Coronary microvascular function, myocardial metabolism, and energetics in hypertrophic cardiomyopathy: insights from positron emission tomography

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Hypertrophic cardiomyopathy (HCM) is a major cause of sudden cardiac death in adolescence, and may lead to heart failure at any age. However, significant heterogeneity in the clinical course and phenotypic expression exists. Next to left ventricular hypertrophy, an impaired myocardial blood flow (MBF) during stress and inefficient cardiac metabolism are other characteristics of HCM. Studies using positron emission tomography (PET) have led to an enhanced understanding of the role that myocardial ischaemia and impaired energetics play in the clinical course of HCM. The blunted vasodilator reserve in the absence of an epicardial coronary stenosis is the result of microvascular dysfunction. Microvascular dysfunction, in turn, represents a predisposing factor for myocardial ischaemia, which may lead to cardiac dysfunction and fibrosis. Correspondingly, the severity of microvascular dysfunction has been shown to serve as a major predictor of mortality. Myocardial energetics in HCM has been studied with similar interest as mounting evidence suggests that mechano-energetic uncoupling may play a central role in its pathogenesis. Although prognostic data related to an impaired energetic state in HCM are lacking, it may hold prognostic relevance. Consequently, enhancing perfusion and restoring energetics have gained considerable attention as potential strategies to alter the natural course of HCM. In this regard, myocardial perfusion and metabolic imaging serves as a valuable tool to monitor the effects of therapeutic interventions on the pathophysiology of HCM.

Keywords
Myocardial perfusion • Myocardial metabolism • HCM • PET • Microvascular dysfunction

Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disease with an estimated prevalence of 1:500, and over 900 documented mutations.1 HCM is the most common cause of sudden cardiac death in adolescence and may lead to heart failure at any age, although significant heterogeneity in phenotypic expression exists.2 The hallmark of HCM is (asymmetrical) left ventricular hypertrophy. However, the discovery of myocardial perfusion defects and abnormal energy handling, by the use of semi-quantitative imaging techniques such as single photon emission computed tomography (SPECT) and nuclear magnetic resonance (NMR) spectroscopy more than two decades ago, revealed that the pathophysiology of HCM was not merely limited to cardiac hypertrophy and adverse remodelling.3,4

The introduction of positron emission tomography (PET) has led to an enhanced understanding of the role that myocardial ischaemia 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, the severity of which serves as an independent predictor of clinical deterioration and death.5 Similarly, growing evidence suggests that an increased energy expenditure relative to work, i.e. reduced mechanical efficiency (ME), is an early feature in HCM and may play a causal role in the onset of mechanical failure of the heart.6–10 Although prognostic data related to an impaired energetic state in HCM are lacking, it is believed to hold prognostic relevance in analogy to patients with dilated cardiomyopathy (DCM), who exhibit similar reduced myocardial efficiency.11

Consequently, treatment strategies aimed at augmenting perfusion and energetics constitute a promising avenue in the treatment
of HCM.\textsuperscript{12} In this regard, myocardial perfusion and metabolic imaging with PET has also served as a valuable tool to monitor treatment effects.\textsuperscript{13} 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 separately.

**Myocardial perfusion**

**Technical aspects**

PET facilitates accurate, non-invasive quantification of the MBF in absolute terms, as opposed to SPECT, which yields qualitative imaging. Although both techniques allow for regional assessment of perfusion defects, an important technical advantage of PET is the higher spatial resolution, enabling the detection of subtle differences in regional perfusion, which is especially useful when studying cardiac pathology in which regional disease expression is a hallmark, such as HCM.

To date, several tracers for quantification of MBF with PET exist, the most widely used being \([^{15}\text{O}]\text{water}\), \([^{13}\text{N}]\text{ammonia}\), and \([^{82}\text{Rb}]\text{rubidium}\). \([^{15}\text{O}]\text{water}\) is a freely diffusible, metabolically inert molecule with a near complete myocardial extraction, independent of flow rate and metabolic state.\textsuperscript{14} In comparison, uptake of \([^{13}\text{N}]\text{ammonia}\) and that of \([^{82}\text{Rb}]\text{rubidium}\) depend on active transportation of the tracer molecule across the cardiomyocyte membrane, thereby affecting their extraction fraction at higher flow rates and requiring additional correction. \([^{15}\text{O}]\text{water}\) and \([^{13}\text{N}]\text{ammonia}\) show similar accuracy as quantitative perfusion tracers in normal myocardium.\textsuperscript{15} However, their equivalence in jeopardized myocardium warrants further investigation, inasmuch as the kinetic modelling of \([^{13}\text{N}]\text{ammonia}\) and \([^{82}\text{Rb}]\text{rubidium}\) is based upon myocardial tracer uptake, which may be altered in metabolically impaired myocardium or in the presence of scar.\textsuperscript{16}

**Transmural myocardial blood flow**

Global resting MBF in HCM patients is generally preserved,\textsuperscript{17} although significant heterogeneity in regional perfusion is frequently observed, with reduced values reported in areas exhibiting hypertrophy.\textsuperscript{5,17,18}

Vasodilator perfusion, on the other hand, is significantly reduced compared with age-matched controls. Early myocardial perfusion SPECT studies already noted significant perfusion defects during treadmill exercise.\textsuperscript{19,20} PET studies during pharmacologically induced stress or vasodilation have confirmed that these perfusion defects are caused by an impaired vasodilatory capacity of the coronary arterioles, thereby blunting hyperaemic MBF (hMBF).\textsuperscript{21} A blunted hMBF in HCM in the absence of an epicardial coronary stenosis is indicative of microvascular dysfunction.\textsuperscript{5} Microvascular function may be impaired for several reasons in HCM. Histological examination has revealed remodelling of intramural coronary arterioles resulting in a decreased cross-sectional arteriolar lumen area,\textsuperscript{22} and concomitant increase in coronary vascular resistance. This remodelling affects vessels across the entire myocardium, possibly explaining why hMBF is frequently hampered in non-hypertrophied areas as well.\textsuperscript{21} Similar remodelling of coronary arterioles has been observed in patients with LVH due to aortic stenosis and hypertension.\textsuperscript{23} Additionally, features such as interstitial fibrosis and reduced capillary density may also contribute to impairment of perfusion.\textsuperscript{24}

**Subendocardial vs. subepicardial perfusion**

In addition to pathological remodelling of the microvascular anatomy, increased LV loading conditions and wall stress, i.e. extra-vascular compressive forces, due to left ventricular outflow tract (LVOT) obstruction and impaired diastolic relaxation, respectively, may further compromise microcirculatory function.\textsuperscript{25} In HCM, the coronary vasodilator reserve (CVR) is more severely blunted in patients with LVOT obstruction compared with patients without,\textsuperscript{19} and perfusion defects are typically most pronounced at the subendocardial myocardial level. Under baseline conditions, perfusion is tightly autoregulated in the microvascular bed in response to varying oxygen demand. However, during maximal vasodilation these extracardiac forces, rather than autoregulatory mechanisms, become the main determinant of MBF. According to Laplace’s law, wall tension increases from the subepicardial to subendocardial layer, creating an opposite transmural hyperaemic perfusion gradient, especially in the presence of augmented LV loading conditions.

**Myocardial oxygen consumption**

**Technical aspects**

PET-mediated semi-quantification of oxygen usage can be performed with \([^{11}\text{C}]\text{acetate}\).\textsuperscript{26} Acetate is metabolized completely in the Krebs cycle where it is oxidized and the \([^{11}\text{C}]\text{activity}\) is transported to carbon-11 labelled dioxide. Since the heart is an aerobic organ, relying almost exclusively on oxidation of metabolic substrates for the generation of energy, myocardial \([^{11}\text{C}]\text{acetate}\) clearance therefore equals the oxidative flux through mitochondria. As a result of the tight coupling between the Krebs cycle and oxidative phosphorylation, the early clearance rate of \([^{11}\text{C}]\text{acetate}\) after i.v. administration strongly correlates with myocardial oxygen consumption (MVO\textsubscript{2}) (Figure 1) under a wide range of physiological conditions, and therefore serves as an index of oxygen usage.\textsuperscript{27} Next to exponential curve fitting, other methodological approaches to (semi)quantify oxidative metabolism include the use of a tracer kinetic model which enables estimation of MVO\textsubscript{2} in absolute terms, albeit less validated and hence currently limited to research protocols.\textsuperscript{28}

**Myocardial oxygen consumption in HCM**

It has been shown that myocardial oxidative metabolism per gram of myocardial tissue in HCM is comparable with controls,\textsuperscript{6,29} or slightly decreased.\textsuperscript{7,9} However, oxygen usage was consistently reduced in hypertrophied segments, i.e. the interventricular septum, when compared with the lateral wall,\textsuperscript{5–9} whereas oxygen usage in healthy subjects is comparable among LV segments.\textsuperscript{6,7} Several mechanisms may explain these findings. First, hypokinesia of hypertrophied segments as indicated by impaired circumferential shortening,\textsuperscript{5,17,18,30} or decreased systolic wall thickening,\textsuperscript{5} 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. Finally, regional uncoupling between oxidative metabolism and function as a result of abnormal energy handling and altered substrate metabolism may affect non-invasive estimation of oxygen consumption as well.

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. This is presumably attributable to increased RV loading due to LV diastolic dysfunction. [11C]acetate PET studies in patients with 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.

Myocardial energy efficiency

Technical aspects

By combining estimates of stroke work (SW) and MVO2 of the LV, myocardial ME can be calculated according to the following equation:

\[
ME = \frac{SW \cdot HR}{1.33 \times 10^{-4} \cdot MVO2 \cdot LVM^{20}}
\]

where the numerator basically defines the amount of energy produced by the LV per minute in absolute terms (i.e. in units of joule), and the denominator defines the amount of energy consumed by the LV per minute in joules. Consequently, the ratio indicates the conversion of MVO2 to ‘useful’ cardiac work, and reflects the energy efficiency of the myocardium.

Myocardial efficiency in HCM

Non-invasive studies have demonstrated that myocardial efficiency is significantly reduced in HCM patients, averaging at nearly half the values observed in healthy subjects. Although oxygen consumption is generally unaltered, SW is disproportionally decreased in relation to MVO2. Patients with LVH due to hypertension show similar normalization of MVO2 at the cost of work generation, suggesting that mechano-energetic uncoupling is a hallmark of pathological hypertrophy itself. Correspondingly, the left ventricular mass (LVM) was shown to be an independent predictor of impaired efficiency in HCM patients. 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 when compared with the non-hypertrophied lateral wall. Nonetheless, the relationship between deteriorated energetics in HCM and cardiac hypertrophy appears to be bidirectional at the least. 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. Altogether, these findings suggest the presence of additional mechanisms that affect myocardial metabolism across the entire myocardium. Repetitive stunning or myocardial hibernation due to ischaemia is associated with reduced energy efficiency.
myopathy, regardless of its cause.36,37 altered substrate metabolism is a final common pathway in cardio- and replacement fibrosis,17,39 causing heart failure and potential arrhythmias on the long term. Hence, microvascular dysfunction could also contribute to this pathophysiological cascade. Other potential mechanisms that may affect myocardial efficiency include altered substrate metabolism. For example, PET studies using \(^{18}\text{F}\)-fluorodeoxyglucose (FDG) as a marker of glucose metabolism have revealed reduced FDG activity in the hypertrophied septum.9 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.29 Similar findings of increased myocardial FFA dependence have been noted in patients with DCM, suggesting that altered substrate metabolism is a final common pathway in cardiomyopathy, regardless of its cause.36,37

Proposed HCM pathogenesis

Severe microvascular dysfunction represents a predisposing factor for myocardial ischaemia, and leads to contractile dysfunction and replacement fibrosis,17,39 causing heart failure and potential arrhythmias on the long term. Hence, microvascular dysfunction is considered to play an important role in HCM pathogenesis, as depicted in Figure 3. Recent evidence has shown, however, that phenotype-negative carriers of the MYBPC3 mutation are characterized by reduced myocardial efficiency in the absence of myocardial perfusion defects.40 Correspondingly, early studies regarding myocardial phosphate metabolism in HCM using \(^{31}\text{P}\) NMR spectroscopy already showed an accumulation of low-energy phosphates (i.e. an increased Pi/PCr ratio), indicating a decreased mitochondrial ATP reserve.1 These results imply that impaired energetics are, at least in part, the direct result of ATP-wastage by mutated sarcomeres, and may precede coronary microvascular dysfunction in the pathophysiological cascade. Interestingly, subtle abnormalities in LV relaxation (a highly energy-requiring process) can already be observed in asymptomatic HCM mutation carriers.41 HCM-causing mutations increase sarcromeric Ca\(^{2+}\) sensitivity, ATPase activity, and the energetic cost of myocyte contraction. These abnormalities led to the hypothesis that the pathophysiology of HCM may primarily be attributable to excessive sarcomeric energy use, incremental cardiomyocyte strain, and concomitant up-regulation of pro-remodelling neurohormonal feedback loops such as the renin–angiotensin–aldosterone system.42 The resulting cardiomyocyte hypertrophy, interstitial collagen deposition, and myofibre disarray, accompanied by microvascular dysfunction due to vascular remodelling, limit cardiomyocyte oxygen delivery and further exacerbate the primary energy deficiency (Figure 3).

Effects of therapeutic interventions

Enhancing myocardial perfusion and augmenting mechanical efficiency by pharmacological antagonization of the neurohormonal system or cardiac resynchronization therapy has been proved to favourably affect outcome in patients with DCM.43,44 Hence, similar treatment strategies are a promising new avenue in HCM. In the following paragraph, the effects of various therapeutic interventions on the aforementioned pathophysiological principles underlying abnormal myocardial perfusion and energy efficiency in HCM will be discussed in detail according to (semi-)recent PET literature.

Improving myocardial perfusion

Left ventricular afterload conditions and wall stress

Numerous studies have shown that relief of LVOT obstruction may reduce stress perfusion defects in HCM.13,45–48 LVOT obstruction can be relieved by septal reduction therapies (i.e. non-surgical alcohol septal ablation (ASA) or surgical myectomy) or dual chamber pacing, and alleviate symptoms in drug-refractory patients with obstructive HCM.46,49 A recent study investigating the long-term effect of septal reduction therapies on myocardial perfusion expanded upon early semi-quantitative SPECT investigations. It was found that relief of LVOT obstruction by ASA resulted in a significant improvement in the global CVR,13 and was predominantly attributable to an increase in hMBF. Furthermore, it was shown that hMBF was mainly augmented at the subendocardial level after relief of LVOT obstruction, the increments of which were directly related to the absolute reduction in afterload.25,46 Complementary to these results, another study showed that improvement of the CVR following septal myectomy was mainly caused by a reduction of resting MBF.45 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. A similar mode of action has been observed in dual chamber pacing, where right ventricular apex pacing may reduce the LVOT gradient by inducing mechanical

**Figure 2** Aligned scatter plot depicting previously published results for mechanical efficiency values in controls,6 carriers,39 HCM patients,6 and obstructive HCM patients before ASA (pre-ASA HOCM), and after ASA (post-ASA HOCM).13

**Figure 3**
dyssynchrony and an abnormal septum motion. Contemporary PET studies show that the CVR of the hypertrophied septum was significantly increased, resulting in a more homogeneous distribution of perfusion.\textsuperscript{50}

Diastolic dysfunction and perfusion
During systole, perfusion of the subendocardium is compromised due to the epicardial origin of the coronary vasculature, and requires compensatory recovery during diastole. Hence, shortened diastolic perfusion as a result of prolonged relaxation may hamper hMBF as well. Correspondingly, treatment with calcium-antagonist verapamil may ameliorate myocardial perfusion defects at the subendocardial level,\textsuperscript{51,52} by exerting negative inotropic effects, augmenting myocardial relaxation, and hence improving diastolic perfusion.

Myocardial capillary density and coronary remodelling
In addition to the short-term effects of afterload reduction on microvascular function by altering the LV haemodynamic profile, regression of LVH and reversed coronary arteriolar remodelling on the long term may also improve perfusion in HCM, in analogy to patients with pressure-overload cardiomyopathy due to aortic stenosis\textsuperscript{53} or hypertension.\textsuperscript{54}

Figure 3 Schematic representation of proposed HCM pathogenesis. Intrinsic as well as extrinsic factors contribute to microvascular dysfunction in HCM, which in turn causes LV dysfunction, fibrosis, and impairment of myocardial efficiency. Conversely, myocardial fibrosis may also contribute to microvascular dysfunction (dotted line). Furthermore, recent evidence suggests a direct link between the sarcomeric mutation and impaired energetics.

Enhancing myocardial energetics
Myocardial oxygen metabolism and mechanical efficiency
Limited data are available regarding the effect of therapeutic interventions on myocardial metabolism and energy efficiency in HCM. Early invasive data in obstructive HCM already showed a direct relationship between the magnitude of postoperative reduction in LVOT gradient following septal myectomy, and reduction in oxygen usage.\textsuperscript{46} In a more recent study investigating the effects of ASA on mechanical efficiency by the use of PET, relief of LVOT obstruction by ASA did not significantly affect mean MVO\textsubscript{2} in seven patients.\textsuperscript{13} However, due to a substantial reduction in the LVM as a result of reversed remodelling 6 months after the procedure, the amount of work per gram of myocardial tissue was significantly increased, thereby significantly increasing the mechanical efficiency from 15 to 20\% (Figure 2). Recent evidence also suggests that the beneficial effects of ASA extend beyond the LV and may favourably affect RV energetics as well by reducing RV afterload and oxygen usage.\textsuperscript{31}

Contrary to the potentially beneficial effects of the relief of LVOT obstruction on myocardial energetics by septal reduction therapies, dual chamber pacing induces mechanical dyssynchrony of the LV (i.e. contraction of the interventricular septum and of the lateral
Conflict of interest: none declared.

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