EXPERT OPINION AND POSITION PAPER

Clinical application of stress echocardiography in valvular heart disease

An expert consensus of the Working Group on Valvular Heart Disease of the Polish Cardiac Society

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ABSTRACT

Valvular heart diseases (VHDs) constitute an increasing problem both as a consequence of population aging and as the sequelae of other heart diseases. Accurate diagnosis is essential for correct clinical decision-making; however, in many patients, transthoracic and transesophageal echocardiography is insufficient. Stress echocardiography (SE) proved to be a useful tool allowing for simultaneous assessment of left ventricular contractile reserve and HVD hemodynamics under conditions of physiological or pharmacological stress. It is recommended for assessing the severity of VHD, guiding the choice of treatment, as well as for surgical risk stratification. It can be applied both in asymptomatic patients with severe VHD and in symptomatic individuals with moderate disease. In patients with VHD, SE can be performed either as exercise stress echocardiography (ESE) or dobutamine stress echocardiography (DSE). The first modality is recommended to unmask symptoms or abnormal blood pressure response in patients with aortic stenosis (AS) who report to be asymptomatic or in those with mitral stenosis with discordance between clinical symptoms and the severity of valve disease on transthoracic echocardiography. In asymptomatic patients with paradoxical low-flow, low-gradient (LFLG) AS, ESE can be used to assess the severity of stenosis. On the other hand, low-dose DSE can be a useful diagnostic tool in classical LFLG AS, providing information on stenosis severity and contractile reserve. Moreover, SE is indicated in patients with prosthetic valve when there is discordance between symptoms and echocardiographic findings. It is also recommended in high-risk surgical patients with VHD with poor functional capacity and more than 2 clinical risk factors. The present paper discusses in detail the use of SE in VHD.

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Introduction The first Polish registry of echocardiography studies (Pol-STRESS [Polish Stress Echocardiography Registry]) and a European report on cardiac imaging studies show that stress echocardiography (SE) is currently a well-recognized imaging modality, predominantly used in the diagnosis of coronary artery disease and valvular heart disease (VHD).[1,2] It is currently recommended by numerous guidelines of the European Society of Cardiology (ESC) as a noninvasive test with high sensitivity and specificity. The test uses various stressors (most often exercise and dobutamine) that enhance left ventricular (LV) contractility, increase blood flow through the valve orifices, or lead to an imbalance between myocardial oxygen supply and demand. Stress-induced ischemia generates new or worsening regional wall motion abnormalities as well as changes in blood flow through the heart valves.[3]

For more than a decade, Polish[4] and European[5] experts in cardiac imaging as well as the ESC guidelines for the management of patients with VHD[6] have recommended the use of SE for assessing the severity of VHD, guiding the choice of treatment, and for surgical risk stratification. The examination is indicated in asymptomatic patients with severe VHD or in symptomatic individuals with moderate disease. A special group of patients are those with low-flow, low-gradient (LFLG) aortic stenosis (AS) and reduced LV ejection fraction (LVEF) as well as those with so-called paradoxical LFLG AS in which LVEF is preserved. Stress echocardiography is also recommended in patients with mitral stenosis (MS) as well as mitral (MR) and tricuspid regurgitation (TR). Finally, it may be performed to identify patients at increased risk of pulmonary hypertension.[7]

Stress echocardiography: laboratory equipment and patient preparation The SE laboratory should be equipped with a resuscitation kit containing an automated external defibrillator, a bag valve mask, and basic emergency drugs with infusion fluids. β-Blockers or nitroglycerin should be available to reverse dobutamine action. Blood pressure monitors and electrocardiogram machines are also indispensable.

Before SE, it is important to collect detailed medical history, including contraindications to the examination. Stress echocardiography should not be performed in patients with unstable coronary artery disease, decompensated heart failure, severe arrhythmia, myocarditis, endocarditis, and pericarditis, while contraindications to dobutamine SE (DSE) include uncontrolled high blood pressure and hypertrophic cardiomyopathy with high LV outflow tract (LVOT) gradient. The examination should be done in a fasting state or at least 4 hours after a light meal. Before the examination, patients should avoid physical exertion, drinking strong coffee, tea, or other energy drinks, as well as smoking. Discontinuation of medications masking the symptoms or affecting the test result (eg, β-blockers, nitrates) may be considered prior to testing. Patients should provide written informed consent to undergo the examination.

Before the examination, resting echocardiography should be performed to assess the quality of the images. If echogenicity is decreased, the reliability of the test is questionable and SE is not recommended in such patients. The choice of a stress test modality depends on the presence of indications and contraindications as well as the physician's experience and preference.

Stress echocardiography was confirmed to be safe.[8,9] The safety of exercise SE (ESE) is comparable to that of a standard exercise stress test. As for DSE, the most common adverse effects include trembling, flushing, headaches, and palpitation.

Stress echocardiography protocols in valvular heart disease Valvular heart disease is diagnosed using ESE and DSE.[3,7] The choice of the modality and protocol depends on indications and the patient's clinical status. Considering the very short duration of imaging, it is important to predefine the echocardiographic parameters and to acquire the images in a specific order depending on the aim of the test. During SE, blood pressure monitoring, 12-lead electrocardiogram recording, and assessment of clinical status are mandatory.

Exercise SE requires the patient's cooperation and ability to perform physical exercise. It is a symptom-limited test conducted using a semi-supine bicycle or treadmill. Semi-supine bicycle exercise echocardiography allows detailed image acquisition throughout the test, from low to peak workload. The patient pedals at a constant cadence (60 rpm) against the increasing workload (starting at 25 W with increments of 25 W at 3-minute intervals). The images are acquired at baseline, at 25 to 50 W, on achieving a heart rate of 100 to 120 bpm, at peak stress, and during recovery. In severe valve disease, LV images should be acquired first to assess contractile reserve and changes in global longitudinal strain (GLS). In contrast, in asymptomatic patients with LFLG AS with preserved LVEF, images allowing the assessment of disease severity and LV flow reserve should be acquired first. The semi-supine bicycle is the only ESE modality that enables the estimation of systolic pulmonary artery pressure (SPAP) by assessing TR. Treadmill exercise is another ESE modality, but it does not allow imaging during exercise. Images are typically acquired after peak exercise (within 90 seconds after termination), immediately after the patient has been moved to an echocardiography bed. Therefore, this modality cannot be used to identify abnormalities at low workload. The commonly used treadmill protocols are the Bruce and modified Bruce protocols.

Dobutamine SE allows image acquisition at low, intermediate, and peak levels of stress. The DSE protocol involves continuous intravenous dobutamine infusion, starting at a dose of 5 µg/kg/min, uptitrated by 5 to 10 µg/kg/min every 3 to 8 minutes, up to 40 µg/kg/min. The maximum dose in the assessment of patients with AS is 20 µg/kg/min. Image acquisition should start 2 to 3 minutes after each increment of dobutamine dose. Due to the vasodilatory effect of dobutamine, DSE does not allow an assessment of SPAP and MR severity.

Stress echocardiography in low-flow, low-gradient aortic stenosis Low-flow, low-gradient AS is defined as the presence of a mean transvalvular gradient of less than 40 mm Hg, an effective aortic valve area (AVA) of less than 1 cm^2 (0.6 cm^2/m^2 body surface area), and a stroke volume (SV) index of less than 35 ml/m^2. It may be classic (with reduced LVEF) or paradoxical (with preserved LVEF).

Low-dose DSE can be a useful diagnostic tool in classical LFLG AS, providing information on stenosis severity (changes in the mean transvalvular gradient and AVA in response to the increase in flow rate) and LV contractile reserve (changes in SV and LVEF). The DSE protocol for the assessment of classical LFLG AS starts at a low dobutamine dose of 2.5 or 5 µg/kg/min, uptitrated at 3- to 5-minute increments to a maximum dose of 20 µg/kg/min.[10] High doses should be avoided due to the increased risk of arrhythmia and possible overestimation of stenosis severity during the accelerated flow rate caused by high drug concentrations.[10]

The minimum acquired dataset at baseline and at each stage of infusion should include aortic flow velocity measured with continuous-wave Doppler (optimally recorded from the window with the highest velocity signal), LVOT flow velocity measured with pulsed-wave Doppler, and LV contractile reserve assessed in the parasternal long-axis and apical 4- and 2-chamber views. The LVOT diameter is measured at baseline, and the value is used to calculate the AVA by the continuity equation throughout the test.[3,10] A DSE report should include peak transvalvular flow velocity, mean gradient, SV, and AVA at each stage of the test; LVEF should be measured at least at baseline and at peak stress.

Classical low-flow, low-gradient aortic stenosis Clinically significant findings of DSE in classical LFLG AS are as follows:[10,11]

1 an increase in the mean transaortic gradient above 30 mm Hg (optimally >40 mm Hg) with an AVA of less than 1 cm^2 at any stage of dobutamine infusion, which indicates true-severe AS;
2 an increase in AVA above 1 cm^2, which indicates absence of severe stenosis;
3 no increase in SV to 20% or higher indicating the lack of contractile (flow) reserve, which is a predictor of high perioperative mortality.[12] However, it should be emphasized that this abnormality does not preclude an improvement in the patient's clinical status and late survival after surgical or transcatheter aortic valve replacement. Therefore, the absence of LV flow reserve on DSE should not preclude consideration for aortic valve replacement.[3,12]

In some patients, a discordance between a small AVA and low gradient is maintained throughout DSE, making it difficult to determine the severity of stenosis. In this population, typically presenting with not sufficient increase in transvalvular flow rate, the so called projected AVA can be calculated, which provides an estimate of the AVA at normal transvalvular flow rate (ie, 250 ml/s),[10,13] using the following formula:

$$\text{Projected AVA} = AVA_{rest} + (\Delta AVA/\Delta Q) \times (250 - Q_{rest})$$

where AVA_{rest} and Q_{rest} are the AVA and mean transvalvular flow rate (ie, SV/LV ejection time) measured at rest, while ΔAVA and ΔQ are the absolute changes in the AVA and mean transvalvular flow rate measured during DSE. To obtain a reliable measurement of the projected AVA, a minimum increase of 15% (optimally ≥20%) in transvalvular flow rate during dobutamine infusion is required.[12] A projected AVA of less than 1 cm^2 confirm the presence of true-severe AS.

In patients with classical LFLG AS, in whom DSE cannot be used to differentiate between true- and pseudo-severe stenosis because of inadequate increase in transvalvular flow rate, multidetector computed tomography (MDCT) should be applied to assess aortic valve calcification (FIGURE 1).[3,10]

Paradoxical low-flow, low-gradient aortic stenosis Currently, DSE is not recommended as a diagnostic tool in paradoxical LFLG AS because of limited evidence and an increased risk of hemodynamic abnormalities due to dobutamine-induced abnormal LV filling pressure, LVOT obstruction, and subsequent hypotension in patients who typically have pronounced LV concentric remodeling with a small LV cavity size and restrictive physiology pattern.[10,11] The gold standard for assessing stenosis severity in this population is MDCT (FIGURE 1), while ESE can be used in patients with no or mild symptoms.

Before using additional tests, it is important to note that resting AVA in patients with transvalvular flow rate exceeding 200 ml/s is unlikely to change during stress.[14]

Stress echocardiography in patients with asymptomatic severe aortic stenosis

Recommendations Patients with severe high-gradient AS, defined as an AVA of less than 1 cm^2 and a mean pressure gradient (MPG) exceeding 40 mm Hg at rest, who present with symptoms (class I, level of evidence B) and / or LV systolic

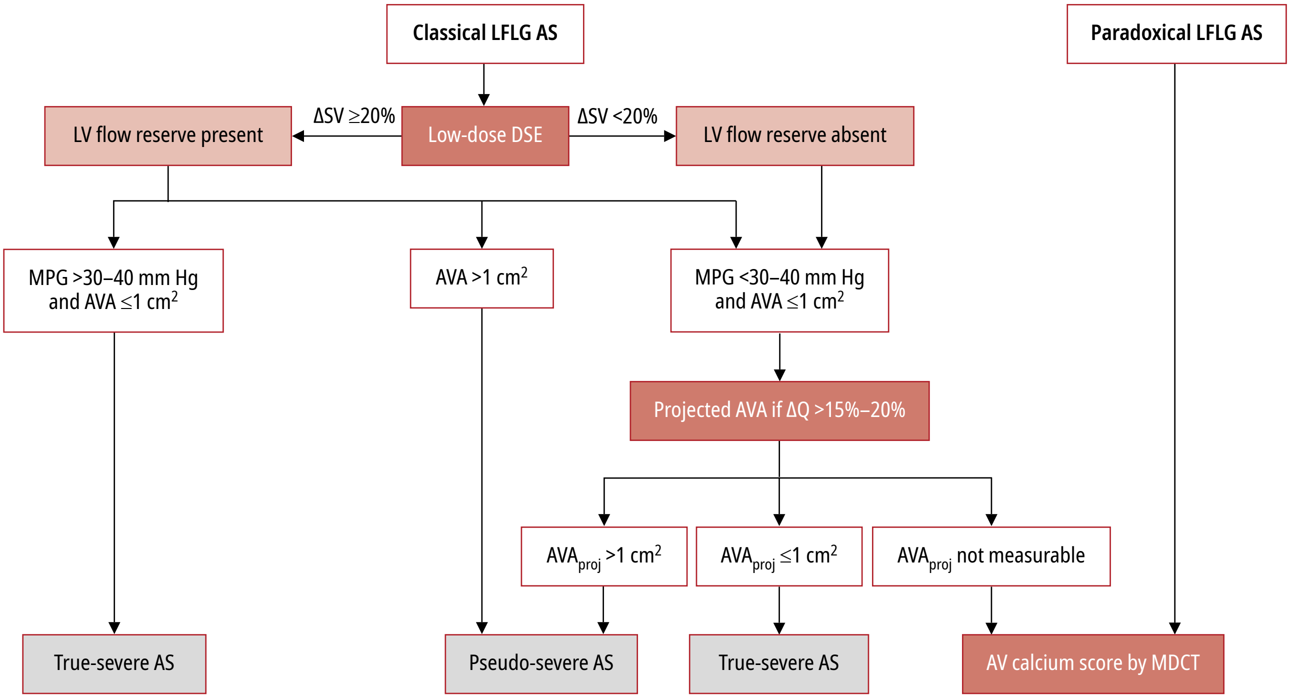

FIGURE 1 Algorithm for differentiation between true-severe and pseudo-severe low-flow, low-gradient aortic stenosis using dobutamine stress echocardiography and multidetector computed tomography

Abbreviations: AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; Δ, changes from rest to peak stress; DSE, dobutamine stress echocardiography; LFLG, low--flow, low-gradient; LV, left ventricular; MDCT, multidetector computed tomography; MPG, mean pressure gradient; SV, stroke volume

dysfunction (class I, level of evidence C) should be referred for surgical aortic valve replacement (SAVR) or, in some cases, for transcatheter aortic valve implantation.[6] In patients with asymptomatic AS, an exercise stress test is recommended to reveal symptoms or abnormal blood pressure response to exercise.[3,6] However, the exercise test does not always allow to detect every high-risk patient with asymptomatic AS; therefore, other diagnostic tools are being sought. Importantly, the exercise test is contraindicated in symptomatic patients with severe AS.[3]

Clinical indications In patients with asymptomatic severe paradoxical LFLG AS, SE can be used to determine stenosis severity.[7,16] In physically active patients with severe AS, ESE has been shown to be useful for unmasking symptoms and for risk stratification.[15]

Test parameters **Modalities** In patients with asymptomatic AS, ESE can be performed using either a treadmill or bicycle ergometer protocol. Dobutamine SE is contraindicated in severe high-gradient AS and not recommended in paradoxical LFFG AS.[7]

Protocols The commonly used treadmill protocols are the Bruce and modified Bruce protocols.[3] Bicycle exercise echocardiography may be performed with an upright or, ideally, a semi-supine bicycle. The latter allows image acquisition throughout the test as it does not require the change of the patient's position.[3,7] Imaging at low workload allows an assessment of contractile reserve and changes in GLS, which may reveal subclinical LV systolic dysfunction.[7]

Interpretation of the test Echocardiographic parameters that should be assessed during ESE are shown in TABLE 1.

Global longitudinal strain seems to outweigh LVEF in terms of predicting symptoms and cardiovascular events in patients with asymptomatic severe high-gradient AS with preserved LVEF, although the precise cutoff values have not yet been determined.[3,6]

Definitions of abnormal results and the cutoff values for clinical and echocardiographic parameters are presented in TABLE 2.

Impact on management Therapeutic decision-making in patients with asymptomatic severe AS who undergo ESE is presented in TABLE 3.

Stress echocardiography in aortic regurgitation Surgical aortic valve replacement is indicated in patients with symptomatic severe aortic regurgitation (AR; class I indication, level of evidence B).[6]

Clinical indications In patients with severe AR who report to be asymptomatic, exercise testing

TABLE 1 Targeted parameters to be assessed during exercise stress echocardiography in patients with severe asymptomatic aortic stenosis

Sequence of 2D and Doppler image acquisition	Levels of 2D and Doppler image acquisition	ESE result	ESE report
– 2D LV apical views – MR and TR color-flow Doppler – TR CW Doppler (for SPAP estimation) – AV CW Doppler (for gradient estimation) – LVOT PW Doppler	– Baseline – Low workload – Peak exercise	Symptoms ± drop / no increase in LVEF and / or GLS ± regional wall motion abnormalities ± SPAP increase ± MR development / exacerbation ± gradient increase ± projected AVA ≤ or >1 cm² for paradoxical LFLG AS	Severe AS with symptoms on exertion / SPAP / dynamic MR / lack of contractile reserve / exercise-induced ischemia / noncompliant valve

Abbreviations: 2D, 2-dimensional; CW, continuous-wave; ESE, exercise stress echocardiography; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PW, pulsed-wave; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; others, see FIGURE 1

TABLE 2 Criteria for abnormal exercise stress echocardiography findings and cutoff values for echocardiographic markers of poor prognosis in patients with asymptomatic aortic stenosis [3,7,16]

Symptoms	Angina, dyspnea, dizziness, syncope and near-syncope, fatigue at low workload
Ischemia	≥2-mm ST-segment depression in comparison with baseline
	New or worsening regional wall motion abnormalities
Arrhythmias	Nonsustained and or sustained ventricular tachycardia
Specific targeted features	For high gradient AS: a marked (>18–20 mm Hg) increase in MPG, deterioration of LV systolic function, lack of LV functional reserve (increase in LVEF <5%), and exercise SPAP >60 mm Hg
	For paradoxical LFLG AS: a marked (up to >30–40 mm Hg) increase in MPG with projected AVA ≤1 cm², deterioration of LV systolic function, and exercise SPAP >60 mm Hg

Abbreviations: MPG, mean pressure gradient; others, see FIGURE 1 and TABLE 1

TABLE 3 Therapeutic decision-making in patients with asymptomatic severe aortic stenosis undergoing exercise stress echocardiography[3,6,15]

SAVR is indicated in patients with asymptomatic severe AS and abnormal exercise test with the presence of exercise-limiting symptoms (IC).
SAVR should be considered in patients with asymptomatic severe AS and abnormal exercise test showing a reduction in blood pressure below baseline values (IIa C)
Patients with asymptomatic severe AS with an exercise-induced increase in SPAP or limitation of contractile reserve (increase in LVEF <5%) may require closer clinical and echocardiographic monitoring.
If predictors of rapid symptom onset and poor prognosis are present, early SAVR may be justified in patients with asymptomatic severe AS, particularly at low surgical risk. These predictors include exercise-induced increase in MPG >20 mm Hg.
Stress tests should determine the recommended level of physical activity.

Abbreviations: SAVR, surgical aortic valve replacement; others, see FIGURE 1, TABLE 1, and TABLE 2

is recommended to reveal symptoms.[3] In patients with nonsevere AR, an exercise test can be performed to exclude symptoms.[3]

Test parameters **Modalities** For the assessment of symptoms, ESE is preferred over DSE.

Protocols Supine bicycle exercise is most appropriate for the assessment of contractile reserve. Images should be acquired at baseline, low workload, and peak exercise when using a supine bicycle, and at baseline and immediately postexercise when using a treadmill.

The minimum acquired dataset should include 2-dimensional (2D) LV views, TR by continuous-wave Doppler for estimation of SPAP, and MR by color-flow Doppler, obtained in this order.

Interpretation of the test For severe AR without symptoms: detection of symptoms with or without contractile reserve. For nonsevere AR with symptoms: exercise-induced ischemia ± pulmonary hypertension ± dynamic MR.

Impact on management Surgical aortic valve replacement is indicated in patients with severe AR and symptoms revealed by exercise testing (class I indication, level of evidence B).[6] The lack of contractile reserve (<5% increase in LVEF) was found to predict the development of LV systolic dysfunction at follow-up or after SAVR. Rest and exercise longitudinal function assessment by tissue Doppler imaging parameters may reveal early signs of LV systolic dysfunction.[3]

Stress echocardiography in mitral regurgitation Due to the presence of a dynamic component in valve disease, a full clinical assessment of a patient with acquired valvular disease should in principle be carried out both at rest and during exercise. The dynamic component is particularly evident in MR. On the one hand, changes in the function of the LV and subvalvular apparatus during exercise (exercise-induced asynchrony, ischemia, changes in LV shape) can lead to alterations in the degree of valvular leakage. On the other hand, the progression of MR leads to an elevation of pulmonary pressure by increasing the left atrial volume and pressure overload. For this reason, in the majority of patients with MR, exercise testing is the most optimal modality.[1,2] Owing to its pharmacodynamic profile (vasodilatory effect), dobutamine is not an appropriate stressor because it can limit functional regurgitation, making it difficult to interpret test results. However, DSE may be used in ischemic MR when it is important to assess not only mitral valve (MV) leakage but also contractile reserve or ischemia in the posterior, inferior, and lateral segments (circumflex and right coronary artery territory) as well as papillary muscle function. Improved contractility and valve sealing at a low dobutamine dose followed by deterioration and unsealing at a high dose (a biphasic response) indicates the need for revascularization in this area.

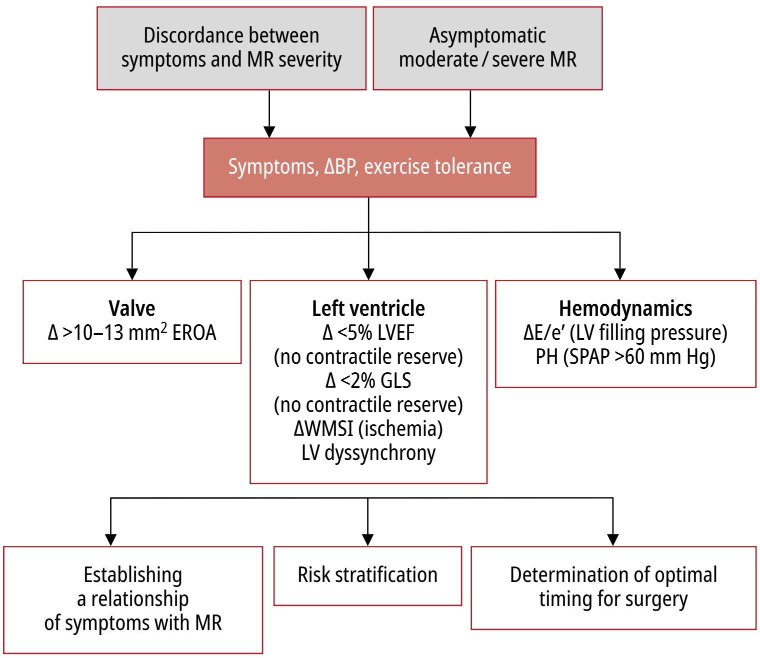

FIGURE 2 Indications, interpretation of the test, and basic goals of exercise or dobutamine stress echocardiography in patients with mitral regurgitation. Valvular function, left and right ventricular function, and hemodynamic consequences of valve disease are assessed individually.[3]

Abbreviations: EROA, effective regurgitant orifice area; GLS, global longitudinal strain; ΔBP, a change in blood pressure; others, see FIGURE 1 and TABLE 1

Stress echocardiography should be performed when the reported symptoms are disproportionate to the degree of MR on resting echocardiography. This applies both to patients with paroxysmal dyspnea (transient pulmonary edema) and mild / moderate ischemic MR on resting echocardiography and to asymptomatic patients with hemodynamically significant mitral defect (ie, moderate or severe MR irrespective of etiology). When adapting to altered hemodynamic conditions, elderly patients with heart defect often reduce their physical activity, thus masking clinical symptoms. With stress echocardiography, it is possible to objectively assess exercise capacity and to determine whether reported dyspnea and reduced exercise tolerance are related to heart valve disease or comorbidities (lung disease, musculoskeletal disorders, anemia) or simply to poor adaptation to exercise (lack of training).[2,3] Undoubtedly, the greatest benefit of exercise testing for the patient is the possibility to determine MR severity and establish the optimal timing for surgery (FIGURE 2). For example, in a young asymptomatic female patient with hemodynamically significant organic MR (eg, Barlow syndrome, fibroelastic deficiency) who is planning pregnancy, determination of specific targeted parameters during ESE (PSAP >50 mm Hg, <5% increase in LVEF, <2% increase in GLS) guides decision-making about early surgical valve repair.

Due to the specific protocol of ESE, the number of echocardiographic parameters that can be obtained during the test is limited. In practice, only parameters that can be measured at each stage of exercise and that have diagnostic value for clinical assessment are recorded (FIGURE 3). Echocardiographic results are evaluated online (2D measurements, Doppler) and offline (LV and right ventricular strain measurements). Bicycle stress test should be offered to elderly and less well-trained individuals, while younger people may also be tested using the treadmill. However, it is important to note that image acquisition is easier with a bicycle (2D + Doppler) than with a treadmill. The stress test in a patient with MR is limited by symptoms or the heart rate that allows a legible and reliable recording of echocardiographic parameters (typically around 100–120 bpm). The diagnostic endpoints as well as criteria for test termination are summarized in TABLE 4.

The interpretation of echocardiographic parameters depends on the etiology of MR and concomitant resting clinical symptoms. In symptomatic patients with a moderate degree of organic MR at rest, an increase in MR severity (≥1 grade), dynamic pulmonary hypertension (SPAP >60 mm Hg), absence of LV contractile reserve (5% increase in LVEF, <2% increase in GLS), and a limited right ventricular contractile reserve (tricuspid annular plane

BP, ECG, symptom monitoring

Baseline	25–75 W	100–120 bpm	Max load	Recovery
LV function	LV function	LV function	LV function	LV function
Regional wall motion abnormalities	Regional contractility abnormalities	Regional contractility abnormalities	Regional contractility abnormalities	Regional contractility abnormalities
LV strain	–	LV strain	LV strain	-
MR	MR	MR	MR	MR
RVSP	–	RVSP	RVSP	-
RV function	–	RV function	RV function	-

FIGURE 3 Exercise test protocol using a bicycle ergometer or treadmill in a patient with mitral regurgitation. Left ventricular global and regional function and severity of mitral regurgitation are monitored throughout the test. RV function, RVSP, LV strain, and EROA are assessed at baseline and at peak exercise. Abbreviations: ECG, electrocardiogram; RV, right ventricular; others, see FIGURE 1, TABLE 4, and FIGURE 2

systolic excursion <19 mm) are all parameters of poor long-term prognosis. On the other hand, in patients with severe organic MR without symptoms, the evaluation should focus mainly on the presence of clinical symptoms (dyspnea), dynamic pulmonary hypertension (SPAP >60 mm Hg), and LV contractile reserve, without the need to assess the degree of MR. An increase in effective regurgitant orifice area (EROA), which is usually observed in these patients during exercise, has no prognostic value.[1]

In patients with ischemic MR and LV systolic dysfunction, an exercise-induced increase in EROA of more than 13 mm^2 indicates advanced postinfarction LV remodeling and may guide the decision on simultaneous revascularization and MV annuloplasty. On the other hand, the reduction of EROA or complete sealing of the valve after exercise confirms the presence of contractile reserve and the absence of ischemia in the posterior, inferior, and lateral wall, which indicates good prognosis. The most common indications for stress testing with regards to MR etiology are summarized in TABLE 5.

Stress echocardiography in mitral stenosis

Stress echocardiography is indicated in patients with discordance between clinical symptoms and the degree of MS on resting echocardiography. It not only allows a more accurate hemodynamic evaluation of native MV disease but also a dynamic assessment of both MV prosthesis (when obstruction or patient–prosthesis mismatch [PPM] is suspected) and the MV after repair (when iatrogenic functional MS is suspected).[3,6,17]

The first group of patients with indications for SE comprises symptomatic individuals with resting echocardiography findings suggesting nonsignificant MS (ie, MV area [MVA] >1.5 cm^2). During SE, MV impaired compliance to the stress-induced increase in flow may result in a significant rise in mean diastolic gradient (MDG).

The second group with indications for SE includes patients without symptoms or with atypical symptoms despite the MVA suggesting hemodynamically significant MS, in whom stress testing may provoke symptoms. The test is indicated when the MVA is lower than 1.5 cm^2 and higher than 1 cm^2 in patients planning pregnancy or referred for major surgery and when the MVA is lower than 1 cm^2 in the remaining patients.

In patients after MV replacement or repair, SE is typically indicated when MS symptoms are present and the resting MDG is about 5 mm Hg or slightly higher. Symptomatic patients after surgical repair of functional MR (typically after undersized rigid ring annuloplasty) constitute a specific subgroup. In these patients, systolic LV dysfunction may result in low flow at rest. Therefore, SE should be considered already at an MDG exceeding >3 mm Hg,[3] as it may unmask functional MS.

The preferred SE modality is supine bicycle exercise. Tricuspid regurgitation velocity for estimation of SPAP and mitral valve for the measurement of MDG are recorded with continuous-wave Doppler at at different stages of ESE. If dedicated equipment is unavailable, a standard exercise test (bicycle, treadmill) may be used,

TABLE 4 Diagnostic endpoints and criteria for test cessation in patients with mitral regurgitation

Diagnostic endpoints	Criteria for test cessation
Maximum dobutamine dose (simultaneous MR and contractile reserve assessment)	Symptoms: muscle fatigue, dyspnea, angina
Maximum tolerated workload	Ischemia (ST-segment depression ≥2 mm compared with baseline)
Target heart rate	Systemic arterial hypertension (220/120 mm Hg) or symptomatic hypotension (>40 mm Hg decrease)
Pulmonary hypertension (RVSP >60 mm Hg)	New regional contractility abnormalities
Severe MR	Arrhythmia (VT, SVT, AF, multifocal ventricular ectopy)

Abbreviations: AF, atrial fibrillation; RVSP, right ventricular systolic pressure; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia; others, see TABLE 1

TABLE 5 The most frequent indications for exercise testing in patients with mitral regurgitation depending on etiology

Functional MR	Organic MR
Ischemic MR: assessment of indications for simultaneous myocardial revascularization and mitral valve repair / replacement	Asymptomatic patients, assessment of MR severity, determination of optimal timing for mitral valve surgery
HCM: assessment of MR severity and indications for concomitant MR repair / replacement	Asymptomatic patients before planned pregnancy, assessment of MR severity, determination of optimal timing for mitral valve surgery
Diagnostic workup of paroxysmal nocturnal dyspnea and low exercise tolerance in patients with moderate MR	Symptomatic patients with moderate MR, assessment of MR severity and exercise tolerance as well as the etiology of dyspnea

Abbreviations: HCM, hypertrophic cardiomyopathy; others, see TABLE 1

with echocardiographic assessment limited to baseline and postexercise. Alternatively, a DSE with a maximum infusion rate of 20 µg/kg/min can be performed. Due to the specificity of dobutamine's action, only MDG is assessed.[3,17]

An SPAP exceeding 60 mm Hg on exertion is considered a marker of hemodynamically significant MS. The criteria for MDG assessment are presented in TABLE 6.

Stress echocardiography assessment of the tricuspid valve Assessment of TR during exercise is used for evaluating the severity of left heart valve diseases and their hemodynamic consequences. Semi-supine bicycle exercise is the preferred modality allowing the estimation of SPAP by TR assessment. Transtricuspid pressure gradient should be recorded at every stage of the stress test in the assessment of AS and AR as well as MS and MR.[7] An exercise-induced SPAP higher than 60 mm Hg is a predictor of poor prognosis.[7] It is important to record TR jet velocity by continuous-wave Doppler at low workload, because the increase in SPAP from low workload is a marker of more significant hemodynamic consequences of valve disease.[3] Importantly, exercise SPAP is not included in the diagnostic criteria of pulmonary hypertension.

Stress echocardiography in patients with prosthetic valve The evaluation of prosthetic valve function usually requires extensive clinical experience. The diagnostic workup is hindered by the different models and sizes of valves that cause varying degrees of flow obstruction. When prosthetic valve dysfunction is suspected, transthoracic echocardiography complemented by transesophageal examination may be insufficient.[6,18] Fluoroscopy, and sometimes computed tomography, may be helpful in patients with a mechanical prosthetic valve.[10] Stress echocardiography may provide additional diagnostic value. The current recommendations of the European Association of Cardiovascular Imaging and American Society of Echocardiography provide guidelines for applications and performance of SE in patients with prosthetic valve.[3] The test is indicated when there is discordance between the patient's symptomatic status and transthoracic echocardiography and / or transesophageal echocardiography findings. In patients with no or mild symptoms, the preferred modality is ESE with semi-supine bicycle. In patients with moderate or severe symptoms, low-dose DSE (up to 20 µg/kg/min) is recommended.

Stress echocardiography is used to diagnose prosthetic valve stenosis or PPM (when the size of the implanted valve is too small) in patients with a mildly elevated transprosthetic gradient at rest. A marked increase in transprosthetic gradient during SE (by >20 mm Hg in the aortic position and by >10 mm Hg in the mitral position) indicates prosthesis stenosis or PPM, especially at a simultaneous rise in SPAP (>60 mm Hg). Another important indication for SE with dobutamine is the assessment of aortic prosthesis at low cardiac output to differentiate true

TABLE 6 Diagnostic criteria for clinically significant mitral stenosis based on mean diastolic gradient estimated by stress echocardiography [3,17]

Clinical setting	Cutoff value
Native MV stenosis	Absolute MDG value (depending on stress test): >15 mm Hg (ESE) >18 mm Hg (DSE)
Suspicion of PPM or prosthesis dysfunction	ΔMDG (depending on recommendations): >10 mm Hg[3] >12 mm Hg[17]
Functional MS after MV repair	ΔMDG: >7 mm Hg

Abbreviations: Δ, changes from rest to peak stress; MDG, mean diastolic gradient; MS, mitral stenosis; MV, mitral valve; PPM, patient–prosthesis mismatch; others, see FIGURE 1 and TABLE 1

from pseudo-stenosis or mismatch. Indications for DSE include low flow rate (stroke volume index <35 ml/m^2), a relatively low gradient, and small effective orifice area (EOA; <1 cm^2), a small indexed EOA (<0.85 cm^2/m^2), and abnormal Doppler velocity index (<0.35). In patients with pseudo-stenosis or mismatch, a dobutamine-induced increase in the valve EOA ($\geq$0.3 cm^2) with no or minimal elevation in gradients is observed. On the other hand, in true stenosis, a marked increase in gradient is noted with no or minimal increase in EOA (<0.3 cm^2). Differentiation is limited by the lack of an increase in the transprosthetic flow of at least 20%.

Novel quantitative techniques for stress echocardiography in valve heart disease

In recent decades, practical experience in advanced techniques for quantitative assessment of myocardial function has considerably increased, especially regarding the measurement of GLS. Also 3-dimensional (3D) echocardiography has been increasingly widely used for a more accurate measurement of cardiac volumes and other parameters such as true anatomical area of the LVOT. However, these methods are rarely applied in SE protocols. Despite a significant progress in transthoracic imaging quality, 3D echocardiography does not always provide sufficient endocardial border visualization, especially at peak stress of dobutamine or exercise protocols. The clinical significance of stress parameters obtained using 3D echocardiography has not been elucidated. The simplest SE protocol incorporating this modality should include additional full-volume registrations of the LV with a refresh rate of more than 15 volumes/s at rest and peak stress.

The preliminary clinical experience with GLS measurement is limited to patients with asymptomatic AS assessed for early markers of myocardial dysfunction, which are potentially useful to predict prognosis or guide referral for surgery. In healthy individuals, GLS increases during exercise by one-fourth of the baseline value, and the increase is more pronounced in the apical than basal segments. In patients with AS, there is no or mild increase in GLS (up to one-tenth of the baseline value),[19] which correlates with abnormal exercise test result.[20] Basal longitudinal strain during exercise of less than –18% is associated with worse prognosis.[21] Preliminary observations also indicate the usefulness of LV global work index in patients with AS. Global work index is a secondary parameter estimated based on LV pressure–strain loops calculated from speckle tracking echocardiographic data.

In patients with asymptomatic primary MR, the exercise-induced increase in GLS by 2% or higher can be used as a marker of LV contractile reserve, which was associated with better 2-year prognosis.[22]

Stress echocardiography protocol with image acquisition for speckle tracking–based deformation analysis should include 3 apical LV views, optimized for full chamber-wall registration with a frame rate exceeding 40 Hz (optimally, 60–80 Hz) at rest and peak stress.

The use of contrast agents to improve SE imaging of valve disease is limited to the assessment of regional wall motion. In these cases, commercially available transpulmonary contrast agents may be used to improve endocardial border delineation. Contrast agents are not recommended to enhance the Doppler spectrum, especially during exercise. In the lack of sufficient operator experience, this may lead to inaccuracies in border detection.

In conclusion, exercise measurement of GLS in the setting of VHD may be practiced in experienced centers in asymptomatic or mildly symptomatic patients with severe AS or primary MR with preserved LV function at rest. The use of novel techniques in SE assessment of other valve diseases should be investigated in future studies.

Stress echocardiography before noncardiac surgery in patients with valvular heart disease Noninvasive cardiovascular tests constitute a part of preoperative cardiovascular risk assessment. Patients with VHD who are referred for noncardiac surgery are at higher risk of cardiovascular morbidity and mortality. Therefore, echocardiography should be performed before noncardiac surgery in any patient suspected for VHD to confirm the diagnosis and assess disease severity. Patients with symptomatic severe AS, symptomatic hemodynamically significant MS, or MS with an SPAP exceeding 50 mm Hg require valve replacement or percutaneous coronary intervention before elective noncardiac surgery. Noncardiac surgery is safe in asymptomatic patients with asymptomatic severe MR or AR and preserved LV function. The presence of symptoms and LV dysfunction is associated with a mild increase in perioperative risk; however, valvular repair is rarely performed before noncardiac procedures.[6]

The preoperative management of VHD patients who do not fulfill the above criteria is similar to that in the general population. When choosing appropriate diagnostic tests (eg, stress echocardiography) for preoperative evaluation, one should consider individual functional capacity, clinical risk factors, and surgical risk depending on the type of surgery. The clinical risk factors include ischemic heart disease, heart failure, stroke or transient ischemic attack, renal dysfunction, and diabetes mellitus requiring insulin therapy. Surgical risk according to the type of surgery is estimated as low-risk (<1%; eg, eye surgery), intermediate-risk (1%–5%; eg, cholecystectomy), and high-risk (>5%; eg, aortic surgery).[23]

Stress echocardiography is recommended before high-risk surgery in patients with poor (<4 metabolic equivalents) functional capacity and more than 2 clinical risk factors (class I, level of evidence C). It may also be considered in patients with 1 or 2 clinical risk factors (class IIb, level of evidence C). A similar recommendation is made for intermediate-risk surgical patients. Considering the low risk of cardiovascular events in patients referred for low-risk surgery, routine screening with noninvasive stress tests is not recommended in this group (class III, level of evidence C).[23]

Exercise stress echocardiography is the preferred modality. In patients with limited ability to exercise, DSE is usually performed.[23-25] As SE has a high negative predictive value, negative outcome is associated with a very low cardiovascular risk in patients undergoing noncardiac surgery.

SUPPLEMENTARY MATERIAL

The Polish version of the paper is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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