Chapter 5

Effects of Alcohol Septal Ablation on Coronary Microvascular Function and Myocardial Energetics in Hypertrophic Obstructive Cardiomyopathy


Abstract

Background: To investigate the effects of alcohol septal ablation (ASA) on microcirculatory function and myocardial energetics in patients with hypertrophic cardiomyopathy (HCM) and left ventricular outflow tract (LVOT) obstruction.

Methods: In fifteen HCM patients who underwent ASA, echocardiography was performed prior to and 6 months after the procedure to assess LVOTG. Additionally, $[^{15}\text{O}]$water PET was performed to obtain resting myocardial blood flow (MBF) and coronary vasodilator reserve (CVR). Changes in LV mass (LVM) and volumes were assessed by CMR. Myocardial oxygen consumption (MVO$_2$) was evaluated by $[^{11}\text{C}]$acetate PET in a subset of 7 patients to calculate myocardial external efficiency (MEE).

Results: After ASA, peak LVOTG decreased from 41±32 to 23±19 mmHg, $p=0.04$, as well as LVM (215±74 to 169±63 g, $p<0.001$). MBF remained unchanged (0.94±0.23 to 0.98±0.15 mL.min$^{-1}$.g$^{-1}$, $p=0.45$), whereas CVR increased (2.55±1.23 to 3.05±1.24, $p=0.05$). Preoperatively, the endo-to-epicardial MBF ratio was lower during hyperemia compared to rest (0.80±0.18 vs. 1.18±0.15, $p<0.001$). After ASA, the endo-to-epi hMBF ratio increased to 1.03±0.26 ($p=0.02$). Delta CVR was correlated to delta LVOTG ($r=-0.82$, $p<0.001$) and delta LVM ($r=-0.54$, $p=0.04$). MEE increased from 15±6 to 20±9% ($p=0.04$).

Conclusion: Coronary microvascular dysfunction in obstructive HCM is at least in part reversible by relief of LVOT obstruction. After ASA, hMBF and CVR increased predominantly in the subendocardium. The improvement in CVR was closely correlated to the absolute reduction in peak LVOTG, suggesting a pronounced effect of LV loading conditions on microvascular function of the subendocardium. Furthermore, ASA has favourable effects on myocardial energetics.
Introduction

In approximately one quarter patients affected by hypertrophic cardiomyopathy (HCM), the disease process of asymmetrical septal hypertrophy is complicated by dynamic left ventricular outflow tract (LVOT) obstruction due to bulging of the thickened septum into the outflow tract and abnormal anterior motion of the of the mitral valve during systole.(26) Recent studies have demonstrated that the increased LV loading condition accompanied with LVOT obstruction is associated with coronary microvascular dysfunction.(20,42) The poorer prognosis of outflow tract obstruction in HCM is, at least in part, believed to be mediated by the induction of myocardial ischaemia.(6,9,26,27) Furthermore, myocardial energetics and efficiency are impaired in HCM.(15,39,46) The latter may, in analogy with dilated cardiomyopathy, hold prognostic relevance.(22,31,32) Treatment strategies to alter the clinical course of HCM may therefore be targeted at enhancing coronary microvascular function and/or restoring myocardial energetics.

Alcohol septal ablation (ASA) reduces LVOT obstruction and alleviates symptoms in patients with HCM.(40) Although randomized trials are lacking, relief of LVOT obstruction is associated with a more favourable prognosis.(33) The reduction in LV loading conditions and regression of LV hypertrophy (LVH), due to reversed remodeling, could restore perfusion and improve myocardial energetics.(48) Indeed, previous investigations suggest that perfusion reserve is improved after LVOT obstruction relief.(3,4,16,34,41,51) These studies, however, have been conducted with semi-quantitative perfusion indices. Furthermore, data regarding the effects of ASA on myocardial energetics and efficiency are currently lacking. The present study was therefore conducted to study the effects of ASA on coronary microvascular dysfunction and energetics in patients with HCM, using positron emission tomography (PET), echocardiography, and cardiovascular magnetic resonance imaging (CMR).(19,21)

Methods

Fifteen patients with obstructive HCM undergoing ASA (10 men and 5 women, mean age 55 ± 9 years) were enrolled in the study. HCM was diagnosed by the presence of a nondilated and hypertrophied LV, in the absence of any other systemic or cardiac causes of LV hypertrophy, on 2-dimensional (2D) echocardiography (maximal wall thickness > 15 mm in adult patients). All patients exhibited an asymmetrical pattern of septal hypertrophy. Coronary angiography was only performed prior to inclusion, in order to exclude coronary
artery disease (CAD) and myocardial bridging. The indication for ASA was based on a significant peak LVOT gradient (LVOTG ≥ 50 mmHg at rest or during Valsalva maneuver measured with Doppler echocardiography) and symptoms (New York Heart Association (NYHA) Class II or III, despite medical therapy). The ASA procedure was performed as described previously.\cite{49} The imaging protocol consisted of echocardiography, PET and CMR within one week prior to and 6 months after ASA. Medication was kept constant during the study. The study was approved by the medical ethics committees of all participating centers and all patients gave written informed consent.

**Imaging protocol**

**PET**

All scans were performed in 2D mode, using an ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tennessee, USA). The protocol was performed as previously described.\cite{18,21} In short, after overnight fasting, myocardial blood flow (MBF) was measured using 1100 MBq of oxygen-15-labeled water under resting conditions and during pharmacologically induced hyperemia with adenosine (140 μg•kg⁻¹•min⁻¹), and oxidative metabolism was assessed using 550 MBq [¹¹C]acetate.

Transaxial parametric MBF images were generated as described previously,\cite{2} as well as maximum intensity [¹¹C]acetate uptake images. Subsequently, these images were reoriented according to the anatomic axis of the heart and slices were displayed as short-axis slices. The same reslicing parameters were applied to the dynamic [¹⁵O]water and [¹¹C]acetate images. Regions of interest (ROIs) were defined on these images corresponding to septal, anterior, lateral, and inferior walls of the left ventricle in the basal, mid, and apical planes.\cite{18} ROIs that did not display water / acetate uptake after ASA (i.e. indicative of scar tissue) were excluded from analysis. Additional ROIs were defined in the left atrial and right ventricular chamber. This latter set of ROIs was projected onto the dynamic [¹⁵O]water images in order to generate tissue time activity curves (TAC). These TACs were used as image-derived input functions and for use in spill-over correction of myocardial tissue TACs. Using the standard single tissue compartment model together with these input functions, MBF (mL•min⁻¹•g⁻¹ of perfusable tissue) was determined for all myocardial tissue time activity curves. Corrections were made for left and right ventricular spillover effects by use of the method described by Hermansen et al.\cite{13} Kmono was fitted from the washout phase of the [¹¹C]acetate scan as an index of oxidative metabolism.\cite{21} For the [¹⁵O]water images, additional subendocardial and subepicardial layers were
identified by dividing myocardial ROIs with a central line. Coronary vasodilator reserve (CVR) was calculated as the ratio of hyperemic MBF to resting MBF. As resting MBF is related to the LV rate-pressure-product (LV RPP = (systolic blood pressure + peak LVOTG) • heart rate (HR)), corrected resting MBF (MBF • LV RPP⁻¹ • 10.000) was also determined. Additionally, LV RPP during hyperemia was calculated. Resting coronary microvascular resistance (CMVR) was calculated by dividing mean arterial pressure (MAP) with MBF, whilst minimal CMVR was derived in a similar fashion, only during infusion of adenosine.(19)

**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 < 50 ms, 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).(10) Subsequently, a stack of 10-12 short axis slices were acquired for full coverage of the LV.(25) Cine images were acquired during one breath-hold in mild expiration. Left ventricular volume analysis was performed by manually drawing epicardial and endocardial contours on all ED and end-systolic (ES) LV short-axis images. Global LV function parameters, including ED volume (LVEDV), ES volume (LVESV), and LV mass (LVM), were then derived from the cine images with use of the MASS software package (MEDIS, Leiden, The Netherlands). The forward stroke volume (SV) was obtained from the velocity-encoded phase-contrast aortic flow maps by dividing the forward cardiac output by HR.

Delayed contrast enhanced (DCE) images were acquired 10-15 minutes after intravenous administration of 0.2 mmol•kg⁻¹ gadolinium, by using a 2D segmented inversion-recovery prepared gradient-echo sequence. Inversion-recovery time was 250-300 ms. Hyperenhancement was defined as an area of signal enhancement greater than 5 SD of the signal of nonenhanced myocardium.
Echocardiography

Transthoracic echocardiography was performed using a Vivid 7 (General Electrics-Vingmed, Milwaukee, Wisconsin, USA), according to the ACC/AHA/ASE guidelines.(7) Pulsed-wave Doppler was used to derive the peak outflow tract pressure gradient (peak LVOTG) across the subvalvular obstruction, as well as the mean LVOTG. Mitral regurgitation (MR) and systolic anterior motion of the mitral valve (SAM) were graded qualitatively. LV ejection time (LVET) was measured on the continuous wave Doppler trace from the opening to the closure of the aortic valve.

Diastolic perfusion time calculation

The R-R interval was measured at rest and during hyperemia on the ECG obtained during the PET scan. Diastolic perfusion time (DPT) (seconds • min⁻¹) = (R-R interval - LVET) • heart rate was subsequently calculated during rest and hyperemia.

Myocardial external efficiency

MEE was calculated according to the equation depicted below.(21,46) External work (EW) was defined as the product of SV derived by MRI and mean LVOTG plus mean arterial pressure (MAP). The caloric equivalent of 1 mmHg•mL is $1.33 \cdot 10^{-4}$ J, whereas 1 mL O₂ is $\approx 20$ J.

$$MEE = \frac{EW \cdot HR \cdot 1.33 \cdot 10^{-4}}{MVo_2 \cdot LVM \cdot 20}$$

Statistics

Data were expressed as mean ± SD. For comparison of two data sets, a paired or unpaired Student’s t test was performed where appropriate. For the comparison of multiple data sets, one-way analysis of variance (ANOVA) was applied with post hoc Bonferroni adjustment for inequality. Linear regression was used to analyze the relationship between variables. All analyses were performed using SPSS 14 (SPSS Inc., Chicago, Illinois, USA). A p value < 0.05 was considered statistically significant.
Results

Study population characteristics

Baseline and follow up characteristics are depicted in table 1. All HCM patients except three, in whom side effects were considered intolerable, used β-receptor blockers and/or Ca\textsuperscript{2+} channel-blockers. Baseline peak LVOTG during the imaging protocol averaged 41 ± 32 mmHg. After ASA, peak LVOTG was significantly reduced to 23 ± 19 mmHg ($p = 0.04$). Thirteen patients exhibited a certain degree of MR at baseline (grade 1, $n = 4$; grade 2, $n = 6$; grade 3, $n = 3$; grade 4, $n = 0$). NYHA class at baseline was 2.7 ± 0.61, and was significantly reduced to 1.9 ± 0.42 after ASA ($p = 0.01$).

<table>
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<th>Baseline (n = 15)</th>
<th>Follow up (n = 15)</th>
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<tr>
<td>peak LVOTG (mmHg)</td>
<td>41 ± 32</td>
<td>23 ± 19</td>
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<td>MI (grade)</td>
<td>1.8 ± 0.9</td>
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<td><strong>CMR</strong></td>
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<td>LVM (g)</td>
<td>215 ± 74</td>
<td>169 ± 63</td>
<td>&lt;0.001</td>
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<td>LVEDV (mL)</td>
<td>192 ± 30</td>
<td>184 ± 28</td>
<td>0.23</td>
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<td>LVESV (mL)</td>
<td>72 ± 6</td>
<td>71 ± 22</td>
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<td>SV (mL)</td>
<td>86 ± 27</td>
<td>92 ± 18</td>
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<td>LA-size (mL)</td>
<td>161 ± 71</td>
<td>138 ± 56</td>
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Table 1. Echocardiographic and cardiovascular magnetic resonance data at baseline and during follow up. LVOTG, left ventricular outflow tract gradient; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LA-size, left atrial size.
**Hemodynamic data**

Heart rates were comparable between baseline and follow-up studies, both at rest and during hyperemia (Table 2). Systolic blood pressure (SBP) at rest was significantly increased ($p = 0.04$). To the contrary, there was no difference in resting diastolic blood pressure (DBP), resting LV mean arterial pressure (MAP), or hyperemic blood pressures. Resting LV RPP was not significantly altered after ASA (10292 ± 3884 to 8979 ± 1949 mmHg•bpm•min^{-1}, $p = 0.34$), nor was hyperemic LV RPP (13137 ± 4338 to 11795 ± 2884 mmHg•bpm•min^{-1}, $p = 0.29$).

<table>
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<tr>
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<th>Rest</th>
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<td>62 ± 9</td>
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<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>127 ± 26</td>
<td>139 ± 22</td>
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<td><strong>DBP (mmHg)</strong></td>
<td>74 ± 9</td>
<td>77 ± 7</td>
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<tr>
<td><strong>LV MAP (mmHg)</strong></td>
<td>105 ± 16</td>
<td>105 ± 13</td>
</tr>
<tr>
<td><strong>LV RPP (mmHg •bpm•min^{-1})</strong></td>
<td>10292 ± 3884</td>
<td>8979 ± 1949</td>
</tr>
</tbody>
</table>

*Table 2.* Hemodynamics during the PET studies at baseline and during follow up. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LV MAP, left ventricular + mean arterial pressure; LV RPP, left ventricular rate-pressure product.

**LVM, LV dimensions and DCE**

As listed in Table 1, LVM decreased significantly, LVEDV and LVESV were not significantly altered, whereas SV increased and LA size decreased.

On average, infarct size was $16 \pm 6 \text{ g}$ at 6 months after ASA, and covered $9 \pm 4\%$ of total LVM. In all patients, the infarct extended transmurally throughout the interventricular septum, predominantly involving the antero- and inferobasal
segments. There was no evidence for infarct-related hyperenhancement in remote myocardial segments.

**Transmural MBF**

ASA did not significantly affect global resting transmural MBF (0.94 ± 0.23 to 0.98 ± 0.15 mL·min⁻¹·g⁻¹, p = 0.45) (Fig. 1A), or MBF corr (1.00 ± 0.37 to 1.12 ± 0.34 mL·min⁻¹·g⁻¹, p = 0.10). Preoperatively, the distribution pattern of resting MBF was somewhat heterogeneous, with lower MBF in the septum than the lateral wall, although not reaching statistical significance (p = 0.15, Table 3). After ASA, a similar heterogeneous distribution pattern of transmural resting MBF was observed (p = 0.10).

Global transmural hMBF did increase significantly postoperatively from 2.25 ± 0.91 to 2.94 ± 1.18 mL·min⁻¹·g⁻¹ (p = 0.013, Fig. 1A), as well as CVR (2.55 ± 1.23 to 3.05 ± 1.24, p = 0.05) and CVR corr (2.38 ± 0.99 to 2.88 ± 1.14, p = 0.03). Preoperatively, regional perfusion differences at rest became homogeneous during adenosine infusion, with hMBF not being significantly different between the septum and lateral wall (p = 0.61, Table 3). After ASA, the distribution pattern of hMBF remained homogeneous (p = 0.38).

![Figure 1A](image_url)

**Figure 1A.** Baseline and follow up data for global transmural MBF at rest and during hyperemia, and (B) the endo-to-epicardial MBF ratio at rest and during hyperemia.
Endo-to-epicardial MBF

As listed in Table 3, endocardial MBF at baseline was higher than epicardial MBF, although not reaching statistical significance. During hyperemia, endocardial MBF increased to a lesser extent than epicardial MBF, resulting in a decreased endo-to-epicardial hMBF ratio, compared to rest (0.80 ± 0.18 vs. 1.18 ± 0.15, \( p < 0.001 \), Fig. 1B). After ASA, the endo-to-epicardial MBF ratio at rest was not significantly altered. The endo-to-epicardial hMBF ratio, however, did increase (\( p = 0.02 \), Fig. 1B), mainly due to a significant increase in endocardial hMBF (\( p = 0.004 \), Table 3). As a result, CVR was increased in the subendocardium after ASA (\( p = 0.03 \)), but not in the subepicardium (\( p = 0.90 \), Table 3).

![Figure 1B](image)

**Figure 1B.** Baseline and follow up data the endo-to-epicardial MBF ratio at rest and during hyperemia.

Coronary microvascular resistance and diastolic perfusion time

CMVR at rest was comparable between baseline and follow-up (102 ± 26 to 101 ± 14 mmHg•ml⁻¹•min⁻¹•g⁻¹, \( p = 0.88 \)), whereas minimal CMVR was slightly decreased after ASA, although not reaching statistical significance (42 ± 18 to 34 ± 16 mmHg•ml⁻¹•min⁻¹•g⁻¹, \( p = 0.07 \)). ASA did not affect DPT at rest (40.6 ± 4.0 vs. 40.6 ± 2.3 s•min⁻¹, \( p = 0.97 \)), or during hyperemia (32.8 ± 4.9 vs 32.8 ± 4.1 s•min⁻¹, \( p = 0.98 \)).
<table>
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<tr>
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<th>Rest</th>
<th>Hyperemia</th>
<th>CVR</th>
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<tr>
<td></td>
<td>Endo</td>
<td>Epi</td>
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<tr>
<td>Endo/Epi</td>
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<tr>
<td>Baseline</td>
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<td>0.89 ± 0.26</td>
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<tr>
<td>Follow up</td>
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<td>Baseline</td>
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<td>Follow up</td>
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<td>$p$</td>
<td>0.76</td>
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Table 3. Subendocardial, subepicardial and regional MBF, hMBF and CVR at baseline and during follow up. *Endo and Epi, subendocardial and subepicardial blood flow (expressed in mL/min⁻¹•g⁻¹); CVR, coronary vasodilator reserve.* 

* $p < 0.01$ vs. rest.
Myocardial oxygen consumption and myocardial efficiency

Table 4 lists the estimated MVO$_2$ and MEE values of 7 HCM patients at baseline and after ASA. MVO$_2$ was comparable between studies ($p = 0.25$), whereas MEE increased significantly from $15 \pm 6\%$ to $20 \pm 9\%$ (Fig. 2).

![Graph showing myocardial efficiency comparison between baseline and follow-up](image)

Figure 2. Baseline and follow up data for myocardial efficiency.

Univariate relationships between variables

Univariate regression analysis revealed a significant relationship between the absolute change in workload (as defined by the LV RPP) and the absolute change in resting MBF ($r = 0.71$, $p = 0.004$), hMBF ($r = -0.50$, $p = 0.05$) and CVR ($r = -0.79$, $p < 0.001$). Additionally, the absolute change in resting LV RPP after ASA was directly correlated to the absolute change in MVO$_2$ ($r = 0.74$, $p = 0.05$).
There was no relationship between the absolute change in LVOTG and change in resting MBF after ASA. The absolute change in LVOTG was, however, inversely related to the absolute change in CVR (Fig. 3).

**Figure 3.** Linear relationship between the absolute change in CVR and the absolute change in peak LVOTG at six months after ASA. The dotted lines represent the 95% confidence interval of the regression line.

There was also no relationship between regression of LVH (as defined by the absolute change in LVM) and the absolute change in transmural resting MBF, but a significant inverse relationship with the absolute change in LVM and CVR (Fig. 4).

There was a significant relationship between the absolute change in hyperemic DPT and CVR (Fig. 5).
Figure 4. Linear relationship between the absolute change in CVR and the absolute change in LVM at six months after ASA. The dotted lines represent the 95% confidence interval of the regression line.

Figure 5. Linear relationship between the absolute change in CVR and the absolute change in hyperemic DPT at six months after ASA. The dotted lines represent the 95% confidence interval of the regression line.
<table>
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<tr>
<th>Patient no.</th>
<th>EW (mmHg•mL)</th>
<th>HR (bpm)</th>
<th>LVM (g)</th>
<th>MVO$_2$ (mL•min$^{-1}$•g$^{-1}$)</th>
<th>MEE (%)</th>
<th>EW (mmHg•mL)</th>
<th>HR (bpm)</th>
<th>LVM (g)</th>
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<tr>
<td>Mean ± SD</td>
<td>8375 ± 2385</td>
<td>63 ± 7</td>
<td>231 ± 100</td>
<td>0.12 ± 0.03</td>
<td>15 ± 6</td>
<td>8390 ± 1998</td>
<td>68 ± 13</td>
<td>188 ± 79*</td>
<td>0.13 ± 0.03</td>
<td>20 ± 9*</td>
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</table>

Table 4. Cardiovascular magnetic resonance, oxidative metabolism and myocardial efficiency data of the subset of HCM patients. *p < 0.05 vs. baseline. EW, external work; HR, heart rate; LVM, left ventricular mass; MVO$_2$, myocardial oxygen consumption; MEE, myocardial external efficiency.
Discussion

In the present study, transmural hMBF and CVR were significantly increased after ASA, indicating that impairment of microcirculatory function in obstructive HCM is, at least in part, reversible by relief of LVOT obstruction. The improvement in CVR was attributable to increased hMBF, especially in the subendocardial layers, and was closely correlated to the absolute reduction in peak LVOTG, as well as to regression of LVM albeit to lesser extent. As a result, the endo-to-epicardial hMBF ratio increased after ASA, suggesting a pronounced effect of LV loading conditions on microvascular function of the subendocardium. These results expand on previous semi-quantitative investigations regarding the effects of relief of LVOT obstruction on perfusion in HCM patients, by using $^{15}$Owater PET to study absolute changes in regional MBF. In addition, it was demonstrated for the first time that myocardial efficiency improves after ASA in patients with LVOT obstruction due to HCM, by use of $^{11}$Cacetate PET.

Effects of ASA on transmural MBF

The blunted CVR that characterizes HCM, in the absence of epicardial coronary stenosis, is indicative of microvascular dysfunction.(6) In these patients, CVR is predominantly limited by an inadequate increase in MBF in response to adenosine,(24,35,43) compared to age-matched healthy subjects.(47) Microcirculatory function is impaired for several reasons in HCM. Histological examination has revealed remodeling of intramural coronary arterioles resulting in a decreased cross-sectional arteriolar lumen area,(28,45) and concomitant increase in coronary vascular resistance.(23) Additionally, pathological LVH is accompanied by a decreased capillary-to-myocyte ratio,(23,45) i.e. a relative reduction in capillary density, the extent of which has been shown to independently predict the reduction in hMBF in HCM,(20) when calculated on the basis of milliliters per gram of myocardial tissue.

The absolute increase in CVR after ASA was correlated to regression of LVM. Albeit a moderately strong relationship, the results are in accordance to a recent study conducted by Soliman et al.(41) Similar results have been found in patients with pressure-overload cardiomyopathy due to aortic stenosis,(14,36) or hypertension,(1) indicating that restoration of the capillary density by regression of afterload dependent LVH or reversed remodeling of arteriolar walls has favourable microcirculatory effects.

In addition to the aforementioned morphological features, LV loading conditions and wall stress, i.e. extravascular compressive forces, can further compromise microcirculatory function.(42) In HCM, CVR is more severely blunted in patients
with LVOT obstruction compared to patients without,\(^{5,17}\) and the absolute reduction in CVR has been shown to parallel the severity of LVOT obstruction.\(^{4}\) Whilst patients with LVOT obstruction due to aortic stenosis show similar blunting of CVR,\(^{37}\) coronary arteriole remodeling is absent in these patients,\(^{44}\) providing additional evidence that augmented extravascular resistance substantially impedes perfusion. During maximal vasodilatation, these extravascular forces in addition to intravascular resistance, rather than autoregulatory mechanisms itself, become the main determinant of MBF.\(^{19}\) In line with this hypothesis, the improvement in CVR after ASA was directly correlated to the absolute reduction in peak LVOTG. Contrary to these results, Jörg-Ciopor et al. showed that improvement of CVR following septal myectomy was mainly caused by a reduction of resting MBF.\(^{17}\) However, since pre-interventional MBF was not studied, the results were compared to a group of medically treated HOCM patients, thereby impeding valid interpretation of the effects of treatment on myocardial perfusion in the myectomy group. In addition, the RPP in the medically treated group was higher as compared to the myectomy group, and inasmuch as resting MBF is autoregulated according to oxygen demand, this may explain the differences in resting MBF between groups.

**Effects of ASA on endo-to-epicardial MBF**

According to Laplace’s law, wall tension increases from the subepi-to-subendocardial layer, hence creating an opposite transmural hyperemic perfusion pattern, especially in the presence of augmented LV loading conditions.\(^{8}\) Indeed, relief of the LVOT obstruction significantly improved the endo-to-epicardial MBF ratio during hyperemia. Interestingly, endocardial CVR was increased by nearly 30%, whereas epicardial CVR was not at all affected by ASA.

Diastolic filling of the epicardial arterioles and accompanied subepicardium precedes perfusion of the subendocardial layers, due to the epicardial origin of the coronary vasculature. The physiological implication is that during systole, perfusion at the subendocardium is compromised, requiring compensatory recovery from diastolic perfusion. A shortened DPT as a result of LVOT obstruction may theoretically hamper perfusion. Accordingly, a moderately strong positive correlation was found between the absolute change in CVR and hyperemic DPT after relief of LVOT obstruction, the strength of which was increased when only subendocardial CVR was included \(r = 0.68, p = 0.01\). Although absolute myocardial perfusion is related to DPT, as previously documented in patients with aortic valve stenosis as well,\(^{38}\) mean DPT did not significantly change between baseline and follow up. Hence, the observed changes in CVR after ASA cannot be attributed to changes in diastolic perfusion.
Effects of ASA on LVM and LV dimensions

Relief of LVOT obstruction by ASA or surgical myectomy of the septum has been associated with reversed remodeling of the LV in previous HCM investigations.\(^{(29,51)}\) This can be ascribed to a combination of alcohol induced scarring and thinning of the hypertrophied septum and regression of afterload dependent LVH, the latter presumably contributing most to LV mass reduction.\(^{(48)}\)

In our study, LVEDV and LVESV were not significantly changed postoperatively, contrary to other investigations who generally report significant increases in LV volumes.\(^{(29,30,48,50)}\) LA dimensions, however, were significantly decreased postoperatively, likely reflecting favourable effects of ASA on diastolic function and reduction of mitral regurgitation.\(^{(11)}\)

Effects of ASA on myocardial oxygen consumption and efficiency

Only limited data is available on the effect of ASA on MVO\(_2\). In the current study, both MVO\(_2\) and LV RPP as an indirect marker of MVO\(_2\) were not significantly affected by ASA. Individual changes in MVO\(_2\), however, could be related to the changes in LV RPP, suggesting that decrements in oxidative metabolism after ASA can mainly be ascribed to reduced workload due to relief of LVOT obstruction, as described earlier by Cannon et al.\(^{(4)}\)

Previously, it was demonstrated that mechanical external efficiency (MEE) is decreased compared to healthy subjects, and could independently be predicted by SV and LVM.\(^{(46)}\) Although peak LVOTG was significantly reduced postoperatively, the total amount of work delivered by the LV was not altered, and was mainly attributable to a significant increase in forward SV. However, due to a substantial reduction in LVM, the amount of work per gram of myocardial tissue was significantly increased. The absence of a concomitant increase in MVO\(_2\) per gram of myocardial tissue resulted in an increased MEE.

Technical considerations

Rimoldi and coworkers have previously validated \(^{[15O]}\)water measurements of subendo-to-subepicardial MBF in pigs, by comparison with radioactive microspheres, using a PET scanner with a similar resolution \((\sim 6.5\) mm\) as in this study.\(^{(38)}\) It was demonstrated that PET subendo- and subepicardial perfusion are in fairly good agreement with the microsphere values, over a wide range of MBF \((0.30 – 4.46\) mL/min/g\). Since the pigs had a small LV wall thickness \((\sim 10\) mm\), flow measurements were affected by partial-volume effects, due to the limited scanner resolution. Hence, this could have influenced our results as well.
In human hearts, however, $[{^{15}\text{O}}]$water PET measurements are less confounded by partial-volume effects due to a larger LV wall thickness, especially in the currently studied hypertrophied hearts. Furthermore, Rimoldi et al. found that transmural flow differences were actually underestimated, i.e. subendocardial perfusion was overestimated and subepicardial perfusion was underestimated, because of the large spillover component between both myocardial layers. Thinning of the myocardial wall after ASA will increase partial-volume effects, due to treatment induced scarring of the septum and regression of afterload-dependent LVH. As a result, the actual border between the endocardial and epicardial layer may also be changed. The effect on measurements of global endo-to-epicardial flow ratios is expected to be minimal, however, inasmuch as significant postoperative reduction of LV wall thickness occurs only in the septum (~16%), and is small throughout remote myocardium (~10%).(48) Furthermore, postoperative hMBF was comparable between the subendo- and subepicardial layers. Hence, flow measurements in both layers do not suffer from spillover from one another, as they are similar in tracer activity, thereby leaving the subendo-to-subepicardial hMBF ratio unaffected by partial-volume effects. Altogether, this suggests that the actual treatment-induced improvement in the subendo-to-subepicardial hMBF ratio may be greater than currently measured, due to overestimation of the baseline endo-to-epicardial hMBF ratio. In this matter, however, future PET studies incorporating improved spatial resolution seem warranted.

**Limitations**

Despite the fact that all patients had a significant LVOTG at the time of inclusion either at rest or during Valsalva maneuver, the degree of LVOT obstruction during preoperative imaging varied considerably intra-individually, and a significant LVOT obstruction at rest (i.e. $\geq 50$ mmHg at rest) was observed in only 60% of patients (i.e. 9 had significant LVOT obstruction at rest, 6 only during provocation). The pressure gradient across the LVOT in HCM has been shown to be dependent upon ventricular filling and myocardial inotropy, and the results therefore underline the dynamic aspect of LVOT obstruction in these patients.(12) Consequently, however, the absolute reduction of LVOTG by ASA was limited in a number of patients, especially with provokable obstruction only, and even resulted in a substantial increase in one subject. Although unsuccessful reduction of LVOT obstruction in these subjects is not uncommon,(48,49) and presumably explains the substantial variations in MBF improvement following ASA, the data require validation in a cohort of HCM patients with severe resting obstruction. Nevertheless, the results clearly indicate a significant overall benefit in coronary vasodilatory capacity after ASA in the currently studied cohort, the
largest improvement of which was observed in subjects with the greatest absolute LVOTG reduction.

LVOTG was determined during resting conditions and related to hyperemic perfusion induced by adenosine infusion. During vasodilating stress, however, pre- and afterload values may indeed be altered. Although data are lacking, in HCM patients adenosine likely augments LVOTG. In addition, hyperemic diastolic perfusion time was calculated under the presumption that ejection time between rest and stress conditions was the same. This may have introduced bias into the relationship between diastolic perfusion time, LVOTG and MBF.

Only a limited number of HCM patients was studied with $[^{11}\text{C}]$acetate PET, and therefore the results regarding the effects of ASA on myocardial efficiency should be interpreted with care. Additionally, due to $[^{11}\text{C}]$acetate kinetics, myocardial scar tissue is not included in estimates of oxidative metabolism. To prevent underestimation of myocardial efficiency after ASA, the septally located alcohol induced infarct zone was subtracted from total LVM when calculating MEE.

The noninvasive estimation of EW in HCM is hampered by the presence of mitral regurgitation, because part of the blood volume is ejected into the low-pressure LA during systole, as indicated by the discrepancy between LV enddiastolic and -systolic volumes and SV. We largely circumvented this issue by using forward SV only, acquired by MRI flow measurements in the ascending aorta.

The continued use of medication during the study protocol could have introduced bias in the results. On the other hand, inasmuch as medication was kept constant, intra-individual variability was expected to be minimal between studies. Additionally, myocardial haemodynamics and $[^{15}\text{O}]$water PET studies were obtained simultaneously to further minimize intra-individual changes.

**Conclusion**

Coronary microvascular dysfunction in obstructive HCM is at least in part reversible by relief of LVOT obstruction. After ASA, hMBF and CVR were predominantly increased in the subendocardial layers of the myocardium. The improvement in CVR was closely related to the absolute reduction in peak LVOTG, and to a lesser degree to regression of LVM. These results suggest a pronounced effect of LV loading conditions on microvascular function of the subendocardium, in addition to LV hypertrophy. Furthermore, ASA has favourable effects on myocardial energetics in HCM.
References


PART II


