Chapter 3

Determinants of Myocardial Energetics and Efficiency in Symptomatic Hypertrophic Cardiomyopathy


Abstract

**Background:** Next to hypertrophy, hypertrophic cardiomyopathy (HCM) is characterized by alterations in myocardial energetics. A small number of studies have shown that myocardial external efficiency (MEE), defined by external work (EW) in relation to myocardial oxidative metabolism (MVO₂), is reduced. The present study was conducted to identify determinants of MEE in patients with HCM by use of dynamic positron emission tomography (PET) and cardiovascular magnetic resonance imaging (CMR).

**Methods:** Twenty patients with HCM (12 men, mean age 55.2 ± 13.9 years) and 11 healthy controls (7 men, mean age 48.1 ± 10 years) were studied with ¹¹C-acetate PET to assess MVO₂. CMR was performed to determine LV volumes, mass (LVM). Univariate and multivariate analyses were employed to determine independent predictors of myocardial efficiency.

**Results:** Between study groups, MVO₂ (controls, 0.12 ± 0.04 mL·min⁻¹·g⁻¹, HCM, 0.13 ± 0.05 mL·min⁻¹·g⁻¹, P = 0.64) and EW (controls, 9139 ± 2484 mmHg·mL, HCM, 9368 ± 2907 mmHg·mL, P = 0.83) were comparable, whereas LVM was significantly higher (controls, 99 ± 21 g, HCM, 200 ± 76 g, P < 0.001) and MEE was decreased in HCM patients (controls, 35 ± 8%, HCM, 21 ± 10%, P < 0.001). MEE was related to stroke volume (SV), LV outflow tract gradient, NT-proBNP, and serum free fatty acid levels (all P < 0.05). Multivariate analysis revealed that SV (β = 0.74, P < 0.001) and LVM (β = -0.43, P = 0.013) were independently related to MEE.

**Conclusion:** HCM is characterized by unaltered MVO₂, impaired EW generation per gram of myocardial tissue and subsequent deteriorated myocardial efficiency. Mechanical external efficiency could independently be predicted by SV and LVM.
Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease phenotypically expressed by left ventricular (LV) hypertrophy, which predominantly affects the interventricular septum (1). In addition, HCM is characterized by alterations in myocardial energy metabolism. Ishiwata et al. demonstrated that cardiac work in relation to oxidative metabolism, i.e. myocardial efficiency, was reduced not only in the hypertrophied septum but also in the lateral wall (2). Similarly, an impaired energetic status as reflected by the phosphocreatine / adenosine triphosphate ratio, derived by $^{31}$P spectroscopy, has been documented in different stages of the disease process (3-6). Although prognostic data related to an impaired energetic state in HCM are lacking, in analogy with other cardiomyopathies, it is believed to be of prognostic relevance (7;8). Insights into the mechanism and causative factors of altered energy metabolism could therefore be of clinical importance in risk stratification, and the development and application of (new) therapeutic approaches. Recent advances in imaging techniques offer the possibility to accurately assess myocardial oxygen consumption (MVO$_2$), regional mechanical work, and tissue characteristics non-invasively using dynamic positron emission tomography (PET) (9;10) and cardiac magnetic resonance imaging (CMR) (11-13), respectively. The present study was conducted to identify the determinants of impaired myocardial energetics and efficiency in patients with symptomatic HCM with the use of these currently available advanced imaging techniques.

Methods

Subjects

Twenty patients with symptomatic HCM were enrolled in the study. HCM was diagnosed according to the presence of a hypertrophied and non-dilated left ventricle on two-dimensional echocardiography in the absence of any other systemic or cardiac disease (maximal wall thickness >15 mm in adults or >13 mm in relatives of a HCM patient) (14). All patients were using betablockers or calcium channel blocking agents, which were not discontinued. Eleven healthy adults with normal physical examination, two-dimensional echocardiography and electrocardiogram without a relevant medical history served as controls. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands.
Imaging protocols

PET

All PET scans were obtained under resting conditions after overnight fasting, in two-dimensional mode, by use of an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn). A transmission scan was performed using three rod sources filled with $^{68}$Ga/$^{68}$Ge solution. Subsequently, 550 MBq of $^{11}$C-acetate was injected and simultaneously a dynamic 29 frame acquisition was performed lasting 48 min (12×10, 3×20, 4×60, 3×120 and 7×300 sec). During the PET acquisition, venous blood was drawn and N\textsubscript{H}$_2$-terminal pro-brain natriuretic peptide (NT-proBNP, expressed in ng/L), hemoglobin (Hb), free fatty acids (FFA), glucose, and lactate levels were determined. Blood pressure and heart rate were recorded at regular intervals during the PET studies.

CMR

CMR studies were performed on a 1.5-Tesla whole body scanner (Magnetom Sonata, Siemens, Erlangen, Germany), using a six-channel phased-array body coil.

After survey scans, a retro-triggered, balanced steady-state free precession gradient-echo sequence was used for cine imaging. Image parameters were: slice thickness 5 mm, slice gap 5 mm, temporal resolution <50ms, repetition time 3.2 ms, echo time 1.54 ms, flip angle 60 degrees and a typical image resolution of 1.3*1.6 mm. The number of phases within the cardiac cycle was set at twenty.

After the 4-, 3-, and 2-chamber view cines were obtained, a stack of 6-10 transversely oriented slices was planned on an end-diastolic (ED) 2-chamber view at the level of the lower leading edge of the mitral valve annulus to cover the left atrium (LA) (15). Then, a stack of 10-12 short axis slices were acquired for full coverage of the LV used for assessing LV volumes, mass and ejection fraction (Fig 1). The method of planning the image acquisition for LV coverage has been described previously (16). Cine images were acquired during one breath-hold in mild expiration.

Aortic flow measurements were performed with a nonbreath-hold, retrospective, ECG-triggered, phase-contrast velocity mapping sequence with the encoding velocity set at 150 cm s$^{-1}$. The image plane was planned on a coronal view of the thorax, perpendicular to the ascending aorta. Acquisition of the entire cardiac cycle was achieved by setting the acquisition window to 120% of the cardiac cycle length. To minimize the effects of Eddy Currents and Maxwell gradients on velocity acquisition, patients were positioned in the isocenter of the scanner.
Cine imaging with myocardial tagging was applied to create noninvasive markers (tags) within the myocardium for calculation of strain (11). Three short-axis tagged images with complementary spatial modulation of magnetization tagging for improved strain calculations were acquired as previously described (17).

Delayed contrast enhanced (DCE) images were acquired 10-15 minutes after intravenous administration of 0.2 mmol/kg Gadolinium, by using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence. Inversion-recovery time was 250-300 ms. Fig. 1 illustrates examples of CMR cine and tagging images during ED and end-systole (ES) as well as a DCE image and phase-contrast velocity map, all representative for the HCM phenotype.

**Echocardiography**

Transthoracic two-dimensional echocardiography was performed on Vivid 7 (General Electrics-Vingmed, Milwaukee, WI). The peak pressure gradient over the LV outflow tract (LVOTG) was estimated by use of pulsed-wave Doppler at rest.

**Data analysis**

**PET**

Data were transferred to a SUN workstation and analyzed using Siemens/CTI software and MATLAB. Regions of interest (ROIs) were defined manually on the maximum intensity ¹¹C-acetate short axis images at the basal, midventricular and apical level of the left ventricle according to a 13-segment model as described previously in detail (18). This set of ROIs was projected onto the ¹¹C-acetate images to generate time-activity curves (TAC). The linear myocardial wash-out part of the ¹¹C-acetate TAC was determined automatically and fitted in a monoexponential fashion to determine $K_{monc}$, which corresponds to oxidative metabolism (10). For each individual PET data set, average, septal and lateral wall $K_{monc}$ values were determined. Average $K_{monc}$ was derived from the weighed mean of all segmental $K_{monc}$ values, whereas regionally corresponding segments were combined to generate septal and lateral wall $K_{monc}$. To derive $MVO_2$ from average $K_{monc}$, a relationship between $K_{monc}$ and myocardial oxygen metabolism (mL·min⁻¹·g⁻¹), previously established in humans, was used, where $K_{monc} = 0.0027(MVO_2) + 0.0197$ (19). Since $MVO_2$ expresses the oxygen consumption per minute, myocardial oxygen consumption per beat was also determined ($MVO_2(beat) = MVO_2/HR$).
Figure 1. Examples of CMR short-axis cine images at (A) end-diastole and (A’) end-systole. CMR short-axis tagging images at (B) end-diastole and (B’) end-systole with characteristically decreased septal deformation compared to the lateral wall at end-systole. C. CMR short-axis delayed contrast enhancement image with a patchy appearance. D. Aortic velocity-encoded phase-contrast flow map. S, septum; L, lateral wall.

CMR

Left ventricular volume analysis was performed by manually drawing epicardial and endocardial contours on all ED and ES LV short-axis images. Global LV function parameters, including ED volume (LVEDV), ES volume (LVESV), ejection fraction (LVEF), and myocardial mass, were then derived from the cine images with use of the MASS software package (MEDIS, Leiden, The Netherlands). For LA diameter analysis, epicardial contours were drawn on all LA data sets in ES. The forward SV was obtained from the velocity-encoded phase-contrast aortic flow maps by dividing the forward cardiac output by heart rate (HR).
The tagging images were used to generate circumferential strain curves for each myocardial segment. Subsequently, circumferential shortening ($E_{cc}$), which reflects maximum myocardial contraction, was derived for each segment from the strain curves (17). Since circumferential shortening is determined by the shortening of myofibers, $E_{cc}$ is expressed as a negative value. Similar average, septal and lateral wall segmentation was used as described for the PET data. Finally, each myocardial segment was evaluated for the presence of hyperenhancement, which was defined as an area of signal enhancement greater than 5 SD of the signal of nonenhanced myocardium. The extent of DCE was expressed as the percentage of the total myocardial tissue area studied.

**Calculation of myocardial efficiency**

As illustrated by Fig. 2, total mechanical energy 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. The pressure-volume area (PVA) was defined as the sum of external work (EW) and potential energy (PE).

![Diagram of pressure-volume area](image)

**Figure 2.** Schematic representation of a pressure-volume area (PVA). *EW*, external work; *PE*, potential energy; *ESPVR*, end-systolic pressure-volume relation; *EDPVR*, end-diastolic pressure-volume relation
External work was determined according to the factor of mean arterial pressure (MAP) and forward stroke volume (SV). In the HCM group, individually obtained estimations of the LVOTG were added to the MAP to ensure accurate estimations of actual LV pressures in case of outflow tract obstruction. Since the end-diastolic pressure-volume point was not available, it was set to zero. The slope of the ESPVR, $E_{es(1b)}$, expressed in mm Hg mL$^{-1}$, was estimated by use of a previously validated single-beat method (20). Subsequently, the x-axis intercept of the ESPVR was calculated from which point PE and, thus, PVA could be calculated. When the x-axis intercept was negative, it was set to zero. The caloric equivalent of 1 mmHg · mL equals $1.33 \cdot 10^{-4}$ J, whereas 1 mL of O$_2$ is $\approx 20$ J. Subsequently, mechanical external efficiency (MEE) was calculated according to the equation below (10).

$$\text{MEE} = \frac{\text{EW} \cdot \text{HR} \cdot 1.33 \cdot 10^{-4}}{\text{MVO}_2 \cdot \text{LVM} \cdot 20}$$

Mechanical efficiency (ME) was similarly calculated by substituting EW for PVA area. In addition, the ratio between EW and PVA served as an index for mechanical conversion efficiency. Regional efficiency was determined as the ratio between regional $E_{cc}$ and the corresponding $\text{MVO}_2(\text{beat})$, where more negative values indicate increased efficiency.

**Statistics**

Results are displayed as mean ± SD. Differences between the patients with HCM and controls were assessed by the unpaired Student’s $t$-test. The significance of intraindividual differences between the septum and lateral wall were determined with the paired Student's $t$-test. Correlations between variables were evaluated with linear equation analysis. Univariate and multivariate analyses were employed to determine independent predictors of mechanical external efficiency. In the multivariate analyses, stepwise manual backward selection was applied with a removing probability for each variable of $\geq 0.1$. All tests were two-sided and $P$ values < 0.05 were considered statistically significant. Analyses were performed using SPSS 15.0 (Chicago, Illinois).
Results

Characteristics of both study groups are shown in table 1. Left ventricular mass (LVM), left atrial size (LA-size), NT-proBNP, serum FFA and DCE were all significantly increased in the HCM group. No significant difference between groups was found for sex, age, body surface area (BSA), forward stroke volume (SV), left ventricular ejection fraction (LVEF), hemoglobin (Hb), and serum lactate and glucose levels.

<table>
<thead>
<tr>
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<th>HCM (N = 20)</th>
<th>Controls (N = 11)</th>
<th>P</th>
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<tbody>
<tr>
<td>Sex</td>
<td>12 men</td>
<td>7 men</td>
<td>0.85</td>
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<tr>
<td>Age (yr)</td>
<td>55 ± 14</td>
<td>48 ± 10</td>
<td>0.15</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>0.72</td>
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<tr>
<td>LVM (g)</td>
<td>200 ± 76</td>
<td>99 ± 21</td>
<td>0.001</td>
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<td>SV (mL)</td>
<td>87 ± 24</td>
<td>102 ± 26</td>
<td>0.12</td>
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<tr>
<td>LVEF (%)</td>
<td>61 ± 7</td>
<td>61 ± 5</td>
<td>0.98</td>
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<tr>
<td>LA-size (mm)</td>
<td>144 ± 41</td>
<td>101 ± 21</td>
<td>0.003</td>
</tr>
<tr>
<td>NT-proBNP (ng·L⁻¹)</td>
<td>619 ± 638</td>
<td>61 ± 53</td>
<td>0.001</td>
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<tr>
<td>Hb (mmol·L⁻¹)</td>
<td>8.5 ± 0.4</td>
<td>8.3 ± 0.5</td>
<td>0.34</td>
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<tr>
<td>FFA (mmol·L⁻¹)</td>
<td>0.70 ± 0.20</td>
<td>0.52 ± 0.23</td>
<td>0.041</td>
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<tr>
<td>Glucose (mmol·L⁻¹)</td>
<td>5.2 ± 1.3</td>
<td>5.6 ± 0.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Lactate (mmol·L⁻¹)</td>
<td>1.10 ± 0.61</td>
<td>1.46 ± 0.65</td>
<td>0.15</td>
</tr>
<tr>
<td>DCE (%)</td>
<td>4.1 ± 2.4</td>
<td>0</td>
<td>&lt; 0.001</td>
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Table 1. Study population characteristics. BSA, body surface area; LVM, left ventricular mass; SV, stroke volume; LVEF, left ventricular ejection fraction; LA-size, maximal left atrial size; NT-proBNP, NH₂-terminal pro-brain natriuretic peptide; Hb, hemoglobin; FFA, free fatty acids; DCE, delayed contrast enhancement.
Hemodynamics

Hemodynamic parameters obtained during PET for the HCM and control group are presented in table 2. Left ventricular outflow tract gradients as well as mean LV pressures were significantly higher in HCM patients (both $P < 0.001$), whereas arterial blood pressures and heart rates were comparable.

<table>
<thead>
<tr>
<th></th>
<th>HCM</th>
<th>Controls</th>
<th>$P$</th>
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<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>128 ± 21</td>
<td>122 ± 12</td>
<td>0.48</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>70 ± 8</td>
<td>73 ± 9</td>
<td>0.46</td>
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<tr>
<td>LVOTG (mmHg)</td>
<td>22 ± 11</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
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<td>LVMAP (mmHg)</td>
<td>113 ± 23</td>
<td>89 ± 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>63 ± 10</td>
<td>67 ± 11</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Oxygen metabolism</strong></td>
<td></td>
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<tr>
<td>$MVO_2$ (mL·min$^{-1}$·g$^{-1}$)</td>
<td>0.13 ± 0.05</td>
<td>0.12 ± 0.04</td>
<td>0.64</td>
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<tr>
<td><strong>Contractile function</strong></td>
<td></td>
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<tr>
<td>$E_{es(sb)}$ (mmHg·mL$^{-1}$)</td>
<td>1.42 ± 0.61</td>
<td>1.15 ± 0.36</td>
<td>0.30</td>
</tr>
<tr>
<td>EW (mmHg·mL)</td>
<td>9368 ± 2907</td>
<td>9139 ± 2484</td>
<td>0.83</td>
</tr>
<tr>
<td>PE (mmHg·mL)</td>
<td>3507 ± 1216</td>
<td>2921 ± 910</td>
<td>0.17</td>
</tr>
<tr>
<td>PVA (mmHg·mL)</td>
<td>12875 ± 3704</td>
<td>12060 ± 3004</td>
<td>0.54</td>
</tr>
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</table>

**Table 2.** Hemodynamics, myocardial oxygen metabolism and contractile parameters. $BP$, blood pressure; $LVOTG$, Left ventricular outflow tract gradient; $LVMAP$, left ventricular mean arterial pressure; $MVO_2$, myocardial oxygen consumption; $E_{es(sb)}$, single-beat estimation of $E_{es}$; $EW$, external work; $PE$, potential energy; $PVA$, pressure volume area.
Myocardial metabolism and contractile parameters

PET derived estimates of myocardial oxygen consumption and MRI obtained contractile parameters are also depicted in table 2. MVO$_2$ was comparable between groups ($P = 0.64$), as well as $E_{es(sib)}$ ($P = 0.30$). In addition, no significant differences were found between groups for EW ($P = 0.83$), PE ($P = 0.17$) and PVA ($P = 0.54$).

Myocardial efficiency
Table 3 lists the estimated efficiency values of HCM patients and controls. Mechanical external efficiency was significantly decreased in the HCM group as compared to the control group ($P < 0.001$), as well as ME ($P < 0.001$). In contrast, mechanical conversion efficiency did not differ between groups ($P = 0.80$).

<table>
<thead>
<tr>
<th></th>
<th>HCM</th>
<th>Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical external efficiency (EW/MVO$_2$)</td>
<td>21 ± 10%</td>
<td>35 ± 8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mechanical efficiency (PVA/MVO$_2$)</td>
<td>30 ± 14%</td>
<td>51 ± 12%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mechanical conversion efficiency (EW/PVA)</td>
<td>70 ± 6%</td>
<td>70 ± 7%</td>
<td>0.80</td>
</tr>
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</table>

Table 3. Myocardial efficiency. EW, external work; PVA, pressure volume area; MVO$_2$, myocardial oxygen consumption.

Determinants of mechanical external efficiency

The results of univariate and multivariate regression analyses of MEE are depicted in table 4. Mechanical external efficiency was significantly and positively correlated to SV, whereas an inverse correlation was observed with LVOTG, NT-proBNP levels and FFA. When multivariate analysis was performed, SV and LVM remained independent predictors of MEE, and these two factors could predict 83% of MEE values.
Table 4. Univariate and multivariate regression analysis of determinants of MEE in patients with HCM. BSA, body surface area; LA-size, maximal left atrial size; LVM, left ventricular mass; SV, forward stroke volume; LVEF, left ventricular ejection fraction; NT-proBNP, NH2-terminal pro-brain natriuretic.

**Regional myocardial metabolism and efficiency**

Fig. 3 A represents MVO2 values for the septum and lateral wall in HCM patients and control subjects. In the HCM group, septal MVO2(beat) was significantly lower compared to the lateral wall (1.82 ± 0.63 · 10⁻³ mL · beat⁻¹ · g⁻¹ and 1.91 ± 0.65 · 10⁻³ mL · beat⁻¹ · g⁻¹ respectively, P = 0.006). In contrast, septal MVO2(beat) in the control group was comparable to the lateral wall (1.95 ± 0.55 · 10⁻³ mL · beat⁻¹ · g⁻¹ and 1.89 ± 0.57 · 10⁻³ mL · beat⁻¹ · g⁻¹ respectively, P = 0.69). Regional Ecc values for the septum and lateral wall in the HCM and control group are depicted in Fig. 3 B. In the HCM group, septal Ecc averaged -13.0 ± 2.5% and was significantly lower compared to the lateral wall (-15.8 ± 1.9%, P < 0.001), whereas in the
control group $E_{cc}$ did not display regional differences (septum, $-17.7 \pm 1.8\%$, lateral wall, $-18.6 \pm 2.6\%$, $P = 0.22$). Consequently, regional efficiency of septum averaged $-7740 \pm 2927$ and was significantly lower compared to the lateral wall in the HCM group ($-8917 \pm 3767$, $P = 0.006$). In contrast, regional efficiency in the control group was comparable between the septum and lateral wall ($-10187 \pm 3507$ and $-10924 \pm 4401$, respectively, $P = 0.21$) as illustrated by Fig. 3 C. Between groups, regional efficiency of the septum was significantly decreased in the HCM group ($P = 0.05$), whereas the lateral wall was comparable ($P = 0.20$).

Figure 3 A. Regional MVO$_2$ of the septum and lateral free wall in the control and HCM group. B. Regional $E_{cc}$ of the septum and lateral free wall in the control and HCM group. C. Regional efficiency of the septum and lateral free wall in the control and HCM group. MVO$_2$, myocardial oxygen consumption; HCM, hypertrophic cardiomyopathy.
**Discussion**

The present study demonstrates that MVO$_2$ and EW in HCM patients are comparable to controls. External work generated per gram of myocardial tissue, however, is impaired in HCM, resulting in decreased mechanical external efficiency. In addition, septal contractility was declined compared to the lateral wall resulting in significant heterogeneity of regional efficiency. Therefore, symptomatic HCM is characterized by a disproportional reduction of work in relation to oxygen expenditure, from both a global and a regional point of view.

**Myocardial metabolism and contractile parameters**

The present finding of unaltered MVO$_2$ in patients with symptomatic HCM is in line with previous invasive investigations (21;22;23). Similarly, noninvasive $^{11}$C-acetate studies in HCM have demonstrated MVO$_2$ in HCM to be comparable to controls (24), or slightly decreased (2;25).

The current results show that both left ventricular EW and PVA are comparable between HCM and controls. However, when corrected for LV mass, EW and PVA generated per gram of myocardium were significantly decreased in HCM, in line with other invasive (22), and noninvasive studies (2;24). Although not reaching statistical significance, a trend towards an increased slope of the ESPVR was observed in the HCM study group, consistent with an invasive study by Meliga and coworkers in 10 symptomatic patients with obstructive HCM (26).

**Myocardial efficiency**

Despite unaltered oxygen usage, EW and PVA per gram of myocardium are disproportionately decreased in relation to oxygen consumption, and therefore occur at the expense of myocardial efficiency (2;24). In line with the currently presented data, an early invasive study by Thompson and coworkers in 13 patients with obstructive HCM revealed a MEE of 21% (22). Patients with essential hypertension and LVH show similar pseudonormalization of MVO$_2$ accompanied by decreased EW generation per gram of myocardium (27), suggesting that mechanoenergetic uncoupling is a distinctive feature in pathological hypertrophy (8;10).

Whether deteriorated energetics in HCM is the consequence of LVH, or the cause of LVH, remains unclear. Nonetheless, impaired energy metabolism in HCM exists even in the absence of LVH, suggesting that compromised energetics, due to
detrimental effects of sarcomere mutations, play a causal role in the early stages of hypertrophy development (28). Concordantly, HCM cardiomyocytes exhibiting sarcomeric mutations, show inefficient ATP utilization, resulting in an increased cost of force generation and consequent excess demand on myocytes (29). Clearly, more studies regarding this issue are warranted.

In contrast to the above, mechanical conversion efficiency remained unaltered between groups and was fairly consistent with investigations in healthy adults (30;31). This indicates that, despite impaired PVA due to inefficient energetics, the transferral ratio from energy production to effective work is sustained.

**Regional efficiency**

HCM hearts exhibit marked heterogeneity in regional contractile properties (32-34). Correspondingly, we have shown that septal $E_c$ was significantly decreased as compared to the lateral wall in the HCM group. Hence, patients with HCM exhibited marked heterogeneity in regional efficiency, especially due to deteriorated energetics of hypertrophied septum, whereas no significant differences in regional efficiency were observed in the control group. Interestingly, regional efficiency of the lateral wall tended to be lower in HCM patients, when compared to controls, also suggesting global impairment of energetics in HCM patients. Ishiwata et al. have produced similar results indicating a decreased work production to oxygen expenditure ratio in the septum, compared to the lateral wall in HCM (2). A potential explanation for these regional differences, besides the extent in hypertrophy, could be the characteristic presence of myofiber disarray in HCM, which can predominantly be found in the interventricular septum located at the insertions with the right ventricle. These oppositely contracting myocytes do not result in an effective contraction pattern and therefore may contribute to reduced mechanical efficiency (35).

**Determinants of MEE**

As depicted in Fig. 4, deteriorated MEE was independently correlated to smaller SV and increased LVM. Since SV and LVM are, among other cardiac parameters, used to calculate MEE, these results are not startling. Nevertheless, these factors appear to be stronger determinants of MEE than outflow tract obstruction, heart rate, blood pressure, or global strain, consequently suggesting a larger potential for therapeutic interventions regarding preservation of SV and/or regression of LVM (24). In addition, the present study reveals that increased hemodynamic pre- and afterload conditions, reflected by NT-proBNP levels and outflow tract
obstruction, are also important factors related to MEE. Where the extent of DCE has been shown to be of independent predictive value to impaired efficiency in patients with HCM (36), this could not be reproduced in the present study.

Finally, next to higher FFA serum concentrations in HCM, we also observed a significant inverse relation between FFA and MEE in these patients. These increased serum levels of FFA may be related to an augmented sympathetic drive, a well-documented phenomenon in cardiomyopathy and heart failure. This change in metabolic milieu, in turn, may induce a metabolic switch from myocardial glucose to FFA oxidation (24). As substrate metabolism affects the ratio of adenosine triphosphate (ATP) produced per oxygen molecule consumed, i.e. glucose metabolism yields 11% to 13% more ATP per unit of oxygen consumption compared with FFA metabolism, this potential metabolic switch affects mechanical efficiency and could explain the observed correlation between MEE and serum FFA levels in the present study.(10) On the other hand, Tadamura and coworkers observed a switch from FFA to the more efficient glucose oxidation in the presence of hypertrophy (25). Although it is clear that substrate metabolism in HCM is subject to changes and affects efficiency, future investigations in carefully selected study groups are warranted to further demarcate this issue.

**Clinical implications**

The current results could provide new insight into the currently applied therapeutic approaches in HCM. Restoring favorable myocardial energetics and, thereby possibly augmenting LV function and improving prognosis, would require preservation of SV and regression of LVM. Surgical myectomy or alcohol ablation of the interventricular septum in HCM patients reduces LVM, by relief of LV outflow tract obstruction, thereby decreasing extravascular compression forces and inducing chamber remodeling (37;38;39). Therefore, regression of afterload-dependent LVH after such a procedure may result in more favorable myocardial energetics in HCM patients.

**Study Limitations**

In the present study we used a previously obtained relationship, obtained in healthy humans, to extrapolate MVO₂ from regional ¹¹C-acetate clearance rates. However, it is unkown whether this relation is valid in HCM patients, since Kₘₙ₀ is dependent on arterial input, extraction and washout of tracer, altered hemodynamic and metabolic condition of the myocardium.
Furthermore, noninvasive estimation of work and contractile function is hindered by some important factors. The presence of valvular disease, such as mitral regurgitation in the HCM group could lead to overestimation of SV, and thus efficiency, because part of the LV volume is ejected in the low-pressured left atrium during systole. We circumvented the latter issue by using forward SV only, acquired by MRI flow measurements in the aortic root. In addition, EW is represented as a rectangle in the present study (Fig. 2), not taking into account the area under the EDPVR curve. This results in overestimated EW and subsequent overestimation of MEE values, especially in patients with decreased LV diastolic elastance (i.e. patients with HCM). A range of PV-loops under different loading conditions (e.g. by vena cava inferior occlusion) is warranted to accurately determine the EDPVR as well as the ESPVR. However, with a recently proposed single-beat method, E_{es(sb)} could be obtained non-invasively. The left ventricular end-systolic elastance ensues a parabolic shape, and therefore little underestimation or overestimation of E_{es} cannot be ruled out.

**Conclusion**

Symptomatic HCM is characterized by unaltered MVO_2, impaired EW generation per gram of myocardial tissue and subsequent deteriorated myocardial efficiency. Mechanical external efficiency could independently be predicted by SV and LVM.
Reference List

Chapter 3


