

TREADMILLS, BIKES, AND DRUGS

ROLE OF STRESS IN CLINICAL DECISION MAKING

Early Identification of Decompensated Aortic Regurgitation With Stress Echocardiography



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INTRODUCTION

Most patients with chronic aortic regurgitation (AR) have a slow and insidious disease progression with an estimated annual progression (aortic valve replacement [AVR] or death) rate of approximately 6%.¹ The optimal timing for surgical intervention continues to be debated. Current guidelines recommend AVR for patients with severe AR at the onset of symptoms or once left ventricular (LV) ejection fraction (LVEF) is <55% (class I) or with significant cavity dilatation defined as LV end-systolic diameter of (LVESD) > 50 mm, indexed LVESD > 25 mm (class IIa), or progressive severe LV dilation (LV end-diastolic diameter [LVEDD] > 65 mm; class IIb).² However, adverse LV remodeling including subclinical LV dysfunction and fibrosis often precedes these guideline-recommended thresholds and prevents postoperative myocardial recovery.

Here we present a patient with long-standing asymptomatic AR who did not meet the current guideline criteria for surgical intervention but demonstrated LV systolic dysfunction during exercise echocardiography, prompting referral for AVR. This case highlights the capacity of stress echocardiography to evaluate contractile reserve (CR) and uncover subclinical LV systolic dysfunction due to decompensated AR and identify patients who might benefit from earlier intervention.

CASE PRESENTATION

A 63-year-old man with a medical history of hypertension and hyperlipidemia was referred to the cardiac valve clinic for evaluation of asymptomatic AR noted incidentally on a screening echocardiogram performed to evaluate a heart murmur. The patient reported being

VIDEO HIGHLIGHTS

Video 1: Transthoracic parasternal long-axis view of aortic valve with color Doppler showing severe AR.

Video 2: Transesophageal short-axis view of the aortic annulus showing fenestration of right coronary cusp in color Doppler comparison mode.

Video 3: Transesophageal focused three-chamber view in color Doppler comparison mode demonstrating severe eccentric regurgitant jet.

Video 4: Transthoracic echocardiogram apical four-chamber view showing normal LV wall motions at rest.

Video 5: Transthoracic echocardiogram apical four-chamber view showing hypokinesia of the apex and inferoseptum at peak stress.

Video 6: Transthoracic echocardiogram apical two-chamber view showing normal LV wall motions at rest.

Video 7: Transthoracic echocardiogram apical two-chamber view showing LV wall motions at peak stress.

Video 8: Transthoracic echocardiogram apical three-chamber view showing normal LV wall motions at rest.

Video 9: Transthoracic echocardiogram apical three-chamber view showing hypokinesia of anteroseptum at peak stress.

Video 10: Coronary angiogram showing patent epicardial vessels.

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well, exercising regularly, and performing vigorous physical activity without any cardiovascular symptoms. On physical examination, the patient had a normal body habitus without marfanoid features. His blood pressure was 110/54 mm Hg, and his heart rate was regular at 70 bpm. Cardiac examination revealed a prominent apical impulse, LV third heart sound (S3), and diastolic decrescendo blowing murmur (grade III/IV) best heard over the right second intercostal space. Chest examination revealed bilateral normal air entry with no added sounds. The rest of the physical examination was unremarkable. An echocardiogram performed in the valve clinic revealed severe AR (regurgitant volume 98 mL), normal LV systolic function, and normal cavity dimensions with LVESD measuring 37 mm and LVEDD measuring 55 mm (Figure 1A,B, Video 1). A transesophageal echocardiogram was performed for definitive evaluation of the severity and mechanism of AR and revealed a mildly thickened trileaflet aortic valve with focal prolapse and fenestration of the right coronary cusp as

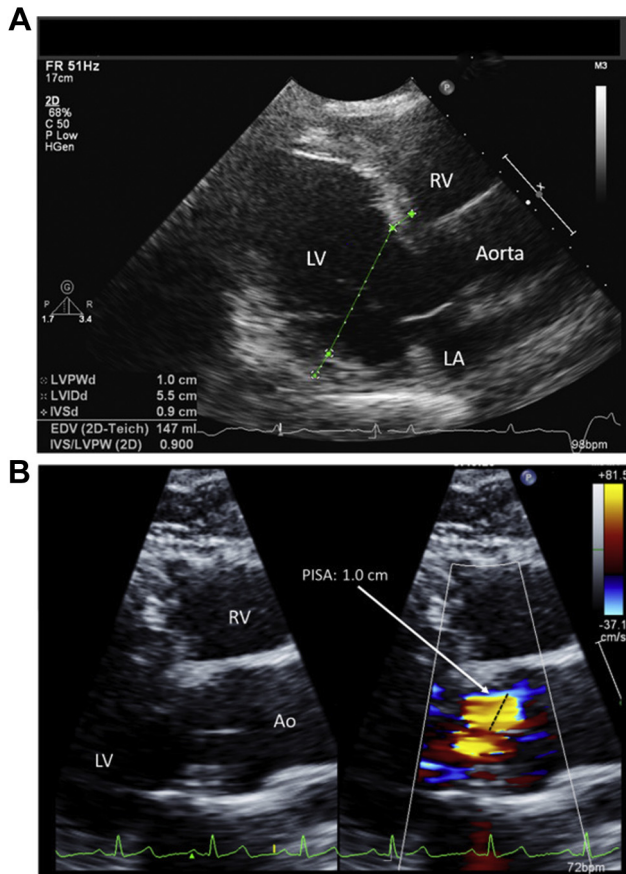


Figure 1 (A) Transthoracic parasternal long-axis view showing LVEDD, measuring 55 mm. (B) Transthoracic parasternal long-axis view of aortic valve with color Doppler showing proximal isovelocity surface area measurement (arrow; Supplemental Video 1, available at www.onlinejase.com). Ao, Aorta; LA, left atrium; RV, right ventricle.

the etiology of AR while confirming the severity (Figure 2 and Figure 3, Videos 2 and 3). In the absence of an indication for AVR, he was followed in the cardiac valve clinic annually with serial echocardiograms. Four years later, an echocardiogram revealed mild cavity dilatation (LVEDD of 62 mm and LVESD of 42 mm, indexed LVESD of 19 mm), with LVEF of 60%. The patient remained asymptomatic while leading his normal active lifestyle. He then underwent a stress echocardiogram for objective assessment of his functional status and symptoms. He exercised for 8 minutes on a standard Bruce protocol (10 metabolic equivalents, 100% of maximum predicted heart rate) with an appropriate systolic blood pressure response from resting blood pressure of 140/55 mm Hg to 190/80 mm Hg before developing mild dyspnea. Electrocardiogram had nondiagnostic ST-segment depressions at peak exercise in the anterolateral leads that persisted late into the recovery phase. An echocardiogram at peak stress revealed severe LV cavity dilatation (LVEDD of 72 mm and LVESD of 55 mm) along with hypokinesis of the apex, anteroseptum, and inferoseptum resulting in a depressed LVEF of 40% (Figure 4, Videos 4-9). Subsequent coronary angiography showed no obstructive disease (Figure 5A,B, Video 10), indicating that the exercise-induced LV dysfunction represented subclinical LV dysfunction due to adverse ventricular remodeling from AR. He underwent surgical AVR without any complications. Although LV systolic function was low-normal (LVEF 50%-55%) 2 months postoperatively, a repeat study a year later showed normal cavity dimensions (LVEDD of 53 mm and LVESD of 27 mm) and a recovered LV systolic function with an estimated LVEF of 60%. The patient continued to maintain an excellent functional status.

DISCUSSION

Natural history studies of patients with significant AR have demonstrated that the majority of patients remained asymptomatic with normal systolic function for over a decade but also identified a subset of patients who had already developed irreversible LV dysfunction before the onset of the symptoms.^{3,4} Current guidelines recommend AVR for severe AR at the onset of symptoms, LV systolic dysfunction

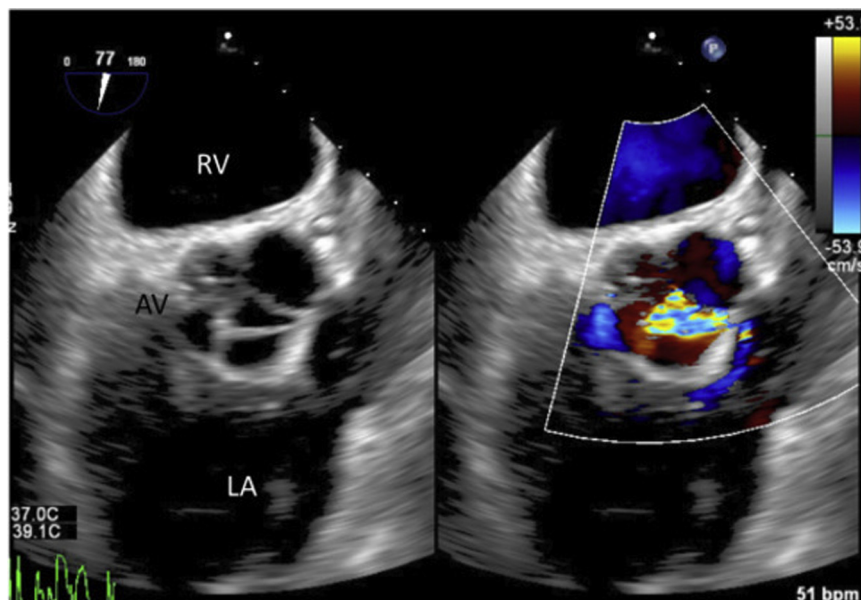


Figure 2 Transesophageal short-axis view of the aortic annulus showing fenestration of right coronary cusp in color Doppler comparison mode (Supplemental Video 2, available at www.onlinejase.com). Ao, Aorta; LA, left atrium; RV, right ventricle.

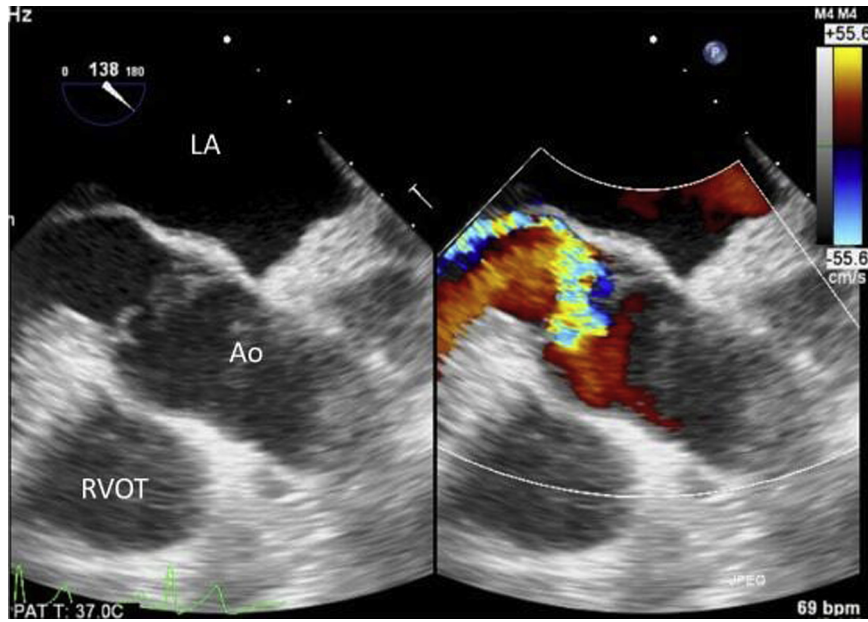


Figure 3 Transesophageal focused three-chamber view in color Doppler comparison mode demonstrating severe eccentric regurgitant jet with vena contracta > 0.6 cm (Supplemental Video 3, available at www.onlinejase.com). Ao, Aorta; LA, left atrium; RVOT, right ventricular outflow tract.

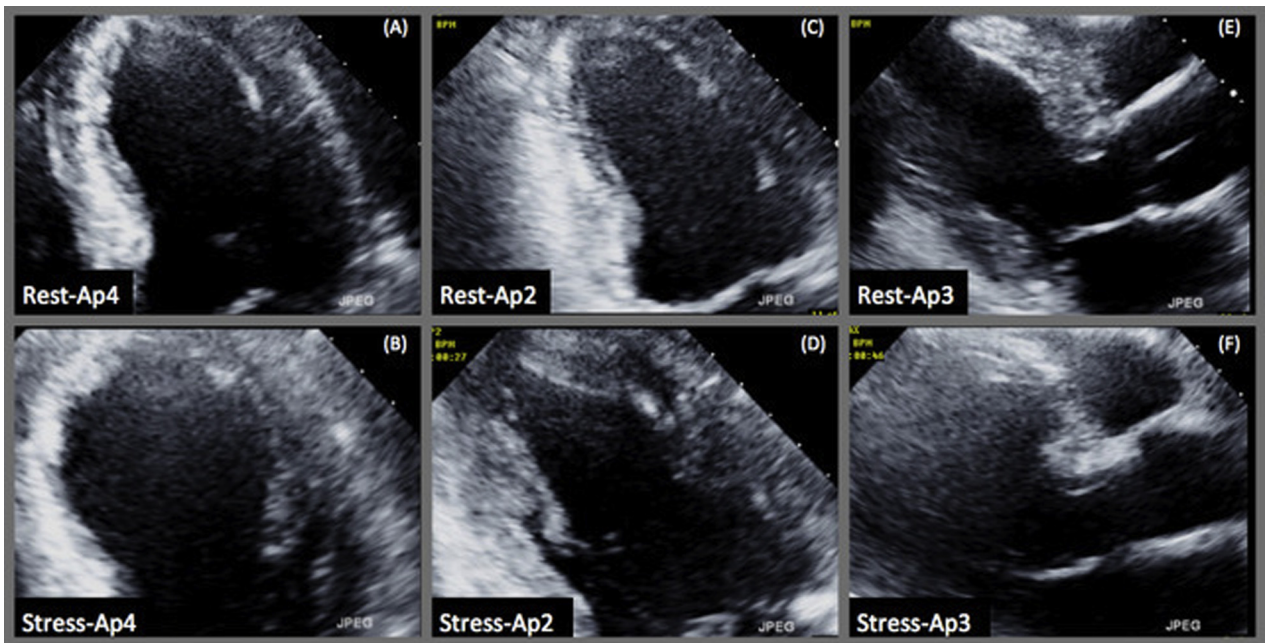


Figure 4 Stress echocardiogram apical four-chamber view showing hypokinesia of the apex and inferoseptum. (A) Four-chamber end-systolic frame at rest (Supplemental Video 4, available at www.onlinejase.com). (B) Four-chamber end-systolic frame at peak stress (Supplemental Video 5, available at www.onlinejase.com). (C) Two-chamber end-systolic frame at rest (Supplemental Video 6, available at www.onlinejase.com). (D) Two-chamber end-systolic frame at peak stress (Supplemental Video 7, available at www.onlinejase.com). (E) Three-chamber end-systolic frame at rest (Supplemental Video 8, available at www.onlinejase.com). (F) Three-chamber end-systolic at peak stress (Supplemental Video 9, available at www.onlinejase.com).

(LVEF < 55%), or significant LV dilations (LVESD > 50 mm or indexed LVESD > 25 mm/m²).² However, there is growing concern that the guidelines are too restrictive, delaying referral for surgery and increasing the risk of permanent LV remodeling and worse prognosis.^{3,5} De Meester *et al*⁶ demonstrated that adjusted 10-year

survival, cardiovascular survival, and survival free of heart failure admission were all better in patients without guideline-based triggers for AR surgery than in patients operated on for class I (with symptoms and/or reduced LVEF) or class IIa (LVESD > 50 mm or LVESD/body surface area > 25 mm/m²) indications. A study by Scognamiglio *et al*⁷

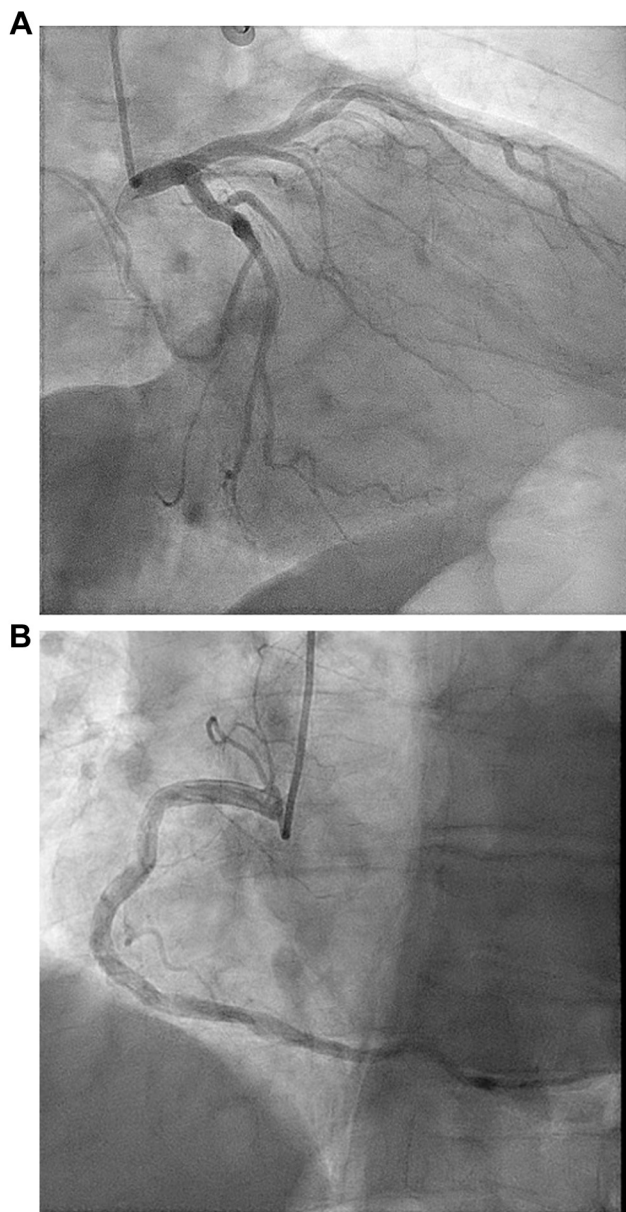


Figure 5 Left (A) and right (B) coronary angiograms showing patent epicardial vessels (Supplemental Video 10, available at www.onlinejase.com).

demonstrated that subclinical irreversible myocardial damage can occur in clinically well-compensated patients who are closely monitored for the development of guideline-recommended surgical indications. Several other studies have shown similar results and suggested that early surgery in patients with AR is associated with significant longer-term survival benefits.^{8,9}

In the current guidelines, the role of routine exercise stress echocardiography (ESE) is limited to evaluating patients with AR whose symptoms are equivocal.^{3,10} But ESE can be an invaluable tool that can not only unmask symptoms but can also assess for lack of CR (defined as the absence of an exercise-induced increase in LVEF or stroke volume increase of <20%)¹¹ and detect subclinical LV dysfunction in asymptomatic patients who would receive a signif-

icant mortality benefit from AVR compared with delaying surgery until the onset of guideline triggers for AVR.

Lee *et al*¹² evaluated the predictive value ESE in asymptomatic severe AR with preserved LV systolic function and demonstrated that the absence of CR (>4% augmentation of LVEF postexercise) in ESE is independently associated with deterioration of symptoms or LV systolic function in these patients. It was also noted by Park and colleagues¹³ that while CR (>5% augmentation of LVEF during exercise) is best related to baseline resting LV end-systolic dimension index, one-third of patients were found to have discordance between the presence of CR and the LV dimension recommended for AVR in minimally symptomatic patients with severe AR. Wahi *et al*¹⁴ followed medically and surgically treated patients who underwent an exercise echocardiogram and observed that CR on exercise echocardiography is a better predictor of LV decompensation than resting indices in asymptomatic patients with AR. Additionally, in patients undergoing AVR, CR had a better correlation with resting ejection fraction on postoperative follow-up.¹⁴

The lack of LV CR during exercise in asymptomatic patients with severe AR likely represents subclinical LV dysfunction due to advanced cardiac remodeling with cellular and extracellular structural changes, including myocardial fibrosis as a result of the pressure and volume overload exerted on the left ventricle (LV) by AR.¹⁵ The exact mechanism of regional wall motion abnormalities in our patient is not clear. However, it is well understood that patients with severe AR have diminished coronary perfusion due to reduced diastolic pressure gradient between the aorta and LV as well as decreased coronary flow reserve.⁵ Exercise in the presence of reduced coronary flow perfusion pressure and flow reserve could potentially cause regional myocardial oxygen supply demand mismatch leading to subendocardial myocardial ischemia and regional dysfunction. Further, this case illustrates the fact that severe valvular heart disease (e.g., severe AR) can lead to false-positive ESE and should be considered in differential diagnosis of positive stress echocardiogram. The presence of myocardial fibrosis has a significant prognostic value. Malahfji and colleagues¹⁵ demonstrated in patients with moderate or severe AR that myocardial scar detected by cardiac magnetic resonance imaging is independently associated with a 2.5-fold increase in mortality and that AVR was associated with a reduction in risk of mortality in these patients.¹⁵ In conclusion, these data suggest that loss of CR in exercise echocardiography may be an earlier marker of LV decompensation, prognosticating advanced and in some cases irreversible LV remodeling, and thus can be used to risk stratify asymptomatic patients with severe AR and preserved LV systolic function influencing the optimal timing of AVR.

In our patient, exercise echocardiography detected subclinical LV systolic dysfunction in an asymptomatic patient with hemodynamically significant AR who did not meet the criteria for surgery, preventing a delay in the necessary valve replacement. Poor CR on stress echocardiography in patients with severe AR, as demonstrated here, is a marker of early decompensation that is not well appreciated by the resting echocardiographic indices endorsed by current guidelines and could be considered another indication for AVR to prevent irreversible ventricular remodeling.

CONCLUSION

Conservative management is appropriate for the majority of asymptomatic patients with chronic severe AR. However, the transition from the compensated to the early decompensated stage in severe AR may represent an optimal window for surgical intervention, albeit

one that is narrow and challenging to detect. Routine stress echocardiography may identify subclinical LV systolic dysfunction in patients with severe AR who may benefit from AVR but are not presently captured by guideline-based indications. Further research on the longitudinal outcomes of patients with AR and stress-induced LV systolic dysfunction is needed to determine the optimal timing of AVR.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.case.2021.07.012>.

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