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Rapid early rise in heart rate on treadmill exercise in patients with asymptomatic moderate or severe aortic stenosis: a new prognostic marker?

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ABSTRACT

Objective To examine the clinical significance and prognostic value of an early rapid rise in heart rate (RR-HR) in asymptomatic patients with moderate or severe aortic stenosis (AS).

Methods We retrospectively assessed the prospectively collected data from 306 patients (age 65±12 years, 33% women) with moderate (n=204) or severe AS (n=102) with a median follow-up of 25 months (mean 34.9±34.6 months). All had echocardiography and modified Bruce exercise treadmill tests (ETT). RR-HR was defined as achieving 85% target HR or ≥50% increase from baseline in the first 6 min. The outcome measures were revealed symptoms during ETT, aortic valve replacement (AVR) and all-cause mortality.

Results RR-HR occurred in 77 (25%) and 64% developed revealed symptoms (postive predictive value 64% and negative predictive value 84%). On univariate Cox regression analyses in patients with severe AS, RR-HR was associated with AVR (HR 3.32, 95% CI 2.03 to 5.45, p<0.001) but not with all-cause mortality (HR 0.04, 95% CI 0.13 to 9.21, p=0.798). In patients with moderate AS, RR-HR was associated with all-cause mortality (HR 2.67, 95% CI 1.09 to 6.56, p=0.032), but not with AVR (HR 1.35, 95% CI 0.92 to 1.98, p=0.127). These associations remained significant in multivariate Cox regression analyses after adjustment for age, sex, hypertension, coronary artery disease, abnormal blood pressure response, Doppler stroke volume and mean pressure gradient (both p<0.001).

Conclusions RR-HR was associated with the development of revealed symptoms. It predicted revealed symptoms on serial ETT, AVR in severe AS and all-cause mortality in moderate AS. RR-HR may be a useful new measure to define risk in AS.

INTRODUCTION

International guidelines recommend formal exercise testing for patients with apparently asymptomatic severe aortic stenosis (AS) because revealed symptoms are a class I indication for aortic valve replacement (AVR) and an abnormal blood pressure (BP) response a class IIa indication.[1] Despite this exercise testing is underutilised,[2] partly for logistic reasons and partly from concern over safety although we recently showed that the risk of adverse events is close to zero.[3] There is also lingering concern that revealed symptoms are subjective and less valid than spontaneous symptoms taken from the history.[4] However, we showed that the stroke volume fell during early exercise in those developing symptoms but rose in those remaining symptom free.[5] The cardiac index was similar in the two groups suggesting that an augmented rise in heart rate (HR) in those deveanloping symptoms occurred as an adaptive response to maintain cardiac output.[5] It is therefore possible thatan early rapid rise in HR (RR-HR) may identify patients who develop symptoms later in exercise. It is our practice to exercise patients with moderate AS since their prognosis may not be benign.[6–8] We recently showed that symptoms were revealed in nearly 20% with moderate AS and 40% with severe AS.[3] The aim of the present study was therefore to determine in patients with moderate or severe AS whether: (1) an early RR-HR during an exercise treadmill test (ETT) preceded the development of revealed symptoms later in the test and (2) whether it predicted events during follow-up.

METHODS

Patient population

The Exercise Testing in Aortic Stenosis (EXTAS) study is a retrospective cohort study of data collected prospectively between January 2000 and May 2017.[3] A total of 651 patients aged >18 years with moderate (effective orifice area 1.0–1.5 cm^2) or severe (effective orifice area <1.0 cm^2) AS[9 10] were assessed in a specialist heart valve clinic at Guy's and St Thomas' Hospital. All patients underwent an ETT at presentation and most were

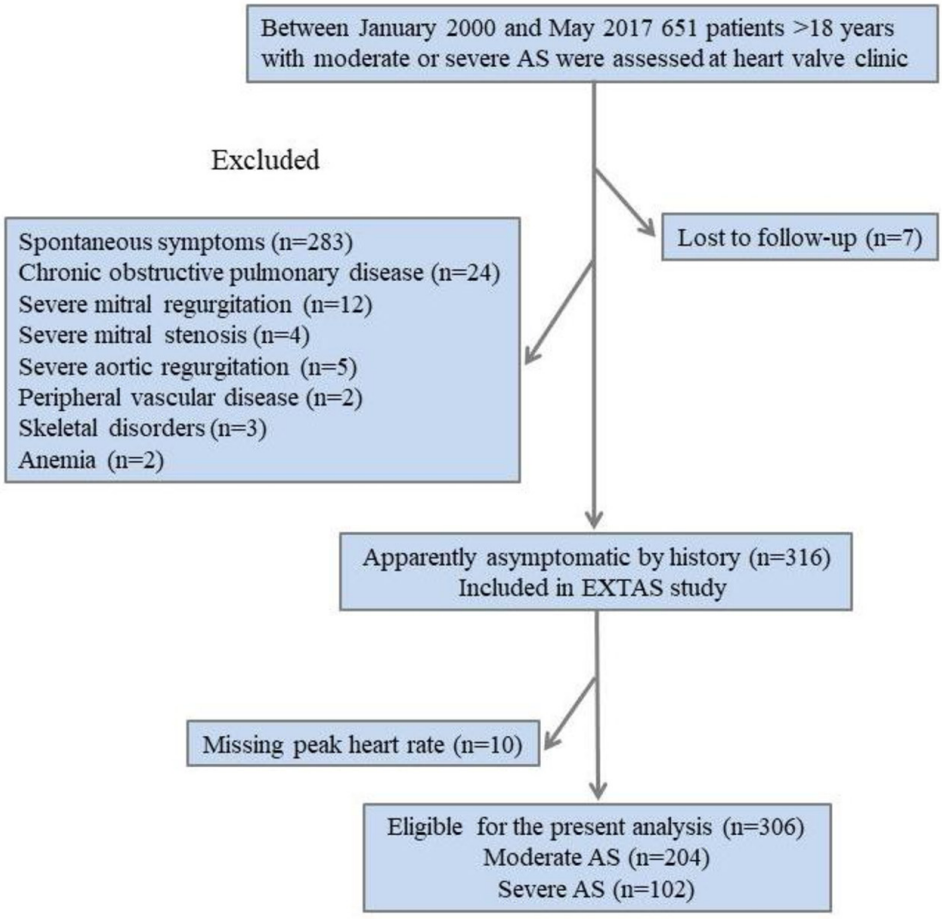

Figure 1 Flow chart of the study population. AS, aortic stenosis; EXTAS, Exercise Testing in Aortic Stenosis.

restudied when their AS crossed the threshold between moderate and severe, and thereafter annually. Baseline data including clinical characteristics, ETT and echocardiography was used in the present analysis. A total of 283 patients were excluded from the study because of the presence of spontaneous symptoms justifying surgery, 21 patients due to more than moderate disease of other valves (12 patients with severe mitral regurgitation, four with severe mitral stenosis and five with severe aortic regurgitation), 24 owing to chronic obstructive pulmonary disease, two to peripheral vascular disease, three to skeletal disorders and two to anaemia. The remaining 316 patients (49%) were apparently asymptomatic on the history and eligible for ETT. Of these, 10 patients were excluded due to an unrecorded peak HR, leaving 306 available for the present analysis (figure 1). Hypercholesterolaemia was defined as treatment with lipid-lowering drugs. Obesity was defined as body mass index ≥30 kg/m^2. Resting clinic BP prior to ETT was measured with a semiautomatic device with the patient resting for 5–10 min in the sitting position. Hypertension was defined from a history of elevated BP values, past or current treatment with antihypertensive agents or a BP at the baseline clinic visit >140/90 mm Hg.[3] The double product (rate pressure product), a prognostically validated index of myocardial oxygen consumption, was defined as systolic BP multiplied by the peak HR.[11] Prior to surgical or transcutaneous AVR, all patients underwent conventional coronary angiography. Coronary artery disease was defined as previous myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, or angiographic evidence of coronary artery disease (>70% stenosis of one or more main epicardial artery). The study was managed and conducted in accordance with the Declaration of Helsinki and latest Good Clinical Practice guidelines.

ETT protocol

ETTs were performed according to American College of Cardiology/American Heart Association practice guidelines using a Bruce protocol modified by two warm-up stages so most patients at any age can exercise for 9 min which is equivalent to 3 min of a standard Bruce protocol.[12 13] The test was stopped prematurely for symptoms (significant breathlessness or any chest constriction or dizziness), progressive ventricular ectopy >3 beats, new atrial fibrillation, a sustained fall in systolic BP >20 mm Hg from the previous stage or more than 5 mm ST segment depression.[3] Significant symptoms (breathlessness, chest tightness, dizziness, the presence of distress, inability to speak and facial pallor) were differentiated clinically from physiological breathlessness at high workload.[3] An

abnormal BP response was defined as a sustained fall in systolic BP ≥20 mm Hg below the previous stage or baseline level.[14] The following measures were recorded: exercise time, exercise capacity in metabolic equivalents (METs), maximum systolic and diastolic BP, ST segment depression in mm. One MET is defined as the energy expended at rest which is equal to a body oxygen consumption of nearly 3.5 mL/kg of body weight for an average adult.[15] METs were calculated from the speed and gradient of the treadmill by the machine's software using the formula (METS=((speed×0.1)+(gradient/100×1.8×speed)+3.5)/3.5), where speed is measured in m/s and gradient as a percentage. Predicted peak HR was calculated according to the Astrand formula (220-age).[16] An early RR-HR during ETT was defined as achieving at least 85% of target HR or ≥50% increase from baseline within the first 6 min. Six minutes was chosen because it represents the end of the warm-up phase. However, there is little in the literature to guide this definition.

Transthoracic echocardiography

Echocardiographic data were obtained using commercially available ultrasound systems (Vingmed system 5, 7, 9 GE Medical, Milwaukee, Wisconsin, USA, or a Philips 'Epiq 7' cardiac ultrasound machine). The recommended methodology for the assessment of severity of AS, left ventricular (LV) wall thicknesses, chamber dimensions, stroke volume and ejection fraction was standardised as part of our retrospective analysis and measured according to prevailing joint European and US guidance.[9 10 17] LV hypertrophy was diagnosed as LV mass >46.7 g/$m^{2.7}$ in women and 49.2 g/$m^{2.7}$ in men, respectively, and relative wall thickness as 2 x LV posterior wall thickness/LV internal radius at end-diastole, and considered increased if ≥0.430.[17] The ratio of PP to SVi (PP/SVi) was used as an indirect measure of systemic arterial stiffness.[18] LV stroke work was defined as: systolic BP·SV converted to gram-metres by multiplying by 0.0144).[19] Valvuloarterial impedance (Z_{va}), a measure of resting global LV afterload was calculated as: (systolic BP+mean aortic pressure gradient)/stroke volume index.[20]

Study end points

Outcomes were revealed symptoms on ETT, AVR (either surgical or via a transcatheter approach) and all-cause mortality. Indications for AVR on patients asymptomatic on the history were revealed symptoms on ETT or spontaneous symptoms developing during follow-up. Follow-up time was calculated from the baseline ETT until AVR, death or censoring on 19 September 2017.

Statistical analyses

SPSS V.24.0 was used for data management and statistical analyses. Continuous variables were presented as mean±SD and categorical variables as percentages. Comparison between groups was by a Student's t-test or χ^2 test for parametric and non-parametric data as appropriate. Correlates of RR-HR during ETT were tested in univariate and multivariate logistic regression analyses. Bivariate associations between continuous variables were performed with Pearson's correlation coefficients. Kaplan-Meier curves were used to examine cumulative event rates and the difference between groups was tested using a log-rank test. Cox proportional hazard models were used to assess the association between RR-HR and outcomes. A p value of <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

The mean age of the study population was 65±12 years and 67% were men and 33% women. At baseline, 204 (66.7%) had moderate AS and 102 (33.3%) had severe AS. Patients with severe AS were older, but did not differ in body surface area, smoking status and clinic BP compared with patients with moderate AS (table 1). Patients with moderate AS were more likely to have coronary artery disease and hypercholesterolaemia, while there was no difference in the proportion of other comorbidities. ACE inhibitors were more frequently used by patients with severe AS (table 1). LV ejection fraction, systemic arterial stiffness (pulse pressure/stroke volume index), stroke work and the prevalence of LV hypertrophy were comparable in both groups, while valvuloarterial impedance was significantly higher in patients with severe AS (table 1).

Exercise treadmill parameters

There were no significant differences in exercise measurements between patients with moderate and severe AS (table 2).

Symptoms were revealed in 87 (28.4%) patients more frequently with severe than moderate AS (36.3 vs 24.5%; p=0.032). Women had shorter exercise duration than men (8.2±4.2 vs 10.4±4.3 min, p<0.001) and lower METs (7.6±4.3 vs 9.2±4.5; p=0.003), but achieved similar peak HR (134±27 vs 134±24 bpm; p=0.986).

Early RR-HR

An early RR-HR occurred in 77 (25%) patients. These were older and had a higher proportion of females, obesity and hypertension than those with a normal HR response (table 3).

Z_{va} was significantly higher, left atrium was larger and aortic root was smaller in the RR-HR group, but there were no differences in the severity of AS, stroke volume index, resting HR or LV mass between the groups. Patients with RR-HR had shorter exercise times than those with a normal HR response (5.3±2.3 min vs 11.2±3.9 min; p<0.001) and 49 (64%) developed limiting symptoms later in the same exercise test. In a univariate logistic regression analysis, beta blocker treatment was not associated with RR-HR (OR 0.67, 95% CI 0.30 to 1.45, p=0.298). The positive predictive value (PPV) of RR-HR for revealed symptoms was 64% and negative predictive value (NPV) 84%. Of those with revealed symptoms, 56% had RR-HR (PPV 56% and NPV 87%).

Table 1 Baseline clinical and echocardiographic characteristics of the study population according to the severity of AS

	Total (n=306)	Moderate AS (n=204)	Severe AS (n=102)	P value
Demographic and clinical data				
Age, years	65±12	64±12	69±11	<0.01
Male, female %	67, 33	70, 30	61, 39	0.134
Obesity	80 (26%)	55 (27%)	25 (25%)	0.944
Smokers	147 (48%)	96 (47%)	51 (50%)	0.586
Coronary artery disease	152 (50%)	118 (58%)	36 (35%)	0.001
Diabetes mellitus	43 (14%)	31 (15%)	12 (12%)	0.409
Previous stroke or transient ischaemic attack	37 (12%)	28 (14%)	9 (9%)	0.233
Atrial fibrillation	43 (14%)	21 (10%)	22 (21%)	0.056
Hypercholesterolaemia	202 (66%)	144 (71%)	58 (57%)	0.029
Clinic systolic BP, mm Hg	142±19	140±18	145±21	0.052
Clinic diastolic BP, mm Hg	82±13	81±12	86±11	0.001
Hypertension	223 (73%)	146 (72%)	77 (75%)	0.565
Antihypertensive treatment	199 (65%)	133 (65%)	66 (65%)	0.992
Beta blockers	101 (33%)	65 (32%)	36 (35%)	0.805
Diuretics	92 (30%)	63 (31%)	29 (28%)	0.581
Calcium blockers	80 (26%)	49 (24%)	31 (29%)	0.618
ACE inhibitors	60 (20%)	49 (24%)	11 (11%)	0.036
ARB inhibitors	37 (12%)	27 (13%)	10 (10%)	0.447
Alpha blockers	25 (8%)	19 (9%)	6 (6%)	0.368
Echocardiographic data				
LV end-diastolic diameter, cm	4.6±0.7	4.6±0.6	4.5±0.7	0.301
Interventricular septal thickness, cm	1.29±0.26	1.27±0.25	1.35±0.28	<0.018
Posterior wall thickness, cm	1.12±0.22	1.10±0.20	1.15±0.26	<0.036
LV mass index, g/m$^{2.7}$	52±17	50±16	55±20	0.098
LV hypertrophy	165 (54%)	106 (52%)	60 (59%)	0.357
LV ejection fraction %	60±7	60±7	60±6	0.821
Peak aortic jet velocity, m/s	3.7±0.6	3.4±0.5	4.4±0.5	<0.001
Mean aortic gradient, mm Hg	34±13	28±8	47±12	<0.001
Effective orifice area, cm^2	0.94±0.22	1.04±0.20	0.74±0.14	<0.001
Doppler stroke volume index, mL/m^2	43±13	44±15	41±10	0.206
PP/SVi, mm Hg/mL/m^2	1.46±0.57	1.44±0.56	1.50±0.60	0.512
Z_{va}, mm Hg/mL/m^2	4.37±1.25	4.08±1.20	4.85±1.19	<0.001
LV stroke work, g-m/bpm	159.9±52.7	161.3±56.7	157.9±44.7	0.606

ARB, angiotensin II receptor blocker; AS, aortic stenosis; BP, blood pressure; LV, left ventricular; PP/SVi, pulse pressure/stroke volume index; Z_{va}, valvuloarterial impedance; bpm, beats per minute.

Predictors of early RR-HR during ETT

Univariate predictors of RR-HR are presented in table 4. In a multivariate logistic regression analysis, older age, female sex, obesity and lower LV ejection fraction remained significant predictors of RR-HR (table 4). In the subset of patients without revealed symptoms, RR-HR was associated with female gender, coronary artery disease and lower LV ejection fraction (table 4).

The association of early RR-HR during ETT with outcomes

During a mean follow-up period of 34.9±34.6 months, 254 (84%) patients experienced an event, 226 AVR and 28 all-cause death. AVR occurred in 164 (72%) of 229 with a normal HR response and in 62 (81%; p=0.151) of 77 with RR-HR. Death occurred in 20 (8.7%) with a normal HR response and in eight (10.4%; p=0.679) with RR-HR. On univariate Cox regression analyses in the entire study population, RR-HR was associated with AVR (HR 1.75, 95% CI 1.30 to 2.34; p<0.001), but not with all-cause mortality (HR 1.97, 95% CI 0.87 to 4.48; p=0.106). In the total population, after adjustment for age, sex, hypertension, coronary artery disease, abnormal BP response, Doppler stroke volume and

Table 2 Baseline resting and exercise treadmill test measures of the study population according to the severity of AS

	Total (n=306)	Moderate AS (n=204)	Severe AS (n=102)	P value
Pre-ETT heart rate, bpm	77±15	76±15	78±16	0.471
Pre-ETT systolic BP, mm Hg	141±19	141±19	143±19	0.395
Pre-ETT diastolic BP, mm Hg	85±11	84±11	86±11	0.098
Peak heart rate, bpm	134±25	134±26	134±23	0.802
Peak systolic BP, mm Hg	166±26	167±26	165±25	0.401
Peak diastolic BP, mm Hg	90±16	90±16	91±16	0.441
Abnormal BP response	113 (37%)	72 (36%)	42 (41%)	0.388
Target heart rate achieved, %	86±15	85±15	89±14	0.080
Rapid early rise in heart rate	77 (25%)	49 (24%)	28 (28%)	0.452
Exercise duration, min	9.7±4.4	9.8±4.7	9.6±3.6	0.648
METs	8.5±4.5	9.0±4.8	8.0±3.9	0.063
Revealed symptoms	87 (28.4%)	50 (24.5%)	37 (36.3%)	0.032
Double product, mm Hg · bpm	1.90±0.46	1.91±0.48	1.90±0.43	0.874

AS, aortic stenosis; BP, blood pressure; ETT, exercise treadmill test; METs, metabolic equivalents; bpm, beats per minute.

mean pressure gradient, RR-HR remained an independent predictor of AVR (HR 2.15, 95% CI 1.44 to 3.22, p<0.001) (table 5).

The symptom-free survival in patients with RR-HR was significantly lower at 1 and 2 years compared with those with normal HR response (figure 2A).

To determine whether RR-HR had prognostic use independent of revealed symptoms, we examined the subset of patients who were asymptomatic on the baseline ETT. RR-HR was a significant predictor of revealed symptoms developing spontaneously or on subsequent follow-up ETTs both in univariate (HR 1.82, 95% CI 1.09 to 3.05, p=0.022) and multivariate Cox regression models (HR 2.14, 95% CI 1.07 to 4.27, p=0.030) (table 5). Symptom-free survival at 1 and 2 years in this subgroup was also significantly lower compared with patients with a normal HR response (figure 2B).

We further analysed patients with moderate and severe AS separately using univariate Cox regression models. In patients with moderate AS, RR-HR was associated with all-cause mortality (HR 2.67, 95% CI 1.09 to 6.56, p=0.032) and significantly lower 1 and 2 years freedom from all-cause mortality in Kaplan-Meier survival plots (figure 2C), but not with AVR (HR 1.35, 95% CI 0.92 to 1.98, p=0.127). By contrast, in patients with severe AS, RR-HR was associated with AVR (HR 3.32, 95% CI 2.03 to 5.45, p<0.001) (figure 2D), but not with all-cause mortality (HR 0.04, 95% CI 0.13 to 9.21, p=0.798). Similarly, in multivariate Cox regression analyses, the association between RR-HR and all-cause mortality in patients with moderate AS and between RR-HR and AVR in severe AS remained significant after adjustment for age, sex, hypertension, coronary artery disease, abnormal BP response, Doppler stroke volume and mean pressure gradient (table 6).

DISCUSSION

Exercise testing is recommended in asymptomatic severe AS to reveal symptoms or detect a BP drop which are class I and class IIa indications for AVR.[1] We now describe a new exercise measurement with additional important prognostic implications, an early rapid rise in heart rate (RR-HR). This was associated with revealed symptoms later in the same test and predicted AVR in patients with severe AS and all-cause death in patients with moderate AS.

A RR-HR was associated with the development of symptoms later in the test. There is remaining uncertainty over the possible subjectivity of revealed symptoms as an indication for surgery. However, an associated haemodynamic change helps to corroborate its validity. We previously showed that the stroke volume falls at the start of exercise and before symptoms develop in patients with severe AS.[5] Others have shown a failure of LV ejection fraction to rise as an adverse prognostic sign.[19] We suggest that RR-HR is a compensatory mechanism to maintain cardiac output. Although the PPV for revealed symptoms was only 64%, the NPV was 84% suggesting that in the presence of equivocal symptoms a normal HR response might provide reassurance. Conversely, if the result of ETT based on symptoms is inconclusive, a RR-HR may strengthen the clinical significance of symptoms and indicate a true positive ETT.

Clearly, patients with revealed symptoms have an indication for AVR. However, in patients who remained asymptomatic on baseline ETT, RR-HR predicted the development of revealed symptoms on serial testing suggesting that it has additional prognostic potential and might be used to identify a group for more frequent follow-up.

It was in patients with moderate AS that RR-HR might be most useful. This group is seen as having a benign

Table 3 Baseline clinical, echocardiographic and ETT test data of the study population according to rate of heart rate rise during ETT

	Total (n=306)	Normal HR response (n=229)	Rapid early rise in HR (n=77)	P value
Demographic and clinical data				
Age, years	65±12	64±12	70±10	<0.001
Male, Female %	67, 33	70, 30	56, 44	0.024
Body mass index, kg/m^2	28±10	27±4	31±17	0.060
Obesity	80 (26%)	41 (18%)	35 (46%)	<0.001
Coronary artery disease	152 (50%)	106 (46%)	46 (60%)	0.062
Diabetes mellitus	43 (14%)	28 (12%)	15 (20%)	0.093
Hypercholesterolaemia	202 (66%)	148 (65%)	54 (71%)	0.326
Clinic systolic BP, mm Hg	142±19	141±19	144±20	0.225
Clinic diastolic BP, mm Hg	82±13	82±12	82±15	0.844
Hypertension	223 (73%)	160 (70%)	63 (82%)	0.027
Beta blockers treatment	101 (33%)	80 (35%)	21 (27%)	0.296
Echocardiographic data				
Aortic root diameter, cm	3.3±0.5	3.4±0.5	3.2±0.4	0.028
Left atrium diameter, cm	3.8±0.7	3.7±0.7	4.0±0.7	0.006
LV end-diastolic diameter, cm	4.6±0.7	4.6±0.6	4.5±0.7	0.234
LV mass index, g/m$^{2.7}$	52±17	52±16	51±20	0.320
LV ejection fraction, %	60±7	61±7	58±7	0.030
Mean aortic gradient, mm Hg	34±13	34±12	36±17	0.293
Effective orifice area, cm^2	0.94±0.22	0.95±0.22	0.91±0.22	0.213
Doppler stroke volume index, mL/m^2	43±13	43±12	41±15	0.293
Z_{va}, mm Hg/mL/m^2	4.37±1.25	4.25±1.17	4.70±1.43	0.034
ETT data				
Pre-ETT heart rate, bpm	77±15	76±14	79±16	0.218
Pre-ETT systolic BP, mm Hg	141±19	141±19	143±18	0.290
Pre-ETT diastolic BP, mm Hg	85±11	85±11	85±12	0.860
Peak heart rate, bpm	134±25	134±27	131±19	0.257
Peak systolic BP, mm Hg	166±26	166±26	167±26	0.838
Peak diastolic BP, mm Hg	90±16	90±16	90±18	0.924
Target heart rate achieved, %	86±15	86±16	87±12	0.377
Abnormal BP response	113 (37%)	83 (36)	30 (39)	0.763
Exercise duration, min	9.7±4.4	11.2±3.9	5.3±2.3	<0.001
METs	8.5±4.5	9.9±4.4	5.0±2.5	<0.001
Revealed symptoms	87 (28.4%)	38 (16.6%)	49 (63.6%)	<0.001

BP, blood pressure; ETT, exercise treadmill test; LV, left ventricular; METs, metabolic equivalents; Z_{va}, valvuloarterial impedance; bpm, beats per minute.

prognosis but we showed that RR-HR predicted death even when corrected for age, gender, hypertension, coronary artery disease, abnormal BP response, Doppler stroke volume and mean pressure gradient. We and others have previously shown that 20% of patients with moderate AS develop revealed symptoms compared with 40% with severe AS.[3 21] Patients with moderate AS have a significantly increased risk of myocardial infarction at the time of non-cardiac surgery, as demonstrated by Agrawal *et al*, 2.5% compared with 3.5% for severe AS and 1.0% for controls.[7] This may partly be because of underestimation of the grade of AS or because of low aortic valve compliance or high combined LV outflow impedance. However, the presence of associated coronary artery disease is likely the most important factor. Patients with apparently moderate AS who are not exercised to reveal symptoms would not be considered for AVR leaving them at risk of dying from more severe AS

Table 4 Covariates of rapid early rise in heart rate in univariate and multivariate logistic regression analyses

	Total study population (n=306)				Patients without revealed symptoms during ETT1 (n=219)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, year	1.05 (1.02 to 1.08)	<0.001	1.07 (1.03 to 1.12)	0.002	1.04 (1.01 to 1.089	0.024	0.99 (0.93 to 1.06)	0.817
Female sex	1.84 (1.08 to 3.13)	0.025	2.43 (1.08 to 5.46)	0.010	4.03 (1.73 to 9.25)	0.001	6.88 (1.42 to 33.22)	0.016
BMI, kg/m^2	1.11 (1.04 to 1.18)	0.002	–	–	1.11 (1.01 to 1.23)	0.037	–	–
Obesity	3.89 (2.07 to 7.28)	<0.001	4.96 (2.13 to 11.57)	<0.001	3.73 (1.40 to 9.96)	0.009	1.32 (0.27 to 6.49)	0.732
Hypertension	2.05 (1.07 to 3.90)	0.029	1.04 (0.40 to 2.72)	0.935	2.64 (0.88 to 7.94)	0.085	–	–
Coronary artery disease	1.78 (0.97 to 3.25)	0.063	–	–	3.63 (1.11 to 11.87)	0.033	8.60 (1.33 to 55.51)	0.024
EOA, cm^2	0.46 (0.13 to 1.56)	0.213	–	–	2.28 (0.39 to 13.36)	0.362	–	–
Lower LV FS, %	1.06 (1.00 to 1.11)	0.036	–	–	1.07 (1.00 to 1.14)	0.037	–	–
Lower LV EF, %	1.05 (1.01 to 1.10)	0.013	1.09 (1.02 to 1.16)	0.018	1.07 (1.01 to 1.13)	0.032	1.12 (1.01 to 1.24)	0.043
Lower Doppler SV, mL	1.01 (0.99 to 1.02)	0.453	–	–	1.03 (1.00 to 1.06)	0.054	–	–
LV mass index, g/m$^{2.7}$	0.99 (0.98 to 1.02)	0.330	–	–	1.00 (0.97 to 1.03)	0.902	–	–
Z_{va}, mm Hg/mL/m^2	1.32 (1.02 to 1.70)	0.038	1.14 (0.86 to 1.51)	0.374	1.26 (0.83 to 1.92)	0.286	–	–

BMI, body mass index; EF, ejection fraction; EOA, effective orifice area; FS, fractional shortening; LV, left ventricular; METs, metabolic equivalents; SV, stroke volume; Z_{va}, valvuloarterial impedance.

Table 5 Multivariate Cox regression analyses for AVR in the total population and for the development of spontaneous or revealed symptoms on serial testing in patients who were asymptomatic on the baseline study

	Total study population (n=306) AVR		Asymptomatic on ETT (n=219) Revealed symptoms	
	HR (95% CI)	P value	HR (95% CI)	P value
Rapid early rise in heart rate	2.15 (1.44 to 3.22)	<0.001	2.14 (1.07 to 4.27)	0.03
Age, year	1.02 (1.00 to 1.03)	0.025	1.05 (1.02 to 1.08)	<0.001
Male sex	1.82 (1.22 to 2.73)	0.004	1.16 (0.66 to 2.01)	0.611
Hypertension	0.83 (0.56 to 1.24)	0.368	0.94 (0.47 to 1.91)	0.871
Doppler stroke volume, mL	1.00 (0.99 to 1.01)	0.354	1.00 (0.99 to 1.02)	0.570
Mean pressure gradient, mm Hg	1.05 (1.03 to 1.06)	<0.001	1.02 (0.99 to 1.02)	0.063
Abnormal blood pressure response	1.24 (0.86 to 1.80)	0.253	1.87 (0.93 to 3.79)	0.081
Coronary artery disease	0.99 (0.68 to 1.47)	0.993	0.88 (0.42 to 1.84)	0.940

AVR, aortic valve replacement; ETT, excercise treadmill test.

than realised or associated coronary artery disease or both. Death might occur spontaneously or at the time of non-cardiac surgery or a major trauma or illness for which the AS reduces cardiac reserve.[22] Our patients with moderate AS had a higher prevalence of hypercholesterolaemia and coronary artery disease and a comparable

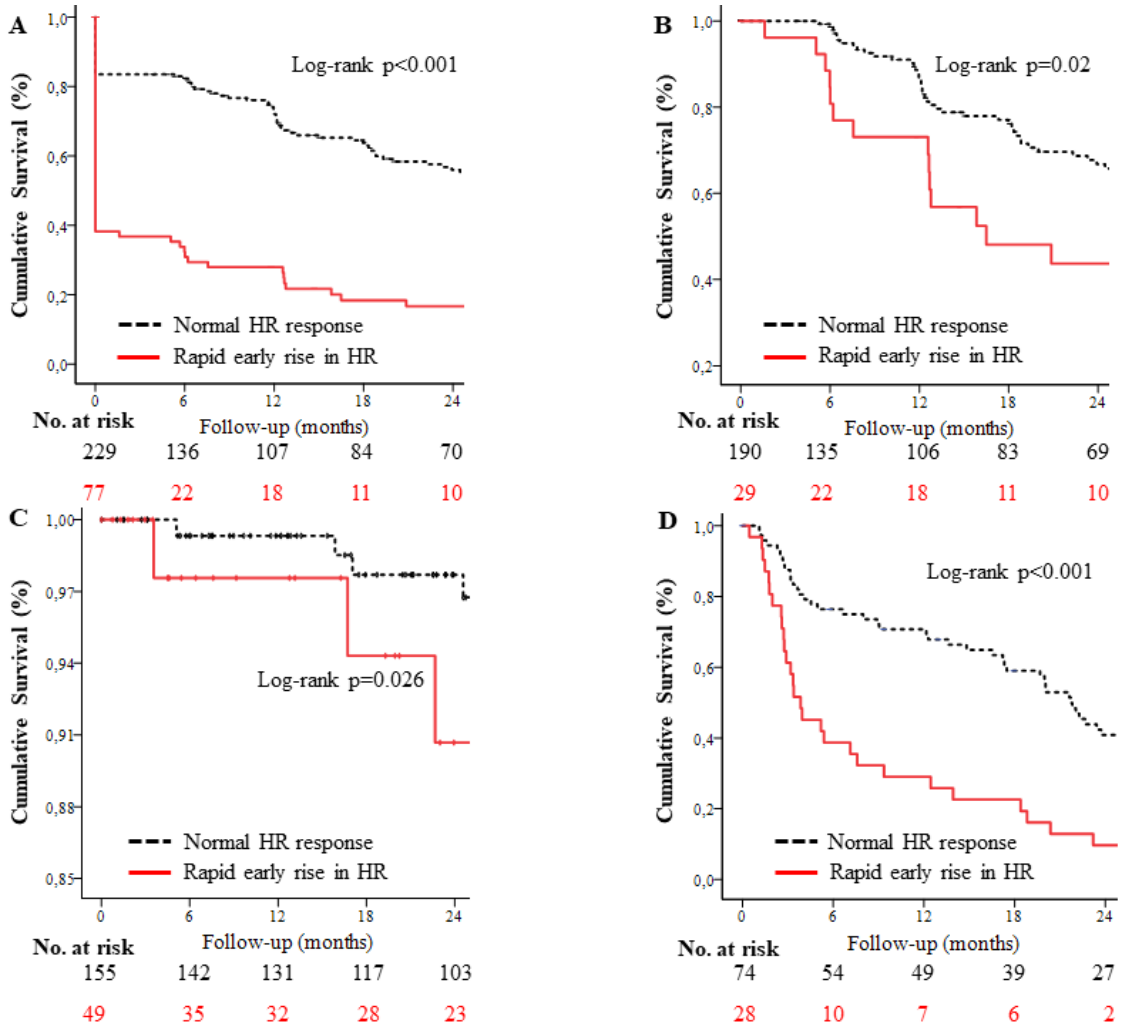

Figure 2 Kaplan-Meier curves showing the probability of symptom-free survival according to the rate of heart rate rise during exercise testing in (A) for the whole study population, and in (B) for the subset of patients who did not develop revealed symptoms on the baseline exercise test and (C) shows event-free survival from all-cause mortality in patients with moderate aortic stenosis and (D) shows event-free survival from aortic valve replacement in patients with severe aortic stenosis.

Table 6 Multivariate Cox regression analyses for all-cause mortality in patients with moderate AS or AVR in patients with severe AS

	Moderate AS (n=204)		Severe AS (n=102)	
	All-cause mortality		AVR	
	HR (95% CI)	P value	HR (95% CI)	P value
Rapid early rise in heart rate	16.02 (1.83 to 140.02)	0.012	3.21 (1.70 to 6.08)	<0.001
Age, year	1.13 (1.01 to 1.23)	0.044	1.00 (0.97 to 1.03	0.897
Male sex	8.37 (0.43 to 165.06)	0.162	2.16 (1.08 to 4.29)	0.029
Hypertension	0.11 (0.01 to 2.11)	0.143	0.90 (0.44 to 1.87)	0.781
Doppler stroke volume, mL	1.00 (0.95 to 1.05)	0.990	0.99 (0.98 to 1.01)	0.733
Mean pressure gradient, mm Hg	1.17 (1.00 to 1.36)	0.045	1.03 (1.00 to 1.05)	0.043
Abnormal blood pressure response	0.19 (0.02 to 2.24)	0.185	1.86 (1.00 to 3.44	0.049
Coronary artery disease	14.63 (0.42 to 514.15)	0.140	1.35 (0.74 to 2.47)	0.333

AS, aortic stenosis; AVR, aortic valve replacement.

prevalence of hypertension-mediated organ damage compared with those with severe AS. These factors are also associated with a higher rate of progression of AS.[23] A RR-HR might therefore be an indication for further evaluation of patients with apparently moderate AS, for example, with stress echocardiography looking for wall motion abnormalities.

There is little previously published work for comparison. In patients with coronary artery disease, a RR-HR in the first 1 min of individualised bicycle exercise defined as ≥12 bpm above the median increase predicted a higher risk of death and non-fatal myocardial infarction than in those with a normal rise in HR.[24] An excessive HR increase in response to mental stress before exercise in the general population is also associated with a relatively high risk of sudden death and non-cardiac deaths.[25] By contrast, a study using standardised treadmill exercise similar to our methodology showed that HR-RR was associated with a relatively low risk of cardiac events in patients referred for clinical exercise testing including some with coronary artery disease.[26] There is little comparable literature in patients with AS as studies have mainly focused on symptoms and BP response.[14 21 27–29] We showed several other risk factors including higher age, male gender and mean pressure gradient were associated with all-cause mortality or risk of AVR as already shown.[30]

Limitations

This was a retrospective analysis of prospectively collected clinical information but the information on hospital databases was close to complete. We did not perform routine stress echocardiography to look for changes in transaortic gradient and the development of wall motion abnormalities or pulmonary hypertension. The definition of RR-HR was arbitrary but based on clinical judgement, and it is possible that better thresholds could be determined using a larger database.

CONCLUSIONS

An early RR-HR during ETT was associated with the development of revealed symptoms later in the same ETT. In patients who remained asymptomatic on exercise, it predicted revealed symptoms on serial ETT and predicted AVR in severe AS and all-cause mortality in moderate AS. We believe this new measure should be included with symptom onset and BP response in research studies and it may in the future help decide on the need for surgery or further investigation.

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