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Mitral Valve Area During Exercise After Restrictive Mitral Valve Annuloplasty

Importance of Diastolic Anterior Leaflet Tethering

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ABSTRACT

BACKGROUND Restrictive mitral valve annuloplasty (RMA) for secondary mitral regurgitation might cause functional mitral stenosis, yet its clinical impact and underlying pathophysiological mechanisms remain debated.

OBJECTIVES The purpose of our study was to assess the hemodynamic and clinical impact of effective orifice area (EOA) after RMA and its relationship with diastolic anterior leaflet (AL) tethering at rest and during exercise.

METHODS Consecutive RMA patients ($n = 39$) underwent a symptom-limited supine bicycle exercise test with Doppler echocardiography and respiratory gas analysis. EOA, transmitral flow rate, mean transmitral gradient, and systolic pulmonary arterial pressure were assessed at different stages of exercise. AL opening angles were measured at rest and peak exercise. Mortality and heart failure readmission data were collected for at least 20 months after surgery.

RESULTS EOA and AL opening angle were 1.5 ± 0.4 cm^2 and $68 \pm 10°$, respectively, at rest ($r = 0.4$; $p = 0.014$). EOA increased significantly to 2.0 ± 0.5 cm^2 at peak exercise ($p < 0.001$), showing an improved correlation with AL opening angle ($r = 0.6$; $p < 0.001$). Indexed EOA (EOAi) at peak exercise was an independent predictor of exercise capacity (maximal oxygen uptake, $p = 0.004$) and was independently associated with freedom from all-cause mortality or hospital admission for heart failure ($p = 0.034$). Patients with exercise EOAi <0.9 cm^2/m^2 ($n = 14$) compared with ≥ 0.9 cm^2/m^2 ($n = 25$) had a significantly worse outcome ($p = 0.048$). In multivariate analysis, AL opening angle at peak exercise ($p = 0.037$) was the strongest predictor of exercise EOAi.

CONCLUSIONS In RMA patients, EOA increases during exercise despite fixed annular size. Diastolic AL tethering plays a key role in this dynamic process, with increasing AL opening during exercise being associated with higher exercise EOA. EOAi at peak exercise is a strong and independent predictor of exercise capacity and is associated with clinical outcome. Our findings stress the importance of maximizing AL opening by targeting the subvalvular apparatus in future repair algorithms for secondary mitral regurgitation. (J Am Coll Cardiol 2015;65:452–61) © 2015 by the American College of Cardiology Foundation.

Secondary mitral regurgitation (MR) in ischemic and/or dilated heart disease is associated with an unfavorable prognosis (1,2). Restrictive mitral valve annuloplasty (RMA) has evolved as the gold standard treatment for severe secondary MR (3-6); however, recurrence of MR after RMA has an

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incidence of approximately 30% (7), and mitral valve replacement (MVR) has been proposed as a potential alternative in selected patients (8-11). In addition, several studies have demonstrated the occurrence of moderate mitral stenosis (defined as mean transmitral pressure gradient [TMG] >5 mm Hg or mitral valve area <1.5 cm^2) after RMA (12-16). Functional mitral stenosis after RMA is generally attributed to undersizing of the annular ring, yet the subvalvular apparatus might play a role as well. Importantly, the impact of such functional mitral stenosis on exercise capacity and clinical outcome remains unclear, mainly because most studies have based stenosis grading on the mean TMG at rest (13,14,16-19). However, this parameter is certainly flow dependent, potentially masking severe stenosis in low-flow patients (15). There are currently few data on the use of less flow-dependent parameters such as the effective orifice area (EOA) to quantify stenosis in RMA patients.

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The aim of this study was to investigate the hemodynamic, functional, and clinical impact of EOA after RMA and its relationship with diastolic anterior leaflet (AL) tethering at rest and during exercise.

METHODS

STUDY DESIGN AND STUDY POPULATION. We included consecutive patients who underwent RMA with a complete semirigid Physio ring (Edwards Lifesciences, Irvine, California), undersized by 1 or 2 sizes to obtain a minimal coaptation length of 8 mm in the A2-P2 segment, for secondary MR (Carpentier class IIIb, i.e., systolic leaflet restriction) between July 2007 and September 2012 at a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium). Exclusion criteria were structural leaflet abnormalities at surgical inspection, inability to undergo a supine bicycle exercise test, more than mild aortic regurgitation (AR) (vena contracta width >3 mm), and more than mild MR recurrence (vena contracta width >3 mm) at rest or during exercise. Eligible patients underwent a comprehensive resting transthoracic echocardiography (TTE) examination, followed by a semisupine symptom-limited bicycle exercise test with concomitantly performed TTE. The study complied with the Declaration of Helsinki, the protocol was approved by the local ethics committee, and written informed consent was obtained from all participating patients.

ECHOCARDIOGRAPHIC MEASUREMENTS. Resting and exercise echocardiography was performed with a commercially available system (Philips Medical Systems, IE33, Andover, Massachusetts). Standard 2-dimensional and Doppler images were acquired in the left lateral decubitus position and stored digitally for offline analysis in the CardioView software (TomTec Imaging Systems, Unterschleissheim, Germany). All measurements were averaged over 3 consecutive cardiac cycles for patients in sinus rhythm and 5 consecutive cycles for patients with atrial fibrillation according to the guidelines of the American Society of Echocardiography. The modified Simpson's biplane method was used to calculate ejection fraction at rest and peak exercise (20). Peak and mean TMG were calculated using the modified Bernoulli equation on the continuous-wave transmitral Doppler signal, with EOA calculated by the continuity equation (21). Systolic pulmonary artery pressure (sPAP) was calculated using the modified Bernoulli equation on the transtricuspid continuous-wave signal, while adding an estimate of right atrial pressure (22). Because patients with more than mild MR and AR were excluded, mean transmitral flow rate was defined as the ratio of left ventricular (LV) stroke volume (measured from pulsed wave Doppler in the LV outflow tract) over diastolic filling time. During each stage of exercise, LV stroke volume, transmitral flow rate, peak and mean TMG, sPAP, and EOA were assessed. The mitral AL opening angle was measured on 2-dimensional TTE in an apical long-axis view, both at rest and at peak exercise. Measures were taken at peak E-wave, and the angle of the maximal excursion of the AL was measured with respect to the plane of the prosthetic annular ring (**Central Illustration**).

EXERCISE TEST. All participating patients underwent a symptom-limited graded bicycle test in the semisupine position on a tilting exercise table. Workload was initiated at 20 W, with increments of 20 W every 3 min. In patients with poor general condition, an adjusted protocol was applied with 10 W of initial workload and increments of 10 W every 3 min. Blood pressure, a 12-lead electrocardiogram, ergospirometry (Jaeger, Würzburg, Germany), and echocardiography measurements were recorded at each stage.

CLINICAL ENDPOINTS. All-cause mortality and heart failure admissions (defined as hospitalization because of signs or symptoms of congestion that warranted treatment with parenteral drugs) were registered in all study patients from the day of surgery until July 31, 2014, which yielded a follow-up of at least

ABBREVIATIONS AND ACRONYMS

AL = anterior (mitral) leaflet
AR = aortic regurgitation
EOA = effective orifice area
EOAi = indexed effective orifice area
LV = left ventricle
MR = mitral regurgitation
MVR = mitral valve replacement
RMA = restrictive mitral valve annuloplasty
TMG = transmitral pressure gradient
TTE = transthoracic echocardiography
VO_2max = maximal oxygen uptake