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Regurgitant Volume Informs Rate of Progressive Cardiac Dysfunction in Asymptomatic Patients With Chronic Aortic or Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study hypothesized that regurgitation severity, as determined by using the regurgitant volume index, would better delineate differential cardiac dysfunction in asymptomatic patients with moderate to severe aortic regurgitation (AR) and mitral regurgitation (MR).

BACKGROUND Frequent surveillance echocardiography is considered appropriate in asymptomatic patients with moderate to severe AR and MR. However, the evidence to support this practice and to define the appropriate frequency is limited.

METHODS This was an observational cohort study of consecutive patients with moderate to severe asymptomatic AR or MR who underwent exercise echocardiography. Our cohort included 130 patients with moderate to severe asymptomatic MR and 130 patients with moderate to severe asymptomatic AR who were matched according to age and regurgitant volume index. All patients underwent yearly echocardiographic follow-up studies. Regurgitation severity was determined according to regurgitant volume index, with a level ≥30 ml/m^2 considered a marker of severe regurgitation.

RESULTS During follow-up, regardless of etiology, patients with severe regurgitation demonstrated increasing left ventricular volume indexes (4.2 ± 1.5 ml/m^2 per year; p = 0.01) and decreasing left ventricular ejection fractions (1.3 ± 0.4% per year; p = 0.002). In patients with moderate regurgitation, left ventricular volumes and ejection fractions did not significantly change. In addition, patients with severe regurgitation experienced a similar drop in contractility (end-systolic pressure/end-systolic volume ratio and single-beat pre-load recruitable stroke work) during follow-up independent of regurgitation etiology. Contractility parameters did not change in patients with moderate regurgitation.

CONCLUSIONS These asymptomatic patients with moderate AR or MR had stable cardiac function during 3 years of follow-up; thus, frequent echocardiography without a change in clinical status may not be necessary. In the setting of severe regurgitation, further cardiac deterioration occurred at a similar rate and manner irrespective of whether the dysfunction was related to AR or MR. (J Am Coll Cardiol Img 2015;8:14–23) © 2015 by the American College of Cardiology Foundation.

Details regarding follow-up at appropriate intervals and the subsequent management of asymptomatic patients with aortic regurgitation (AR) and mitral regurgitation (MR) have been debated (1–5). Current appropriate use criteria recommend routine surveillance echocardiography in patients with moderate to severe valvular regurgitation and no change in clinical status (6). However, the evidence to support this practice is limited and, as noted, there is no distinction according to whether the lesion is moderate or severe and involves either the aortic or mitral valve. Although patients with

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severe MR and AR demonstrate adverse remodeling with increased left ventricular (LV) volumes and decreased ejection fractions over time, the natural history of patients with less severe regurgitation is unclear (7,8). Furthermore, in the setting of the same amount of regurgitation, an assessment for a divergent decline in cardiac function according to valve lesion has not been performed. Such an evaluation would be clinically relevant because it would better define which parameters should be monitored and would more precisely determine the appropriate timing for interval echocardiography. Therefore, we investigated whether regurgitant volume would inform the rate of differential decline in cardiac function in asymptomatic patients with moderate to severe MR or AR.

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METHODS

STUDY SAMPLE. This was an observational cohort study of consecutive patients with moderate to severe isolated asymptomatic AR or MR who underwent exercise echocardiography at the Cleveland Clinic between January 2007 and January 2012 (9,10). Patients with AR and MR were matched according to age (within 5 years) and regurgitant volume index (within 5 ml/m^2) by using a random number generator to assure lack of bias. Because age is a strong predictor of progression of any disease and has a profound impact on cellular mechanisms that determine myocardial response to overload (11), we used age to match AR and MR patients to exclude the effect of this factor. All patients had preserved LV size and function according to valvular heart disease guidelines (2). These included the following: for AR, LV ejection fraction >50%, LV end-diastolic diameter <70 mm, LV end-systolic diameter <50 mm, or LV end-systolic diameter/body surface area <25 mm/m^2; and for MR, LV ejection fraction >60% or LV end-systolic diameter <45 mm. All patients underwent at least 1 yearly echocardiographic follow-up study, according to the guidelines. We excluded patients with more than mild concomitant valvular disease, atrial fibrillation or flutter, and stress-induced myocardial ischemia or scar. All patients underwent symptom-limited exercise treadmill testing using standard treadmill protocols with 12-lead electrocardiography monitoring. The maximal exercise tolerance was expressed as estimated metabolic equivalents (METs). Predicted exercise capacity was calculated in accordance with described nomograms (predicted METs; in male subjects, 18 − [0.15 × age]; in female subjects, 14.7 − [0.13 × age]) (12), and percent predicted METs were described as the difference between actual and predicted METs divided by predicted METs. The protocol was approved by the Cleveland Clinic Institutional Review Board.

ECHOCARDIOGRAPHIC ASSESSMENT. Transthoracic echocardiography was performed by experienced sonographers using a commercially available ultrasound machine (Vivid 7 or Vivid 9, GE Vingmed, Horten, Norway; Sonos 5500 or iE33, Philips Healthcare, Andover, Massachusetts). Measurements and recordings were obtained according to the American Society of Echocardiography recommendations (13). Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial volume (LAV), and LV ejection fraction were calculated by using the biplane Simpson disk method using 2-dimensional images and indexed to body surface area. The LV mass was estimated from the formula of Devereux and Reichek (14). Right ventricular systolic pressure (RVSP) was estimated from the maximal continuous wave Doppler velocity of the tricuspid regurgitant jet by using a systolic transtricuspid pressure gradient calculated according to the modified Bernoulli equation. Quantification of regurgitant volume was performed by using the quantitative Doppler method: the difference between valve stroke volume and systemic stroke volume (15). LV meridional end-systolic wall stress (ESS_m), as a measure of LV afterload, was calculated from the formula of Grossman et al. (16). Because the averaged body surface area in our population was 2.0 m^2 and because the cutoff value for severe regurgitant volume is 60 ml for both AR and MR according to the current guidelines (15), we selected the indexed value of ≥30 ml/m^2 to indicate severe valve regurgitation to eliminate the impact of body size on gradation of regurgitant severity.

CONTRACTILITY ASSESSMENT. Two markers of contractility were used: end-systolic pressure-volume ratio (ESPVR) (a surrogate for LV systolic elastance) and single-beat pre-load recruitable stroke work (PRSW). End-systolic pressure was calculated using estimations from the previous study (i.e., end-systolic pressure = 0.9 × brachial systolic pressure) (17). ESPVR and PRSW were calculated using the following formulas: ESPVR = end-systolic pressure/left ventricular end-systolic volume index [LVESVI]; PRSW = (stroke volume × mean aortic pressure)/(0.28 × LVEDV + 0.28 × LV wall volume) (18,19). Because ESPVR and

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

ESPVR = end-systolic pressure-volume ratio

ESS_m = meridional end-systolic wall stress

LAV = left atrial volume

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEDVI = left ventricular end-diastolic volume index

LVESV = left ventricular end-systolic volume

LVESVI = left ventricular end-systolic volume index

METs = metabolic equivalents

MR = mitral regurgitation

PRSW = single-beat pre-load recruitable stroke work

RVSP = right ventricular systolic pressure