Stress Echocardiography in Regurgitant Valve Disease

Patrizio Lancellotti, MD, PhD; Julien Magne, PhD

Because of its wide availability, low cost, versatility, and clinical use, stress echocardiography has become increasingly recognized as a valuable tool in the assessment of patients with regurgitant valvular heart disease. Exercise testing is favored compared with pharmacological stress testing for risk stratification in asymptomatic patients and can identify what might otherwise be considered as a moderate valve disease. It has been shown to provide insights into exertional symptoms disproportionate to resting hemodynamics in these patients and to facilitate individual risk stratification. Aggravation of valvular regurgitation severity, exercise-induced pulmonary hypertension (PHT), impaired left ventricular (LV) contractile reserve, inducible ischemia, dynamic LV dyssynchrony, and altered exercise capacity, together with the development of symptoms during exercise echocardiography, provide the clinician with straightforward prognostic information, therefore enabling a more accurate definition of the optimal timing of intervention in patients with valvular regurgitation. In contrast, dobutamine stress echocardiography has little value in cases of valvular regurgitation. Dobutamine infusion is almost systematically associated with a decrease in the severity of regurgitation; however, it might be of interest in the detection of LV contractile reserve and inducible ischemia.

Exercise Echocardiography and Protocols

The most common form of exercise used in conjunction with echocardiography is immediate postexercise imaging on a treadmill or upright bicycle ergometer. However, semisupine exercise testing on an appropriate tilted table allows continuous echocardiographic monitoring, which represents an advantageous tool for quantifying changes in valvular regurgitation severity, LV function, and pulmonary pressure (Table). This exercise stress echocardiography modality (ie, per-exercise echocardiography) is the most used in Europe, and we strongly suggest this approach in the setting of valvular heart disease to detect evanescent changes. A symptom-limited graded exercise test is recommended, and ≥80% of the age-predicted upper heart rate should be reached in the absence of symptoms. The test is adapted to the clinical conditions and should be performed under the supervision of an experienced person. Typically, the initial workload of 25 W is maintained for 2 minutes, and the workload is increased every 2 minutes by 25 W. An increase in steps of 10 W seems to be more appropriate in patients with a low level of physical activity (ie, heart failure).

Exercise echocardiography enables the assessment of various echocardiographic parameters related to the valves, the hemodynamics, and the LV (Figure 1). Because some valve-related exercise changes are evanescent, peak exercise imaging is mandatory. Apart from changes in E/e′—an estimate of LV filling pressure—that are obtained at low-level exercise (≈95–105 bpm, before e′ and a′ wave fusion), all other parameters should be obtained throughout the test. The kinetic changes in LV contractile function and transri- cuspoid pressure gradient need to be assessed, especially in patients with mitral regurgitation (MR). A rapid increase in pressure gradients can indicate a more severe disease process or an absence of pulmonary vascular function adaptation, low pulmonary compliance, and markedly increased pulmonary resistance. Nonetheless, the dynamic changes in systolic pulmonary arterial pressure (SPAP) and the occurrence of exercise PHT should be interpreted with caution and analyzed in light of age, exercise load, and changes in systemic blood pressure and cardiac output. A worsening in wall motion from the baseline classically indicates an inducible ischemia as a result of exhausted coronary reserve, with or without coronary artery disease. The absence of LV contractile reserve is characterized by a small change in the LV ejection fraction or the longitudinal function (derived from tissue Doppler imaging or 2-dimensional speckle tracking).

In practice, image recordings are obtained in a stepwise order at baseline, low, medium, and high levels of exercise and at peak test. Figure 1 shows an example of exercise stress test protocol.

Mitral Regurgitation

MR is a common and progressive disease that is difficult to manage. MR is roughly classified as primary (ie, organic/structural: intrinsic valvular disease) or secondary (ie, functional/nonstructural: without evident structural abnormalities of the mitral valve). The clinical value of exercise echocardiography has been extensively demonstrated in patients with MR.

Primary MR

Exercise-Induced Changes in MR

An asymptomatic 42-year-old man diagnosed in 2007 with mitral valve prolapse inducing moderate MR was referred to
our echocardiography laboratory for an exercise stress echocardiography. The patient had no reference to comorbidities and medication. Previous echocardiography reported the presence of moderate primary MR without harmful consequences to the LV (ie, no dilation/dysfunction) and no PHT. The resting echocardiogram confirmed these previous findings and noted the presence of a P2 prolapse, an A2 billowing without obvious leaflet tissue redundancy, and calcification of the anterior mitral annulus. The presence of moderate MR was confirmed by the quantitative assessment of MR severity (ie, an average of both proximal isovelocity surface area (PISA) and Doppler volumetric methods; effective regurgitant orifice [ERO], 27 mm²; regurgitant volume, 49 mL; Figure 2). The LV dimension was normal, the LV ejection fraction was 63% using the Simpson method, and the SPAP was 35 mmHg. The patient reached an exercise load of 125 W (9 metabolic equivalents

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<th>Characteristics</th>
<th>Upright/Treadmill Exercise Test</th>
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<tr>
<td>Image acquisition</td>
<td>Rest</td>
<td>+</td>
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<td></td>
<td>Intermediate level</td>
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<td></td>
<td>Postexercise</td>
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<td>Postexercise</td>
<td>(within 90 s after test termination)</td>
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<td>Advantages</td>
<td>Same position for image acquisition</td>
<td>-</td>
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<td></td>
<td>Kinetic of changes in SPAP, in MR</td>
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<td>E/e' at low level</td>
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<td>Contractile reserve</td>
<td>+ (if at peak test present)</td>
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<td></td>
<td>Biphasic wall motion changes</td>
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<td>Ischemic threshold</td>
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<td>Limitations related to the change in posture for image acquisition</td>
<td>Changes in loading conditions</td>
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<td>Drop in heart rate and blood pressure</td>
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MR indicates mitral regurgitation; and SPAP, systolic pulmonary arterial pressure.

Figure 1. Stepwise Doppler echocardiography image acquisitions in patients with mitral regurgitation (MR) or aortic regurgitation. *Estimation of left ventricular (LV) filling pressure (E/e' ratio) could be obtained only if chronotropic conditions permit it; SPAP indicates systolic pulmonary arterial pressure.
and stopped exercising suddenly as a result of exertional dyspnea. Throughout the test, echocardiography revealed a marked increase in MR severity (ERO, 53 mm²; regurgitant volume, 77 mL). The SPAP also increased significantly (76 mmHg) during the test.

This case emphasizes the fact that primary MR may be dynamic and significantly worsen during exercise, frequently resulting in the development of exercise PHT. As a result of these exercise findings, it was decided that this patient would be followed up closely every 6 months rather than being monitored every 1 to 2 years as recommended in the guidelines. After 1.5-year follow-up, the patient developed severe MR at rest and overt signs of low-exercise abnormal dyspnea and was then referred for mitral valve repair.

**Dynamic PHT**

A 57-year-old inactive woman with moderate obesity (body mass index, 32 kg/m²), diabetes mellitus, systemic hypertension, and a loud systolic murmur was referred to our echocardiographic laboratory in June 2009. The patient reported ambiguous symptoms, such as mild dyspnea when climbing stairs, and had a normal sinus rhythm. At rest, the echocardiogram revealed the presence of a mitral flail leaflet associated with severe MR. The LV ejection fraction was normal (68%), the LV was not dilated (LV end-systolic diameter, 38 mm), and the SPAP was slightly elevated (44 mmHg). At a low level of exercise (ie, 75 W), the MR degree seemed to be more severe than at rest (quantification inaccurate because of poor quality images). Concomitantly, the patient developed severe dyspnea and stopped the test. In contrast to MR severity quantification, the measurement of SPAP was feasible and showed exercise PHT (SPAP, 87 mmHg). This case also underlines the fact that exercise can induce an increase in MR severity that can trigger exercise PHT and dyspnea. During follow-up, the patient developed resting dyspnea and fatigue and underwent isolated mitral valve surgery in July 2010.

**Contractile Functional Reserve**

A 68-year-old asymptomatic man with moderate-to-severe MR (ERO, 36 mm²; regurgitant volume, 54 mL) caused by Barlow disease was examined in our heart valve clinic in September 2011. The patient had no valvular indication for surgery. During exercise, the patient exhibited a significant increase in MR severity (ERO, 57 mm²; regurgitant volume, 70 mL) and an apparent increase in LV ejection fraction (from 65% to 72%), suggesting the presence of LV contractile reserve. Conversely, the analysis of 2-dimensional speckle tracking of myocardial deformation during exercise depicted a significant decrease in global longitudinal strain (GLS) from −26% to −17%, which indicated the absence of LV contractile reserve. The brain natriuretic peptide level measurement increased significantly from rest (89 pg/mL) to peak test (176 pg/mL). Cardiac magnetic resonance was performed and identified the presence of mid-wall myocardial fibrosis highlighted by late gadolinium hyper-enhancement (Figure 3), despite the absence of coronary artery disease. One year later, the patient was admitted for a first episode of heart failure with reduced LV ejection fraction (43%) and was successfully operated in January 2013. This case demonstrates that the absence of LV contractile reserve as assessed by 2-dimensional speckle tracking measurement of long-axis function can identify the presence of latent subclinical LV myocardial dysfunction, whereas the LV ejection fraction frequently
underestimates the extent of intrinsic myocardial dysfunction. In addition, no improvement in LV longitudinal function during exercise may be related to the presence of myocardial fibrosis and increased LV wall stress, as revealed by an elevated brain natriuretic peptide level at rest and during exercise.

Discussion
In asymptomatic patients with ≥moderate primary MR, exercise stress echocardiography may reveal dynamic MR (ie, a marked increase in MR severity) in approximately one third of cases. More importantly, between 32% and 66% of patients with moderate MR may develop severe MR during exercise.5 This phenomenon is often associated with exercise-induced PHT because of the close relationship between the increase in MR and SPAP.6,8 Both dynamic MR and exercise PHT may precipitate symptom onset in the short-term follow-up. The level of increase in SPAP depends on the ability to recruit the pulmonary vasculature successfully to accommodate increased blood flow with exercise, the contribution (or proportion) of the reduction in cross-sectional area of pulmonary circulation, the changes in pulmonary vascular compliance, resistance and impedance, and the increase in left atrial pressure, each of which may be abnormal at rest. In addition, the level of exercise SPAP should be cautiously interpreted in light of patient’s age and exercise workload.

Exercise stress echocardiography may also enable the identification of latent LV myocardial dysfunction.9–11 The absence of LV contractile reserve, as assessed by 2-dimensional speckle tracking measurement of LV GLS, is a powerful marker of reduced cardiac event–free survival and predicts early postoperative LV decompensation.11

During exercise, the increase in LV function allows adequate adaptation of LV forward stroke volume and cardiac output to central and peripheral demands. In addition to chronotropic adaptation, LV improves contractility with an increase in longitudinal shortening and circumferential and radial thickening. However, the long-axis function (longitudinal myocardial fibers) is known to be more sensitive to any myocardial disease process than the short-axis (circumferential fibers) function. Hence, GLS is the first to be reduced in the presence of intrinsic myocardial dysfunction even if the LV ejection fraction remains preserved. Patients with a slight increase in LV GLS <2% at exercise are those with limited LV contractile reserve. Recent studies have shown that GLS correlates more accurately with brain natriuretic peptide level than LV ejection fraction, both at rest and during exercise.12,13 The lack of specificity of exercise changes in LV ejection reflects its load dependency. Indeed, the increase in MR during exercise is artificially accompanied by an increase in LV ejection fraction even in the presence of latent LV dysfunction. Conversely, exercise changes in GLS are less load-dependent and less affected by the dynamic behavior of MR.

In the current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines, exercise PHT is now considered as a class IIb indication for mitral valve repair in asymptomatic patients without LV dysfunction/dilatation.1,2 Consequently, patients with an exercise-induced marked increase in MR severity and exercise PHT
could benefit from early elective mitral valve surgery. In addition, because the lack of LV contractile reserve is independently associated with reduced cardiac event–free survival, elective surgery could also be contemplated in asymptomatic patients with severe MR. When treated medically, these patients should be followed up very closely (ie, 3–6 months). Conversely, asymptomatic patients without exercise PHT or with LV contractile reserve could be monitored annually. Nevertheless, such a management strategy for asymptomatic patients with primary MR requires validation in large prospective trials.

In daily practice, exercise Doppler echocardiography is a reasonable method to use in asymptomatic patients with moderate-to-severe primary MR with preserved LV ejection fraction for immediate risk stratification and to guide the timing of mitral valve surgery, especially for those in whom the risk-to-benefit ratio of surgical intervention is uncertain (doubt about reparability, elderly patients, or comorbidities). The clinical value of serial testing needs to be addressed.

**Secondary Dynamic MR**

**Inducible Ischemia and Dynamic MR**

A 61-year-old noninsulin-dependent diabetic patient with chronic obstructive pulmonary disease (GOLD II), was admitted with acute pulmonary edema in 2005. Other risk factors were active smoking, systemic hypertension, and overweight. No angina pectoris was noted. She was in sinus rhythm (92 bpm) and had a normal blood pressure (140/80 mm Hg). Troponin was in the lower normal range, and ECG showed a sinus rhythm with negative T waves in the inferolateral leads. After stabilization, she underwent a comprehensive echocardiogram completed by an exercise test. At rest, mild MR and inferoposterior hypokinesia were noted. During exercise, the degree of MR increased significantly, which induced severe PHT (Figure 4, Movie I in the online-only Data Supplement). At low-level exercise, wall motion improved in the posterior region but deteriorated at a high workload, indicating the presence of severe right coronary stenosis (red arrow).

**Figure 4.** Dynamic increase in mitral regurgitation severity during exercise echocardiography. ERO indicates effective regurgitant orifice; R Vol, regurgitant volume; and TTPG, transtricuspid pressure gradient (an estimate of pulmonary arterial systolic pressure).

**Figure 5.** Exercise echocardiographic recordings (end-systolic frames) showing a biphasic response (viable myocardium at jeopardy) characterized by an improvement in wall motion at low level of exercise followed by a subsequent deterioration at high level of exercise (white arrows) secondary to severe right coronary stenosis (red arrow).
of a biphasic response (viable myocardium at jeopardy; Figure 5, Movie II in the online-only Data Supplement). Coronary angiography showed a right coronary artery stenosis, which was dilated and stented. The LV function normalized and the dynamic behavior of MR disappeared during control exercise echocardiography performed a month later. This case demonstrates that dynamic MR may sometimes be secondary to transient ischemia.

**Exercise Dyssynchrony and MR Changes**

A 57-year-old patient (risk factors: smoking, hypertension, hypercholesterolemia) who had an inferior acute ST-segment elevation myocardial infarction in 1997. At that time, he underwent elective percutaneous coronary angioplasty completed by the implantation of a bare metal stent in the right coronary artery. Before hospital discharge, a pacemaker was implanted for high atrioventricular block. He was in New York Heart
Association Class II under medical treatment. After a couple of years, his clinical condition deteriorated (New York Heart Association Class III), and he developed several episodes of acute dyspnea, despite maximum tolerated drug therapy (lisinopril 20 mg, bisoprolol 10 mg, spironolactone 25 mg, furosemide 40 mg, nitrates before exertion). The QRS duration was 118 ms. In resting Doppler echocardiography, the LV systolic function was severely impaired (ejection fraction 28%) with severe inferoposterior wall motion dyssynergy. The mitral valve was markedly deformed, and significant MR was observed. A moderate septolateral dyssynchrony and a slight LV apical rocking motion were also noted. An exercise Doppler echocardiography was performed to evaluate the functional capacity, but the test was interrupted because of significant dyspnea. Color Doppler identified a severe dynamic increase in MR with an ERO of 45 mm² (Movie III in the online-only Data Supplement). The SPAP reached 87 mmHg (transtricuspid pressure gradient, 77 mmHg), which was slightly increased under baseline conditions. The degree and extent of LV dyssynchrony also increased during exercise (Figure 6). No ischemia was observed (Movie IV in the online-only Data Supplement). Taking into account these data, a decision was made to refer the patient for biventricular pacing implantation. After cardiac resynchronization therapy, his clinical condition improved. However, he came back a year later with acute heart failure because of recurrent inferior myocardial infarction, which resulted in a loss of effective pacemaker stimulation (Figure 7). This case demonstrates that exercise aggravation of dyssynchrony and MR can trigger exertional dyspnea and clinical deterioration in systolic heart failure.

Pulmonary Edema and Dynamic MR
An 83-year-old patient with severe ischemic LV dysfunction because of anterolateral myocardial infarction and marked LV remodeling. In 2005, he was admitted to our intensive care unit with acute pulmonary edema. A few days after stabilization, coronary angiography excluded any significant coronary stenosis. The medical treatment was then progressively intensified (bisoprolol 5 mg, perindopril 5 mg, spironolactone 25 mg, furosemide 80 mg). Before hospital discharge, an exercise echocardiography was performed. The resting echocardiographic evaluation confirmed the presence of severe LV dysfunction (ejection fraction, 22%) and showed moderate MR. After 4 minutes, he stopped because of severe dyspnea (35 W). The heart rate changed slightly (73–78 bpm), whereas the blood pressure increased significantly (104/66–164/85 mmHg). There was no chest pain and ECG modifications. The test demonstrated no viability in the anterior wall, and the MR became severe with marked PHT (Figure 8A and 8B; Movie Va and Vb in the online-only Data Supplement). A diagnosis of acute heart failure worsening because of dynamic MR was then suspected, and the patient was sent home. A few weeks after discharge, he was readmitted with a second episode of acute pulmonary edema, and again he came through this event with medical therapy. However, the echocardiogram performed during the episode showed significant MR (Figure 8C, Movie VII in the online-only Data Supplement), which confirmed that dynamic MR could trigger pulmonary edema in patients with systolic LV dysfunction. He passed away after the 6-month follow-up.
Discussion
When present, secondary MR may exhibit a broad range of severity and convey a worse outcome. Rarely, exercise-induced increase in MR occurs as a consequence of acute transient ischemia (case 1). This type of dynamic MR is often clinically revealed by a flash pulmonary edema and may be easily identified using exercise stress echocardiography. It should indicate coronary angiography to demonstrate the presence of a significant right or circumflex coronary artery stenosis, which when dilated solves the problem.

In chronic secondary MR, although there is a correlation between the rise in MR during exercise and the increase in SPAP, the degree of MR at rest is unrelated to the magnitude of MR changes during exercise. Dynamic MR is strongly related to exercise-induced changes in mitral valve configuration at both ends of tethered leaflets and to intermittent changes in LV synchronicity (case 2). Characteristically, dynamic secondary MR occurs independently of detectable myocardial ischemia. The increase in MR is more pronounced in patients with exercise-limiting dyspnea and in those hospitalized for acute pulmonary edema (case 3), and the acute increase in MR during exercise independently predicts cardiac death and heart failure admission. An exercise increase by >13 mmHg in MR ERO has been identified as the cutoff point for predicting an increased risk of cardiac events. Considering the adverse prognostic implications of dynamic exercise MR in patients with moderate secondary MR, the development of dyspnea secondary to increased severity of MR and PHT during exercise echocardiography is considered as a further incentive to perform a combined mitral valve repair at the time of surgical coronary revascularization (European Society of Cardiology class IIa). Of note, combined surgery, such as biventricular pacing (case 2), can potentially reduce the dynamic component of MR during exercise.

In daily practice, exercise Doppler echocardiography can provide useful information in the following cases of patients with secondary MR: (1) those with exertional dyspnea out of proportion with the severity of resting LV dysfunction or MR, (2) those in whom acute pulmonary edema occurs without an obvious contributing factor, (3) those with moderate MR.

Figure 9. Echocardiographic assessment of an asymptomatic patient with severe aortic regurgitation. At rest, left ventricular ejection fraction (LVEF) is in the low normal range, as well as the peak systolic velocity (Sv), obtained by tissue Doppler imaging. During exercise, the LVEF decreases slightly, and the increase in Sv is low, suggesting the presence of latent left ventricular dysfunction. After aortic valve replacement, a moderate LV dysfunction persisted.
before surgical revascularization, (4) those in whom individual risk stratification is requested, and (5) those operated on for mitral valve problems but with persistent postoperative PHT.

Aortic Regurgitation
Severe aortic regurgitation (AR) gradually leads to LV dysfunction, heart failure symptoms, and increased risk of sudden death. Symptomatic patients have an excessive mortality rate and a firm indication for aortic valve replacement.

Absence of Contractile Reserve
A 57-year-old patient who has been regularly followed in our heart valve clinic for severe asymptomatic AR. Cardiovascular risk factors include cigarette smoking, hypercholesterolemia normalized with simvastatin, and well-controlled systemic hypertension (candesartan 16 mg QD). At the last echocardiographic check-up, borderline values in terms of LV end-systolic diameter were observed (end-systolic diameter, 53 mm). She denied having any symptoms, but described a limitation in her daily life activities. An exercise echocardiography was performed and failed to demonstrate any rise in LV ejection fraction at exercise (Movie VIII in the online-only Data Supplement). Such an absence in contractile reserve was confirmed by the small increment in peak systolic velocities using tissue Doppler imaging. A moderate dyspnea was noted at peak test. Taking everything into account (severe AR, absence of contractile reserve, borderline values in terms of diameters, moderate exercise dyspnea), she was referred for an aortic valve replacement. After the intervention, a moderate LV dysfunction was observed (ejection fraction, 45%). This case demonstrates that exercise echocardiography could also be used to unmask latent LV dysfunction in AR (Figure 9).

Discussion
Exercise stress testing is reasonable for the assessment of functional capacity and symptomatic status in patients with severe AR and equivocal symptoms (American College of Cardiology/American Heart Association, class IIa). However, only a few studies with a small number of patients have evaluated AR with quantitative exercise stress imaging.19–25 When performed, attention should be focused on LV ejection fraction at exercise. Using radionuclide ventriculography, Borer et al26 showed abnormal exercise LV ejection fraction to be common in patients with AR and normal LV function at rest. However, the observed magnitude of change in ejection fraction from rest to exercise seems to be related not only to myocardial contractile function, but also to severity of volume overload and exercise-induced changes in preload and peripheral resistances. In asymptomatic or minimally symptomatic patients with AR, Bonow et al21,22 showed that the LV ejection fraction response to stress was related to the degree of LV dilatation at rest, with reduction of exercise ejection fraction in the majority of patients with an end-systolic diameter >50 mm. Conversely, Goldman et al23 found no correlation between the ejection fraction response to exercise and the resting LV dimensions or ejection fraction in patients with AR.23 However, the subgroup with an abnormal ejection fraction response to exercise was characterized by an increase in peak systolic wall stress. When the changes in LV ejection fraction with exercise were normalized for the changes in end-systolic wall stress, Borer et al20 showed that this complex parameter independently predicted the outcome. Subsequent studies confirmed that failure to reduce end-systolic volume or increase the ejection fraction at exercise was specific for predicting LV dysfunction at follow-up, with earlier need for surgery24 and higher event rates.25–26 Limited data support the use of exercise echocardiography in patients with AR. In 61 patients with asymptomatic or minimally symptomatic AR, Wahi et al27 reported that contractile reserve on exercise echocardiography was a better predictor of LV decompensation after surgery than resting indices of LV function. The absence of contractile reserve—decrease in LV ejection fraction by 5% at exercise—seems, thus, to identify the presence of latent LV dysfunction earlier than conventional echocardiographic parameters obtained at rest.19 Recently, Park et al28 reported a significant discordance between the presence of contractile reserve and the LV dimension recommended for aortic valve replacement. In their study, one third of patients with larger dimensions were contractile reserve (+), whereas one third of patients with smaller LV dimensions not qualifying for surgery did not have contractile reserve, suggesting that exercise test may be able to further stratify the current guidelines for aortic valve replacement. Color tissue Doppler imaging for measuring systolic mitral annulus velocities may be used as a surrogate marker of long-axis and subclinical LV dysfunction.

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None.

References


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