Curr Treat Options Cardio Med (2017) 19:17
DOI 10.1007/s11936-017-0516-8

Valvular Heart Disease (J Dal-Bianco, Section Editor)

Exercise Testing and Stress Imaging in Mitral Valve Disease

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This article is part of the Topical Collection on *Valvular Heart Disease*

Keywords Mitral valve disease · Valvular heart disease · Echocardiography · Exercise

Opinion statement

Mitral valve disease represented by mitral stenosis and mitral regurgitation is the second most frequent valvulopathy. Mitral stenosis leads to an increased left atrial pressure whereas mitral regurgitation leads to an increased left atrial pressure associated with a volume overload. Secondary to an upstream transmission of this overpressure, both mitral stenosis and regurgitation lead to pulmonary hypertension and right heart failure. In addition, mitral regurgitation also leads to left ventricular dilatation and dysfunction with left heart failure. Depending on the anatomy of the valvular and subvalvular apparatus, valve repair (percutaneous mitral commissurotomy for mitral stenosis and valvuloplasty for mitral regurgitation) might be possible. If the anatomy is not favorable, valve replacement by mechanical or biological prosthesis is indicated. Most of the intervention indications are based on clinical symptoms and resting transthoracic echocardiography. Outcomes of patients operated based upon resting echo abnormalities might however not be optimal. Therefore early intervention might be beneficial based upon abnormal exercise testing, which has been demonstrated to more sensitive to identify high-risk patients. In this last decade, especially exercise echocardiography has been found to be a crucial tool in the management of patients with mitral valve disease.

Published online: 13 March 2017

Introduction

Mitral valvulopathy is composed by mitral stenosis (MS) and primary/secondary mitral regurgitation (MR) [1]. MS leads to an increase in left atrial pressure (LAP) with an upstream transmission of this overpressure into the pulmonary vascular bed eventually creating pulmonary hypertension (PH). Primary or secondary MR also leads to an upstream transmission of increased LAP and to a left ventricular (LV) volume overload, which contributes to LV dilatation and dysfunction. All these changes in hemodynamic conditions contribute to the onset of cardiovascular symptoms, which are closely correlated to a poor outcome. Therefore, the occurrences of cardiovascular symptoms or LV dysfunction are clear indications for mitral valve surgery (valvular replacement or valvuloplasty as appropriate) [1, 2••]. However, some patients may underestimate their symptoms or rapidly evolve from an asymptomatic state to LV dysfunction or resting PH. In this subset of patients, the post-operative outcome may not be optimal.

The concept of exercise assessment of mitral parameters and pulmonary hemodynamics has emerged over the last decade with the aim to identify a subgroup of higher risk patients that may benefit either from early elective surgery (even without symptoms) or a close follow-up in a heart valve clinic [3•, 4]. The goal of exercise evaluation is to separate patients with an abnormal exercise adaptation (abnormal increase in transmitral gradient for MS or abnormal increase in MR parameters for primary MR or exercise-induced pulmonary hypertension (EIPH) in secondary MR), whom are at higher risk of post-operative LV dysfunction or persistent PH.

The aim of this review is to highlight studies of interest in the field of exercise echocardiography and mitral valve disease and to highlight useful information for the management of patients in daily clinical practice.

Exercise echocardiography in normal subjects

Some prerequisites on exercise protocol and pulmonary circulation hemodynamics in normal conditions are required for a complete understanding of exercise echocardiography studies.

Normal adaption of the pulmonary circulatory system during exercise

There is a three- to fourfold increase in cardiac output (CO) secondary to increased oxygen demand. The pulmonary vascular bed is a low resistance high compliance system and has the ability to recruit and distend pulmonary arterial vessels in response to the increase in flow and volume. This leads to a drop in pulmonary vascular resistance (PVR) and only a moderate increase in pulmonary arterial pressure (PAP) [5•]. Exercise pulmonary arterial vasodilation has been demonstrated by La Gerche et al. [6]. Fourty athletes and 15 non-athletes were studied with exercise echocardiography with pulmonary transit agitated contrast (PTAC) assessment at peak exercise. At rest, PTAC was not present as pulmonary capillaries are smaller than contrast bubbles. Patients were classified into high or low PTAC, depending on the number of bubbles in the LV cavity. As compared to low PTAC, patients with high PTAC demonstrated higher exercise CO (16 ± 3 vs. 14 ± 3 L/min; $p < 0.001$), lower exercise systolic PAP (52 ± 10 vs. 63 ± 14 mmHg; $p = 0.003$), and lower exercise PVR (2.9 ± 1.0 vs. 4.6 ± 1.8 mmHg/L/min). These results suggested that recruitment of pulmonary arterial vasodilatation results in a drop in PVR and a lower increase in PAP during exercise.

Protocol used for exercise echocardiography assessment

Exercise echocardiography is usually performed in a semi-supine position allowing a good compromise between the feasibility of exercise and the ability to acquire adequate quality echocardiography images during the exercise.

It is recommended to begin at 25 W and to increase the workload by 25 W every 2 min until onset of symptoms, exhaustion, or achievement of the maximal predicted heart rate.

Blood pressure, heart rate, and 12-lead electrocardiography are recorded at rest and at each exercise level. Echocardiographic parameters (valvular parameters and sPAP) should be recorded at rest, at peak exercise, and during recovery. If possible, recording these parameters during the exercise at each level may be informative.

Exercise echocardiography assessment of PAP and PVR in healthy subjects

In the last few years, exercise echocardiography has been studied to understand the adaptation of the vascular bed to exercise in healthy subjects [7, 8]. However, normal values of PAP during exercise should be considered carefully due to confounding factors (i.e., age, CO, and exercise protocol).

Mahjoub et al. [9] demonstrated the age dependency of PAP in 70 healthy volunteers. sPAP, as assessed by echocardiography, increased from 27 ± 4 to 34 ± 6 mmHg at 25 W and to 51 ± 9 mmHg at peak exercise. Older patients (>60 years) presented with a higher exercise sPAP (56 ± 9 mmHg) than younger patients (49 ± 7 mmHg, $p = 0.02$). In addition, 36% of 60 to 70 years patients presented a peak exercise sPAP ≥60 mmHg, so as 50% of subjects older than 70 years. Thus, exercise sPAP is related to age and the cutoff value of 60 mmHg at peak exercise should be interpreted with caution, depending on age.

Argiento et al. [8] studied the feasibility of exercise PAP assessment by echocardiography and confirmed the age and gender dependency of PAP in 124 healthy subjects. Eleven individuals were excluded due to insufficient quality of echocardiographic images. The final study group included 57 women and 56 men aged from 19 to 63 years. The average slope of mPAP-CO was 1.5 ± 0.5 mmHg/L/min (normal range from 0.5 to 2.5 mmHg/L/min) and the distensibility coefficient α was 1.3 ± 1% $mmHg^{-1}$. Consistently with right heart catheterization (RHC) studies, upper limits of normal values of mPAP at exercise would be 34 mmHg at a CO <10 L/min, 45 mmHg between 10 and 20 L/min, and 52 mmHg for CO >30 L/min. Finally, there were differences regarding age and gender. At peak exercise, men achieved higher workload (153 ± 34 vs. 198 ± 54 W; $p < 0.001$), CO (15 ± 3 vs. 21 ± 4 L/min; $p < 0.001$), mPAP (31 ± 7 vs. 36 ± 6 mmHg; $p < 0.001$), and PVR (1.4 ± 0.4 vs. 1.3 ± 0.3 Woods units; $p < 0.05$). There was no gender difference for exercise LAP (10 ± 1 vs. 10 ± 1 mmHg) and indexed PVR (2.4 ± 0.8 vs. 2.5 ± 0.6 Woods units/m^2). α coefficient was higher in women at peak exercise (1.4 ± 1.1 vs. 0.9 ± 0.4% $mmHg^{-1}$; $p < 0.01$).

Therefore, it is now well accepted that the normal value of the slope mPAP-CO is smaller than 3 mmHg/L/min or sPAP <50 mmHg if CO is under 10 L/min.

Age and flow adjustment should be integrated in results interpretation (integration of LVCO in the interpretation of sPAP or assess the slope of PAP-CO).

Mitral stenosis

With decline of rheumatic fever in developed countries, the incidence and prevalence of rheumatic MS have clearly decreased over the last decades. Worldwide however, MS remains present in daily practice and is clearly linked to an increase in morbidity and mortality [1]. At the beginning of the disease, patients remain asymptomatic with a good outcome. At end stage disease, the onset of atrial fibrillation, thromboembolism, heart failure, and PH is associated with a decreased survival. Transition between these two stages may be rapid. The treatment of MS is either percutaneous mitral comissurotomy (PMC) or valve replacement depending on the valve characteristics and patients' profile and comorbidity [10].

Classical indications for PMC are as follows:

- Symptomatic patients without unfavorable characteristics (old age, previous commissurotomy, NYHA class IV, permanent atrial fibrillation, severe PH, Echo score >8, Cormier score 3, very small mitral valve area, severe tricuspid regurgitation) (class I B),
- Symptomatic patients with contraindication or high risk for surgery (class I C),
- Asymptomatic patients without unfavorable characteristics and high thromboembolic risk and/or high risk of hemodynamic decompensation (sPAP >50 mmHg at rest) (class II A) [1].

Mitral valve replacement is considered for the same conditions in patients not suitable for PMC.

Exercise echocardiography in mitral stenosis

There are few data on exercise assessment in MS patients. In this particular condition, both dobutamine stress (DSE) and exercise echocardiography have been explored and compared [11]. Even though exercise assessment is clearly more physiologic, DSE may also be performed in patients with MS.

DSE has been shown to be a useful tool to identify patients with a worse outcome. Reis et al. [12] included 53 patients with moderate to severe MS and performed a DSE in all patients. After a mean follow-up of 60 months, 29 patients presented with cardiovascular complications. In a multivariable analysis, the increase of mean transmitral gradient (MTMG) was the best predictor of adverse events with a cutoff value of 18 mmHg. Finally, the authors concluded that, in addition to conventional management, DSE might increase the detection of high-risk patients presenting moderate mitral stenosis. More recently, Brochet et al. [13] explored 48 "asymptomatic" patients presenting moderate to severe MS. Exercise echocardiography allowed identification of patients who underestimated their symptoms, since 46% of them described dyspnea during test. Interestingly, there were no significant differences between patients with or without exercise dyspnea regarding resting or exercise MS severity and PAP. However, patients with dyspnea exhibited a more rapid increase in exercise PAP. Thus, the cutoff value of sPAP >60 mmHg at exercise did not discriminate "false asymptomatic" patients but an early increase in relative sPAP >90% at 60 W revealed an abnormal risk of developing dyspnea or requiring valvular intervention during follow-up (Fig. 1).

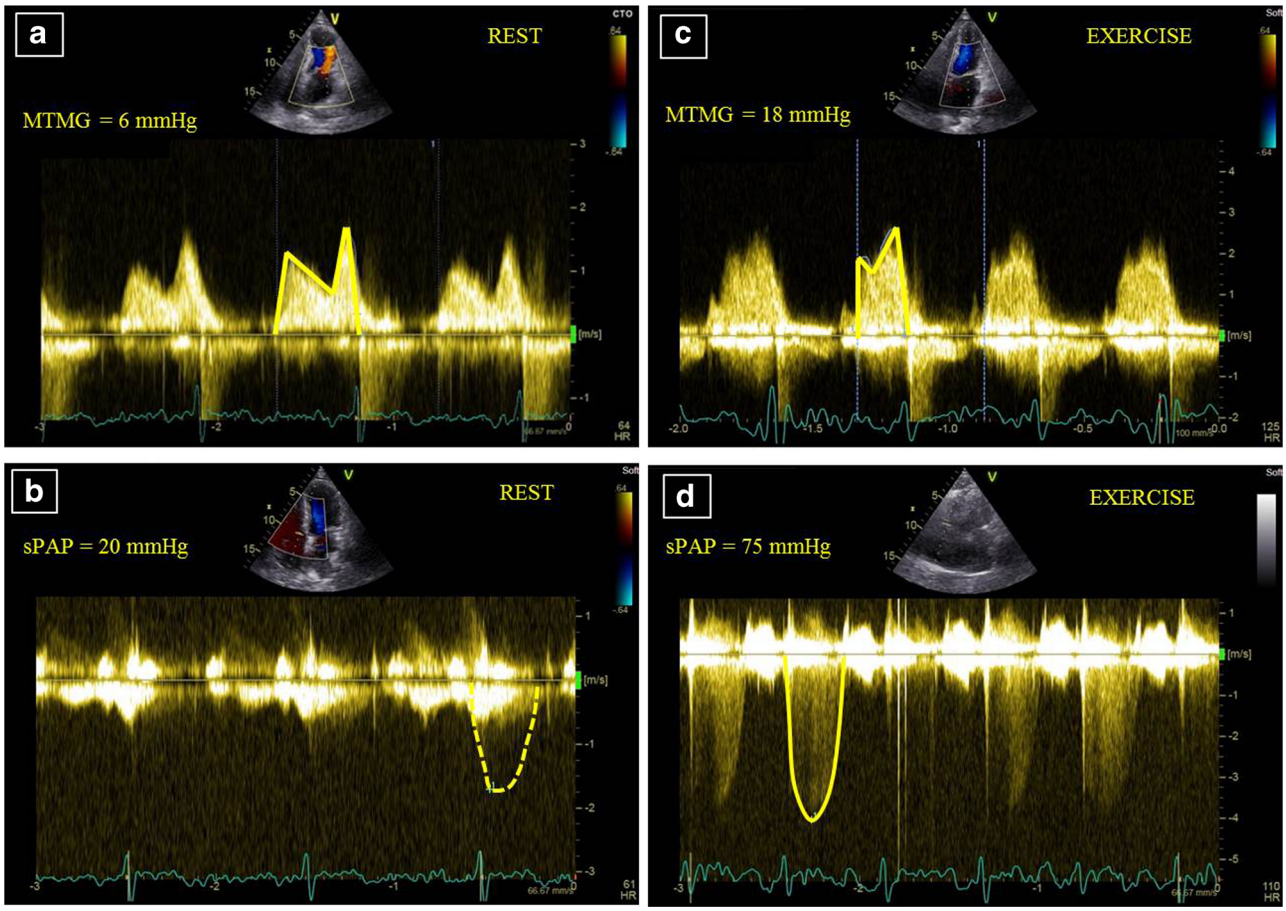

Fig. 1. Exercise echocardiography in a 58-year-old women with moderate mitral stenosis and exercise dyspnea. **a** Resting mean transmitral gradient (*MTMG*) showing moderate mitral stenosis (mean gradient 6 mmHg and mitral area estimated at 1.6 cm^2). **b** Resting systolic pulmonary arterial pressure (sPAP) assessed by transtricuspid gradient (probably underestimated due to very mild tricuspid regurgitation at rest) and right atrial pressure. **c** Exercise transmitral gradient showing a significant increase in mean gradient at peak exercise. Patient presented with dyspnea with limited exercise workload (75 W). **d** Exercise sPAP showing an abnormal increase in sPAP (>60 mmHg) and in slope of PAP-CO (>3 mmHg/L/min).

Finally, atrioventricular compliance seems to play an important role in the increase of PAP during exercise in patients with MS [14, 15] and may be integrated in the interpretation of exercise echocardiography in MS patients. Reasonably, it has been demonstrated that patients with a low atrioventricular compliance (≤4 mL/mmHg) had greater increase in exercise PAP, which was correlated to dyspnea. In addition, this parameter was directly linked to a decrease in functional capacity.

Therefore, exercise echocardiography has been integrated in the latest American guidelines [2••], PMC may be considered when valve anatomy is suitable, in patients with mild-moderate MS (mitral valve area (MVA) >1.5 cm^2) and abnormal increase in MTMG >15 mmHg during exercise (class II b). It has been proposed to closely follow-up patients without any symptoms and presenting significant MS (MVA <1.5 cm^2) associated with EIPH (>60 mmHg) or an increase in MTMG >15 mmHg [4] (resting and exercise key values listed in Table 1).

Table 1. Key values in mitral stenosis and level of recommendation for treatment

Parameters	Key value	Level	Guidelines
Mitral valve area	≤1.5 cm^2		European
Resting MTMG	>10 mmHg		European
Resting sPAP	>50 mmHg	IIa	European
Exercise increase in MTMG	>15 mmHg	IIb	American

MTMG mean transmitral gradient, *sPAP* systolic pulmonary arterial pressure

Primary mitral regurgitation

Degenerative MR is the second most frequent valvular heart disease in Europe [1]. MR results in an increased LA pressure and an upstream transmission of pressure to pulmonary vascular bed. Chronic PAP elevation may lead to definitive remodeling of pulmonary vessels and increase post-operative mortality. In acute MR, mainly represented by chordal rupture or papillary muscle rupture, the indication of surgery is not debated as the acute volume and pressure overload is always poorly tolerated and related to a poor outcome. In chronic primary MR, surgery is currently indicated in the following:

- Symptomatic patients with LV ejection fraction (LVEF) >30% and LV end-systolic diameter (ESD) <55 mm (class I)
- Asymptomatic patients with LV dysfunction (<60%) and/or LV dilatation (ESD >45 mm) (class I).

  Mitral surgery should also be considered in the following:

- Asymptomatic patients with onset of atrial fibrillation or resting PH (PAP >50 mmHg) or with flail leaflet and suitable for a valve repair and with LVESD >40 mm (class IIa)
- In patients with severe LV dysfunction (<30%), LV dilatation (LVESD >55 mm) refractory to medical therapy, surgery should be discussed if there is a high likelihood of durable repair (class IIa) or a low likelihood of durable repair (class IIb).

  Surgical indications are no longer questioned in symptomatic patients or in patients with LV dysfunction and/or dilatation or with resting PH, but the role of early/preemptive surgery in asymptomatic patients with high-risk profile is more controversial and has been debated in the last few years.

Exercise echocardiography in primary mitral regurgitation

Exercise echocardiography has been proposed as a useful method to identify patients at higher risk who may beneficiate from an early elective surgery. Magne et al. [16] performed a comprehensive resting and exercise echocardiography study in 78 patients (age 61 ± 13 years, 56% men) with moderate to severe degenerative MR. Resting PH and EIPH were defined as previously

described in the guidelines [1]. EIPH was present in 46% of study patients. Patients with EIPH had more severe MR at peak exercise (higher exercise effective regurgitant orifice (ERO) area and regurgitant volume (RV)). Age, resting sPAP, and exercise MR parameters were associated with EIPH. After a mean follow-up of 19 ± 14 months, 49% patients developed symptoms. Patients who developed symptoms had higher resting-to-exercise changes in effective regurgitant orifice and regurgitant volume. Patients with EIPH had lower rate of symptom-free survival at 1 and 2 years. EIPH remained significantly associated with symptom-free survival regardless of the statistical method of analysis (adjustment for age, sex, resting, and exercise data). A peak exercise sPAP >56 mmHg was the best cutoff to predict the onset of symptoms (specificity 73% and sensibility 82%). Exercise echocardiography in primary MR allows a better understanding of the pathophysiology of the valvular mechanics at exercise and its consequences on pulmonary hemodynamics. Patients with greater MR at exercise and thus higher sPAP are at higher risk of cardiovascular events during follow-up. Therefore, a early/preemptive surgery has been proposed for this specific subgroup [1].

More recently, Kusunose et al. [17] have studied exercise RV function in addition to exercise sPAP, as a predictive parameter of event-free survival in patients with primary MR. They studied 196 patients at rest and during exercise. They defined four groups depending on the median of exercise sPAP (54 mmHg) and exercise TAPSE (19 mm). They showed that patients with EIPH (exercise sPAP >54 mmHg) but no exercise RV dysfunction (TAPSE >19 mm) had a better 4-year event-free survival (71%) than patients with EIPH and RV dysfunction (25%). These results suggest that there is probably a continuum of the valvular consequences on the pulmonary vasculature and that EIPH may lead to exercise RV dysfunction corresponding to patients with a very high risk in the subgroup of EIPH patients.

Finally, the presence of pre-operative EIPH has been correlated with an increased risk of cardiac events in the post-operative period (19). Magne et al. [18•] studied 102 patients with primary MR, NYHA ≤2, no LV dysfunction, and/or dilatation. All patients underwent comprehensive exercise echocardiography and were followed prospectively. Baseline EIPH was defined as a peak exercise sPAP >60 mmHg. Surgery was indicated based on the current guidelines. After a mean follow-up of 50 months, 26% of patients presented cardiac events. Patients with EIPH at baseline had higher post-operative complications (39 vs. 12%, $p < 0.05$). This was confirmed even after exclusion of atrial fibrillation criteria (39 vs. 9%, $p < 0.05$). Event-free survival was lower in patients presenting baseline EIPH (60 ± 8 vs. 88 ± 5%, $p = 0.007$). After Cox multivariate analysis, EIPH remained significantly associated with onset of post-operative cardiac complications (resting and exercise key values listed in Table 2).

Secondary mitral regurgitation

Secondary or "functional" MR represents a complex situation where LV dysfunction/dilatation directly impacts the functioning of the subvalvular and valvular apparatus. Two different situations may be encountered. The first one is transient myocardial ischemia of the inferolateral myocardial wall and/or papillary muscle leading to MR increase during exercise, usually revealing a

Table 2. Key values in degenerative mitral regurgitation and level of recommendation for treatment

Parameters	Cutoff	Level	Guidelines
EROA	≥40 mm^2		European
RV	≥60 mL		European
LVEF	>30 < 60%	I	European
LVESD	≥45 < 55 mm	I	European
LVESD	≥40 mm with flail leaflet	IIa	European
Resting sPAP	>50 mmHg	IIa	European
Left atrial volume	≥60 mL/m^2	IIb	European
Exercise sPAP	≥60 mmHg	IIb	European

EROA effective regurgitant orifice area, *RV* regurgitant volume, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter, *sPAP* systolic pulmonary arterial pressure

coronary artery disease. The second one is represented by a chronic ischemic or non-ischemic cardiomyopathy leading to LV remodeling with a mitral annulus dilatation and tethering of the subvalvular apparatus. Chronic secondary MR is related to increased morbidity and mortality, and surgery is currently indicated in the following:

- Patients with severe MR undergoing coronary artery bypass graft (CABG) and LVEF >30% (class I),
- Patients with moderate MR undergoing CABG, especially in case of dyspnea and abnormal MR severity increase with exercise (class IIa),
- Symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence of myocardial viability (class IIa),
- Patients with severe MR, LVEF >30%, who remain symptomatic despite optimal medical management (including cardiac resynchronization therapy if indicated) and have low comorbidity, when revascularization is not indicated (class IIb)

  The inbalance between leaflet tethering and closing forces which is exaggerated during exercise by increased LV filling pressure can lead to an acute chronic increase of significant secondary MR consequently resulting in EIPH, which is associated with a worse prognosis [19–21].

  Therefore, exercise echocardiography is actually suggested [1] in case of LV dysfunction associated with the following situations: dyspnea during exercise out of proportion with resting MR severity and LV dysfunction, acute pulmonary edema without obvious causes, moderate secondary MR before surgical revascularization, and risk stratification of mortality in heart failure patients.

Exercise echocardiography and secondary mitral regurgitation

It has been demonstrated that resting echocardiography cannot predict the severity of MR during exercise [22]. Lancellotti et al. [22] studied 70 patients

with at least moderate secondary MR and LV systolic dysfunction (EF <45%). All patients underwent an exercise echocardiography and predictors of exercise-induced change in MR parameters were evaluated. Resting echocardiographic parameters of MR did not correlate with exercise-induced change in EROA. Predictors of abnormal increase in exercise ERO were changes in systolic annular area for all infarct categories, in tenting area and wall motion score in the global population and those with inferior infarction, and in apical displacement of mitral leaflets for patients with anterior myocardial infarction (MI).

Piérard and Lancellotti [21] also demonstrated the clinical impact of dynamic MR in patients with post MI LV dysfunction. Compared to patients who did not experience pulmonary edema, patients presenting with recent pulmonary edema exhibited at peak exercise, a lower increase in LVEF, a greater increasing in tenting area, in EROA (16 ± 10 vs. 2 ± 9 mm^2, $p < 0.001$) and regurgitant volume (RV) (26 ± 14 vs. 5 ± 14 mL, $p < 0.001$), and in PAP (29 ± 10 vs. 13 ± 11 mmHg, $p < 0.001$). Of note, there were no significant differences for demographic parameters and resting echocardiographic data. Finally, in a multivariable analysis, exercise-induced changes in the EROA, in PAP, and in LVEF were independently associated with a history of recent pulmonary edema.

Finally, Lancellotti et al. [23] later confirmed these results. They prospectively enrolled 161 patients with chronic ischemic cardiomyopathy, LV dysfunction, and at least moderate secondary MR. After a mean follow-up of 35 months, 20 patients had cardiac surgery, 23 died, 22 were hospitalized for heart failure, and 15 had acute coronary syndromes. In a multivariable analysis, best predictors for mortality and heart failure were an increase during exercise ≥13 mm^2 in EROA and a greater increase in PAP. Resting MR severity was only predictor of cardiac death.

Therefore, the latest European guidelines [1] recommend mitral surgery in patients with moderate MR undergoing CABG, especially in case of exercise dyspnea and abnormal increase in MR severity during exercise (class IIa) (resting and exercise key values listed in Table 3).

Conclusion

Exercise assessment in mitral valve disease clearly offers useful information in terms of understanding the pathophysiology, individual risk stratification, and patient management.

Table 3. Key values in functional regurgitation and level of recommendation for treatment

Parameters	Cutoff	Level	Guidelines
EROA	≥20 mm^2		European
RV	≥30 mL		European
LVEF	>30% and CABG	I	European
LVEF	<30% with viability and revascularization	IIa	European
Exercise increase in EROA	Moderate MR and CABG	IIa	European

CABG coronary artery bypass grafting, *EROA* indicates effective regurgitant orifice area, *RV* regurgitant volume, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation

In primary mitral regurgitation, the place of exercise echocardiographic assessment is now clearly defined, and surgery is indicated when an abnormal increase in PAP during exercise occurs in asymptomatic patients.

In secondary mitral regurgitation, exercise echocardiography has been identified as a very interesting tool, especially for risk stratification. However, due to the complexity of the disease, its place to define the indication and the timing of surgery remains debated.

In mitral stenosis, exercise stress echocardiography may be interesting in a defined subset of patients, and is integrated in the management of MS patients in the American guidelines.

Further prospective studies are clearly needed to further define the role of exercise echocardiography in the management of patients presenting with secondary mitral regurgitation and mitral stenosis.

Compliance with Ethical Standards

Conflict of Interest
Damien Voilliot and Patrizio Lancellotti each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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