Chapter 9

General Discussion

Adapted from Review: Coronary Microvascular Function, Myocardial Metabolism, and Energy Efficiency in Hypertrophic Cardiomyopathy – New Insights from Positron Emission Tomography

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Submitted
Abstract

Hypertrophic cardiomyopathy (HCM) is a major cause of sudden cardiac death in adolescence and heart failure at any age. However, significant heterogeneity in clinical course and phenotypic expression exist. Next to left ventricular hypertrophy, an impaired myocardial blood flow (MBF) during stress and inefficient cardiac metabolism are other hallmarks of HCM. Positron emission tomography (PET) has led to an enhanced understanding of the role that myocardial ischemia and impaired energetics play in the clinical course of HCM. The blunted vasodilatory response during stress in the absence of coronary stenosis is the result of microvascular dysfunction. Microvascular dysfunction, in turn, represents a predisposing factor for myocardial ischemia, which may lead to cardiac dysfunction and fibrosis. Correspondingly, the severity of microvascular dysfunction has been shown to serve as a major predictor of morbidity and mortality. Myocardial energetics in HCM have been studied with similar interest since the development of substrate-based tracers, and growing evidence suggests that mechano-energetic uncoupling plays a central role in the pathogenesis. Although prognostic data related to an impaired energetic state in HCM are lacking, it is believed to hold strong prognostic relevance. Currently, microvascular dysfunction and impaired myocardial energetics are considered major determinants of the HCM pathogenesis. Consequently, treatment strategies aimed at enhancing perfusion and augmenting energetics are a promising avenue in the treatment of HCM. In this regard, myocardial perfusion and metabolic imaging serves as a valuable tool for the development of (new) therapeutics, and monitor the clinical effect of existing interventions.
Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disease with an estimated prevalence of 1:500, and over 100 documented mutations.(1) HCM is the most common cause of sudden cardiac death (SCD) in adolescence, and a major cause of heart failure at any age, although significant heterogeneity in phenotypic expression exists.(2) One of the hallmarks of HCM is asymmetrical left ventricular hypertrophy (LVH). However, the discovery of myocardial perfusion defects and abnormal energy handling, by use of semi-quantitative imaging techniques in the early 90’s, revealed that the pathophysiology of HCM was not merely limited to cardiac hypertrophy and adverse remodeling.(3-7)

More recently, the introduction of positron emission tomography (PET) has led to an enhanced understanding of the role that myocardial ischemia and impaired energetics play in HCM. For example, it was shown that myocardial blood flow (MBF) during stress is significantly impaired in HCM due to microvascular dysfunction,(8) the severity of which serves as an independent predictor of clinical deterioration and death.(9) Similarly, growing evidence suggests that an increased energy expenditure relative to work, i.e. reduced mechanical efficiency, is an early feature of HCM and may play a causal role in mechanical failure of the heart.(10-14) Although prognostic data related to an impaired energetic state in HCM are lacking, it is believed to hold prognostic relevance in analogy to other cardiomyopathies.(15,16)

Consequently, treatment strategies aimed at augmenting perfusion and energetics are a promising avenue in the treatment of HCM.(17) In this matter, myocardial perfusion and metabolic imaging serves as a valuable tool for the development of (new) therapeutics, and monitor the clinical effect of existing interventions, such as biventricular pacing and septal reduction therapies.(18) This review discusses results from clinical PET studies in HCM regarding myocardial perfusion, metabolism, and energy efficiency. In addition, the effect of therapeutic interventions on these parameters will be discussed.

Myocardial perfusion

Technical aspects

PET facilitates accurate, non-invasive quantification of myocardial blood flow (MBF) in absolute terms, as opposed to single photon emission computed tomography (SPECT)-based semi-quantification.(19) In addition, these parameters can be investigated on a regional level, which is especially useful
when investigating cardiac diseases in which regional disease expression is a hallmark, such as HCM.

To date, the most reliable tracer for quantification of MBF in HCM with PET is $^{[15]}\text{O}\text{H}_2\text{O}$.\(^{(20-22)}\) $^{[15]}\text{O}\text{H}_2\text{O}$ is a freely diffusible, metabolically inert molecule with a nearly complete extraction, independent of flow rate and metabolic state. Therefore, regional differences in dynamic tissue responses depend solely on perfusion, rendering this tracer ideal for quantification of perfusion. Conversely, the extraction fraction of other widely used perfusion tracers such as $^{[13]}\text{N}\text{Am}_2\text{O}$ and $^{82}\text{Rb}_2\text{O}$ decreases with increasing flow rates, leading to underestimation of perfusion with higher flow values.\(^{(23)}\) In addition, inasmuch as myocardial uptake of these tracers is dependent upon active transportation of the molecule across the cell membrane, the presence of interstitial fibrosis and scarring, both frequently seen in HCM, affect tracer kinetics and may reduce the reliability of perfusion estimates in these subjects.\(^{(24)}\)

*Transmural myocardial blood flow*

Global resting MBF in HCM patients is generally preserved,\(^{(25)}\) although significant heterogeneity in regional perfusion is frequently observed, with reduced values reportedly in areas exhibiting hypertrophy.\(^{(8,9,18,25-28)}\)

Hyperemic MBF (hMBF), on the other hand, is significantly reduced compared to age-matched controls. Early studies using semi-quantitative measurements of MBF in HCM already reported significant perfusion defects during physical exercise.\(^{(6,7)}\) More recently, PET studies have revealed that these stress induced perfusion defects are caused by an inadequate increase in MBF in response to adenosine, thereby blunting coronary vasodilatory reserve (CVR).\(^{(28,29)}\) The blunted CVR in HCM in the absence of epicardial coronary stenosis, is indicative of microvascular dysfunction.\(^{(9)}\) Microcirculatory function may be impaired for several reasons in HCM. Histological examination has revealed remodeling of intramural coronary arterioles resulting in a decreased cross-sectional arteriolar lumen area,\(^{(30)}\) and concomitant increase in coronary vascular resistance. This remodeling affects vessels across the entire myocardium, possibly explaining why hMBF is frequently hampered across the entire myocardium, also affecting non-hypertrophied areas.\(^{(29)}\) Additionally, pathological LVH is accompanied by a decreased capillary-to-myocyte ratio,\(^{(31)}\) i.e. a relative reduction in capillary density, the extent of which has been shown to independently predict the reduction in hMBF in HCM, when calculated on the basis of milliliters per gram of myocardial tissue. Similarly, patients with LVH due to hypertension or aortic stenosis also have reduced hMBF.\(^{(21,22)}\)
Microvascular dysfunction, in turn, represents a predisposing factor for myocardial ischemia, which may lead to contractile dysfunction and scarring, causing heart failure and potential arrhythmias on the long term (Fig. 1). Correspondingly, myocardial segments with a severe perfusion reserve deficit are at increased risk for developing contractile dysfunction during follow-up, (32) and these segments generally exhibit the largest amount of fibrosis, as reflect by delayed contrast enhancement.(25,33,34)

Subendocardial versus subepicardial perfusion

In addition to the aforementioned morphological features, LV loading conditions and wall stress, i.e. extravascular compressive forces, can further compromise microcirculatory function.(35,36) In HCM, CVR is more severely blunted in patients with LV outflow tract (LVOT) obstruction compared to patients without,(6,37) and the absolute reduction in CVR has been shown to parallel the severity of LVOT obstruction.(18,38) Moreover, these patients exhibit a typical pattern of reduced CVR at the subendocardial regions of the heart. Under baseline conditions, perfusion is tightly autoregulated in the microvascular bed in response to varying oxygen demand of the myocardium. However, during
maximal vasodilatation these extravascular forces in addition to intravascular resistance, rather than autoregulatory mechanisms itself, become the main determinant of MBF.\(^{(35)}\) According to Laplace’s law, wall tension increases from the subepi-to-subendocardial layer, creating an opposite transmural hyperemic perfusion pattern, especially in the presence of augmented LV loading conditions.\(^{(39)}\) Whilst patients with LVOT obstruction due to aortic stenosis show similar blunting of CVR,\(^{(40)}\) coronary arteriole remodeling is absent in these patients,\(^{(41)}\) providing additional evidence that augmented extravascular resistance substantially impedes perfusion.

**Myocardial oxidative metabolism**

*Technical aspects*

PET-mediated semi-quantification of oxygen usage can be performed with \([^{11}C]\)acetate.\(^{(42)}\) Acetate is metabolized completely in the Krebs-cycle where it is oxidized and the \(^{11}C\)-activity is transported to carbon-11 labeled dioxide (\(^{11}CO_2\)). Inasmuch as the heart is an almost entirely aerobic organ, myocardial \([^{11}C]\)acetate clearance therefore equals the oxidative flux through mitochondrion and can be used as index of myocardial oxidative metabolism. Several approaches to (semi-)quantify oxidative metabolism have been proposed, the simplest being exponential curve fitting. Armbrecht and coworkers showed that the rapid phase of \([^{11}C]\)acetate clearance represents the dynamic flux of \(^{11}C\)-activity through the Krebs-cycle.\(^{(43)}\) The corresponding rate constant (\(K_{\text{mono}}\)) closely correlates to \(MVO_2\) (Fig. 2). However, several factors hamper the accuracy of monoexponential curve, including spillover effects from blood-to-myocardium and vice versa, a falsely high \(^{11}C\) activity of the arterial input function due to incomplete myocardial extraction of \([^{11}C]\)acetate, and a subjective selection of data points on the time-activity curve (TAC). Theoretically, a compartment model increases the accuracy of \(MVO_2\) estimates with \([^{11}C]\)acetate PET by describing the myocardial kinetics of \([^{11}C]\)acetate and considering the effects of recirculating vascular \(^{11}C\)-activity and spillover altogether. Indeed, previous investigations in humans suggest that the use of a tracer kinetic model allows for more consistent noninvasive estimates of \(MVO_2\) in human subjects, compared to monoexponential curve fitting.\(^{(44,45)}\)
Myocardial oxygen consumption

It has been shown that myocardial oxidative metabolism per gram of myocardial tissue in HCM is comparable to controls,(10,46) or slightly decreased.(11,13) However, oxygen usage was consistently reduced in hypertrophied segments, i.e. the interventricular septum, as compared to the lateral wall,(10-13) whereas oxygen usage in healthy subjects is comparable among LV segments.(10,11) Several mechanisms may explain these findings. First, hypokinesia of hypertrophied segments as indicated by impaired circumferential shortening(10,25,27,47) or decreased systolic wall thickening,(33) as indices of contractile function, may reduce oxygen demand. Secondly, an increased diffusion distance as a result of a relative decrease in capillary density may reduce oxygen uptake by the cardiomyocyte.(30) Finally, regional uncoupling between oxidative metabolism and function as a result of abnormal energy handling and altered substrate metabolism, may affect noninvasive estimation of oxygen consumption as well.(48)

Where LV oxygen consumption remains largely unaltered during the HCM disease process, a recent study showed that oxygen usage of the RV is augmented, resulting in an altered ratio of right to left oxygen consumption.(49)
This is presumably attributable to increased RV loading due to LV diastolic dysfunction. [11C]acetate PET studies in patients with dilated cardiomyopathy (DCM) have shown a similar exaggerated metabolic imbalance between the RV and LV, a higher ratio of which (≥ 0.8) was associated with a significant decrease in exercise capacity. (50)

**Myocardial efficiency**

*Technical aspects*

As illustrated in Fig. 3, stroke work (SW) is represented by the area between the end-systolic pressure-volume relation (ESPVR), the end-diastolic pressure-volume relation (EDPVR), and the pressure-volume loop of the cardiac cycle. In practice, SW can be calculated relatively accurate and straightforward by multiplying mean arterial pressure (MAP) with stroke volume (SV). SV can be routinely derived by various imaging techniques, such as magnetic resonance imaging, echocardiography, and nuclear imaging. In case of HCM patients with LVOT obstruction, individually obtained measurement of the gradient across the aortic valve should be included to ensure accurate estimations of actual LV pressures.

By combining noninvasive estimates of MVO$_2$ and SW, mechanical efficiency can be calculated according to the equation below;

$$ME = \frac{SW \cdot HR \cdot 1.33 \cdot 10^{-4}}{MVO_2 \cdot LVM \cdot 20}$$

where HR is heart rate and LV mass (LVM) is measured in grams. It needs to be emphasized that SW and MVO$_2$ in this equation are expressed in absolute terms (i.e., joule), hence the calorific equivalents of 1 mmHg·mL ($\approx 1.33 \cdot 10^{-4}$ J), and 1 mL of O$_2$ ($\approx 20$ J). The most commonly employed method to estimate oxidative metabolism noninvasively, however, is by monoexponential curve fitting which yields an index of MVO$_2$. Therefore, an alternative efficiency index called the work metabolic index (WMI) has been introduced, where SVI is stroke volume index and SBP is systolic blood pressure.

$$WMI = \frac{SBP \cdot SVI \cdot HR}{[11C]acetate clearance}$$
Myocardial efficiency in HCM

Noninvasive studies have demonstrated that myocardial mechanical efficiency is significantly reduced in HCM patients,\(^{(11-13)}\) averaging at nearly half the values observed in healthy subjects (Fig. 4).\(^{(10)}\) Although oxygen consumption is generally unaltered, stroke work is disproportionately decreased in relation to MVO\(_2\). Patients with LVH due to hypertension show similar normalization of MVO\(_2\) at the cost of work generation, suggesting that mechanoenergetic uncoupling is a hallmark of pathological hypertrophy itself.\(^{(51)}\) Correspondingly, LVM was shown to be an independent predictor of impaired efficiency in HCM patients.\(^{(10)}\) Additional evidence for this hypothesis is provided by the presence of marked heterogeneity in regional efficiency, and concomitant findings of a lower mechanical efficiency in the hypertrophied septum as compared to the non-hypertrophied lateral wall.\(^{(10,11)}\)

Nonetheless, the relationship between deteriorated energetics in HCM and cardiac hypertrophy appears to be bidirectional. After all, impaired energy metabolism in HCM has even been noted in the absence of LVH, suggesting that compromised energetics play a causal role in the early stages of hypertrophy development.\(^{(52)}\) In addition, although regional differences in myocardial energetics exist, mechanical efficiency of the non-hypertrophied lateral wall tended to be lower in HCM patients, when compared to controls.\(^{(10,11)}\)
Altogether, these findings suggest the presence of additional mechanisms that affect myocardial metabolism across the entire myocardium. Repetitive stunning or myocardial hibernation due to ischemia are associated with reduced energy efficiency as well. Therefore, the presence of microvascular dysfunction, a widespread phenomenon in HCM also affecting non-hypertrophied segments, may play an essential role in this matter. However, inasmuch as a recent study revealed that phenotype-negative carriers of the MYBPC3 mutation are characterized by reduced mechanical efficiency, in the absence of myocardial perfusion defects, this may only be applicable to later stages of the disease. These results imply that impaired energetics are, at least in part, the primary result of inefficient ATP-usage by mutated sarcomeres (Fig. 1).

Figure 4. Aligned scatter plot depicting previously published results for mechanical efficiency values in controls, carriers, HCM patients, obstructive HCM patients before ASA (Pre-ASA HOCM), and after ASA (Post-ASA HOCM). ASA, alcohol septal ablation.
Effects of therapeutic interventions

To date, microvascular dysfunction and impaired myocardial energetics are considered major determinants of HCM. Enhancing myocardial perfusion and augmenting mechanical efficiency by pharmacological antagonization of the neurohormonal system or cardiac resynchronization therapy, has been proven to favourably affect outcome in patients with dilated cardiomyopathy.(55-57) Hence, treatment strategies aimed at enhancing coronary microvascular function and/or restoring myocardial energetics are a promising new avenue and may alter the clinical course of HCM.(58) In this matter, PET has served as a valuable tool for monitoring the clinical effect of new and existing therapies, and providing an in-depth understanding of their mode of action.(59)

Pharmacological therapies

Of the available calcium channel blocking agents, verapamil is highly effective in the treatment of anginal complaints in HCM.(60) Although extensive research has been performed regarding the effect of verapamil on myocardial ischemia, the exact mode of action by which verapamil improves symptoms remains unclear. Early SPECT studies showed that verapamil ameliorates silent myocardial perfusion defects during exercise.(61-63) More recent PET studies, on the other hand, have revealed that verapamil does not significantly affect myocardial perfusion.(64,65) However, some evidence was found of increased subendocardial MBF during treatment with high-dose verapamil. Inasmuch as verapamil also exerts negative inotropic effects, these changes may also be attributed to a reduction in subendocardial strain and wall stress, resulting in improved diastolic perfusion.

To date, noninvasive data regarding the effect of beta-blocking agents on myocardial oxygen consumption and efficiency in HCM are lacking. In analogy to patients with non-ischemic dilated cardiomyopathy, beta-blockade in HCM may reduce ischemia and improve outcome by limiting myocardial oxygen demand and augment mechanical efficiency, respectively.(56)

Dual chamber pacing

Dual chamber pacing succesfully reduces subjective symptoms and improves exercise capacity in patients with obstructive,(66) and non-obstructive HCM.(67) Although dual chamber pacing in obstructive HCM has been associated with a reduction in LVOT gradient, presumably by causing abnormal septal motion, the mechanism by which pacing relieves complaints in non-obstructive HCM is less clear.(68) In both subgroups, reduction of regional perfusion defects have been noted by use of exercise thallium-201 scintigraphy, especially in the
hypertrophied septum. Contemporary PET studies have provided more elaborate results by investigating the effect of pacing on absolute MBF in patients with obstructive HCM. It was shown that CVR of the hypertrophied septum was significantly increased, resulting in more homogeneous distribution of perfusion. In addition, resting MBF was significantly decreased during pacing in all myocardial segments, suggesting a concomitant reduction in global oxygen demand due to relief of LVOT obstruction.

**Septal reduction therapies**

Non-surgical alcohol septal ablation (ASA) and surgical myectomy reduce LVOT obstruction and alleviate symptoms in drug-refractory patients with obstructive HCM. Relief of LVOT obstruction is associated with a more favourable prognosis, although prospective randomized trials are currently lacking. LVH has previously been identified as an independent predictor of MBF, and is strongly associated with impaired energetics on a global and regional level. Hence, the reduction in LV loading conditions and regression of LV hypertrophy (LVH), due to reversed remodeling, could restore perfusion and improve myocardial energetics.

**Transmural myocardial blood flow**

Numerous studies have suggested that perfusion defects in HCM are in part reversible by relief of LVOT obstruction. However, the exact mechanism of action remained unexplained. Results from two recent studies investigating the long-term effect of septal reduction on myocardial perfusion have expanded on the aforementioned semi-quantitative investigations, by using PET to study absolute changes in regional MBF. It was found that relief of LVOT obstruction resulted in a significant improvement in global CVR, which was mainly attributable to an increased hyperemic MBF. Contrary to these results, another study showed that improvement of CVR following septal myectomy was mainly caused by a reduction of resting MBF. Inasmuch as MBF under baseline conditions is autoregulated according to oxygen demand, a reduction in LV afterload may reduce metabolic demand, and thus resting perfusion. It should be noted, however, that pre-interventional MBF was not studied, and the results were compared to a group of medically treated patients with obstructive HCM, thereby significantly hampering the inferences that can be drawn from this study.

In addition to reducing LV afterload as a means of enhancing microvascular function, regression of LVH has also been associated with improved perfusion in HCM. Similar results have been found in patients with pressure-overload...
cardiomyopathy due to aortic stenosis,(78) or hypertension,(79) indicating that restoration of the capillary density may have favourable microcirculatory effects as well.

**Subendocardial versus subepicardial blood flow**

The exaggerated LV loading conditions present in obstructive HCM limit microvascular function especially at the subendocardium. Correspondingly, it has been shown that CVR is mainly augmented in these regions after relief of LVOT obstruction, the increments of which directly related to the absolute reduction in afterload.(35,38) Conversely, epicardial CVR was not at all affected by ASA, providing additional evidence that extravascular forces exert pronounced effects on microvascular perfusion in obstructive HCM.

**Myocardial oxygen consumption and mechanical efficiency**

Limited data is available regarding the effect of septal reduction therapies on myocardial metabolism, let alone on mechanical efficiency. An early invasive study in 13 patients with obstructive HCM showed that septal myectomy reduced MVO$_2$, and that the reduction in basal oxygen usage was directly related to the magnitude of postoperative reduction in LVOT gradient.(38) Moreover, a postoperative switch from lactate production to lactate consumption was observed, suggesting that the reduction in myocardial oxygen demand resulted in more efficient substrate metabolism by use of oxidative phosphorylation, rather than anaerobic dissimilation. In a more recent study investigating the effects of ASA on mechanical efficiency, relief of LVOT obstruction did not significantly affect mean MVO$_2$ in 7 patients.(7) Individual changes in MVO$_2$ after ASA, however, were related to changes in the rate-pressure product, as an index of LV workload. The same study revealed that, despite a significant reduction in the LVOT gradient after ASA, the total amount of work delivered by the LV was not altered either, and could be attributed to a concomitant increase in SV. Due to a substantial reduction in LVM as a result of reversed remodeling 6 months after the procedure, however, the amount of work per gram of myocardial tissue was significantly increased. Inasmuch as oxygen usage was unchanged, mechanical efficiency significantly improved from 15% to 20%. Next to reducing myocardial oxygen usage as a means of increasing substrate availability and improving efficient energy handling, relief of LVOT obstruction may also have beneficial effects by increasing oxygen supply and limiting myocardial ischemia, as previously discussed.
**Right ventricular metabolism and energetics**

Relief of LVOT obstruction reduces right ventricular (RV) afterload as well, presumably improving LV diastolic function. (80) Correspondingly, it has recently been shown that a reduction in RV workload after ASA is associated with decreased oxygen usage. (49) Hence, the beneficial effects of ASA extend beyond the LV and may favourably affect RV energetics as well. More studies are warranted to further elucidate RV energetics in HCM.

**Myocardial substrate metabolism**

As mentioned earlier, myocardial efficiency may be favourably affected by improving the balance between myocardial oxygen supply and metabolic demand. Altered substrate metabolism, however, should not be disregarded as potential underlying mechanism. For example, PET studies using $^{18}$F-fluorodeoxyglucose (FDG) as a marker of glucose metabolism have revealed reduced FDG activity in the hypertrophied septum. (12, 81) Conversely, free fatty acid (FFA) uptake appears to be augmented in these areas, and inasmuch as FFA is a less energy efficient fuel, this may also contribute to reduced mechanical efficiency. (46) Concomitantly, interventions that induce a switch to a more energy-efficiency fuel, such as glucose, may improve energy efficiency and favourably affect cardiac function. This is underlined by a recent study, demonstrating that correction of energy deficiency in symptomatic HCM with perhexilllin was associated with improved exercise capacity. (17) Unfortunately, data on LV substrate metabolism in HCM are scarce, and future studies are clearly warranted to address these matters.

**Conclusions and future perspectives**

The development of PET has introduced a new era of myocardial imaging in heart disease. Although the clinical application of PET remains limited, as it is cost-expensive and carries radiation burden, its use in study protocols has produced tantalizing new insights into the pathophysiology of HCM. Over the past few years, myocardial ischemia and impaired energetics have gained considerable attention as potential mechanisms of disease in HCM, and are now considered major determinants of its natural course of disease. Recent findings of reduced myocardial efficiency in phenotype-negative HCM carriers even suggest a causative role for energy deficiency in the pathophysiology of HCM. Although an imbalance between oxidative metabolism and cardiac function is rather unspecific, it appears to be a sensitive marker of myocardial pathology and hold prognostic relevance. Clinical trials focussing on long-term outcome need to be performed, however, to determine the incremental prognostic value
of myocardial energetics in HCM. Nonetheless, developing therapeutic strategies specifically aimed at improving myocardial perfusion and energy handling is a promising new avenue in the treatment of HCM. Evaluation of new treatment strategies in a relatively small number of patients by use of PET can provide important insights into the potential mode of action, and is a step toward testing interventions in large clinical trials.
Reference list


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