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Changes in the severity of aortic regurgitation at peak effort during exercise☆

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ABSTRACT

Background: Chronic aortic regurgitation can be well tolerated for a long time. Some patients with normal ventricular function can even reach high levels of sporting performance. How the severity of regurgitation may change during exercise, however, is little known, although some studies suggest it diminishes. The present work examines, during exercise, the functional capacity, ventricular function, and regurgitation fraction (RF) in asymptomatic subjects with moderate or severe aortic regurgitation with preserved ejection fraction.
Methods: The study subjects ($n = 32$; 23 men, 9 women) were patients referred to our echocardiography laboratory with moderate or severe aortic regurgitation, preserved left ventricular systolic function, and sinus rhythm into NYHA functional class I. All underwent transthoracic echocardiography at rest and at peak effort during an exercise protocol involving an inclined cycloergometer. Left atrial and ventricular volume indices were recorded, along with diastolic and systolic function, cardiac index, peripheral resistance, and RF.
Results: The mean age of the subjects was 43.8 ± 18.2 years; 59% suffered moderate regurgitation, 41% severe aortic regurgitation, and 84% had a dilated left ventricle. All subjects managed exercise loads adequate for their age. Peak effort was associated with a significant reduction (mean 44.5% [range 10–95%]) in the RF (21.8 ± 13.2 vs. 39.3% ± 14.7% at rest; $p = 0.0001$). The absolute reduction in the RF at peak effort was greater among the subjects with severe aortic regurgitation (21.2% vs. 13.3% in those with moderate regurgitation; $p = 0.018$).
Conclusions: The RF becomes smaller during exercise in asymptomatic subjects with moderate or severe aortic regurgitation and preserved ventricular function.

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1. Introduction

Chronic moderate or even severe aortic regurgitation can be well tolerated over an extended period of time [1–4]. It has been reported that patients with either condition, but with preserved ventricular function, can have good functional capacities and even reach high levels of sporting performance [5,6]. Some studies suggest the severity of aortic regurgitation to diminish with exercise, but definitive evidence for this is lacking [7]. The aim of the present work was to examine the functional capacity and ventricular function of subjects with moderate and severe aortic regurgitation (but who were asymptomatic and had a normal ejection fraction) and examine the aortic regurgitation fraction (RF) at rest and under conditions of peak effort.

2. Materials and methods

2.1. Selection of study subjects

The study subjects were all those referred to our echocardiography laboratory at a tertiary level hospital (between January 2009 and December 2010) for moderate or severe aortic regurgitation (according to the criteria of the European Association of Echocardiography [8]) who also showed preserved left ventricular systolic function and sinus rhythm and fell into NYHA functional class I. Subjects who required a valve replacement [9,10], with associated aortic stenosis, mitral, or tricuspid valve disease of class >1 (on a scale of 4), with persistent arrhythmia, who had a poor acoustic window, systemic disease, physical, or mental abnormalities that prevented the undertaking of exercise, or who

Abbreviations: Acolor, Maximum area of the regurgitation jet; iSVR, Width of the left ventricular ejection tract regurgitation jet; LVeDD, Left ventricular end-diastolic diameter; LVeSD, Left ventricular end-systolic diameter; HR, Heart rate; ShFr, Shortening fraction; RF, Regurgitation fraction; CI, Cardiac index; LAVI, Left atrial volume index; LVEDVI, Left ventricular end-diastolic volume index; LVESVI, Left ventricular end-systolic volume index; iSVR, Index of systemic vascular resistance; bpm, beats per minute; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BSA, body surface area; LVOT, Left ventricular outflow tract; SV Mi, Mitral stroke volume; SV LVOT, Stroke volume in the left ventricular outflow tract; VTI, Velocity time integral.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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were in an NHYA functional class higher than I were excluded. All subjects gave their informed consent to be included in the study.

2.2. Methods

The body weight, height, body surface area (BSA) (determined using the Mosteller equation), resting heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) of all subjects were measured. All subjects also underwent a resting 12 lead ECG examination and a transthoracic ultrasound exploration using a General Electric Vivid 7 device equipped with 2.0 and 4.0 MHz Phased Array transducers. All tests were performed according to the recommendations of the American Society of Echocardiography [11] and undertaken by appropriately certified and experienced cardiologists.

The subjects then began an exercise protocol on an inclined cycloergometer (General Electric Vivid 7) specially designed for obtaining echocardiographic images during exercise. The initial load was 25 W, increasing by 25 W every 2 min until the subject reached peak effort, at which point the HR, SBP, and DBP were recorded again, and ECG and echocardiography were performed once more.

2.3. Echocardiographic variables measured

2.3.1. Echocardiogram

Left atrial volume index (LAVI), left ventricular end-diastolic (LVeDD) and end-systolic (LVeSD) diameters, and the left ventricular diastolic (LVEDVI) and systolic (LVESVI) volume indices (biplanar method) were measured.

2.3.2. Ventricular function

General indices of ventricular function, including the ejection fraction (determined by the Simpson biplanar method), the shortening fraction (ShFr), and the cardiac index (CI) as determined using Eq. (1):

$$\mathrm{CI} = \left[\mathrm{VTI\ LVOT} \times \pi \times (D/2)^2 \mathrm{LVOT}\right] \times \mathrm{HR/sc} \quad (1)$$

where LVOT is the left ventricular outflow tract, *D* is the diameter, and VTI LVOT is the corresponding velocity time integral of the flow in the LVOT.

Normal systolic ventricular function was defined as an ejection fraction of >50%. The severity of aortic regurgitation was identified according to the criteria of the European Society of Cardiology and the American College of Cardiology [10,11]. For this, the following measurements were taken: the width of the LVOT jet (wLVOTj), the maximum area of the regurgitation jet (Acolor) (color Doppler) in the plane of maximum visualization, the width of the *vena contracta*, the reversal flow in the aortic arch and abdominal aorta, and the RF. The latter was calculated from the diameters of the LVOT and mitral annulus and the corresponding velocity time integrals (VTI LVOT and VTI Mi). The stroke volume (SV) was calculated for both the LVOT (SV LVOT) and at the mitral level (SV Mi) as the product of the VTI and the area of the LVOT (understanding both to be circular). The RF was finally determined according to Eq. (2):

$$\mathrm{RF} = [(\mathrm{SV\ LVOT\text{-}SV\ Mi})/\mathrm{SV\ LVOT}] \times 100 \quad (2)$$

2.3.3. Diastolic function variables

Mitral filling *E* and *A* waves, the *E/A* ratio, the mean velocity of displacement of the mitral annulus (*e′*) (measured on the septal and lateral sides), and the *E/e′* ratio were obtained.

At the point of peak effort during exercise, the following variables were also recorded: duration of exercise, exercise load attained (in Watts), percentage of the maximum theoretical HR (220-age), and regurgitation severity (as reflected by the wLVOTj, Acolor, *vena contracta*, RF, percentage change with respect to baseline RF, mitral filling *E* wave, *e′*, *E/e′*, and CI.) The index of systemic vascular resistance (iSVR) was determined at baseline and peak effort according to Eq. (3):

$$\mathrm{iSVR} = (\mathrm{mean\ blood\ pressure} - \mathrm{mean\ right\ atrial\ blood\ pressure})/\mathrm{CI} \times 79.9 \quad (3)$$

where mean blood pressure was determined as (2 × DBP + SBP) / 3, and the blood pressure in the right atrium was assumed to be a normal 5 mmHg.

2.4. Statistical analysis

Continuous variables were recorded as means ± standard deviation (SD) or medians plus interquartile range. Categorical variables were recorded as absolute values or percentages. The Shapiro–Wilk test was used to check sample distribution. Given the sample size, the Wilcoxon signed-rank test was used to examine the differences between baseline and peak effort values for continuous hemodynamic and echocardiographic variables. The Mann–Whitney *U* test was used to examine the change in the RF between those with moderate and severe abnormalities. Spearman Rho correlation coefficients were calculated to examine linear associations. All calculations were made using SPSS Statistics v.20.0 software.

3. Results

The mean age of the 32 study subjects was 43.8 ± 18.2 years (median 42 [IRQ 37–50]). Twenty three (72%) were men. Nineteen (59%) suffered moderate aortic regurgitation and 13 (41%) severe regurgitation. Table 1 shows the etiologies behind their conditions.

Table 2 shows the subjects resting (baseline) hemodynamic and echocardiographic values, and Table 3 the comparison of values for the measured variables at rest and at peak effort.

Some 46.9% of the subjects showed an increased left atrial volume (≥34 ml/m^2); 84.4% had a left ventricular volume of >75 ml/m^2. In 53.1% of subjects, the LVeDD was >60 mm, but in none was it >74 mm. The LVeSD was never >55 mm. No subject received specific pharmacological treatment for aortic regurgitation.

At peak effort, significant increases were noted in SBP (166.4 ± 24.5 vs. 137.2 ± 18.7 mmHg at rest; $p < 0.001$) and DBP (82.2 ± 17.0 vs. 69.9 ± 10.3 mmHg; $p < 0.001$). A mean 83.2% ± 8.1% of the theoretical HR (220-age) was reached. All patients managed exercise loads appropriate for their age [12]. The most common reason for ending the exercise test was leg fatigue or poor adaptation to the cycloergometer. Exercise was associated with a significant reduction in the SV LVOT (82.2 ± 18.5 vs. 111.3 ± 2.5 ml; $p < 0.001$), but not in the SV Mi (65.5 ± 16.3 vs. 64.1 ± 17.7 ml; no significant difference). An increase was seen in the CI at peak exercise (6.7 ± 1.6 vs. 4.0 ± 1.3 l/min/m^2; $p < 0.001$) associated with an increased HR (146 ± 15.7 vs. 64.5 ± 8.7 bpm; $p < 0.0001$), along with a reduction in the values reflecting the severity of regurgitation: wLVOTj 9.4 ± 3.8 vs. 11 ± 3.3 at rest mm, $p = 0.012$; Acolor 4.9 ± 2.2 vs. 5.6 ± 2.4 cm^2, p 0.028; and RF 21.8 ± 13.2 vs. 39.3% ± 14.7%, $p < 0.001$ (Fig. 1). In most cases, color Doppler variables reflecting the severity of regurgitation could not be recorded due to tachycardia. Overall, a mean reduction of 44.5% ± 26.6% (range 10–95%; mean absolute reduction 17.4% ± 11.9%) was recorded for the RF. The reduction in the RF was greater in the subjects with severe regurgitation (mean overall reduction 59.6% vs. 30.2% in those with moderate aortic regurgitation $p < 0.05$; absolute reduction 21.2% vs. 13.3%; $p = 0.018$) (Fig. 2).

An increase was seen in the velocity of the *E* wave at peak effort (131 ± 19.7 vs. 74 ± 15 cm/s at rest; $p < 0.001$), as well as in *e′* (15.4 ± 5 vs. 9.8 ± 2.8 cm/s; $p < 0.001$), along with a slight but significant increase in the *E/e′* ratio (9.4 ± 3.2 vs. 7.9 ± 2; $p = 0.008$).

A positive correlation was detected between the duration of exercise and the baseline ventricular volumes ($R = 0.7$ with LVEDVI, $R = 0.73$ with LVESVI; $p < 0.0001$ for both). The RF at peak effort showed a trend toward a negative correlation with the duration of exercise ($R = -0.35$; $p = 0.06$).

4. Discussion

The present results show that the RF becomes smaller with exercise in asymptomatic subjects with aortic regurgitation but preserved ventricular function. This reduction is greater in subjects with more severe regurgitation at rest. No relationship was seen between the reaching of any particular HR and this reduction, but those subjects who were able to exercise for longer showed a trend ($p = 0.06$) toward a smaller RF at peak effort. In a magnetic resonance study involving 12 subjects with aortic regurgitation, Stern et al. [7] reached the same conclusions

Table 1
Etiology of aortic regurgitation.

Bicuspid aortic valve	13 (41%)
Dilation of ascending aorta	6 (19%)
Annular ectasia	5 (16%)
Myxoid valve degeneration	5 (16%)
Valve sclerosis	2 (6%)
Subaortic stenosis (postsurgery)	1 (3%)

Table 2
Patient characteristics and resting values.

n (%) women/men	9 (28%)/23 (72%)
AGE (years)	43.8 ± 18.2
HR (bpm)	64.5 ± 8.7
SBP (mm Hg)	137.2 ± 18.7
DBP (mm Hg)	69.9 ± 10.3
LAVI (ml/m^2)	31.3 ± 8.3
LVeDD (mm)	59.9 ± 8.7
LVeSD (mm)	42.4 ± 6.7
ShFr (%)	31.7 ± 4.8
LVEDVI (ml/m^2)	104.4 ± 25.7
LVESVI (ml/m^2)	44.9 ± 13.2
Ejection Fr (Simpson %)	57.1 ± 5.7
wLVOTj (mm)	11.1 ± 3.3
Acolor (cm^2)	5.63 ± 2.4
SVMi (ml)	65.5 ± 16.3
SVLVOT (ml)	111.3 ± 2.5
RF (%)	39.3 ± 14.7
CI (l/min/m2)	4.0 (± 1.28
E/*A*	1.39 ± 0.54
e′ (cm/s)	9.8 ± 2.8
E/*e*′	7.9 ± 2.1
iRVS (dyne·s/cm^5/m^2)	1901 ± 629

when comparing results collected at rest and at sub-peak effort during exercise.

A number of explanations may account for the good functional capacity of such subjects, and indeed the high level sporting performance achieved by certain athletes with valve abnormalities. It may be that the tachycardia that occurs during exercise shortens the diastolic period and thus the time over which regurgitation can occur. Although no linear correlation was found between the HR and the reduction in the RF, this does not rule out that exercise-induced tachycardia may have an important influence on the latter. The reduction in peripheral resistance during exercise (the consequence of arteriolar and capillary dilation in the peripheral muscles) might also favor a reduction in retrograde flow, with the increase in DBP seen at peak effort explained by the reduction in the RF. Alternatively, the increase in the ventricular volume of subjects with aortic regurgitation, caused by the volume overload, might contribute toward the adaptation of the heart to exercise. This might serve as an adaptive mechanism that increases cardiac output, favoring the capacity to exercise. In the present work, a strong correlation was seen between the ventricular volumes at rest and the duration of exercise. In addition, exercise might increase the tolerance of the heart to aortic regurgitation [13], reducing the RF during exercise and improving the diastolic function.

Although the present subjects only reached a mean 83.2% of the maximum theoretical HR, it is well known that hemodynamic changes occur at sub-peak effort. In a study of the cardiac dynamics of subjects

Table 3
Comparison of values for the measured variables at rest and at peak effort.

	At rest	Peak effort	*P*
Duration exercise (s)		594.3 ± 204.8	
Watts		134.4 ± 44.8	
HR (bpm)	64.5 ± 8.7	146.1 ± 15.7	0.0001
% maximum theoretical HR		83.2 ± 8.1	
SBP (mmHg)	137.2 ± 18.7	166.4 ± 24.5	0.0001
DBP (mmHg)	69.9 ± 10.3	82.2 ± 17.0	0.0001
SVMi (ml)	65.5 ± 16.3	64.1 ± 17.7	NS
SVLVOT (ml)	111.3 ± 2.5	82.2 ± 18.5	0.0001
RF (%)	39.3 ± 14.7	21.8 ± 13.2	0.0001
IC (l/min/m^2)	4.0 ± 1.28	6.70 ± 1.65	0.0001
e′ (cm/s)	9.8 ± 2.8	15.41 ± 5.02	0.0001
E/*e*′	7.9 ± 2.1	9.39 ± 3.2	0.008
iRVS (dyne·s/cm^5/m^2)	1901 ± 629	1339 ± 423	0.0001
Absolute reduction in RF (%)		17.5 ± 11.9	
Overall reduction in RF (%)		44.5 ± 26.6	

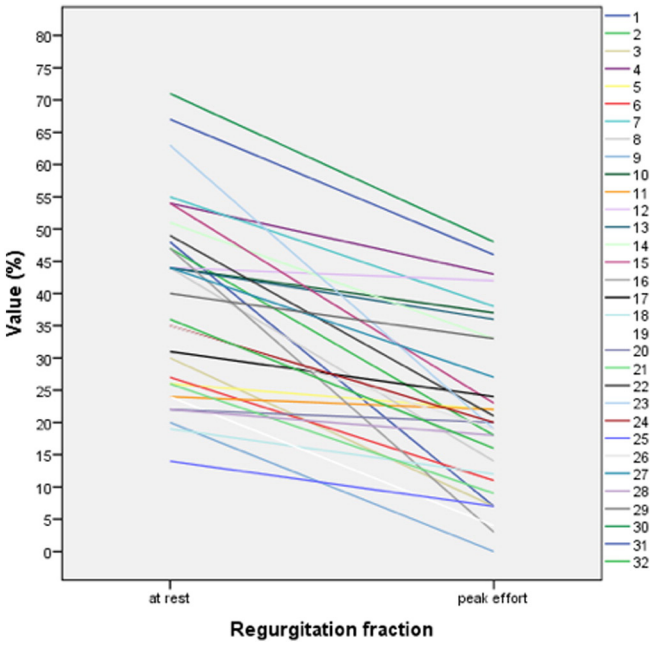

Fig. 1. Reduction in the regurgitation fraction at peak effort.

at sub-peak and peak effort (on a cycloergometer), Astrand et al. [14] observed a maximum volume/beat ratio at just 40–60% maximum oxygen consumption.

While the present results show that stress tests can be used to determine the functional capacity and ventricular function of patients [15,16], they question their use as a tool for determining by how much exercise worsens aortic regurgitation [17]; indeed, the results clearly show that it might improve. This finding should be taken into account when taking clinical decisions [18].

5. Study limitations

The sample size was rather small to be entirely confident of the factors associated with a reduction in regurgitation.

The determination of the RF by Doppler echocardiography is subject to unreal assumptions regarding the shape of the valves; the values obtained must therefore be somewhat inaccurate. However, the same

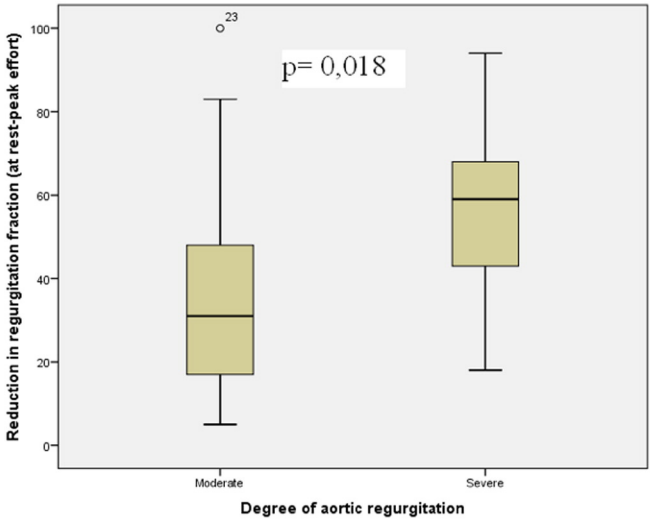

Fig. 2. Comparison of the reduction in the regurgitation fraction in subjects with moderate and with severe regurgitation at peak effort.

error would have affected readings taken at rest and at peak effort; thus, the percentage change in RF obtained is, at least, reliable.

The difficulty in acquiring adequate echocardiographic recordings during exercise also implies some inaccuracy in associated calculations. It also makes it very difficult to estimate the severity of valve failure by color Doppler methods, with most of the present subjects it was impossible to obtain good images during exercise. Difficulties in obtaining the necessary images also made it impossible to determine the ejection fraction during exercise.

A number of the present subjects experienced difficulty in adapting to the cycloergometer, preventing high HRs from being reached. Although it was initially thought that the inability to reach the maximum theoretical HR might be a drawback, sub-peak effort allows for longer exploration times and better tolerance to exercise on the part of the subject. Further, since many hemodynamic variables change even at low exercise loads, this limitation need not negatively influence the conclusions that can be drawn.

6. Conclusions

The RF fell significantly at peak effort in subjects with moderate-severe aortic regurgitation but preserved ventricular function. This helps explain why, as long as ventricular function is preserved, this valve disease can be well tolerated and not negatively affect sporting performance.

Conflicts of interest

None.

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