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Exercise stress echocardiography in patients with valvular heart disease

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Abstract

Stress echocardiography is recommended for the assessment of asymptomatic patients with severe valvular heart disease (VHD) when there is discrepancy between symptoms and resting markers of severity. The aim of this study is to determine the prognostic value of exercise stress echocardiography in patients with common valve lesions. One hundred and fifteen patients with VHD (aortic stenosis ($n=28$); aortic regurgitation ($n=35$); mitral regurgitation, ($n=26$); mitral stenosis ($n=26$)), and age- and sex-matched controls ($n=39$) with normal ejection fraction underwent exercise stress echocardiography. The primary endpoint was a composite of death or hospitalization for heart failure. Asymptomatic VHD patients had lower exercise capacity than controls and 37% of patients achieved $<85\%$ of their predicted metabolic equivalents (METs). There were three deaths and four hospital admissions, and 24 patients underwent surgery during follow-up. An abnormal stress echocardiogram (METs <5 , blood pressure rise <20 mmHg, or pulmonary artery pressure post exercise >60 mmHg) was associated with an increased risk of death or hospital admission (14% vs 1%, $P<0.0001$). The assessment of contractile reserve did not offer additional predictive value. In conclusion, an abnormal stress echocardiogram is associated with death and hospitalization with heart failure at 2 years. Stress echocardiography should be considered as part of the routine follow-up of all asymptomatic patients with VHD.

Key Words

- ▶ stress echocardiography
- ▶ valvular heart disease
- ▶ exercise testing
- ▶ echocardiography

Introduction

Valvular heart disease (VHD) remains a common cause of cardiovascular morbidity and mortality worldwide. The development of acute valvular lesions such as acute aortic or mitral regurgitation (MR) often present with signs of acute severe heart failure and the prognosis without urgent cardiac surgery is poor. In contrast, patients with chronic valve disease may remain asymptomatic for many years. Previous studies have demonstrated that during this asymptomatic phase, the prognosis remains relatively favourable, but once symptoms develop, the prognosis

without valve surgery becomes poor (1, 2, 3, 4, 5). Consequently, the assessment of symptomatic status in patients with VHD forms a key factor in current guidelines on the management of VHD (6, 7). However, due to the often slowly progressive nature of VHD, defining the exact onset of symptoms in patients with VHD can be difficult. In addition, many patients who remain asymptomatic can develop significant dilatation of cardiac chambers and impairment of ventricular function or pulmonary hypertension prior to developing overt symptoms. In many patients, the assessment of the severity of the underlying

valve disease can be problematic, with discordant markers of severity on resting echocardiography, and a number of patients may complain of symptoms despite objectively mild or moderate valve disease at rest.

To overcome these difficulties, current guidelines (6, 7, 8) recommend the use of exercise testing in patients with valve disease. However, this is mainly consensus-driven, and it is unclear whether performing exercise testing in VHD patients who do not have an indication for valve surgery based on clinical assessment and resting echocardiography alone translates to a clinical benefit for these patients.

The aim of this study is therefore to determine the value of performing exercise testing in patients with common valvular heart lesions without an established indication for surgery according to current guidelines. We aim to determine whether patients who demonstrate adverse features on stress echocardiography have a worse outcome during follow-up than those with normal exercise stress echocardiograms. A secondary aim was to compare the value of exercise stress echocardiography across different valve lesions.

Methods

Patient selection

Asymptomatic patients with severe valve disease, patients with a discrepancy between symptoms and Doppler echocardiography performed at rest or those with equivocal symptoms were identified from echocardiogram reports and outpatient clinics in the Auckland region. These comprised patients with isolated aortic stenosis (AS), aortic regurgitation (AR), MR and mitral stenosis (MS). All patients had normal left ventricular (LV) ejection fraction (EF) (AS $\geq 50\%$, AR $> 50\%$, MR $\geq 60\%$, MS $\geq 50\%$) (8, 9, 10). Exclusion criteria included ischaemic heart disease, significant renal impairment (creatinine $> 160 \mu\text{mol/l}$), respiratory disease, a contraindication to exercise testing, additional valvular lesions graded greater than mild or an established indication for valve surgery according to the ACC/AHA guideline criteria (8, 11). All patients eligible for inclusion were invited to participate. The patients' symptomatic status was assessed according to the New York Heart Association criteria by an experienced cardiologist blinded to echocardiographic data. Control subjects were volunteers from the local community who were age and sex matched. They were recruited by advertisement and had no clinical evidence of cardiovascular or respiratory disease. The study was approved by the Northern X Ethics Committee, Auckland.

All patients gave written consent after a full explanation of the purpose and nature of all procedures used.

Echocardiography

All echocardiograms were performed by experienced sonographers on cardiac ultrasound scanners (Vivid 7, General Electric, Vingmed Ultrasound, Horten, Norway). All patients underwent comprehensive examination including M-mode, 2D, Doppler and tissue Doppler echocardiography. All analysis was performed offline (Echopac PC, GE Medical, Milwaukee, WI, USA) by an experienced cardiologist blinded to the results of the patients' clinical assessment. All measurements were averaged from at least three, or in cases of atrial fibrillation, five cardiac cycles. The LV end-systolic and end-diastolic volumes and EF were measured from the apical four-chamber view using the modified Simpson's single-plane method (12). This method was chosen to allow comparison with the post-exercise volumes. The left atrial area was measured in the apical four-chamber view (13).

Quantitative and qualitative measures of AS and regurgitation severity were made according to American Society of Echocardiography guidelines (9, 10). Quantitative measures of AS severity included peak velocity, mean pressure drop and aortic valve area. Assessment of AR severity included the AR jet:LVOT width ratio, AR pressure half time, peak diastolic and end-diastolic flow velocities in the descending thoracic and abdominal aorta.

The severity of MR was assessed by quantitative Doppler with mitral and aortic stroke volumes (14) and by the proximal isovelocity surface area (PISA) method (15). The volumes obtained from the two methods were averaged to give a mean regurgitant volume (16). The mitral valve area (MVA) was obtained using direct planimetry, pressure half-time and continuity methods (17, 18, 19). The median MVA from these three methods was used for analysis. Mean trans-mitral pressure gradients were obtained by tracing the continuous wave Doppler signal across the mitral valve (20).

To facilitate estimation of right ventricular systolic pressure, agitated saline was injected to enhance the tricuspid regurgitation profile (21). The peak pulmonary artery systolic pressure (PAP) was derived using the simplified Bernoulli equation from the peak tricuspid regurgitant jet and added to an estimate of right atrial pressure obtained from imaging of the inferior vena cava (22). Left atrial area, LV volumes, valve areas and effective regurgitant orifice areas were indexed to body surface area (23).

Exercise stress echocardiography

All patients underwent symptom-limited exercise testing on a motorized treadmill. A standard Bruce protocol was used for patients with MR. However, it was noted that there was significant clustering of exercise times at the end of each stage, and this was felt to adversely affect the objectivity of the determination of exercise capacity. Consequently, for subsequent patients, the protocol was adjusted so that the speed and/or incline of the treadmill were increased at 1-min intervals. The maximum workload at the end of each 3-min stage remained equivalent to that of the standard Bruce protocol. Exercise was stopped for significant dyspnoea, chest discomfort, presyncope, fatigue or at patient request.

Immediately after exercise, echocardiographic images were obtained in the apical four-chamber view, first for LV volumes then for tricuspid regurgitant jet velocity with agitated saline enhancement. In all patients, data were obtained within 1 min of peak exercise.

Outcome measures

Patients continued with their regular clinical follow-up with their usual cardiologist in accordance with established guidelines (8). Their clinical cardiologist decided the requirement for, and timing of, any valve intervention blinded to exercise echo data. The only exception to this was if there were major abnormalities detected on stress echocardiography, in which case the cardiologist was informed. Follow-up data was collected for 2 years from the date of enrolment. The main outcomes were death, hospitalisation for heart failure and the need for valve replacement surgery. The primary clinical outcome was a composite of death and hospitalisation for acute heart failure. The secondary endpoint was a composite of death, heart failure and valve surgery.

Adverse features on treadmill testing were defined as low exercise capacity (<5 metabolic equivalents (METs) on treadmill exercise (24)), an abnormal blood pressure response to exercise (<20 mmHg rise with exercise) (8), exercise-induced pulmonary hypertension (PAP >60 mmHg post exercise (8)) and poor contractile reserve ($<4\%$ increase in EF post exercise) (24, 25).

Statistical analysis

Two sample Student's *t*-tests were used for comparing continuous variables between patient groups. Comparison of all valves vs the control group, and valve sub-groups was performed using the χ^2 or Fisher's exact tests for

categorical data where appropriate. For continuous variables, two independent samples Student's *t*-test was used for comparing all valves vs controls group. For comparison between subgroup of valves, one-way ANOVA was performed. Prediction accuracies were reported by area under the receiver operating characteristic curve (AUC) and its 95% CI. Kaplan–Meier curves were used to visualize the time to first clinical event across different stress echocardiographic parameters. XLSTAT (version 2014.4.06, Addinsoft 1995–2014, Paris, France) was used for analysis. All tests were two-tailed and a *P* value of <0.05 was considered statistically significant.

Results

All patients who agreed to participate completed all aspects of the study. One hundred and fifteen patients with valve disease and 39 control subjects were recruited: isolated MR ($n=26$), AR ($n=35$), AS ($n=28$) and MS ($n=26$) or normal valves ($n=39$) (Table 1).

Eighty-one (70%) VHD patients were assessed as asymptomatic (NYHA class 1). The remainder had mild or equivocal symptoms but did not fulfil criteria for surgery based on their assessment of valve severity according to Doppler echocardiography and clinical assessment performed at rest. Across all VHD patients, 37 (32%) patients had severe valve disease, 69 (60%) patients had moderate valve disease and nine (8%) patients had mild disease but had symptoms out of keeping with their echocardiographic findings at rest. No patients had evidence of regional wall motion abnormalities at rest or immediately post exercise.

Normal exercise echocardiograms

Sixty-four VHD patients (56%) had normal stress echocardiograms. Most patients with AR had normal studies. In contrast, only four patients (15%) with MS had a normal stress echocardiogram (Table 1). Although patients with VHD and normal exercise stress echocardiograms were younger than controls (48 ± 15 vs 55 ± 15 years; $P=0.02$), they had lower exercise capacity (11.1 ± 2.9 vs 12.5 ± 3.1 METs; $P=0.02$). In addition, patients with VHD and normal stress echocardiograms had larger left atria, larger left ventricles and higher PAP than controls (Table 1).

Abnormal stress echocardiograms

Fifty-one (44%) patients with VHD had abnormal stress echocardiograms and were older than those with VHD

Table 1 Clinical characteristics and exercise echocardiogram data for patients and controls.

Patient characteristics	Controls (n=39)	Normal ESE (n=64)	Abnormal ESE (n=51)	P value (normal ESE vs controls)	P value (abnormal vs normal ESE)
Baseline characteristics					
Mitral regurgitation n (%)		16 (25)	10 (20)		0.49
Mitral stenosis n (%)		4 (6)	22 (43)		<0.0001
Aortic stenosis n (%)		10 (16)	18 (35)		0.01
Aortic regurgitation n (%)		34 (53)	1 (2)		<0.0001
Age (years)	55±15	48±14	58±15	0.02	<0.0001
BMI (kg/m ²)	26±4	28±4	29±5	0.01	0.46
Sex male n (%)	23 (59)	50 (78)	23 (45)	0.06	<0.001
NYHA	0 (0)	11 (17)	23 (45)	0.07	0.001
Resting echocardiography					
Left atrial area index (cm ² /m ²)	11±2	12±4	16±6	0.01	<0.0001
Left ventricular end diastolic volume Index (mls/m ²)	52±13	77±28	54±19	<0.0001	<0.0001
Left ventricular end-systolic volume Index (mls/m ²)	19±7	57±30	39±18	<0.0001	<0.0001
Left ventricular ejection fraction (%)	64 (8)	64±6	63±8	0.71	0.38
Pulmonary artery pressure (mm Hg)	24±4	29±6	37±13	<0.0001	<0.0001
Exercise echocardiography					
Left ventricular end diastolic volume Index (mls/m ²)	34±13	57±20	40±18	<0.0001	<0.0001
Left ventricular end-systolic volume Index (mls/m ²)	9±5	17±9	12±7	<0.0001	0.004
Left ventricular ejection fraction (%)	78±8	71±8	71±10	<0.0001	0.87
Change in ejection fraction (%)	13±7	7±8	7±16	0.001	0.79
Pulmonary artery pressure (mm Hg)	41±9	46±8	64±20	0.02	<0.0001
Metabolic equivalents (METs)	12.5±3.1	11.1±2.9	7.4±2.9	0.019	<0.0001
Systolic blood pressure rise (mm Hg)	46±15	50±18	11±18	0.25	<0.0001
% of predicted METs (%)	133±38	106±33	82±41	<0.0001	0.001
Peak heart rate (bpm)	153±16	143±21	136±25	0.02	0.14
% peak heart rate (%)	93±13	78±24	84±13	<0.0001	0.13

and normal exercise echocardiograms (58 ± 15 vs 48 ± 15 years; $P < 0.0001$). Patients with abnormal stress echocardiograms had larger left atria, larger ventricles and higher PAP compared to patients with VHD and normal stress echocardiograms.

Symptomatic status

Eighty-one patients were assessed in NYHA class 1. However, despite being asymptomatic, they had worse exercise capacity than control subjects (10.3 ± 3.4 vs 12.5 ± 3.1 METs; $P = 0.001$). Patients with NYHA class 2 symptoms had a lower exercise capacity than those in NYHA class 1 (7.2 ± 2.3 vs 10.3 ± 3.4 , $P < 0.0001$) despite only two patients (with equivocal symptoms) having evidence of severe disease at rest (5% vs 43%, $P < 0.0001$). Five patients (6%) who were deemed to be asymptomatic at baseline had an exercise capacity of < 5 METs. Twenty-eight patients (82%) who were deemed to be symptomatic had an exercise capacity greater than five METs. However, when exercise capacity was stratified according to age, 30 (37%) asymptomatic patients

achieved $< 85\%$ of their age-predicted exercise capacity. In contrast, 14 (41%) patients who were classed as symptomatic achieved more than 85% of their age-predicted METs. Overall, the use of objective exercise capacity (workload $> 85\%$ age-predicted METs) resulted in the re-classification of symptomatic status in 38% of patients. Reclassification of symptomatic status was seen most frequently in patients with AR and MS, suggesting that accurate assessment of symptomatic status is most difficult in these groups of patients.

Outcome data

There were three deaths, four hospital admissions for heart failure and 24 patients underwent surgery during the 2-year follow-up period (Table 2). Patients with an abnormal exercise test were more likely to die (5% vs 1%, $P < 0.001$) or be hospitalised with heart failure (9% vs 0%, $P = 0.0009$) during follow up. Exercise-induced pulmonary hypertension was the only isolated adverse feature on exercise testing that was different in patients who died or those who underwent surgery during follow up.

Table 2 Relative proportions of patients with adverse features on stress echocardiography with adverse outcome.

Stress echo parameters	Death		Admission		Surgery		Death/Admission		Any outcome	
	n (%)	P	n (%)	P	n (%)	P	n (%)	P	n (%)	P
Abnormal BP	2 (5)	0.22	4 (10)	0.005	10 (26)	0.37	6 (15)	0.003	11 (28)	0.23
Normal BP	1 (1)		0 (0)		14 (18)		1 (1)		14 (18)	
METS < 5	0 (0)	0.55	3 (25)	<0.0001	1 (8)	0.26	3 (25)	0.004	1 (8)	0.23
METS > 5	3 (3)		1 (1)		23 (22)		4 (4)		24 (23)	
PAP > 60 mmHg	2 (8)	0.02	2 (9)	0.02	7 (30)	0.07	3 (13)	0.004	7 (30)	0.005
PAP < 60 mmHg	1 (2)		2 (4)		10 (21)		3 (3)		11 (12)	
Abnormal ESE*	2 (5)	<0.0001	4 (9)	0.0009	10 (23)	<0.0001	6 (14)	<0.0001	11 (25)	<0.0001
Normal ESE	1 (1)		0 (0)		7 (10)		1 (1)		7 (10)	
EF increase ≤ 4%	1 (3)	0.98	1 (3)	0.7	7 (18)	0.58	0 (0)	0.35	2 (17)	0.63
EF increase > 4%	2 (3)		3 (4)		17 (22)		7 (7)		23 (23)	

BP, blood pressure; METs, metabolic equivalents; PAP, pulmonary artery pressure; ESE, exercise stress echocardiogram; EF, ejection fraction.

*Abnormal ESE is at least one of BP rise < 20 mmHg, Exercise tolerance < 5 Mets or PAP post exercise > 60 mmHg.

Patients who were admitted to hospital had lower exercise capacity, higher pulmonary artery pressure and lower blood pressure rise with exercise. In contrast, poor contractile reserve (EF ≤ 4%) did not identify patients with adverse outcome. Exercise capacity was the single best predictor of death or heart failure admission (Table 3).

Patients with an abnormal stress echocardiogram were more likely to meet the primary endpoint of death or hospitalisation (Fig. 1) but not the combined endpoint of death, hospitalisation or need for surgery during follow up (Fig. 2).

Comparison between different valve lesions

Patients with an established indication for surgery were excluded from this study. In keeping with the inclusion of some patients with degenerative AS, these patients were significantly older than the patients in other valve groups (Table 4). Patients with stenotic valve lesions had a lower rise in systolic blood pressure than those with regurgitant valve lesions (AS 16 ± 23, MS 14 ± 15, AR 59 ± 18, MR 34 ± 19 mmHg; $P < 0.0001$). Patients with MS were the most likely to have exercise limitation, with 88% of patients

failing to achieve > 85% of their age-predicted exercise capacity. However, symptomatic status at rest did not correspond to exercise capacity on exercise stress echocardiography in almost a third of patients, regardless of the underlying valve lesion (Table 4).

Discussion

This study demonstrates that adverse features found on stress echocardiography in patients with common VHDs are associated with a worse prognosis during a 2-year follow-up period. This is despite these patients not fulfilling any criteria for surgical intervention at the time of enrolment. In particular, patients with exercise-induced pulmonary hypertension were more likely to die during follow-up. In addition, patients with at least one adverse feature on stress echocardiography were more likely to be hospitalised with heart failure or meet the combined endpoint of death and heart failure admission.

A number of other studies have assessed the role of exercise testing in VHD. The most evidence is in asymptomatic patients with severe AS and relates primarily to exercise electrocardiography (ECG). Previous

Table 3 The predictive accuracy of exercise stress echo parameters for clinical outcomes during follow-up.

Stress echo parameters	Death		Admission		Death/admission		Operation		Any event	
	AUC	P	AUC	P	AUC	P	AUC	P	AUC	P
Exercise capacity (METS)	0.73 (0.57, 0.89)	0.005	0.94 (0.93, 0.96)	<0.0001	0.86 (0.76, 0.96)	<0.0001	0.58 (0.46, 0.69)	0.21	0.65 (0.54, 0.76)	0.007
BP rise (mmHg)	0.52 (0, 1.0)	0.92	0.86 (0.78, 0.93)	<0.0001	0.72 (0.49, 0.95)	0.07	0.51 (0.36, 0.66)	0.9	0.58 (0.45, 0.71)	0.22
Post exercise PAP (mm HG)	0.50 (0, 1.0)	1	0.73 (0.58, 0.87)	0.002	0.66 (0.36, 0.96)	0.3	0.56 (0.40, 0.72)	0.44	0.58 (0.43, 0.73)	0.3
Change in EF (%)	0.41 (0, 0.83)	0.68	0.31 (0, 0.64)	0.25	0.35 (0.10, 0.59)	0.22	0.55 (0.43, 0.67)	0.43	0.46 (0.34, 0.58)	0.48

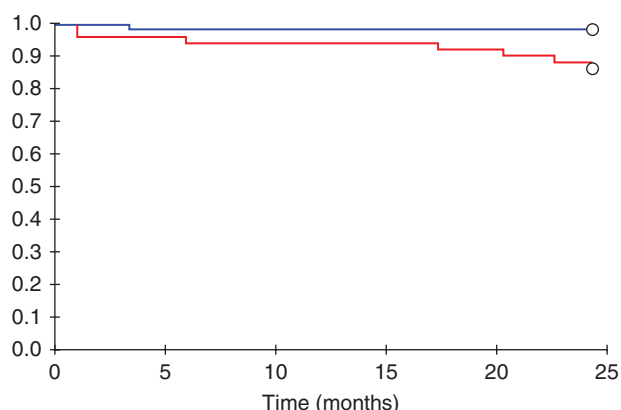


Figure 1

Kaplan-Meier curves showing event free survival (death or hospitalisation with heart failure) for patients with a normal stress echocardiogram (blue line) and an abnormal stress echocardiogram (red line) over 2-year follow up ($P=0.01$).

studies have suggested that an abnormal exercise test defined as the development of symptoms, ST depression or a failure to augment BP by >20 mmHg predicted the future onset of symptoms (26, 27) and sudden cardiac death during follow-up (26). More recently, a study by Das *et al.* (28) confirmed the finding that the development of symptoms with exercise was superior to clinical history and resting echocardiography in predicting future onset of symptoms. However, they also found that the presence of an abnormal BP response to exercise was less helpful. The additional value of exercise stress echocardiography over exercise ECG is less clear. Lancellotti *et al.* (29) and Marechaux *et al.* (30) found that an exercise-induced increase in mean pressure drop of more than 18 mmHg or 20 mmHg respectively was associated with an increased risk of symptom onset or death. However, in patients with reduced LV functional reserve, the ability to generate a significant pressure drop across a stenotic valve may be reduced and this finding should be interpreted with caution. The role of exercise echocardiography in AR is even less clear. A few studies have looked at the presence of exercise-induced LV dysfunction in patients with AR. Wahi *et al.* (31) found that failure to augment LV systolic function at peak exercise was predictive of LV decompensation. In addition, we have previously demonstrated that even in AR patients who have an appropriate increase in EF with exercise, assessment of global longitudinal strain post exercise can detect early LV dysfunction (32).

Similarly, in MR a number of studies have demonstrated that MR can worsen with exercise and that the absence of contractile reserve is associated with reduced

event-free survival and can predict early postoperative LV dysfunction (33, 34). Exercise echocardiography was formally a class 1 recommendation in asymptomatic patients with moderate or severe MS and symptomatic patients with mild MS (8). However, there are no outcome data to support this and it is a level of evidence C.

In this study, patients who were deemed to be asymptomatic by clinical assessment alone did indeed have a better objectively measured exercise capacity than those who were symptomatic. The asymptomatic group did have a much greater proportion of patients with severe VHD although, in accordance with current guidelines, symptomatic patients with severe valve disease were excluded from undergoing stress echocardiography. It was striking that despite thorough clinical assessment by an experienced cardiologist, a significant number of apparently asymptomatic patients had extremely poor exercise capacity when subject to exercise stress echocardiography and that reclassification of symptomatic status occurred in a third of patients across all valve groups. This is in keeping with the findings of other studies, which have highlighted the difficulty in the accurate assessment of symptomatic status in patients with valve disease.

Previous guidelines (8) recommended exercise stress echocardiography for asymptomatic patients with severe AS (peak velocity >4 m/s or mean gradient >40 mmHg), in asymptomatic moderate or severe MS (MVA <1.5 cm²) and symptomatic patients with mild MS. For patients with MS, a rise in PAP of >60 mmHg or a pulmonary capillary wedge pressure of >25 mmHg was considered an indication for intervention. However, the most recent

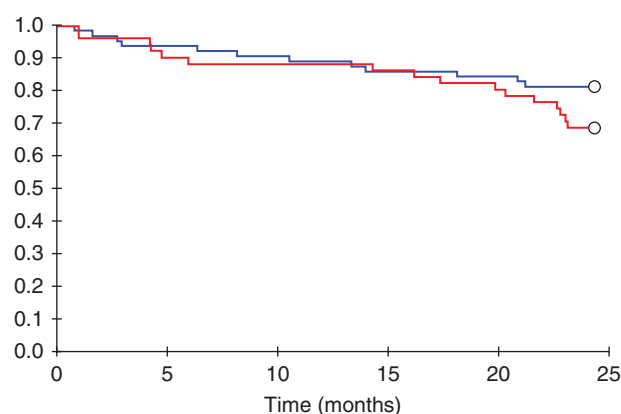


Figure 2

Kaplan-Meier curves showing event free survival (death or hospitalisation with heart failure, valve surgery) for patients with a normal stress echocardiogram (blue line) and an abnormal stress echocardiogram (red line) over 2-year follow up ($P=0.19$).

Table 4 Patient characteristics and exercise data for patients with different valve lesions.

	Controls	Aortic regurgitation	Aortic stenosis	Mitral regurgitation	Mitral stenosis	All valves	P value (all valve vs controls)	P value (comparison between subgroups)
Number of subjects	39	35	28	26	26	115		
Age (mean \pm s.d.)	55.4 \pm 15.1	43.5 \pm 13.5	66.0 \pm 9.0	52.7 \pm 14.5	50.1 \pm 14.8	52.5 \pm 15.5	0.3707	<0.0001
NYHA class, n (%)	–	3 (9)	11 (39)	10 (38)	10 (38)	34 (30)	0.0001	0.0137
Exercise capacity (mean \pm s.d.)	12.5 \pm 3.1	11.2 \pm 3.5	9.6 \pm 3.0	9.8 \pm 2.3	6.5 \pm 2.8	9.4 \pm 3.4	<0.0001	<0.0001
% peak heart rate (mean \pm s.d.)	93 \pm 13	77 \pm 11	84 \pm 12	90 \pm 10	87 \pm 13	84 \pm 13	<0.0001	0.0002
BP rise (mean \pm s.d.)	46 \pm 15	59 \pm 18	16 \pm 23	34 \pm 19	14 \pm 15	33 \pm 27	0.0002	<0.0001
METS <5, n (%)	0 (0)	1 (3)	0 (0)	0 (0)	12 (46)	13 (11)	0.0395	<0.0001
METS <85% predicted, n (%)	4 (10)	12 (34)	5 (18)	10 (38)	23 (88)	50 (43)	0.0002	<0.0001
Change in NYHA (all), n (%)	–	13 (37)	8 (29)	10 (38)	13 (50)	44 (38)	<0.0001	0.4490
NYHA 1 to 2, n (%)	–	11 (31)	1 (4)	5 (19)	13 (50)	30 (26)	0.0004	0.0010
NYHA 2 to 1, n (%)	–	2 (6)	7 (25)	5 (19)	0 (0)	14 (12)	0.0215	0.0091

ACC/AHA (6) guidelines no longer specifically consider exercise-induced pulmonary hypertension as a criteria to intervene but instead prompt the clinician to reassess the patient's symptomatic status. Stress echocardiography is now only considered a class 1 indication in patients in whom there is a discrepancy between symptom status and clinical assessment and Doppler echocardiographic markers of severity at rest (6). Exercise stress echocardiography is recommended in patients with chronic MR where there is a discrepancy between symptoms and severity at rest. In addition, they suggest that exercise treadmill testing can be useful to establish symptoms status and exercise tolerance. No specific recommendations are made for stress echocardiography in AR other than it may be helpful to define symptom status.

Patients with an established indication for surgery were excluded from this study in keeping with current guidelines. Consequently, given that in some cases intervention is now considered at an earlier stage for patients with valve disease, the patients in this study consist of a lower-risk cohort than in some previously published studies. This may be reflected in the lower than expected event rate during follow-up. However, despite this we found a significantly poorer outcome across a range of different valvular heart lesions for patients with an abnormal exercise stress echocardiogram. Although the best single predictor of adverse outcome was exercise capacity, the addition of a poor BP response to exercise and exercise-induced pulmonary hypertension (PAP >60 mmHg) offered incremental prognostic information and was clearly associated with an increased rate of death

or admission with heart failure over the 2-year follow-up period. Conversely, the measurement of contractile reserve as assessed by change in EF is probably not helpful and should not be considered routinely.

These findings suggest that stress echocardiography, with the measurement of pulmonary pressure post exercise, should be considered more frequently in the assessment of asymptomatic patients with VHD. It remains unclear whether earlier intervention following a positive exercise stress echocardiogram can improve the long-term outcome of these patients. Although this needs to be the subject of future research, it remains difficult to investigate this, as in clinical practice, patients with adverse features on exercise stress echocardiography, particularly those with poor exercise capacity, will have their symptomatic status re-classified and may require referral for valve surgery.

We performed exercise stress echocardiography using a treadmill rather than a semi-supine ergometer. The cycle ergometer has a number of advantages in the assessment of VHD. In particular, it allows images to be obtained during exercise, thereby allowing additional measurements such as changes in valve gradients or quantitative assessment of MR severity during exercise to be obtained. However, cycle ergometers are not widely available outside mainland Europe. In addition to their widespread availability, treadmill exercise has a number of other advantages. Firstly, it is more physiological and patients are more readily able to equate performance on a treadmill to their exercise capacity in day-to-day activities. Secondly, patients are often able to achieve higher workloads and higher heart rates with treadmill exercise.

This was demonstrated by the fact that most patients achieved >85% of their maximum heart rate during this study. However, when using treadmill exercise with a standard Bruce protocol for the MR cohort, we found significant clustering of patients' exercise times that coincided with the end of each 3-min stage. This probably represents a goal-orientated approach to exercise and perhaps affects the true objective determination of exercise capacity. Consequently, for other valve groups we adapted the Bruce protocol such that the speed and/or incline increased at 1-min intervals. The protocol was adapted to ensure that the exercise capacity in METS at the end of each 3-min interval remain unchanged when compared to the standard Bruce protocol (Supplementary Table 1, see section on supplementary data given at the end of this article). This resulted in a more even spread of exercise times across VHD patients. This suggests that when using treadmill exercise in order to objectively assess exercise capacity, the use of a more graduated protocol such as the one used in this study should be considered.

Study limitations

This study did not specifically assess the role of more detailed PISA-based markers of severity during exercise in MR or increased valve gradients with exercise in AS that have previously been shown to predict outcome (30, 33). In addition, we did not assess the role of global longitudinal strain post exercise, which may identify a higher-risk cohort of patients with VHD (34). Although feasible, these markers are much more difficult to assess particularly during exercise and as above requires the use of a semi-supine tilting ergometer to perform reliably. Furthermore, it is difficult to compare these variables across different types of valve lesions. Instead, we chose to focus on easily measurable and directly comparable variables such as exercise capacity, BP rise with exercise, and PAP. Although we also assessed the presence of CR, defined by a change in EF post exercise, this was not predictive of adverse outcome. Measurement of exercise capacity, BP response to exercise and PAP is straightforward and hence more readily incorporated into clinical practice. A further limitation is that although the total number of patients within the study is reasonable, the number of adverse events during follow-up was lower than expected. This may reflect the overall low-risk cohort of patients recruited within the study. Given the low rate of adverse events it was not possible to perform regression analysis to determine the effect of other predictors such as age and sex on adverse outcome. Although patients with an abnormal stress

echocardiogram were older than those with a normal stress echocardiogram, the patients within this cohort, most of whom had severe VHD, were typically younger than seen in many valve clinics due to the high prevalence of rheumatic fever. In addition, the number of patients within each valve group is relatively small and hence detailed comparison between valve lesions is not possible.

Conclusion

The clinical assessment of symptomatic status is unreliable and a significant number of patients with VHD who do not meet the criteria for surgery based on clinical assessment and resting echocardiography perform badly during exercise stress echocardiography. The finding of an abnormal exercise echo is predictive of an increased risk of death or hospitalization with heart failure the next 2 years. Exercise stress echocardiography or, if not available, exercise ECG should be considered as part of the routine follow-up of asymptomatic patients with VHD.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/ERP-15-0015>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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