



The role of exercise echocardiography in the management of mitral valve disease

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Abstract

Purpose Exercise echocardiography can assess the dynamic component of mitral valve (MV) disease and may therefore be helpful for the clinical decision-making by the heart team. The purpose of this study is to determine the role of exercise echocardiography in the management of disproportionately symptomatic or otherwise atypical patients with mitral regurgitation (MR) and stenosis (MS) in clinical practice.

Methods Data of 14 MR and 14 MS patients, including echocardiograms at rest, were presented retrospectively to an experienced heart team to determine treatment strategy. Subsequently, exercise echo data were provided whereupon once again the treatment strategy was determined. This resulted in: value of exercise echo by means of 1) alteration or 2) confirmation of treatment strategy or 3) no additional value.

Results During exercise the echocardiographic severity of MV disease increased in 9 (64 %) MR and 8 (57 %) MS patients. Based upon alteration or confirmation of the treatment strategy, the value of exercise echocardiography in the management of MR and MS was 86 % and 57 %, respectively.

Conclusion This study showed that physical exercise echo can have an important role in the clinical decision-making of challenging patients with MV disease. Exercise echocardiography had additional value to the treatment strategy in 71 % of these patients.

Keywords Exercise echocardiography · Physical exercise echocardiography · Mitral valve disease · Mitral regurgitation · Mitral stenosis · Clinical practice

Introduction

Mitral valve (MV) disease is a dynamic entity. Consequently, patients can present as being asymptomatic or disproportionately symptomatic in relation to the degree of severity of their valve disease on the resting echo [1]. Management of MV disease can therefore be challenging.

Exercise echocardiography

Echocardiography has been the most important and cost-effective diagnostic imaging tool in clinical cardiology for more than 30 years [2]. Rest echocardiography is nowadays recommended in the diagnostic work-up of MV disease [3, 4] and has also shown to be of additional value in other valve diseases [5]. Further echocardiographic development has created new opportunities among which stress echocardiography, performed by exercise or dobutamine. Exercise echo is already widely accepted as an important diagnostic and prognostic tool in the assessment of coronary artery disease [1]. Exercise echocardiography is now also increasingly being performed in the evaluation of MV disease and has a place in the current European Society of Cardiology (ESC) guidelines. Compared with dobutamine stress echo, the main advantage of exercise echo is the direct evaluation of symptoms, exercise capacity and haemodynamic consequences of MV disease. In mitral stenosis (MS), dobutamine stress

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echo is an alternative when physical exercise cannot be performed (except for the evaluation of pulmonary pressure) [6]. However, in mitral regurgitation (MR) it is not useful due to its reduction in afterload and beneficial effect on the MR [6, 7].

As exercise echocardiography can assess the dynamic component of MR or MS, it may be helpful for clinical decision-making.

Exercise echo in mitral regurgitation

MR is the second most frequent valve disease in Western countries after aortic stenosis [8]. It can be classified as organic or functional. Two-dimensional (2D) echocardiography is the recommended method to confirm MR and must include an assessment of severity, mechanism, reparability and clinical consequences [3].

Exercise echocardiography is useful in experienced hands to quantify exercise-induced changes in organic MR, systolic pulmonary artery pressure (SPAP) and LV function [3]. The influence of exercise echo testing is evidenced by the ESC recommendations: surgery may be considered in asymptomatic patients with severe organic MR, preserved LV function and SPAP ≥ 60 mmHg during exercise (class IIb, level of evidence C) [3]. However, a prospective trial to clarify the best treatment option in these patients started in 2013 (Dutch AMR trial) [9].

In patients with moderate functional MR, development of exercise-induced dyspnoea and increased MR severity, associated with pulmonary hypertension, are further incentives to indicate surgery (class IIa, level of evidence C) [3]. Nevertheless due to the low level of evidence, the exact value of exercise echo in the management of MR remains unclear.

Exercise echo in mitral stenosis

With the reduction in rheumatic fever, MS is now less frequently seen in industrialised countries. However, MS results in significant morbidity and mortality rates worldwide. Echocardiography is the main diagnostic method to assess severity, consequences and the extent of anatomic lesions. MS prognosis dramatically worsens with the development of symptoms [10]. Following the ESC guidelines, exercise testing is indicated in asymptomatic patients or patients with symptoms equivocal or discordant with the MS severity [3]. When analysing exercise-induced changes in symptoms, SPAP and valve gradients may provide extra information [3, 11]. Moreover, following the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, further (invasive) intervention may be considered in (even mild) symptomatic patients, with a significant increase in SPAP >60 mmHg or a rise in valve gradient to >15 mmHg during exercise (class IIB, level of evidence C) [4]. Furthermore percutaneous mitral balloon valvotomy is indicated in asymptomatic patients with moderate to severe

MS and favourable characteristics, who reach an SPAP >50 mmHg at rest or >60 mmHg during exercise (in the absence of a left atrium thrombus or moderate to severe MR) (class I, level of evidence C) [4].

Exercise echocardiography is now increasingly being performed according to the guidelines and beyond: i.e. in disproportionately symptomatic patients in relation to their MV disease severity. The present study analysed the role of physical exercise echocardiography for the evaluation and management of disproportionately symptomatic or otherwise atypical patients with MV disease.

Materials and methods

Study population

We retrospectively evaluated 28 resting and corresponding exercise echocardiograms performed for the evaluation of MV disease in the University Medical Center of Utrecht (2009–2011).

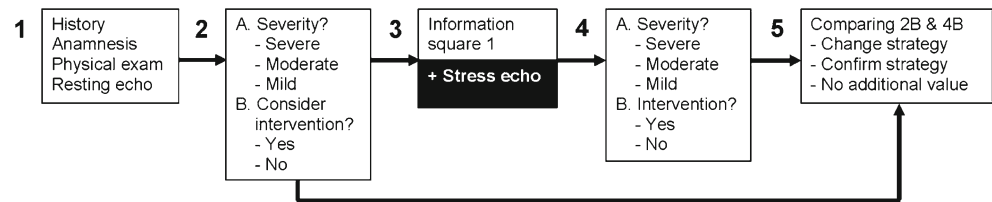
Expert panel

Patient records were reviewed by an experienced heart team consisting of a cardiologist and cardiothoracic surgeon. The expert panel was provided with all available patient data including resting echocardiogram, whereupon they determined if intervention should be considered. Subsequently, exercise echo data were provided after which the expert panel once more decided if they would perform an intervention or watchful waiting strategy. Based on the preferred treatment strategies, depending on resting and exercise echo data respectively, three different outcomes were scored: value of exercise echo by means of either 1) change or 2) confirmation of the treatment strategy or 3) no additional value. Finally a change and/or confirmation determined the true additional value of exercise echocardiography (Fig. 1).

Exercise echo protocol

The exercise protocol was tailored to the capacity of the patient. Hence, 16 patients underwent exercise testing on a semi-supine bicycle (Fig. 2). In 12 patients alternative exercise testing was done, using a stepper or by performing knee bends. ECG and blood pressure (non-invasively) were measured before, every 3 min during and after exercise. Symptoms were continuously monitored. An adjusted protocol was used starting with a mean resistance of 30 (± 12) Watts, which the physician manually increased by 10–25 Watts every 2–3 min. Exercise testing was performed until >85 % of the age-predicted maximal heart rate was reached or when exhaustion or recognisable symptoms occurred.

Fig. 1 Study methods: the decision flowchart per patient, used by the expert panel (1 to 5)



All patients underwent 2D transthoracic echocardiography (TTE) during physical exercise on a semi-supine bicycle or in the left lateral decubitus position directly after exercise. MR mechanism and severity were classified both on colour Doppler and according to the recommendations for quality echocardiography laboratory operations [12]. Measurement of tricuspid regurgitation (TR) jet velocity was performed in the parasternal short-axis or in the apical four-chamber view, resulting in right ventricular systolic pressure (RVSP) by adding the right atrial pressure (RAP) to the peak TR gradient. The mean transmitral gradient was measured by tracing the area-under-the-curve of the mitral E and A waves obtained by continuous Doppler in the apical views.

Examinations were performed with the Philips 5500 or Philips IE33 (Philips Medical Systems, Andover, Massachusetts, USA) echo machines. All datasets were archived on the hospital server as video loops and freeze frames in a digital format (DICOM). Off-line analysis was performed using Xcelera software.

Results

Mitral regurgitation

Patient characteristics

The MR group consisted of 14 patients (7 organic and 7 functional MR). Mean age was 66 (31–78) years. All patients

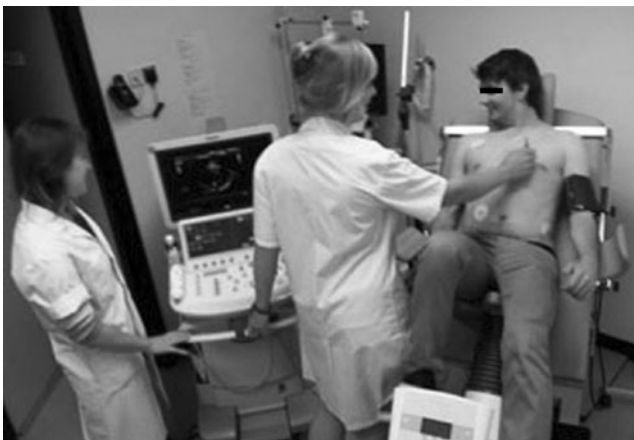


Fig. 2 Exercise echocardiography on a semi-supine bicycle in the University Medical Center of Utrecht

were symptomatic. The LV function was normal in 11 patients (79 %).

MR severity at rest was classified at baseline: 1 severe, 4 moderate and 7 mild. Two patients had clinical suspicion of MR but no regurgitation on resting images (Tables 1 and 2).

Exercise echo

The mean heart rate during exercise was 131 (80–160) beats per minute (bpm). Nine patients (64 %) reached >85 % of the age-predicted maximal heart rate (mean 145 ± 12 bpm). In 43 % β -adrenergic blocking medication was used. Severity of MR during exercise increased in 9/14 patients (64 %). During exercise, 4 patients had severe MR. Exercise RVSP was ≥ 60 mmHg in 5 (36 %) subjects, of whom 3 (60 %) were diagnosed with severe MR during exercise (Table 2). In 10 patients (71 %) stress RVSP was higher compared with the resting value (5 patients ≥ 60 mmHg), and in 4 subjects a change in RVSP could not be determined. Figure 3a shows the increase in mean RVSP from 29.9 ± 4.5 mmHg at rest to 54.2 ± 15.8 mmHg during exercise.

Clinical management

Based on the judgment of the expert panel an intervention was indicated in 5 MR patients (80 % new indication); 4 patients in this group had severe MR during exercise (of whom 1 already had severe MR at rest) and in 4 patients exercise RVSP was ≥ 60 mmHg (Table 2). In 1 patient with RVSP ≥ 60 mmHg during exercise but at the same time moderate MR, an intervention was not recommended.

Figure 4a demonstrates a change in recommended treatment strategy for MR patients in 29 % and confirmation in 57 %. The value of physical exercise echocardiography in the management of MR was demonstrated in 86 %.

Mitral stenosis

Patient characteristics

The MS group consisted of 14 patients of whom 7 (50 %) had organic disease and 7 (50 %) had MS after mitral valve repair (MVR). Mean age was 56 (29–83) years and 86 % were symptomatic. LV function was normal in 93 %. Severity of MS at rest was classified at baseline: 1 severe, 11 moderate and 2 mild (Tables 1 and 3).

Table 1 Baseline characteristics

Baseline	MR	MS
Patient characteristics		
Study group	14	14
Age (range)	66 (31–78)	56 (29–83)
Gender:		
Male (%)	50	29
Female (%)	50	71
Left ventricular function		
Normal	11	13
Dysfunctional ^a	3	1
Mitral valve disease		
Symptomatic	14	12
Severity in rest:		
Severe	1	1
Moderate	4	11
Mild	7	2
None	2	0
Exercise protocol		
Semi-supine bicycle	10	6
Alternative exercise test ^b	4	8

MR mitral regurgitation, MS mitral stenosis

^a According to the ESC guidelines: left ventricular ejection fraction of $\leq 60\%$ or left ventricular end systolic dimension of ≥ 45 mm [4]

^b Using a stepper or performing knee bends

Exercise echo

During exercise echocardiography the mean heart rate was 115 (80–150) bpm. Four patients (29 %) achieved $>85\%$ of the age-predicted maximal heart rate (mean 143 ± 9 bpm). Of these patients 71 % used β -adrenergic blocking medication. MS severity during exercise increased in 8/14 patients (57 %). Seven patients had severe MS during exercise. Exercise-induced RVSP was ≥ 60 mmHg in 4 (29 %) of the MS patients. Three of them (75 %) were diagnosed with severe MS during exercise. Stress mean gradient values increased to >15 mmHg in 7 (50 %) patients. All were diagnosed with severe MS during exercise (Table 3).

RVSP increased in 11 patients (79 %) during exercise (4 patients ≥ 60 mmHg), whereas in 2 cases RVSP could not be determined. One patient showed a slight decrease in RVSP. However, with severe MS and exercise-induced mean gradient >15 mmHg, intervention was still recommended in this patient by the expert panel.

Figure 3b and c show a rise in mean RVSP and mean gradient during exercise from 34.9 ± 9.0 mmHg to 52.1 ± 17.8 mmHg and from 6.9 ± 2.4 mmHg to 15.9 ± 7.3 mmHg, respectively.

Clinical management

The expert panel recommended an intervention in every patient who developed severe MS during exercise (7). For 6 patients this indication was new (Table 3). In all 7 subjects exercise-induced mean gradient was >15 mmHg and 3 (43 %) had an RVSP ≥ 60 mmHg. Of the patients with exercise RVSP ≥ 60 mmHg, 75 % received an indication for surgery.

Figure 4b shows a change in recommended treatment strategy in 43 % of all MS patients and confirmation in 14 %. The value of physical exercise echocardiography in the management of MS was seen in 57 %.

Discussion

The present study is remarkable for its objective to define the clinical value of exercise echocardiography for decision-making in challenging patients with MS or MR who cannot easily be classified by the guidelines.

As clearly described by Van de Heyning et al. [13], several articles have already pointed out the increasing evidence for exercise echo in determining dynamic changes in MV disease and to identify high-risk patients who may benefit from (early) intervention. In addition, our study showed that exercise echocardiography was of additional value in the clinical decision-making in 20/28 (71 %) of all patients, demonstrating 10 patients with a change and 10 patients with confirmation of treatment strategy.

Exercise-induced changes in MV disease severity

Data supporting exercise-induced changes in echocardiographic parameters to quantify MR are limited [3, 11]. Only an exercise-induced increase of the effective regurgitant orifice area (EROA) by ≥ 13 mm has shown to be associated with a significant increase in relative risk of death and hospitalisation for cardiac decompensation in functional MR [14]. Unfortunately EROA is difficult to measure, especially during exercise. Furthermore, exercise echocardiography has only shown to be useful in observing symptoms caused by an increase in MR severity in symptomatic patients with mild rheumatic MR at rest [15].

In our study MS severity was mainly based on the mean gradient value. Determining MS severity by mean gradient using exercise echocardiography has proven to be feasible and well correlated with invasive measurements [16–18]. Previous studies also demonstrated marked elevations in mean gradient after peak exercise in patients with predominantly MS [19–23]. Further (invasive) intervention may therefore be considered in (even mild) symptomatic patients with a significant increase in valve gradient to >15 mmHg during exercise (class IIB, level of evidence C) [4].

Table 2 Results in mitral regurgitation patients

MR patient	Diagnosis at rest	Symptoms	Consider intervention at rest	LV function at rest	RVSP at rest	RVSP during stress	Diagnosis during stress	Intervention during stress	Decision based on	Additional value stress echo
1	Mild	Yes	No	Normal	27.6	60.0	Severe	Yes	Severity and RVSP	Yes change
2	Mild	Yes	No	Normal	25.0	46.0	Moderate	No	Severity and RVSP	Yes confirmation
3	Mild	Yes	No	Normal	22.3	51.0	Mild	No	Severity and RVSP	Yes confirmation
4	Severe	Yes	Yes	Normal	39.0	70.0	Severe	Yes	Severity and RVSP	Yes confirmation
5	Mild	Yes	No	Normal	27.4	40.0	Moderate	No	Other ^a	No
6	Mild	Yes	No	Reduced	NA	NA	Moderate	No	Other ^a	No
7	Moderate	Yes	No	Reduced	35.5	75.2	Moderate	Yes	RVSP	Yes change
8	Mild	Yes	No	Normal	33.3	50.7	Moderate	No	Severity and RVSP	Yes confirmation
9	None	Yes	No	Normal	NA	25.0	Mild	No	Severity and RVSP	Yes confirmation
10	Mild	Yes	No	Reduced	28.9	41.0	Moderate	No	Severity and RVSP	Yes confirmation
11	None	Yes	No	Normal	30.8	64.2	Severe	Yes	Severity and RVSP	Yes change
12	Moderate	Yes	No	Normal	30.5	NA	Mild	No	Severity	Yes confirmation
13	Moderate	Yes	No	Normal	27.6	NA	Severe	Yes	Severity	Yes change
14	Moderate	Yes	No	Normal	30.9	73.1	Moderate	No	Severity	Yes confirmation

MR mitral regurgitation, LV left ventricular, RVSP right ventricular systolic pressure, NA not available

^a other: the expert panel decision is based on criteria different from the exercise echo results, for example ischaemic heart disease as a cause, co-morbidity or high surgical risks

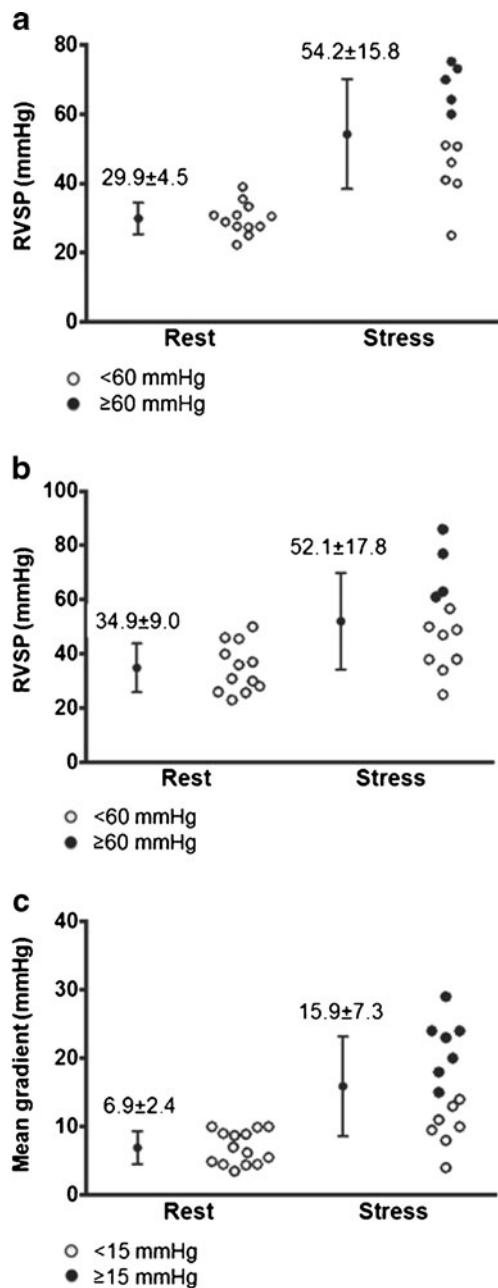


Fig. 3 Right ventricular systolic pressure (RVSP) values in patients with mitral regurgitation (a) and mitral stenosis (b) and mean gradient values in mitral stenosis (c) during rest and exercise echocardiography

As a result, in all 7 MS subjects with an exercise-induced mean gradient >15 mmHg, our expert panel recommended an intervention. However, the proposed cut-off value by the guidelines (>15 mmHg) is arbitrary, consensus driven and not supported by solid evidence.

Exercise-induced changes in pulmonary pressures

Echocardiography has been validated as the principal tool for measuring pulmonary pressures in daily practice, although

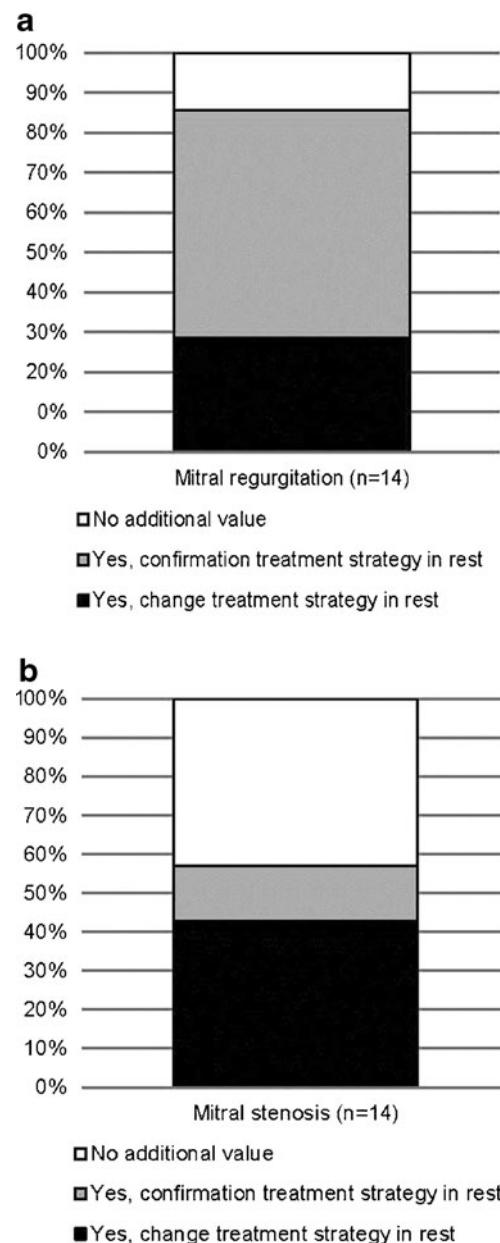


Fig. 4 The value of exercise echocardiography in mitral regurgitation (a) and mitral stenosis (b)

discrepancy exists on the correlation between echocardiographic findings and invasive measurements [24]. Guidelines regarding MS urge to consider further intervention in symptomatic patients with significant elevation of SPAP (>60 mmHg) during exercise [19, 25, 26]. Furthermore, marked pulmonary hypertension (SPAP >50 mmHg at rest or >60 mmHg during exercise) is associated with a poor prognosis in patients with LV dysfunction [27]. Despite a low level of evidence, echocardiographic measurement of an exercise-induced SPAP ≥60 mmHg has therefore also been suggested as cut-off value for considering MVR in asymptomatic patients with severe organic MR and preserved LV

Table 3 Results in mitral stenosis patients

MS patient	Diagnosis at rest	Symptoms	Consider intervention at rest	LV function at rest	RVSP at rest	Mean gradient at rest	RVSP during stress	Mean gradient during stress	Diagnosis during stress	Intervention during stress	Decision based on	Additional value stress echo
1	Severe	Yes	Yes	Normal	28.1	10.0	38.0	24	Severe	Yes	Severity and mean gradient	Yes confirmation
2	Moderate	No	No	Normal	45.6	4.9	50.0	4	Moderate	No	Severity, RVSP and mean gradient	Yes confirmation
3	Moderate	Yes	No	Normal	40.0	10.0	63.0	18	Severe	Yes	Severity, RVSP and mean gradient	Yes change
4	Moderate	Yes	No	Normal	NA	5.5	NA	9.5	Moderate	No	Other ^a	No
5	Moderate	Yes	No	Normal	23.0	6.2	56.7	11	Moderate	No	Other ^a	No
6	Moderate	Yes	No	Reduced	36.0	8.7	25.0	20	Severe	Yes	Severity and mean gradient	Yes change
7	Moderate	Yes	No	Normal	46.0	9.9	61.0	15	Severe	Yes	Severity, RVSP and mean gradient	Yes change
8	Moderate	Yes	No	Normal	30.9	4.5	38.0	10	Moderate	No	Other ^a	No
9	Moderate	Yes	No	Normal	25.7	8.9	48.9	14	Moderate	No	Other ^a	No
10	Moderate	Yes	No	Normal	50.0	9.0	86.0	23	Severe	Yes	Severity, RVSP and mean gradient	Yes change
11	Mild	Yes	No	Normal	37.0	3.5	77.0	8	Moderate	No	Other ^a	No
12	Moderate	Yes	No	Normal	26.0	7.0	34.0	29	Severe	Yes	Severity and mean gradient	Yes change
13	Mild	Yes	No	Normal	NA	4.5	NA	13	Moderate	No	Other ^a	No
14	Moderate	No	No	Normal	30.0	4.4	47.0	24	Severe	Yes	Severity and mean gradient	Yes change

MS mitral stenosis, LV left ventricular, RVSP right ventricular systolic pressure, NA not available

^a other: the expert panel decision is based on criteria different from the exercise echo results, for example ischaemic heart disease as a cause, co-morbidity or high surgical risks

function [3]. Moreover, Lebrun et al. showed that SPAP values were greatest in patients with marked dynamic MR, and well correlated with increases in regurgitant volume (PISA method) [28].

However, no reference values exist for physiological exercise-induced changes in SPAP. Also other factors than MV disease can play a role in the dynamic changes during exercise, e.g. alterations of pulmonary resistance and neuro-hormonal activation [28].

In absence of right-sided flow obstruction, SPAP and RVSP values were equal in this study. Although stress RVSP peak values of 35–45 mmHg are regarded as physiological [29–31] in (young, male) endurance athletes and older patients (≥ 60 years), peak-exercise values of >60 mmHg have been reported [32, 33]. The prognostic significance of this marked increase has not been defined. It has been advocated to integrate age and level of exercise with the exercise-induced SPAP response to determine abnormal elevation of pulmonary pressures [24, 29, 33]. In our study a stress SPAP of ≥ 60 mmHg in patients with less than maximal workload was classified as pathological.

The expert panel's decision was influenced by the RVSP measurement during exercise in 13 (46 %) of all patients. In 15 patients management was determined based on other criteria, e.g. an increase in mean gradient (an intervention was recommended in all MS patients with mean gradient >15 mmHg).

Value of exercise echocardiography

For optimal exercise testing, a heart rate of >85 % of the age-predicted maximal heart rate was obligatory. In 64 % of the MR patients this criteria was achieved, versus only 29 % of the MS patients. Moreover, the total mean heart rate appeared to be lower in MS compared with MR (115 versus 131 bpm). Both remarks can be explained by the use of more β -adrenergic blocking agents in the MS population compared with MR patients (71 % versus 43 %).

Although exercise echocardiography is only recommended in asymptomatic patients with severe MR [3], in this study we analysed symptomatic MR patients. Apparently, in daily clinical practice exercise echocardiography is more and more supposed to be of additional value in disproportionately symptomatic patients. Furthermore, the additional value in 12 symptomatic (86 %) and 2 asymptomatic (14 %) MS patients certainly fits within the earlier described guideline recommendations for exercise echocardiography in both asymptomatic and symptomatic MS [3, 4].

Limitations

This study was retrospective with its inherent limitations. The decision to perform an exercise echocardiography had

already been made by the physician, thus our patient population is a selected one. Because patient numbers were rather small, no subanalysis for specific MR or MS aetiologies could be performed. We also did not focus on the exact difference in LV function by measuring ejection fraction at rest and during exercise, but in our patient cohort it appeared to be less of importance. Finally, the expert panel judgment did not account for the interaction between patient and treating physician as this is not possible in this type of research. This might ultimately have resulted in a different treatment strategy by the expert panel compared with the treating physician.

Only 2 patients were asymptomatic at rest. Evaluation of symptomatic patients remains subjective and is solely based on the patient's history and cardiologist's interpretation. Nevertheless, being symptomatic is of utmost importance in the recommended guidelines for MV surgery and therefore important in determining the best treatment strategy [3, 4]. Thus, exercise echocardiography also serves as an important additional tool to unmask specific symptoms in atypical patients.

Concerning the technical limitations, evaluation of echocardiographic examination is sometimes limited by a poor imaging window, which is even more difficult during exercise. Therefore considerable experience is needed to obtain good quality echo studies. Moreover, patients may be unable to exercise, or perform a submaximal test. Furthermore, while exercise-related symptoms may sometimes be difficult to interpret and remain subjective, additional haemodynamic parameters during exercise are indispensable. However these (noninvasive) measurements can be difficult to perform during exercise, differ in accuracy and may not be fully established.

Future prospective

A prospective trial is needed to confirm the value of exercise echocardiography in the management of MV disease. Subanalysis of various mechanisms is necessary since they are based on different aetiologies and are diagnosed and treated accordingly.

A validated and standardised exercise protocol is necessary in order to compare exercise echo results. Exercise endpoints should be determined at >85 % of the age-predicted maximum heart rate, or the occurrence of recognisable symptoms.

Furthermore, there may be an important role for real-time three dimensional (3D) echocardiography as an alternative for 2D exercise echocardiography [34].

Conclusion

Exercise echocardiography is an important tool to unravel dynamic changes and monitor symptomatic responses occurring in

MV disease during physical exercise. It can support the heart team in determining the best treatment strategy in disproportionately symptomatic or otherwise atypical patients, as seen in 71 % of our study patients. A prospective trial is needed to support our findings by confirming the additional value of exercise echocardiography in patients with MV disease and its different aetiologies.

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Conflicts of interest None declared.

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