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Exercise echocardiography in the evaluation of functional mitral regurgitation: A systematic review of the literature

Damian Cieślikowski, Tomasz Baron and Tomasz Grodzicki

Chair of Internal Medicine and Gerontology,
Jagiellonian University *Collegium Medicum*, Cracow, Poland

Abstract

Background: *The aim of this article is to present a systematic review of publications regarding the role of exercise echocardiography in the evaluation of functional mitral regurgitation.*

Methods: *The PubMed database was searched using the following combination of keywords: "mitral" and "regurgitation" and "exercise" and "echocardiography". Initially, a list of 152 articles published between 1977 and 2007 was retrieved. Following application of the exclusion criteria, the list was shortened to 18 original scientific papers. Different groups of patients were analyzed in these studies, but mainly patients with ischemic left ventricular systolic dysfunction with at least mild mitral regurgitation were included. All participants underwent echocardiography, which included resting examination and certain stress tests, i.e. exercise tests using a cycloergometer or a treadmill as well as pharmacological stress. The main evaluated echocardiographic parameters were regurgitant volume, effective regurgitant orifice area (ERO), left ventricular geometry and function, and systolic pulmonary artery pressure.*

Results: *Exercise-induced changes in mitral regurgitation parameters were strongly associated with the risk of pulmonary edema, mortality, exercise tolerance and the severity of ischemic heart disease. The most important echocardiographic variable was an increase in ERO of more than 13 mm^2 during exercise.*

Conclusions: *Published scientific evidence demonstrates the significance of exercise echocardiography in patients with functional mitral regurgitation in relation to its dynamic character, the possibility of a considerable increase in the severity of even mild mitral regurgitant jet with changing loading conditions and especially with increased left ventricular afterload.* (Cardiol J 2007; 14: 436–446)

Key words: mitral regurgitation, exercise echocardiography

Address for correspondence:
Damian Cieślikowski
Chair of Internal Medicine and Gerontology
Jagiellonian University *Collegium Medicum*
Śniadeckich 10, 31–531 Cracow, Poland
Tel. +48 12 424 88 00, fax: +48 12 423 10 80
e-mail: damianci@poczta.onet.pl
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Introduction

Functional mitral regurgitation (MR) is a particular type of MR that is not related to organic lesions within the valve leaflets or the subvalvular apparatus but results from abnormal left ventricular geometry related to chamber dilation and remodeling [1]. MR is most commonly found in patients with heart failure of ischemic origin, especially following a previous inferoposterior myocardial infarction; thus, it is frequently referred to as chronic ischemic MR.

It is estimated that MR develops in approximately 60% of patients with heart failure. The pathogenesis of MR in these patients is related, among other factors, to restricted posterior and/or anterior leaflet motion, particularly in patients following a previous myocardial infarction. Other factors include dilation of the mitral annulus and lack of leaflet coaptation, displacement of the papillary muscles in relation to the mitral annulus and altered tension of the chordae tendinae. Chronic ischemic papillary muscle dysfunction and progressively spherical left ventricular chamber geometry also contribute to MR [2]. Two major pathophysiological hypotheses explaining MR in these circumstances have been proposed, one stressing the role of left ventricular dilatation as well as expanded and flattened mitral annulus, and the other putting more emphasis on changes within the subvalvular apparatus, including altered position and dysfunction of the papillary muscles leading to their abnormal interactions with the valve leaflets.

Resting echocardiographic study is currently considered insufficient for complete evaluation of MR. This has resulted in the increased popularity of echocardiographic stress tests that were previously used mainly in the evaluation of ischemic heart disease and myocardial viability [3]. The aim of this review is to summarize current knowledge on the role of exercise echocardiography in the evaluation of MR by comparing methods, results and conclusions in the published studies on this subject.

Literature selection

Publications selected for the purpose of the current literature review were retrieved from the PubMed database. Using keywords "mitral AND regurgitation AND exercise AND echocardiography" and restricting the search to papers with an abstract available, published in English and describing work performed in humans, we identified 178 studies published from 1978 until July 2007. Two of the authors independently reviewed all publications, considering their relevance to the investigated subject. We only included papers describing changes in echocardiographic parameters of functional, nonrheumatic MR during stress tests.

Most of the excluded studies (n = 30) dealt with the echocardiographic evaluation of heart failure, with MR as a secondary finding that was assessed only in resting conditions. A further 22 studies were excluded because no changes of echocardiographic parameters during exercise were evaluated (stress tests were performed in some of these studies, but only to evaluate left ventricular function or exercise tolerance). We also excluded 20 studies related to the echocardiographic evaluation of patients undergoing surgical treatment of MR, in which only resting studies were performed. Some excluded studies assessed the role of exercise echocardiography in the evaluation of ischemic heart disease (n = 3), primary cardiomyopathies (n = 9), tricuspid regurgitation (n = 5), aortic regurgitation (n = 4), mitral stenosis treated with commissurotomy (n = 9), and complex valvular heart disease (n = 4). In addition, we did not include studies in patients with rheumatic MR (n = 6) or MR complicating mitral valve prolapse (n = 17). Twelve studies on the role of exercise echocardiography in children or in congenital heart disease were excluded, as were papers dealing with cardiac arrhythmia (n = 4), myocardial damage following radiotherapy (n=2) or storage diseases (n = 1), studies based exclusively or mainly on the invasive evaluation of MR during cardiac catheterization (n = 3) and studies in which echocardiography was performed in healthy subjects during exercise (n = 4). Finally, two other review papers were excluded.

In the end, we were left with the remaining 21 original studies on the role of exercise echocardiography in the functional evaluation of MR. Among these studies, 17 publications were available in full-text versions and they were used as the basis for the present literature review. We also included current European Society of Cardiology (ESC) guidelines on the management of valvular heart disease regarding the appropriate selection of patients referred for surgical treatment of MR, and one publication dealing with the role of stress echocardiography in prognostic evaluation following surgical treatment [4].

Study populations

Patient selection is an important factor in the echocardiographic evaluation of MR during exercise.

Table 1. Patient characteristics in the studies included in the review. NA — not available.

Publi-cation no.	N	Age	Patient characteristics
1	74	65 ± 11	LVEF < 45%, 2 subgroups: 1) patients following at least one episode of pulmonary edema (n = 28) 2) patients with no history of pulmonary edema (n = 46)
2	70	NA	LVEF < 45% and a previous myocardial infarction, including an anterior wall (n = 28), inferior wall (n = 31) or inferoanterior wall infarction (n = 11)
14	40	54 ± 8	LVEF < 45% and a previous myocardial infarction, resting MR
16	98	NA	LVEF < 45%; 82 patients treated medically and 16 patients treated surgically. 10 patients in NYHA class I, 63 in NYHA class II and 25 in NYHA class III. Previous myocardial infarction, including an anterior wall (n = 43), inferior wall (n = 41), or inferoanterior wall infarction (n = 14). Duration of follow-up: 19 ± 8 months
17	161	NA	Patients with left ventricular systolic dysfunction and at least mild resting MR, including 20 patients treated surgically and 141 patients treated medically. Duration of follow-up: 35 ± 11 months
7	25	53 ± 12	Fractional shortening < 25%, LVEDD > 60 mm, impaired exercise tolerance (MVO_2 < 20 mL/min/kg). NYHA class I or II — 12 patients, NYHA class III or IV — 13 patients
15	17	64 ± 8	Patients with heart failure (NYHA class I–II) and documented left ventricular systolic dysfunction (LVEF: 35 ± 15%, LVEDD: 57 ± 9 mm)
8	17	NA	MR and severe heart failure (NYHA class III–IV)
18	27	NA	LVEF < 35%, LVEDD > 58 mm; 26 patients with IHD; NYHA class I — 3 patients, class II — 14 patients, class III — 10 patients
3	513	58 ± 11	Patients with documented IHD or evaluated for IHD. Resting MR was present in some subjects (n =164)
6	120	61 ± 10	Patients with IHD, including 54 with a previous myocardial infarction. LVEF < 45% in 23 subjects
5	47	51 ± 12	MR more than 1+, LVEF > 50%, no IHD; 2 patients had chronic atrial fibrillation. The control group consisted of 17 healthy volunteers
11	32	41 ± 14	MR 3+ or 4+. LVEF > 50%, no IHD, sinus rhythm
10	42	46–79	IHD: Group 1 — 27 patients undergoing an exercise test. Resting MR in 14 subjects, Group 2 — 15 patients undergoing percutaneous coronary intervention
9	12	52–78	NYHA class III–IV, mean LVEF approx. 24%, resting MR
12	70	NA	Dilated cardiomyopathy (of ischemic origin in 51% of patients), LVEF < 25 ± 8% (62% of patients in NYHA class III/IV), intra- and interventricular asynchrony, resting MR
13	21	Mean 67	Patients with severe left ventricular systolic dysfunction (mean LVEF 22%, LVEDD: 69 ± 4 mm), left bundle branch block (QRS duration 175 ± 16 ms) and resting MR, undergoing cardiac resynchronization therapy

NA — not available; LVEDD — left ventricular end-diastolic dimension; MVO_2 — maximal oxygen uptake; LVEF — left ventricular ejection fraction; MR — mitral regurgitation; IHD — ischemic heart disease

Patient characteristics in the publications selected for our review had many common features (Table 1). The exclusion criteria included organic mitral valve disease, e.g. rheumatic mitral stenosis or MR, and coexisting severe aortic regurgitation that could confound the echocardiographic evaluation of MR due to the presence of a large aortic regurgitant jet. Patients with a recent acute coronary syndrome were also excluded (to avoid inclusion of patients with acute MR complicating an acute inferior wall myocardial infarction), as were patients with significant intraventricular conduction delay.

In half of the studies, echocardiography was considered not to be interpretable in patients with atrial fibrillation or flutter. In addition, exercise echocardiography was not performed in patients with technically poor resting images.

The differences between the selected studies were mainly related to the size of the study population (ranging from 25 to 513 patients), the severity of heart failure symptoms and signs, inclusion

of patients with atrial fibrillation and the etiology of functional MR.

In particular, MR was mostly related to left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) < 45%], with only Leung et al. [5] studying patients with normal or relatively normal EF and isolated MR . In the study by Peteiro et al. [6] on ischemic MR, systolic dysfunction was present in only 23% of the subjects. Patients in New York Heart Association (NYHA) class IV heart failure were excluded from most studies, but three studies dealt with MR mainly or exclusively in patients with advanced heart failure, i.e. NYHA class III–IV [7–9].

Most authors recruited patients with various etiologies of MR, but mainly with MR of ischemic origin – most patients suffered from a previous myocardial infarction, and the minority was patients with MR of non-ischemic origin, e.g. idiopathic dilated cardiomyopathy. Four studies included only patients with ischemic MR [2, 3, 6, 10]. In contrast, Leung et al. [5] and Kim et al. [11] excluded all patients with established ischemic heart disease documented by coronary angiography.

Exercise/stress test protocols

In different studies, dynamic changes of MR echocardiographic parameters were elicited in different ways, using specified stress test protocols that were summarized in Table 2. In most studies, exercise testing was used, with additional pharmacologic stress testing performed in one study. Exercise tests using a cycloergometer were performed in 7 studies, treadmill exercise testing was used in 6 studies and in one study some subjects were tested using a treadmill and some were tested using a cycloergometer. In two studies, isometric handgrip exercise was used. One study evaluated the effect of both exercise and dobutamine or nitroglycerin stress on MR echocardiographic parameters [9]. In contrast, Fehrenbacher et al. [10] used another form of stress to induce transient ischemic MR, i.e. temporary myocardial ischemia during percutaneous coronary intervention (PCI).

Table 2. Stress test protocols in the studies included in the review.

Publication no.	Stress test protocol
1, 2, 13, 16, 17, 18	Symptom-limited, maximal exercise stress test using semi-supine bicycle ergometry. Initial workload 25 W for 6 minutes, increased by 25 W every 2 minutes. Termination criteria: dyspnea or physical exhaustion
7	Three-stage exercise stress test using bicycle ergometry: 1. Initial study, or selection test was performed to select appropriate subjects. Two further stages were the actual study tests 2. Second-stage study to determine maximal workload as measured by MVO_2 3. Stress test using the following protocol: initial workload 10 W increased by 10 W every 1 minute. Measurements were performed in semisupine and left lateral decubitus positions during three subsequent stress levels, i.e. 30, 60 and 90% of MVO_2
15	Spiroergometry using a cycloergometer. Echocardiographic measurements were performed at 80 and 150% of the anaerobic threshold
8	Isometric handgrip exercise
3, 6, 11, 12, 14	Treadmill exercise test using the Bruce protocol. Termination criteria: physical exhaustion, ST segment depression ST > 2 mm, new wall motion abnormalities, cardiac arrhythmia, blood pressure > 240/110 mm Hg, hypotensive response
5	In some subjects, treadmill exercise test using the Bruce protocol was performed (23 patients with MR, 10 subjects in the control group), and bicycle ergometry using a standard protocol was used in the remaining subjects
10	A. In group 1, treadmill exercise test using the Bruce protocol was performed B. In group 2, percutaneous coronary intervention was the provocative stress test, leading to transient myocardial ischemia during balloon dilatation
9	Stress testing included several stages: 1. Isometric handgrip exercise for 5–7 minutes. Measurements were performed at a workload equal to 30% of the previously estimated maximal workload 2. Resting dobutamine infusion protocol. Initial dose 3 μg/kg/min, increased by 2 μg/kg/min every 10 minutes up to a maximal dose of 13 μg/kg/min 3. Isometric handgrip exercise with simultaneous dobutamine infusion protocol 4. Resting nitroglycerin protocol. Initial dose, 10 μg/min, then 15, 25 and 35 μg/min, given every 15 minutes 5. Isometric handgrip exercise with simultaneous nitroglycerin protocol

Termination criteria for the exercise stress test usually included severe dyspnea or physical exhaustion. In most studies, patient groups were selected to avoid chest pain or ST-T segment changes, i.e. clinical and electrocardiographic manifestations of exercise-induced ischemia. Thus, any potential effect of myocardial ischemic changes related to exercise on the valvular function during stress was likely eliminated. With this assumption, exercise-induced changes in MR were in most studies related to changing hemodynamic conditions, e.g. to increased left ventricular afterload during isometric exercise. In contrast, studies by Peteiro et al. [3] and Fehrenbacher et al. [11] focused on MR changes that were primarily related to regional wall motion abnormalities induced by transient myocardial ischemia during exercise.

Echocardiographic parameters

Comprehensive echocardiographic evaluation in patients with functional MR includes numerous parameters summarized in Table 3. Quantitative and semiquantitative measures of the severity of the regurgitant jet, including regurgitant volume (RVol) and fraction, vena contracta width (VCW) and effective regurgitant orifice area (ERO), are among the most important parameters. Some measurements are directly related to the altered geometry of the mitral valve, including mitral annulus diameter and area, the distance from the coaptation point to the mitral annulus plane (so-called coaptation height), the area defined by the coaptation point and the mitral annulus plane (so-called tenting area) and papillary muscle displacement. Other parameters

Table 3. Echocardiographic parameters used in the evaluation of mitral regurgitation.

Echocardiographic parameter	Publication number																
	1	2	14	16	17	7	15	8	18	3	6	5	11	10	9	12	13
Mitral regurgitant jet volume (RVol)	+			+		+		+	+			+	+		+	+	+
Regurgitant jet fraction (RVol/LV stroke volume)						+		+				+	+		+		
ERO	+	+	+	+	+			+								+	+
Mitral regurgitant jet area										+	+			+			
Regurgitant jet/LA area						+	+		+								
VCW									+								
Tricuspid regurgitation	+			+	+				+				+			+	+
Mitral annulus diameter			+			+			+					+		+	
Mitral annulus area		+											+				
Coaptation height		+	+			+								+			
Tenting area	+	+	+														
LVDF				+						+	+		+				
WMSI	+	+	+							+	+			+			
LADA	+		+										+				
LVEDD																	
LVESD					+	+	+		+		+		+			+	
LVEDV																	
LVESV	+	+	+	+								+		+	+	+	
LVSI			+			+											
LVEF	+	+	+	+	+	+	+			+	+	+		+		+	+
LVSV						+	+	+				+	+		+		
CO						+						+					

LA — left atrium; LV — left ventricle; VCW — vena contracta width; ERO — effective regurgitation orifice area; LVEDD — LV end-diastolic dimension; LVESD — LV end-systolic dimension; LVEDV — LV end-diastolic volume; LVESV — LV end-systolic volume; LVSV — LV stroke volume; WMSI — LV wall motion score index; LVDEF — LV diastolic function; LADA — dimensions and/or area; LVSI — sphericity index; LVEF — left ventricular ejection fraction; CO — cardiac output

are related to the sequelae of MR, most importantly pulmonary hypertension, with systolic pulmonary artery pressure (sPAP) measured indirectly using tricuspid regurgitation gradient. As functional MR is in most cases secondary to left ventricular dysfunction, evaluation of global left ventricular systolic function (as expressed by systolic and diastolic dimensions of the left ventricle, LVEF and the sphericity index), regional wall motion abnormalities (as expressed by wall motion score index [WMSI]) and diastolic function is imperative. Two studies included parameters of intra- and interventricular asynchrony [12, 13]. The measure of intraventricular asynchrony is the difference of pre-ejection period duration (from the beginning of the QRS complex to the beginning of the S wave by tissue Doppler imaging) between the most initially contracting and the most delayed basal segment of the left ventricle. In turn, interventricular asynchrony may be determined based on the difference between aortic and pulmonary ejection times.

Individual studies included in the review were characterized by quantitative and qualitative differences concerning the evaluated echocardiographic parameters. Some studies focused on a single variable describing MR, e.g. regurgitant jet area (Peteiro et al. [3]), while some others included much more comprehensive MR evaluation, particularly the study by Lancellotti et al. [2]. This was the only study in our review that included a thorough evaluation of changes in the subvalvular apparatus, such as anterior displacement of the anterior and posterior papillary muscles (APM-anterior, PPM-anterior), apical displacement of the posterior papillary muscle (PPM-fibrosa) and lateral displacement of the papillary muscles. The geometry of the mitral apparatus was also thoroughly evaluated in the study by Giga et al. [14]. Most studies focused on two echocardiographic approaches to estimate the severity of MR, Doppler evaluation and proximal isovelocity surface area method (PISA). Averaged measurements made using these approaches were then used in the calculation of RVol and ERO. Although the data in the literature are not entirely consistent and there is still no single gold standard for the quantitative evaluation of the regurgitant jet, most studies indicate ERO as the most important parameter. One newer and currently very popular parameter is VCW, but in contrast to ERO this is only a semiquantitative measure of the severity of MR. Regurgitant fraction is a more reliable indicator of the severity of MR than RVol because with severely impaired global left ventricular systolic function, small RVol falsely indicates mild MR, and adjusting this value for small stroke volume gives a larger regurgitant fraction that is consistent with more severe MR.

Some studies included data obtained using other diagnostic modalities in addition to echocardiography, such as right heart catheterization [8, 9, 11], coronary angiography [3, 6, 10], and evaluation of MVO_2 using spiroergometry [6, 7, 15]. These additional data were considered in relation to echocardiographic measurements to give the most comprehensive picture of left ventricular dysfunction in patients with MR.

Results of the studies

All studies included in the review focused on comparisons between the results of echocardiographic evaluation at rest and during exercise or pharmacologic stress. Table 4 summarizes the main

Table 4. Results of the studies included in the review.

Publication no.	Results of the stress testing
1	In patients with a history of pulmonary edema, a significantly higher increase in ERO, RVol, tricuspid regurgitation gradient and tenting area, and an insignificantly lower increase in LVEF were found during exercise compared to the patients without a history of pulmonary edema. These exercise-induced changes in the severity of MR did not correlate with baseline, i.e. resting MR severity
2	An increase in ERO during exercise was not related to baseline ERO values or to indices of global left ventricular function. A significant correlation was found with measures of valve geometry, in a particular tenting area (following a prior inferior wall myocardial infarction) and mitral annulus area. Among indices of local remodeling, a significant correlation was found for WMSI (following an inferior wall myocardial infarction), APM, PPM and coaptation height (following an anterior wall infarct). In 18% of subjects, ERO decreased in relation to preserved contractile reserve
14	ERO during stress was significantly related to exercise-induced changes in coaptation height, tenting area, mitral annulus diameter, WMSI and left ventricular sphericity index. No correlation was found with ERO at rest

cont. →

Table 4. cont. Results of the studies included in the review.

Publication no.	Results of the stress testing
16	Resting ERO and RVol values were higher, and E wave deceleration time was shorter in patients who died during follow-up. During exercise, an increase in RVol, ERO and tricuspid regurgitation gradient was significantly higher in non-survivors compared to survivors (among the latter, a decrease in ERO was even found in 14% of patients). Exercise-induced changes in ERO did not correlate with baseline values: 17 of 24 patients with large increases in ERO during exercise (> 13 mm^2) had mild MR at rest, and only 10 of 27 patients with severe MR at baseline (ERO > 20 mm^2) showed an exercise-induced increase in ERO of > 13 mm^2
17	An increase in ERO of >13 mm^2 was related to a higher risk of admission due to cardiac decompensation, as was an increase in right ventricular systolic pressure. Resting ERO exceeding 20 mm^2 was an independent predictor of mortality. High values of LVEDV and LVESV and the lack of contractile reserve were additional prognostic factors of adverse outcome
7	Patients with marked exercise intolerance (unchanged or decreased LVEF during stress and MVO_2 < 50 mL/min/kg) showed higher increase in RVol, ERO, left ventricular sphericity index and coaptation height, and higher left atrial pressures during exercise tests compared to other subjects
15	During exercise, an increase in a MR jet/LA ratio was found, and this index correlated with left ventricular stroke volume and MVO_2
8	Isometric exercise in patients with severe heart failure was associated with an increase in RVol and ERO. The severity of MR was proportional to the decrease in left ventricular stroke volume during exercise
18	RVol estimated using PISA method correlated significantly with Doppler measurements. Dynamic changes in RVol were significantly related to the changes in tricuspid gradient and VCW, if the increase in RVol was large, i.e. > 13 mL (correlation with VCW was not significant in the group with a small increase in RVol). No significant correlation was found between the increases in RVol and regurgitant jet to left atrial area ratio. Patients in whom the exercise test was terminated due to dyspnea showed significantly higher increases in RVol compared to those in whom the exercise test was terminated due to fatigue
3	The patients were divided into 3 groups based on changes of MR during exercise: Group 1, development of new MR or an increase in the severity of pre-existing MR (n = 70), Group 2, no changes of MR (n = 112), Group 3, MR absent both at rest and during exercise (n = 307). Patients with dynamic changes of MR (Group 1) showed more reduced global and regional left ventricular systolic function, more frequent decrease in LVEF during exercise, the most pronounced reversible wall motion abnormalities, the lowest values of double product, the shortest duration of exercise, the highest incidence of chest pain, ST segment changes and hypotensive response during exercise and the highest rate of three-vessel coronary artery disease
6	Development of MR during exercise (n = 15) or an increase in the severity of pre-existing MR (n = 17) was significantly related to a decrease in LVEF, an increase in LVESV, the occurrence of regional wall motion abnormalities, the pseudonormalization pattern of the E/A ratio and a higher rate of multivessel coronary artery disease
5	During the exercise test: 1. All patients with MR reached lower MVO_2 and cardiac output (CO) values compared to the control group 2. In both evaluated groups, correlation between CO and MVO_2 was higher compared to that of the baseline values of both parameters 3. Patients with an increase in RVol also had lower CO and higher regurgitant fraction during exercise compared to the other patients 4. Patients in whom the exercise test was terminated due to dyspnea reached lower MVO_2 and CO values compared to the other patients 5. Patients with an increase in LVESV showed lower CO and MVO_2 during exercise 6. Independent determinants of MVO_2 included CO during exercise, age (decrease in MVO_2 with age) and gender (lower MVO_2 values in women). Resting CO showed weaker but still significant cor relation with MVO_2
11	Among all evaluated echocardiographic parameters, only E wave peak velocity and pulmonary venous backward flow (PVa) velocity were significantly related to the duration of exercise during the treadmill test and thus to exercise tolerance
10	In Group 1, MR was absent in rest and during exercise in 52% of patients (no MR, Group 1A), developed only during exercise in 15% of patients (transient MR, Group 1B) and was constantly present in the remaining 33% of patients (chronic MR, Group 1C). In Group 2, MR was absent

cont. →

Table 4. cont. Results of the studies included in the review.

Publication no.	Results of the stress testing
	during PCI in 53% of patients (Group 2A) but developed in 47% of patients (Group 2B). During exercise, a marked increase in coaptation height was seen in Group 1C (exacerbation of chronic MR), and an even greater increase was seen in Group 1B (development of new MR), proportion al to the increase in LVESV. No significant differences of mitral annulus diameter were found between rest and exercise. Regional wall motion abnormalities markedly increased or developed during stress in Groups 1B and 2B. Group 1C showed a much smaller increase in regional wall motion abnormalities, but persistent hypokinesis or dyskinesis was seen
9	1. During exercise, an increase in RVol and LVEDD and a decrease in CO and LVESD were noted 2. During dobutamine infusion, a decrease in RVol, LVEDD and LVESD, and an increase in CO wereseen 3. The use of dobutamine during exercise test resulted in smaller increase in RVol and higher stroke volume compared to exercise without dobutamine 4. Administration of nitroglycer in resulted in a decrease in RVol, LVEDD and LVESD, and an increase in CO 5. The use of nitro glycerin during the exercise test resulted in a smaller increase in RVol and higher stroke volume compared to exercise without nitroglycerin
12	Changes in RVol and ERO during exercise were significantly related to baseline (resting) measures of intra- and interventricular asynchrony
13	The use of CRT resulted in a significant decrease of resting ERO and RVol, less dynamic exercise-induced changes in MR during the stress test and was related to an improvement in left ventricular function (as measured by dP/dt ratio). However, no improvement in regard to sPAP was seen

results of the individual studies. To give a general oversight, we did not give numeric values of the particular measurements but showed trends regarding these parameters that were noted during the stress tests and listed correlations found between individual echocardiographic parameters and between echocardiographic and clinical data.

Discussion

From the practical point of view, the most important findings are those with direct clinical implications, such as prognostic value of dynamic MR changes, the effect on exercise tolerance and a causal relationship with pulmonary edema.

Prognostic value

The severity of MR in patients with heart failure is an independent (in regard to left ventricular dysfunction itself, e.g. as indicated by low LVEF) prognostic factor of adverse outcomes during long-term follow-up. Exercise-induced changes of MR are particularly important in this regard and support the role of stress tests. Significant prognostic value was found for resting ERO > 20 mm^2, exercise-induced increase in ERO of > 13 mm^2, and shortened E wave deceleration time, an indicator of high left ventricular filling pressures that are found not only in MR but also in diastolic heart failure. Severe MR is associated with marked pulmonary hypertension, high filling pressures, left ventricular volume overload and accelerated progression of adverse myocardial remodeling leading to end-stage heart failure. Patients with MR are at elevated risk of episodes of pulmonary edema and malignant ventricular arrhythmias that may result in sudden death [16, 17]. Mitral valve repair [often concomitantly with coronary artery bypass grafting (CABG)] improves long-term prognosis.

Exercise tolerance

Functional MR is an additional factor resulting in impaired exercise tolerance and lower quality of life in patients with heart failure, together with systolic dysfunction and low LVEF [7, 15]. Backward flow from the left ventricle to the left atrium during systole limits stroke volume, and thus results in reduced cardiac output and impaired exercise tolerance. If sufficient contractile reserve is maintained, cardiac output may be increased during exercise and the severity of MR does not increase, or even diminishes. With severe left ventricular dysfunction (low cardiac reserve), the increase in contractility during stress is limited, and increased afterload results in a marked decrease in cardiac output and more severe MR. Even mild to moderate MR at rest may become a significant factor limiting stroke volume during stress and lead to the impairment of exercise tolerance. With increasing exercise-induced changes in MR in

patients with heart failure, and in particular with the increase in ERO, exercise tolerance worsens, but in fact left ventricular systolic dysfunction is the underlying cause [8].

In contrast, other factors determine exercise tolerance in patients with isolated MR, i.e. those without left ventricular dysfunction and with no significant obstructive coronary lesions. Peak exercise cardiac output and constitutional factors (age, gender) proved to be the most important determinants while RVol and its changes during stress were not significantly related to exercise tolerance; the same is true of LVEF, which is by definition normal in such patients [5]. Some parameters of left ventricular diastolic function, such as peak E wave velocity and pulmonary venous backward flow (PVa) velocity, were also of importance in this specific form of MR [11].

Risk of pulmonary edema

Exercise-induced changes in the severity of MR are also related to the risk of pulmonary edema, as highlighted by Pierard et al. [1]. Marked increase in the severity of even mild MR at rest may result in a large increase in the pulmonary capillary wedge pressure, leading to pulmonary edema. The main risk factor for pulmonary edema related to worsening of MR in patients with heart failure is an increase in ERO of > 13 mm^2 during stress. Thus, evaluation of MR by exercise echocardiography may be useful in patients with chronic stable heart failure who experienced flash pulmonary edema of unknown cause, if some more obvious causes such as discontinuation of medications, an acute coronary syndrome, or tachyarrhythmia have been excluded.

Others

Findings from other studies are important mainly for research purposes, as they contribute to better elucidation of the pathophysiology of MR and help determine appropriate evaluation of functional MR. In those studies, the sensitivity and specificity of two different echocardiographic approaches to evaluate MR was compared [18], exercise-induced changes in MR were related to the parameters of global and regional left ventricular remodeling as well as to changes in the subvalvular apparatus [2] and mitral valve geometry [14], the effects of pharmacologic stress were evaluated [9], dynamic changes in ischemic MR were related to the degree of left ventricular dysfunction and the severity of ischemic heart disease [3], and factors affecting the presence and severity of chronic and transient ischemic MR were compared [10]. Of particular importance, Ennezat et al. [12] evaluated indices of inter- and intraventricular asynchrony as predictors of MR worsening during exercise in patients with severe dilated cardiomyopathy [12]. In another study, cardiac resynchronization therapy not only improved left ventricular function but also significantly decreased the severity of MR both at rest and during stress [13].

Some factors affecting changes in functional MR during exercise have been elucidated. The main predictors of dynamic ERO changes in patients with ischemic MR include mitral annulus area measured in systole (regardless of the localization of infarct), tenting area, WMSI (in patients with a prior inferior wall myocardial infarction) and coaptation height (in patients following an anterior wall infarct) [2].

Echocardiographic evaluation of ischemic MR during exercise stress test gives a lot of important data not only regarding left ventricular dysfunction but also on the severity of ischemic heart disease [3, 6]. It has been proven that the development of new MR or worsening of its severity during stress is related to an increased rate of clinically and/or electrocardiographically positive results of an exercise test and an increased prevalence of multivessel coronary artery disease as documented by coronary angiography.

Summary of the findings

Our review suggests that the mechanisms of dynamic changes in MR during exercise are complex and not entirely clear. In particular, afterload increase during stress (related to increased systemic vascular resistance and blood pressure) worsens the dysfunction of failing left ventricle. These exercise-induced changes include increased sphericity of the left ventricle chamber, distension of the valve annulus (in particular in its posterior aspect), further papillary muscle displacement, and abnormal coaptation of the mitral leaflets [7]. All these alterations result in an increased ERO and explain the increasing severity of MR with exercise in those studies that excluded any direct of effect of exercise-induced ischemic changes in the myocardium on the mitral valve function. In contrast, classic ischemic MR worsens or develops mainly due to the worsening of regional wall motion abnormalities in the left ventricular myocardium, especially in those segments that affect papillary muscle function during exercise [3]. In particular, ischemia within the posterobasal segments of the left ventricle results in local dyssynergy leading to subvalvular apparatus destabilization. These finding imply two

mechanisms of MR worsening during exercise: hemodynamic overload and a direct effect of exercise-induced ischemia.

Of particular interest are changes in MR during pharmacologic stress, as evaluated by Keren et al. [9]. Dobutamine decreases the severity of MR by increasing myocardial contractility by β_1-adrenergic receptor stimulation and decreasing afterload, thus leading to improved left ventricular function. A biphasic effect of dobutamine on myocardial segments that are hypokinetic at rest (e.g. hibernated myocardium) is seen: a low dose of dobutamine (up to 15 μg/kg/min) increases contractility, while larger doses increase myocardial oxygen demand and result in increased hypokinesis of poorly perfused regions, which might result in an increased severity of MR if segments related to the papillary muscle function are affected. In that study, however, only a small dose of dobutamine was used (up to 13 μg/kg/min) that increased contractility of the hibernated myocardium and improved contractile reserve, resulting in a decreased severity of MR. A lack of beneficial effects of dobutamine in some patients may be related, among other factors, to severely decreased cardiac reserve or β-adrenergic receptor desensitization due to chronically increased adrenergic stimulation that is typical for heart failure.

Finally, one should focus on the indications for surgical treatment of functional MR, and in particular ischemic MR. According to the ESC guidelines, these procedures are definitely beneficial (Class I recommendation) in patients with severe chronic ischemic MR and impaired left ventricular function (LVEF > 30%), who are referred for CABG. Such treatment may also be indicated (Class IIa recommendation) in patients with moderate MR undergoing CABG, and patients with severe MR and severely depressed global left ventricular function (LVEF < 30%), if concomitant coronary revascularization is feasible. If the latter is not possible (i.e. in patients with severe MR, LVEF < 30% who are not candidates for CABG), mitral valve repair is contraindicated due to a high surgical risk (Class III recommendation). However, some patients with severe MR and LVEF < 30%, in whom CABG is not feasible, may be candidates for mitral valve surgery (Class IIb recommendation) if intensive medical treatment has been proven ineffective [19]. However, echocardiographic evaluation is currently not considered a definitive diagnostic modality to determine the need for surgical treatment as this role is still relegated to invasive studies, particularly ventriculography. A search for echocardiographic parameters that would allow the decision to proceed with medical or surgical treatment being made without the need for invasive studies might prove a significant challenge. On the other hand, stress echocardiography is useful in predicting the outcome of surgical treatment as it allows the assessment of the contractile reserve. An example could by the study by Lee et al. [14], who evaluated prognosis in patients with severe asymptomatic MR undergoing valve surgery. In this study, outcomes were better in patients with preserved contractile reserve while patients without contractile reserve more frequently developed significant postoperative left ventricular dysfunction.

Conclusions

Our literature review suggests an important role of exercise echocardiography in the evaluation of functional MR. The echocardiographic examination during exercise or pharmacologic stress has a significant advantage over the resting study as it allows evaluation of the dynamic nature of MR. This is useful not only for research purposes, i.e. studying the pathophysiology of MR, but also has important practical implications. Exercise-induced changes in MR reflect the degree of left ventricular dysfunction, the extent of adverse remodeling of the left ventricle, the severity of ischemic heart disease (in case of ischemic MR), exercise tolerance level and the risk of an episode of flash pulmonary edema. In particular, the degree of MR worsening during exercise is strongly related to adverse long-term outcomes in patients with heart failure. Among numerous echocardiographic parameters that may be used to characterize MR, currently the most important one appears to be ERO. Several studies indicate that an increase in ERO of more than 13 mm^2 during exercise predicts potentially adverse sequelae of MR, including high mortality. It may be thus expected that exercise echocardiography, currently regarded as only one of the number of recommended diagnostic modalities, will soon become an essential, standard tool in the evaluation of functional MR.

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