Myocardial efficiency is an important determinant of functional improvement after aortic valve replacement in aortic valve stenosis patients: a combined PET and CMR study

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Abstract

Aims
The pathophysiology underlying aortic valve stenosis (AVS)-induced cardiac dysfunction and reduced exercise capacity is unclear. We hypothesize that improvement of myocardial external efficiency (MEE) – the ratio between external work and myocardial oxygen consumption (MVO$_2$) – underlies functional improvement of AVS patients after aortic valve replacement (AVR). Therefore, the aim of this proof-of-concept study was to investigate whether myocardial efficiency is reduced in patients with cardiac hypertrophy caused by AVS and to assess the effect of AVR on myocardial efficiency in relation to exercise capacity.

Methods
Echocardiography, cardiopulmonary exercise test, [$^{11}$C]-acetate positron emission tomography and cardiovascular magnetic resonance imaging were performed in 10 AVS patients prior to (pre-AVR) and 4 months after AVR (post-AVR). Fourteen healthy individuals served as control group.

Results
MEE was significantly lower in pre-AVR patients (32 ± 7%) than in controls (49 ± 6%). AVR significantly decreased left ventricle mass and MVO$_2$. Also, external work significantly decreased post-AVR reaching similar values as in controls. AVR significantly improved MEE from 32 ± 7% to 37 ± 5% ($P = 0.02$). Moreover, significant correlations were present between the AVR-induced increase in MEE and changes in both exercise work ($r = 0.74$, $P = 0.01$) and peak VO$_2$ ($r = 0.67$, $P = 0.03$). However, four AVS patients did not show improved MEE, which was associated with no or minimal improvement in exercise parameters.

Conclusions
MEE is significantly reduced in patients with AVS-induced hypertrophy. Improved MEE is an important predictor of AVR-induced improvement of exercise capacity in AVS patients. Future investigation is needed to confirm our observations in a large prospective, multicenter clinical trial.
Effect of aortic valve replacement on myocardial efficiency

Introduction

Aortic valve stenosis (AVS) is the most frequent degenerative valvular heart disease in the Western world with a prevalence of 25% in people aged >65.1, 2 AVS is characterized by pressure overload of the left ventricle (LV), which results in compensatory LV hypertrophy (LVH) to reduce wall stress.2 Although, initially LVH is compensatory, AVS-induced remodelling of the heart becomes maladaptive leading to the development of heart failure and increased risk of sudden cardiac death.3, 4 The pathophysiology underlying AVS-induced cardiac dysfunction and ultimately heart failure is not completely understood. A study in hypertensive patients with LVH revealed a reduction in myocardial efficiency, i.e. the ratio of cardiac work to myocardial oxygen consumption (MVO\textsubscript{2}), which may predispose these patients to heart failure.5 However, the effects of AVS on MVO\textsubscript{2} and myocardial efficiency has not been elucidated yet.6, 7 Hicks et al. found a higher MVO\textsubscript{2} in AVS hearts, while Schwitter et al. reported a lower MVO\textsubscript{2} at a given index of overall LV performance suggesting greater mechanical efficiency in AVS patients than in healthy controls. Clearly, effects of AVS on cardiac work and MVO\textsubscript{2} of the heart, i.e. myocardial efficiency, remain to be established.

Aortic valve replacement (AVR) is the primary treatment in symptomatic AVS patients.8 AVR induced reduction in LV loading leads to reversed remodelling of the LV and is associated with a favourable prognosis.9-15 However, improvement of cardiac performance is variable, as some patients show deterioration of functional status and exercise capacity after AVR.16, 17 Impaired myocardial efficiency may underlie differences in the time to recovery after AVR. Limited information is present regarding the effects of AVR on myocardial energetics.

Therefore, the purpose of the present study was to investigate myocardial efficiency in patients with AVS induced hypertrophy and to assess the effect of AVR on myocardial efficiency in relation to exercise capacity. Myocardial efficiency was quantified non-invasively using \textsuperscript{[11]C}-acetate positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) imaging in AVS patients before and 4 months after AVR and in a healthy control group (baseline value).18, 19 AVR-induced changes in myocardial efficiency were correlated with parameters of exercise capacity assessed during cardiopulmonary exercise testing.

Methods

Study population

The study protocol was in agreement with principles outlined in the Declaration of Helsinki and was approved by the Medical Ethics Review Committees of the
participating hospitals (VU University Medical Center and Onze Lieve Vrouwe Gasthuis in Amsterdam, The Netherlands). All participants gave written informed consent prior to inclusion. Ten AVS patients (mean age 62 ± 10 years, 7 males), eligible for AVR, were enrolled into the study between May 2012 and May 2013. Inclusion criteria were the presence of symptomatic isolated AVS with a peak transvalvular gradient of >50 mmHg (mean transvalvular gradient ranged between 34 and 68 mmHg) and an aortic valve area < 1 cm².

**Exclusion criteria** were (previously documented) aortic regurgitation more than Grade 1, moderate to severe mitral regurgitation, the presence of coronary artery disease (coronary artery stenosis >30%), poor LV function (ejection fraction <50%), a history of diabetes mellitus or hypertension (defined as a systemic blood pressure ≥140/90 mmHg), contraindications to magnetic resonance imaging, and significant renal dysfunction defined as an estimated glomerular filtration rate <30 mL·min⁻¹·1.73m².

In addition, 14 healthy subjects (mean age 48 ± 11 years, 9 males) were included as a control group. Control subjects were considered to be at low risk for coronary artery disease based on clinical history, electrocardiographic findings, and echocardiographic studies.

**Study design**

All AVS patients underwent a transthoracic echocardiography, PET imaging using [¹¹C]-acetate, CMR imaging, and a cardiopulmonary exercise test (CPET) on the same day within 2 weeks prior to AVR (pre-AVR). The same examinations were repeated 4 months after AVR (post-AVR). A 4-month follow-up was based on previous studies, which showed reversed remodelling early after AVR. Control subjects underwent baseline in vivo measurements only.

**Cardiac imaging protocols**

**Transthoracic echocardiography**

Echocardiography was performed according to the American Society of Echocardiography guidelines. Continuous wave Doppler was used to derive LV outflow tract gradient and peak aortic valve pressure gradient. Diastolic function was assessed using a combination of early mitral annular velocities. Color-coded tissue Doppler imaging was applied to the apical four-chamber view to determine mean early (e‘) velocity at the septal and lateral mitral annulus. E/e‘, both septal and lateral, was calculated as an index of LV filling pressure.
CMR and [$^{11}$C]-acetate PET
The study protocol comprised [$^{11}$C]-acetate PET and CMR imaging. A detailed version of the methods describing the protocol and accuracy regarding the in vivo imaging modalities can be found in the online supplement. [$^{11}$C]-acetate PET imaging was performed to indirectly quantify oxygen metabolism using the rate constant $k_2$, $k_2$ represents the rate of transfer of radioactivity from tissue to blood, of which myocardial oxygen consumption ($MVO_2$) can be derived as described previously. Data of the control group were acquired as described previously. For the AVS group, [$^{11}$C]-acetate scans were obtained on a Gemini TF-64 PET/CT scanner (Philips Healthcare, Best, The Netherlands). CMR was performed on a 1.5 T whole body scanner (Magnetom Sonata or Avanto, Siemens, Erlangen, Germany), using a six-channel phased-array body coil. A contiguous, short-axis, steady-state free precession stack was acquired extending from the mitral valve annulus to the LV apex, to obtain global LV function parameters, including ED volume (LVEDV), ES volume (LVESV), stroke volume (SV), LV ejection fraction (LVEF) and LV mass (LVM). Subsequently, a stack of 6-10 transversely orientated slices was planned on an end-diastolic two-chamber view at the level of the lower leading edge of the mitral valve annulus to cover the left atrium (LA). Cine imaging with myocardial tagging was applied to create non-invasive markers (tags) within the myocardium for the calculation of peak systolic circumferential strain (SCS). Late gadolinium enhancement (LGE) images were acquired 10-15 min after intravenous administration of 0.2 mmol kg$^{-1}$ gadolinium.

Myocardial external efficiency
External work (EW) was defined as the product of SV derived by CMR and mean arterial pressure (MAP). In the AVS group, individually obtained estimations of the aortic valve gradient were added to the MAP to ensure accurate estimations of actual LV pressures. Subsequently, myocardial external efficiency (MEE) was calculated according to the equation below:

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

in which $\text{HR}$ is the heart rate and the constants represent the caloric equivalent of 1 mmHg·mL EW, which is $1.33 \cdot 10^{-4}$ J, whereas 1 mL O$_2$ corresponds to 20 J.
Chapter 4

Cardiopulmonary exercise test
A cyclo ergometry exercise was performed using a ramp protocol of 10-20 W·min$^{-1}$. Patients cycled until they reached the point of exhaustion or symptom limitation. Breath-by-breath gas exchange analysis was performed. Respiratory gases were sampled continuously via a mouthpiece and analysed for oxygen and, using an infrared sensor, for carbon dioxide. Using this method, peak oxygen consumption (peak VO$_2$), defined as the highest VO$_2$ achieved during exercise, was determined before and after surgery.

Statistics
Data analyses and statistics were performed using Prism version 5.0 (Graphpad Software, Inc., La Jolla, CA, USA) and SPSS version 20 (IBM, Armonk, NY, USA). Data were expressed as mean ± SD. Individual data sets (pre-AVR, post-AVR and controls) were tested for normality using the Shapiro–Wilk test. Normality was assumed when $P > 0.05$ and variances were equal. When the normality assumption was not violated, a paired two-tailed Student’s $t$-test was performed to investigate differences among baseline and follow-up measurements; otherwise, a Mann–Whitney U test was used. A value of $P < 0.05$ was considered statistically significant. Linear regression was used to analyse the relationship between variables.

Results

Characteristics of pre-AVR patients compared with controls
Baseline characteristics of pre-AVR patients and control subjects are summarized in Tables 1 and 2. Patients were significantly older than control subjects (mean age 62 ± 10 and 48 ± 11 years, respectively, $P < 0.01$). No significant differences were observed between groups for gender. Six patients were classified as New York Heart Association (NYHA) functional Class II and four as Class III. LGE was observed in three pre-AVR patients with a mean of 1.2 ± 2.7% in the total group. LVEDV and LVESV tended to be higher in pre-AVR patients compared with controls but did not reach statistical significance. LVM, LA max volume, and NT-pro-BNP were significantly higher, while global peak SCS was significantly lower in pre-AVR patients compared with controls (Figure 1), indicating a decrease in myocardial contractile function. Global $e'$ was significantly lower, while global $E/e'$ was significantly higher in AVS patients, indicating impaired diastolic function (Figure 1 and Table 2). External work was significantly higher in pre-AVR patients than in controls (15439 ± 2631 vs 10117 ± 2268 mmHg·ml, $P < 0.001$). Myocardial efficiency was significantly lower in pre-AVR patients than in controls (32 ± 7 vs 49 ± 6%, $P < 0.001$; Figure 1).
Table 1. Characteristics of patients before valve replacement and control subjects

<table>
<thead>
<tr>
<th></th>
<th>pre-AVR (n = 10)</th>
<th>Controls (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>7 men (70%)</td>
<td>9 men (64%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 10*</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.99 ± 0.16</td>
<td>2.01 ± 0.20</td>
</tr>
<tr>
<td>Aortic valve gradient (mmHg)</td>
<td>88 ± 20</td>
<td>0</td>
</tr>
<tr>
<td>NYHA class of heart failure</td>
<td>2.4 ± 0.5</td>
<td>0</td>
</tr>
<tr>
<td>LGE (yes/no)</td>
<td>3/7</td>
<td>0/14</td>
</tr>
<tr>
<td>LGE (%)</td>
<td>1.2 ± 2.7</td>
<td>0</td>
</tr>
</tbody>
</table>

Haemodynamic parameters obtained during [11C]-acetate PET acquisition. Data are presented as mean ± SD. Pre-AVR, before valve replacement; NYHA, New York Heart Association; LGE, late gadolinium enhancement. *P < 0.05 pre-AVR vs. controls.

Predictors of myocardial efficiency

Univariate analysis revealed a significant correlation of both LV systolic parameters, global peak SCS and LVEF, with myocardial efficiency (Figures 2A and B). In addition, impaired diastolic function was associated with lower myocardial efficiency, illustrated by a significant correlation between global e´ and myocardial efficiency (Figure 2C). LA maximum volume index and LVM index also significantly correlated with myocardial efficiency (Figures 2D and E). These findings indicate a close relationship of myocardial efficiency with both systolic and diastolic function of the heart.
Figure 1. Scatter plots depicting peak aortic valve gradient (A), LVM index (B), global peak systolic circumferential strain (C), global e' (D), external work (E), myocardial oxygen consumption (F), and myocardial external efficiency (G) values for pre-AVR, post-AVR, and control patients.
Effect of aortic valve replacement on myocardial efficiency

Figure 2. Correlations of myocardial external efficiency with global peak systolic circumferential strain (A), LVEF (B), EFglobal e (C), LA maximum volume (D) and LVM index (E).

Represent the 95% confidence interval of the regression line.
## Table 2. CMR, $^{11}$C-acetate PET, and echocardiography data before and after AVR

<table>
<thead>
<tr>
<th></th>
<th>Pre-AVR ($n = 10$)</th>
<th>Post-AVR ($n = 10$)</th>
<th>Controls ($n = 14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical treatment</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1 (10)</td>
<td>9 (90)</td>
<td>0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0</td>
<td>7 (70)</td>
<td>0</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>CMR parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (mL·m$^{-2}$)</td>
<td>101 ± 19</td>
<td>88 ± 16$^\dagger$</td>
<td>93 ± 15</td>
</tr>
<tr>
<td>LVESV (mL·m$^{-2}$)</td>
<td>43 ± 14</td>
<td>35 ± 9$^\dagger$</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>SV (mL·m$^{-2}$)</td>
<td>58 ± 11</td>
<td>53 ± 9</td>
<td>57 ± 7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 ± 7</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>LVM (g·m$^{-2}$)</td>
<td>104 ± 21$^*$</td>
<td>74 ± 15$^*$</td>
<td>49 ± 6</td>
</tr>
<tr>
<td>LA max volume (mL·m$^{-2}$)</td>
<td>59 ± 7$^*$</td>
<td>49 ± 9$^*$</td>
<td>46 ± 6</td>
</tr>
<tr>
<td>Global peak SCS (%)</td>
<td>$-16.2 ± 1.5^*$</td>
<td>$-19.0 ± 1.5^*$</td>
<td>$-19.3 ± 1.7$</td>
</tr>
<tr>
<td><strong>Echocardiographic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global e’</td>
<td>6.2 ± 1.2$^*$</td>
<td>8.9 ± 1.6$^*$</td>
<td>11.7 ± 2.4</td>
</tr>
<tr>
<td>Global E/e’</td>
<td>13 ± 3$^*$</td>
<td>10 ± 2$^*$</td>
<td>8 ± 2</td>
</tr>
<tr>
<td><strong>PET &amp; haemodynamic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_2$ (per minute)</td>
<td>0.09 ± 0.02</td>
<td>0.07 ± 0.01$^\dagger$</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120 ± 11</td>
<td>122 ± 12</td>
<td>123 ± 13</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>69 ± 10</td>
<td>72 ± 9</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>LV MAP (mmHg)</td>
<td>86 ± 9</td>
<td>88 ± 8</td>
<td>88 ± 8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>69 ± 10</td>
</tr>
<tr>
<td><strong>Metabolic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-pro-BNP (ng·L$^{-1}$)</td>
<td>439 ± 537$^*$</td>
<td>247 ± 151$^*$</td>
<td>63 ± 55</td>
</tr>
<tr>
<td>Hb (mmol·L$^{-1}$)</td>
<td>8.9 ± 0.7$^*$</td>
<td>8.8 ± 1.0</td>
<td>8.3 ± 0.4</td>
</tr>
<tr>
<td>Glucose (mmol·L$^{-1}$)</td>
<td>6.2 ± 0.7$^*$</td>
<td>5.9 ± 0.6</td>
<td>5.5 ± 0.8</td>
</tr>
<tr>
<td>FFA (mmol·L$^{-1}$)</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Lactate (mmol·L$^{-1}$)</td>
<td>1.4 ± 0.5</td>
<td>1.8 ± 1.0</td>
<td>1.4 ± 0.6</td>
</tr>
</tbody>
</table>

Values are $n$ (%) or mean ± SD. All volumes and mass are indexed to body surface area. pre-AVR, before valve replacement; post-AVR, 4 months after valve replacement; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; SV, stroke volume; LVEF, LV ejection fraction; LVM, LV mass; LA, left atrial; SCS, systolic circumferential strain; $k_2$, average $^{11}$C-acetate clearance rate constant; BP, blood pressure; MAP, mean arterial pressure; NT-proBNP, NH$_2$-terminal pro-brain natriuretic peptide; Hb, haemoglobin; FFA, free fatty acid; $^*P < 0.05$ pre-AVR or post-AVR vs. controls. $^\dagger P < 0.05$ pre-AVR vs. post-AVR.
**Effects of AVR**

After AVR, peak aortic valve gradient decreased from $88 \pm 20$ to $24 \pm 12$ mmHg ($P < 0.001$; Figure 1A). Seven of the 10 patients showed symptomatic clinical improvement as indicated by an improvement in average NYHA class from $2.4 \pm 0.5$ to $1.6 \pm 0.5$ ($P = 0.003$). After AVR, no significant change in blood pressure and heart rate was observed. The effects of AVR on LV and LA dimensions, functional parameters, and metabolic parameters are presented in Table 2.

AVR resulted in reversed cardiac remodelling evident from significant decreases in LVEDV, LVESV, LVM as well as LA maximum volume (Figure 3 and Table 2). LVM index significantly decreased in all AVS patients, although remained significantly higher than in controls (Figure 1B). Global peak SCS significantly improved from $-16.2 \pm 1.5$ to $-19.0 \pm 1.5\%$ ($P = 0.001$), indicating an improvement in myocardial contractile function (Figure 1C). Global e´ also significantly increased from $6.2 \pm 1.2$ to $8.9 \pm 1.6$ cm$\cdot$s$^{-1}$ ($P = 0.001$), though it was still significantly lower than the value observed in control subjects (Figure 1D). No significant changes were observed for the fasting metabolic parameters such as glucose, FFA, lactate, haemoglobin and NT-pro-BNP (Table 2). External work significantly decreased from $15439 \pm 2631$ pre-AVR to $10774 \pm 2446$ mmHg$\cdot$mL post-AVR ($P < 0.001$), reaching a similar value as observed in controls ($10117 \pm 2268$ mmHg$\cdot$mL; Figure 1E). $k_2$, representing the rate of $[^{11}\text{C}]$-acetate washout, significantly decreased, indicating lower oxygen consumption after AVR (Table 2). Indeed, $\text{MVO}_2$ significantly decreased from $0.11 \pm 0.03$ to $0.09 \pm 0.02$ mL$\cdot$min$^{-1}$$\cdot$g$^{-1}$ ($P = 0.02$; Figure 1F). Consequently, AVR resulted in a significant improvement in myocardial efficiency from $32 \pm 7$ to $37 \pm 5\%$, ($P = 0.02$; Figure 1G).

**Exercise parameters**

After AVR, maximum exercise work significantly increased from $148 \pm 61$ to $159 \pm 61$ W ($P < 0.01$). In addition, peak VO$_2$ increased from $2.00 \pm 0.64$ to $2.13 \pm 0.59$ L$\cdot$min$^{-1}$ ($P = 0.05$). Peak VO$_2$$\cdot$kg$^{-1}$ increased from $24.1 \pm 7.0$ to $25.5 \pm 6.6$ mL$\cdot$kg$^{-1}$$\cdot$min$^{-1}$ but did not reach statistical significance ($P = 0.08$). There was a significant relationship of absolute change in myocardial efficiency ($\Delta$MEE) and absolute changes in both exercise work ($\Delta$Work) and peak VO$_2$ ($\Delta$peak VO$_2$; Figure 4), indicating that an improvement of myocardial efficiency is associated with increased exercise capacity in patients. As can be seen, four patients (grey dots) did not show an improvement in myocardial efficiency, which was associated with no or minimal improvement in exercise parameters.
Figure 3. Reversed remodelling after AVR. From left to right, cardiac magnetic resonance cine of a 2-chamber view, parametric images of $[^{13}]$C-acetate washout ($k_2$) with corresponding polar maps in pre- and post-AVR condition. As can be seen clearly, reversed remodelling occurred after AVR, evident from reduction in LVEDV, LVM, LA volume, and oxygen metabolism.

Figure 4. Linear relationship between changes in myocardial external efficiency (MEE) with changes in both exercise work (A) and peak VO$_2$ (B). AVS patients are indicated by open dots, whereas those without MEE improvement are indicated by grey dots. AVS patients with LGE are marked with an asterisk. The dotted lines represent the 95% confidence interval of the regression line.
Discussion

The present study demonstrates the results of a comprehensive investigation on the effects of AVR on myocardial efficiency in AVS patients without co-morbidities. Non-invasive quantification of myocardial efficiency, derived from combined \(^{11}\text{C}\)-acetate PET and CMR studies, revealed significantly lower myocardial efficiency in AVS patients in comparison with controls. At 4-month follow-up, the detrimental effects of AVS were partially reversed by AVR in patients with normal coronary arteries and preserved ejection fraction. This was evident from a regression of LV hypertrophy and improvement of myocardial efficiency. Interestingly, improvement of myocardial efficiency closely correlated with increased exercise capacity.

Effects of AVR on LV geometry, systolic function, and diastolic function

AVS causes pressure overload of the LV leading to concentric hypertrophy of the LV wall. This compensatory mechanism results in a reduction of wall stress (afterload) according to the Laplace equation, which helps to preserve systolic performance. However, LV hypertrophy also has disadvantages such as a reduction in coronary flow reserve, diastolic dysfunction and is associated with increased mortality.\(^{13,29-31}\) AVR reduces pressure overload of the LV causing reversed remodelling. In the present study, already at 4 months of follow-up, AVR resulted in a significant reduction in LVEDV, LVESV, LVM, and LA maximum volume index, though, in accordance with previous studies, values remained higher than control values.\(^{9-11}\)

There may be several explanations for incomplete reversed LV remodelling. At 4 months of follow-up, the process of reversed remodelling may still be ongoing. Moreover, AVR does not completely reduce aortic valve pressure gradients to normal values, which might limit the reversed remodelling process. Thirdly, when severe aortic stenosis is present for a longer period of time, increased deposition of interstitial fibrosis leading to diastolic dysfunction may hinder the process of reversed remodelling. Flett et al.\(^{32}\) described a higher amount of diffuse myocardial fibrosis in severe AVS patients, which significantly correlated with the severity of diastolic dysfunction. In the present study, diastolic dysfunction was present in all AVS patients. Diastolic function significantly improved after AVR, illustrated by an increase in global e’ and a decrease in global E/e’ but did not reach values as in controls, indicating irreversible changes within the myocardial extracellular matrix. Although cardiac remodelling was only partially reversed 4 months after AVR, global peak SCS was normalized to control values indicating improved contractile function of the heart.
**Effects of AVR on MVO\(_2\) and myocardial efficiency**

The present finding of higher k\(_2\) values and thus higher MVO\(_2\) in pre-AVR patients compared with controls is in line with previous studies\(^6\),\(^{33}\) AVR significantly reduced k\(_2\) and MVO\(_2\) (Figure 1 and Table 2), indicating that the AVR-induced reduction in LV workload improves myocardial oxygen metabolism.

An important finding of the present study is that AVR improves myocardial efficiency in AVS patients. As can be seen in Figure 1G, however, not all patients showed an improvement in myocardial efficiency following AVR, which might explain the difference in symptomatic improvement between patients. AVS patients without improvement in myocardial efficiency tended to have less reversed remodelling and minimal change in MVO\(_2\) after AVR compared with AVS patients with improved myocardial efficiency (not shown). In addition, there was no relation between medication use with LV remodelling and changes in myocardial efficiency, as three out of four AVS patients without improvement in myocardial efficiency received dual therapy with a beta-blocker and ACE inhibitor. Furthermore, the limited effects of AVR on LV remodelling and myocardial efficiency could not be explained by a higher post-AVR gradient through the aortic valve or the extent of gradient reduction, suggesting that there might be an intrinsic myocardial defect causing reduced reversibility. Yarbrough *et al.* reported that chronic LV pressure overload not only leads to cardiomyocyte hypertrophy, but also causes irreversible changes in extracellular matrix composition and accumulation of extracellular matrix components resulting in diastolic dysfunction, which could hamper the reversed remodelling process after AVR.\(^9\)

Furthermore, a close correlation was found between absolute changes in myocardial efficiency and those in exercise parameters such as work and peak VO\(_2\) (Figure 4), i.e. patients who did not show improved myocardial efficiency also did not show improvement in exercise capacity. All AVS patients with myocardial efficiency improvement showed improvement in NYHA functional class. Three out of four patients without improvement in myocardial efficiency did not show improvement in NYHA functional class. No relation was observed between the presence of focal fibrosis assessed with LGE and changes in myocardial efficiency or exercise capacity. However, as mentioned earlier, Flett *et al.*\(^{32}\) observed a good correlation between the extent of diffuse myocardial fibrosis and diastolic dysfunction and impaired functional capacity of AVS patients. These findings suggest that there might be a relation between the extent of diffuse myocardial fibrosis and myocardial efficiency impairment, as we also found a close correlation between myocardial efficiency and the diastolic function of the heart. In our study, we did not observe a relation between \(\Delta\)MEE and the presence of fibrosis as determined by LGE (Figure 4).
Overall, the present study shows that myocardial efficiency is an important determinant of exercise capacity in AVS patients. The data indicate that the AVR-induced gradient reduction does not result in complete reversed remodelling and improved myocardial efficiency in all patients, which may be due to irreversible changes in the myocardium.

**Study limitations and clinical implications**

A limited number of patients were studied, and therefore, results should be interpreted with care. Nonetheless, sample sizes were large enough to reveal AVR-induced changes in the LV. This proof-of-concept study is the first study providing evidence of beneficial effects of AVR on myocardial efficiency in AVS patients and its relation with improved exercise capacity after AVR. However, the limited number of patients does not permit strong conclusions on pathophysiology. Another limitation was that AVS patients were significantly older than controls.

Age has been associated with alterations of myocardial metabolism and might influence myocardial efficiency.\textsuperscript{34} In the present study, however, univariate analysis revealed that age was not a predictor of myocardial efficiency (not shown). To avoid influences of other confounding factors on myocardial efficiency, AVS patients with hypertension, diabetes mellitus or coronary artery disease were excluded.

In conclusion, our study shows that myocardial efficiency is significantly reduced in patients with AVS-induced hypertrophy. The finding of a close relationship between myocardial efficiency with both systolic and diastolic functional parameters indicates that impairment of myocardial efficiency is an important determinant of cardiac failure in AVS patients. Moreover, improved myocardial efficiency is an important predictor of AVR-induced improvement of exercise capacity in AVS patients. Our proof-of-concept study warrants a future large prospective, multicenter clinical trial to confirm our observations.

**Funding**

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**Conflict of interest**

None declared.
References


