Predictors of exercise capacity and symptoms in severe aortic stenosis

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Aims
This study investigated the association between invasive and non-invasive estimates of left ventricular (LV) filling pressure and exercise capacity, in order to find new potential candidates for risk markers in severe aortic valve stenosis (AS).

Methods and results
Twenty-nine patients with AS, aortic valve area (AVA) <1 cm², performed a symptom-limited multistage supine bicycle exercise test. Immediately before the exercise test, the pulmonary capillary wedge pressure (PCWP), Doppler index for LV filling (E/e’), and left atrial (LA) volume were measured. Symptomatic status was determined by senior staff doctors blinded to the results of this study. All patients terminated the exercise test because of dyspnoea. There were no significant differences in AVA between asymptomatic patients (n=9) and symptomatic patients (n=20), and AVA did not correlate with exercise capacity (r=−0.16, P=NS). In contrast, PCWP, LA volume, and E/e’ were significantly increased in the symptomatic group and they all correlated with exercise capacity (r=−0.66, −0.75, and −0.62, respectively, P<0.001). Receiver operating characteristic curve analysis confirmed that PCWP, LA volume index, and E/e’ all provided incremental information [area under the curve (AUC) = 0.90, 0.92, and 0.90, respectively, P<0.05] over AVA index (AUC = 0.66, NS) in predicting symptomatic status.

Conclusion
PCWP, LA volume, or E/e’ is closely related to exercise capacity and symptomatic status, and may therefore be important markers of disease severity in AS.


Keywords
Severe aortic valve stenosis • Left ventricular filling pressure • Exercise capacity • Symptomatic status

Introduction
The classic symptoms of aortic valve stenosis (AS) include exertional dyspnoea, chest pain, and syncope/dizziness. Although the prognosis in asymptomatic patients with AS is relatively benign, the risk is abruptly increased when symptoms appear emphasizing the pivotal importance of early accurate detection of symptoms.1–4 The symptoms of AS, however, are often unspecific and may be caused by co-morbidities especially in elderly frail patients, where aortic valve area (AVA) is only weakly related to symptoms. Exercise testing in selected cases may improve identification of patients who benefit from valve replacement, but exercise testing is tedious and rarely applied in the general population with AS.5 Thus, it would be beneficial to identify changes in cardiac structure or hemodynamics that could aid accurate identification of symptomatic patients with diminished exercise tolerance.

Exertional dyspnoea in AS is an important prognostic factor and is likely caused by elevated filling pressure.6,7 Thus, early detection of increased filling pressure may be a warning sign of increased risk in patients thought to be only mildly symptomatic or asymptomatic. Invasive measurements of left ventricular (LV) filling pressure are not feasible for routine use, but studies indicate that echocardiographic parameters such as the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e’) recorded by Doppler and tissue Doppler echocardiography may accurately detect increased LV filling pressure at rest.8,9
Furthermore, increased left atrial (LA) volume in the absence of significant mitral regurgitation has been suggested to reflect long-standing LA pressure overload and thus a valuable parameter reflecting both the duration and severity of the diastolic dysfunction in other cardiac conditions.\(^{10,11}\)

The aim of the present study was therefore to determine whether the association of LV filling pressure measured invasively or non-invasively is related to exercise capacity and symptomatic status in severe AS, and thereby identify potential new prognostic factors in these patients.

**Methods**

**Study population**

Twenty-nine patients, with severe AS (AVA < 1 cm\(^2\)), in sinus rhythm and no symptoms at rest, referred for evaluation for aortic valve replacement were recruited. Patients with significant mitral valve disease (more than mild), severe angina pectoris, and patients who were unable to perform an exercise test of other reasons were excluded. The patients were divided in two groups by the caring staff physicians to be either symptomatic or asymptomatic. This decision was made blinded for the results of supine exercise testing and estimates of LV filling pressure, but could be based on all other available data, including a previous standard exercise test, if performed.

The attending physician recorded history of diabetes mellitus, hypertension, and chronic obstructive pulmonary disease. A coronary angiogram was performed as part of the planned diagnostic work-up of the patients. Coronary artery disease (CAD) was graded by the number of involved vessels and left main disease. The present study is a baseline substudy to a study investigating acute haemodynamic effects of treatment with angiotensin-converting enzyme (ACE)-inhibitors in severe AS (ACCESS). Accordingly, no patients received ACE-inhibitors at the time of inclusion. The exercise test was performed in the supine position as a part of the protocol for this study.

**Echocardiography**

Preceding the exercise test, all patients underwent a two-dimensional and Doppler echocardiographic examination using a General Electric Vivid 7 cardiac ultrasound system (Horton, Norway). Images were stored digitally for off-line analysis using the GE EchoPac analysis software, version 6.12 (Horton, Norway). These analyses were performed blinded to measurements of pulmonary capillary wedge pressure (PCWP), exercise capacity, and symptomatic status of the patients. The severity of AS was quantified by estimating the effective valve area using the continuity equation with the time velocity–time integral ratio of a pulsed wave Doppler profile of blood flow in the LV outflow tract and continuous wave across the aortic valve.\(^{12,13}\) Care was taken to align the Doppler cursor as parallel as possible with the flow across the valve. The AVA was indexed to body surface area (AVAI).

LV internal diameters and wall thickness were measured at end-diastole and end-systole in two-dimensional parasternal long-axis view.\(^{14}\) End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula.\(^{15}\) LV hypertrophy was considered present, when LV mass indexed by body surface area was > 104 g/m\(^2\) in women and > 116 g/m\(^2\) in men.\(^{16}\) LV ejection fraction was calculated from the biplane method of disks. An LV ejection fraction > 50% was considered preserved. LA volume was measured in ventricular end-systole from the frame preceding mitral valve opening by the modified Simpson’s monoplane method in the apical four-chamber view. The plane of the mitral annulus represented the inferior border of LA. Pulmonary veins were excluded from the LA tracing according to guidelines.\(^{14}\) LA volume was indexed to body surface area. Early (E) and late (A) transmitral inflow velocities were recorded in the apical four-chamber view, with the sample volume placed between the tips of the mitral leaflets during diastole. Pulsed wave tissue Doppler loops were acquired with the Doppler sample volume placed in the septal mitral annulus.\(^{17}\) At least three cardiac cycles were measured and averaged for all echocardiographic parameters. Concomitant heart valve disease as mitral or tricuspid valve disease was evaluated as defined by the guidelines of the American College of Cardiology/American Heart Association.\(^{17}\)

**Invasive haemodynamic measurements**

PCWP and cardiac index were measured at rest in the supine position using a 7.5 F triple-lumen Swan–Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, CA, USA). The right heart catheterization was performed by introducing the catheter under local anaesthetic via the internal jugular vein.

**Exercise testing**

Immediately following the echocardiogram and the invasive measurements, all patients performed a multistage symptom-limited supine cycle exercise test using an Angio V2 ergometer (Lode BV, The Netherlands). Workload was increased by 25 W every other minute until exhaustion. Exercise capacity was defined as the duration of the exercise test. Brachial blood pressure was measured by cuff using a regularly calibrated aneroid sphygmomanometer with the patient in the supine position. Blood pressure was measured at baseline and every other minute until maximal workload was reached. A 12-lead electrocardiogram was continuously monitored. Patient’s medications, including beta-blockers, were not withheld during the study. The test was interrupted if the subjects experienced severe symptoms of angina, significant ventricular arrhythmia, dizziness, or a drop in blood pressure according to the European guidelines.\(^{18}\) All the investigations were performed under strict surveillance in a setting of an intensive cardiac care unit.

**Ethics**

The study was approved by the Regional Ethics Committee (J. no. 02 269334) and all patients gave written informed consent to participate.

**Statistics**

Continuous variables are expressed as mean ± SD and categorical variables as number and per cent. Comparisons of groups are done using Student’s t-test for continuous data. Pearson’s correlation and linear regression analysis was used for correlation analysis. Spearman’s correlation analysis was used to analyse the relation of different variables with exercise capacity. The area under the receiver operating characteristic (ROC) curve and the derived sensitivity and specificity of the different values of PCWP, E/e’, and LA volume index were calculated to discriminate symptomatic from asymptomatic patients adjusted for AVAI. The ROC plots were also used to determine the ideal cut-off value that more accurately discriminated asymptomatic from symptomatic patients. Logistic and linear regression analysis were used to assess independent covariates for symptomatic status and exercise capacity, respectively. A P-value < 0.05 was considered statistically significant. The coefficient of variation (CV)\(^{19}\) for repeated measures on the same recording was analysed for E/e’ and LA volume. The SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA), was used for statistical analysis.
Results

Patient characteristics
Mean AVA was 0.71 ± 0.17 cm². Most of the patients (79%) had preserved LV ejection fraction (56 ± 8%) and LV hypertrophy was present in 69%. Mean exercise duration time was 6.3 ± 2.0 min and was significantly shorter in patients classified as symptomatic than in asymptomatic patients (5.3 ± 1.0 vs. 8.5 ± 2.0 min, P = 0.002). All patients terminated the exercise test because of dyspnoea. Blood pressure dropped in four patients at peak exercise and no patients developed ventricular arrhythmia or complaints of dizziness. The exercise test was performed without any complications.

Characteristics of the patients are summarized in Table 1. PCWP, LA volume, and E/e’ were significantly higher (21.4 ± 7.0 vs. 12.4 ± 2.5 mmHg, 54 ± 14 vs. 37 ± 6 mL/m², and 21.3 ± 4.9 vs. 14.7 ± 2.7, respectively, P < 0.01) in the symptomatic patients, despite similar valve area (0.71 ± 0.2 vs. 0.75 ± 0.1 cm², NS) between groups. No statistical differences in other parameters included in Table 1 were identified. The intra-observer variation of E/e’ measured on repeated recordings by the same person was CV = 8% and the inter-observer variation was CV = 10% in 16 randomly selected patients. The variation of LA volume on repeated recordings by the same person was CV = 7% and the inter-observer variation was CV = 11% in 16 randomly selected patients.

In the asymptomatic group, two (22%) were women. Three (33%) of the patients had CAD involving no more than one vessel, four (44%) had hypertension, one (11%) had chronic obstructive pulmonary disease, and one (11%) had diabetes mellitus. In the symptomatic patients, eight (40%) were women. Six (30%) of the patients had CAD. One vessel was involved in four patients, two vessels in one patient, and three vessels in one patient. Fourteen (70%) had hypertension, two (10%) had chronic obstructive pulmonary disease, and six (30%) had diabetes mellitus. Symptomatic patients received more diuretic than asymptomatic patients (diuretics: 22 vs. 60%). The use of beta-blockers, calcium antagonists, and statins were 33 vs. 40%, 11 vs. 25%, and 56 vs. 80% in asymptomatic and symptomatic patients, respectively. None of the patients had tricuspid regurgitation more than mild–moderate.

Estimates of left ventricular filling pressure, exercise capacity, and symptoms
PCWP correlated closely with LA volume index (r = 0.84, P < 0.0001) and E/e’ (r = 0.69, P < 0.0001), whereas PCWP was not related to AVAI (r = −0.16, NS) (Figure 1). Even though LV ejection fraction was preserved in most patients and did not correlate with exercise capacity (r = 0.22, NS), estimates for LV filling pressure had a moderately negative correlation with LVEF (r = −0.40, P = 0.02) (Figure 1). PCWP, LA volume index, and E/e’ measured at rest were all significantly correlated with exercise capacity (r = −0.66, −0.75, and −0.62, respectively, P < 0.001 for all) (Figure 2). ROC curve analysis confirmed that PCWP, LA volume index, and E/e’ all provided incremental information [area under the curve (AUC) = 0.90, 0.92, and 0.90, respectively, P < 0.05] over AVAI (AUC = 0.66, NS) in predicting symptomatic status (Figure 3). From the ROC curve analysis, the optimal cut-off value for PCWP at 15 mmHg measured at rest predicted whether patients were symptomatic during exercise with a sensitivity of 71% and a specificity of 90%. Accordingly, an LA volume index at 41 mL/m² identified the symptomatic patients with a sensitivity of 80% and a specificity of 80% and an E/e’ ratio at 17 predicted symptoms with a sensitivity of 75% and a specificity of 80%. In a logistic regression analysis that also included AVAI, LV ejection fraction, LV mass, and CAD, PCWP was the only parameter that was independently related to symptomatic status. Similar results were found in a linear regression model of exercise capacity, which included the same covariates. Using E/e’ or LA volume index instead of PCWP resulted in similar findings in both models (P < 0.05 for all). This was also the case if unadjusted values for AVA were used.

Discussion
Invasive and non-invasive estimates for LV filling pressure were found to be accurate predictors of exercise capacity and symptomatic status in patients with severe AS. Both LA volume and E/e’ were confirmed also to be useful non-invasive estimates of PCWP in these patients. Finally, we found a strong negative correlation between PCWP, E/e’, and LA volume and exercise capacity which was incremental to AVA.

Previous studies of exercise testing in severe AS have demonstrated that reduced exercise capacity most often is due to exertional dyspnoea, which at the same time seems to be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients with severe aortic stenosis</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>Gender [female, n (%)]</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.90 ± 0.17</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150 ± 28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 10</td>
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<tr>
<td>Aortic valve area (cm²)</td>
<td>0.71 ± 0.17</td>
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<tr>
<td>Aortic valve area index (cm²/m²)</td>
<td>0.39 ± 0.07</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56 ± 8</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>224 ± 51</td>
</tr>
<tr>
<td>E deceleration Time (ms)</td>
<td>230 ± 47</td>
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<tr>
<td>E/A ratio</td>
<td>1.05 ± 0.3</td>
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<tr>
<td>E/e’ ratio</td>
<td>19.2 ± 5.0</td>
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<tr>
<td>Left atrial volume index (mL/m²)</td>
<td>49 ± 14</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>18.6 ± 7.0</td>
</tr>
<tr>
<td>Cardiac index (mL/min/m²)</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Cardiac output (mL/min)</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>80 ± 15</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>6.3 ± 2.0</td>
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associated with the poorest prognosis. In the present study, we also found that patients considered asymptomatic had a better exercise capacity than symptomatic patients, although overlap between groups was observed. Even though previous studies have demonstrated that exercise testing is an excellent tool to reveal symptoms in apparently asymptomatic patients, exercise testing is only performed in <6% of these patients according to recent reports. Reasons for the seemingly low utilization of exercise testing may include fear of complications, inexperience in exercise testing in these patients, or possibly because it is considered inconvenient and time-consuming. Although symptomatic status and exercise capacity are the most important criteria for identification of patients who will benefit from aortic valve replacement, we sought to generate a model to identify an easy and low-cost measure, which is related to both parameters at rest.

Exercise intolerance, and especially development of pulmonary congestion in patients with heart failure, is usually caused by increased pulmonary venous pressure due to increased LA pressure. It is well known that systolic dysfunction relates relatively poorly with exercise capacity, whereas estimates of LV filling pressure seem to be more closely related to exercise capacity. However, patients with valvular heart disease are excluded in most studies investigating this issue. In the present study, we did not find any significant differences in LV ejection fraction between asymptomatic and symptomatic patients and no association between LV ejection fraction and exercise capacity in severe AS. Instead, the results clearly demonstrated a close relation between invasive/non-invasive estimates of LV filling pressure and exercise capacity as well as symptomatic status in patients with severe AS.

Previous studies have shown that the diastolic \( E/e' \) ratio can estimate PCWP irrespective of LVEF, and recently, one study indicated that this also to be the case in patients with AS. Furthermore, a close relation between non-invasive measurements of LV filling pressure and exercise capacity has been demonstrated in patients with suspected CAD, hypertrophic cardiomyopathy, and systolic heart failure. The cut-off values identified in the present study for identifying symptomatic patients are comparable to generally accepted cut-off values for severe abnormal filling pressures. Although PCWP and \( E/e' \) are influenced by instantaneous changes in loading conditions, LA volume is thought to be closely related to chronic LA pressure overload, thus reflecting the cumulative effect of impaired LV filling pressure over time. Being less susceptible to transient changes in loading conditions could explain why LA volume seemed to be the most accurate predictor of exercise capacity and symptomatic status in the present study.

**Figure 1** Correlations of pulmonary capillary wedge pressure with the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (\( E/e' \)), left atrial volume, aortic valve area, and left ventricular ejection fraction in patients with severe aortic stenosis.
Grading of the severity of AS is usually based on AVA and mean gradient determined by echocardiography. The prognostic impact of the degree of stenosis has been studied in patients with a wide range of disease severity from mild to severe stenosis. However, even in prospective studies, AVA and mean gradient provide little protective risk stratification. 1–4 In the present study, AVA was not related to symptomatic status or exercise capacity. Therefore, there is still a need for additional selection criteria based on objective measurements of cardiac dysfunction. Estimates of LV filling pressure might potentially be such an additive measure for follow-up of these patients.

There are some limitations to this study. The strength of the study and the statistical analysis is limited by the relatively small number of patients. A large cohort of patients would have allowed a more robust and comprehensive multivariate analysis clarifying the role of associated CAD, reduced LV function, LV hypertrophy, and co-morbidities such as chronic obstructive pulmonary disease in relation to exercise capacity and symptomatic status. Furthermore, large-scale longitudinal studies are needed to further confirm the prognostic value of these parameters in patients with AS. In this study, exercise capacity was defined by the exercise time in minutes with the working load increased by 25 W every other minute. Using gas exchange techniques might have provided more accurate information of exercise capacity. However, previous studies have confirmed the close relation between these techniques and exercise duration time. 33–35 Furthermore, symptomatic patients with AS are often identified by dismissed exercise tolerance, making exercise time during increasing workload an reasonable surrogate parameter for exercise capacity in this study.

**Conclusion**

PCWP, $\text{E/E} _a$, and LA volume at rest are closely related to exercise capacity and provide incremental information to valve area in predicting symptomatic status in severe AS. PCWP, LA volume, or $\text{E/E} _a$ may be the important prognostic factor and reflects the haemodynamic consequence of AS.

**Conflict of interest:** none declared.

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References