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Determinants of an abnormal response to exercise in patients with asymptomatic valvular aortic stenosis

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Aim Patients with asymptomatic aortic stenosis (AS) and abnormal haemodynamic responses to exercise testing are at increased risk of cardiac events. This study assesses the Doppler echocardiographic determinants of a positive exercise test in a cohort of asymptomatic patients with AS.
Methods and results One hundred and twenty-eight patients with AS underwent quantitative Doppler echocardiographic measurements at rest and during exercise test. Of these patients, 60 had an abnormal response to exercise. Two independent determinants of an abnormal exercise response were selected in multivariate analysis: a larger increase in mean transaortic pressure gradient ($P = 0.00014$) and a limited contractile reserve—latent left ventricular dysfunction—as indicated by smaller changes in ejection fraction ($P = 0.0002$). Limiting symptoms were associated with greater increase in mean transaortic pressure gradient, smaller changes in systolic blood pressure and a lower ejection fraction at peak exercise. The increase in pressure gradient was associated with smaller exercise-induced changes in aortic valve area and in ejection fraction and new or worsening mitral regurgitation during exercise.
Conclusion Abnormal responses to exercise in asymptomatic AS patients are mediated by a larger increase in mean transaortic pressure gradient and/or a limited contractile reserve characterized by an inadequate increase in ejection fraction at exercise.

Introduction

Valvular aortic stenosis (AS) is a prevalent condition and a progressive disease. When symptoms appear, usually after a long asymptomatic period, prompt surgical replacement of the aortic valve is warranted.[1] The risk of sudden death is very low in asymptomatic patients, even with severe AS.[2–4] It may however occur soon after the onset of symptoms[5] or if the waiting period for surgery is too long.[6] Ideally, the surgical decision should be made quickly after the emergence of symptoms. It is clinically important to identify patients who are falsely classified as asymptomatic and to predict whether an asymptomatic patient with AS might rapidly become symptomatic. In this situation, exercise testing is safe and provides better risk stratification than resting echocardiography.[7,8] It allows the identification of a subset of asymptomatic patients with AS at higher risk of clinical deterioration and adverse outcome during followup.[9–11] An abnormal response to exercise has thus been considered for use in referring asymptomatic patients with severe AS for aortic valve replacement.[12,13] However, a recent European survey revealed that few patients with asymptomatic AS are submitted to an exercise test.[14] The determinants of a positive exercise test have never been examined. We therefore prospectively performed exercise Doppler echocardiography in asymptomatic patients with AS to identify which parameters were associated with an abnormal response to exercise.

Material and methods

Patients

We prospectively included 136 consecutive patients who met the following criteria: significant valvular AS with an aortic valve area $\leq$1.0 cm^2, no symptoms according to history taken by the referring physician, normal left ventricular (LV) ejection fraction ($\geq$55%) as calculated by two-dimensional echocardiography and capability to perform an exercise test. Eight patients who developed significant myocardial ischaemia on exercise echocardiography (new regional wall motion abnormalities) were excluded from the final study analysis. None of the remaining patients had the following exclusion criteria: more than trivial aortic regurgitation, intraventricular

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conduction abnormality and significant arrhythmias including atrial fibrillation. The mean age was 69 ± 11 years (range 41–85 years). Calcific degenerative AS was observed in 121 of the 128 patients (94.5%); AS was the consequence of rheumatic fever in the 7 other patients. A history of arterial hypertension was noted in 57 patients, 36 patients were current smokers, 51 had dyslipidaemia and 26 were diabetic. All patients gave informed consent and the study was approved by the hospital ethics committee.

Exercise testing

Symptom-limited exercise testing was performed on a tilting exercise table. The initial workload of 25 W was maintained for 2 min and the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded at rest and every 2 min during exercise. Exercise test was interrupted promptly when age related maximum heart rate was reached or in case of typical chest pain, limiting breathlessness, dizziness, muscular exhaustion, hypotension (drop in systolic blood pressure ≥20 mmHg) or significant ventricular arrhythmia. Abnormalities in the ST segment were no reason to stop the stress exam. The test was considered abnormal if the patient presented ≥1 of the following criteria: angina, evidence of dyspnoea, dizziness, syncope or near-syncope, ≥2 mm ST segment depression in comparison to baseline levels, rise in systolic blood during exercise <20 mmHg or a fall in blood pressure and complex ventricular arrhythmias (ventricular tachycardia, more than 4 premature ventricular complexes in a row).[13]

Exercise Doppler echocardiography

Echocardiographic examinations were performed continuously during exercise in a semi-supine position using a VIVID 7 ultrasound machine (General Electric Healthcare, Little Chalfont, UK). All echocardiographic and Doppler data were obtained at rest and at peak exercise and were stored on optical disk for off-line analysis. For each measurement, at least two cardiac cycles were averaged. Continuous wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation.[2] Aortic velocities were recorded during test and at peak exercise. Aortic valve area was calculated from the continuity equation.[3] LV end-diastolic and end-systolic volumes and ejection fraction were measured by the biapical Simpson disk method.

Statistical analysis

Continuous variables are expressed as mean ± SD. Student's *t*-test was used to assess differences between mean values and categorical variables were compared with chi-square test and Fisher's exact test when appropriate. To detect independent predictors of a positive exercise test, a logistic multivariate analysis was performed (Statistica version 6). Receiver-operator characteristic curve analysis was used to determine the cut-off values that best distinguished the issues. $P < 0.05$ was considered significant.

Results

Baseline and exercise Doppler echocardiography

In baseline conditions, aortic valve area ranged from 0.45 to 1.0 cm^2 (mean 0.83 ± 0.14 cm^2) and mean transaortic pressure gradient ranged from 26 to 81 mmHg (mean 41 ± 12 mmHg) (*Figure 1*). Mean LV ejection fraction was 67 ± 8% (range 55–85%). During test, heart rate and systolic blood pressure increased significantly ($P < 0.0001$). Exercise-induced changes in peak and mean transvalvular pressure gradients ranged from −18 to +61 mmHg (mean 20 ± 16 mmHg) and from −9 to 42 mmHg (mean 14 ± 10 mmHg), respectively. Changes in calculated aortic valve area ranged from −0.33 cm^2 to +0.52 cm^2 (mean 0.08 ± 0.20 cm^2) and those in LV ejection fraction ranged from −18% to 19%

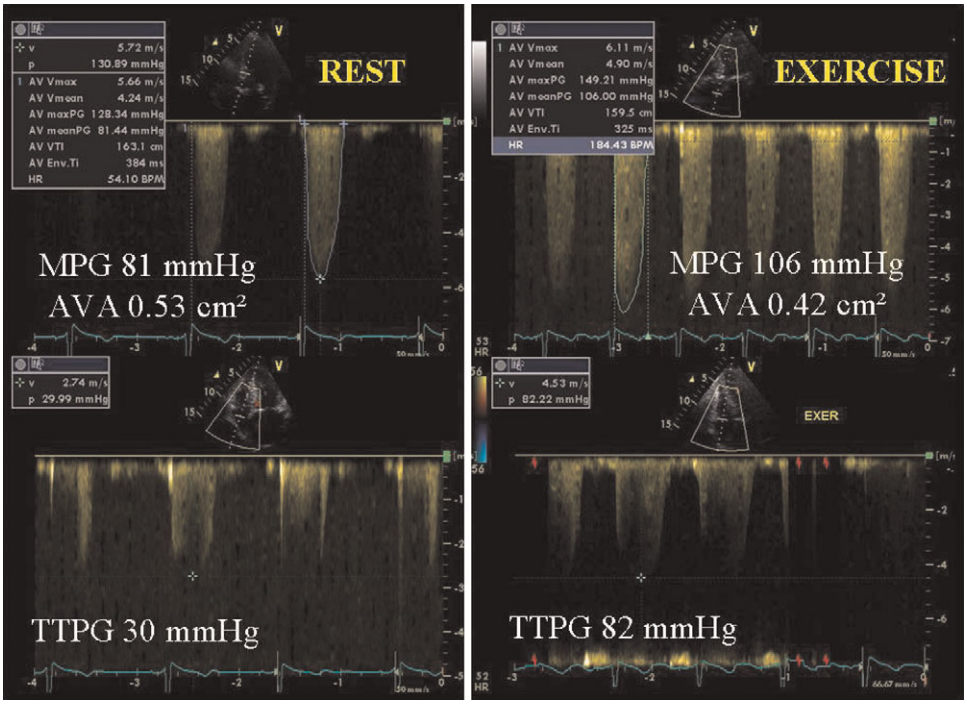

Figure 1 Example of a patient with abnormal exercise test in whom significant increase in mean transaortic pressure gradient (MPG) was observed during rest. Note that the aortic valve area (AVA) was smaller at peak exercise. This patient had also a marked rise in transtricuspid pressure gradient (TTPG), an estimate of systolic arterial pulmonary pressure.

Table 1 Predictors of abnormal exercise test

Variables	Normal test $n = 68$	Abnormal test $n = 60$	*P*
Rest haemodynamics and echo			
Heart rate (beats/min)	75 ± 11	74 ± 14	NS
Systolic arterial pressure (mmHg)	145 ± 20	143 ± 19	NS
LV end-diastolic volume (mL)	95 ± 28	99 ± 25	NS
LV end-systolic volume (mL)	34 ± 15	32 ± 11	NS
LV ejection fraction (%)	66 ± 7	68 ± 8	NS
Aortic valve area (cm^2)	0.85 ± 0.15	0.81 ± 0.14	NS
Peak aortic pressure gradient (mmHg)	61 ± 16	71 ± 22	0.004
Mean aortic pressure gradient (mmHg)	40 ± 9	43 ± 14	NS
Exercises–rest difference			
Heart rate (beats/min)	50 ± 20	46 ± 18	NS
Systolic arterial pressure (mmHg)	33 ± 20	19 ± 21	0.0003
LV end-diastolic volume (mL)	7.0 ± 18	8.6 ± 16	NS
LV end-systolic volume (mL)	−8.2 ± 11.5	1.9 ± 10	0.0018
LV ejection fraction (%)	6.6 ± 7.8	0.9 ± 8.2	<0.0001
Aortic valve area (cm^2)	0.11 ± 0.19	0.04 ± 0.17	0.032
Peak aortic pressure gradient (mmHg)	17 ± 13	24 ± 17	0.019
Mean aortic pressure gradient (mmHg)	10.5 ± 7	18 ± 11	<0.0001
Mean aortic pressure gradient 17 mmHg	12 (18%)	35 (58%)	<0.0001

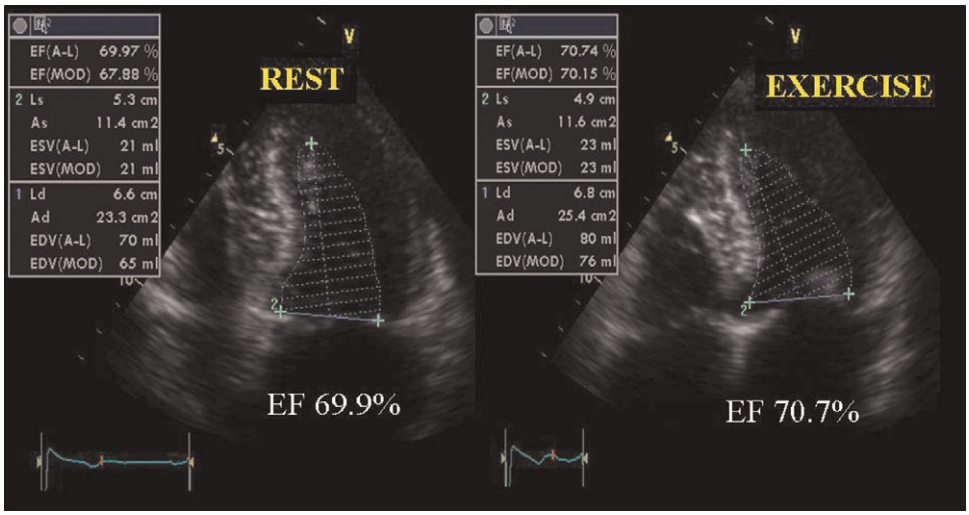

Figure 2 Example of a patient with abnormal exercise test and no contractile reserve (slight change in ejection fraction (EF)).

(mean 3.0 ± 8.8%). New or worsening (at least 1 grade) mitral regurgitation occurred in 44 (34%) patients. Transtricuspid pressure gradient was recorded at rest in 81 patients (25 ± 9 mmHg) and during exercise in 85 (48 ± 15 mmHg) ($P < 0.0001$).

Determinants of abnormal exercise test

Exercise testing was abnormal in 60 (47%) patients who had ≥1 criteria of positivity. Among these, 30 experienced symptoms during the test: 3 patients had angina, 25 had dyspnoea and 2 developed both symptoms. No patient had dizziness or syncope. Twenty-three patients had a ≥2 mm ST segment depression, 23 had a fall or a <20 mmHg rise in systolic blood pressure, and non-sustained ventricular tachycardia was recorded in 1 patient. The echocardiographic characteristics of patients with negative versus positive exercise test are shown in *Table 1*. In multivariate analysis, two independent predictors of an abnormal response to exercise were selected stepwise: a higher increase in mean transvalvular pressure gradient ($P = 0.0014$, odds ratio 1.08) and a decrease or lower increase in LV ejection fraction ($P = 0.0002$, odds ratio 0.90) (*Figure 2*). Using categorical variable, a ≥17 mmHg increase in mean pressure gradient was selected as the best cut-off value associated with positivity of the exercise test ($P = 0.00033$, odds ratio 4.9).

Relations between abnormal responses

The development of symptoms during exercise in 30 of the 128 patients was associated in multivariate analysis with a

Table 2 Characteristics of patients with exercise-induced symptoms

	No symptoms ($n = 98$)	Symptoms ($n = 30$)	P
Mitral regurgitation at rest	40 (41%)	22 (73%)	0.0016
Aortic valve area at rest (cm^2)	0.85 ± 0.15	0.77 ± 0.12	0.006
LV ejection fraction at exercise (%)	71 ± 9	66 ± 8	0.0086
Aortic valve area at exercise (cm^2)	0.89 ± 0.20	0.81 ± 0.21	0.0067
Peak aortic pressure gradient (mmHg)	83 ± 23	95 ± 21	0.012
Mean aortic pressure gradient (mmHg)	54 ± 15	60 ± 15	0.049
LV ejection fraction diff (%)	4.0 ± 8.8	0.2 ± 7.4	0.0021
Aortic valve area diff (cm^2)	0.11 ± 0.21	0.022 ± 0.16	0.039
Mean aortic pressure gradient diff (mmHg)	13 ± 10	18 ± 10	0.007
Worsening mitral regurgitation	27 (28%)	17 (57%)	0.0033
Systolic arterial pressure diff (mmHg)	29 ± 21	18 ± 24	0.017

Diff, difference exercise-rest.

Table 3 Covariates of exercise-induced changes in mean aortic pressure gradient

	17 mmHg $n = 81$	17 mmHg $n = 47$	P
Transtricuspid pressure gradient at exercise (mmHg)	45 ± 14	53 ± 17	0.014
Aortic valve area at exercise (cm^2)	0.97 ± 0.30	0.83 ± 0.23	0.00078
LV ejection fraction at exercise (%)	71 ± 9.1	67.7 ± 8.6	0.03
Aortic valve area diff (cm^2)	0.13 ± 0.21	0.012 ± 0.16	0.00076
LV ejection fraction diff (%)	4.9 ± 8.9	0.28 ± 7.7	0.00097
Transtricuspid pressure gradient diff (mmHg)	21 ± 14	28 ± 16	0.047
Worsening mitral regurgitation	22 (27%)	22 (47%)	0.025
ST segment depression	5 (6.1%)	18 (38%)	0.00002
Angina + dyspnoea	13 (16%)	17 (36%)	0.009

Diff, difference exercise-rest; LV, left ventricular.

higher increase in mean pressure gradient during exercise ($P = 0.0018$, odds ratio 1.1), a smaller exercise-induced change in systolic arterial pressure (0.01, odds ratio 0.97), and a lower LV ejection fraction at peak test ($P = 0.017$, odds ratio 0.92) (*Table 2*). Exercise-induced increase in mean transvalvular pressure gradient was $\geq$17 mmHg in 47 patients who differed from the 81 other patients in several characteristics (*Table 3*). Multivariate analysis selected new or worsening mitral regurgitation during exercise ($P = 0.024$, odds ratio 2.6) and a low exercise-induced difference in aortic valve area ($P = 0.028$, odds ratio 0.71) and in ejection fraction ($P = 0.0086$, odds ratio 0.94) as covariates associated with a $\geq$17 mmHg increase in mean pressure gradient. There was no relationship between the changes in the gradient with exercise and the baseline gradient ($r = -0.02$, $P =$ NS). A fall or a $<$20 mmHg increase in systolic blood pressure during exercise was associated with two independent parameters: the presence of mitral regurgitation at rest ($P = 0.021$) and a decrease or lower increase in ejection fraction during exercise ($P = 0.015$). Two independent variables were related to $\geq$2 mm ST segment depression during exercise: a smaller aortic valve area at rest ($P = 0.021$) and a larger exercise-induced increase in mean pressure gradient ($P = 0.0012$).

Discussion

During exercise, the haemodynamic and functional consequences of AS can be reliably assessed by quantitative Doppler echocardiography. The present study confirms and extends previous reports showing that, although asymptomatic in their daily life, a significant proportion of patients with significant AS develop an abnormal response to exercise. A $\geq$17 mmHg increase in mean transaortic pressure gradient and a reduction or low increase in LV ejection fraction during exercise characterized patients with an abnormal test. These two abnormalities are potentially related to two different conditions: greater leaflet stiffness in some patients and impairment of LV functional reserve in other patients.

Although it is acknowledged that the benefit is not proven, selective aortic valve surgery has been recommended in asymptomatic patients who are haemodynamically compromised by AS.[15] Indeed, it is difficult to make a truly asymptomatic patient feel better,[16,17] but distinguishing between asymptomatic and mildly symptomatic patients is not always easy. History-taking is often unsatisfactory; patients can deny symptoms and the physician may be unable to accurately elicit symptoms. The prognostic value of exercise testing in asymptomatic patients with AS has emerged from the studies of Amato *et al.*[7] and Alborino *et al.*[8] Despite negative history taking, exercise testing was positive in two thirds of the population in both studies. An abnormal exercise test was superior to resting echocardiography for identifying patients with a high rate of need for valve replacement. These data have been recently confirmed by the group of Chambers[9] and our group.[11] Haemodynamic effects of exercise in valvular AS have been studied during catheterization[18,19]; Doppler recordings have been obtained immediately after exercise.[2,20–22] The present study is one of the first that aimed to obtain Doppler haemodynamics during exercise in patients with asymptomatic AS. We used a dedicated table with the patient lying in a comfortable position that permitted adequate recording of Doppler velocities: this is technically less demanding than recording these data

quickly and accurately immediately after exercise. The risk of developing dizziness or syncope may potentially be reduced in the semi-supine position: such symptom did not develop in any patient, as compared with a 11% incidence of dizziness during treadmill test in the study by Amato and colleagues.[7]

The exercise test was positive in more than one third of our patients. Such an abnormal response was associated with a higher increase in mean pressure gradient and with a limited LV contractile reserve—latent LV dysfunction—as indicated by a decrease or smaller increase in LV ejection fraction.

A large exercise-induced increase in mean pressure gradient correlated with a decrease or a smaller increase in valve area with exercise. This suggests that patients exhibiting this type of response have greater valvular stiffness and a more rigid anatomic orifice, unable to increase with exercise. Our findings are consistent with the observations of Das *et al.*, who submitted asymptomatic patients to dobutamine stress echocardiography.[23] Valve compliance was calculated during the pharmacological test and was found to be lower in patients limited by symptoms on treadmill exercise testing. In contrast, their patients with a greater valve compliance remained asymptomatic during exercise as were our patients who had significant increases in calculated orifice area, probably related to increased opening of less stiff leaflets.

The increase in pressure gradient was also associated with lower changes in LV ejection fraction and new or worsening mitral regurgitation reflecting the inadequate LV adaptation to exercise due probably to afterload mismatch.[24]

Limiting symptoms on exercise testing relate in part to blunted changes in systolic blood pressure which is the witness that peripheral demands (vasodilatation) exceed the rise in cardiac output (substantial pump failure). Such subjects may be at higher risk of developing overt symptoms during follow-up and may already have irreversible myocardial damage that could cause a greater complication rate, even after valve replacement.[25,26]

This study has some limitations. Continuous wave recordings were made only from the apical position. The right parasternal window was not used, because it was not possible to tilt the table to the right. This may have resulted in underestimation in peak velocity in some patients, but similarly at rest and during exercise. Although less demanding than recording Doppler echocardiographic data shortly after exercise, a learning curve is required to obtain reliable measures during exercise. Recordings during rest might be affected by noise artefacts.

Exercise-induced dyspnoea may have been related to other causes. We did not attempt to evaluate valve compliance and indices of LV diastolic function in this study. Nearly all patients examined had at least moderate or severe calcification of the aortic valve. The specific effect of valvular calcification was thus not assessable. The influence of coronary artery disease on our results was not assessed since 33 patients underwent coronary angiography. Of note, multivessel disease was observed in 13, single vessel stenosis in 1 and non-significant coronary stenosis ($<$50%) in 6. The decision to perform surgery was made by individual cardiologists in charge of the patients.

We conclude that in asymptomatic patients with significant AS, exercise Doppler echocardiography is safe and provides a comprehensive evaluation of the haemodynamic repercussion of AS.

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