Effects of alcohol septal ablation on coronary microvascular function and myocardial energetics in hypertrophic obstructive cardiomyopathy

Stefan A. J. Timmer,1 Paul Knaapen,1 Tjeerd Germans,1 Pieter A. Dijkmans,1 Mark Lubberink,2 Jurrien M. ten Berg,4 Folkert J. ten Cate,5 Iris K. Rüssel,3 Marco J. W. Götte,1 Adriaan A. Lammertasma,2 and Albert C. van Rossum1

1Department of Cardiology, 2Department of Nuclear Medicine and PET Research, and 3Department of Physics and Medical Technology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam; 4Department of Cardiology, St. Antonius Hospital, Nieuwegein; and 5Department of Cardiology, Thoraxcenter Erasmus Medical Center, Rotterdam, The Netherlands

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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 favorable 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 semiquantitative 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 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 of 55 ± 9 yr) 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 LVH, 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, to exclude coronary artery disease 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 (49). The imaging protocol consisted of echocardiography, PET, and CMR within 1 wk before and 6 mo after ASA. Medication was kept constant during the study. The study was approved by the VU University Medical Center, St. Antonius Hosp-

Address for reprint requests and other correspondence: P. Knaapen, Dept. of Cardiology, 5F, VU Univ. Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands (e-mail: p.knaapen@vumc.nl).
Imaging Protocol

PET. All scans were performed in 2D mode, using an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN). The protocol was performed as previously described (18, 21). In short, after overnight fasting, myocardial blood flow (MBF) was measured using 1,100 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 (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 LV in the basal, mid, and apical planes (18). ROIs that did not display water/acetate uptake after ASA (i.e., indicative of scar tissue) were excluded from analysis. Additionally ROIs were defined in the left atrial and right ventricular chamber. This latter set of ROIs was projected onto the dynamic [¹⁵O]water images to generate tissue time activity curves (TACs). These TACs were used as image-derived input functions and for use in spill-over correction of myocardial tissue TACs. With the use of the standard single tissue compartment model together with these input functions, MBF (ml·min⁻¹·g⁻¹ of perfusible 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. (13). An̄mono was fitted from the washout phase of the [¹¹C]acetate scan as an index of oxidative metabolism (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 (hMBF) 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 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, while 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 as follows: 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°, and a typical image resolution: 1.3 × 1.6 mm. The number of phases within the cardiac cycle was set at 20.

After the four-, three-, and two-chamber view cines were obtained, a stack of 6–10 transversely oriented slices was planned on an end-diastolic (ED) two-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. LV 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 images were acquired 10–15 min after intravenous administration of 0.2 mmol/kg 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 >5 SD of the signal of nonenhanced myocardium.

Echoangiography. Transthoracic echocardiography was performed using a Vivid 7 (General Electrics-Vingmed, Milwaukee, WI), 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 and systolic anterior motion of the mitral valve 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) (s/min) = (R-R interval − LVET)·HR was subsequently calculated during rest and hyperemia.

Myocardial External Efficiency

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 MAP. The caloric equivalent of 1 mmHg·ml is 1.33·10⁻⁴ J, whereas 1 ml O₂ is ~ 20 J.

\[
MEE = \frac{EW \cdot HR \cdot 1.33 \cdot 10^{-4}}{MV_{O2} \cdot LVM \cdot 20}
\]

Statistics

Data are expressed as means ± 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 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, Chicago, IL). 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 ß-receptor blockers and/or Ca²⁺ 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 mitral regurgitation 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).

Hemodynamic Data

HRs were comparable between baseline and follow-up studies, both at rest and during hyperemia (Table 2). Systolic blood pressure at rest was significantly increased (P = 0.04). To the contrary, there was no difference in resting diastolic blood pressure, resting LV MAP, or hyperemic blood pressures.
Resting LV RPP was not significantly altered after ASA (10,292 ± 3,884 to 8,979 ± 1,949 mmHg·beats·min⁻¹·min⁻¹; P = 0.34) nor was hyperemic LV RPP (13,137 ± 4,338 to 11,795 ± 2,884 mmHg·min; P = 0.29).

**LVM, LV Dimensions, and Delayed Contrast Enhanced Images**

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

On average, infarct size was 16 ± 6 g at 6 mo after ASA and covered 9 ± 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 corrected MBF (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 corrected CVR (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).

**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 with rest (0.80 ± 0.23 to 0.72 ± 0.22; P = 0.05).

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**Table 1. Echocardiographic and cardiovascular magnetic resonance data at baseline and during follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 15)</th>
<th>Follow-up (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LVOTG, mmHg</td>
<td>41 ± 32</td>
<td>23 ± 19</td>
<td>0.04</td>
</tr>
<tr>
<td>MR (grade)</td>
<td>1.8 ± 0.9</td>
<td>1.5 ± 0.7</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Cardiovascular magnetic resonance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM, g</td>
<td>215 ± 74</td>
<td>169 ± 63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>192 ± 30</td>
<td>184 ± 28</td>
<td>0.23</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>72 ± 6</td>
<td>71 ± 22</td>
<td>0.85</td>
</tr>
<tr>
<td>SV, ml</td>
<td>86 ± 27</td>
<td>92 ± 18</td>
<td>0.02</td>
</tr>
<tr>
<td>LA size, ml</td>
<td>161 ± 71</td>
<td>138 ± 56</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are means ± SD. LVOTG, left ventricular outflow tract gradient; MR, mitral regurgitation; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LA size, left atrial size.

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**Table 2. Hemodynamics during the PET studies at baseline and during follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
<th>Hyperemia</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60 ± 11</td>
<td>62 ± 9</td>
<td>0.70</td>
<td>85 ± 14</td>
<td>87 ± 10</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>127 ± 26</td>
<td>139 ± 22</td>
<td>0.04</td>
<td>114 ± 17</td>
<td>120 ± 23</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74 ± 9</td>
<td>77 ± 7</td>
<td>0.18</td>
<td>66 ± 9</td>
<td>65 ± 7</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>LV MAP, mmHg</td>
<td>105 ± 16</td>
<td>105 ± 13</td>
<td>0.91</td>
<td>98 ± 14</td>
<td>92 ± 15</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>LV RPP, mmHg·min</td>
<td>10,292 ± 3,884</td>
<td>8,979 ± 1,949</td>
<td>0.34</td>
<td>13,137 ± 4,338</td>
<td>11,795 ± 2,884</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. 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.
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).

**CMVR and DPT**

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; P = 0.97) or during hyperemia (32.8 ± 4.9 vs. 32.8 ± 4.1 s/min; P = 0.98).

**Myocardial Oxygen Consumption and Myocardial Efficiency**

Table 4 lists the estimated myocardial oxygen consumption (MV̇O₂) and MEE values of 7 HCM patients at baseline and after ASA. MV̇O₂ was comparable between studies (P = 0.25), whereas MEE increased significantly from 15 ± 6 to 20 ± 9% (Fig. 2).

**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 MV̇O₂ (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).

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).

**DISCUSSION**

In the present study, transmural hMBF and CVR were significantly increased after ASA, indicating that impairment

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**Table 3. Subendocardial, subepicardial and regional MBF, hyperemic MBF, and CVR at baseline and during follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Endo</th>
<th>Epi</th>
<th>P</th>
<th>Endo/Epi</th>
<th>Endo</th>
<th>Epi</th>
<th>P</th>
<th>Endo/Epi</th>
<th>Endo</th>
<th>Epi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>1.03 ± 0.24</td>
<td>0.89 ± 0.26</td>
<td>0.14</td>
<td>1.18 ± 0.15</td>
<td>1.89 ± 0.84*</td>
<td>2.43 ± 0.94*</td>
<td>0.11</td>
<td>0.80 ± 0.18*</td>
<td>1.99 ± 1.11</td>
<td>2.94 ± 1.38</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>1.10 ± 0.15</td>
<td>0.94 ± 0.18</td>
<td>0.01</td>
<td>1.18 ± 0.16</td>
<td>2.82 ± 1.30*</td>
<td>2.71 ± 0.97*</td>
<td>0.80</td>
<td>1.03 ± 0.26</td>
<td>2.63 ± 1.34</td>
<td>2.98 ± 1.21</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.32</td>
<td>0.44</td>
<td></td>
<td>0.88</td>
<td>0.004</td>
<td></td>
<td>0.26</td>
<td></td>
<td>0.02</td>
<td></td>
<td>0.90</td>
</tr>
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</table>

**Table 4. Cardiovascular magnetic resonance, oxidative metabolism, and myocardial efficiency data of the subset of HCM patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>EW, mmHg/ml</th>
<th>HR, beats/min</th>
<th>LVM, g</th>
<th>MV̇O₂, ml·min⁻¹·g⁻¹</th>
<th>MEE, %</th>
<th>EW, mmHg/ml</th>
<th>HR, beats/min</th>
<th>LVM, g</th>
<th>MV̇O₂, ml·min⁻¹·g⁻¹</th>
<th>MEE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12,567</td>
<td>64</td>
<td>203</td>
<td>0.12 ± 0.03</td>
<td>21</td>
<td>10,936</td>
<td>62</td>
<td>161</td>
<td>0.11 ± 0.03</td>
<td>27</td>
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<tr>
<td>2</td>
<td>10,631</td>
<td>67</td>
<td>421</td>
<td>0.08 ± 0.03</td>
<td>14</td>
<td>7,208</td>
<td>93</td>
<td>326</td>
<td>0.14 ± 0.03</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>7,500</td>
<td>69</td>
<td>307</td>
<td>0.12 ± 0.03</td>
<td>9</td>
<td>7,813</td>
<td>52</td>
<td>250</td>
<td>0.09 ± 0.03</td>
<td>13</td>
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<tr>
<td>4</td>
<td>6,486</td>
<td>49</td>
<td>136</td>
<td>0.07 ± 0.03</td>
<td>21</td>
<td>7,840</td>
<td>65</td>
<td>104</td>
<td>0.12 ± 0.03</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>8,260</td>
<td>59</td>
<td>149</td>
<td>0.12 ± 0.03</td>
<td>18</td>
<td>8,573</td>
<td>70</td>
<td>131</td>
<td>0.12 ± 0.03</td>
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<tr>
<td>6</td>
<td>5,980</td>
<td>62</td>
<td>187</td>
<td>0.16 ± 0.03</td>
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<td>5,412</td>
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<td>212</td>
<td>0.14 ± 0.03</td>
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<tr>
<td>7</td>
<td>7,201</td>
<td>70</td>
<td>215</td>
<td>0.13 ± 0.03</td>
<td>12</td>
<td>10,946</td>
<td>64</td>
<td>136</td>
<td>0.17 ± 0.03</td>
<td>24</td>
</tr>
</tbody>
</table>

Means ± SD 8,375 ± 2,385 63 ± 7 231 ± 100 0.12 ± 0.03 15 ± 6 8,390 ± 1,998 68 ± 13 188 ± 79 0.13 ± 0.03 20 ± 9*

Values are means ± SD. Endo and Epi, subendocardial and subepicardial blood flow (expressed in ml·min⁻¹·g⁻¹); MBF, myocardial blood flow; CVR, coronary vasodilator reserve. *P < 0.01 vs. rest.
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 semiquantitative investigations regarding the effects of relief of LVOT obstruction on perfusion in HCM patients by using $^{15}$O-water 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 $^{11}$C-acetate 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 with 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 CVR (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 favorable 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 with patients without (5, 17), and the absolute reduction in CVR has been shown to parallel the severity of LVOT obstruction (4). While 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. (17) showed that improvement of CVR following septal myectomy was mainly caused by a reduction of resting MBF. However, since preinterventional MBF was not studied, the results were compared with a group of medically treated obstructive HCM 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 compared with 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 hyperpermeable 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 subepicardial 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 LVM 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, 48, 50). LA dimensions, however, were significantly decreased postoperatively, likely reflecting favorable effects of ASA on diastolic function and reduction of mitral regurgitation (11).

Effects of ASA on $MVO_2$ and Efficiency

Only limited data are 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 with 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 et al. (38) have previously validated [$^{15}$O]water measurements of subendo-to-subepicardial MBF in pigs, by comparison with radioactive microspheres, using a PET scanner with a similar resolution (~6.5 mm) as in this study. It was demonstrated that PET subendo- and subepicardial perfusion is in fairly good agreement with the microsphere values, over a wide range of MBF (0.30–4.46 ml·min$^{-1}$·g$^{-1}$). Since the pigs had a small LV wall thickness (~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, [$^{15}$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 are 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 intraindividually, and a significant LVOT obstruction at rest (i.e., ≥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 on 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 provocable 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 DPT was calculated under the presumption that ejection time between rest and stress conditions was the same. This may have introduced bias into the relationship among DPT, LVOTG, and MBF.

Only a limited number of HCM patients was studied with [11C]acetate PET, and therefore the results regarding the effects of ASA on myocardial efficiency should be interpreted with care. Additionally, due to [11C]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 was calculated.

The noninvasive estimation of external work in HCM is hampered by the presence of mitral regurgitation, because part of the blood volume is ejected into the low-pressured LA during systole, as indicated by the discrepancy between LV end diastolic 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, intraindividual variability was expected to be minimal between studies. Additionally, myocardial hemodynamics and [15O]water PET studies were obtained simultaneously to further minimize intraindividual 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 LVH. Furthermore, ASA has favorable effects on myocardial energetics in HCM.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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Effects of ASA on perfusion and energetics

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