



REVIEW

Clinical value of exercise Doppler echocardiography in patients with cardiac-valvular disease

Intérêt clinique de l'échocardiographie Doppler à l'effort dans l'évaluation des patients porteurs de valvulopathies

Sylvestre Maréchaux^{a,b}, Annaïk Bellouin^c,
 Anne Sophie Polge^a,
 Marjorie Richardson-Lobbedez^{a,b}, Rémi Lubret^a,
 Philippe Asseman^d, Alain Berrebi^e,
 Christophe Chauvel^f, Jean Louis Vanoverschelde^g,
 Rémi Nevière^{a,b}, Brigitte Jude^b,
 Ghislaine Deklunder^{a,b}, Thierry H. Le Jemtel^h,
 Pierre Vladimir Ennezat^{b,d,*}

^a Département de physiologie, centre hospitalier régional et universitaire de Lille, 59019 Lille, France

^b EA 2693 et 2689, faculté de médecine, université de Lille-2, 59045 Lille, France

^c Département de cardiologie et maladies vasculaires, centre hospitalier régional et universitaire de Rennes, Rennes, France

^d Pôle de cardiologie, centre hospitalier régional et universitaire de Lille, Lille, France

^e Hôpital européen Georges-Pompidou, Paris, France

^f Clinique Saint-Augustin, Bordeaux, France

^g Cliniques universitaires Saint-Luc, UCL, Bruxelles, Belgium

^h Tulane University school of medicine, News Orleans, Los Angeles, USA

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Abbreviations: AR, aortic regurgitation; AO VTI, aortic velocity-time integral; AS, aortic stenosis; AVA, aortic-valve area; LV, left ventricular; LV EF, left ventricular ejection fraction; LVOT VTI, left ventricular-outflow tract velocity-time integral; MPG, mean pressure gradient; MR, mitral regurgitation; MS, mitral stenosis; PASP, pulmonary artery systolic pressure; PISA, proximal isovelocity surface area; RV, right ventricular; RVOT VTI, right ventricular-outflow tract velocity-time integral.

* Corresponding author. Intensive care unit, Cardiology hospital, boulevard Pr-J-Leclercq, 59037 Lille cedex, France.

Fax: +33 03 20 44 65 04.

E-mail address: ennezat@yahoo.com (P.V. Ennezat).

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Summary Besides its usefulness for the detection of exercise-induced ischemia, conventional exercise testing may help to predict the onset of clinical events and the need for surgery in asymptomatic patients with cardiac-valvular disease. Doppler echocardiography examination during exercise recently emerged as a new stress testing modality that may add useful information regarding dynamism of LV function, valve disease severity and pulmonary circulation. Few studies have demonstrated a correlation between the results of exercise Doppler echocardiography and clinical outcome. Preliminary experience needs to be confirmed to warrant routine use of Doppler echocardiography examination during exercise in the evaluation of patients with cardiac-valve disease.

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Résumé Au-delà de son utilité dans la détection d'une ischémie induite par l'effort, le test d'effort conventionnel réalisé chez des patients porteurs de valvulopathies, asymptomatiques, pourrait contribuer à prédire la survenue d'évènements cliniques et aider à poser les indications opératoires. L'échographie doppler pendant un exercice physique apparaît comme une nouvelle modalité d'évaluation pour ces patients apportant des informations complémentaires concernant la dynamique de la fonction ventriculaire gauche, la sévérité de l'atteinte valvulaire et la circulation pulmonaire. Peu d'études ont, à ce jour, établi une corrélation entre les données obtenues par échographie doppler à l'effort et le devenir des patients. Les études préliminaires nécessitent confirmation avant d'utiliser en pratique clinique l'échodoppler cardiaque d'effort pour les patients porteurs de valvulopathies.

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Doppler echocardiographic examination at rest is now the preferred imaging modality for the evaluation of patients with cardiac-valvular disease [1]. Non-invasive hemodynamic quantitative data derived from Doppler echocardiography examination at rest predict outcome and guide timing of valve surgery. Notwithstanding its usefulness for the detection of myocardial ischemia, conventional exercise testing in asymptomatic patients with heart-valve disease may help to predict onset of clinical events and need for surgery. Doppler echocardiography examination during exercise recently emerged as a new stress testing modality that may add useful information regarding dynamism of LV function, valve disease severity and pulmonary circulation. The present review aims to appraise whether Doppler echocardiography examination during exercise effectively adds useful information to that provided by resting Doppler echocardiography examination in the management of patients with cardiac-valvular disease.

Exercise Doppler echocardiography in aortic valve stenosis

Exercise testing even at low workload [2] is clearly contra-indicated in aortic stenosis (AS) patients with clear symptoms or with LV systolic dysfunction (LV EF < 50%). However conventional treadmill exercise testing is useful for unmasking symptoms and risk stratification of patients with severe asymptomatic AS (AVA < 1 cm²), particularly those younger than 70 years (class I level of evidence C) [1]. Importantly, exercise induced fall in systolic blood pressure, ST segment depression do not seem to refine the prognostic value of exercise-elicited symptoms [3]. Interpretation of exercise-elicited dyspnea is somewhat subjective, as

elicited symptoms may not be related to AS, especially in elderly people. Exercise Doppler echocardiography may facilitate interpretation of exercise-elicited symptoms. In contrast to Otto et al., who showed in patients with various degree of AS that postexercise derived Doppler echocardiography parameters do not provide additional prognostic information over those provided by Doppler echocardiography examination at rest [4], Lancellotti et al. found that an exercise-induced increase in mean transvalvular gradient greater than 18 mmHg has a predictive value of poor outcome over that provided by resting echocardiography and conventional exercise testing parameters [5] (Fig. 1). Of note, 75% of events were aortic valve replacement. Alternatively, a fall in LV EF during exercise may blunt the pressure gradient increase across the aortic valve (Fig. 2A), but it correlates with elicited symptoms (Fig. 2B)

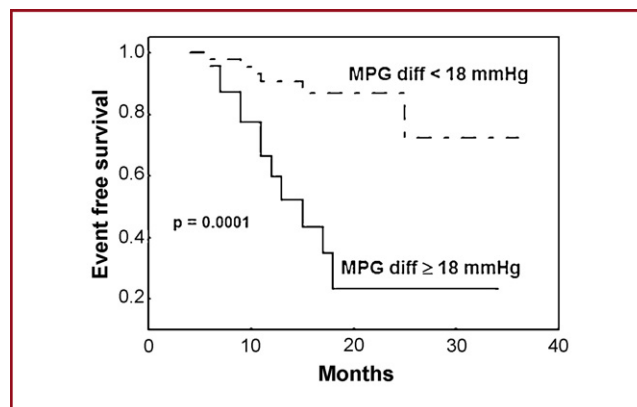


Figure 1. Event-free survival (aortic valve surgery in 75% of cases) according to the difference in mean transaortic gradient up or below 18 mmHg from rest to peak exercise. MPG: mean pressure gradient.

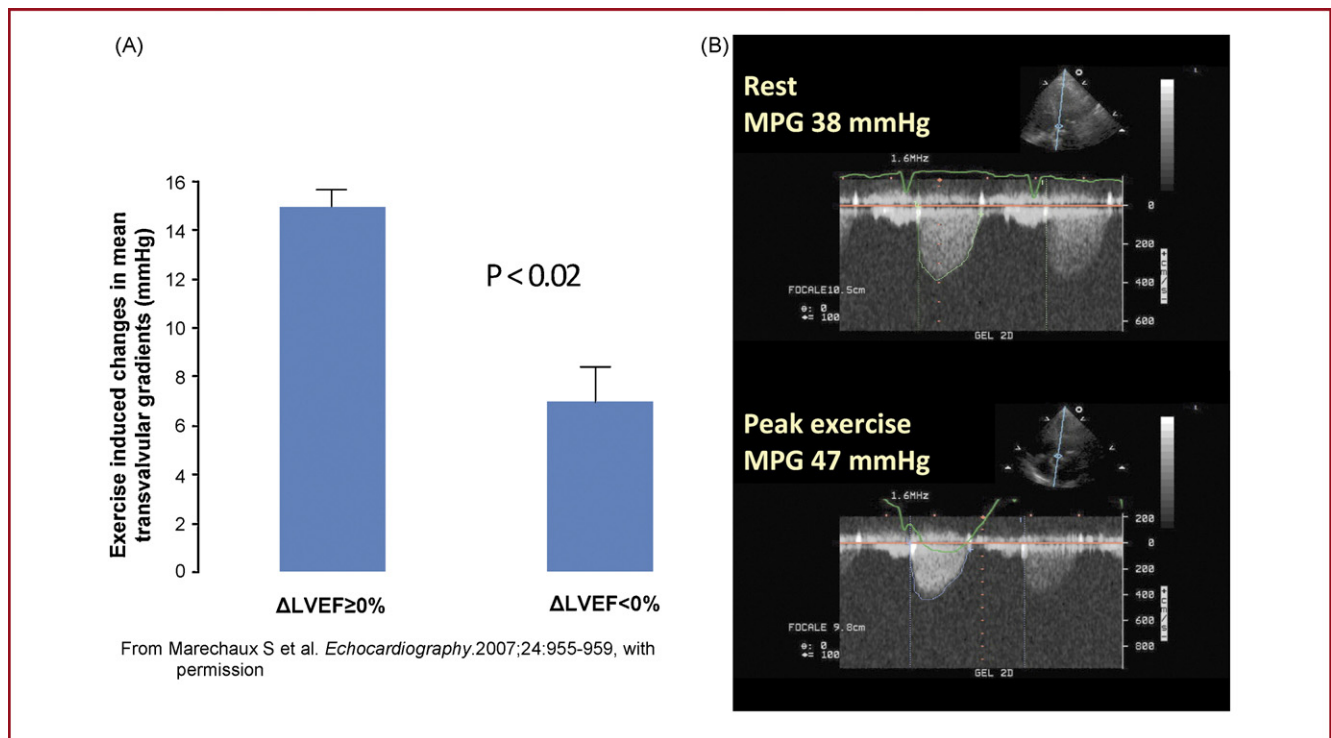


Figure 2. Exercise-induced changes in mean transvalvular gradients according to LV response to exercise. Exercise-induced changes in mean transvalvular gradients were significantly lower in patients with abnormal LV response during exercise (A). B illustrates mean transvalvular gradient at rest and at peak exercise in a patient with tight asymptomatic AVS who ended exercise at 45W because of dyspnea. LV EF decreased concomitantly from 0.65 to 0.55 and exercise-induced change in mean transaortic gradients was +9 mmHg. MPG: mean pressure gradient.

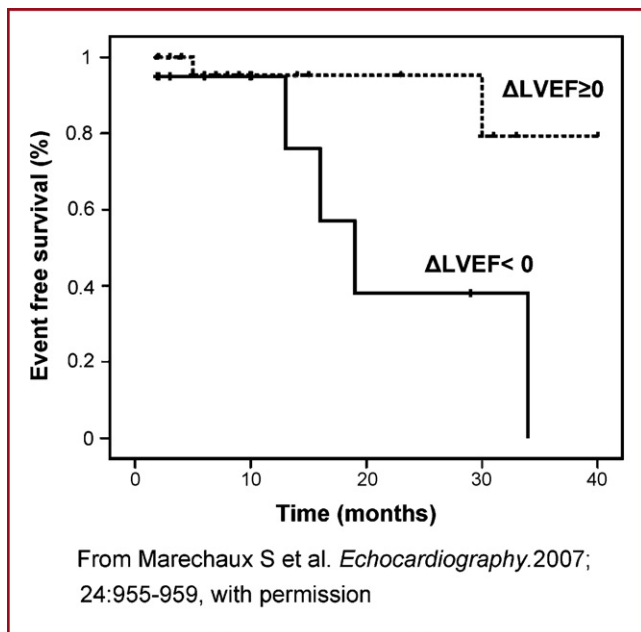


Figure 3. Event-free survival (clinical events) according to LV response to exercise in 50 patients with severe AS. Event-free survival was significantly lower in patients with abnormal LV response to exercise when compared with others.

and subsequent clinical events (Fig. 3) [6]. Event-free survival analysis may explain these apparent discrepancies. In the Euro Heart Survey, lung et al. reported that 20% of patients with AS underwent interventions without having an indication according to the guidelines [7]. Patients undergoing aortic valve replacement incidental to coronary surgery or without experiencing spontaneous symptoms should be censored at the time of the event [4]. Lancellotti et al. also reported that a limited contractile reserve is an independent predictor of exercise-elicited symptoms [8]. Latent LV systolic dysfunction may be uncovered when mitral annulus velocity does not increase immediately after exercise [9]. Whether this last finding correlates with clinical outcome remains to be established.

“In summary”, current guidelines do recommend exercise stress testing that is widely underused for evaluation of asymptomatic AS patients [1]. Preliminary experience needs to be confirmed to warrant routine use of exercise Doppler echocardiography in the assessment of patients with asymptomatic AS.

Exercise Doppler echocardiography in mitral regurgitation

Functional mitral regurgitation (MR)

Functional or secondary MR is defined by valvular incompetence associated with LV systolic dysfunction of ischemic

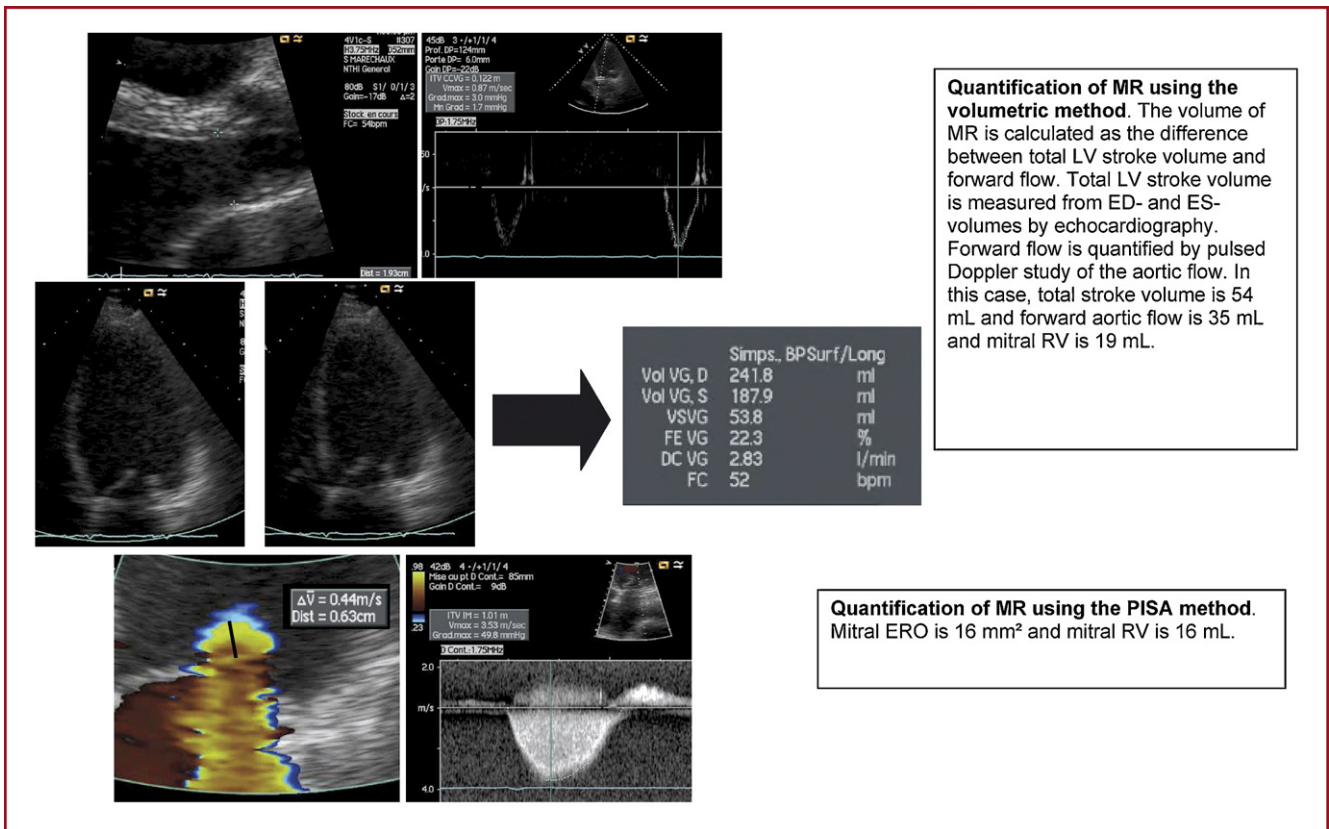


Figure 4. Quantification of MR using either the volumetric method and the PISA method in a same patient. Concomitant quantification using two different methods has to be performed to ascertain the severity of regurgitation and avoid regurgitant volumes that may nearly approach the total stroke volume!

and non-ischemic origin in the absence of any structural mitral-valve abnormality and conveys a poor outcome. While functional MR is dramatically underestimated by physical examination, Doppler echocardiography is exquisitely sensitive for the detection of functional MR [10]. Functional MR is particularly common as chronic-heart failure progresses [11]. Functional MR results from an imbalance between decreased mitral closing forces and increased tethering forces promoting MR [12]. The proximal flow convergence or proximal isovelocity surface area (PISA) method is more accurate for quantitative measurement of MR severity than the color Doppler jet area that is influenced by gain settings, pulse repetition and transducer frequency [13]. Grigioni et al. observed that values for effective regurgitant orifice and regurgitant volume above 20 mm² and 30 mL were associated with higher pulmonary pressures and poor outcome in patients with LV systolic dysfunction after myocardial infarction [14]. However, quantification of MR using the PISA method assumes circular effective regurgitant orifices. The difference between total stroke volume (using the Simpson method and three-dimensional live echocardiography in a near future) and LV forward stroke volume should be systematically computed (Fig. 4) [15]. In our experience, functional MR is usually mild or moderate [11] and the Doppler method using the mitral inflow often overestimates mitral regurgitant volume that may nearly approach the total LV stroke volume, probably because of geometric distortion of mitral annulus.

Functional MR is intrinsically dynamic. Induction of anesthesia, isometric or dynamic exercise and inotropic or vasodilator therapy may significantly alter the severity of functional MR [16–21]. The severity of functional MR during both isometric and dynamic exercise cannot be predicted from its severity at rest (Fig. 5) [19,20]. Exercise-induced changes in mitral severity depend on alterations in tenting area and in LV performance in patients with LV systolic dysfunction due to coronary artery disease [22]. Alterations in LV shape and thereby in mitral valve deformation brought by the volume load imposed by exercise correlated with exercise induced increase in mitral effective regurgitant area in ischemic MR patients without obvious acute coronary insufficiency [22]. In clinical practice, it should be underscored that myocardial ischemia may result in temporary LV papillary muscle-wall dysfunction or in an acute decline in LV function, both contributing to worsen or trigger ischemic MR [23], whatever the culprit ischemic territory [24]. Increased myocardial asynchronism assessed using pulsed-wave tissue Doppler imaging at rest (Fig. 6) and dynamic LV dyssynchrony may also exacerbate functional MR during exercise [20,25,26]. The decrease in LV ejection phase efficiency produced by myocardial asynchronism reduces transmitral force closure and thereby increases functional MR in patients with chronic-heart failure. Conversely, by producing a more efficient LV contraction, cardiac resynchronization therapy increases mitral force closures, thereby limiting the increase in MR brought by exercise in patients with chronic-heart

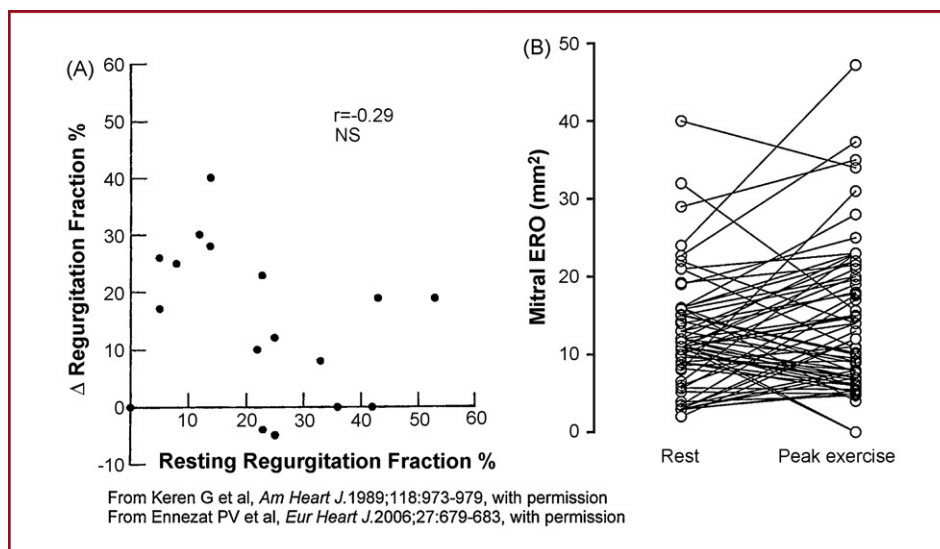


Figure 5. Lack of correlation between severity of mitral regurgitation at rest and at exercise during both isometric (A) and dynamic exercise (B).

failure, LV systolic dysfunction and enlarged QRS [27,28]. Lancellotti et al. observed that mitral effective regurgitant orifice increases in 80% of patients with LV systolic dysfunction due to coronary artery disease. An increase in mitral effective regurgitant orifice of more than 13 mm² was observed in 27% of patients and independently predicted cardiac death [29]. In contrast, we observed that mitral effective regurgitant orifice increases in 52% of patients with ischemic and non-ischemic cardiomyopathy but an increase greater than 13 mm² occurred in only 9% of patients [30]. Whereas the dynamic component of mitral severity did not help to predict outcome, both severity of LV remodelling and right ventricular dysfunction emerged as independent predictors of mortality [30]. However, Lancellotti's patient population differed from ours. We did not exclusively study patients with LV systolic dysfunction due to coronary artery disease without intraventricular conduction abnormality, but also included patients with LV systolic dysfunction due to non-ischemic cardiomyopathy. Adherence to current therapeutic guidelines, including inhibitors of the renin-angiotensin system [31] and long-term beta-adrenergic blockade [32], was substantially greater in our study than in Lancellotti's study [29]. Whether differences in LV systolic dysfunction etiology and treatment account for the disparate findings between Lancellotti's and our study cannot be ascertained from our data, further studies are needed to address these issues. In this context, benefit of surgical valve correction in this setting is an important matter of debate and awaits prospective studies, such as the SIMRAM registry [33].

"In summary", functional MR should be viewed as a ventricular disease and not a valvular disease. Functional MR responds dynamically to exercise, even in selected patients with no evidence of inducible ischemia. Because assessment of exercise wall motion abnormalities in patients with depressed LV function is challenging, worsening of MR during exercise might be a marker of possible active myocardial ischemia [24] and advocates further testing (stress cardiac

MRI, Thallium study and possible coronary angiography). The role of exercise Doppler echocardiography in the risk stratification of chronic-heart failure patients with functional MR remains to be clarified in larger studies. Current guidelines do not recommend the use of exercise Doppler echocardiography in this setting [1]. Lastly, changes in the severity of MR may not be primarily related to functional capacity [20] as patients with chronic-heart failure do not exhaust their cardiopulmonary reserve during symptom-limited maximal bicycle exercise [34].

Organic MR

The assessment of the severity of any valvular disease needs not to rely entirely on one single parameter, but requires an integrated approach, including mechanisms, Doppler and cardiac chamber morphologic data [1]. Because of non-hemispheric radius and wall constraint, quantification of MR volume obtained from the PISA method needs to be confirmed by the difference between LV total stroke volume (measured from end-diastolic and end-systolic volumes by 2D echocardiography) and forward stroke volume method.

Exercise testing may uncover symptoms and depressed peak-aerobic capacity in patients with asymptomatic severe MR, but requires validation [35]. The role of exercise Doppler echocardiography in organic MR has been seldom studied. Absence of LV contractile reserve (defined as a decrease or an increase in LV EF less than 4%) after exercise predicts postoperative LV dysfunction and poor prognosis in asymptomatic patients with moderate to severe MR (Fig. 7) [36]. This study confirms that the assessment of LV systolic function at rest can be misleading due to latent LV systolic dysfunction that exercise testing may unmask. In addition, deterioration of resting LV EF while awaiting surgery may have occurred in this series and advocates the critical need for serial resting and exercise testing in future studies [37]. Whereas assessment of LV EF during exer-

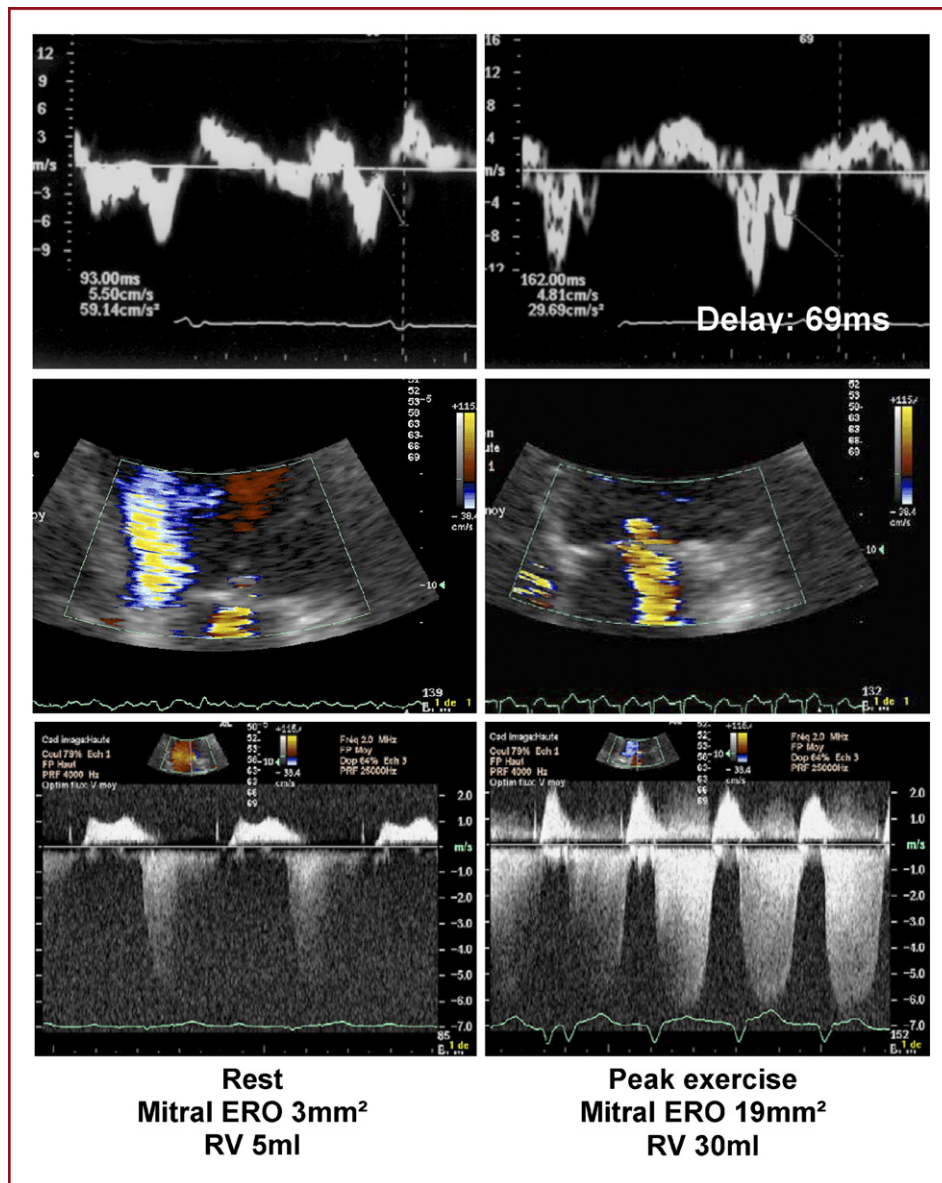


Figure 6. Example of a patient with non-ischemic dilated cardiomyopathy (LV EF = 0.25), left bundle branch block and resting myocardial asynchronism (intra-LV asynchrony = 69 ms) who experienced an increase in functional MR severity (+ 16 mm²) during dynamic exercise.

cise testing is challenging, in our opinion, monitoring aortic velocity time integral and thereby forward output during exercise may be an easier surrogate of contractile reserve than LV EF, but requires validation. In addition, whether blood pressure response during exercise primarily alters MR severity and thereby exercise capacity remains to be demonstrated.

“In summary”, serial clinical and echocardiographic examinations and monitoring of functional capacity are strongly recommended. Careful observation with prompt referral to surgery when either symptoms develop or currently recommended cut-off values for LV size, LV function or pulmonary hypertension are reached results in an outcome similar to that of age and gender matched controls [38]. The usefulness of exercise Doppler echocardiography examination during exercise in optimizing timing of surgery remains to be established in larger series.

Exercise Doppler echocardiography in aortic regurgitation

Once again, integrative approach is also needed to assess resting aortic regurgitation (AR) severity [1]. Only one study addressed the usefulness of Doppler echocardiography examination during exercise in AR patients. Marwick’s group reported that the absence of LV contractile reserve during exercise (defined as a decrease or no increase in LV EF) predicts a poor outcome in patients with severe AR [39]. Of note, an easier surrogate of decrease in LV EF during exercise may be reduction in long-axis contraction at rest [40].

“In summary”, the decision of aortic valve replacement in asymptomatic patients with severe AR is based on Doppler echocardiography data acquired in the resting state. Current guidelines advocate aortic valve replacement when LV EF is equal or less than 50% or LV end-diastolic or LV end-systolic

diameter is greater than 70 mm and 50 mm (or $> 25 \text{ mm/m}^2$ body surface area), respectively. Lastly, surgery is indicated when the ascending aorta is severely dilated independently from AR severity [1].

Exercise Doppler echocardiography in mitral stenosis

Planimetry is the method of choice to assess mitral stenosis (MS) severity at rest. Severe MS at rest is defined when mitral area is less than 1.5 cm^2 [1]. Doppler echocardiography examination during exercise in a small number of patients has shown that:

- exercise induced increase in systolic pulmonary pressure is greater in patients with MS when compared to patients with mitral prosthesis [41];
- mitral valve compliance (i.e. atrio ventricular compliance) is an important determinant of resting and exercise pulmonary artery systolic pressure (PASP) [42];
- peak exercise PASP is inversely related to exercise capacity [43];
- exercise duration mainly depends on resting PASP in patients with low mitral valve compliance and on post-exercise stroke volume in patients with preserved mitral valve compliance [44];
- failure to increase stroke volume during exercise is related to MS severity and limits exercise capacity (Fig. 8) [45,46];
- the transmitral mean pressure gradient commonly increases during exercise, regardless the severity of the stenosis, in accordance with exercise duration and exercise-induced changes in cardiac output [42,47].

However, due to the small number of patients studied, the data regarding exercise Doppler echocardiography and clinical outcome are not robust in patients with MS.

‘‘In summary’’, the limited data available do not advocate a routine use of exercise Doppler echocardiography in MS. Larger series are needed to clarify the role of this tool in the management of patients with MS. However, Doppler echocardiography may be performed during exercise to correlate symptoms with transmitral gradient, cardiac output and pulmonary artery pressure. Indeed, current guidelines recommend exercise testing to elicit symptoms in patients with severe MS and no or doubtful symptoms [1].

Exercise Doppler echocardiography, heart–valve disease and pulmonary pressure

Increase in PASP during exercise may provide useful information in patients with cardiac valve disease [29,41,43,8]. Accurate recording of the maximal tricuspid regurgitant jet velocity by continuous Doppler, although sometimes challenging even in resting conditions, is essential to measure reliably PASP [48]. Doppler estimated pulmonary pressure has been validated against invasive measurement [49], but the normal range values of exercise-induced changes in PASP

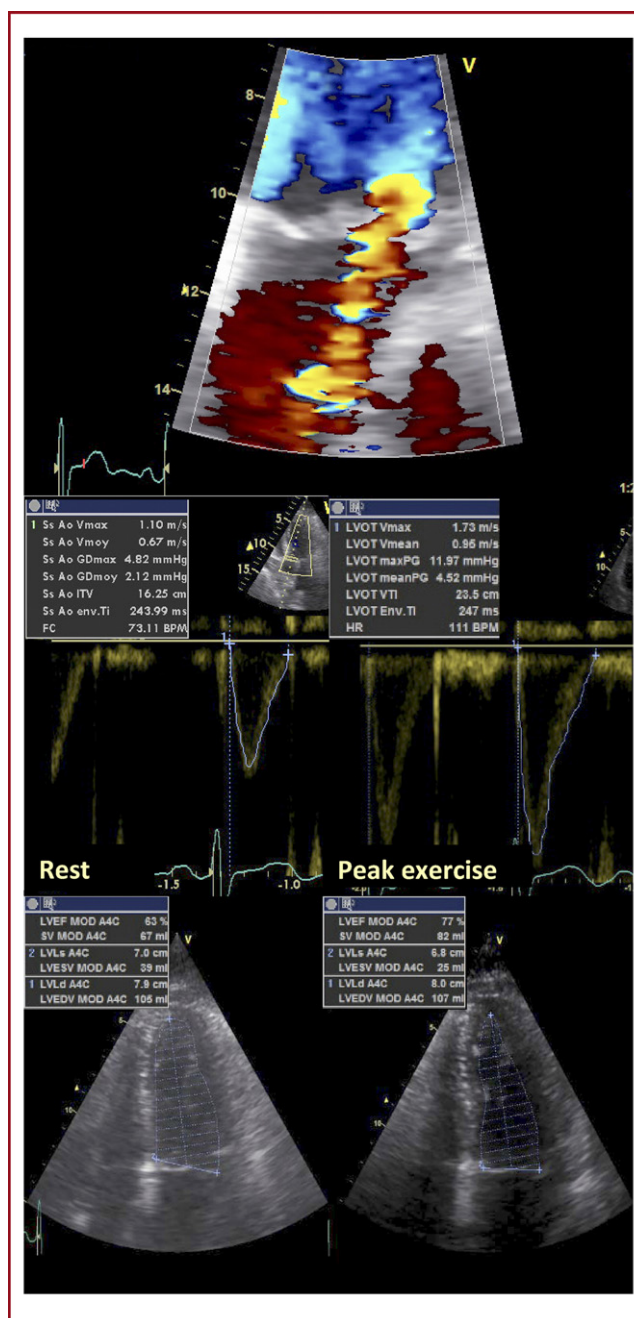


Figure 7. Presence of contractile reserve during exercise in an asymptomatic patient with moderate MR due to posterior mitral valve prolapse. LV EF increases more than 4% during exercise. The rise in left ventricular outflow tract velocity-time integral (LVOT VTI) during exercise suggests that MR does not blunt exercise-induced increase in LV stroke volume.

still needs to be defined. In healthy humans, large changes in pulmonary blood flow are associated with small elevation in PASP in order to maintain a low-pressure circuit [50]. Exercise-induced changes in PASP depends on exercise duration. The clinical significance of a large increase in PASP needs to be interpreted as a function of the duration of exercise and the achieved workload [51]. As occurs in patients with chronic-heart failure due to LV systolic dysfunction [52], exercise-induced changes in pulmonary pressures do

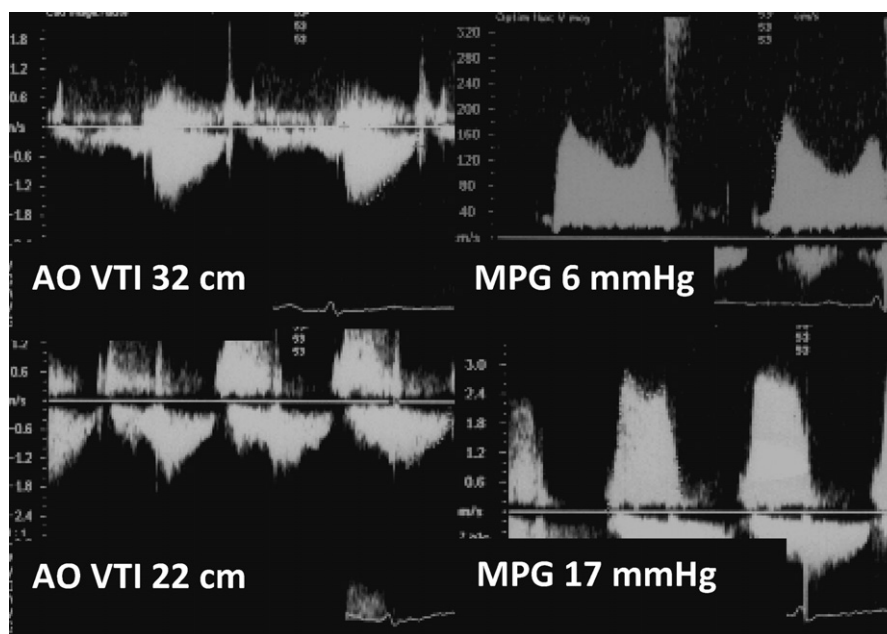


Figure 8. Decrease in aortic VTI and thereby in stroke volume in a patient with severe mitral stenosis. AO VTI: aortic velocity-time integral, MPG: mean pressure gradient.

not entirely depend on changes in pulmonary resistances but also on changes in flow [50]. Changes in right ventricular peak systolic pressure during exercise depend on the contractile reserve of the right ventricle that may be depressed in patients with heart-valvular disease. The key relationship between right ventricular function, dynamic changes in PASP and prognosis advocates to pay great attention to right ventricular function [30]. Bidart et al. elegantly demonstrated that tricuspid regurgitant velocity/right ventricular outflow tract velocity-time integral might discriminate a flow- versus a resistance-mediated mechanism for exercise-induced increase in PASP [53]. Further studies are needed to ascertain the usefulness and the convenience of this parameter.

Conclusions

According to current guidelines, indication for surgery in cardiac valve disease is mainly based on clinical evaluation and thorough Doppler echocardiography examination at rest. In patients with no or doubtful symptoms, conventional upright exercise testing aids decision making by unmasking symptoms, but is still underused (performed in only 5.7% patients with asymptomatic severe AS in the Euro Heart Survey) [7]. Assessment of cardiac valve disease by Doppler echocardiography during exercise is currently investigated. Exercise Doppler echocardiography is indeed a valuable tool to monitor the dynamic components of valvular leaks and stenosis, LV systolic function, forward output and pulmonary pressures and enables to correlate these results with symptoms. Besides the assessment of heart-valvular disease, exercise Doppler echocardiography remains a reliable method for the detection of myocardial ischemia [54,55]. However, available data regarding exercise echocardiography rely on experienced teams. It remains to be established that a wide use of exercise Doppler echocardiography in less

experienced hands may be helpful to improve prognosis of patients with cardiac valve disease and to select the optimal timing for surgery.

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