that the ace of spades pattern observed on the echocardiogram of patients with apical HCM suggests that the intensity of glycolytic activity in this region could be associated with the progression of myocardial hypertrophy, detected by electrocardiographic abnormalities, apical akinesia and abnormal coronary flow reserve (in SPECT images), also allowing to conclude that the metabolic change may be primarily associated with pathophysiological and non-morphological changes.

In addition to the detection of HCM, recent studies demonstrate the importance of cardiac PET in prognostic evaluation, as well as in the prediction of response to septal alcohol ablation (SAA), a therapeutic procedure that can be used in severe obstructive forms. Aoyama et al. studied 30 patients with HCM and no significant CAD, who underwent $^{18}$F-FDG PET, and the results were compared with CMRI with late enhancement protocol. Of the patients analyzed, 12 had the non-obstructive form, 14 had the obstructive form and two had medium-ventricular obstruction. FDG concentration was demonstrated in a limited area in the nonobstructive form, predominating in the anteroseptal region with good correlation between late enhancement on CMRI and intensity of FDG concentration. Such spatial correlation may be associated with the presence of fibrotic myocardium in this region, but an increase in glycolytic metabolism may indicate the risk of fibrosis before its establishment.

In the obstructive form, FDG concentration exceeded the limits of the hypertrophied myocardium and the radiopharmaceutical concentration pattern, as well as its intensity, which did not correspond to the CMRI findings. A possible explanation is that late enhancement evaluates myocardium with established tissue damage, whereas glycolytic metabolism reflects pre-fibrosis disorders.
Another interesting aspect of this study is that the radiotracer concentration patterns were compared to important biochemical tests, such as troponin T and Brain Natriuretic Peptide (BNP). Troponin T had a good correlation with the FDG concentration in the non-obstructive forms, reflecting the ischemia through its many pathways, as mentioned before, while the obstructive form correlated with BNP, a marker of ventricular dysfunction, indicating that the concentration of $^{18}$F-FDG is more extensively observed in the myocardium with dysfunction. Obstructive flow disorders cause metabolic abnormalities not only in the hypertrophied area, but also in the non-directly affected myocardium, with consequent increase in BNP levels.27

In the therapeutic evaluation, patterns before and after SAA were studied. The pattern of concentration in the left ventricular lateral wall, as seen in obstructive cases, improved after SAA. The improvement was attributed to the attenuation of ischemic demand secondary to an increase in the chamber wall pressure. Therefore, the degree and extent of glycolytic metabolism assessed by $^{18}$F-FDG PET may be highly useful in both SAA indication (because it identifies the obstructive HCM pattern) and in post-therapy evaluation.28

### Table 1 – Findings suggestive of hypertrophic cardiomyopathy (HCM) on myocardial perfusion scintigraphy synchronized with electrocardiography (gated-SPECT)

<table>
<thead>
<tr>
<th>Apical HCM</th>
<th>Other forms of HCM</th>
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<tr>
<td>Increased radiopharmaceutical concentration in the apical region</td>
<td>Increased radiopharmaceutical concentration on a myocardial wall, usually in the septal region (Figures 5 and 6)</td>
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<tr>
<td>Solar polar map pattern</td>
<td>Pseudo-regression of tracer concentration on other walls</td>
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<tr>
<td>Ventricular chamber with aoe of space pattern deformity on gated-SPECT images</td>
<td>Abnormal motility of the septal wall without substrate to explain it (e.g.: no history of cardiac surgery, no LBBB on the electrocardiogram) on gated SPECT</td>
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LBBB: left bundle branch block

### Conclusions

In hypertrophic cardiomyopathy, evaluation of myocardial ischemia can be done using scintigraphic techniques, such as SPECT and PET. The presence of perfusion defects is relatively frequent in this cardiomyopathy and is associated with a worse prognosis. Evaluation of perfusion, myocardial blood flow, coronary flow reserve and myocardial metabolism can be performed using the PET technique. The results of cardiac PET have unique importance in the diagnostic and prognostic perfusion evaluation, accessing, with greater specificity and sensitivity, the coronary microcirculation disorders. In the metabolic evaluation, PET can predict outcomes in the forms with and without obstruction, as well as evaluate the therapeutic response of septal alcohol ablation in the cases of more severe obstructive hypertrophic cardiomyopathy, with good correlation with tests established in the daily routine of cardiologists, including laboratory tests (such as T troponin and brain natriuretic peptide) and imaging tests (cardiac magnetic resonance imaging).

Unfortunately, in Brazil, the limited availability of PET technology outside the oncology area limits the experience of
most major centers. However, myocardial perfusion scintigraphy imaging with SPECT is well known and relatively available. Therefore, we should be aware of the perfusion patterns reported in this review, as we may be faced with hypertrophic cardiomyopathy not diagnosed by traditional methods (electrocardiography and echocardiography). In hypertrophic cardiomyopathy, the presence of myocardial ischemia suggests worse prognosis, not necessarily related to obstructive coronary artery disease, and its treatment may reduce the risk of sudden death and heart failure in these patients.

**Authors’ contributions**

Research creation and design: Segundo Neto EMV, Lopes RW, Brandão SCS; Data acquisition: Segundo Neto EMV, Lopes RW, Brandão SCS; Data analysis and interpretation: Segundo Neto EMV, Lopes RW, Brandão SCS; Statistical analysis: Segundo Neto EMV, Lopes RW, Brandão SCS; Manuscript writing: Segundo Neto EMV, Lopes RW, Brandão SCS; Critical revision of the manuscript as for important intellectual content: Segundo Neto EMV, Lopes RW, Brandão SCS.

**Potential Conflicts of Interest**

There are no relevant conflicts of interest.

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**Academic Association**

This study is not associated with any graduate program.
Figure 8 – Operating Characteristic Curve of the PET study receptor of myocardial perfusion with $^{13}$N-ammonia and use of dipyridamole in patients with hypertrophic cardiomyopathy. The area under the curve was 0.727, with $p < 0.03$. The cutoff value of the myocardial flow reserve was ≤1.35 mL/minute/g, predictive of events during follow-up on average of 4.0 ± 2.2 years. Source: Adaptation authorized by Castagnoli H, et al. 2016

References


