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Mechanisms of Effort Intolerance in Patients With Rheumatic Mitral Stenosis

Combined Echocardiography and Cardiopulmonary Stress Protocol

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ABSTRACT

OBJECTIVES This study sought to evaluate mechanisms of effort intolerance in patients with rheumatic mitral stenosis (MS).

BACKGROUND Combined stress echocardiography and cardiopulmonary testing allows assessment of cardiac function, hemodynamics, and oxygen extraction (A-Vo_2 difference).

METHODS Using semirecumbent bicycle exercise, 20 patients with rheumatic MS (valve area 1.36 ± 0.4 cm^2) were compared to 20 control subjects at 4 pre-defined activity stages (rest, unloaded, anaerobic threshold, and peak). Various echocardiographic parameters (left ventricular volumes, ejection fraction, stroke volume, mitral valve gradient, mitral valve area, tissue s′ and e′) and ventilatory parameters (peak oxygen consumption [Vo_2] and A-Vo_2 difference) were measured during 8 to 12 min of graded exercise.

RESULTS Comparing patients with MS to control subjects, significant differences (both between groups and for group by time interaction) were seen in multiple parameters (heart rate, stroke volume, end-diastolic volume, ejection fraction, s′, e′, Vo_2, and tidal volume). Exercise responses were all attenuated compared to control subjects. Comparing patients with MS and poor exercise tolerance (<80% of expected) to other subjects with MS, we found attenuated increases in tidal volume ($p = 0.0003$), heart rate ($p = 0.0009$), and mitral area ($p = 0.04$) in the poor exercise tolerance group. These patients also displayed different end-diastolic volume behavior over time (group by time interaction $p = 0.05$). In multivariable analysis, peak heart rate response ($p = 0.01$), tidal volume response ($p = 0.0001$), and peak A-Vo_2 difference ($p = 0.03$) were the only independent predictors of exercise capacity in patients with MS; systolic pulmonary pressure, mitral valve gradient, and mitral valve area were not.

CONCLUSIONS In patients with rheumatic MS, exercise intolerance is predominantly the result of restrictive lung function, chronotropic incompetence, limited stroke volume reserve, and peripheral factors, and not simply impaired valvular function. Combined stress echocardiography and cardiopulmonary testing can be helpful in determining mechanisms of exercise intolerance in patients with MS. (J Am Coll Cardiol Img 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Multiple mechanisms are held responsible for the limited exercise capacity of patients with rheumatic mitral stenosis (MS). Studies of exercise limitation in MS have predominantly used exercise tests combined with catheterization (1) or the equilibrium cardiac output (CO) rebreathing technique (2) to calculate CO and peripheral muscle oxygen extraction. The studies were limited by: 1) the invasive nature of the catheterization techniques, resulting in selection bias in those studies;

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ABBREVIATIONS AND ACRONYMS

AT = anaerobic threshold

A-Vo_2 difference = arterial-venous oxygen content difference

CO = cardiac output

CPET = cardiopulmonary exercise (stress) test

EF = ejection fraction

HR = heart rate

LV = left ventricle

MS = mitral stenosis

NYHA = New York Heart Association

RER = respiratory exchange ratio

SE = stress echocardiography

SPAP = systolic pulmonary artery pressure

SV = stroke volume

and 2) insufficient anatomic data provided with both techniques (3). Therefore, we created a combined cardiopulmonary exercise (stress) test (CPET) and stress echocardiography (SE) protocol that allows assessment of cardiac and peripheral responses to exercise at 4 pre-defined levels (rest, unloaded cycling, anaerobic threshold [AT], and peak). Our aims were: 1) to test whether cardiovascular response to exercise differs between patients with MS and normal subjects; 2) to look for differences in cardiovascular response to exercise between patients with MS having poor exercise tolerance and those with preserved exercise tolerance; and 3) to assess the independent factors associated with limited exercise capacity in patients with MS.

METHODS

STUDY POPULATION. Between January 2013 and July 2015, we performed 173 combined CPET and SE examinations. The study included all consecutive patients who had rheumatic MS (N = 20). There were no selection criteria for the MS group, but because cardiopulmonary stress or SE testing is rarely performed in patients with very severe MS (1) (valve area <1 cm^2) or in asymptomatic or severely symptomatic (New York Heart Association [NYHA] functional class IV) patients, our group consisted mostly of patients in the moderate-to-severe (1) range (valve area 1.0 to 1.5 cm^2) with milder symptoms (NYHA functional class II or III). Control subjects were selected from 37 patients with no cardiac disease who were referred for evaluation of dyspnea; 20 were selected after matching for age, gender, and ejection fraction (EF). Nine of these patients were determined to have dyspnea on the basis of peripheral factors; the other 11 had normal exercise capacity. Subanalysis was performed in the MS group, comparing the 10 patients who had reduced exercise capacity (<80% of predicted) with the 10 patients who had preserved exercise capacity (>80% of predicted).

A second CPET was performed in 13 patients with MS without echocardiography and without change in medical therapy (including β-blocker if present): 6 of 7 patients who underwent intervention and 7 others who were treated conservatively. The intervention group included 6 patients who had mitral valve replacement (1 of whom refused repeat CPET) and 1 who had balloon valvuloplasty.

In a third analysis, 7 patients with MS underwent repeat CPET combined with SE after withdrawal of β-blocker therapy.

These data were collected in the course of routine clinical care. Observers who performed and analyzed the exercise gas exchange data and the echocardiographic images were blinded to patient group and other characteristics. This retrospective study was approved by our Institutional Review Board at Tel Aviv Medical Center.

EXERCISE PROTOCOL. Exercise was performed as previously described (4). A symptom-limited graded ramp bicycle exercise test was performed in the semisupine position on a tilting dedicated microprocessor controlled eddy current brake SE cycle ergometer (Ergoselect 1000 L, CareFusion, San Diego, California) We estimated the expected peak Vo_2 on the basis of the patient's age, height, and weight after considering the patient's history. We then calculated the work rate increment necessary to reach the patient's estimated peak Vo_2 in 8 to 12 min. The protocol included 3 min of unloaded pedaling, a symptom-limited ramp graded exercise, and 2 min of recovery. Breath-by-breath minute ventilation, carbon dioxide production (Vco_2), and oxygen consumption (Vo_2) were measured using a Medical Graphics metabolic cart (ZAN, nSpire Health Inc., Oberthulba, Germany). Peak Vo_2 was the highest averaged 30-s Vo_2 during exercise. AT was determined manually using the modified V-slope method. The respiratory exchange ratio (RER) was defined as the ratio between Vco_2 and Vo_2 obtained from ventilatory expired gas analysis (2). In 7 patients taking β-blockers during the first exercise test, β-blockers were subsequently withdrawn before a second examination. In patients on β-blocker therapy, chronotropic incompetence on stress testing was determined when <62% of heart rate (HR) reserve was used (5).

EXERCISE ECHOCARDIOGRAPHY TESTING. Echocardiographic images were obtained concurrently with breath-by-breath gas exchange measurements in a continuous manner as previously described (3). Each cycle of imaging included left ventricular (LV) end-diastolic and end-systolic volumes, stroke volume (SV), peak E- and A-wave velocities, deceleration time, and septal e′ and lasted between 30 and 60 s. LV end-diastolic volume, end-systolic volume, and EF were calculated according to the single plane ellipsoid apical 4-chamber area-length method. Left atrial volume was calculated according to the biplane area-length method. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level.