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Exercise Hemodynamics in Valvular Heart Disease

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Abstract Exercise hemodynamics play an important role in the evaluation and management of patients with both severe stenotic or regurgitant valve lesions. Exercise testing in patients with valvular heart disease can help to unmask latent symptoms and define the timing of surgical intervention. Additionally, exercise-induced hemodynamics are an important tool to assess prosthetic valve function. This review summarizes both background literature and recent publications that assess the use of exercise hemodynamics in the evaluation and management of valvular heart disease.

Keywords Valvular heart disease · Heart valve surgery · Exercise · Echocardiography

Introduction

The role of exercise stress testing and pharmacologic stress in the evaluation of coronary artery disease is well established. Exercise stress testing for the assessment of valvular heart disease, although discussed in the literature since the introduction of Doppler echocardiography, is of renewed interest, and included in published American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology guidelines (Table 1) [1, 2]. Exercise testing and exercise hemodynamics have a role in the evaluation of both stenotic and regurgitant valve lesions, and in the evaluation of prosthetic heart valves. This review is intended to briefly summarize pertinent background literature, and review recent publications describing the use of exercise testing in the evaluation and management of heart valve disease.

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Mitral Stenosis

Mitral stenosis (MS) in adults most commonly is caused by rheumatic heart disease and less commonly by severe mitral annular calcification or prosthetic valve dysfunction. Obstruction to left ventricular (LV) filling leads to left atrial hypertension, which is transmitted to the pulmonary venous circulation, where remodeling over time leads to progressive pulmonary arterial hypertension (PAH). In severe disease, left-sided cardiac output is compromised as a result of poor LV filling.

Symptoms tend to be associated with the presence of severe MS, defined by a valve area less than 1.5 cm^2. However, because LV filling is dependent on diastolic filling time, increases in heart rate (due to physical activity, emotional stress, or arrhythmia) can worsen symptoms even in the absence of evidence of severe MS at rest [1]. Exercise testing can be helpful in asymptomatic patients with severe MS by unmasking latent symptoms. In addition, among symptomatic patients with evidence of only mild or moderate MS, exercise testing is useful to evaluate for provocation of high transvalvular gradients or inducible PAH.

Recently, the occurrence of functional MS has been recognized after reduction mitral annuloplasty for the treatment of functional mitral regurgitation (MR), with some estimates of prevalence as high as 50% [3]. In addition to a reduction in the mitral annular area after annuloplasty, diastolic mitral leaflet restriction can occur or

Table 1 Summarized from the ACC/AHA guidelines on the management of patients with valvular heart disease [1]; focus on exercise testing recommendations

Valvular lesion	Patient status	Role of exercise/ stress testing	Strength of recommendation (level of evidence)
Mitral stenosis	Asymptomatic or equivocal symptoms	Assess exercise-induced mean transmitral gradient and PA pressure when discrepancy in resting echocardiographic and clinical findings, symptoms, and signs	I (C)
	Symptomatic	Percutaneous mitral balloon valvotomy may be considered when MV area >1.5 cm^2 if exercise mean transmitral gradient is >15 mmHg, exercise PA pressure >60 mmHg	II b (C)
Mitral regurgitation	Asymptomatic	Exercise tolerance and effects of exercise on PA pressure and mitral regurgitation severity	IIa (C)
		MV surgery is reasonable when exercise-induced PA systolic pressure is >60 mmHg with exercise	
Severe aortic stenosis	Asymptomatic or equivocal symptoms	Elicit occult symptoms (dyspnea, chest pain, lightheadedness)	IIb (B)
		Evaluate for abnormal BP response to exercise[a]	
	Symptomatic patients	Contraindicated	III (B)
Chronic severe aortic regurgitation	Asymptomatic or equivocal symptoms	Assessment of functional capacity	IIa (B)
		Evaluation of symptoms and functional capacity prior to participation in athletic activities	IIa (C)
		May consider surgery if abnormal hemodynamic response to exercise with normal resting LV function	IIb (C)
	Asymptomatic or symptomatic patients	Evaluation with exercise radionuclide ventriculography to assess LV function	IIb (B)
Low-flow low-gradient aortic stenosis and LV dysfunction	Dobutamine infusion is reasonable to assess contractile reserve[b] and severity of aortic stenosis		IIa (B)
	Pseudo-stenosis	Suggested by improvement in stroke volume but little change in gradient, increase in calculated valve area (0.2 cm^2)	
	True stenosis	Suggested by improvement in stroke volume with increase in gradients, fixed valve area	

Adapted from ACC/AHA guidelines on valvular heart disease [1]

[a] Abnormal hemodynamic response = hypotensive or blunted BP response to exercise (< 20 mmHg increase in systolic BP)

[b] Defined as increase in stroke volume by greater than 20%

ACC American College of Cardiology, *AHA* American Heart Association, *BP* blood pressure, *LV* left ventricular, *MV* mitral valve, *PA* pulmonary artery

persist after reduction annuloplasty. In 2010, Kubota et al. [4•] published data from 31 patients after reduction annuloplasty for ischemic mitral regurgitation (IMR). This study found that the mitral valve area was smaller than the annular area in patients with IMR and LV dysfunction, largely due to tethering and reduced leaflet tip opening (Fig. 1). In 13 of 31 patients, the mitral valve area was less than 1.5 cm^2, with associated high mean transvalvular gradients and worsened functional status. A subset of 12 patients was evaluated using exercise echocardiography. In these patients, exercise was associated with a constant mitral annular area but decreased leaflet tip opening and increased anterior leaflet tethering, with an exercise-associated decrease in mitral valve area and an increase in transmitral gradients. This study suggests that functional MS after reduction annuloplasty for IMR is a real phenomenon with physiologic consequences; because the mitral leaflets were more restrictive than was the annulus, the authors suggest that the use of a larger annuloplasty ring might not correct functional MS after reduction annuloplasty.

Mitral Regurgitation

Degenerative Mitral Regurgitation

Degenerative MR, defined as MR caused by an intrinsic degenerative abnormality of the mitral valve, usually is adequately assessed using resting echocardiography with Doppler. ACC/AHA class I indications for surgical inter-

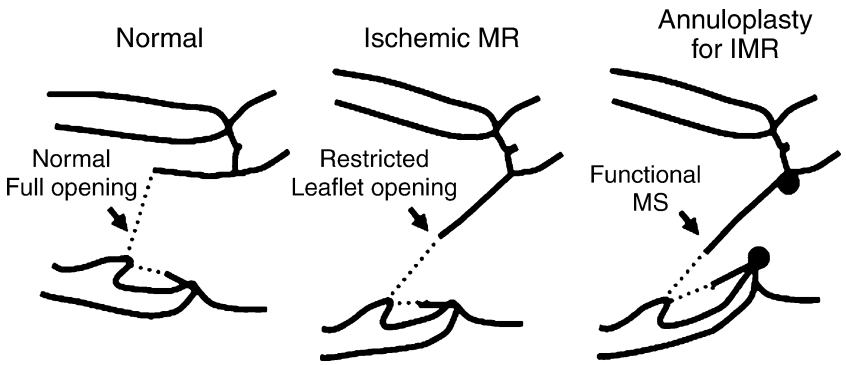

Fig. 1 Schematic demonstrating a proposed mechanism for functional mitral stenosis (MS) following surgical restrictive annuloplasty for ischemic mitral regurgitation (IMR). Valve tethering restricts leaflet mobility and valve opening (*middle*). Following surgical annuloplasty, valve opening limited further, resulting in functional MS (*right*). (*Reprinted from* Kang et al. [5]; with permission from Elsevier)

vention are severe organic MR with symptoms, or with LV dilation or LV systolic dysfunction; class IIa indications include PAH or new-onset atrial fibrillation. In addition, there is increasing interest in earlier surgical intervention among asymptomatic patients with normal LV size and function if successful mitral valve repair is likely [1, 5]. MR and the sequelae of MR can be dynamic phenomena. Exercise echocardiography is a useful tool to evaluate changes in MR severity, LV contractile reserve, and changes in pulmonary artery pressure associated with increased cardiac output.

Non-echocardiographic exercise parameters have utility in estimating prognosis among patients with degenerative MR. In one study published in 2007, Supino et al. [6] evaluated the added prognostic value of exercise treadmill testing in 38 asymptomatic patients with degenerative (nonischemic) MR, and compared these findings to traditional assessment of symptoms. In univariate analysis, a low annual risk of cardiac events was associated with exercise duration ≥15 min, the percent maximum predicted heart rate achieved, and heart rate recovery greater than 29 bpm. On multivariate analysis, only exercise duration had independent prognostic value, with 70% event-free survival rate at 16 years.

In 2010, Magne et al. [7•, 8] published two studies evaluating exercise-induced changes in patients with asymptomatic degenerative MR. One study describes 61 asymptomatic patients with normal LV size and function and at least moderate MR caused by mitral valve prolapse [7•]. With a mean exercise duration of 9 min, an increase in MR severity (defined as an increase in effective regurgitant orifice area ≥10 mm^2) was noted in 30% of patients, confirming that degenerative MR can be dynamic. In addition, 25% of patients with moderate MR at rest developed severe MR with exercise. Exercise-induced changes in MR severity correlated with an increase in pulmonary artery pressure, and with an adverse prognosis; in patients with a regurgitant volume increase ≥15 mL, symptom-free survival was significantly less at 2, 24, and 30 months.

In the second study, echocardiographic predictors of exercise-induced PAH were evaluated, along with its impact on symptoms [8]. In this report, 78 patients were evaluated, including 15% with mild PAH at rest. Exercise-induced PAH (defined as systolic pulmonary artery pressure >60 mmHg) was present in 46% of patients; and associated with significant exercise-induced increases in effective regurgitant orifice area (12.4±2.2 m^2), regurgitant volume (13.8± 3.2 mL), and the development of dyspnea. At a mean follow-up of 19 months, 49% of the study group had developed symptoms. The development of symptoms during follow-up was associated with more severe MR during exercise, and more exercise-induced change in MR severity. A pulmonary artery pressure greater than 56 mmHg was predictive of the onset of symptoms at 2 years.

In summary, prior studies and more recent data suggest that degenerative MR can be dynamic, and therefore incompletely characterized at rest. Multiple functional and echocardiographic parameters may be helpful in determining the optimal timing for surgical intervention in these patients.

Functional MR and IMR

Functional MR (MR caused by dilation or geometric distortion of the left ventricle with normal or functionally normal mitral leaflets) and IMR (functional MR associated with underlying coronary artery disease and ischemic changes in LV size, geometry, or function) are associated with an adverse prognosis [9–11]. The mechanism of functional MR is complex, and includes remodeling of the left ventricle, mitral annular dilation, displacement of one or both papillary muscles, and mitral leaflet tethering.

Functional MR is known to be dynamic, and dependent on loading conditions as well as exercise-induced changes in LV geometry [12–14]. One hallmark study published in 2003 demonstrated that IMR severity at rest is a poor predictor of MR severity with exercise, with a large increase in exercise effective regurgitant orifice area (> 13 mm^2) observed in 28% of patients [14]. In this study, exercise-related changes in IMR severity correlated with an increase in systolic mitral annular area, apical displacement of the papillary muscles among patients with prior anterior myocardial infarction, and an increase in mitral tenting area; but not with effective regurgitant orifice area or LV systolic function at rest. Notably, a decrease in MR severity was observed in 13 of 68 (19%) patients, and associated with the presence of a prior inferior wall myocardial infarction and the presence of recruitable myocardium. In another study published in the same year by the same investigators, an exercise-induced increase in effective regurgitant orifice ≥13 mm^2 was found to be independently associated with cardiac death [15]. Notably, half of the patients who had a significant increase in effective regurgitant orifice in this study had only moderate MR at rest.

In 2010, data were published on exercise-induced changes in IMR severity in patients early after acute myocardial infarction [16]. In these patients, IMR severity was associated with a worsened wall motion score with exercise, indicative of more inducible ischemia, particularly involving the inferior and inferoseptal walls. In another recent publication, patients with heart failure with normal ejection fraction were studied [17]. Among these patients, an increase in functional MR severity with exercise was associated with an increase in systolic mitral leaflet tenting area and an increase in the E/e' ratio, but not with changes in regional LV shape or function. These findings confirm that LV filling pressure can impact functional MR severity even in the absence of LV dilation or geometric distortion.

Three-dimensional echocardiography may be useful for better understanding the complex mechanism of IMR. Recently published data suggest that changes in the degree of LV dysfunction, LV volumes, and resting LV ejection fraction assessed by two-dimensional echocardiography are similar between patients with and without exercise-induced IMR [18•]. However, three-dimensional echocardiographic evaluation showed more pronounced changes in mitral valve deformation patterns and in LV dyssynchrony and sphericity indices among patients with exercise-induced IMR. Taken together, existing knowledge and recently published data suggest that the mechanism of IMR is complex and incompletely characterized at rest, and that the use of both exercise testing and three-dimensional echocardiography could help better define the presence and mechanism of functional MR.

Aortic Stenosis

Asymptomatic Severe Aortic Stenosis

Current guidelines support surgical intervention for aortic stenosis (AS) in the setting of severe AS and symptoms of angina, dyspnea, fatigue, or syncope; or for severe AS and LV systolic dysfunction [1, 2]. Intervention based on symptoms typically relies on historical reporting of symptoms, rather than provocative testing performed with the goal of eliciting symptoms not spontaneously reported. However, symptoms can be insidious in onset, and patients often limit their physical activity to compensate. Exercise testing can be helpful among patients with severe AS who deny symptoms, allowing assessment for symptoms as well as objectively determining exercise tolerance and the hemodynamic response to stress.

Prior studies have shown that asymptomatic patients with severe AS can have blunted blood pressure and heart rate response with exercise, decreased stroke volume, and less than normal augmentation of cardiac output; largely due to an inability to augment LV end-diastolic volume [19]. Although severe symptomatic AS is a contraindication to exercise testing, published data [20–22] and current guidelines [1, 2] reinforce its utility among asymptomatic patients with severe AS. A recently published meta-analysis on exercise stress testing in asymptomatic AS found no complications associated with stress testing in 491 patients, and no cases of sudden death at 1-year follow-up among patients with a normal stress test [23]. Due to an ability to identify occult symptoms, as well as identify higher risk albeit still asymptomatic patients with severe AS, it appears reasonable to use exercise testing among asymptomatic patients with severe AS who would be considered reasonable surgical candidates for aortic valve replacement [24].

Among asymptomatic patients with severe AS, exercise echocardiographic parameters appear to have incremental prognostic value beyond the symptomatic and hemodynamic responses to exercise. In one study published in 2010 of 186 asymptomatic patients with at least moderate AS and normal LV systolic function, echocardiographic parameters including LV hypertrophy and an increase greater than 20 mmHg in exercise-induced mean transvalvular gradient were associated with the need for surgical intervention at 20 months [25].

Two-dimensional echocardiographic strain imaging also has been tested in patients with severe AS. One study published in 2009 evaluated the role of myocardial deformation assessed by two-dimensional strain imaging compared with exercise tolerance to assess prognosis in 60 asymptomatic patients with severe AS [26]. In this study, 65% of patients studied had an abnormal hemodynamic response to exercise. Patients with symptoms or

abnormal exercise hemodynamics had lower global and basal longitudinal strain rates than did patients with normal exercise hemodynamics. A basal strain rate change of more than -13% predicted a more benign course. Although LV ejection fraction was similar to a matched group of normal controls, longitudinal strain patterns were impaired in patients with AS, with exercise basal longitudinal strain showing the largest differences between groups.

A risk score for predicting outcomes in asymptomatic severe AS was proposed in 2009 [27]. Generated from a prospective cohort of 107 patients, factors associated with the predefined end points of death or the need for surgical aortic valve replacement included female sex, elevated N-terminal B-type natriuretic peptide (BNP), and aortic peak jet velocity at rest; yielding a calculated risk score defined as:

$$\text{Risk score} = (2 \times \text{peak velocity}) + (1.5\ [\text{if female sex}]) + (1.5 \times [\text{natural log of BNP}]).$$

A score less than 11 predicted a lower rate of death or need for aortic valve replacement of 10% at 24 months, whereas a score greater than 16 predicted a high-risk group with an event rate of greater than 75% at 24-month follow-up.

A study published in 2009 describes the changes with exercise in invasive measurements of arterial compliance among symptomatic patients with AS [28]. The study found that valvular AS is associated with reduced arterial compliance and increased systemic vascular resistance. With exercise, arterial compliance decreased further among patients with AS compared with normal controls, with the potential to impair cardiac output and contribute to symptoms. Although not practical for routine assessment, this study provides insight into the complex physiology of AS.

Low-Flow Low-Gradient AS

Low-flow low-gradient AS is defined as severe AS with low transvalvular mean gradient (typically <30 mmHg) due to reduced cardiac output (typically in the setting of impaired LV ejection fraction). Patients with impaired LV ejection fraction have higher operative risks at the time of aortic valve replacement compared with patients with preserved LV ejection fraction [29–31].

Dobutamine stress is useful for the determination of LV contractile reserve among patients with low-flow low-gradient AS and low LV ejection fraction [32, 33]. Although the absence of LV contractile reserve during dobutamine infusion is useful for identifying patients at increased perioperative risk [32], postoperative functional status is similar to those with intact contractile reserve [33]. As such, the absence of LV contractile reserve should be considered in assessing operative risks, but generally should not be considered as an absolute contraindication to operative intervention for aortic valve replacement.

Aortic Regurgitation

Chronic aortic regurgitation (AR) is a condition of combined LV volume and pressure overload, with late sequelae of LV systolic dysfunction and heart failure. As in AS, symptoms associated with chronic AR—including dyspnea, fatigue, or decreased exercise tolerance—are insidious in onset. ACC/AHA class I indications for surgical intervention include severe AR and the presence of symptoms, decreased LV systolic function, or marked LV dilation.

Exercise testing using radionuclide ventriculography to assess LV contractile reserve is useful in detecting higher-risk patients with early LV systolic dysfunction despite normal LV ejection fraction at rest [34, 35]. In one recently published retrospective study, the use of exercise radionuclide ventriculography was evaluated for utility in the prediction of postoperative LV dysfunction among 29 patients with chronic severe AR who were referred for surgery [36]. In patients with a preoperative exercise-induced LV ejection fraction increase greater than 5%, postoperative LV volumes were smaller and resting LV ejection fraction improvement was better compared with those with neutral or decreased exercise-induced change in ejection fraction preoperatively.

The same investigators evaluated another group of patients referred for surgery for chronic AR with both pre- and postoperative echocardiography and cardiopulmonary exercise testing [37]. Nearly half of these patients were asymptomatic, and all had a normal LV ejection fraction at rest. LV volumes and LV ejection fraction improved significantly postoperatively, but were independent of preoperative functional classification; and echocardiographic parameters were not predictive of postoperative exercise capacity. However, preoperative exercise parameters (eg, peak maximum oxygen uptake) correlated well with postoperative exercise capacity. Based on these results, the authors suggest that traditional methods of evaluating functional capacity and LV systolic function might not be adequate, and that exercise testing might allow better assessment of optimal surgical timing among patients with chronic severe AR and normal resting LV ejection fraction.

Prosthetic Heart Valves

Essentially all prosthetic heart valves provide an orifice area that is less that of a normal, native valve. Prosthesis-patient

mismatch results if the valve effective orifice area is inadequate for the patient in whom it was implanted. Although echocardiography/Doppler-derived transvalvular gradients are useful and often sufficient to assess prosthetic valve hemodynamics, exercise-associated changes in cardiac output can unmask prosthesis-patient mismatch, manifest as a sharp increase in gradients.

Bileaflet mechanical aortic valve prostheses generally are associated with favorable hemodynamics [38]. However, prosthesis-patient mismatch still can occur, and is usually associated with smaller-sized prostheses [39, 40]. The risk of prosthesis-patient mismatch in the past was greater with the use of bioprostheses, especially with smaller valve sizes. However, supra-annular designs have improved hemodynamics and reduced the risk of prosthesis-patient mismatch associated with many current-generation bioprostheses [41, 42].

One study published in 2009 addressed the influence of prosthesis-patient mismatch on exercise-induced arrhythmias for smaller (19 and 21 mm) mechanical valves and bioprosthesis in patients with isolated AS and normal LV systolic function [43]. In this study, prosthesis-patient mismatch (defined as an indexed effective orifice area$\leq$ 0.75 cm^2/m^2) occurred in 61% of 157 patients. In those with prosthesis-patient mismatch, overall survival and freedom from cardiac-related death were similar to those without prosthesis-patient mismatch. However, mean gradients were higher with exercise in the prosthesis-patient mismatch group and exercise tolerance was worse. Ventricular arrhythmias, including premature contractions and nonsustained ventricular tachycardia, occurred during exercise in 33% of all patients, and were found to correlate most strongly with exercise-induced mean gradients greater than 50 mmHg.

There has been a debate in the literature regarding whether stentless bioprostheses offer superior hemodynamics compared with current-generation supra-annular stented bioprostheses [44–46•, 47–49]. In 2010, a study was published that addressed long-term hemodynamic data for stented and stentless aortic bioprostheses [46•]. In this study, follow-up out to 12 years was reported for a randomized trial comparing the Carpentier Edwards pericardial valve (Edwards Lifesciences; Irvine, CA) with the Toronto stentless porcine aortic bioprosthesis (St. Jude Medical; St. Paul, MN). In 38 of 99 (38%) patients available for follow-up, mean transvalvular gradients decreased initially and then increased after 1 year, although more so in the stented pericardial group. Dobutamine stress was associated with a greater increase in peak and mean gradients among patients with the stented pericardial valve compared with the stentless valve. However, there were no differences between groups in observed LV mass regression, survival, valve-related events, or reoperation.

Exercise testing continues to be used to better characterize prosthetic valve hemodynamics. Although the valve is limited in terms of durability [50], data were published in 2009 that addressed rest and exercise gradients associated with the MitroFlow pericardial bioprosthesis (Sorin Group; Vancouver, BC, Canada). Implanted in the aortic position in 127 patients (of whom 78 were available for follow-up at 6 months), the observed effective orifice area was similar for larger and smaller valve sizes, with small exercise-associated increases in mean gradient [51].

Conclusions

Exercise hemodynamics play an important role in the evaluation and management of patients with valvular heart disease. Exercise testing may unmask latent symptoms and help define the timing of surgical intervention among asymptomatic patients with severe MS, MR AS, or AR. In addition, exercise-induced hemodynamics remain an important tool in helping to characterize prosthetic valve hemodynamics.

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