Cardiopulmonary Exercise Testing in Aortic Stenosis

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This thesis is based on the following studies:

Study I. Le DTV, Jensen GVH, Carstensen S, Kjøller-Hansen L. Cardiopulmonary exercise testing in patients with asymptomatic or equivocal symptomatic aortic stenosis. Feasibility, reproducibility, safety and information obtained on exercise physiology. Cardiology. 2016;133(3):147-56.

Study II. Le DTV, Jensen GVH, Carstensen S, Kjøller-Hansen L. Prognostic value of cardiopulmonary exercise testing in patients with asymptomatic or equivocal symptomatic moderate to severe aortic stenosis. JACC, submitted.

Study III. Le DTV, Jensen GVH, Kjøller-Hansen L. Observed change in peak oxygen consumption after aortic valve replacement and its predictors. Open Heart. 2016 May 26;3(1):e000309. doi: 10.1136/openhrt-2015-000309. eCollection 2016.

Introduction

Symptomatic aortic stenosis is a class I indication for valve replacement (1,2); this equation, however, assumes that symptoms in patients with aortic stenosis are caused by haemodynamic compromise from the aortic stenosis. Dyspnoea and fatigue are by far the most common symptoms in aortic stenosis (3), but they are rather nonspecific and may be caused by other common conditions, such as aging, pulmonary disease, atrial fibrillation, hypertension, obesity, or deconditioning. The use of functional classifications, such as the New York Heart Association (NYHA) or Specific Activity Scale, to assess the hemodynamic compromise from aortic stenosis is clearly limited by suboptimal inter- and intra-rate reproducibility (4), possible or likely bias from knowledge of the severity of the aortic stenosis, and lack of predictive accuracy as with functional class II patients with aortic stenosis (5). On the other hand, symptoms from true hemodynamic compromise may be concealed by a sedentary lifestyle or the gradual adjustment to decreased functional capacity.

Optimization of the premises for the clinical decision of whether a patient with aortic stenosis is truly symptomatic – that is, suffers from hemodynamic compromise from the aortic stenosis – is important because of the risks and complications of aortic valve replacement (AVR). Complications associated with transcatheter AVR – perioperative mortality (1–8%), and complications associated with surgical AVR (3.1–7.7%; stroke, myocardial infarction, bleeding, infection), prosthesis, and anticoagulation treatment (2–3% annually: bleeding, infection) (6,7,8,9) – clearly outweigh the risk of sudden death in true asymptomatic aortic stenosis, which is much less than 1% annually (3,9). Furthermore, AVR often requires a significant convalescence and does not always improve the symptoms or quality of life (1,10,11).

A number of methods are used and recommended (1,2) to evaluate whether patients with aortic stenosis are truly asymptomatic with no significant hemodynamic compromise, but they have limitations:

1. Conventional exercise testing with assessment of exercise capacity, symptoms, and blood pressure response has a low predictive accuracy particularly in patients >70 years old or in functional class II (5) and this is common in patients with equivocal symptomatic aortic stenosis. Conventional exercise testing does not give information on the physiology behind decreased exercise capacity, and will overestimate the calculated METS from the workload achieved (Watts) in the case of haemodynamic compromise (12). Finally, all individuals will experience symptoms, such as some discomfort and dyspnoea, at peak exercise (13).
2. Exercise stress echocardiography with the use of increasing gradients or pulmonary hypertension has predictive value for the progression to an AVR; however, the feasibility (75% in experienced hands), operator dependency, and modest reproducibility of echocardiographic parameters limit its use, especially for the assessment of individual patients (14,15,16).
3. Brain natriuretic peptide (BNP) and its precursor, proBNP, are predictive for the progression to AVR (17,18). Elevated BNP seems to reflect the load on the left ventricle, but also reflects conditions associated with the prognosis other than aortic stenosis (18) and the frequency of elevated BNP remains high post-AVR (19).

It has been suggested that patients with increasing peak transvalvular flow velocity (Vmax) >0.3 m/s per year may benefit from an AVR despite asymptomatic status (1,20). However, a significant proportion of patients may reach this criterion by chance, because it is equivalent to one standard deviation of the difference in test-retest scores with one experienced operator (16).

Studies of patients with asymptomatic or equivocal symptomatic aortic stenosis that form the basis for guideline recommendations are not based on randomized trials, with a number of patients range 50 to 186 (3,5,14,15,20,21,22,23), recruited patients through 5 years (3,5,21) and from several hospitals (23), and

many studies were retrospective (3,20,21,22). None of the studies provided a pre-specified sample size (3,5,14,15,20-23), and the outcome predictors revealed in these studies were found post-hoc (14,15,21,23). Furthermore, in these studies, the composite endpoint was often evaluated by telephone interviews of relatives, primary physicians, or physicians at other institutions (3,22).

When a patient becomes truly symptomatic from aortic stenosis, the underlying pathophysiology is usually an inability to increase or maintain stroke volume (SV) and thereby cardiac output (CO) and oxygen delivery during exercise (3,24). If a patient with aortic stenosis is symptomatic without hemodynamic compromise, the cause is unlikely to be aortic stenosis and improvement with AVR is unlikely.

The peak oxygen consumption (pVO_2) has good reproducibility (25,26) and is a major determinant of prognosis in major cardiac diseases, such as ischemic heart disease and heart failure (27,28,29). This is not surprising because pVO_2 reflects cardiac output during peak exercise and peak oxygen pulse (pO_2pulse: pVO_2/heart rate) reflects stroke volume. The primary limiting factor of pVO_2 is oxygen flow to working muscles, which is primarily dependent on stroke volume, heart rate, and the haemoglobin (Hb) or hematocrit (30). In high-level endurance athletes, the distribution of blood flow to exercising muscles may also play a role, whereas the impact of mitochondrial function is questionable. Training or detraining (bed rest) primarily affects stroke volume (30). In addition to decreased stroke volume, peak heart rate (both may be impaired by lack of effort), anaemia, and abnormal ventilation/perfusion coupling and/or oxygenation will impair pVO_2 (31).

By cardiopulmonary exercise testing (CPX) pVO_2 and pO_2pulse, which reflects cardiac output and stroke volume at peak exercise, respectively, are easily obtained, as are measures reflecting effort, ventilation/perfusion coupling oxygenation, and pulmonary function. Thus CPX reflects objective measure of functional capacity obtained (pVO_2) and elucidates the physiology of pVO_2 (31).

The endpoint progression to AVR is, by far, the dominating event in studies on the predictors of events in patients with asymptomatic or equivocal symptomatic aortic stenosis (3,5,14-17,20-23). The decision to refer for AVR is subjective, and knowledge of test results may inflate the predictive value for progression to AVR, as might the interpretation of minor common symptoms (5,13). Furthermore, AVR does not improve functional capacity and quality of life in all patients (10,11).

In patients with ischemic heart disease it is known that neither symptoms nor coronary anatomy, the finding of coronary artery stenosis, equals ischemia. Revascularization of patients with symptoms and coronary stenosis without physiological evidence of ischemia is now considered inappropriate (32); furthermore, sham operations improve the patients' symptoms by the placebo effect (33,34). Dyspnoea, not feeling well, and tiredness are even less specific symptoms than angina, and patients with aortic stenosis are often older than those with ischemic heart disease. Therefore co-existence of aortic stenosis and symptoms does not always present an association, and AVR could also carry a placebo effect. Demonstration of an objective and physiological background for the patient's symptoms and improvement with AVR is appealing and seems more optimal than current practices.

Accordingly, in asymptomatic or equivocal symptomatic aortic stenosis, it is relevant to study methods that closely reflect the hemodynamic during exercise and the pathophysiology of aortic stenosis to obtain detailed information on the exercise (patho)physiology, and that provide objective and reproducible results. Furthermore, it is relevant to study the outcome and improvement with AVR with methods that are more objective and reproducible and less biased than, for example, the NYHA classification and patient reported "improvement". One such method could be cardiopulmonary exercise testing (CPX).

Hypothesis and Objectives

Hypothesis

In patients who are difficult to assess through standard procedures, cardiopulmonary exercise testing has high feasibility and good reproducibility and gives information on the hemodynamics and exercise physiology beyond that obtained by standard methods.

If evaluation of CPX results do not indicate a significant hemodynamic compromise from aortic stenosis, deferral of AVR is safe and may even result in lower event rates compared to standard methods. If evaluation of CPX results do indicate hemodynamic compromise, AVR is followed by a high rate of improvement in physical capacity.

Not all patients improve or reach near normal pVO_2 with AVR. Predictors of unfavourable and favourable outcomes for post-AVR pVO_2 can be identified.

Objectives

Study I

To evaluate, in patients who are judged, by a cardiologist, as asymptomatic or equivocal symptomatic from moderate or severe aortic stenosis, including those who are difficult to assess, such as those aged >70 years, with Vmax <4 m/s and high valvuloarterial impedance, Vmax >5 m/s, a NYHA II or III classification, COPD, or with impaired blood pressure response or ST depression or symptoms during the exercise test: the feasibility, reproducibility, and information obtained by CPX, to determine predictors of a decreased pVO2, and to assess the safety of reliance upon CPX results for the treatment strategy in such patients.

Study II

To determine the safety of a treatment strategy based on the results from CPX in patients with asymptomatic or equivocal symptomatic from AS without left ventricular dysfunction and if such a treatment strategy would result in: a) a low and acceptable event rate for those without significant hemodynamic compromise from aortic stenosis as determined by CPX and; b) a high rate of improvement in functional capacity with valve replacement in those with significant hemodynamic compromise.

Study III

To determine pVO_2 nine months after single AVR for aortic stenosis without left ventricular dysfunction and comparing postAVR pVO_2 with the predicted pVO_2, to evaluate the changes in pVO_2 with AVR, and to determine predictors of favourable or less favourable outcomes in pVO_2 after AVR.

Methods

Patients and inclusion criteria

Study I and II

The study population was recruited from the outpatient clinic of the Cardiology Department at Roskilde Hospital between 1st March 2010 and 1st October 2011. Patients who were followed in our outpatient clinic or were referred for exercise testing or for

evaluation for AVR and who were judged by a (non-study) cardiologist as asymptomatic or equivocal symptomatic from moderate or severe aortic stenosis (aortic valve area <1.3 cm^2) were eligible for the study. Equivocal symptoms included milder dyspnoea, apparent progression of dyspnoea in COPD-patients, unspecific chest symptoms, or atypical angina and dizziness not clearly related to exercise. The exclusion criteria were a left ventricular ejection fraction <0.50, atrial fibrillation with a resting heart rate >90, or concomitant significant other valvular disease. In patients with aortic stenosis and these exclusion criterias, it is difficult to determine, by CPX, which component is the cause of a hemodynamic compromise.

Study III

Patients referred to single AVR (AVR without revascularization or other valve interventions) from our clinic in the study period from 1st March 2010 1st March 2012 who had a left ventricular ejection fraction not less than 45% in the symptomatic state, had no atrial fibrillation with resting heart rate >90, and were judged able to perform exercise testing were eligible. Such patients were registered and an evaluation, including a CPX 9 months after AVR, was scheduled. Accordingly, the patient group in Study III consisted of patients who were clearly symptomatic by clinical evaluation at first contact in the study period, including patients with hospitalization for heart failure (Group A) and patients from Study I/II who were referred for AVR during the study period (Group B). Group A patients were not subjected to a pre-AVR CPX because they were judged as having unequivocal symptoms from the aortic stenosis. Exercise testing is regarded as a class III indication (not recommended) in such patients (1,2); however, patients in Group B had a pre-AVR CPX after development of symptoms, including those with hospitalization with heart failure or syncope. These patients were well known and evaluated by the study physicians. Therefore, despite symptomatic status, a CPX was found safe and accepted by the ethics committee.

Baseline evaluation (Study I/II)

At baseline, the patients underwent clinical history examinations, NYHA functional classification, echocardiograms, and blood sampling, including for Hb, BNP, and creatinine, and a SF-36 questionnaire was completed. The inclusion criteria, AVA <1.3 cm^2 and classification as asymptomatic or equivocal symptomatic, were based on the referring independent cardiologist's evaluation. A baseline echocardiogram was performed by our cardiologist or technician staff. A CPX with IGR was performed at baseline except in those in Study III who were judged clearly symptomatic at first evaluation (Group A).

Prospective grouping according to CPX outcome at baseline (Study I/II)

Based on the outcome and evaluation of the baseline CPX, patients were prospectively categorized as shown in Table 1.

The evaluation of the CPX results was done without knowledge of the echocardiographic severity of the aortic stenosis and the patient record, whereas the assessment of symptoms during CPX was not.

At the baseline visit, patients categorized into Groups 1 and 2 followed a conservative strategy, whereas Group 3 patients were referred for angiogram and Heart Team evaluation for AVR.

Follow-up

Study I/II

Follow-up was scheduled to a minimum of 12 months with an expected range of 12 to 36 months and mean follow-up of two years. Patients in Groups 1 and 2 and those who did not have AVR in Group 3 were followed with clinical evaluations at 3- to 6-month intervals and with CPX and echocardiography at 6- or 12-month intervals, or if patients presented symptoms between scheduled visits. Patients were instructed to contact the study doctors if new symptoms arose or functional capacity decreased. All patients who reported symptoms and/or a change in functional capacity at or between the visits had full evaluations, including a CPX, and completed a SF-36 questionnaire. The same evaluation and CPX were performed after stabilization and ambulation in patients who experienced syncope or hospitalization for heart failure in study period. If the clinical evaluation, including CPX, indicated new or worsening symptoms or decreasing functional capacity from aortic stenosis, the patient was referred for angiogram and evaluation for AVR. All decisions concerning AVR were taken by an independent Heart Team that included cardiologists and surgeons, from another institution, without knowledge of the details of the CPX and SF-36 results. Patients who had AVR underwent a follow-up CPX, echocardiography, blood sample collection, clinical evaluation and NYHA classification, and completion of the SF-36 questionnaire 9 months after AVR.

The vital status, hospitalizations, and AVR were recorded as of 1st December 2012 from the Danish National Patient Registry, hospital records, and through information obtained during the study. Cause of death was the primary diagnosis in the discharge

Table 1. Criteria for grouping based on the results of baseline CPX.

Group 1 "normal CPX"	pVO_2 >83% of predicted value and pO_2pulse >95% of predicted value.
Group 2 "abnormal CPX results not likely caused by AS"	1. pVO_2 <83% of predicted value and either: a. normal pO_2pulse, defined as >95% of predicted value b. low effort (R <1) c. pulmonary disease with FEV1 or FEV1/FVC <70% of predicted value, low BR, high VE/VCO_2, and normal O_2pulse trajectory 2. pVO_2 >83% and pO_2pulse <95% of predicted values.
Group 3 "abnormal CPX results judged to be caused by AS"	1. pVO_2 <83% of predicted value and decreased O_2pulse <95% of predicted value and good effort with R >1. 2. VE/VCO_2 >32 with normal FEV1 (>80% of predicted value) and non-low breathing reserve (>25) if the pVO_2 and O_2pulse were not much higher than 83% and 95% of the predicted, respectively. 3. Clear exercise-limiting symptoms (angina, severe dizziness and discomfort, and more than usual dyspnoea) and the CPX results pointing to no other cause than aortic stenosis.

summary. For patients who had an AVR before 1st December 2012, a post-AVR evaluation was scheduled for 9 months afterwards.

Study III

At 9 months post-AVR, CPX and evaluation, as described for study I/II patients, were done.

Outcome measures

Study I

The two primary outcome measures were percentage achieved of the predicted pVO_2 and the percentage achieved of the predicted pO_2pulse, reflecting cardiac output and stroke volume, respectively. A pVO_2 <83% of the predicted value by the EACPR/AHA statement (35) represents < the lower 95% CI in the healthy sedentary population and was considered subnormal (36). A pO_2pulse <95% of the predicted value was considered subnormal. This was based on the assumption that 5% less than normal is abnormal. This value corresponds to a pVO_2 of 83% at a peak heart rate of 87% of the predicted value. It may be more appropriate, however, to use a value that corresponds to a pVO_2 of 83% at a peak heart rate of 85% and 83% of the predicted, i.e., a limit of 98% or 100% of the predicted pO_2pulse.

CPX safety was evaluated by registration of adverse events during the test and the safety of relying on CPX evaluation was evaluated by determining vital status and cause of death at 12 months.

Reproducibility was determined by test-retest within 14 days in 15 patients who lived close to our hospital and by calculating the coefficient of reproducibility.

Study II

Primary endpoint

Cardiac death, hospitalization with heart failure, or AVR with improvement.

This endpoint was used as a surrogate for hemodynamic compromise from aortic stenosis.

In patients without significant left ventricular dysfunction, an AVR for true hemodynamic compromising aortic stenosis should improve the patient's physical capacity.

AVR with improvement was defined as a clinically significant improvement from pre-AVR to 9 months post-AVR in either 1) the objective measure pVO_2 or 2) the patient's experienced physical function, as determined by the Physical Component Score (PCS) of the SF-36 Health related quality of life questionnaire. A relative increase in the absolute pVO_2 >5% was considered a clinically significant improvement. This value corresponds to the coefficient of variability by test-retest in our lab (37). This cut-off minimized the chance that the individual patient actually declined – it may be appropriate to refer for AVR when smaller changes in functional capacity or pVO_2 emerge – and is consistent with a high likelihood that the patient actually improved. A relative increase in PCS of 7.5% was regarded as a clinically significant improvement. This value corresponds to the estimated minimal clinical relevant difference (38,39) and to 50% of the mean improvement found after AVR in a previous study of very symptomatic patients (40). PCS was used because it, in contrast to, e.g., symptoms, subjective improvement, or NYHA classification, was regarded as less prone to bias from the placebo effect of AVR, double unblinded assessment, and knowledge of the pre-AVR value.

For patients with an initial conservative strategy, an event rate of the primary endpoint during follow-up <33% was considered low and <50% acceptable.

Secondary endpoints

Safety endpoint. Cardiac (including sudden or unexplained) deaths and hospitalization with heart failure.

Traditional endpoint. Cardiac death, hospitalization with heart failure, or AVR. This endpoint was used for comparisons with other studies. Not all AVRs are performed due to hemodynamic compromise from aortic stenosis, but may be performed because of knowledge of that the patient has a severe aortic stenosis, changes in echocardiographic measures within the limits of intra- or interrater reproducibility, the patient is told that he/she might benefit from AVR, a wish to "get it done", or temporal changes in symptoms or functional capacity that may not be caused by aortic stenosis, or by assessment from different physicians.

A cardiac death rate in patients not recommended AVR of <1% per year was considered low and around 1% per year acceptable. An event rate during mean follow-up of two years for the traditional endpoint of <40% was considered low and <60% acceptable, based on the outcomes of the previous studies on asymptomatic (although younger) patients with comparable echocardiographic severity of the aortic stenosis, showing an estimated event rate at two years of >50% (3,5,14,23,41). A meta-analysis showed an event rate, at 14 months, of 42% (41).

Study III

The primary outcome measure was the percent pVO_2 of the predicted value. An unfavourable outcome was defined as a post-AVR pVO_2 <83% of the predicted value, which corresponds to the lower 95% CI in the healthy sedentary population (36). Although a post-AVR pVO_2 <83% of the predicted value may present an improvement in some patients, this level represents a significant decreased functional capacity and such patients should not be regarded as completely healthy and unlimited.

For the subgroup with a pre-AVR CPX, the percent change from pre- to post-AVR in the absolute pVO_2 was the primary outcome measure. An unfavourable outcome was defined as a >10% decrease from pre-AVR to 9 months post-AVR in the absolute pVO_2; 10% was 2 times the coefficient of variability by test-retest (37). Similarly, a favourable outcome was defined as a >10% increase in the absolute pVO_2.

Determination of predictors of outcome

Study I

Predictors of a pVO_2 <83% of the predicted value. Tested predictors included age and sex (although these were accounted for in the predicted pVO_2), atrial fibrillation, pulmonary disease, diabetes, hypertension, use of beta blockers, Vmax >4 m/s, mean gradient >40 mm Hg, AVAI <0.4 cm^2/m^2 (and post hoc AVAI as a continuous variable), Sa and E/e' (as continuous variables, and according to median and upper and lower quartiles), SVI determined by inert gas rebreathing at submaximal exercise (continuous and post-hoc <35 mL/m^2), peak heart rate (continuous variable), VE/VCO_2 (continuous and post hoc >32), FEV1 (continuous and post hoc <80% of predicted value), and pO2pulse index (continuous) and Zva (>5.5 mm Hg/(mL/m^2), representing median value and cut-off used in other studies (42).

Study II

Tested predictors included decreased exercise capacity (pVO_2 <83% of the predicted value), symptoms or increases in systolic blood pressure <20 mm Hg during the CPX, pO_2pulse <95% of the predicted value as an expression of decreased stroke volume at peak exercise, a respiratory coefficient <1 as an indicator of lack

of effort, BNP >ULN, Vmax >4 m/s and AVAI <0.4 cm^2/m^2. Post-hoc pO_2pulse <100% of the predicted value was tested and used; this corresponds to a pVO_2 <83% of the predicted value at a peak heart rate of 83% of the predicted and so on. Use of this cut-off also partially circumvents bias from the initial grouping and increased the statistical power.

For the statistical methods used to determine predictors, please refer to section 3.9.

Study III

The following preoperative parameters thought to influence outcome were tested: age, sex, atrial fibrillation, presence of pacemaker, chronic obstructive lung disease, diabetes, hypertension, use of beta blockers, Vmax >4 m/s, mean gradient <40 mm Hg (and median value), AVAI <0.4 cm^2/m^2 (and median value), Sa, E/e' and pO_2pulse (dichotomized by their respective median value), and post-hoc postoperative pacemaker and use of beta blockers. Median values were used to increase the power.

Power and sample size calculations

Calculated with significance level at 5% and power of 80%.

Study I

Based on the sample size in previous studies and the estimated number of patients that could be included during two years, a sample size of at least 120, with at least 50 having Vmax >4 m/s, was scheduled.

With the standard deviation of pVO_2 estimated as 20%, a difference in mean values of 10 to 11% in pVO_2 and pO_2pulse would be detected by group sizes of 40 to 50 vs. 80, respectively. With group sizes of 20 vs.110, a difference of 13.5% would be detected.

An observed cardiac death rate of 0, 1 or 2% at one year would have a 95% CI upper level at <3, 4 and 6%, respectively, with n=130.

Study II

With 100 patients in the conservative arm, event rates of 7, 28, 38, and 46% would be significantly different from theoretic values of 15, 40, 50, and 60%, respectively. Cardiac death rates of 0, 1, 2, and 4% would have 95% CI upper levels at <3, 4, 7, and 10%, respectively. A sample size of 20, with baseline CPX pointing to hemodynamic compromise with an event rate of 67% of the primary endpoint (two thirds expected to improve with AVR) and 100 in the conservative arm, would detect an absolute decrease in event rate of 34% (down to 33%, two-thirds of 50% with traditional endpoint improved by AVR).

Study III

It was planned to have 100 post-AVR evaluations (Group A+B) with one-third estimated to undergo a pre-AVR CPX (Group B). With the standard deviation of pVO_2 estimated at 20%, this would detect a difference in the mean post-AVR pVO_2 compared to the predicted of 5%, and a sample size of 35 would detect a difference in the frequency of patients with a change in pVO_2 >10% from pre- to post-AVR from the expected 5 to 16%.

Cardiopulmonary exercise testing

By cardiopulmonary exercise testing, the oxygen and carbon dioxide concentrations, air flow (inspiratory and expiratory), and heart rate (HR) were measured. From these measurements, the oxygen consumption (VO_2), carbon dioxide exhaustion (VCO_2), and ventilation (VE) were calculated. In the present study, breath-by-breath and 10-second interval average measurements were made. Continuous 12 leads ECG monitoring and an Innocor apparatus (Innovision, Odense, Denmark) with a breath-to-breath module and spirometer connected to a bicycle ergometer (Corival) were used. Brachial blood pressure was checked at baseline and every other minute until after the exercise.

Several measures that reflect the cardiorespiratory function and exercise physiology can be determined from the VO_2, VCO_2, VE, and HR.

Peak oxygen uptake (pVO_2). The pVO_2 is the highest value of VO_2 measured during the last stage of exercise and is usually indexed for body weight. VO_2 is associated with cardiac output (CO) and arteriovenous oxygen extraction ($C_{(a-v)}O_2$): $VO_2 = CO \times C_{(a-v)}O_2$, where CO = SV × HR. Since the arteriovenous oxygen extraction does not differ between healthy individuals and patients with cardiac diseases at peak exercise (43,44) within the normal ranges of hemoglobin and oxygen-saturation, pVO_2 has a linear relationship with the CO at peak exercise (45). Given this relationship, it is not surprising that pVO_2 is a major predictor for the prognosis of patients with cardiac diseases (27-29). Furthermore, the pVO_2 is highly reproducible in such patients and has little training effect (25,26). Assuming stable hemoglobin and oxygenation in the individual patient, changes in pVO_2 will reflect changes in CO at peak exercise, which makes pVO_2 very useful for serial monitoring of CO.

It is the exercising muscles, not the body fat, that significantly increase oxygen consumption during exercise. It is, therefore, inappropriate to present pVO_2 only as pVO_2 per kg, which is unfortunately not uncommon in studies. A 20% overweight would result in a 17% subnormal pVO_2.

The recommended predicted (normal) value of pVO_2 is dependent on age, sex, weight, over- and underweight. As recommended by the EACPR/AHA statement, the predicted values were calculated as follows (35,46):

Predicted pVO_2 (mL/min) for sedentary men:

- Cycle factor = 50.72 - 0.372 × age
- Predicted weight = 0.79 × height - 60.7
- Predicted pVO_2 for normal weight men = actual weight × cycle factor
- Predicted pVO_2 for men weighing less than that predicted = ((predicted weight + actual weight)/2) × cycle factor
- Predicted pVO_2 for men weighing more than that predicted = (predicted weight × cycle factor) + 6 × (actual weight - predicted weight)

Predicted pVO_2 (mL/min) for sedentary women:

- Cycle factor = 22.78 - 0.17 × age
- Predicted weight = 0.65 × height - 42.8
- Predicted pVO_2 for normal weight women = (actual weight + 43) × cycle factor
- Predicted pVO_2 for women weighing less than that predicted = ((predicted weight + actual weight + 86)/2) × cycle factor
- Predicted pVO_2 for women weighing more than that predicted = (predicted weight + 43) × cycle factor + 6 × (actual weight - predicted weight)

A pVO_2 <83% of the predicted value corresponds to the lower limit of the 95% CI for normal sedentary individuals (36) and was predefined as abnormal in the present study.

Peak oxygen pulse (pO_2pulse). The pO_2pulse is calculated as pVO_2/pHR. Based on $VO_2 = CO \times C_{(a-v)}O_2$ with CO = SV × HR, the pO_2pulse reflects the SV at peak exercise. Since the $C_{(a-v)}O_2$ at peak exercise is does not change significantly in an individual,

changes in the pO_2pulse reflect changes in the SV at peak exercise, making the pO_2pulse suitable for serial monitoring. A pO_2pulse <95% of the predicted value was pre-specified as subnormal in this study. An estimate of the SV (mL) at peak exercise can be obtained from the equation (pO_2pulse/Hb in g/dL) × 100, because Hb in g/dL then corresponds to the millilitres of oxygen extracted per decilitre (43,44).

VO_2 trajectory. The VO_2 trajectory is obtained by plotting VO_2 against the load. The VO_2 normally increases linearly during incremental exercise and reaches its plateau at the last stage, expressing the maximum tolerable work capacity. An abnormal VO_2 trajectory flattens before the last stage.

O_2pulse trajectory. The O_2pulse trajectory is derived from plotting the O_2pulse against the load. The normal response with exercise is for the O_2pulse to increase with load and for the SV to gradually increase until, or shortly after, the anaerobic threshold is reached, with a small decline thereafter (35,47). An early plateau or a decline in the O_2pulse is considered abnormal, and, if not caused by an abnormal increase in the heart rate, indicates a decline in the SV. In patients with coronary disease, abnormal VO_2 and O_2pulse reflect ischemia, probably caused by ischemia-induced systolic dysfunction (35,47).

In the present study, the load was increased linearly with time, allowing the VO_2 and O_2pulse to be plotted against time. The VO_2 and O_2pulse trajectories were assessed, blinded to all other patient-data, and visually assessed with a ruler for slope and linearity. Examples of normal and abnormal trajectories in two study patients are presented in Figure 1. The patient with the abnormal trajectory shows a flattening in the VO_2 trajectory and a decline in the O_2pulse trajectory beginning at the 4th and last stage, whereas the patient with the normal trajectory shows a linear increase in VO_2 and a continuing rise in the O_2pulse trajectory without a plateau.

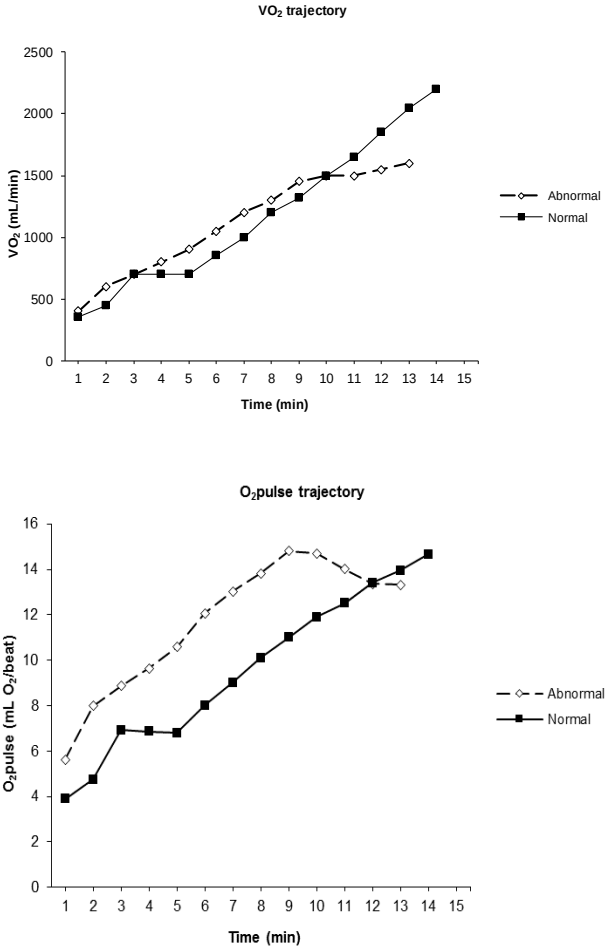
Anaerobic threshold (AT), or VO_2 at AT. The anaerobic threshold is the level of exercise and corresponding VO_2 where lactate accumulates because of an insufficient oxygen supply to oxygen consumption ratio, leading to bicarbonate buffering and an increased VCO_2. Decreased blood flow due to decreased CO results in a decreased AT. The AT is determined from a plot of the VO_2 and VCO_2 versus time/load, and is defined as the VO_2 value where the VCO_2 increases as compared to the VO_2. The AT was computed by the Innocor, using the V-slope method, and was controlled by inspection of the VO_2 versus VCO_2 plot generated and corrected as necessary. The AT was evaluated against the predicted pVO_2. In the bicycle ergometer test, the mean (lower boundary of the 95% CI) ATs for normal sedentary 70-year old men and women are 58% (47%) and 65% (54%) of the predicted pVO_2, respectively (48).

VE/VCO_2. The ventilatory equivalent for carbon dioxide is the ratio of the VE and VCO_2, both measured in L/min; it declines at the beginning of incremental exercise, reaches its nadir when respiratory compensation for lactic acidosis starts, and rises thereafter. A high value at the nadir (>32) suggests increased physiological dead space, a ventilation/pulmonary blood-flow mismatch, as seen in lung diseases and heart failure or non-physiological hyperventilation (31). The VE/VCO_2 slope is often used and the nadir value corresponds to the slope but is more reproducible (49,50).

Respiratory exchange ratio/coefficient (R). R is defined as the ratio of VCO_2 to VO_2. A value <1.0 at peak exercise indicates little lactate production, and thus no flow limitation to the exercising muscles. Faster increases in the load tend to increase R, and severe hyperventilation may decrease R (51).

Predicted peak heart rate (pHR) was calculated as 220 - age, and it is dependent on age, the use of negative chronotropic drugs or a pacemaker implant, effort, and motivation for exercise; it may be reduced by angina or heart failure symptoms during exercise (36,52).

Figure 1



Examples of normal and abnormal trajectories in two study patients.
Top - VO_2 trajectories.
Bottom - O_2pulse trajectories.
Abnormal. Patient with Vmax 5.1 m/s. Normal. Patient with Vmax 3.9 m/s.
As it appears from the description of the exercise protocol (after the first 3 min), one minute presents one step in load.

Spirometry was done prior to the exercise test. Forced expiratory volume in the first second (FEV1) and FVC (forced vital capacity) were determined as the mean of three measures. Breathing reserve (BR) during the exercise test was defined as 40 × FEV1 - maximum per minute ventilation, and a low BR indicates respiratory limitation or hyperventilation (46); a very high BR may indicate lack of effort.

Cardiac output and stroke volume index from inert gas rebreathing (IGR)

Cardiac output may be measured by the Innocor by means of the inert gas rebreathing technique. The method was validated against the invasive thermodilution method (53) and in patients with presumed asymptomatic aortic stenosis (24). The patients inspire an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulphur hexafluoride), from a 4 litre bag for normal-sized persons. In this closed

system, the respiratory gas concentrations are measured by photoacoustic analysers over the next few breaths. The concentration of the soluble inert gas nitrous oxide decreases proportionally with pulmonary blood flow, which then can be calculated by the Innocor; in the absence of shunts, this flow corresponds to the cardiac output. The insoluble inert gas concentration serves as the control. The stroke volume index (SVI) is then calculated from the CO, the corresponding HR, and the patient's calculated body surface.

In the present study, patients were instructed and familiarized with the rebreathing test prior to the exercise test, and a baseline CO was determined as the mean of three rebreathing tests. Patients then had a CPX without the rebreathing test. The AT and pVO_2 were determined and, after 15 minutes of rest, the patient had another incremental exercise test with IGR at the stage beyond the AT. This is the point where the SVI peaks in normal individuals; this strategy will not detect patients who have a sudden decline in SVI at peak exercise. IGR may be difficult at peak exercise due to patient cooperation, and in a previous study, IGR was not feasible in >30% of the patients (24). In the present study, priority was given to a high feasibility of IGR. Patients who have a sudden decline in SVI at peak exercise will show a decline in the O_2pulse or abnormal VO_2 and O_2 trajectories.

Exercise protocol

As recommended (54), patients cycled unloaded for 3 min for familiarization and to obtain a steady state unloaded VO_2 and VCO_2. The load was then increased each minute based on the following: work rate increment per minute (W/min) = (predicted pVO_2 - VO_2 unloaded)/100, resulting in an exercise time of 8 to 10 minutes; exercise time and watts are thus irrelevant. Patients continued to exercise until exhaustion or limiting/disabling symptoms. ECG changes or declines in blood pressure were not stopping criteria unless severe symptoms developed or the CPX revealed hemodynamic compromise.

Quality of life and NYHA class

Health related quality of life (QOL) was determined from the well-validated and widely-used Physical Component Summary (PCS) and the Mental Component Summary (MCS) from the short-form health survey questionnaire (SF-36), calculated by dedicated software (38,55,56). Higher scores indicate higher perceived health. In order to decrease bias from the physician and from the outcomes of the echocardiography and exercise testing, the patients completed the questionnaire at home prior to the tests.

The NYHA class was determined by thorough questioning based on the original criteria at the visits prior to the echocardiography and exercise test.

Echocardiography

All patients underwent two-dimensional and Doppler echocardiography (General Electric Vivid E9, GE Healthcare, Horten, Norway). Apical continuous wave and pulsed wave Doppler recordings were created to obtain the peak flow velocity (Vmax), mean pressure gradient from the velocity time integral, ventricular outflow velocity time integral, and early diastolic inflow velocity (E). The left ventricular outflow diameter was measured along the parasternal long-axis in mid-systole. The aortic valve areal index was calculated using the continuity equation and indexing for body surface. The left ventricular ejection fraction was estimated visually from several two-dimensional projections. Pulsed-tissue Doppler recordings were made from the apex to obtain the early lateral mitral annulus velocity (e'), and E/e' was calculated as an expression of diastolic pressure. Left ventricular systolic function was assessed by the peak systolic tissue velocity (Sa) derived from apical colored tissue Doppler recordings of the mitral annulus, because it is a more sensitive marker of systolic function in patients with aortic stenosis than the ejection fraction (57,58). The mean of the septal and lateral Sa values was used.

Valvuloarterial impedance (Zva)

Zva was calculated as (systolic blood pressure + mean systolic aortic valve gradient)/SVI with the measurements obtained at rest by sphygmomanometer of the brachial blood pressure, by echocardiography, and during the IGR test, respectively. A high Zva was defined as higher than the median in the study population (5.5 mm Hg/(mL/m^2)), which turned out to be the cut-off value used in some important studies (42,59).

Brain natriuretic peptide

Venous blood from the forearm was obtained at resting conditions. The upper level of normal (ULN) was based on the local laboratory reference, which incorporated age and sex.

Statistics

For statistical calculations, the IBM software program SPSS Statistics 20 (New York, NY, United States) was used. Continuous variables are presented as the mean ± standard deviation (SD). Unpaired t-tests were used to compare the means of two groups, while paired t-tests were conducted for within group changes at two time points, and an analysis of variance was done to compare the means of three or more groups. The magnitudes of difference between groups or changes within group are presented as 95% confidence intervals (95% CI). Assumptions for the t-test or ANOVA were assured by generally striving for groups of not much less than 20 patients, by testing and eventually correcting for unequal variances, and by normality plots to determine skewness. The assumption of the t-test is a normal distribution of the mean value with equal variances. Categorical variables are presented as numbers and percentages, and the Fisher's test and the normal approximation to the binomial distribution were used to compare differences between groups. A p-value <0.05 was generally considered statistically significant. However, if two primary outcome measures were used and only one had p<0.05, the level was 0.025. Similarly, if 3 or 4 groups were tested and, e.g., only one between-group comparison had p<0.05, a significance level of 0.017 or 0.013 was used, respectively.

Predictors of binary outcome measures were sought by logistic regression or, if relevant, by Cox-regression analysis. Univariate predictors were identified by a p-value <0.05. For multivariate models, the predictor with the lowest p-value <0.05 was entered in the model and all other predictor variables with a p-value <0.10 were each entered, one at a time, by forward stepwise regression and kept if the predictor had a p-value <0.05. All such predictors were then tested in possible models with three, four, five, and more; predictors and predictor variables with p<0.05 were kept in the final model. Non-binary predictor variables were tested as continuous variables and as binary variables according to median, and dependent on sample size and the upper and lower 25 and 33% percentiles. Goodness of fit of logistic regression models was secured by the Hosmer-Lemeshow method and, in case of continuous predictor variables, linearity assumptions were assured by plots of quartiles. Appropriateness of the Cox regression model was assured by using binary predictor variables and lack of time-dependency (proportional hazard) by the log minus log plot.

Ethics

All included patients gave written informed consent, and the study was approved by the local ethics committee (1-01-83-0002-07).

Summary of results

Baseline characteristics. Studies I and II (Table 2)

The age distribution was typical for current patients evaluated for aortic stenosis, with a mean age of 72.1 ± 9.3 years. The study patients had non-trivial aortic stenosis, with 90% having AVAI <0.6 cm^2/m^2; 71% were judged equivocal symptomatic and 48% judged in NYHA class II. Patients with comorbidities, such as atrial fibrillation, COPD, and undergoing beta blocker therapy, were included because such patients are part of the spectrum of patients with aortic stenosis.

Table 2. Baseline characteristics.

	n=131
Age (years)	72.1±9.3
Male/female ratio	83/48
BMI (kg/m^2)	26.8±4.0
Diabetes mellitus (n)	16 (12%)
Hypertension (n)	78 (60%)
Smoker (n)	24 (18%)
Obstructive lung disease (n)	21 (16%)
Prior revascularization (n)	13 (10%)
Atrial fibrillation (n)	16 (12%)
Pacemaker (n)	4 (3%)
Asymptomatic/Equivocal symptomatic (n)	38/92 (29%/71%)
NYHA class I (n)	68 (52%)
Hemoglobin (mmol/L)	8.8±0.7
Creatinine (µmol/L)	82.9±20.0
LDL cholesterol (mmol/L)	2.96±0.98
BNP >ULN (n)	35 (27%)
Echocardiography	
Vmax (m/s)	3.92±0.77
Vmax >4 m/s (n)	55 (42%)
Mean gradient (mm Hg)	38.2±15.3
Aortic valve area index (cm^2/m^2)	0.45±0.11
Aortic valve area index <0.6 cm^2/m^2 (n)	117 (90%)
Left posterior wall thickness (cm)	1.14±0.25
Sa (cm/s)	5.00±1.23
E/e'	13.3±5.0
Cardiovascular drugs	
Beta blockers (n)	36 (28%)
Digoxin (n)	9 (7%)
ACE-/AT-II inhibitors (n)	47 (36%)
Diuretics (n)	51 (39%)
Calcium-blockers (n)	37 (28%)
Statins (n)	74 (56%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin converting enzyme inhibitor; AT-II inhibitor, angiotensin receptor inhibitor.

Study I

Feasibility

Of 146 eligible patients, 15 did not consent and 131 were recruited. A CPX was feasible in 130 (>99%) and an IGR, with determination of SVI at rest and at submaximal exercise, was feasible in 116 (88.5%). There were no adverse events during the tests.

Reproducibility

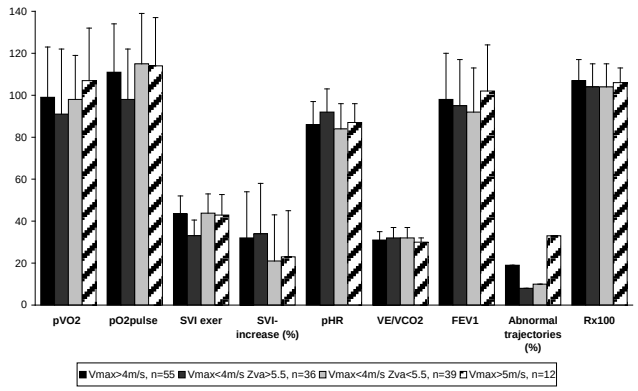
In 15 asymptomatic patients, who accepted a new CPX within 2 weeks of the previous, the coefficients of variability for the pVO_2, pO_2pulse, and SVI at submaximal exercise were 5.4%, 4.6%, and 14.2%, respectively. The kappas for an abnormal O_2pulse and for an abnormal O_2pulse and abnormal VO_2 trajectory were 0.70 and 1.0, respectively.

CPX and IGR results according to Vmax >< 4 m/s and valvuloarterial impedance (Figure 2)

In general, patients were able to exercise to substantial effort according to peak heart rate and the respiratory coefficient. It appears that in these study patients, a Vmax >4 m/s or even >5 m/s does not mean a decreased pVO_2 or pO_2pulse or that SVI does not increase with exercise. The higher frequency of abnormal trajectories in those with a Vmax >5 m/s suggests that, in such patients, a significant decrease in stroke volume during peak exercise is more common but not obligate.

Patients with Vmax <4 m/s but high valvuloarterial impedance exhibited lower pVO_2 and pO_2pulse, concordant with lower stroke volume at peak exercise, but were well able to increase SVI, as determined from IGR, from rest to submaximal exercise. Thus, this group was characterized by a low stroke volume at rest, more than from hemodynamic compromise from aortic stenosis, during exercise.

Figure 2



CPX outcomes according to Vmax and Zva.

pVO_2, pO_2pulse, pHR, and FEV1 in percent of predicted value. SVI exer: SVI from IGR at submaximal exercise. SVI-increase: increased SVI in percent from resting SVI to SVI exer. Group mean values and SD (bars) are presented.

Those with Vmax ≥4 m/s showed slightly lower VE/VCO_2 (p=0.032) compared to those with Vmax <4 m/s.

Those with Vmax <4 m/s and Zva >5.5 mm Hg/(mL· m^2) showed lower pO_2pulse (p=0.003 [0.016])), SVI exer (p<0.001 [<0.001]), higher pHR (p=0.004 [0.077]) and a trend toward lower pVO_2 (p=0.083 [0.10]) compared to the other groups. The P-values in brackets [] represent the p values when patients with atrial fibrillation (n=16) were excluded from analysis.

No differences between these groups were observed for the other parameters displayed in this figure.

Patients with "abnormal" conventional exercise test

In the 25 patients with symptoms during the exercise test, mean pVO_2 was low 84±19% of the predicted value, but achieved, at significant effort, a mean pHR of 85±11% of the predicted value and

an R of 1.07±0.12. The mean VE/VCO_2 was above the normal 34±5.

Those with blood pressure increases <20 mm Hg (n=35) or ST depression ≥2 mm during exercise (n=12) showed similar pVO_2, pO_2pulse, and frequency of abnormal trajectories as those without these characteristics.

Patients with COPD

Patients with COPD showed lower pVO_2 (80.6 vs 99.9%, 95% CI: -29.2 to -9.5%), pHR (80.4 vs. 87.9%, 95% CI: -12.9 to -2.1%), and breathing reserve (30.9 vs. 48.0, 95% CI: -26.8 to -7.5) and exhibited a higher VE/VCO_2 (33.5 vs. 31.1, 95% CI: 2.1 to 12.9) compared to those without COPD. The echocardiographic severity of the aortic stenosis was similar (Vmax and AVAI).

Predictors of a decreased pVO_2

A pVO_2 <83 % of the predicted value was seen in 35 patients (27%), and in this study, was predicted by lower stroke volume index at submaximal exercise, lower peak heart rate (together reflecting cardiac output during exercise), higher VE/VCO_2 (worse ventilation/perfusion coupling), and lower FEV1 (worse pulmonary function) (Table 4), but not by echocardiographic severity of the aortic stenosis or systolic or diastolic function.

Table 3. Characteristics and CPX results in those referred as Asymptomatic vs. Equivocal symptomatic from aortic stenosis.

	Asymptomatic n=38	Equivocal symptomatic n=92	P-value
pVO_2 <83% of predicted (n)	4 (10%)	30 (33%)	0.009
pVO_2 % of predicted (%)	104±19	94±22	0.014
pO_2pulse % of predicted (%)	113±20	107±25	0.15
pO_2pulse/Hb index (mL/m²)	48±8	42±9	0.001
R	1.06±0.09	1.05±0.10	0.5
% pHR of predicted (%)	88±10	86±12	0.3
VE/VCO_2	30±3	32±4	0.003
FEV1 % of predicted (%)	102±18	93±22	0.022
Breathing Reserve	52±23	42±20	0.021
AT % of predicted pVO_2 (%)	65±13	62±17	0.2
SVI rest (mL/m²)	35±8	31±9	0.033
SVI exercise (mL/m²)	45±9	39±9	0.002
Increase SVIexer/SVIrest (%)	31±17	28±24	0.5
AVAI (cm²/m²)	0.43±0.10	0.46±0.11	0.26
V_{max} (m/s)	4.24±0.69	3.79±0.76	0.002
Mean gradient (mm Hg)	43.8±14.9	35.9±14.9	0.007
Age (years)	73±8	72±10	0.6
Atrial fibrillation (n)	2 (5%)	14 (15%)	0.15
COPD (n)	1 (3%)	20 (22%)	0.007
Beta blocker (n)	7 (18%)	28 (30%)	0.2

Table 4. Multivariate predictors of pVO_2 <83% of the predicted.

	Odds Ratio (95% CI)	P-value
SVI-exercise (per mL/m²)	1.09 (1.01;1.17)	0.022
pHR (per % of predicted)	1.06 (1.01;1.12)	0.031
FEV1 (per % of predicted)	1.07 (1.03;1.11)	<0.001
VE/VCO_2 (per unit)	0.80 (0.69;0.93)	0.005
SVI-exercise <35 mL/m²	5.59 (1.80;17.35)	0.003
pHR (per % of predicted)	1.07 (1.02;1.12)	0.008
FEV1 <80% of predicted	5.01 (1.56;16.04)	0.007
VE/VCO_2 >32	6.38 (2.03;20.02)	0.002

Odds ratios were calculated for decreasing SVI, pHR, FEV1, and VE/VCO_2.

The safety of reliance on CPX results for the treatment strategy

At the one-year follow-up, no sudden or cardiac death had occurred in the 130 patients. This included, among the 112 conservatively treated patients, patients with Vmax >5 m/s, an abnormal conventional exercise test, or a NYHA ≥II classification, where the CPX did not point to significant hemodynamic compromise.

Study II

The baseline characteristics, echocardiographic measures, and CPX results for the three groups are presented in Table 5, Table 6, and Figure 3, respectively. A consort diagram for flow of patients in the three groups is presented in Figure 4.

Table 5. Baseline characteristics in the three groups.

	Group 1 n=77	**Group 2** n=35	**Group 3** n=18
Age (years)	72.8±9.9	72.0±7.5	69.2±10.0
Male/female (n)	42/35 *	26/9	15/3
Hypertension	50.6%	80.0%*	55.6%
Diabetes mellitus	11.7%	11.4%	16.7%
Ischemic heart disease	6.5%	20.0%	27.8%
COPD	9.1%	37.1%*	5.6%
Smoker	13%	28.6%	22.2%
Atrial fibrillation	3.9%	31.4%†	11%
Pacemaker	2.6%	2.9%	5.6%
NYHA class ≥ II	36.4%*	68.6%	55.6%
PCS-SF-36	46.9±8.2†	41.1±8.6	40.7±8.8
Body mass index (kg/m²)	26.6±3.7	27.9±5.3	26.2±3.1
Creatinine (µmol/L)	80±20	88±22	83±11
LDL-cholesterol (mmol/L)	3.1±1.0	2.7±0.9	2.2±1.0
Hb (mmol/L)	9.0±0.7	8.9±0.9	8.7±0.7
Cardiovascular drugs			
Beta blockers	19.5%	45.7%*	22.2%
Digoxin	5.2%	11.4%	5.6%
Calcium-blockers	31.2%	25.7%	22.2%
ACE-/AT-II-inhibitors	31.2%	54.3%	22.3%
Diuretics	40.3%	40.0%	27.8%
Statins	54.5%	57.1%	66.6%

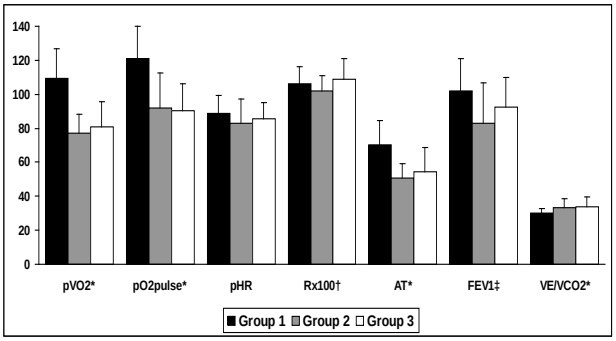
** p<0.01 and † p<0.001 compared to other two groups.*
Group 1: "Normal CPX"
Group 2: "Abnormal CPX results not likely caused by AS"
Group 3: "Abnormal CPX results judged to be caused by AS"

Table 6. Echocardiographic characteristics, stroke volume index, and valvuloarterial impedance at baseline in the three groups.

	Group 1	Group 2	Group 3
V_{max} >4 m/s	48%	23%*	56%
Mean gradient (mm Hg)	39.9±16.1	31.6±10.9*	44.3±15.5
AVAI <0.6 cm^2/m^2	88%	89%	100%
AVAI (cm^2/m^2)	0.45±0.11	0.47±0.09	0.39±0.09*
Sa (cm/s)	5.08±1.16	5.00±1.17	4.62±1.63
E/e'	13.5±5.0	13.4±5.2	12.8±4.2
LVPWd (cm)	1.12±0.23	1.15±0.29	1.21±0.24
SVI resting (mL/m^2)	34±9*	30±9	30±5
SVI submaximal exercise (mL/m^2)	43±9*	36±9	39±9
Systolic blood pressure resting (mm Hg)	132±15	133±19	132±16
Z_{va} (mm Hg/(mL/m^2))	5.46±1.66	5.89±1.52	6.03±1.16

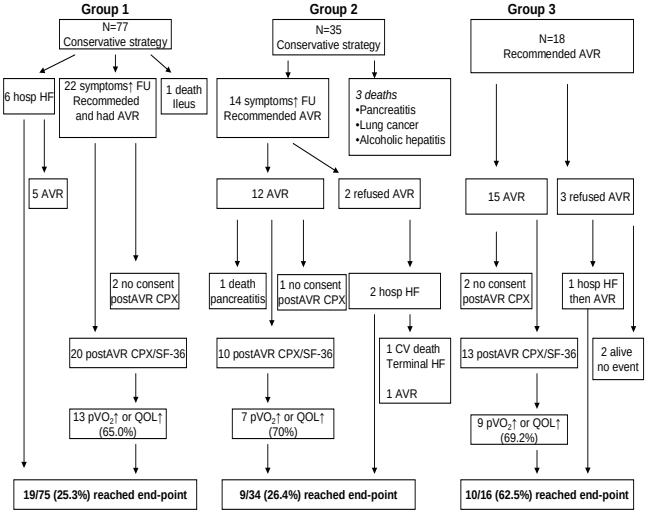
** p<0.01 compared to the two other groups together.*
SVI Stroke volume index measured by inert gas rebreathing.
Zva: Valvuloarterial impedance: (Systolic blood pressure + mean gradient)/SVI rest.
Group 1: "Normal CPX"
Group 2: "Abnormal CPX results not likely caused by AS"
Group 3: "Abnormal CPX results judged to be caused by AS"

Figure 3



CPX results in the 3 groups at baseline.
** p<0.001 for Group 1 vs. Group 2 and Group 3, individually.*
† p=0.011 for Group 2 vs. Group 3 and p=0.013 for Group 2 vs. Group 1.
‡ p<0.001 for Group 1 vs. Group 2.
pVO_2, pO_2pulse, pHR, and FEV1 in percent of predicted value, AT: anaerobic threshold in percent of predicted pVO_2, R: Respiratory coefficient VCO_2/VO_2 at peak exercise (multiplied by 100 for illustration), VE/VCO_2: Ventilation/ expired CO_2 ratio at nadir after AT.

Figure 4



Flow sheet for patients in the three groups.
↑ Symptoms FU: Self-reported new or worsening symptoms at or between follow-up visits.
pVO_2↑: Increase > 5% from just pre-AVR to 9 months post-AVR.
QOL↑: Increase >7.5% in Physical Component Score of the SF-36 health related quality of life questionnaire from pre-AVR to 9 months post-AVR.
CV: Cardiovascular. HF: hospitalization with heart failure.

Outcome in patients where CPX did not indicate significant hemodynamic compromise (Figure 4, Groups 1 + 2)

Safety of reliance on CPX results for treatment of patients. At a mean follow-up of 24.1±5.8 months (range: 12 to 36 months) with complete follow-up, no sudden deaths were observed and no cardiac deaths in patients who had not been recommended for AVR were observed. One patient died of terminal heart failure >8 months after the first recommendation of AVR. In those with an initial conservative strategy, eight (7.1%) patients had a hospitalization with heart failure and two of these had declined AVR previously.

Primary endpoint. This was reached in 25.7% of the study patients (95% CI: 14.6 to 43.1%); there were no differences between groups 1 and 2.

For those with a Vmax >4 m/s vs. <4 m/s, the endpoint was reached in 28.6 vs 24.5% (non-significant), respectively. Because of the lack of post-AVR CPX in three patients (due to lack of consent to post-AVR CPX) the endpoint could be assessed in 109 of 112 patients.

Traditional endpoint. This was reached in 37.5% of the study patients (95% CI: 29.1 to 46.7%). In group 2, the frequency was 40.0%. More patients with Vmax >4 m/s than Vmax <4 m/s reached this endpoint: 48.9 vs. 29.9% (95% CI: 0.8 to 36.1%).

Outcome in patients where CPX did indicate a significant hemodynamic compromise

Group 3

Because of their severe symptoms, five patients (angina n=3, severe dizziness and discomfort n=2) were included in this group despite pVO_2 >83% and pO_2pulse >95%, of which three had pVO_2 >84% and pO_2pulse >95% of the predicted. The primary endpoint was reached in 62.5% (p=0.003 vs. Group 3 vs. Group 1+2). The traditional endpoint is not relevant in this group.

Predictors of endpoints

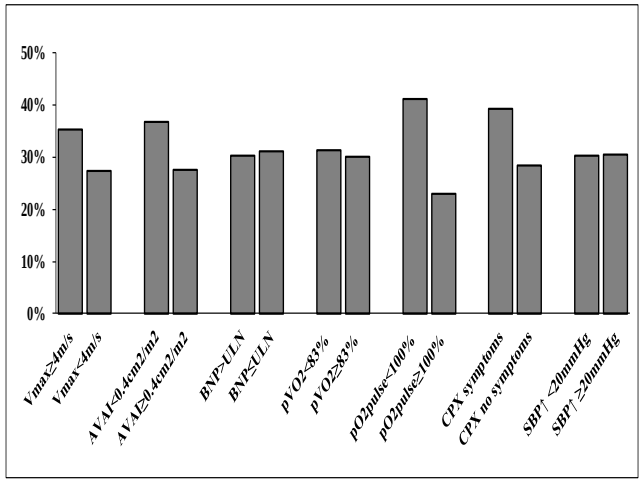
The endpoints in subgroups are presented in Figures 5 and 6.

Primary endpoint. For the entire study population, the only significant predictor was pO_2pulse <100% of the predicted value with OR 2.55 (95% CI: 1.18 to 5.54, p=0.018). If only patients with an initial conservative strategy (Group1+2, n=112) were analysed, the time to endpoint was relevant in this group; a Cox regression analysis showed a trend only for pO_2pulse <100% of the predicted with HR 1.88 (95% CI: 0.89 to 3.97, p=0.096).

Traditional endpoint. This endpoint is only meaningful for Groups 1 and 2. No significant predictors were found by Cox regression analysis. However, as noted above, patients with Vmax >4 m/s showed a higher proportion of the endpoint than those with Vmax <4 m/s.

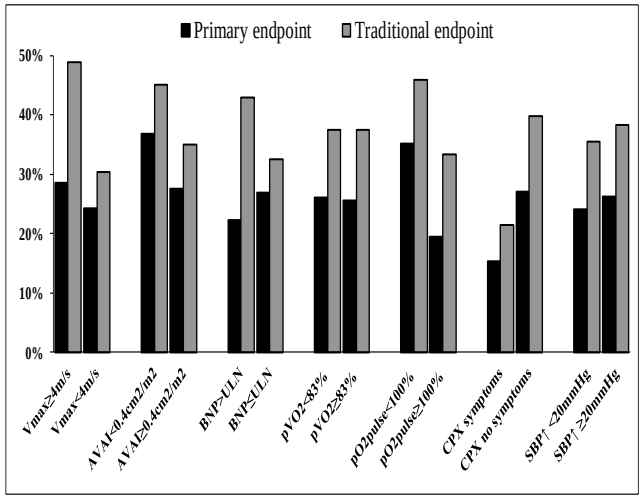
For selection of and how predictors were tested, please refer to the Methods paragraph.

Figure 5



Frequency of primary endpoint in subgroups among all study patients (n=130). *pVO_2 and pO_2pulse in percent of predicted.*

Figure 6



Frequency of endpoint in subgroups among those with an initial conservative strategy (n=112). pVO_2 and pO_2pulse in percent of predicted.

Study III

Baseline characteristics of the 73 patients with a 9-month post-AVR CPX are presented in Table 7.

A flow sheet for the study patients is presented in Figure 7. Characteristics are the pre-AVR values. There were no differences in these characteristics between those who were clearly symptomatic from aortic stenosis and referred for AVR (Group A) and those who were initially judged equivocal symptomatic from aortic stenosis but either because of the results of the initial CPX or because of later development of symptoms had AVR, except for the greater number of patients in the NYHA class than in Group A. Because of a national randomized study of patients >70 years that were eligible for surgery (surgery vs. transcatheter AVR), 20 study patients (Group A: 11, Group B: 9) were randomized to TAVR. Post-AVR, there were no significant differences in the mean achieved vs. the predicted pVO_2 or in the mean change in pVO_2 from pre-AVR between surgical and transcatheter groups. Furthermore, that study was neutral regarding the primary outcome (60).

Table 7. Baseline pre-AVR characteristics.

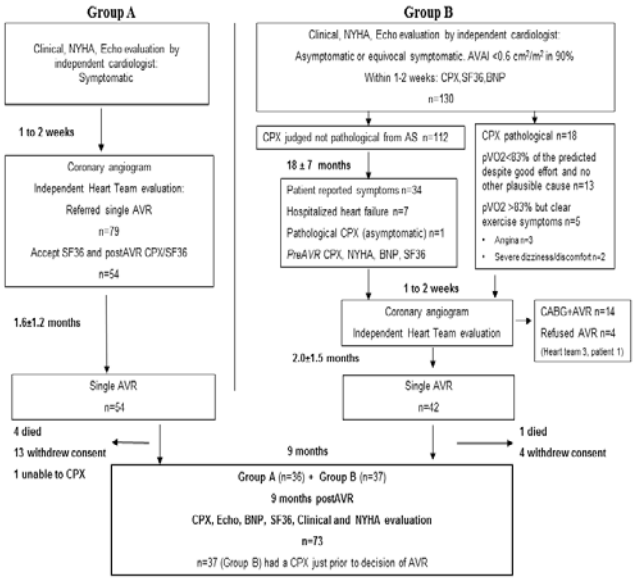
	Baseline Groups A + B n=73
Age (years)	71.6±9.8
Male/female (n)	47/26
BMI (kg/m²)	27.1±4.3
Diabetes mellitus (n)	10 (14%)
Hypertension (n)	47 (64%)
COPD (n)	11 (15%)
Prior PCI/CABG (n)	7 (10%)
Atrial fibrillation (n)	16 (22%)
Pacemaker (n)	5 (6.8%)
Creatinine (µmol/L)	86.±21
LDL cholesterol (mmol/L)	2.9±1.0
Smoker (n)	7 (10%)
AVAI (cm²/m²)	0.39±0.09
Mean gradient (mm Hg)	49.2±15.8
Sa (cm/s)	4.88±±1.43
E/e'	15.6±5.2
LVPWD (cm)	1.20±0.20
Systolic blood pressure (mm Hg)	135±19
Heart rate at rest (beat per minute)	75±13
BNP >ULN (n)	24/54 (44%)
NYHA class ≥II (n)	63 (86.6%)
SF-36 PCS	39.5±9.6
SF-36 MCS	49.8±9.5
Beta blockers (n)	22 (30%)
Digoxin (n)	7 (10%)
ACE-/AT-II inhibitors (n)	30 (41%)
Diureticum (n)	38 (52%)
Calcium blockers (n)	21 (29%)
Statin (n)	43 (59%)
Biologic prostheses (n)	42 (58%)
Mechanic prostheses (n)	10 (14%)
TAVR (n)	20 (27%)
Conduit (n)	1 (1%)

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, AVAI: Aortic valve area index, LVPWD: left ventricular wall thickness end-diastole, TAVR: Transcatheter aortic valve replacement.

Outcome for pVO_2

Nine months after AVR, the mean absolute pVO_2 was 89.2% of the predicted value (95% CI: 84.5 to 93.9%) and 23 patients (31.5%) had a pVO_2 <83% of the predicted value, despite significant effort with average pHR 83±16% of the predicted value and R 1.08±0.10 and improvement in Sa (95% CI: 0.31 to 1.13cm/s) and E/e' (95% CI: -5.6 to -1.3).

Figure 7



Patient flow in Study III.

Among the 37 patients with a pre-AVR and a post-AVR CPX (Group B), a relative increase of 5% and 10% in the absolute pVO_2 compared to the pre-AVR value were observed in 43% and 24% of patients, respectively, and a relative decrease in pVO_2 >10% was observed in 30% (Figure 8).

Predictors of outcome in pVO_2 (Figures 9, 10 and 11)
A pVO_2 <83% post-AVR was independently predicted by preoperative mean gradient <40 mm Hg (OR 4.1, 95% CI: 1.3 to13.1) and preoperative atrial fibrillation (OR 5.5, 95% CI: 1.6 to19.3). A postoperative pacemaker was a predictor by univariate analysis (OR 4.8, 95% CI: 1.4 to 16.9), but not by multivariate analysis.

A decrease in pVO_2 >10% with AVR was independently predicted by preoperative mean gradient <40 mm Hg (OR 14.4; 95% CI: 2.2 to 93.2) and a postoperative pacemaker (OR 6.4, 95% CI: 1.2 to 34.6), the latter likely due to a decreased pHR (76.1% of the predicted). Atrial fibrillation was not a predictor.

An increase in pVO_2 >10% with AVR was independently predicted by preoperative AVAI <0.4 cm^2/m^2 (OR 14.1, 95% CI: 1.35 to 147.5) and pO_2pulse < the median in the study population, i.e., <98% of the predicted value (OR 7.5, 95% CI: 1.09 to 51.5).

Neither Sa, E/e', DM, hypertension, COPD, age, sex, or use of beta blockers (pre- or post-AVR) predicted favourable or unfavourable outcomes for pVO_2.

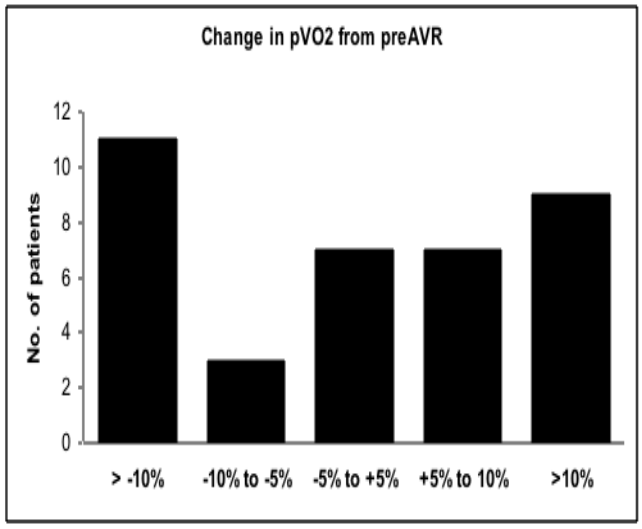
Discussion

Study I

Feasibility of CPX

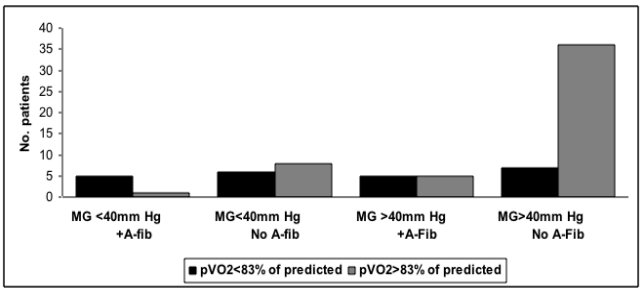
The feasibility of CPX was nearly 100% in this patient group with a mean age of 72.1 years. This observation should be seen in the context that patients who were judged beforehand, by referring cardiologists, as unable to perform the bicycle ergometer test were not referred and included in the study; however, patients with high frailty are seldom considered for AVR if they are only asymptomatic or equivocal symptomatic. This observed feasibility was much higher than that described for obtainment of gradients or pulmonary hypertension during exercise stress echocardiography among patients who are able to exercise, even in very experienced hands (15).

Figure 8



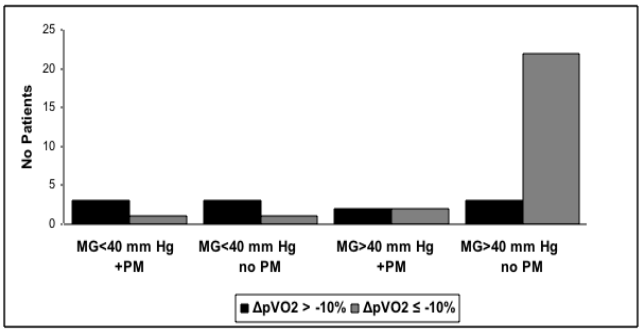
Distribution of percentage change in the patients' absolute pVO_2 from pre-AVR to 9 months post-AVR (Group B, n=37).

Figure 9



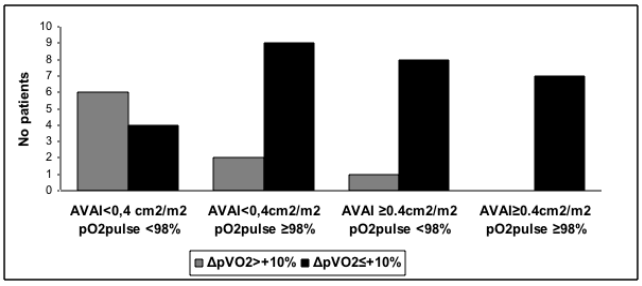
Impact of preoperative mean gradient (MG) <40 mm Hg and atrial fibrillation (A-fib) on risk of having a pVO_2 <83% of the predicted 9 months post-AVR (Groups A + B, n=73).

Figure 10



Impact of preoperative mean gradient (MG) <40 mm Hg and postoperative pacemaker on decline >10% in absolute pVO_2 from pre-AVR to 9 months post-AVR (Group B, n=37).

Figure 11



Impact of preoperative AVAI <0.4 cm^2/m^2 and preoperative pO_2pulse on improvement >10% in absolute pVO_2 from pre-AVR to 9 months post-AVR (Group B, n=37).
98% present the median value of pO_2pulse in the study population.

Reproducibility

The coefficient of variability for the pVO_2 by test-retest scores was similar or better than that found in healthy subjects and in patients with heart failure (26,27), and it was similarly low for other key parameters, such as the pO_2pulse and pHR. The data on the test-retest variability for exercise stress echocardiography in patients with aortic stenosis are sparse, but the variability must be at least equal to, and probably worse than, that for the echocardiographic parameters obtained at rest. Accordingly, the 4–6% coefficient of variability with CPX is clearly less than the coefficient of variability of 7–15% described for the peak and mean gradients and aortic valve area, obtained at rest and in experienced hands (16).

The fact that pVO_2 and pO_2pulse reflect cardiac output and stroke volume, respectively, suggests that, in an individual patient with stable hemoglobin and pulmonary function, changes in pVO_2 and pO_2pulse reflect changes in cardiac output and stroke volume at peak exercise, respectively. This, together with the high feasibility of CPX in patients that are not overtly frail and the good reproducibility, gives CPX a potential as a usable tool for serial testing.

Information from CPX on hemodynamics

It is taught that patients with asymptomatic aortic stenosis of no greater severity than in the present study, are not able to increase their stroke volume during exercise, but are limited to increasing cardiac output only by increases in heart rate (3,61); the findings in the present study contradict this dogma.

An increase in SVI by IGR and pO_2pulse in the normal range and a low frequency of abnormal trajectories was found for patients with Vmax >4 m/s, with Vmax >5 m/s, as well as in patients with Vmax <4 m/s and high valvuloarterial impedance. That asymptomatic or equivocal patients, even with severe aortic stenosis, do increase stroke volume with exercise was also observed in a more recent study of 37 patients (24).

Predictors of a decreased pVO_2. The pVO_2 is determined by the cardiac output (determined by stroke volume and heart rate) and the arteriovenous oxygen extraction. The arteriovenous oxygen extraction is primary determined by hemoglobin (by normal oxygen saturation) (30). In healthy athletes, where cardiac output reaches its maximal possible for the individual without limitations of cardiac conditions, optimal distribution to working muscles likely plays a role, whereas the importance of mitochondrial function is little and debated (30).

In our study, a pVO_2 <83% of the expected logically was independently predicted by decreased stroke volume at peak exercise (lower SVI by IGR or decreasing levels of pO_2pulse), decreased peak heart rate, decreased pulmonary function (decreased FEV1), and suboptimal ventilatory/ perfusion coupling (high VE/VCO_2). The latter may also be increased by inappropriate unphysiological hyperventilation during exercise, leading to breathlessness and decreased effort.

As shown for the patients with COPD, a decreased FEV1 was followed by lower breathing reserve and increased VE/VCO_2, giving dyspnoea at a lower level of exercise, at decreased peak heart rate, and decreased effort.

Resting echocardiographic parameters, such as Vmax, AVAI, Sa, and E/e', did not predict decreased pVO_2 in these patients without significant systolic dysfunction judged asymptomatic or equivocal symptomatic, suggesting that, in such patients, a more severe aortic stenosis does not necessarily imply significant hemodynamic compromise during exercise. That echocardiographic severity of aortic stenosis per se does not predict pVO_2 was also found by Dulgheru et al. (62) in a study of 62 patients.

Patients with Vmax <4 m/s but high valvuloarterial impedance. Patients with these characteristics have, in some observational studies, been shown to have a malignant prognosis on conservative treatment (42). We found that patients with these characteristics, with or without atrial fibrillation, were characterized more by decreased stroke volume at rest and therefore decreased stroke volume during exercise, rather than by lack of increase in stroke volume during exercise as a consequence of hemodynamic burden from the higher valvuloarterial impedance. This observation was done by two separate tests and by two separate methods, SVI from IGR and pO_2pulse from CPX. Our findings suggest that such patients would benefit from exercise training, which increases stroke volume, and medical treatment that decreases afterload and increases diastolic filling and thereby increases stroke volume; this notion requires further study.

Asymptomatic vs. equivocal symptomatic patients. The asymptomatic patients had higher SVI at rest and exercise. This explains the higher gradients, despite more similar AVAI, in asymptomatic vs. equivocal symptomatic patients, and also expresses why both gradients and AVAI should be used in the echocardiographic assessment of aortic stenosis, including in patients without significant left ventricular systolic dysfunction. The stroke volume is affected by the patient's general physical activity (30). The classification as equivocal symptomatic was accompanied, not only by lower stroke volume, which increased with exercise, but also by worse measures of ventilatory response to exercise, suggesting that unaccustomedness to exercise may also determine whether a patient feels dyspnoeic and restricted with exercise.

Symptoms, increase in systolic blood pressure <20 mm Hg, and ST-depression during the exercise test. These characteristics are often regarded as "abnormal exercise test" and an indication for AVR. However, during exercise testing, all persons will sooner or later develop dyspnoea and the experience of dyspnoea is individual, both by the patient and the exercise physician/technician (13). The positive predictive value of the symptom "more than usual dyspnoea" during exercise testing for progressing to "symptoms" in a patient group with similar age and echocardiographic severity of aortic stenosis like ours was 54% (5). Patients with aortic stenosis are often older, may be sedentary, have comorbidities like atrial fibrillation, hypertension, and COPD, and are undergoing medical treatment. Omitting such patients from studies is not helpful for the clinician. Symptoms and decreased functional capacity may not be due to hemodynamic compromise from the aortic stenosis. We observed a significantly decreased pVO_2 and increased VE/VCO_2 in patients with symptoms during the test. However, a decreased pVO_2 is not only an indicator of hemodynamic compromise; if the R is not >1, tissue acidosis is not likely the culprit of a decreased pVO_2, if the pO_2pulse is not decreased, a decreased stroke volume at peak exercise is unlikely, and an increased VE/VCO_2, which also predicts a decreased pVO_2, is also found in primary pulmonary diseases. Using this knowledge and algorithm, 14 of the 25 (of 130) patients, with AVAI 0.49±0.08 cm^2/m^2, who were judged as having more than usual symptoms during the test could safely be deferred initial AVR; this suggests that CPX may increase the specificity of symptoms during the exercise test. It is worth noting that, despite how 71% of the patients in our study were judged equivocal symptomatic, only 25 (19%) were judged as having more than usual symptoms during exercise. This is lower than that reported by Das et al. (5), who judged 37% as having symptoms during the exercise test. This indicates that, in the present study, those who were judged as having symptoms during the CPX had more than trivial symptoms.

The assessment of the CPX was done at a separate occasion than the CPX and without patient records and knowledge of echocardiographic findings, but the assessment of symptoms during the CPX was not. The group of 11 patients with symptoms who were referred for evaluation of AVR had AVAI 0.39±0.11 cm^2/m^2 and this may bias the interpretation of symptoms. However, R was >1, and only three patients had pVO_2 >84% and pO_2pulse of the predicted >95%, indicating that these patients generally had hemodynamic compromise.

We observed no differences in pVO_2, pO_2pulse, and frequency of abnormal trajectories between those with or without ST-depression or increases in systolic blood pressure <20 mm Hg. This observation is in line with the findings by Das et al. (5) and stresses that such observations are rather unspecific.

Study II

In this study population with a mean age of 72 years, judged equivocal symptomatic by a cardiologist, including patients with decreased exercise capacity (pVO_2 <83% of the predicted), COPD,

decreased blood pressure response or with symptoms during the test, high valvuloarterial impedance, or a NYHA classification ≥ II, we found that, based on CPX results, initial deferral of AVR could safely be done in 86% of study patients. Only one patient suffered cardiac death, and this patient had been recommended and had declined AVR much earlier, and the rate of hospitalization for heart failure was low. Of those with an initial conservative strategy on the basis of the CPX results, the primary endpoint progression to hemodynamic compromising aortic stenosis was reached in 25.7%, and those where CPX indicated a hemodynamic compromise from the aortic stenosis, the rate was 62.5%. The traditional endpoint of cardiac death, hospitalization with heart failure or AVR, was reached in 37.5%.

Safety and traditional endpoint

The reported rate of sudden death in patients considered asymptomatic ranges between 0 and 6%, higher with very severe aortic stenosis (3,14,21,23), and generally <1% per year is regarded as acceptable (1). Our rate of 0% during 2 years is statistically significant from a rate of >1.4% per year, an indication of the safety of relying on CPX results, and it should be noted that our study population was significantly older than that of previous studies (14,21).

The event rate of cardiac death or AVR in patients with comparable AVAI to that in the present study ranges from 30% with 12 months follow-up (5), 26% at 15 months follow-up (14), and 50% at 20 months follow-up (23). A meta-analysis on patients of mean age 62 years and mean AVAI 0.47 cm^2/m^2 gave an event rate of 42% at 14 months (41). If one only analyses patients with a Vmax >4 m/s, the event rate in our study of 48.5% was clearly lower than the 79% rate of cardiac death or AVR rate at 2 years found by Otto et al. (3).

Generally, our patients were older than in other studies and with a high proportion of equivocal symptomatic patients, which should increase the event rate. The AVAI was similar to that in other studies but the gradients tended to be lower in those judged equivocal symptomatic (Table 3); however, the lower gradient could be explained by lower stroke volume, suggesting that the use of AVAI for assessment of echocardiographic severity is more appropriate in these patients. Obviously, direct comparisons between different studies are difficult. The comparable AVAI and the higher age and proportion of equivocal symptomatic patients do not suggest that our study patients are at less risk. The lower event rate in our study (37.5% at mean follow-up of 2 years) compared to the above-mentioned studies (3,5,14,23,41) suggests that CPX is a useful tool, compared to standard evaluations, to point those out where AVR can safely be, or should be, deferred with a low and acceptable event rate over the next years.

We did not perform a direct comparison between conventional exercise testing and CPX; however, conventional exercise testing is of limited value in those aged >70 years and in functional class II (5), and other studies included few such patients, a group that constituted more than half of our population. The present study indicates that CPX is also useful in such patients to point those out where AVR can safely be deferred with a low and acceptable event rate over the next years.

Primary endpoint

Because of the limited sample size and low cardiac death rate in studies on asymptomatic equivocal symptomatic patients with aortic stenosis, studies have used composite endpoints (3,5,14-17,20-23,41). Most endpoints are driven by development of symptoms or AVR. Both are subject to knowledge of the severity of the aortic stenosis or knowledge of test results, and this may lead to a biased interpretation of minor symptoms and inflate the predictive value of test results, as pointed out by Das (5) and Bonow (13), who also pointed out the difficulty in determining whether symptoms and decreased exercise capacity are due to cardiac or non-cardiac causes, including age and sedentary lifestyle. In ischemic heart disease, it is now well-recognized that "symptoms" and an anatomic substrate, such as a coronary artery stenosis, do not equal ischemia and that revascularization without physiological demonstration of flow limitation consistent with ischemia is considered inappropriate (32), and that progression to a revascularization without objective ischemia/flow limitation is an inappropriate endpoint (63,64), different from 20 years ago.

The endpoint progression to AVR, as an indicator of progression to hemodynamic important compromise from the aortic stenosis, may be appropriate in many patients, but unlikely in all, according to the discussion above. By using the criteria of AVR with improvement in either an increased pVO_2 or Physical component score of the SF-36 health-related quality of life questionnaire, we aimed at counting only an AVR where a reproducible objective or well-evaluated measure showed that the patient had benefitted from the AVR. If the patient improves after AVR, it is an indication that the patient had hemodynamic compromise from the aortic stenosis. If a patient with aortic stenosis suffers cardiac death (including sudden death) or is hospitalized with heart failure, an aortic stenosis with hemodynamic compromise is likewise likely present and the culprit. Therefore, the endpoint cardiac death, hospitalization with heart failure, or AVR with improvement was chosen as an endpoint as an expression of aortic stenosis with hemodynamic compromise.

A patient with important hemodynamic compromise from aortic stenosis may not improve if the patient has irreversible significant left ventricular dysfunction on a declining slope, which is not likely to be an important issue in this study, or if the patient suffers an important complication secondary to the AVR that impacts the patient 9 months after. In this case, the appropriateness of AVR for that particular patient is ambiguous.

The beneficial effect of AVR is often assessed by improvement in the NYHA class or symptoms. These assessments are prone to severe bias from double unblinded assessment; it is well known that sham operations may improve symptoms (33,34). NYHA classification is considered inadequate to determine a patient's response to therapy and to compare one patient with another and is influenced by patients' perception of their symptoms and physician bias (65); assessment of NYHA post-AVR often leads to gross overestimation of functional capacity. Patients classified NYHA I post-AVR have shown 6 min walking distances of <100 to 260m (66,67), which is much shorter than the expected normal for that age and that of patients with systolic heart failure with a NYHA III/IV classification (68). The use of the PCS, which has been extensively evaluated and accepted for cross-sectional and serial studies (38,55,56), was done single unblinded in the present study but it is difficult for the patient to figure the score out beforehand and to remember the answers a year ago with an AVR between the two time points. The cut-off for improvement in PCS was based on what improvement is judged clinically relevant (38-40).

The cut-off for improvement in pVO_2 was determined by the coefficient of variability by test-retest.

The optimal cut–offs, of course, are unknown. Still, the endpoint an AVR with improvement, either in an adequate objective

measure or in the patient's experience, assessed by a comprehensive and well-evaluated questionnaire seems more adequate than simply AVR done.

By using this criteria of hemodynamic compromise cardiac death, hospitalization with heart failure, or AVR with improvement in either pVO_2 or PCS, we found that when the CPX did not indicate hemodynamic compromise, the endpoint was reached in 25.7%, whereas when CPX indicated hemodynamic compromise, or severely limited symptoms without other explanation in a few patients, the endpoint was reached in 62.5% of patients. The severity of the aortic stenosis did not predict this endpoint, which shows that knowledge of severity of the aortic stenosis did not bias that endpoint. A decreased pO_2pulse <100% of the expected, reflecting decreased stroke volume at peak exercise, predicted the primary endpoint. It may be argued that patients were selected for AVR based on the pO_2pulse, however: first, this may account for a maximum of 9 out of 38 primary endpoints; second, the trend was clear when only patients who were initially treated conservatively were analysed; third, to qualify for the primary endpoint, patients should improve following AVR, which is unlikely if the patient had no hemodynamic compromise; and fourth, the pO_2pulse is just an indicator of stroke volume at peak exercise and therefore a sound predictor from a pathophysiological view.

Why defer AVR?

Although the death rate is low during the 12 months after AVR (~1%) in low-risk patients, the complications and convalescence is substantial (6-9). There is a difference between the 60-year-old with a "very severe" stenosis and the 70-year-old with comorbidities and a "severe" stenosis. Some older patients will eventually die of other causes. Anxiety, caring for spouses, upcoming travels or family occasions often lead to reluctance toward major interventions. AVR is a major intervention and should theoretically only be recommended by the physician to patients with prognostic and/or symptomatic benefit of the intervention. CPX seems useful to safely defer initial AVR in the older population, in equivocal symptomatic patients, and in those in functional class II, where conventional exercise testing seems less useful (5).

Study III

Despite no significant left ventricular dysfunction and how, in this study, the resting systolic and diastolic function improved after single AVR, the mean pVO_2 was less than the predicted and a significant proportion had pVO_2 < the lower 95% CI in the sedentary healthy population (pVO_2 <83% of the predicted). This less optimal outcome was largely driven by patients with atrial fibrillation or with a preoperative mean gradient <40 mm Hg. Surely, a postoperative pVO_2 <83% may present an improvement in a patient; nevertheless, the patient is still significantly limited post-AVR. A significant proportion experienced a decrease in pVO_2 >10%, largely driven by patients with a preoperative mean gradient <40 mm Hg, supporting the negative impact of this parameter, and also by postoperative pacemaker. These findings imply that in patients with a preoperative mean gradient <40 mm Hg or with atrial fibrillation, physicians should not expect or promise the patient normalisation of functional capacity with an AVR, and in such patients, conditions other than the aortic stenosis are often significant culprits of the patient's symptomatic status leading to AVR. Finally, health care personnel and patients should be aware of the risk and negative impact of a pacemaker implant with AVR.

A significant proportion of the patients had an increase in pVO_2 with AVR, driven by patients with severe aortic stenosis (AVAI <0.4 cm^2/m^2) and/or decreased pO_2pulse (< the median in the study population, i.e., <98% of the predicted pO_2pulse). From a pathophysiological view, this finding is sound. Patients with severe aortic stenosis with a decreased stroke volume at peak exercise who have significant hemodynamic compromise and are likely to improve with AVR.

The use of change in pVO_2 to assess change in hemodynamics with AVR is supported by the following: pVO_2 = cardiac output x arteriovenous oxygen extraction. Assuming stable hemoglobin and the patient has not transformed into an endurance athlete, the patients serves as his own control. A change in pVO_2 reflects a change in cardiac output at peak exercise, assuming stable haemoglobin and similar effort. In the present study, pHR and R did not change from pre- to post-AVR, but a slight decrease in Hb was noted. The unchanged anaerobic threshold points out that the impact of the decrease in Hb was negligible and also that possible detraining during convalescence, with a decrease in stroke volume, was not an important issue.

What improvement should be expected with AVR? If the aortic stenosis is hemodynamic important leading to decreased functional capacity and symptoms, improvement should be expected after AVR, unless the left ventricular function is on a declining slope. Complications after AVR and pacemaker implantation will often counteracter improvement, but obviously such conditions are part of the post-AVR setting. There are few studies assessing objective improvement with AVR. Rimington et al. (69) found that 80% of patients showed an increased 6 min walking distance after valve operation ±CABG (48%, n ≈100 with single AVR). These patients, with a mean age of 67 years, were very limited, with a mean 6 min walking distance of 294 m, which corresponds with heart failure patients judged NYHA III (68). In 11 severely symptomatic younger patients, Lee et al. found a mean 12% increase in pVO_2 with AVR (45). Currently, AVR is recommended at the incipience of symptoms. In such patients, Munt et al. (70) found no improvement in exercise capacity from pre- to post-AVR. This may indicate that the conventional exercise test is not sensitive enough, or that the improvement in some were offset by deterioration in others, as was also observed in the present study, either because of complications or that some patients did not have important limitations from hemodynamic compromise from the aortic stenosis.

Representativeness of the study populations

Study I/II. The study results do not apply to all patients with aortic stenosis. An important fraction of patients in the present study had Vmax <4 m/s (58%) but 90% had AVAI < 0.6 cm^2/m^2. Few (9%) had a Vmax >5 m/s. The finding that equivocal symptomatic patients had lower Vmax than and similar AVAI to the asymptomatic patients but lower stroke volumes suggests that the aortic stenosis in patients with lower Vmax was not trivial and could be regarded as severe. It is not difficult to appreciate a tendency to refer asymptomatic patients with higher Vmax and equivocal symptomatic patients with lower Vmax but low AVAI, and patients with comorbidities, for further evaluation. It is exactly in such patients where the cardiologist may be in doubt as to whether the patient is truly asymptomatic or symptomatic from the aortic stenosis or from other causes. The present study included just such patients.

A total of 131 patients were prospectively recruited during 19 months at one institution. For comparisons, the studies that form the basis for guideline recommendations have recruited similar sample sizes: during 5 years (3,5,21), retrospectively (20,22), from

4 different centres (23), or just 69 patients without giving details of the recruiting interval (14). Furthermore, in these studies, the mean age was, on average, 60 years (range of mean age: 49 to 66 years), compared to 72 years in ours.

The event rate for the traditional endpoint in those with a conservative strategy, according to CPX results, was lower than in other studies with similar degrees of aortic stenosis (3,5,14,23), despite the higher age and additional equivocal symptomatic patients in the present study. This indicates either that CPX may be more optimal to exclude or to point out significant hemodynamic compromise than the standard methods used in other studies, or that the threshold for AVR in other studies was low. It would have been interesting to know how many patients improved with AVR in those studies.

Study III. The number of single AVR per year during the study period in our country can be calculated to 110 per 800,000 (the number of inhabitants in our region). For inclusion during 24 months into Group A, 79 patients were screened and found eligible. By the assumptions that: 1) some patients have left ventricular dysfunction, a more acute course, endocarditis, or primary aortic regurgitation, and some patients were not evaluated at our institution (total estimated 30%?); 2) in that period, 37 patients had single AVR in Group B: 106/(0.7 x 110 x 2) ≈69% of eligible patients having AVR could be accounted for. Not all eligible patients in group A gave consent or completed follow-up. There were no differences in baseline characteristics between those who gave consent and completed follow-up versus those who did not. Accordingly, it is reasonable to assume that the included patients are representative for patients undergoing single AVR in the period. The patients, who completed the follow-up, represent ≈47% of all eligible patients.

Is pVO_2 a valid indicator of hemodynamics?

pVO_2 reflects cardiac output at peak exercise (30). pVO_2 = Stroke volume x heart rate x arteriovenous oxygen extraction. The most important cause for the difference in pVO_2 in athletes and sedentary persons is the difference in cardiac output/stroke volume and hemoglobin (30). Deconditioning by, e.g., bed rest, causes decreased stroke volume (30). Improved blood distribution to exercising muscles plays a minor role, and the importance of improved mitochondrial function is little and debated (30). Therefore, it is not surprising that pVO_2 is a predictor of prognosis in most cardiac diseases (27-29,71), including aortic stenosis (71). It was recently shown that pVO_2 and O_2pulse predicted survival with aortic stenosis, in patients who had AVR and also in patients who had no AVR (72). This retrospective study included 155 patients through 15 years, 90% of which were male, overweight with a mean BMI of 29, and the predicted pVO_2 only included age and sex and weight, not as now recommended (35) and used in the present study, which is ideal weight with a small compensation for over- and underweight. Since it is working muscles and not the adipose tissue, that have significantly increased perfusion and oxygen extraction during exercise. This is also a limitation of conventional exercise testing using METS calculated from work rate and weight.

Therefore, a limitation in pVO_2 equals a limitation of cardiac output. Cardiac output may not only be limited by decreased stroke volume from cardiac disease but also by decreased stroke volume secondary to a sedentary lifestyle, lack of increase in heart rate because of lack of effort, and lack of effort secondary to increased dyspnoea with high VE/VCO_2 and low BR as characteristic in patients with pulmonary disease with decreased FEV1, and ventilatory perfusion coupling (31), which is also found in this study in patients with COPD and for the predictors of decreased pVO_2. It appears that, at similar Hb, a change in pVO_2 in an individual will reflect a change in cardiac output. Therefore, pVO_2 is useful to reflect the patient's cardiac output at peak exercise and the serial changes in cardiac output. Because effort and heart rate are of importance for the cardiac output at peak exercise, pHR and R should also be measured.

Study limitations

Representativeness of the study population and the use of an alternative study endpoint were discussed in detail above. Because of the size of the study, that it is the first in its field and therefore the cut-offs for CPX measures were not clearly established earlier, and that some of the predictors were defined post-hoc, the present study may be seen as a pilot study. In this regard it is worth noting that the field of study of asymptomatic or equivocal symptomatic aortic stenosis is constituted of pilot studies without larger follow-up studies (3,5,14,15,20-24).

The CPX was performed during usual medical treatment. Beta blockers were the most common drug prescribed that could have influenced the CPX results; in healthy individuals, beta blockers tend to reduce the pVO_2 and increase the pO_2pulse due to a reduced pHR. In patients with heart disease, the improved diastolic filling and reduced afterload may actually improve the pVO_2. It is therefore important to also assess the pHR, O_2pulse, and the trajectories, as was done in this study. In the present study, we did not find that beta blocker treatment predicted a lower pVO_2, the change in pVO_2 with AVR, or any of the other endpoints. Finally, beta blocker treatment is a part of life in patients with aortic stenosis, both pre- and post-AVR.

A direct, blinded comparison of the performance of CPX versus conventional exercise testing for predicting the endpoints was not undertaken; however, the lack of predictive value per se of the blood pressure response, symptoms, and a subnormal pVO_2 in this study, and the previously reported lack of predictive value of conventional exercise testing in those aged >70 years or in functional class II (5), which represented more than half the study population in the present study, suggests an advantage for CPX. Patients who are severely limited from musculoskeletal or neurological conditions, or with extreme unfamiliarity with even small exercise burdens, may not reveal signs of hemodynamic compromise during the CPX, despite true hemodynamic compromise. In the present study, an R <1 was not associated with a worse outcome, and patients who were judged unable to perform the bicycle ergometer test were not included in the study. However, such frail patients are seldom considered for AVR in the asymptomatic state.

To our knowledge, this is the first study on outcomes based on treatment according to CPX. Therefore, the cut-off values for the pVO_2 and pO_2pulse were selected based on data from healthy sedentary populations and our expectations of what would be subnormal values. Furthermore, a calculated predicted value may not be the absolutely correct for an individual but is regarded as optimal and generally recommended (35). A pVO_2 >83% may be found despite hemodynamic compromise from aortic stenosis, but will then likely be followed by an abnormal pO_2pulse and/or VO_2 trajectory, or a decline during serial testing. The low event rate in Group 1 and the high rate of improvement following an AVR in Group 3, in which only 3 patients had a pVO_2 >83% and pO_2pulse >95% of that predicted, suggest that the cut-off of approximately 83% is adequate. The Mayo group found a level of 80% of the predicted pVO_2 to separate those with a good or adverse prognosis in both operated and non-operated patients (72).

The lack of correction for general overweight in that study population suggests that a higher cut-off is more adequate. The post-hoc finding of a predictive value for a pO_2pulse <100% of that expected implies that this cut-off might be more appropriate than our beforehand selected criteria of <95%, although a type II error may influence the rejection of the 95% cut-off. The optimal cut-off for oxygen pulse is currently unknown, though the present studies point out that a cut-off in the range of 95 to 100% of the predicted for the prediction of which patients will improve with AVR and which may safely defer AVR seems reasonable. In the daily clinic, hard cut-offs are meaningless; the coefficient of variability of most tests restricts that. This counts for pVO_2 and pO_2pulse, as for echocardiographic measures (16) and fractional flow reserve (73).

The cause of death and endpoints was not evaluated by an independent committee; however, all deaths were in-hospital at institutions other than ours, and the cause of death was taken from the diagnosis and discharge summary determined by the doctors at those other institutions. Non-cardiac deaths were also more common than cardiac deaths, both for the operated and non-operated, in a study of 622 patients (mean age: 72 years) with aortic stenosis (74). All AVRs were decided by an independent Heart Team and only one case of hospitalization with heart failure did not lead to AVR, because the patient declined.

Conclusions

In patients who are judged asymptomatic or equivocal symptomatic from at least moderate aortic stenosis and not judged too frail for exercise testing beforehand, CPX is highly feasible and the key measures as pVO_2 and pO_2pulse have good reproducibility.

The majority of patients had pVO_2 and pO_2pulse in the normal range of the predicted value and the stroke volume increased with exercise.

A decreased pVO_2 is logically predicted by lower stroke volume, peak heart rate, and pulmonary function (FEV1), and worse ventilation perfusion coupling (VE/VCO_2), but not by echocardiographic severity of the aortic stenosis.

Equivocal symptomatic patients are characterized by lower pVO_2 and a low AVAI but with lower gradients. Both CPX and inert gas rebreathing confirmed that this was due to a lower stroke volume.

The stroke volume generally increases with exercise also in those with a low resting stroke volume or severe aortic stenosis.

If CPX is judged as pointing against significant hemodynamic compromise, AVR may safely be deferred with a low event rate. The event rate seems lower than that reported by standard assessment. These observations included patients >70 years, in functional class II, with symptoms, ST depression, or blood pressure increase <20 mm Hg during the exercise test, with COPD, or with a decreased pVO_2.

In patients where CPX was judged as pointing to hemodynamic compromise, the rate of AVR with improvement in pVO_2 or Physical Component Score of the SF-36 was high.

A decreased pO_2pulse (<98 to 100% of the expected) may be an important predictor of hemodynamic compromise or progression to hemodynamic compromise.

In patients without significant left ventricular dysfunction, the change in pVO_2 with AVR is heterogeneous and the absolute value often still subnormal. More severe aortic stenosis and decreased pO_2pulse predicted improvement in pVO_2, whereas less severe stenosis, atrial fibrillation, and post-AVR pacemaker predicted decline. These findings may be important for information to patients before AVR and for decision making.

Perspectives

In the present study, the follow-up was only from 1 to 3 years. To assess the prognostic value of CPX, a longer follow-up may be optimal. Unfortunately, it will not be possible to do an optimal study with a longer follow-up of the study patients, because as shown in the present study, AVR does not equal improvement and by now a pre-AVR CPX will be lacking and the primary endpoint thus inaccessible. However, information on deaths, cardiac deaths, and hospitalizations may be obtained and meaningful. A validation study on the predictive importance of a pO_2pulse <100% of the expected would also be beneficial.

The high feasibility and good reproducibility, and because the patient serves as his own control due to serial testing, gives CPX potential as a usable tool for serial assessments in such patients. This should be studied further.

A CPX was performed at the referral for AVR. A study of which CPX parameters and changes in parameters that predicts an improvement post-AVR would be interesting. The importance of changes in the VO_2 and O_2pulse trajectories during the serial testing could be studied.

The IGR is also an interesting method, but the feasibility and reproducibility are somewhat less than those for CPX. To study this method, one has to focus on the cooperative patients and on an IGR and exercise protocol where the maximal tolerable exercise at which an IGR may be performed is used and then do serial IGRs. Such a study in a few selected patients is more basic science.

A randomized study of CPX-driven versus conventional handling, where the endpoint of AVR requires improvement in an objective measure, such as the pVO_2, would be valuable. This would require CPX in all patients and strict blinding methods. There are no randomized and blinded studies on asymptomatic or equivocal symptomatic aortic stenosis.

List of abbreviations

AS = Aortic stenosis	MET = Metabolic equivalent oxygen uptake 3.5 mL/kg·min
AT = VO2 at anaerobic threshold	PCS = Physical Component Summary from the SF-36
AVAI = Aortic valve area index	pHR = Peak heart rate
AVR = Aortic valve implantation (surgical or transcatheter)	pO2pulse = peak oxygen uptake per heart beat
BNP = Brain natriuretic peptide	pVO2 = peak oxygen uptake
BR = Breathing reserve	QOL = Quality of life
$C_{(a-v)}O2$ = Arteriovenous oxygen difference	R = Respiratory coefficient
CI = Confidence interval	Sa = Peak systolic tissue velocity (obtained by colour tissue Doppler echocardiography)
CO = Cardiac output	SBP = Systolic blood pressure
CPX = Cardiopulmonary exercise testing	SD = Standard deviation
E = Early diastolic inflow velocity	SF-36 = Short-form health survey questionnaire
e' = Early lateral mitral annulus velocity	SV(I) = Stroke volume (index)
FEV1 = Forced expiratory volume in 1 second	ULN = Upper level of the normal
FVC = Forced vital capacity	VE/VCO2 = Ventilation/exhausted carbon dioxide ratio
Hb = Hemoglobin	Vmax = Peak flow velocity across the aortic valve
IGR = Inert gas rebreathing	Zva = Valvuloarterial impedance (expression of the global afterload)
MCS = Mental Component Summary from the SF-36	

Summary

Patients with moderate to severe aortic stenosis (AVA <1.3 cm^2) who were judged, by a referring cardiologist, as asymptomatic or equivocal symptomatic from the aortic stenosis were included in the study. Patients with left ventricular ejection fraction <50% were not included. Twenty-nine percent of the referred patients were judged asymptomatic and 71% equivocal symptomatic from their valve disease. The mean age was 72 years and 90% of the patients had an AVA-index <0.6 cm^2/m^2. By clinical evaluation in the outpatient clinic, 48% were judged as having functional limitation corresponding to NYHA≥II. The study participants had cardiopulmonary exercise testing (CPX) at inclusion, and, if relevant, pre- and nine months post-aortic valve replacement (AVR).

CPX was feasible in 130 of 131 study participants recruited across 19 months. The coefficient of variability by test-retest was 5.4% and 4.6% for peak oxygen consumption (pVO_2) and peak oxygen pulse (pO_2pulse= pVO_2/peak heart rate), respectively. The stroke volume generally increased with exercise, also in those with peak flow velocity across the aortic valve (Vmax) >5 m/s, >4 m/s, and <4 m/s but with high valvuloarterial impedance (Zva >5.5 mm Hg/(mL·m^2)). This was found both when assessed by inert gas rebreathing and by the pO_2pulse/hemoglobin index. Both resting and exercise stroke volume were lower for the latter group, with Vmax <4 m/s but high valvuloarterial impedance. A pVO_2 <83% of the predicted, which corresponds to the lower 95% percentile found in the healthy sedentary population, was predicted independently by lower stroke volume during exercise, lower heart rate during exercise, lower FEV1, and by higher ventilation/carbon dioxide exhaustion rate (VE/VCO_2), but not by the severity of the aortic stenosis as determined by echocardiography.

According to the CPX results, the patients were prospectively grouped into 3 groups, as follows: 1) normal pVO_2 (>83% of predicted) and pO_2pulse (>95% of predicted); 2) subnormal pVO_2 or pO_2pulse that according to CPX could be explained by causes other than hemodynamic compromise; 3) subnormal pVO_2 and pO_2pulse. Groups 1 and 2 followed an initial conservative strategy, whereas Group 3 was referred for angiogram and Heart Team evaluation for AVR.

The patients were followed for an average of 24 months and, in Groups 1 and 2, one patient (0.9%) suffered cardiac death and seven were hospitalized with heart failure (6.7%). The patient who died and another patient with heart failure had both previously, during the study, declined AVR. For Groups 1 and 2, the rate of the combined endpoint progression to cardiac death, hospitalization with heart failure, or AVR was 37.5%, which seems lower than what was reported in the literature by conventional assessment and strategy for younger asymptomatic patients with comparable echocardiographic severity of aortic stenosis. The endpoint progression to cardiac death, hospitalization with heart failure, or AVR with improvement in pVO_2 or in the Physical Component Score of the SF-36 health-related quality of life score was reached in 25.6% in Groups 1+2 and in 62.5% in Group 3 (p=0.003). A decreased pO_2pulse, which expresses stroke volume at peak exercise, predicted this endpoint.

In 73 operated patients without left ventricular dysfunction and no coronary stenosis, including 37 patients from the above-mentioned study, a CPX 9 months post-AVR showed that the pVO_2, on average, was less than that predicted (mean 89% of the predicted) and 35% of the patients had a subnormal pVO_2 (<83% of that predicted). A preoperative mean gradient <40 mm Hg across the aortic valve, the presence of atrial fibrillation, and a permanent pacemaker post-AVR all predicted a post-AVR pVO_2 <83% of that predicted. For the 37 patients with a pre-AVR CPX, a postoperative decrease >10% in the absolute pVO_2 was noted in 30% and an increase >10% in 24% of patients. A decrease >10% in pVO_2 was predicted by preoperative mean gradient <40 mm Hg and an increase in pVO_2 was predicted by preoperative AVAI <0.4 cm^2/m^2 and preoperative pO_2pulse <the median in the study population (<98% of that predicted).

Conclusions. In this group of patients, where clinical assessment is difficult and conventional exercise testing is regarded as less useful, CPX showed high feasibility and reproducibility. CPX therefore has potential as a useful tool for serial monitoring. In general, the stroke volume increased during exercise, including in patients with severe aortic stenosis or decreased resting stroke volume. CPX gives information on hemodynamics and the physiologic components that determine decreased pVO_2. CPX seems useful to identify 1) patients with a low risk of cardiac death and low risk of progression to symptoms from the aortic stenosis, and 2) patients with hemodynamic compromise who improve in functional capacity after AVR.

Patients with a preoperative mean gradient <40 mm Hg across the aortic valve, with the presence of atrial fibrillation or who have a permanent pacemaker, postoperatively seem to benefit less from AVR, whereas the benefit seems larger in those with more severe aortic stenosis and a decreased pO_2pulse. These findings may be of importance for decisions and information of patients before AVR.

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