

RESEARCH

The importance of contractile reserve in predicting exercise tolerance in asymptomatic patients with severe aortic stenosis

Jet van Zalen PhD^{1,2,3}, Sveeta Badiani MRCP³, Lesley M Hart HTEC BSE¹, Andrew J Marshall MD MRCP¹, Louisa Beale PhD², Gary Brickley PhD², Sanjeev Bhattacharyya MD MRCP FESC³, Nikhil R Patel MBBS FRCP¹ and Guy W Lloyd FBSE MD FRCP³

¹Department of Cardiology, Eastbourne District General Hospital, Eastbourne, UK

²University of Brighton, Centre for Sport and Exercise Science and Medicine (SESAME), Eastbourne, UK

³St. Bartholomew's Hospital, Barts Heart Centre, London, UK

Correspondence should be addressed to J van Zalen: jet.vanzalen@nhs.net

Abstract

Background: Mortality dramatically rises with the onset of symptoms in patients with severe aortic stenosis (AS). Surgery is indicated when symptoms become apparent or when there is ventricular decompensation. Cardiopulmonary exercise testing (CPET) in combination with exercise echocardiography can unmask symptoms and provides valuable information regarding contractile reserve. The aim of the present study was to determine the prevalence of reduced exercise tolerance and the parameters predicting adverse cardiovascular events.

Methods: Thirty-two patients with asymptomatic severe AS were included in this study. Patients were followed up as part of an enhanced surveillance clinic.

Results: Age was 69 ± 15.7 years, 75% of patients were male. Patients had a raised NT-ProBNP of 301 pg/mL. VO_2 peak was 19.5 ± 6.2 mL/kg/min. Forty-one percent of patients had a reduced % VO_2 peak and this predicted unplanned cardiac hospitalisation ($P = 0.005$). Exercise systolic longitudinal velocity (S') and age were the strongest independent predictors for VO_2 peak ($R^2 = 0.76$; $P < 0.0001$). Exercise S' was the strongest independent predictor for NT-ProBNP ($R^2 = 0.48$; $P = 0.001$).

Conclusion: A large proportion of patients had a lower than predicted VO_2 peak. The major determinant of exercise and NT-ProBNP is the ability of the left ventricle (LV) to augment S' on exercise rather than the severity of aortic valve obstruction or resting structural remodelling of the LV. Reduced exercise tolerance and more adverse remodelling, rather than valve obstruction predicted unplanned hospitalisation. This study demonstrates that for those patients, in whom a watchful waiting is an agreed strategy, a detailed assessment should be undertaken including CPET, exercise echocardiography and biomarkers to ensure those with exercise limitation and risk of decompensation are detected early and treated appropriately.

Key Words

- ▶ cardiopulmonary exercise testing
- ▶ aortic stenosis
- ▶ stress echocardiography
- ▶ exercise

Introduction

Aortic stenosis (AS) results in obstruction of blood flow through the aortic valve. The ventricular response to chronic pressure overload and other consequences of AS such as subtle myocardial ischaemia (1) are also important to understand. The natural history of AS is characterised by an extended latent period which can last between 10 and 20 years. While patients are asymptomatic during this period, it is accepted that prognosis is excellent; however, mortality rises dramatically from the onset of cardiac symptoms (breathlessness, syncope, angina), approximately 25% at 1 year and 50% at 2 years (2, 3). Consequently current guidelines suggest that aortic valve intervention is indicated when patients become symptomatic or if there is echocardiographic evidence of imminent ventricular decompensation (4). A delay to surgery may result in a decrease in myocardial performance, increasing myocardial fibrosis and remodelling which does not fully recover following surgery, and this is associated with a significant increase in late morbidity and mortality (5, 6). Determining why and when patients develop symptoms is not always straightforward especially in an elderly population. Around one-third of 'asymptomatic patients' actually develop cardiac symptoms on exertion (7). Cardiopulmonary exercise testing (CPET) is an objective assessment of patients' exercise tolerance and therefore can assist in unmasking any symptoms (8, 9). Studies have previously reported that over half of the included patients with 'asymptomatic' severe AS have a reduced VO_2 peak implying that a large proportion of self-reported asymptomatic patients are actually limited by symptoms (10, 11). The aims of the study were firstly to determine the level of reduced exercise tolerance in a cohort of patients with severe 'asymptomatic' AS and secondly to determine if exercise tolerance in these symptom-free patients was defined by obstruction to the aortic valve, ventricular remodelling or left ventricular contractile reserve. Thirdly the study aimed to determine which aforementioned parameter best predicted future events during clinical follow-up.

Methods

This was a retrospective longitudinal study of 32 patients with severe AS. Patients were followed up as part of an enhanced surveillance clinic which includes CPET combined with exercise echocardiography and N-terminal pro-type natriuretic peptide (NT-ProBNP) measurements.

Patients who subjectively reported to be asymptomatic were referred into the clinic. All patients had a calculated aortic valve area (AVA) of less than 1.0cm^2 , a peak aortic velocity (V_{max}) of more than 4.0m/sec or a mean aortic pressure gradient (mean PG) greater than 40mmHg . Patients had a left ventricular ejection fraction (LVEF) above 55% and were able to perform CPET testing. Exclusion criteria included self-reported symptoms associated AS, co-morbidities affecting symptoms, a positive test for reversible ischaemia, unable to exercise or poor echocardiographic windows. Excluded patients who were unable to perform exercise were followed up with regular resting transthoracic echocardiograms and symptom assessment.

Echocardiography

Echocardiography was performed using a GE Vivid 9 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. All measurements were made according to the guidelines set by the British Society of Echocardiography (12). At rest, the left ventricular outflow tract (LVOT) diameter and ventricular internal dimensions were measured in zoom mode from the parasternal long axis view, measurements were taken at the level of the mitral valve tips. A protocol was created and the following views were obtained both at rest and at peak exercise. The 2D apical views (4-chamber, 2-chamber, and apical long axis view), a 4-chamber view with tissue velocity imaging (TVI) turned on in the background. Continuous wave and pulse wave Doppler through the aortic valve. The mean PG was measured using the modified Bernoulli equation. AVA was calculated using the continuity equation. LV volumes and LVEF were calculated using Simpson's biplane method in the apical four-chamber and two-chamber views. Q-analysis was used retrospectively to determine the longitudinal systolic velocity (S') where the sample volume was placed at the septal and lateral part of the mitral annulus. Rest and exercise S' (defined as the highest velocity during systole after the end of isovolumetric contraction) was obtained from the lateral and septal annulus and averaged at rest and exercise. The relative wall thickness (RWT) was calculated by multiplying the posterior wall thickness by two and dividing this by the LV end diastolic diameter. A value greater than 0.42 is suggestive of concentric hypertrophy and a value below 0.42 of eccentric hypertrophy (13). Images were obtained in real time and analysed after each study. Images were stored offline.

Cardiopulmonary exercise test

A semi-recumbent tilting cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. At the start of the test a 1-min rest period was included followed by a 3-min unloaded warm up period. Exercise protocols were individually determined based on the patient functional status. Work rate (5, 10, 15 or 20 Watt) increased every minute until voluntary exhaustion aiming for 8–10 min of exercise. Patients were asked to continue their medication as usual. Heart rate (HR), blood pressure and oxygen saturation were monitored throughout. Oxygen uptake (VO_2), carbon dioxide production (VCO_2) and ventilation (V_E) were continuously measured and derived using a calibrated breath-by-breath analyser (Quark, Cosmed, Italy). A respiratory exchange ratio (RER) >1 was used to indicate a good effort. Echocardiography measurements commenced when patients were close to finishing the test when the RER was exceeding 0.95 and if patients were not taking beta blockers in combination with a peak predicted HR greater than 85% of age predicted maximum. Echocardiographic measurements were taken within 90s of finishing exercise. Patients were verbally encouraged to exercise until maximal exertion. All tests were performed according to the exercise testing guidelines (14). $\text{VO}_{2\text{peak}}$ was expressed as the highest value from an average of 30s during the final stage of the exercise test. A predicted VO_2 of less than 84% was considered to be reduced. The oxygen uptake efficiency slope (OUES) is the slope of VO_2 against the logarithm of V_E ($\log\text{V}_E$) (15). The V_E/VCO_2 slope was measured using the whole slope as a marker of the effectiveness of ventilation/perfusion matching.

NT-ProBNP

Blood analysis was performed at rest prior to the appointment. The Roche Elecsys NT-ProBNP assay was used on a Roche Modular E170 immunoassay platform. Serum was collected using standard sampling tubes containing separating gel. Samples were centrifuged. NT-proBNP measurements were carried out using an ELISA technique using two monoclonal antibodies in a sandwich technique and streptavidin-coated microparticles.

Follow-up

CPET combined with exercise echocardiography and the NT-ProBNP measurements were performed during all visits. A consultant cardiologist specialist in cardiac imaging and valve disease determined patients' follow-up.

Data used for the exercise predictive model was the last visit prior aortic valve intervention or the last available follow-up appointment. Data used for cardiac events model were taken from the first test after referral to the clinic. Cardiac admissions (unplanned cardiac admission lasting more than 24h) and aortic valve replacement were based on detailed analysis of hospital case notes and electronic records.

Statistical analyses

Normality of data was tested with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean \pm standard deviation (s.d.) or as a median (interquartile range (IQR)). Categorical data are presented as absolute values and percentages. Pearson or Spearman correlation coefficients were used to determine correlations between $\text{VO}_{2\text{peak}}$ or NT-ProBNP and clinical, demographic and echocardiographic parameters. Potential predictors for $\text{VO}_{2\text{peak}}$ or NT-ProBNP were entered in a multivariate linear regression model. Student *T*-tests were used to determine the differences between patients who were hospitalised versus those that were not. Event rates were estimated using Kaplan–Meier curves and compared using a log-rank test. Receiver-operating characteristics (ROC) curves were used to determine the optimal prognostic threshold value (highest combination of sensitivity/specificity) for hospitalisation. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS version 20.0; SPSS Inc).

Results

A total of 32 patients were included. The average follow-up time was 23 ± 15 months, ranging from 1 up to 64 months over a total of 57 visits. Sixteen patients were referred for aortic valve intervention with an average time to referral of 14 ± 8.8 months, ranging from 0 up to 32 months. Three quarter of the patients were male. All patients had a LVEF within normal range (Table 1). No patients died during follow-up. Median NT-ProBNP was 301 (IQR: 105–571) pg/mL. Average age was 68.8 ± 15.7 years.

Average $\text{VO}_{2\text{peak}}$ was 19.5 ± 6.2 mL/kg/min. Almost half of the patients (41%) had a reduced exercise tolerance based on a predicted $\text{VO}_{2\text{peak}}$ below 84%. Average OUES was 1993 ± 636 (mL/min)/(L/min). In contrast to conventional

Table 1 Demographics for all patients.

Parameter	All patients (n = 32)	VO ₂ peak < 84% predicted (n = 13)	VO ₂ peak > 84% predicted (n = 19)
Age (years)	68.8 ± 15.7	63.5 ± 17.1	72.4 ± 14.0
Weight (kg)	79.3 ± 12.5	80.5 ± 10.3	78.6 ± 14.0
Height (m)	1.72 ± 0.08	1.74 ± 0.06	1.71 ± 0.09
Males (%)	24 (75%)	12 (92%)	12 (63%)
NT-proBNP (pg/mL)	301 (105–571)	155 (91–440)	302 (200–808)
Rest LVEF	62.8 ± 5.4	61.1 ± 4.2	63.8 ± 5.9
RWT	0.43 ± 0.1	0.48 ± 0.1	0.39 ± 0.08
Rest S' (cm/s)	5.5 ± 1.14	5.3 ± 1.0	5.6 ± 1.2
Rest Vmax (cm/s)	4.00 ± 0.5	4.0 ± 0.4	4.0 ± 0.5
Rest mean PG (mmHg)	36.8 ± 9.4	35.3 ± 9.8	37.1 ± 9.3
SV rest (mL)	75.7 ± 17.0	72.0 ± 22.2	75.4 ± 14.0
SV exercise (mL)	80.8 ± 17.8	81.3 ± 23.8	80.5 ± 13.3
Rest AVA (cm ²)	0.88 ± 0.2	0.89 ± 0.04	0.87 ± 0.04
Rest AVAi (cm ² /m ²)	0.47 ± 0.1	0.47 ± 0.03	0.46 ± 0.02
Exercise S'	7.4 ± 1.8	7.2 ± 1.4	7.6 ± 2.1
Exercise Vmax	4.6 ± 0.5	4.6 ± 0.5	4.5 ± 0.6
Exercise mean PG	50.4 ± 13.6	49.8 ± 14.7	51.6 ± 12.0
VO ₂ peak (mL/kg/min)	19.5 ± 6.2	18.9 ± 6.2	19.9 ± 6.3
OUES ((mL/min)/(L/min))	1993 ± 636	1944 ± 470	2025 ± 736
VE/VCO ₂ slope	32.3 ± 5.3	32.4 ± 6.7	32.2 ± 4.2
O ₂ pulse peak	11.7 ± 3.03	11.4 ± 2.4	11.9 ± 3.4
HR peak (beats/min)	133 ± 26.5	131 ± 24.1	132 ± 21.0
Peak WR (watts)	105 ± 56.5	103 ± 51.5	107 ± 61.7
Peak RER	1.07 ± 0.12	1.09 ± 0.15	1.06 ± 0.09

exercise parameters, no patient had a drop in blood pressure during exercise although three patients failed to augment their blood pressure. Four patients were short of breath disproportionate to the level of exercise. No patients suffered from chest pain or syncope during or post exercise.

Regarding the prediction of exercise performance, S' obtained at peak exercise had the strongest correlation with VO₂peak (rho=0.61; P<0.001) (Fig. 1), while augmentation of ejection fraction did not. A relationship was observed between conventional markers of AS obstruction and VO₂peak; Vmax and mean PG at rest showed correlations of rho=0.42 (P=0.02) and rho=0.40 (P=0.02) respectively (Table 2). No relationship was found with stroke volume (SV), AVA or dimensionless velocity index. Resting parameters for systolic function (LVEF or S' likewise did not correlate with VO₂peak). A strong correlation was found with VO₂peak and age (rho=-0.76; P<0.0001 and height (rho=0.45; P=0.009) as expected. During exercise a similar weak association was found with the measures of aortic valve obstruction, Vmax (rho=0.43, P=0.02) and mean PG (rho=0.43, P=0.02) but again no correlation was observed for LVEF, SV or AVA during exercise and VO₂peak (Table 2). In multivariate analysis, exercise S' and age were the strongest independent predictors for VO₂peak with a R² for the model of 0.76 and a beta-coefficient for exercise S' of 1.004 (0.03–1.98); P=0.04 and -0.29 (-0.41 to -0.18; P<0.0001) for age.

A further predictive model for the log NT-ProBNP demonstrated a good relationship with exercise S' (r=0.75), but no relationship was observed for Vmax, mean PG or the AVA (Table 3). Multivariate analyses demonstrated that exercise S' was the strongest predictor for NT-ProBNP with an R² of 0.48 and a beta-coefficient of -0.24 (-0.37 to -0.10); P=0.001.

No patients died during follow-up; however, nine patients required unplanned cardiac admission. Patients who required cardiac admission had a lower percentage predicted VO₂ (77±15.5% vs 92±18.0%; P=0.03) and a greater RWT (0.49±0.11 vs 0.40±0.08; P=0.02). VO₂peak below 84% was a strong predictor for cardiac hospitalisation. A ROC analysis was performed for hospitalisation and % predicted VO₂ had the largest area under the curve R²=0.76 (95% CI: 0.57–0.96). A cut-off of 84.5% for %predicted VO₂ showed a sensitivity and specificity of 78 and 74% respectively (Fig. 2). A Kaplan-Meier curve was generated using this cut-off (Fig. 3). A total of 16 patients were referred for aortic valve intervention during follow-up. No significant predictors were found for exercise S' and hospitalisation. The only difference between those who were referred for surgery and those who continued with watchful waiting was a higher mean PG at rest (33.0mmHg±7.2 vs 39.7±10.3, P=0.049 respectively).

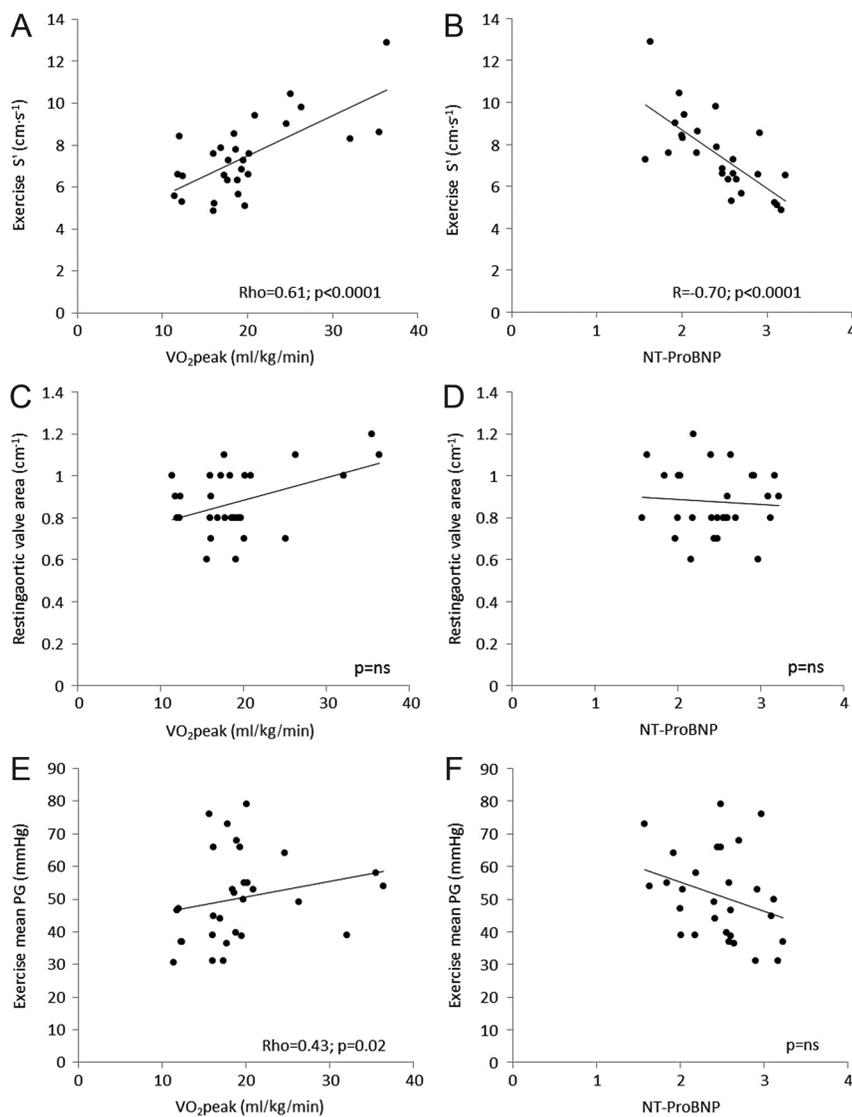


Figure 1
Regression analyses with confidence intervals for (A) VO_2 peak and exercise S' ; (B) VO_2 peak and AVA; (C) VO_2 peak and exercise mean PG; (D) log NT-ProBNP and exercise S' ; (E) log NT-ProBNP and AVA; (F) log NT-ProBNP and exercise mean PG.

Discussion

This study demonstrated that a large proportion of supposedly asymptomatic patients had a lower than predicted $\%VO_2$ peak suggesting that patients have exercise intolerance, this is in agreement with previous reports in the literature (10, 11). In this study CPET identified a much higher proportion of symptomatic individuals than would have been identified if traditional parameters currently recommended in guideline documents (including symptoms and fall in blood pressure) (16). Furthermore a reduced exercise tolerance and more adverse ventricular remodelling, rather than valve obstruction, predicted unplanned hospitalisation, whereas the only difference between those who went for surgery was a higher mean PG suggesting that clinicians may be more influenced

by conventional measures of aortic valve obstruction. Supporting the hypothesis that ventricular response is at least as important as valvular obstruction. Exercise tolerance in this population was poorly correlated with conventional clinical measures of aortic valve severity, even under circumstances of flow augmentation, but was heavily dependent on the ability of the LV to augment longitudinal function during exercise. Furthermore, a similar inverse relationship with NT-ProBNP was observed for exercise S' , whereas other parameters of LV function or valve obstruction were not related.

The severity of AS and the LV response to chronic pressure afterload resulting in myocardial hypertrophy and fibrosis contribute to the progression to the point where patients develop symptoms, adverse events and therefore require surgery (1, 17, 18).

Table 2 Correlation (Spearman's) between VO₂ peak and echocardiographic parameters at rest and exercise (latest visit).

	VO ₂ peak (mL/kg/min)
Demographics	
Age (years)	-0.76*
Weight (kg)	0.19
Height (m)	0.45*
Resting parameters	
S' rest (cm/s)	0.16
LVEF rest (%)	-0.17
RWT	-0.21
Rest max V (cm/s)	0.42 [§]
Rest mean PG (mmHg)	0.40 [§]
Rest SV	0.26
Rest AVA (cm ²)	0.21
Rest AVAi (cm ² /m ²)	-0.19
Dimensionless index	-0.14
Exercise parameters	
S' exercise (cm/s)	0.57*
LVEF exercise (%)	0.25
Exercise max V (cm/s)	0.39 [§]
Exercise mean PG (mmHg)	0.43 [§]
SV exercise	0.25
Exercise AVA (cm ²)	0.28
ΔS' from rest to exercise	0.44 [§]
Δ mean PG from rest to exercise	0.16
Δ SV from rest to exercise	-0.05

**P* < 0.001; [§]*P* < 0.05.

AVA, aortic valve area; AVAi, aortic valve area indexed; LVEF, left ventricular ejection fraction; mean PG, mean pressure gradient; S', systolic longitudinal velocity measured by tissue velocity imaging; SV, stroke volume; Vmax, peak velocity through the aortic valve; VO₂peak, peak oxygen consumption.

Increased hypertrophy leads to impaired LV relaxation, reduced LV compliance and greater metabolic demands (19), and this has been associated with the progression of heart failure (20). However, the extent of LV hypertrophy only weakly correlates with the severity of AS (21, 22, 23). Focal scar burden within the myocardium is strongly correlated with outcome following aortic valve replacement (AVR) and prognosis (23, 24), suggesting that ventricular response to afterload results in irreversible cellular myocardial changes which modulate outcome. LVEF is the standard parameter used for assessing global systolic dysfunction and a current indicator for aortic valve intervention (4, 16). LVEF reduction, used in isolation, is unsatisfactory as in this circumstance reduction is a late manifestation of ventricular decompensation and myocardial fibrosis (25, 26). Furthermore, in AS, it is common to overestimate systolic function for simple geometric reasons, as ventricular volumes are reduced due to concentric hypertrophy (27), leading to a small stroke volume for a given LVEF. As our current model of systolic function is clearly incomplete, more subtle and

predictive parameters to describe ventricular performance are required.

Longitudinal systolic function is more sensitive in detecting early myocardial dysfunction (28). When assessed by strain rate imaging (27, 29, 30), it predicts adverse event more accurately (31) than LVEF in patients with AS. A recent meta-analysis demonstrated that in asymptomatic patients with severe AS and normal LVEF, impaired global longitudinal strain is associated with reduced survival (32). Lancellotti *et al.* included 126 asymptomatic patients with severe AS and found that patients with impaired longitudinal function have a greater risk of developing cardiac events (19). Annular or myocardial longitudinal velocity are an alternative, well-established method of quantifying longitudinal systolic function (33, 34). Although unlike 2D strain imaging, TVI is angle dependent, but it has the advantage of being much less dependent on overall 2D image quality making it useful in most patients and during stress echocardiography. Alternative means of estimating LV dysfunction is the use of systemic biomarkers. Significant associations have been found between NT-ProBNP and myocardial longitudinal contractility and the degree of symptoms in asymptomatic patients with severe AS (36). Rajani and colleagues included 38 patients with moderate and severe AS and found that blood BNP levels strongly predicted patients who became symptomatic during exercise (37). NT-ProBNP is able to unmask early ventricular decompensation; however, the influence of age and sex and the threshold used to determine adverse events differ greatly between studies. Guidelines including reference values should be established to implement the use of NT-ProBNP in a clinical setting in patients with severe AS.

In this study, confirming the results of many others, the standard clinical markers of AS severity correlated very poorly with predicted exercise limitation or outcomes. The only resting parameter which was associated with exercise tolerance was the mean PG; however, this was only a weak relationship. The poor correlation between resting echo findings and objective exercise limitation has been previously demonstrated in the literature (10, 11). Exercise parameters, which do seem to predict prognosis in some studies, have not previously predicted exercise tolerance (10). As far as we are aware, no previous evaluations to date have investigated longitudinal velocity in relation to CPET at exercise.

This paper clearly demonstrates a relationship between longitudinal velocity and VO₂peak, not explained by other clinical parameters. The results are considerably

Table 3 Correlation (Spearman's) between NT-ProBNP and echocardiographic parameters at rest and exercise (latest visit).

	Log NT-ProBNP
Demographics	
Age (years)	0.55*
Weight (kg)	0.23
Height (m)	-0.31
Resting parameters	
S' rest (cm/s)	-0.30
LVEF rest (%)	-0.06
Rest max V (cm/s)	-0.23
Rest mean PG (mmHg)	0.28
Rest SV	-0.06
Rest AVA (cm ²)	-0.01
Rest AVAi (cm ² /m ²)	0.14
Dimensionless index	0.02
Exercise echocardiography parameters	
S' exercise (cm/s)	-0.75*
LVEF exercise (%)	-0.46
Exercise max V (cm/s)	-0.32
Exercise mean PG (mmHg)	-0.35
Exercise SV	-0.44 [§]
Exercise AVA (cm ²)	-0.31
ΔS' from rest to exercise	-0.58*
Δ mean PG from rest to exercise	0.22
Δ SV from rest to exercise	-0.33
Cardiopulmonary exercise testing parameters	
VO ₂ peak (mL/kg/min)	-0.51*
OUES ((mL/min)/(L/min))	-0.46 [§]
V _E /VCO ₂ slope	0.34

**P* < 0.001; [§]*P* < 0.05.

BSA, body surface area; NT-ProBNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; S', systolic longitudinal velocity measured by tissue velocity imaging; Vmax, peak velocity through the aortic valve; mean PG, mean pressure gradient; AVA, aortic valve area; AVAi, aortic valve area indexed; VO₂peak, peak oxygen consumption; OUES, oxygen uptake efficiency slope.

more plausible because of the co-existing inverse, and is among other measured parameters a unique, relationship with log NT-ProBNP, thus suggesting that patients with lower longitudinal systolic reserve have on average, higher intracardiac pressures. We have previously documented the importance of systolic velocity reserve in a variety of different clinical conditions (38, 39) and its importance seems to be confirmed here in patients with AS.

Both stress echocardiography and CPET have been used to establish the likelihood of future cardiac events. Exercise echocardiography provides additional information including the haemodynamic changes that occur during exercise. An increase in mean PG of 18 mmHg or more on exercise is an independent predictor for death and hospital admissions (36). A study by Maréchaux *et al.*, included 186 asymptomatic patients with at least moderate AS (mean PG >35 mmHg)

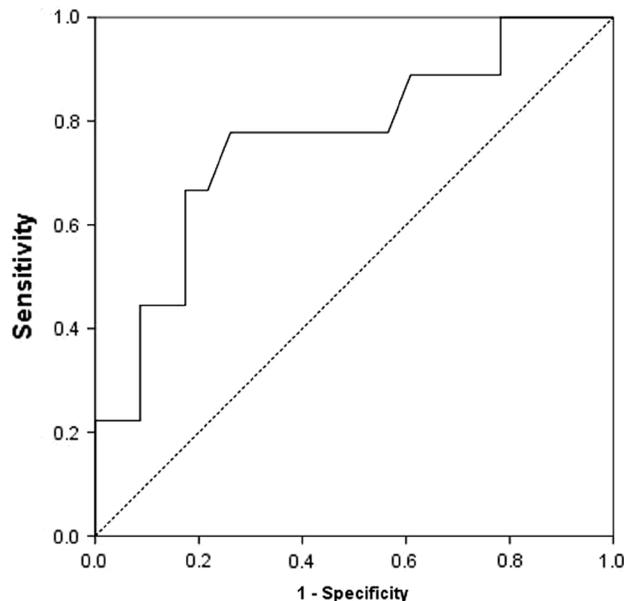


Figure 2

ROC curve for hospitalisation. % predicted VO₂ has the largest area under curve *r*² = 0.76 (95% CI: 0.57–0.96).

and preserved LV function (40). A nine-fold increase in event rate (AVR or death) was found in patients with an increase in mean PG of more than 20 mmHg on exercise; the increase in gradient could not be predicted from resting clinical or echocardiographic data. In our cohort, eight patients demonstrated an increase in gradient of more than 20 mmHg. Three of these eight patients were referred for AVR. However, this was not associated with cardiac hospitalisation or referral for AVR and is probably due to the small numbers with a high gradient on exercise. Resting mean PG was higher for patients referred for AVR compared to those who were not suggesting that clinicians are more influenced by conventional measures of aortic valve obstruction. Our study suggests that exercise performance from CPET is the strongest predictor of cardiac hospitalisation. The parameter investigated was % predicted VO₂peak but not VO₂peak, this is a surprising finding, and probably because % predicted VO₂peak is indexed for normative values (height, weight, age included). Indexing VO₂peak provides the ability to compare patients with different ages, weights and heights. However, normative values for S' are currently unknown, and needed to be able to undertake comparable analyses. A recent study by Domanski and colleagues found that a VO₂peak of less than 85% was a predicted value associated with lower event-free survival in 51 asymptomatic patients

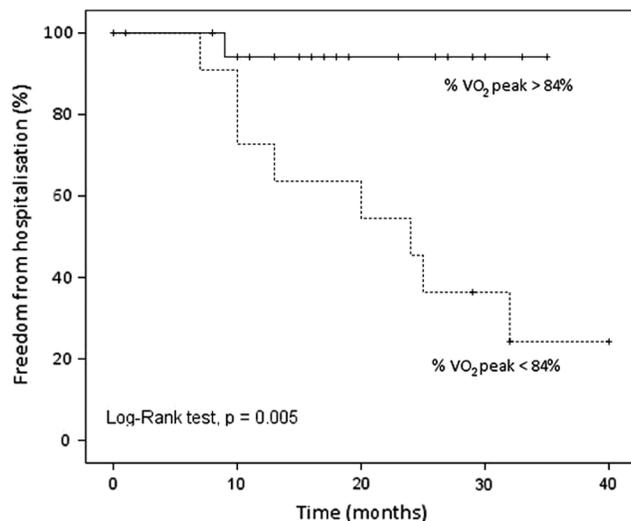


Figure 3
Hospitalisation curve for patients with a VO_{2peak} above and below 84% at the first visit to the clinic.

with severe AS (10). Our data agree with this finding. In the Domanski paper, no parameters obtained during stress echocardiography were able to predict events concluding that CPET should be incorporated when patients are placed in the watchful waiting category. However, authors did not include any parameters describing longitudinal function during exercise in the analyses. Longitudinal function has previously shown good prognostic power for future events (38).

Limitations

The study was retrospective and based around protocolled clinical evaluation. Strain analysis either by TVI or by speckle tracking was not used in this study, and this might have provided further insights into global and regional deformation. However the major benefit of S' is the simplicity and high reproducibility. Furthermore, a recumbent cycle ergometer was used instead of the traditional upright cycle ergometer. The use of the recumbent cycle ergometer is necessary in order to obtain exercise echocardiographic parameters of good quality. A small unpublished study found a good relationship and reasonable agreement between the upright and the semi-recumbent cycle ergometers. And finally the clinical decision to refer to surgery was carried out by a consultant cardiologist who had all information available (stress echocardiographic, CPET and NT-ProBNP parameters) but might have been biased, we were unable to determine which parameter was used in the decision to send patients for surgical intervention.

Conclusion

A large percentage of patients with supposedly asymptomatic severe AS with normal ejection fraction have a lower than predicted VO_2 . This is more dependent upon the ability of the LV to augment longitudinal function on exercise than the level of obstruction at the aortic valve (either at rest or with augmented flow) or the resting structural remodelling of the LV. Exercise S' was not only independently associated with VO_{2peak} but also NT-ProBNP which further confirms that the relationship is stronger than conventional AS severity and LV remodelling parameters. The burden of unplanned hospitalisation was high, and this was predictable when patients had lower than predicted VO_{2peak} . More patients were unmasked as having abnormal exercise performance using CPET than conventional exercise parameters advocated in current guidelines. This suggests that where watchful waiting is an agreed strategy, a detailed assessment should be undertaken including CPET, exercise echocardiography and biomarkers to ensure those with exercise limitation and risk of decompensation are detected early and treated appropriately. The combination of exercise echocardiography and CPET in this setting can therefore unmask patients with exercise limitation and subtle changes in LV performance not identified by current treadmill based guidelines as well as demonstrating, but still predict adverse cardiac events.

Declaration of interest

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