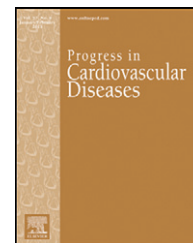


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Exercise Testing in Mitral Regurgitation

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ABSTRACT

Mitral regurgitation (MR) is the second most common valvular heart disease referred for corrective surgery. Diagnostic and management dilemmas are not uncommon when dealing with MR patients. Exercise testing plays an important role in sorting out some of these clinical challenges. In primary asymptomatic MR, exercise testing allows symptom assessment, confident link of symptoms to valve disease severity, safe deferral of surgery for the next 1-year in patients with preserved exercise capacity, insights into the mechanism of exercise-induced dyspnea and helps in individual risk stratification. Moreover, exercise testing in the form of exercise stress echocardiography is also useful in the evaluation of patients with secondary ischemic MR for risk stratification as well as for the detection of patients with moderate ischemic MR in whom mitral valve repair at the time of surgical revascularization may add benefit.

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Statement of conflict of interest: see page XX.

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Abbreviations and Acronyms

ACC = American College
Cardiology

AF = Atrial fibrillation

BNP = Brain natriuretic peptide

BP = Blood pressure

CPET = Cardiopulmonary exer-
cise testing

CRT = Cardiac resynchronization
therapy

EROA = Effective regurgitant ori-
fice area

ESC = European Society of
Cardiology

ESE = Exercise stress
echocardiography

GLS = Global longitudinal strain

HF = Heart failure

HRR = heart rate recovery

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection
fraction

MR = Mitral regurgitation

MV = Mitral valve

PAP = Pulmonary artery pressure

PH = Pulmonary hypertension

RV = Right ventricular

RVSP = Right ventricular systolic
pressure

SBP = Systolic blood pressure

SMR = Secondary mitral
regurgitation

SPAP = Systolic pulmonary artery
pressure

VHD = Valvular heart disease

VO2 = Oxygen consumption

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Mitral valve (MV) re-
gurgitation (MR) is the
second most common
valvular heart disease
(VHD) referred for cor-
rective surgery.¹ It is
also the valvulopathy
that poses the most
clinical dilemmas.
Conventionally, MR is
classified in primary
or secondary MR.
Rarely, mixed forms
of MR may be encoun-
tered. In primary MR,
it is the MV apparatus
(i.e. leaflets, annulus,
chordae or combina-
tion) that carries the
disease. The left ven-
tricle (LV), left atrium
(LA) and pulmonary
vascular bed suffer
from the conse-
quences of the chron-
ic volume overload
imposed by the MR.
To the opposite, sec-
ondary MR is the re-
sult of a diseased LV,
while MV apparatus is
intact. It is the MV
that suffers from the
consequences of the
LV dysfunction and
dilatation by becom-
ing incompetent. In
turn, secondary MR is
also a contributor to
LV dilatation and dys-
function. The cardinal
symptom of MR is
exercise-dyspnea or,

their risk stratification capabilities exercise testing is advo-
cated by the current guidelines on the management of VHD.^{2,3}
This review will address the role of exercise testing in both
primary and secondary MR.

Primary MR

The complex tale of exercise testing – why do we even bother?

When present and if uncorrected, MR impacts patient's
survival.⁴ Surgery and, more recently, transcatheter therapies
(for high surgical risk patients) are the only available
treatments that improve patient's outcome.^{5,6} Based on the
current evidence, surgery is recommended (Class I) in
patients with severe MR when they are symptomatic (but
have a LV ejection fraction (LVEF) >30%) or have overt LV
systolic dysfunction (i.e. LVEF ≤60% but >30% or an
end-systolic LV diameter ≥45 mm (for European Society of
Cardiology ESC)/≥40 mm [for American College of Cardiology
(ACC)/American Heart Association (AHA)]).^{2,3} Although, these
indications for surgery appear crystal clear, in clinical practice
things may get complicated.

Linking symptoms to MR

Since surgery is indicated once the patient becomes symp-
tomatic, identifying those who are truly asymptomatic is
fundamental. Exercise stress testing is an objective way of
confirming the absence of symptoms and to define one's true
functional capacity, compared against age-gender predicted
standards. Not infrequently, patients adapt their daily activ-
ities in order to avoid symptoms. However, exercise-induced
dyspnea as presenting symptom may be subjective and
difficult to objectively link to valve disease itself, since
dyspnea may have multiple causes (deconditioning, obesity,
pulmonary disease, etc.). To this regard, exercise stress
echocardiography (ESE) may be used as a rewarding modality
to assess the true hemodynamic consequences of MR and to
match symptoms with the severity of cardiac involvement
secondary to MR.

Exercise testing in truly asymptomatic patients

The management of asymptomatic patients with severe
primary MR and no LV enlargement or dysfunction remains
a source of debate. The recent ACC/AHA guidelines, however,
advocate MV repair (Class IIa) in these patients when there is
>95% likelihood of a successful and durable repair without
residual MR, and a <1% expected mortality rate in a center of
excellence.^{3,7} Similar reasonable indication exists in the ESC
guidelines but in patients with flail MV or significantly dilated
LA(IIa).² Other reasonable triggers for surgery (class IIa)

in the advanced form, signs and symptoms of overt heart
failure. However, in developed countries, due to the high
accessibility to the medical system, the diagnosis is usually
made earlier in the disease's course, when patients are still
asymptomatic. For secondary MR and patients with asymp-
tomatic primary MR, the full clinical impact of the disease is
underestimated whenever work-up ends with a simple
transthoracic echocardiography (TTE). To this regard and for

Table 1 – Summary of different modalities and protocols used in exercise testing.

| Modality | Protocol | Associated Modality | Timing of Imaging |
|---------------------|----------------|---|-------------------|
| Treadmill | Bruce | Echocardiography | Post-exercise |
| Upstanding bicycle | Modified Bruce | Pulmonary gas exchange analysis (CPET) | Post-exercise |
| Semi-supine bicycle | Naughton | Echocardiography and pulmonary gas exchange analysis (CPET) | During exercise |

include increased systolic pulmonary artery pressure (SPAP >50 mm Hg), or development of atrial fibrillation (AF).^{8–10} So, since prophylactic surgery is not unanimously contemplated in all asymptomatic patients with severe MR, patient's management is often dictated by individual risk stratification. ESE provides a series of prognostic features that could help clinical decision-making; early guidance to mitral valve intervention, closer follow-up, or safe watchful waiting.^{11–19}

Exercise testing modalities and protocols

ESE can be performed using either a treadmill or bicycle ergometer, with a symptom-limited protocol in which the workload is gradually increased in stages (Table 1). The most common treadmill protocol used is the Bruce (or modified) protocol, in which the expected exercise level for a given age and sex can be expressed as functional aerobic capacity. Image acquisition takes place rapidly after exercise cessation and focuses first on regional wall motion (hence LV regional and global systolic function) and right ventricular (RV) systolic pressure (RVSP).^{17,18} When compared with cycle ergometer, treadmill exercise has the advantage of reaching higher workloads and heart rates. Semi-supine bicycle exercise is usually the preferred approach because it allows the assessment of multiple stress parameters during each step of exercise testing (Figs. 1–3). At peak exercise, focus is set on the LV systolic function, MR severity, E/e' (an estimate of LV filling pressure), RVSP and RV function (Fig. 1).²⁰ The patient pedals at a constant cadence against an increasing workload, which starts at 25 W (50 W for younger patients) with increments of 25 watts every 2 or 3 min. Adequate bicycle stress testing requires the patient's cooperation and coordination to perform the pedaling action and this may be a disadvantage.²⁰ Appearance of symptoms should be assessed regularly, and blood pressure (BP), heart rate and a 12-lead ECG should be monitored continuously during the examination. Criteria for interruption are the target heart rate achievement, or onset of typical chest pain, ≥ 2 mm horizontal or downsloping ST segment depression, limiting breathlessness, dizziness, hypotension (systolic BP/SBP drop below baseline), complex ventricular arrhythmia and muscular exhaustion. Of note, cardiopulmonary exercise testing (CPET) with measurement of gas exchange, which has the advantage of providing quantitative evaluation of maximal exercise capacity, can also be useful in patients with primary MR.²¹ CPET can be combined with echocardiographic evaluation.

Clinical value of standard exercise testing

BP response to exercise is clinically meaningful and easy to access. A drop in SBP during exercise may reflect the

time-point during exercise testing at which severe MR is compromising the ability of the LV to increase cardiac output. In the light of recent research, treadmill exercise may be useful to identify a subset of asymptomatic patients with severe primary MR in whom conservative treatment may be initially deferred.^{17,18} In fact, in case of preserved exercise capacity, delaying MV surgery by ≥ 1 year did not adversely affect outcomes.¹⁸ Conversely, patients achieving <85% of predicted metabolic equivalents which may be observed in up to 30%, or those with an abnormal heart rate recovery (HRR; <18 beat drop in heart rate over 1 min in recovery; probably a marker of impaired vagal activity) have an increased risk of events (all-cause mortality, myocardial infarction, stroke, AF or progression to congestive heart failure/HF), which might be used as incentive findings for referring patients to surgery. In daily practice, the clinical usefulness of exercise capacity assessment may be hampered by several confounding factors since it is the result of the integrated function of the cardiovascular, respiratory and musculoskeletal systems. Therefore, once a patient with altered exercise capacity is detected, the next step is to corroborate it with MR consequences.

CPET as a complementary tool

MR may negatively affect exercise capacity through a reduction of cardiac output and its resulting retrograde pressure elevation in the pulmonary venous systems. The interest of CPET in patients with severe asymptomatic primary MR results from its ability to assess their pulmonary hemodynamic status (ventilatory efficiency), and their aerobic capacity (cardiac output adaptation to exercise). Peak oxygen consumption (peak VO₂) may be considered as a marker of the degree to which primary MR may compromise cardiac output and therefore aerobic capacity. Recent studies have shown that age-gender predicted VO₂ varies widely in these patients with severe asymptomatic primary MR.¹⁹ Up to 20% of them actually have reduced functional capacity ($\leq 84\%$ age-gender expected peak VO₂), which related to E/e', lower stroke volume, the presence of AF, but not to the severity of MR. In this study, reduced functional capacity (i.e. peak VO₂ $\leq 84\%$ age-gender predicted peak VO₂) was an independent marker of higher mid-term risk of clinical events (death, HF or new severe symptoms, new atrial arrhythmia) or surgery.¹⁹ Interestingly, in patients with asymptomatic moderate to severe primary MR, exercise pulmonary hypertension (PH), a predictor of symptom onset, is an independent echocardiographic determinant of peak VO₂ and VE/VCOE slope, an estimate of ventilator efficiency.^{21,22} In practice, although of interest, especially for longitudinal monitoring, CPET is rarely used in patients with MR.

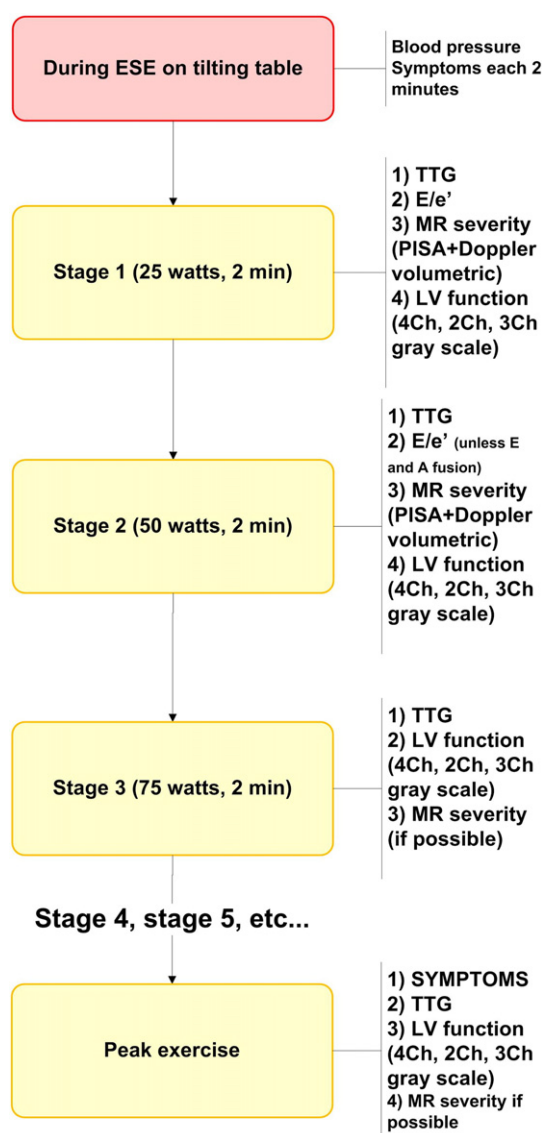


Fig. 1 – Flow-chart on how to perform an exercise stress echocardiography on a semi-supine tilting table. ESE-exercise stress echocardiography; TTG-transtricuspid systolic pressure gradient; E/e'-ratio between early diastolic velocity at the mitral leaflet's tips to early diastolic velocity by TDI at the level of the medial mitral annulus; MR-mitral regurgitation; LV-left ventricle; 4Ch-apical four chambers view; 2Ch-apical two chambers view; 3Ch-apical three chambers view.

The added value of ESE

In patients with primary MR, ESE, as any other exercise test, may be used to provoke symptoms. SBP drop and abnormal HRR may also be detected. However, in our experience, ESE has a remarkable added value in the understanding of hemodynamics, linking symptoms to changing hemodynamics, risk stratification, and ultimately management of patients with primary MR. Although there is less evidence available, the test seems also reasonable in symptomatic patients with at least moderate MR.^{12,15} The increase in MR severity (≥ 1 grade),^{12,23} exercise

induced PH (exercise systolic pulmonary artery pressure or SPAP ≥ 60 mm Hg),^{15,16,24} the absence of LV contractile reserve ($< 5\%$ increase in EF or $< -2\%$ increment in global longitudinal strain (GLS)),^{11,25} and failure of the right ventricle to cope with the excessively high pulmonary artery pressure (PAP) during exercise (quantified by tricuspid annular plane systolic excursion < 18 mm)²⁴ are all parameters of poor prognosis in asymptomatic patients with severe primary MR. Their systematic assessment during ESE is recommended, whenever possible.

Exercise-induced changes in MR severity

Primary MR may be a highly dynamic entity.^{12,26} In chronic asymptomatic primary MR, marked exercise-induced augmentation in MR severity (Effective Regurgitant Orifice Area or EROA ≥ 10 mm² and regurgitant volume ≥ 15 ml) is present in 1/3 of patients and unrelated to resting MR severity.¹² The magnitude of this augmentation is correlated with exercise-induced variation in SPAP and reduced symptom-free survival.^{12,27}

Exercise-induced PH

In severe primary MR, progressive increase in LV filling pressures and LA pressure leads to a backward passive rise in pressure in the pulmonary veins and to post-capillary PH. When present at rest, PH is a marker of poor outcome and surgery is advised (class IIa indication in both guidelines).^{2,3} However, in truly asymptomatic patients, PH at rest is a seldom finding. Conversely, exercise PH is more common (up to 46% in one study) in this group of asymptomatic patients,²⁷ even when no PH is noted at rest.^{16,27} Patients who developed exercise PH and stop exercise for dyspnea have higher increase in regurgitant volumes and larger increase in EROA with exercise.²⁷ Hence, at least in part, the increase in MR severity with exercise may be reflected by the increase in PAP (Fig. 2). Also, exercise PH predicts symptoms onset.²⁷ A recent study showed that at 3-year follow-up, only 20% of the patients with exercise PH at baseline remained free of symptoms.^{24,27} Exercise PH is also associated with a higher rate of cardiac death, HF hospitalization, stroke or AF after MV surgery.^{13,27} PH at exercise (> 60 mm Hg, class IIb) can also be considered as a trigger for MV repair in low risk patients.²

In practice, abnormal values of SPAP during exercise should be considered carefully due to confounding factors (i.e., age, cardiac output, and exercise protocol). The timing and magnitude of exercise-induced changes in SPAP within the exercise test protocol rather than SPAP at peak exercise, seems to contain most of the information regarding pulmonary vascular function adaptation.²⁸ Slowly progressing increase in SPAP during exercise with development of exercise PH at end-stages should not necessarily be labeled as abnormal, especially in elderly patients or in those reaching age-gender predicted workload. This may be perceived as normal adaptation to exercise.²⁹ Conversely, early and steep increases in SPAP (> 60 mm Hg) at the first stages of exercise followed by a plateau often imply an advanced disease process with exercise symptoms and RV dysfunction.³⁰

LV systolic function reserve to exercise

In MR, the LV dimensions and LVEF reflect the heart's ability to adapt to increased volume load.³¹ However, LV contractile function may already be impaired even in the setting of a preserved LVEF at rest. Lack of contractile reserve ($< 4\%$ increase in LVEF or a

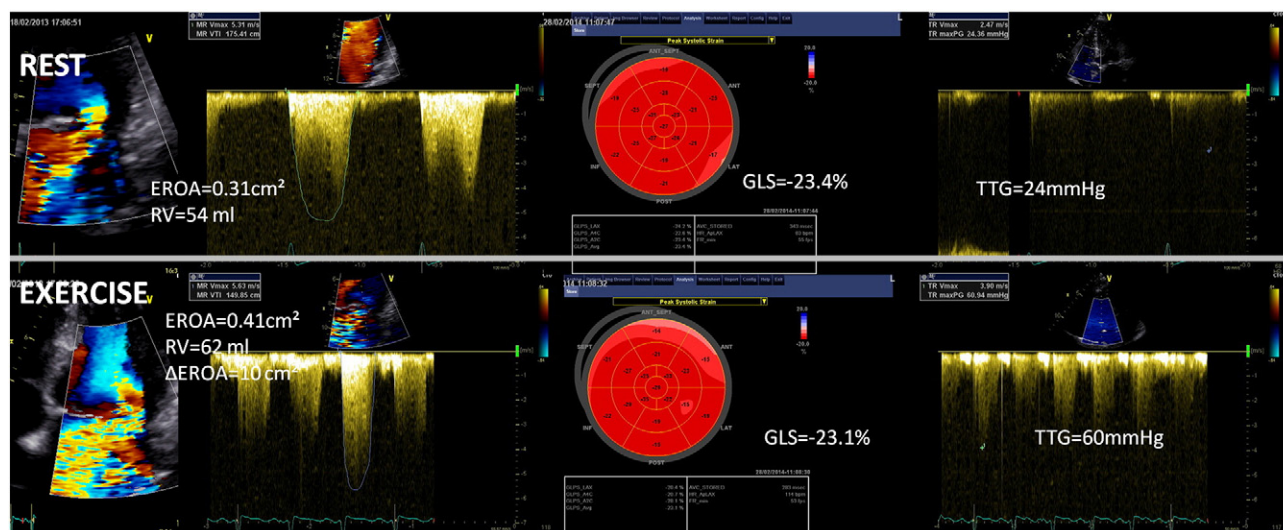


Fig. 2 – Asymptomatic female patient with moderate primary MR at rest due to posterior leaflet prolapse. There is no severe LV dilatation (end-diastolic diameter of 48 mm, end-systolic diameter of 33 mm). LV systolic function is normal, with preserved LV longitudinal function at rest (GLS = -23.4%). There is no pulmonary hypertension at rest (TTG = 24 mm Hg). During exercise (lower panel) MR becomes severe (Δ EROA = 10 mm², Δ RV = 8 ml), there is no increase in GLS and the patient develops severe pulmonary hypertension at the heart rate of 120 bpm and at the second stage of exercise protocol (50 W). She stops the exercise test for dyspnea. MR-mitral regurgitation; LV-left ventricle; EROA-effective regurgitant orifice area; RV-regurgitant volume; GLS-global longitudinal strain by speckle tracking; TTG-transtricuspid systolic pressure gradient.

post-exercise end-systolic volume index >25 cm³/m²) is an early marker of impaired myocyte contractility and predicts post-operative LV function after MV surgery, as well as symptom development and progressive deterioration of LV function in medically treated patients.³¹ Recent studies have suggested that 2D strain imaging obtained at rest and during exercise could be more sensitive at detecting subclinical LV dysfunction.^{11,32,33} A GLS below -20% is associated with LV systolic dysfunction after MV surgery,³¹ and is a predictor of poorer event-free survival.^{11,33} Moreover, the absence of contractile reserve ($<-2\%$ increase in global longitudinal strain during exercise) predicts postoperative LV dysfunction as well as a 2-fold increase in risk of cardiac events at follow-up (cardiovascular death, symptoms or development of LV systolic dysfunction, hospitalization for acute pulmonary edema or HF) in medically-treated patients with a better sensitivity and specificity than an inadequate increase in LVEF.¹¹ In practice, GLS using 2D speckle tracking imaging is the recommended approach; it can be successfully used during exercise, especially in the low stages when heart rate is in adequacy with the frame rate.^{11,33}

Biomarkers during exercise testing

Brain natriuretic peptide (BNP) – a biomarker synthesized and secreted by cardiac myocytes in response to increased intracavitary pressure and wall stress, is a valuable surrogate marker of MR consequences on the LV, LA and PAP both at rest and during exercise.^{34–36} A recent study has shown that in asymptomatic patients with moderate or severe primary MR and normal LV dimensions and function, elevated exercise BNP was independently associated with a higher risk of cardiac events at mid-term follow-up.¹⁴ The main

determinants of exercise BNP levels were resting LV filling pressures, LA enlargement and exercise induced LV longitudinal dysfunction, i.e. lower exercise GLS. An exercise BNP level ≥ 64 pg/ml was the best cut-off value to predict cardiac events.¹⁴ Further studies are needed to confirm the added value of exercise BNP in patients with primary MR.

A summary of all exercise testing derived parameters associated with poor outcome in asymptomatic patients with severe primary MR is provided in Table 2. A schematic representation of exercise testing modalities in the management of patients with primary MR is shown in Fig. 3.

Secondary MR

Chronic secondary MR (SMR) is frequently encountered in HF patients with LV systolic dysfunction of ischemic or non-ischemic etiology.³⁷ It develops due to a combination of mitral leaflet tethering secondary to LV dilatation/deformation with papillary displacement/disco-ordination, annular dilatation/dysfunction, insufficient LV-generated closing forces due to reduction of LV contractility, and global LV/papillary muscle dyssynchrony; SMR is dynamic and affected by changes in hemodynamic conditions, which occur during exercise. Hence, ESE gives the perfect opportunity for the clinician to take a glimpse into the complexity of secondary MR in each individual patient and offers valuable clinical information.

Role of ESE

ESE is a reliable tool to assess the dynamic nature of chronic secondary MR (Fig. 4). Based on our experience, ESE may be of

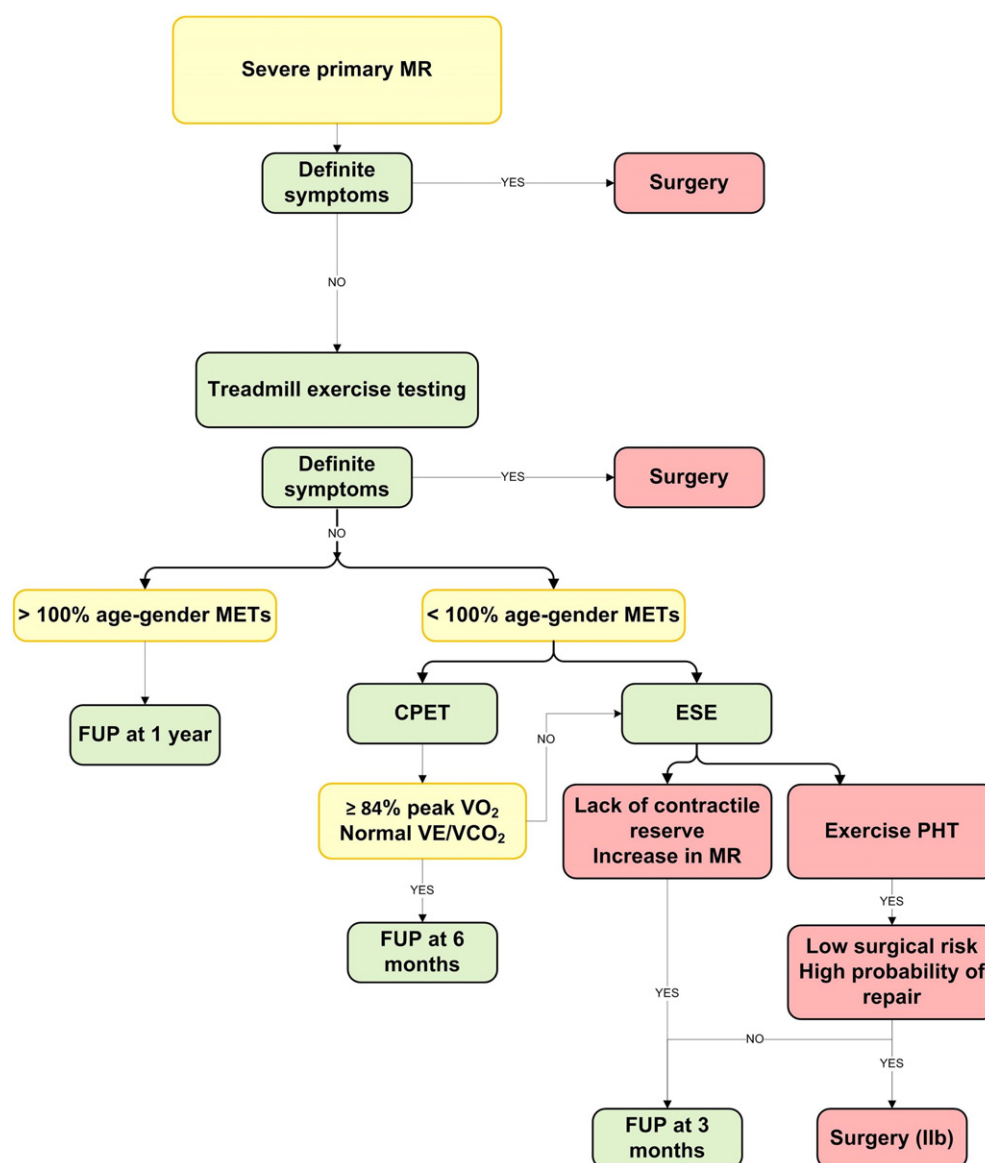


Fig. 3 – Flow-chart on the management of a patient with severe primary MR. MR-mitral regurgitation; METs-metabolic equivalents; FUP-follow-up; CPET-cardiopulmonary exercise testing; ESE-exercise stress echocardiography; peak VO₂-peak oxygen consumption; VE/VCO₂ the slope of the linear relationship between ventilation (VE) and carbon dioxide output (VCO₂); PHT-pulmonary hypertension.

interest in the following conditions: 1) in patients with LV dysfunction who present with exertional dyspnea out of proportion to the severity of resting LV dysfunction or MR severity, 2) in patients in whom acute pulmonary edema occurs without any obvious cause; 3) to unmask patients at high risk of mortality and HF (increase in MR severity and PH with exercise); 4) before surgical revascularization in patients with moderate MR and 5) following surgery, to identify persistence of PH and explain the absence of functional class improvement.³⁸⁻⁴⁰

The severity of SMR at rest is unrelated to the magnitude of MR changes during exercise. About 30% of patients may have a marked increase in MR with exercise accompanied by an increase in SPAP.⁴¹ The degree of exercise-induced changes in MR severity relates to changes in LV remodelling,⁴² in valvular

deformation and^{41,42} in LV and papillary muscles synchronicity.⁴³ Rarely, transient myocardial ischemia may lead to transient SMR. The induction of ischemia during ESE can be easily detected by new or worsening wall motion abnormalities secondary to a hemodynamically significant stenosis of the right or circumflex coronary artery. Myocardial revascularization alone may solve MR in such cases.

The magnitude of increase in MR and SPAP is more pronounced in patients with exercise-limiting dyspnea and in those hospitalized for acute pulmonary edema.³⁸ The increase in MR degree during exercise (i.e. increase in EROA ≥ 13 mm²) independently predicts cardiac death and HF admission in patients with systolic heart failure and at least mild secondary ischemic MR.³⁹ The best predictive cut-off value for the increase in SPAP associated with the outcome is

Table 2 – Parameters of poor prognosis in asymptomatic primary MR.

| Parameter | Type of Exercise Testing | Study |
|---|--|---|
| Symptom development | Any type | |
| <85% age-gender-predicted METs | Treadmill exercise testing | Naji et al. ^{17,18} |
| Abnormal heart rate recovery (<18 beats drop in heart rate over 1 min in recovery) | Treadmill exercise testing | Naji et al. ^{17,18} |
| ≤84% age-gender expected peak VO ₂ | Cardiopulmonary exercise testing | Messika-Zeitoun et al. ¹⁹ |
| Exercise induced increase in EROA ≥10 mm ² or in regurgitant volume ≥15 ml | Exercise stress echocardiography | Magne et al. ¹² |
| Exercise induced systolic pulmonary artery pressure ≥60 mm Hg | Exercise stress echocardiography and post exercise stress echocardiography | Magne et al. ¹³ Kusunose et al. ²⁴ |
| Exercise TAPSE <18 mm | Post-exercise stress echocardiography | Kusunose et al. ²⁴ |
| <4% increase in LVEF post exercise | Post-exercise echocardiography | Lee et al. ³¹ |
| <-2% increase in GLS during low level exercise stages | Exercise stress echocardiography | Magne et al. ¹¹ |
| Exercise BNP levels ≥64 pg/ml | Any type, blood sample drawn 5 min after exercise cessation | Magne et al. ¹⁴ |

Peak VO₂-peak oxygen consumption; EROA-effective regurgitant orifice area as assessed by PISA method; TAPSE-tricuspid annulus plane systolic excursion; LVEF-left ventricle ejection fraction; LV-left ventricle; GLS-global longitudinal strain as assessed by speckle tracking analysis; BNP-brain natriuretic peptide.

21 mm Hg. Exercise induced PH (i.e. SPAP > 60 mm Hg) is common in secondary MR patients, up to 40% of patients in one study (Fig. 4).⁴⁰ It seems to be related more to exercise MR severity and LV diastolic function than to NYHA class. Moreover, exercise PH has proven to be a powerful predictor of the occurrence of HF decompensation, cardiac-related death, or combined cardiovascular events in these patients.⁴⁰ The presence of viable myocardium predicts LV reverse remodelling and a better outcome after revascularization, beta-blocker therapy and cardiac resynchronization therapy CRT.⁴⁴ LV reverse remodelling and reduced mitral apparatus deformation after CRT are associated with a reduction in both resting and exercise-induced MR and an improvement in cardiopulmonary performance.⁴⁵ Moreover, SMR decreases more significantly in patients with viability in the region of the pacing lead after CRT.⁴⁶

Considering the adverse prognostic implications of the increase in MR severity with exercise in patients with moderate SMR, the ESC guidelines suggested combined MV repair at the time of surgical coronary revascularization in

patients in whom such a response has been demonstrated with ESE (Class IIa).

Conclusions

Exercise testing, in its many forms, is useful for the evaluation of asymptomatic patients with primary MR. It allows symptom assessment, confident link of symptoms to VHD severity (ESE, CPET), safe deferral of surgery for the next 1-year if the patient proves to have a preserved exercise capacity, insights into the mechanism of exercise induced dyspnea (CPET and ESE) and helps in risk stratification of truly asymptomatic patients through the assessment of exercise-induced PH, LV dysfunction and MR increase in severity. For all these reasons, exercise testing should be encouraged in asymptomatic patients with primary MR. Moreover, ESE is useful in the evaluation of patients with ischemic SMR for risk stratification as well as for the detection of those with moderate ischemic MR in whom MV repair at the time of surgical

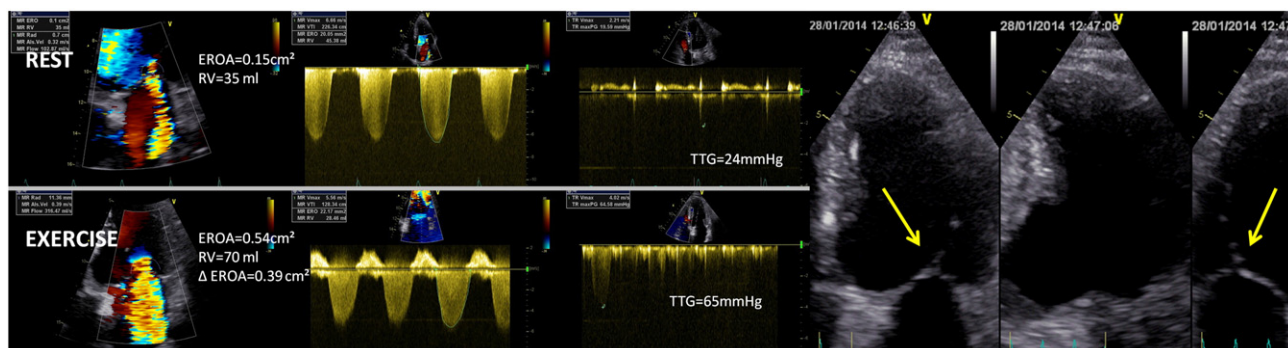


Fig. 4 – High-risk patient with secondary ischemic MR. At rest, upper panel, there is moderate ischemic MR, important tethering on the mitral valve leaflets (yellow arrows) and no pulmonary hypertension. During exercise (lower panel), there is a severe increase in MR (exercise induces change in EROA of 0.39 cm²) accompanied by pulmonary hypertension and dyspnea. This is a high-risk patient for future heart failure episodes or mortality. MR-mitral regurgitation; EROA-effective regurgitant orifice area; RV-regurgitant volume; TTG-transtricuspid systolic pressure gradient.

revascularization may add benefit. The role of ESE in non-ischemic forms of secondary MR is not yet established and should be further explored.

Statement of conflict of interest

There is no conflict of interest of any of the listed authors.

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