Residual compromised myocardial contractile reserve after valve replacement for aortic stenosis

Ying Zhao1,2, Michael Y. Henein1,3*, Stellan Mörner1,3, Sandra Gustavsson1, Anders Holmgren1,4, and Per Lindqvist1,3

1Heart Centre, Umeå University, Umeå, Sweden; 2Ultrasound Department, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; 3Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; and 4Department of Surgery and Perioperative Sciences, Umeå University, Umeå, Sweden

Received 11 September 2011; accepted after revision 24 October 2011; online publish-ahead-of-print 18 November 2011

Objective
Despite recovery of left ventricular (LV) function and morphology after aortic valve replacement (AVR) for aortic stenosis (AS), its relationship with exercise capacity remains unknown. Twenty-one AVR patients (age 61 ± 12 years, 14 male) with normal ejection fraction (EF, 64 ± 7%) and 21 age- and sex-matched controls (57 ± 9 years, 10 male, EF 68 ± 8%) were studied.

Methods and results
All subjects performed semi-supine bicycle exercise and speckle tracking echocardiography (STE) study. Peak oxygen consumption (pVO2) was collected during semi-supine bicycle exercise. Systolic (GLSRs) and early diastolic (GLSRe) longitudinal strain rate using STE and Doppler echocardiographic parameters were measured at rest, submaximal, peak exercise, and 4 min after exercise. The two groups had comparable resting echocardiographic measurements. At peak exercise, pVO2 was lower in patients than controls (18.5 ± 4.5 vs. 22.1 ± 4.3 L/min/kg, P < 0.05). GLSRs (0.98 ± 0.28 vs. 1.55 ± 0.30 1/s, P < 0.001), septal Sm (7.9 ± 1.4 vs. 11.1 ± 2.3 cm/s, P < 0.001) and their changes between rest and peak exercise (DGLSRs: 0.16 ± 0.33 vs. 0.68 ± 0.27 1/s, P < 0.001; DSm 2.29 ± 2.23 vs. 4.63 ± 2.29 cm/s, P < 0.01) were significantly lower in patients than controls. There was no correlation between pVO2 and any echocardiographic measurements in controls. In patients, pVO2 correlated with peak exercise GLSRs (r = 0.60, P = 0.0007), septal Sm (r = 0.65, P = 0.002), and Em (r = 0.57, P = 0.009). In a multivariate model, peak exercise GLSRs (β = 7.18, P = 0.03) was the only independent predictor of pVO2 in the patients group.

Conclusion
Exercise capacity is subnormal after AVR for AS, irrespective of normal LVEF suggesting residual compromised myocardial functional reserve.

Keywords
Exercise echocardiography • Aortic valve replacement • Strain rate • Reserve

Introduction
Left ventricular (LV) function is known to be abnormal in hypertrophied cavities due to aortic stenosis (AS).1,2 Although LV ejection fraction (EF) might remain normal in most symptomatic and asymptomatic AS patients, long-axis function is known to be functionally abnormal because of subendocardial ischaemia and fibrosis.3,4 Furthermore, these resting disturbances have been shown by different imaging techniques to worsen with exercise in asymptomatic patients.5–8 On the other hand, aortic valve replacement (AVR) results in significant regression of myocardial hypertrophy, improvement of segmental as well as global systolic and diastolic function.9–11 It is generally believed that after AVR, along with the release of the outflow tract obstruction and the improvement of LV function, patients’ exercise capacity also improves.12,13 This concept has not been objectively tested, since patients usually deny symptoms and hence the lack of clinical need to investigate their exercise capacity. We hypothesize that

* Corresponding author. Tel: +46 90 785 0000, Fax: +46 90 137 633, Email: michael.henein@medicin.umu.se

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Despite complete alleviation of symptoms following AVR and normal LVEF, patients remain with compromised myocardial functional reserve. In this study, we were set out to assess LV myocardial function in detail during exercise, using 2D speckle tracking echocardiography (STE) technique in a group of AVR patients with normal EF.

Methods

Study population

We studied 21 consecutive severe AS patients (age 61 ± 12 years, 14 male) who underwent surgical AVR at the Heart Centre of Umeå University Hospital. Severe AS was defined as aortic valve area <1.0 cm² and/or mean transvalvular gradient ≥40 mmHg. Patients were excluded if they had impaired LV systolic function (EF < 50%) or were not in sinus rhythm. All patients had undergone cardiac catheterization before surgery to exclude high-grade lesions, none of whom had more than mild additional valve disease, or had undergone other valve or coronary artery bypass procedures. Other exclusion criteria were signs of left atrial pressure (E/A > 2 and isovolumic relaxation time <40 ms), pulmonary hypertension (RV-RA peak pressure drop >40 mmHg), or chronic obstructive pulmonary disease. After 28 ± 12 months (range 12–48 months) of AVR, patients were invited to have an exercise echocardiogram simultaneously with peak oxygen consumption (pVO₂) and blood pressure measurements. All patients were asymptomatic at the time of exercise echocardiographic examination. Brain natriuretic peptide levels (BNP) were also analysed before and at peak exercise using the conventionally available biochemical assay (Triage MeterPro). Twenty-one healthy men, aged 57 ± 9 years, 10 males, selected from the general population constituted the control group, none of whom had any cardiovascular or systemic disease or other cardiovascular risks. Patients and controls had given an informed consent to participate in the study, which was approved by the local Ethics Committee of Umeå.

Supine ergometer exercise test

The study participants underwent a semi-supine (slightly left lateral) bicycle exercise test (GE ergometer, model 900, Ergoline GmbH, Germany) with an increasing workload (10 W) every 2 min. The workload started at 30 W and the Borg scale for exertion level was reported and blood pressure was taken using cuff sphygmomanometer. VO₂ measurements were collected using Metamax breath by breath system (CORTEX Biophysik GmbH-Nonnenstrasse 39-D-04229 Leipzig-Germany). The mean value of VO₂ was continuously calculated within 10 s and the peak exercise value was taken. A 12-lead ECG was continuously monitored throughout exercise, and recorded on paper at the end of each stage to exclude any evidence for exercise-related myocardial ischaemia or arrhythmias. The exercise was stopped if the patient developed limiting breathlessness/chest discomfort, ST-segment depression of ≥1 mm, more than three consecutive ventricular premature beats, or hypotension (defined as a fall in systolic blood pressure of at least 20 mmHg from baseline). Exercise endpoint for controls was exhaustion.

Echocardiography

Resting and exercise echocardiographic examinations were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) equipped with an adult 1.5–4.3 MHz phased array transducer. At rest, standard views from the parasternal long- and short-axis and apical four-chamber views were obtained. Blood flow velocities were acquired using pulsed and continuous wave Doppler, respectively, as proposed by the American Society of Echocardiography. Five consecutive loops of the four-chamber view with and without colour Doppler were acquired at the last minute of each work load and were stored digitally. Measurements were made at all exercise (Ex) stages. In this study, we present data from the following stages: (i) pre Exercise = immediately before exercise (resting echo); (ii) submaximal exercise = at a heart rate (HR) of 100–110 bps; (iii) peak exercise = a Borg scale of level 17; and (iv) 4 min after peak exercise. Recordings were acquired with a superimposed ECG. Analysis of the acquired studies was made using commercially available software (General Electric, EchoPac version 8.0.1, Waukesha, Wisconsin, USA).

Measurements

Conventional echocardiographic measurements

Left atrial (LA) and LV cavity dimensions including septal and posterior wall thickness were taken from the parasternal long-axis view using the M-mode technique. LV volumes were measured at end-systole (LVESV) and end-diastole (LVEDV) from the apical four-chamber view and the LVEF was calculated using single-plane Simpson’s model. Stroke volume (SV) was measured as the product of LV outflow tract (LVOT) cross-sectional area multiplied by its flow velocity time integral from the spectral Doppler recordings of the LVOT velocities. Cardiac output (CO) was determined as the product of the SV and the heart rate. All volumetric data were adjusted to body surface area. LV filling velocities were acquired using pulsed wave Doppler recording of the transmitral early (E) and late (A) diastolic velocities, then E/A ratio was calculated. LV long-axis myocardial velocities Sm and Em were measured in systole and early diastole, respectively using tissue Doppler imaging technique with the sample volume placed at the basal segments of the lateral and septal wall. E/Em was also calculated with Em was the average of septal and lateral values.

Left ventricular longitudinal strain rate

From the apical four-chamber view, global longitudinal strain rate (GLSR) was studied using STE on the grey scale images with a temporal resolution of ~70 frame/s. LV cavity was traced manually from the innermost endocardial edge at end-systole and the software automatically defined the longitudinal SR throughout the cardiac cycle. Adequate tracking was verified and was manually corrected, if necessary. GLSR was measured as the mean of six segments from the apical four-chamber view (basal, middle, and apical levels of septal and lateral wall). From the acquired recordings, systolic (GLSRs), early (GLSRe), and late diastolic (GLSRd) strain rate values were measured. When filling was of the summation pattern, the single diastolic wave was taken as the GLSRe. Usually, LV longitudinal SR was a negative value during systole (SRs) and positive value during diastole (SRd). In this study, the systolic SR was presented as positive value in order to avoid any potential confusion when the linear regression model is performed.

Statistical analysis

Statistical analysis was undertaken using Statistical Package of Social Science version 18 (SPSS, Inc., Chicago, IL, USA). All continuous variables were presented as mean ± SD. Comparisons between groups were made using unpaired Student’s t-test for normally distributed data and Mann–Whitney U test if necessary. BNP comparison was made using Mann–Whitney U test. χ² test was used to analyse gender difference between the two groups. Univariate linear
Exercise echocardiography after aortic valve replacement

regression (Pearson’s coefficient) was performed to study the correlation between pVO₂ and echocardiographic parameters at rest and during exercise. The variables in the univariate regression model which reached statistical significance entered into a multiple regression model to determine the independent predictors of pVO₂. A P-value < 0.05 was considered significant.

Reproducibility
Intra- and inter-observer variabilities were assessed in 10 randomly chosen subjects for STE systolic and diastolic GLSR at rest and during exercise. Coefficient of variation was calculated as the ratio of the standard deviation of the variables to their corresponding mean from the original data set.¹⁸

Results

Baseline clinical and echocardiographic characteristics
Age and gender were comparable between patients and controls. Ten of the 21 patients had additional systemic hypertension causing a slightly raised mean systolic blood pressure values compared with controls (P < 0.05), three had diabetes, three had previous strokes. LV cavity dimensions and EF were not different between groups, but septal and posterior wall thickness were higher (P < 0.01) and LA was larger (P < 0.01) in patients. E/A was not different, BNP was significantly raised in patients (73 ± 72 vs. 14 ± 11 pg/mL, P < 0.001) but remained within conventional limits of LV dysfunction (Table 1).

Exercise echocardiography
Exercise echocardiography was successfully performed in all controls who reached Borg scale of level 17, without any complications. Seventeen patients reached Borg 17 and four patients reached Borg 15 without complaint of chest pain. Peak VO₂ was lower (18.5 ± 4.5 vs. 22.1 ± 4.3 L/min/kg, P < 0.05) and the BNP level was higher at peak exercise (103 ± 82 vs. 25 ± 22 pg/mL, P < 0.001) in patients compared with controls. The systolic BP was not different between patients and controls at submaximal and peak exercise (Tables 2 and 3).

Conventional echocardiographic measurements
LVEF, HR, and LV volume indices were not different between the two groups at rest. However, at submaximal and peak exercise, patients had significantly lower EF (P < 0.001) and higher indexed LVESV (P < 0.05) although they achieved similar HR, CO, and indexed SV with respect to controls. Patients had limited increase in EF (P < 0.05) and CO (P < 0.05) than controls during exercise. Four minutes after exercise, all these parameters recovered to the normal level.

Septal and lateral Sm, E/Em were comparable between the two groups but patients had lower Em (P < 0.01) at rest. At submaximal and peak exercise, septal and lateral Sm and Em in patients were lower (P < 0.01) and E/Em higher than controls (P < 0.01). Consequently, the delta changes of these parameters between rest and peak exercise were less (P < 0.05) but E/Em was higher (P < 0.05) in patients. The change in Em was not significant but had a tendency to be lower in patients (P = 0.08). Four minutes after exercise, septal and lateral Sm, Em were still lower (P < 0.01) and E/Em higher (P < 0.01) than controls but within normal range.

Left ventricular longitudinal strain rate
GLSRs and GLSRe were not different between groups at rest. At submaximal and peak exercise, both systolic and early diastolic SR were significantly lower (P < 0.01) in patients than controls. The magnitude of increase in GLSRs and GLSRe between rest and peak exercise was also lower (P < 0.05) in patients than controls. Four minutes after exercise, the longitudinal strain rates recovered to normal values with no difference from controls (Figures 1 and 2).

Relationship between pVO₂ and cardiac function parameters
There was no correlation between pVO₂ and any echocardiographic measurement in controls. In patients, pVO₂ correlated with peak exercise GLSRs (r = 0.60, P = 0.007), septal Sm (r = 0.65, P = 0.002), and Em (r = 0.57, P = 0.009). In the multivariate model, GLSRs at peak exercise (β = 7.18, P = 0.03) was the only independent predictor of pVO₂ in patients (Figure 3).

Difference between mechanical and biological prosthesis valve
Seven patients had biological prosthesis valve who were older than the remaining 14 mechanical prosthesis valve patients (70 ± 7 vs. 55 ± 11 years, P = 0.01). The extracorporeal circulation (ECC) time was 97 ± 25 min, and occlusion cross-clamping time (OT) was 70 ± 18 min for the whole patients group. Biological valve patients tended to have longer ECC (112 ± 35 vs. 90 ± 15 min, P = 0.15) and OT (84 ± 23 vs. 63 ± 10 min, P = 0.05) but did not reach the statistical significance. Biological prosthesis valve

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients and controls</th>
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<tbody>
<tr>
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<td>Patients (n = 21)</td>
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<td>Age, years</td>
<td>61 ± 12</td>
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<td>Female/Male</td>
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<td>SBP, mmHg</td>
<td>137 ± 16</td>
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<td>DBP, mmHg</td>
<td>79 ± 7</td>
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<td>LAD, mm</td>
<td>38 ± 7</td>
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<td>LVEDD, mm</td>
<td>48 ± 4</td>
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<td>LVESD, mm</td>
<td>30 ± 4</td>
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<td>IVST, mm</td>
<td>11.1 ± 1.3</td>
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<td>PWT, mm</td>
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<td>LVEF, %</td>
<td>64 ± 7</td>
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<td>E/A</td>
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<td>BNP, pg/mL</td>
<td>73 ± 72</td>
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All values are presented as mean ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVEF, left ventricular ejection fraction; E/A, early/late diastolic velocity; BNP, brain natriuretic peptide.
Table 2  Comparison between patients and controls group during exercise

<table>
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<tr>
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<th>Controls</th>
<th>P-value</th>
<th>Rest</th>
<th>Controls</th>
<th>P-value</th>
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<th>Controls</th>
<th>P-value</th>
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<td></td>
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<td>Controls</td>
<td></td>
<td>Patients</td>
<td>Controls</td>
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<td>Patients</td>
<td>Controls</td>
<td></td>
<td>Patients</td>
<td>Controls</td>
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<td>HR, bpm</td>
<td>75 ± 13</td>
<td>70 ± 9</td>
<td>0.19</td>
<td>103 ± 7</td>
<td>107 ± 5</td>
<td>0.05</td>
<td>126 ± 19</td>
<td>128 ± 13</td>
<td>0.68</td>
<td>91 ± 14</td>
<td>83 ± 11</td>
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<tr>
<td>SBP, mmHg</td>
<td>137 ± 16</td>
<td>127 ± 10</td>
<td>0.04</td>
<td>165 ± 20</td>
<td>161 ± 18</td>
<td>0.50</td>
<td>187 ± 21</td>
<td>185 ± 14</td>
<td>0.72</td>
<td>144 ± 18</td>
<td>130 ± 11</td>
<td>0.01</td>
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<td>LVEDVI, mL/m²</td>
<td>49 ± 9</td>
<td>46 ± 14</td>
<td>0.44</td>
<td>45 ± 13</td>
<td>46 ± 11</td>
<td>0.79</td>
<td>41 ± 16</td>
<td>44 ± 14</td>
<td>0.41</td>
<td>42 ± 12</td>
<td>44 ± 9</td>
<td>0.63</td>
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<td>LVESVI, mL/m²</td>
<td>18 ± 5</td>
<td>16 ± 6</td>
<td>0.21</td>
<td>15 ± 5</td>
<td>12 ± 5</td>
<td>0.02</td>
<td>13 ± 5</td>
<td>9 ± 4</td>
<td>0.01</td>
<td>16 ± 5</td>
<td>16 ± 4</td>
<td>0.87</td>
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<td>LVEF, %</td>
<td>63 ± 5</td>
<td>66 ± 7</td>
<td>0.29</td>
<td>66 ± 6</td>
<td>75 ± 5</td>
<td>&lt;0.001</td>
<td>70 ± 7</td>
<td>80 ± 6</td>
<td>&lt;0.001</td>
<td>62 ± 5</td>
<td>64 ± 5</td>
<td>0.19</td>
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<td>SVI, mL/m²</td>
<td>31 ± 6</td>
<td>31 ± 9</td>
<td>0.79</td>
<td>30 ± 9</td>
<td>34 ± 7</td>
<td>0.09</td>
<td>30 ± 10</td>
<td>35 ± 11</td>
<td>0.13</td>
<td>26 ± 8</td>
<td>28 ± 5</td>
<td>0.41</td>
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<td>CO, L/min</td>
<td>4.5 ± 0.8</td>
<td>3.9 ± 1.2</td>
<td>0.06</td>
<td>6.1 ± 1.9</td>
<td>6.9 ± 1.5</td>
<td>0.18</td>
<td>7.1 ± 3.2</td>
<td>8.4 ± 2.8</td>
<td>0.17</td>
<td>4.7 ± 1.5</td>
<td>4.3 ± 1.0</td>
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<td>Lat Sm, cm/s</td>
<td>7.5 ± 2.2</td>
<td>8.5 ± 1.4</td>
<td>0.08</td>
<td>8.9 ± 1.6</td>
<td>11.6 ± 2.5</td>
<td>&lt;0.001</td>
<td>11.0 ± 2.8</td>
<td>14.2 ± 2.5</td>
<td>&lt;0.001</td>
<td>8.9 ± 2.4</td>
<td>10.9 ± 2.2</td>
<td>0.01</td>
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<td>Sep Sm, cm/s</td>
<td>5.6 ± 1.3</td>
<td>6.5 ± 1.4</td>
<td>0.05</td>
<td>7.1 ± 1.1</td>
<td>9.4 ± 1.7</td>
<td>&lt;0.001</td>
<td>7.9 ± 1.4</td>
<td>11.1 ± 2.3</td>
<td>&lt;0.001</td>
<td>5.9 ± 1.1</td>
<td>8.2 ± 1.6</td>
<td>&lt;0.001</td>
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<td>Mitr E, cm/s</td>
<td>69 ± 21</td>
<td>76 ± 24</td>
<td>0.33</td>
<td>107 ± 24</td>
<td>98 ± 25</td>
<td>0.26</td>
<td>128 ± 22</td>
<td>118 ± 29</td>
<td>0.23</td>
<td>76 ± 22</td>
<td>68 ± 16</td>
<td>0.24</td>
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<td>Em, cm/s</td>
<td>9.0 ± 2.2</td>
<td>11.2 ± 2.8</td>
<td>0.007</td>
<td>12.2 ± 2.8</td>
<td>15.3 ± 4.1</td>
<td>0.008</td>
<td>13.5 ± 2.4</td>
<td>17.8 ± 3.9</td>
<td>&lt;0.001</td>
<td>10.1 ± 1.9</td>
<td>12.6 ± 2.8</td>
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<td>E/Em</td>
<td>8.1 ± 3.2</td>
<td>7.2 ± 2.9</td>
<td>0.34</td>
<td>9.2 ± 2.8</td>
<td>6.8 ± 2.4</td>
<td>0.005</td>
<td>9.7 ± 2.4</td>
<td>6.8 ± 1.9</td>
<td>&lt;0.001</td>
<td>7.7 ± 2.7</td>
<td>5.7 ± 1.8</td>
<td>0.009</td>
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<tr>
<td>GLSRe, s⁻¹</td>
<td>0.08 ± 0.21</td>
<td>0.08 ± 0.11</td>
<td>0.20</td>
<td>1.00 ± 0.23</td>
<td>1.34 ± 0.25</td>
<td>&lt;0.001</td>
<td>0.98 ± 0.28</td>
<td>1.55 ± 0.30</td>
<td>&lt;0.001</td>
<td>0.82 ± 0.25</td>
<td>0.99 ± 0.28</td>
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<td>GLSRe, s⁻²</td>
<td>0.08 ± 0.34</td>
<td>1.06 ± 0.31</td>
<td>0.10</td>
<td>1.15 ± 0.33</td>
<td>1.58 ± 0.65</td>
<td>0.01</td>
<td>1.03 ± 0.39</td>
<td>1.75 ± 0.88</td>
<td>0.001</td>
<td>0.88 ± 0.32</td>
<td>1.12 ± 0.47</td>
<td>0.07</td>
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</table>

All values are presented as mean ± SD.
HR, heart rate; SBP, systolic blood pressure; LV, left ventricle; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; SVI, stroke volume index; CO, cardiac output; Sm, systolic myocardial velocity; Em, early diastolic myocardial velocity; GLSRe, global longitudinal systolic myocardial strain rate; GLSRe, global longitudinal early diastolic myocardial strain rate.
patients had higher BNP level at rest (116 ± 61 vs. 52 ± 68 pg/mL, 
P = 0.01) and peak exercise (146 ± 64 vs. 82 ± 83 pg/mL, 
P = 0.03) and lower pVO₂ (15.5 ± 2.8 vs. 20.2 ± 4.5 L/min/kg, 
P = 0.03) than mechanical valve patients. However, the echocardiographic
parameters during exercise were not different between the two 

The changes between peak exercise and rest in patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 21)</th>
<th>Controls (n = 21)</th>
<th>P-value</th>
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<td>LVEDVI, mL/m²</td>
<td>−8.39 ± 12.33</td>
<td>−2.14 ± 12.07</td>
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<td>LVESVI, mL/m²</td>
<td>−5.36 ± 4.78</td>
<td>−6.90 ± 4.34</td>
<td>0.28</td>
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<td>EF, %</td>
<td>6.68 ± 9.60</td>
<td>13.97 ± 9.10</td>
<td>0.02</td>
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<td>SVI, mL/m²</td>
<td>−1.25 ± 8.37</td>
<td>4.55 ± 10.63</td>
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<td>CO, l/min</td>
<td>2.49 ± 3.02</td>
<td>4.43 ± 2.68</td>
<td>0.04</td>
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<td>Lateral Sm, cm/s</td>
<td>3.57 ± 3.98</td>
<td>5.74 ± 2.09</td>
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<td>Septal Sm, cm/s</td>
<td>2.29 ± 2.23</td>
<td>4.63 ± 2.29</td>
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<td>Mitral E, cm/s</td>
<td>59 ± 24</td>
<td>42 ± 37</td>
<td>0.09</td>
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<tr>
<td>Em, cm/s</td>
<td>4.50 ± 2.43</td>
<td>6.56 ± 4.63</td>
<td>0.08</td>
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<tr>
<td>E/Em</td>
<td>1.66 ± 2.73</td>
<td>−0.33 ± 3.11</td>
<td>0.03</td>
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<td>GLSRs, s⁻¹</td>
<td>0.16 ± 0.33</td>
<td>0.68 ± 0.27</td>
<td>&lt;0.001</td>
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<td>GLSRe, s⁻¹</td>
<td>0.14 ± 0.48</td>
<td>0.70 ± 0.93</td>
<td>0.03</td>
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</table>

All values are presented as mean ± SD. Abbreviations are same with Table 2.

Exercise echocardiography after aortic valve replacement

Table 3

Discussion

Findings

After AVR, patients had normal systolic and diastolic function at rest. At peak exercise, patients had less pVO₂ than controls. Also with exercise, patients demonstrated global as well as segmental systolic and diastolic dysfunction in the form of attenuated increase in the EF, global strain rate as well as segmental myocardial velocities at both submaximal and peak exercise. During recovery, GLSRs and GLSRe recovered to resting values with myocardial velocity measurements remaining abnormal but within normal range. Finally, in a multivariate regression model, only GLSRs at peak exercise

Figure 1

An example of left ventricular strain rate measurements at rest and peak exercise (Ex) in a healthy control and a patient. Systolic and early diastolic global longitudinal strain rates are similar at rest but are lower at peak exercise in patients than controls. SR, strain rate.
correlated with pVO\textsubscript{2} in the patients group. Finally, the echocardiographic measurements were not different between mechanical and biological prosthetic valves during exercise.

**Data interpretation**

Exercise provokes greater peripheral oxygen demands which require reciprocal increase in myocardial global and segmental function.\textsuperscript{19} Our patients showed a less increase in the CO with exercise despite similar heart rate to that of controls, thus suggesting maintained myocardial oxygen demand–supply balance. No patient developed symptoms during exercise or signs of ventricular dysfunction based on ECG and 2D echo analysis. However, we found clear evidence for global myocardial dysfunction, in the form of limited EF rise, and global strain rate as well as indirect signs of raised filling pressures. In addition, there was clear evidence for abnormal segmental function in the form of limited increase in myocardial velocities with exercise. The combination of these disturbances was not an incidental finding but was related to pVO\textsubscript{2} in patients. Furthermore, systolic myocardial longitudinal strain rate was the only independent predictor of pVO\textsubscript{2}, suggesting a direct relationship.

In the absence of exercise-induced ischaemic dysfunction, particularly in the setting of AS and dramatic increase of pre-operative afterload we cannot ignore the potential role of subendocardial fibrosis in explaining our findings. With disease progression, myocardial perfusion is decreased and systolic wall stress increased as a response to myocardial hypertrophy. These predominantly affect subendocardial layer in the form of ischaemic dysfunction followed by fibrosis.\textsuperscript{4} The extent of myocardial fibrosis has been found to closely correlate with longitudinal myocardial function 'subendocardial' in patients with increased pressure afterload.\textsuperscript{20,21} This has been previously reported at rest, but now it seems to have a significant effect on patients’ exercise capacity. Such disturbance of LV function is unlikely to be related to AVR, which itself resulted in myocardial mass regression and improvement of overall cardiac function, but more likely reflect the chronic effect of outflow tract obstruction on the myocardium. The current guidelines recommendation of AVR for AS depends on symptoms, which commonly occur when patients develop ventricular disease, which might be, to some extent, irreversible despite maintained EF, at rest.\textsuperscript{22,23} Our findings therefore, reflect those disturbances in the form of compromised myocardial longitudinal SR reserve and limited EF increase with exercise. Although after AVR, the wall stress is still higher than normals due to incomplete recovery of LV hypertrophy and the fibrotic myocardium, the modest rise in BNP levels with stress roles out the possibility of residually raised wall stress as a potential mechanism. With a mean follow-up period of 2 years after AVR, it seems unlikely for such changes to improve. This finding is supported by the previously reported lack of improvement of exercise capacity after AVR despite improvement of resting systolic function.\textsuperscript{24} It is also supported by histological findings after AVR, which showed incomplete regression of structural abnormalities of LV hypertrophy at intermediate follow-up and residually increased relative interstitial fibrosis which existed even 6–7 years after surgery.\textsuperscript{25}

Few studies have used exercise/stress echocardiography in assessing aortic valve substitute function.\textsuperscript{26–29} Most of them aimed at comparing patients exercise capacity and ventricular functional parameters’ response to various valve substitutes. In our study, we also addressed this issue and did not find significant differences between mechanical and biological prosthesis valve. Importantly, this study is the first of its nature to assess objectively patients exercise capacity and cardiac function after AVR. It is also the first to indentify significant myocardial function disturbances which predicted exercise capacity. Similar findings need to be reproduced in a larger cohort of patients.

**Clinical implications**

The important findings of this study are that AS results in reduced myocardial functional reserve which is likely to be irreversible,
even after AVR. These disturbances could not be detected at rest but were associated with limited increase in exercise capacity. Therefore, they stress the hypothesis that earlier removal of the outflow tract obstruction even before symptoms develop might limit the irreversible myocardial damage.

**Limitations**

Our patients did not have an exercise test before AVR, since they all had symptoms justifying direct surgical intervention. We wished to assess the relationship between pVO₂ and the chronicity of AS severity before surgery but these data were not available, since patients had most pre-operative studies at the referring centre/hospital. We cannot exclude the impact of hypertension on the longitudinal dysfunction during exercise, since 50% of our patients had documented hypertension. It is known that there is normal difference in gender response to exercise, but we were unable to assess similar difference in our study because of the small cohort. Also, the study number is small which carries with it the common statistical limitations. We only obtained apical four-chamber view for the data analysis due to the short acquisition time during exercise, the short-axis radial and circumferential myocardial deformation analysis could have add more information. We analysed strain rate data because it is more robust and reproducible especially at a high heart rate. It also provides the diastolic information which may be limited had we only relied on strain measurements.

**Conclusion**

Exercise capacity is subnormal after AVR for AS, irrespective of normal LVEF. Although valve replacement normalizes resting LV longitudinal function, the residual compromised myocardial
functional reserve remains an exercise limiting step, possibly reflecting the chronicity of the myocardial dysfunction before surgery.

**Acknowledgements**

Karin Holmström and Maria Backlund for managing oxygen consumption test and blood samples.

**Conflict of interest:** none declared.

**Funding**

This study was supported by The Swedish Heart and Lung Foundation, The Medical Faculty of Umeå University and The Heart Foundation of Northern Sweden.

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