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Exercise capacity and peak oxygen consumption in asymptomatic patients with chronic aortic regurgitation☆

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ABSTRACT

Background: In patients with chronic, hemodynamically significant aortic regurgitation (AR), a long period of left ventricular remodeling usually occurs prior to the development of symptoms or left ventricular dysfunction. The value of cardiopulmonary exercise testing in patients with asymptomatic AR is not established.
Material and methods: Sixty-six asymptomatic patients aged 44 ± 14 years with hemodynamically significant, chronic AR and no indication for aortic valve replacement were evaluated by echocardiography, cardiac magnetic resonance imaging and exercise testing with measurement of peak oxygen consumption.
Results: The average left ventricular end diastolic volume was 244 ± 62 ml and the aortic regurgitant fraction 34 ± 13%. At an average of 35.8 ± 8.9 ml/kg/min, peak oxygen consumption was well preserved. As in healthy individuals, a high peak oxygen consumption was associated with a relatively large LV end diastolic volume ($r = 0.51$; $p < 0.001$) and a low resting heart rate ($r = -0.37$; $p = 0.002$). The aortic regurgitant fraction was not predictive of maximum oxygen consumption. Higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were independently associated with poorer exercise capacity and oxygen uptake (adjusted $\beta -0.35$; $p = 0.003$).
Conclusion: Our results suggest that in asymptomatic patients with moderate to severe AR and moderately dilated left ventricles, remodeling is primarily adaptive. An increased level of NT-proBNP is associated with a reduced capacity for work and reduced oxygen consumption, possibly heralding the onset of adverse remodeling.

1. Introduction

Aortic regurgitation is the third most common valvular heart disease in the developed world [1,2], affecting 0.5% of the American population [2]. In moderate to severe, chronic aortic regurgitation, patients typically experience a prolonged phase of stability [3–5], characterized by adaptive changes. During this period, an increased left ventricular end-diastolic volume, increased chamber compliance and a combination of eccentric and concentric hypertrophy ensures that net forward cardiac output is preserved [6,7], and the patients remain asymptomatic. With time, however, the initially adaptive left ventricular dilatation tends to progress, and overt heart failure may ensue unless aortic valve replacement is performed [3–5,8].

Peak cardiac output is a major determinant of exercise capacity and peak oxygen consumption [9]. In heart failure, cardiac function is the main factor limiting ergospirometric performance, and peak oxygen consumption is associated with disease severity [10]. In patients with severe heart failure, prognosis is more strongly associated with peak oxygen consumption than with left ventricular function.

Previous studies have shown that there is an association between peak oxygen consumption and symptoms [11], left ventricular end diastolic volume [12] and pulmonary capillary wedge pressure during exercise [13] in patients with aortic regurgitation. However, these historical materials have included patients with severely dilated left ventricles, impaired left ventricular systolic function and symptomatic heart failure. According to current guidelines, these patients have a clear indication for aortic valve replacement [14].

Given the large demand on the cardiovascular system during maximal physical exertion, a reduction in peak oxygen consumption might precede overt left ventricular dysfunction at rest in patients with aortic regurgitation. A subtle reduction in exercise capacity might thus portend progression towards symptomatic disease, and could conceivably be used for stratification for aortic valve surgery. However, exercise

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capacity and peak oxygen consumption have not been reported in patients with hemodynamically significant aortic regurgitation, but no current indication for surgery.

In a cohort of patients with moderate to severe aortic regurgitation, modest left ventricular enlargement and preserved left ventricular systolic function, we measured exercise capacity and peak oxygen consumption. We aimed to investigate if exercise capacity or peak oxygen consumption were reduced in these patients, and whether exercise test parameters were associated with indices of left ventricular dimension and function and the size of the valvular regurgitation.

2. Material and methods

2.1. Patient population

This study comprises patients aged between 18 and 70 years with asymptomatic, hemodynamically significant aortic regurgitation, normal left ventricular ejection fraction (>50%) and a left ventricular end-diastolic internal diameter > 5.0 cm (or >3.0 cm/m^2 body surface area), who participated in a randomized, controlled trial assessing the effect of sustained release metoprolol on left ventricular size and function in patients with aortic regurgitation [15]. The trial complies with the Declaration of Helsinki and was approved by the appropriate Regional Committees for Medical and Health Research Ethics. All patients provided written, informed consent. We did not include patients with symptoms of heart failure; coronary heart disease; significant aortic stenosis (valvular area < 1.5 cm^2 as estimated by echocardiography); other, hemodynamically significant valvular disease or congenital heart disease; or indication for aortic valve replacement (severe aortic regurgitation in conjunction with: symptoms, a left ventricular ejection fraction <50%, or left ventricular end diastolic internal diameter > 7.0 cm or end systolic internal diameter > 5.0 cm).

2.2. Exercise test and gas exchange measurements

Maximal, upright, symptom-limited exercise tests were performed using an electrically braked bicycle ergometer. The tests employed an individualized, stepwise protocol where we increased the workload incrementally every minute so as to reach the age, gender and weight adjusted expected maximum load [16] after approximately 10 min. Simultaneous gas exchange monitoring and hemodynamic monitoring were performed. (Cardiovit CS-200, Schiller, Baar, Switzerland and Ganshorn PowerCube, Ganshorn, Niederlauer, Germany). Before each test, the equipment was calibrated using reference gases and a 2000 cm^3 syringe. Heart rate and blood pressure were recorded at regular intervals throughout the test. We rated patient exertion using Borg's Rating of Perceived Exertion scale, ranging from 7 (very, very light) to 20 (maximum exertion) [17].

Peak oxygen consumption was defined as the VO_2 achieved at maximum load at the end of the exercise. The value was expressed in l/min, in ml per kg/min and as a percentage of the age-, weight and gender-adjusted expected value calculated as recommended by Wasserman et al. [18] The ventilation (VE)/VCO2 slope was calculated by drawing a straight line fitted through the points on the VE/VCO2 plot. The anaerobic threshold was defined as the VCO2/VO2 breakpoint, where the relationship between CO2 excretion and oxygen consumption becomes steeper with increasing effort, signifying the onset of excess lactate production. This breakpoint was determined by drawing straight lines through the points on the VCO2/O2 plot in the early and late phases of the exercise test. The intersection point between these two lines was taken to represent the anaerobic threshold [19].

2.3. Imaging

All image analyses were performed at Oslo University Hospital, Rikshospitalet. Image analyses were performed by operators blinded to the results of the exercise test.

2.3.1. Echocardiography

Echocardiography was performed with Vivid E9 ultrasound scanners (GE Vingmed Ultrasound, Horten, Norway). Patients were examined in the lateral recumbent position after >5 min of rest. Three heartbeats were recorded with each registration. Cine loops were digitally stored and later analyzed off line using Echo-Pac (GE Vingmed). 2D parameters and conventional Doppler parameters were measured off line according to current recommendations. Left ventricular ejection fraction was measured by Simpson's biplane method. The severity of the aortic regurgitation was determined by an integrative approach combining valvular morphology, regurgitant jet evaluation and left ventricular size [14].

2.3.2. Magnetic resonance imaging

We used Siemens 1.5 T scanners (Siemens Avanto; Siemens Medical Systems, Erlangen, Germany) for magnetic resonance imaging. Left ventricular long- and short axis images were acquired using a breath-hold, prospectively ECG-triggered, segmented, balanced, steady-state free precession gradient-echo cine sequence with minimum echo and repetition times, 6 mm slice thickness, 10 mm short-axis interslice increment, spatial resolution 1.9 mm × 1.3 mm, and a temporal resolution <50 ms. Left and right ventricular endocardial borders were traced manually at a PACS work station (Sectra Medical Systems AB, Linköping, Sweden), and ventricular volumes, stroke volumes and ejection fractions were calculated by short axis slice summation. The aortic regurgitation volume was calculated as the difference between the left and right ventricular stroke volumes, and the aortic regurgitation fraction was reported as the aortic regurgitation volume as percentage of the left ventricular stroke volume. We assessed inter- and intraobserver reproducibility by repeat analysis of magnetic resonance images in 15 randomly selected patients.

2.4. Blood sampling and laboratory analysis

Peripheral blood samples were obtained for routine panel analyses. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined by an electrochemiluminescence immunoassay (Roche proBNP II) on a MODULAR E 170 analytical platform (Roche Diagnostics, Mannheim, Germany).

2.5. Statistics

Numerical values are presented as mean values (SD) or median (interquartile range) as appropriate. Differences between patient subgroups were analyzed by students T-test. Associations between peak work load and maximum oxygen uptake, respectively, and other patient characteristics were determined by linear, least squares regression analyses. Skewed parameters, notably NT-proBNP, were log-transformed prior to statistical analysis. Patient variables with a univariate association statistically significant at a p-level of <0.05, were then analyzed in multiple linear regression models (enter), with maximum work load and peak VO2 as the dependent variables. We employed analysis of covariance to assess the predictive value of NT-proBNP, adjusting for other, significant predictors of peak oxygen consumption. All statistical analyses were performed with the Statistical Package for Social Sciences version 18 software (SPSS Inc. Chicago, IL). Two-sided probability values were considered significant at $p < 0.05$. In a *post hoc* sample size estimation, the number of study subjects needed to demonstrate a one metabolic equivalent reduction in peak oxygen in patients with AR compared with matched, historical control subjects was 57, given an expected average peak oxygen consumption of 33.6 (SD 7.5) ml/kg/min, a power of 0.8 and a one-sided α of 0.05.

3. Results

3.1. Patient selection

Seventy-five patients were enrolled in the metoprolol study. This article reports baseline results from the 66 patients who completed the bicycle cardiopulmonary exercise test. In five patients, the test was performed on a treadmill, one patient was paraplegic, one patient could not perform exercise testing due to recent ankle surgery, and in two patients, gas exchange could not be measured or the gas exchange results were considered non-physiological and the values were discarded. (Fig. 1) All measurements were obtained prior to treatment with metoprolol/placebo, and no patient received beta receptor antagonists at baseline. Patient characteristics are presented in Table 1.

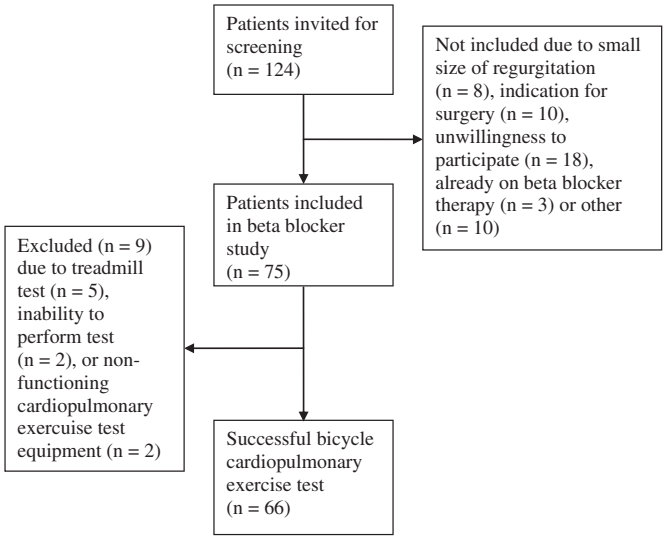

Fig. 1. Patient inclusion.