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Assessment of valvular heart diseases using exercise electrocardiography and stress echocardiography: still needed approach?

Ocena choroby zastawkowej serca za pomocą elektrokardiografii wysiłkowej i echokardiografii obciążeniowej: czy te badania są nadal potrzebne?

Sigita Glaveckaite[1,2], Petrikonyte Dovile[3], Latveniene Lidija[2], Laucevicius Aleksandras[1,2]

[1]Department of Cardiovascular Medicine, Vilnius University, Vilnius, Lithuania
[2]Centre of Cardiology and Angiology, Vilnius University, Hospital Santaros Klinikos, Vilnius, Lithuania
[3]Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Abstract

The role of exercise electrocardiography (ECG) and stress echocardiography (SE) in the management of patients with valvular heart diseases (VHD) has been reviewed in this article relying on the recent evidence and the recommendations of the European Society of Cardiology/European Association of Cardio-Thoracic Surgery (ESC/EACTS) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of VHD. Both guidelines emphasise the role of exercise ECG to unmask objectively the occurrence of symptoms in patients, who deny symptoms or have doubtful symptoms; however, the role of SE to assess the haemodynamic component of VHD and unmask subclinical myocardial dysfunction is questioned. The above-mentioned guidelines strongly recommend deciding regarding valve surgery according to the presence of symptoms and the left ventricular (LV) morphological and functional parameters assessed at rest. SE can be useful in selected VHD patients for the determination of prognosis, clarification of symptoms and deciding on the timing of surgery. Despite existing evidence, there is still a need for randomised clinical outcome trials evaluating the role of stress imaging in the daily practise decision-making.

Keywords: exercise electrocardiography, stress echocardiography, dobutamine echocardiography, exercise echocardiography, stress imaging, valvular heart diseases

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Introduction

Most of the patients having severe VHD are asymptomatic. However, not every asymptomatic patient is certainly without symptoms, because many valve diseases progress slowly, thus patients gradually limit their daily activity levels and may not recognise any symptoms [1]. The main purpose of the exercise testing is to unmask objectively the occurrence of symptoms in patients, who deny symptoms or have doubtful symptoms, and is especially useful for risk stratification in aortic stenosis (AS) [2]. According to ACC/AHA guidelines, exercise testing is reasonable in patients with asymptomatic severe VHD in order to confirm the absence of symptoms, assess the haemodynamic response

Address for correspondence: Sigita Glaveckaite, Assocc. Proffesor, Department of Cardiovascular Medicine, Vilnius University, Centre of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Santariskiu str. 2, 08661 Vilnius, Litwa, e-mail: sigita.glaveckaite@santa.lt

to exercise and determine the prognosis (IIaB) [3]. Additionally, exercise testing can be useful for determination of the level of authorised physical activity, including participation in sports [2]. Therefore both the above-mentioned guidelines strongly support the use of exercise testing in the assessment of VHD [2, 3]. Importantly, the predictive values of functional stress tests used for the diagnosis of coronary heart disease (CHD) may not apply in the presence of VHD and these tests are generally not used in the setting of advanced VHD [4].

SE is more sophisticated test than simple exercise ECG, because it evaluates clinical responses during exercise, together with the assessment of the haemodynamic changes that can be missed at rest. The problem with SE is that this modality is not widely accessible, could be technically demanding, and requires specific expertise. The purpose of this review article is to update the evidence and recommendations regarding the role of exercise ECG and SE, especially exercise echocardiography (EE), in the management of VHD patients.

Stress protocols

Before performing stress testing in patients with VHD, a comprehensive clinical evaluation, including a complete resting transthoracic echocardiogram, is obligated in order to rule out the presence of symptom and to identify potential contraindications. Patients with a significant left VHD are referred to surgery as soon as they experience symptoms. The contraindications to perform a SE in VHD are almost the same as for the evaluation of CHD: 1) clear to VHD related symptoms; 2) clear indications for valve surgery (i.e., symptomatic severe AS or mitral stenosis (MS); 3) high blood pressure (BP) (systolic > 200 mm Hg or diastolic > 110 mm Hg); 4) uncontrolled or symptomatic arrhythmias; 5) systemic illness; 6) physical or mental diseases making the adequate performing of an exercise test impossible [5, 6].

While performing the stress test, stress may be induced physically by exercise or pharmacologically, e.g. by dobutamine. Exercise testing is preferred over pharmacological stress for evaluation of patients with VHD, as the exercise capacity is a significant predictor of the outcome [7]. Pharmacological stress with dobutamine has limited utility in the setting of VHD, except in patients having the true low-flow, low-gradient aortic stenosis (LFLG AS). Exercise test can be performed by using either treadmill or supine/semi-supine bicycle. Supine/semi-supine bicycle is a better technique, because of its' possibility to perform imaging during exercise, while with treadmill, imaging may be performed only before and after exercise [1]. Post-exercise echocardiography can also be performed, but the time to acquire images during recovery is short and it is technically demanding. In our clinic, bicycle exercise ECG is performed in supine or semi-supine position and EE is performed using semi-supine bicycle. Semi-supine bicycle with tilting and rotating table, which is the preferred approach in Europe, is more physiological and permits optimal image acquisition during each step of exercise testing, i.e., per-exercise echocardiography. This modality is strongly suggested by the experts of VHD to detect quickly disappearing changes [8]. Treadmill exercise testing using modified Bruce protocol is more commonly used in North America, and is mentioned in ACC/AHA guidelines as the preferred exercise modality [3].

While performing EE for VHD patient, a symptom-limited graded approach is recommended, trying to reach at least 85% of the age-predicted heart rate in the absence of symptoms. Patients should continue taking their usual medication(s), because abnormal exercise testing results while patients are taking suboptimal therapy might be confusing for clinical decision-making. The test should be performed under the supervision of an experienced and trained operator (sonographer or cardiologist) with continuous monitoring of BP, 12-lead ECG, heart rate (HR) and appearance of symptoms (hypotension, ventricular arrhythmia and etc.). Additional echocardiographic valve parameters, the LV and the haemodynamic consequences of valve disease (e.g. pulmonary arterial pressure) are recorded at rest, at each increment of workload (if not possible, only at peak exercise) and during recovery. The workload should be adjusted for each patient, i.e. we begin a test with a workload of 50 W and increase it by 25 W every 3 minutes in a younger patient with AS, whereas an initial workload of 25 W with an increase of workload by 10 or 25 W (depending on patients' functional status) every 2 minutes is more suitable and comfortable for an older patient with LV dysfunction and ischaemic mitral regurgitation (MR) [5, 6]. Exercise testing should be interrupted, when the target HR is reached or if the patient presents with the typical chest pain, dizziness, hypotension (decrease in systolic BP ≥ 20 mm Hg), limiting dyspnoea, significant complex ventricular arrhythmia, or muscular exhaustion. The test is considered positive if the patient encounters ≥ 1 of the following criteria: typical angina, limiting dyspnoea, ≥ 2 mm horizontal or down-sloping ST segment depression, syncope or near syncope, decrease or < 20 mm Hg increase in systolic BP, or complex ventricular arrhythmias [6].

Dobutamine stress echocardiography (DSE) is useful approach is the setting of a true LFLG AS. We use a low-dose dobutamine protocol starting with 5 μg/kg per minute and increase it by 5 μg/kg per minute every 3 minutes up to a maximum dobutamine dose of 20 μg/kg per minute. We recommend discontinuation of β-blockers ≥ 24 hour before the test, because they may attenuate the response of the myocardium to inotropic stimulation. At each dose of dobutamine, we acquire echocardiographic data for measurement of peak aortic velocity, mean trans-aortic gradient (MTAG), aortic valve area (AVA), stroke volume

(SV) and left ventricular ejection fraction (LVEF). Performing DSE is mandatory to measure flow reserve, also termed contractile reserve, which is defined as > 20% increase in SV. Flow reserve is calculated as follows: flow reserve (%) = (SV_{peak} – SV_{rest})/SV_{rest} × 100 where SV = 0.785 × LVOT (left ventricular outflow tract) diameter^2 × LVOT TVI (time velocity integral), respectively, at rest and at peak stress. The endpoints for terminating infusion of dobutamine are: (1) HR > 220 – age; (2) systolic BP < 80 mm Hg or > 220 mm Hg; (3) ischaemia detected using ECG (> 5 mm flat or down-sloping ST depression); (4) complex ventricular arrhythmias or rapid new atrial arrhythmias; (5) breathlessness, angina, dizziness, or syncope; and (6) maximum dose reached (20 µg/kg per minute) [9].

Exercise testing in the setting of VHD has previously been demonstrated to be safe [7, 10], especially when a bicycle in semi-supine or supine position is used because of a lower risk of haemodynamic collapse in this position compared with treadmill test.

Indications

Asymptomatic severe AS [asymptomatic severe high-flow, high-gradient (HFHG) AS

The onset of symptoms in severe HFHG AS (peak aortic velocity ≥ 4 m/s, MTAG ≥ 40 mm Hg, and AVA ≤ 1.0 cm^2 or AVA index ≤ 0.60 cm^2/m^2) is the main indication for aortic valve replacement (AVR) and the main contraindication for exercise testing [11]. However, about one third of patients who deny symptoms, develop symptoms on exertion, and this can be unmasked by performing exercise ECG [12]. Patients with symptoms provoked by exercise testing should be considered symptomatic, even if their clinical history is equivocal. An exercise test is considered normal if the patient remains asymptomatic (no angina, limiting dyspnoea at low workload (i.e., during the first steps of exercise), syncope (or near-syncope) during the test with an adequate increase in systolic BP (> 20 mm Hg) and absence of complex ventricular arrhythmias. A positive exercise test (i.e. hypotension or failure to increase BP > 20 mm Hg, symptoms and ST-segment abnormalities) in patients with severe AS has prognostic significance — predicts the rapid occurrence of symptoms and cardiac death [11, 13]. It is important to know, that during exercise in > 80% of patients with AS, horizontal or down-sloping ST-depression > 2 mm is seen and those ST segment changes are nonspecific for diagnosis of CHD.

EE has an additive prognostic value over clinical findings, echocardiography at rest, and exercise ECG. While performing EE, an increase in MTAG by ≥ 18–20 mm Hg shows the increased risk of cardiac events and reflects more severe AS with a noncompliant, rigid aortic valve [14–16]. Changes in LV function during exercise also carry important prognostic information. Limited contractile reserve (i.e., a decrease or a limited increase in LVEF) is associated with faster development of symptoms and increased risk of cardiovascular death [17, 18]. Standard LVEF measurements are insensitive to detect subclinical LV systolic dysfunction, therefore more sophisticated technique, such as assessment of longitudinal LV function (i.e. analysing global longitudinal strain (GLS) by using 2-dimensional speckle tracking) seems to be a more powerful predictor of the occurrence of symptoms, exercise intolerance, and outcomes in AS [19, 20]. Other haemodynamically important parameters, such as increase of LV filling pressure or systolic pulmonary artery pressure (SPAP) with exercise, might predict the occurrence of symptoms in HFHG AS patients (Figure 1) [21, 22]. We still need prospective clinical trials evaluating the role of exercise-induced echocardiographic changes, such as increase in MTAG, limited LV contractile reserve or exercise-induced pulmonary hypertension as clear indications of AVR in severe asymptomatic HFHG AS.

As reported in several prospective and retrospective studies, the exercise testing is safe in asymptomatic patients with AS [23]. Exercise testing is recommended in physically active patients for unmasking symptoms and for risk stratification of asymptomatic patients with severe aortic stenosis [2].

Clinical practice implications (Table 1):

- current ESC/EACTS and AHA/ACC guidelines agree, that exercise testing is useful in patients with asymptomatic severe AS. Guidelines recommend/consider surgical AVR in asymptomatic severe AS and symptoms on exercise testing clearly related to AS (ESC/EACTS IC; ACC/AHA IIaB) or fall in BP at exercise below baseline (ESC/EACTS IIaC; ACC/AHA IIaB) [2, 3];
- regarding exercise stress echocardiography, ESC/EACTS guidelines says, that it may provide prognostic information in asymptomatic severe AS by assessing the increase in MTAG and change in LV function during exercise [2];
- exercise testing should not be performed in symptomatic patients with AS, when the aortic velocity is 4.0 m per second or greater or mean pressure gradient is 40 mm Hg or higher (ACC/AHA IIIB) [3].

Low-flow, low-gradient aortic stenosis (LFLG AS) with reduced LV ejection fraction

LFLG AS with LV dysfunction refers to the patients with severe AS (AVA < 1.0 cm^2; ≤ 1.0 cm^2 in ACC/AHA guidelines), low MTAG (< 40 mm Hg), impaired LVEF (< 40%; < 50% in ACC/AHA guidelines) and low-flow condition (SV index < 35 mL/m^2) [2, 3, 9]. However, when the MTAG is < 40 mm Hg, a small AVA does not definitely confirm severe AS and two different situations can be observed: 1) true severe AS with reduced LVEF caused by excessive

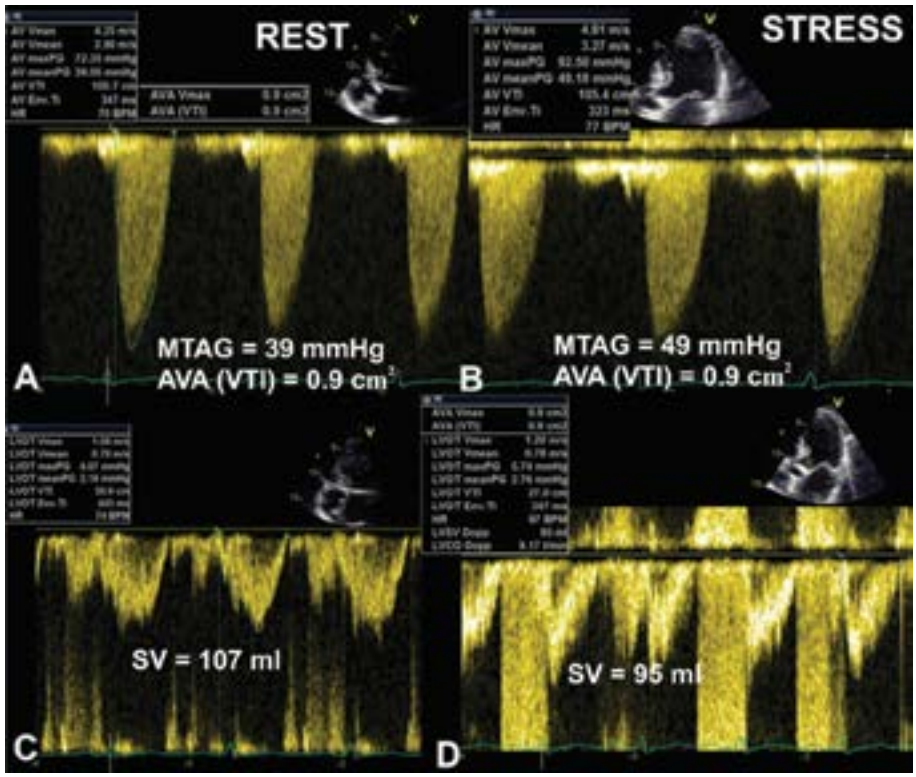

Figure 1A–D. Doppler findings at rest (**left panels**) and at exercise (**right panels**) obtained while performing EE in asymptomatic patient with severe AS. Although increase in MTAG was ~10 mm Hg (nonsignificant) (**A** and **B**), exercise-induced dyspnoea, decrease in LVEF (from 55 to 45%) and SV by 12 mL (**C** and **D**) and increase in trans-tricuspid gradient (from 45 to 79 mm Hg) were observed, all of which represent haemodynamically significant symptomatic AS. The patient underwent surgical AVR-; AV — aortic valve; AVA — aortic valve area; AV Env; Ti — aortic time interval; HR — heart rate; LVCO — left ventricular cardiac output; LVOT — left ventricular outflow tract; LVSV — left ventricular stroke volume; maxPG — maximal pressure gradient; meanPG — mean pressure gradient; MTAG — mean trans-aortic gradient; SV — stroke volume; SVI — stroke volume index; Vmax — maximal velocity; Vmean — mean velocity; VTI — velocity time integral

afterload and concomitant myocardial dysfunction; 2) pseudo-severe AS caused by primary myocardial dysfunction with only moderate AS and reduced aortic leaflet opening due to a low trans-aortic volume flow rate. DSE is helpful in this setting by distinguishing truly severe AS from pseudo-severe AS (Figure 2). The main objective of DSE is to increase the trans-valvular flow rate using the above-mentioned dobutamine protocol (up to 20 μg/kg per minute) to achieve a steady state and avoid tachyarrhythmia or ischaemia [9]. Truly severe AS is defined as an increase in MTAG to > 40 mm Hg, a minimal changes in AVA (< 0.3 cm^2) and/or AVA during dobutamine stress ≤ 1.0–1.2 cm^2, and particularly the presence of flow reserve (i.e., > 20% increase in SV) during low dose DSE [2]. Pseudo-severe AS is characterised by a significant increase in AVA (≥ 0.3 cm^2) and/or an AVA with dobutamine stress > 1.2 cm^2, and an MTAG remaining < 40 mm Hg, explained by greater opening of the aortic valve leaflets with increasing volume flow rate during pharmacological stress. Low-dose DSE by differentiating between true severe and pseudo-severe AS, helps to identify patients, that will significantly benefit from AVR, i.e. patients with true severe AS and impaired LV function. Patients with pseudo-severe AS, in contrary, do not benefit from AVR and may also have a higher perioperative mortality [9]. The latter patients should be treated with aggressive heart failure therapy and they might require AVR if medical therapy fails to improve their condition and/or if the stenosis progresses to the severe stage [24].

In addition to the above-described patient groups, low-dose DSE helps to identify a third group of patients who fail to show an increase in SV > 20% with dobutamine, referred to as "lack of flow or contractile reserve" (Figure 3). This subgroup of patients appears to have a very poor prognosis [3]. Despite high surgical mortality, 5-year mortality is significantly lower after AVR (31%) compared with medical therapy alone (87%) in this patients group [25]. In such patients, AS severity often remains indeterminate after DSE and another imaging modality, such as aortic calcification quantification using multislice computed tomography (CT), might be useful to assess stenosis severity and indications for surgery (Figure 2).

Table 1. Summary of indications for exercise ECG and stress imaging in VHD

VHD	Stress protocol	Parameters to monitor*	Criteria indicating significant lesion	ESC/EACTS and ACC/AHA guidelines	
				Exercise ECG	Stress imaging
Asymptomatic HFHG AS	Exercise ECG or EE	Symptoms, BP response, MTAG *(LVEF, SPAP, GLS, E/Ea**)*	Development of symptoms, fall in BP below baseline, increase in MTAG > 20 mm Hg	**Decision to perform AVR:** ESC/EACTS — IC (symptoms) or IIaC (fall in BP), ACC/AHA — IIaB (symptoms or fall in BP)	EE may provide prognostic information (increase in MTAG and change in LVEF) (ESC/EACTS)
Symptomatic LFLG AS	Low dose DSE only	V_{max}, MTAG, SV, AVA *(LVEF, AVA_{proj})*	SV > 20%, $V_{max} \geq 4.0$ m/s, MTAG ≥ 40 mm Hg, increase in AVA < 0.3 cm^2, AVA ≤ 1.0–1.2 cm^2	No recommendations	**Decision to perform AVR:** ESC/EACTS IC (with flow reserve), IIaC (without flow reserve); ACC/AHA — IIaB (with flow reserve)
Asymptomatic severe AR	Exercise ECG	Symptoms, functional capacity	Development of symptoms, decreased functional capacity	Can be used (ACC/AHA)/should be performed (ESC/EACTS) for objective assessment of exercise capacity and symptom status	No recommendations
Asymptomatic at least moderate MS or symptomatic mild MS	Stress (preferably exercise) echocardiography	Symptoms, functional capacity, MTMG, SPAP	SPAP > 60 mm Hg, MTMG > 15 mm Hg, symptoms, decreased functional capacity	Indicated in asymptomatic patients or patients having equivocal or discordant symptoms with the severity of MS (ESC/EACTS)	**EE recommended:** ACC/AHA IC (may provide additional objective information ESC/EACTS) **Decision to perform PMC:** ACC/AHA IIbC (MTMG > 15 mm Hg)
Asymptomatic severe/symptomatic moderate primary MR	Exercise ECG, EE, cardio-pulmonary exercise testing	Symptoms, functional capacity, SPAP *(EROA, LV contractile reserve)*	Development of symptoms, decreased functional capacity, SPAP ≥ 60 mm Hg	**Should be considered:** ACC/AHA IIaC	**EE should be considered:** ACC/AHA IIaB **Decision to perform MV repair:** no recommendations in both guidelines
Severe/moderate secondary MR	DSE, EE, SPECT, PET, CMR	Symptoms, inotropic reserve (viability), *(SPAP, EROA)*	Viability, increase in EROA ≥ 13 mm^2	No recommendations	ESC/EACTS guidelines recommend to consider EE in moderate MR **For viability assessment:** ECC/AHA IC, ESC/EACTS may be useful **Decision to perform MV correction during CABG:** severe MR (ESC/EACTS IC, ACC/AHA IIaC), moderate MR (ESC/EACTS likely to be considered in the presence of viability and low comorbidity, ACC/AHA IIbB-R)

*In italics there are indicated parameters not mentioned in the both guidelines and more clinical trial data are needed for use them routinely in clinical practice; **measured before E and A wave fusion; AVA — aortic valve area; BP — blood pressure; DSE — dobutamine stress echocardiography; E — diastolic mitral inflow velocity; Ea — early diastolic annulus velocity; ECG — electrocardiogram; EROA — effective regurgitant orifice area; EE — exercise echocardiography; GLS — global longitudinal strain; LV — left ventricular; LVEF — left ventricular ejection fraction; MTAG — mean trans-aortic gradient; MTMG — mean trans-mitral gradient; MVR — mitral valve replacement; PHT — pulmonary hypertension; PMC — percutaneous mitral commissurotomy; RVol — regurgitant volume; SPAP — systolic pulmonary artery pressure; SV — stroke volume; TAPSE — tricuspid annular plane systolic excursion

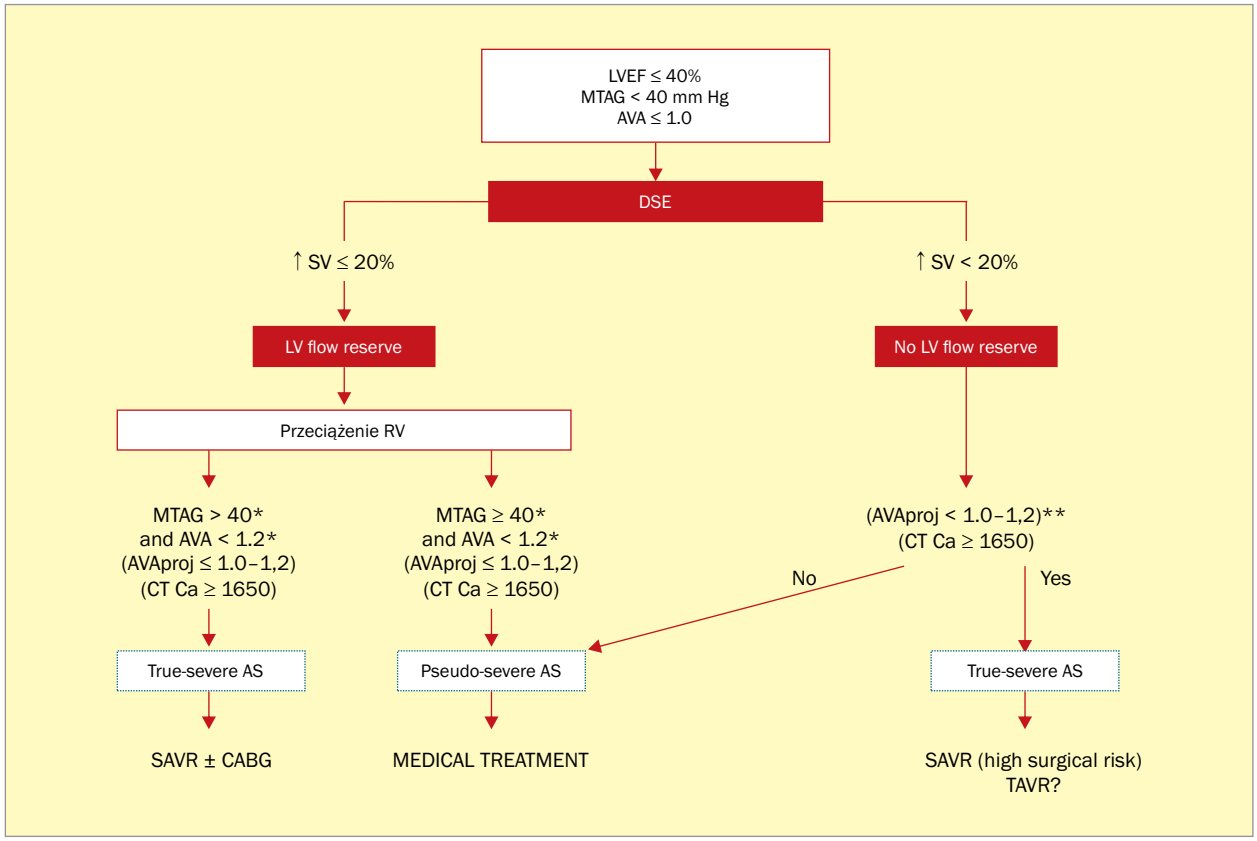

Figure 2. Clinical decision-making algorithm in severe LFLG AS with reduced LVEF. Parameters between parentheses represent new indices requiring further validation; AVA — aortic valve area;, AVA_{proj}. — projected AVA at normal flow rate; MTAG — mean trans-aortic gradient; Ca — calcium score (Agatston unit) (see text for more profound explanation); SV — stroke volume; SAVR — surgical aortic valve replacement, TAVR — trans-catheter aortic valve replacement; *cut-off points could be slightly different depending on a study; **see text for explanation. Adapted with permission from [28]

Instead of one suggested cut-off value for calcium score in Figure 2, ESC/EACTS guidelines recommend to use more precise assessment of likelihood of severe AS: severe AS very likely if Agatston calcium score is ≥ 3000 in men and ≥ 1600 in women; severe AS is likely if Agatston calcium score is ≥ 2000 in men and ≥ 1200 in women and severe AS is likely if Agatston calcium score is < 1600 in men and < 800 in women [2].

Some patients may have an equivocal response to DSE (i.e., a peak trans-aortic gradient of 30 mm Hg and an AVA of 0.8 cm^2) due to variable increases in flow. In those cases, interpretation of the DSE results is difficult without considering the relative changes in flow. To solve the above-mentioned problem, the researchers of the TOPAS (truly or pseudo-severe aortic stenosis) trial proposed to calculate the projected AVA that would have occurred at a standardised flow rate of 250 mL/s (AVA_{proj}). Projected AVA has been shown to be more closely related to actual AS severity, myocardial blood flow impairment, flow reserve, and survival than the traditional DSE parameters [26, 27]. The AVA_{proj} is calculated as follows:

$AVA_{proj} = (AVA_{peak} - AVA_{rest})/(Q_{peak} - Q_{rest}) \times (250 - Q_{rest}) + AVA_{rest}$, where AVA_{rest} and Q_{rest}, and AVA_{peak} and Q_{peak} are AVA calculated by continuity equation and Q by dividing SV (mL) by LV ejection time (s) at rest and at peak DSE, respectively [11]. An $AVA_{proj} \leq 1.0$ cm^2 is considered to be severe, but the full role of the AVA_{proj} still needs evaluation by randomised clinical studies in the future.

Clinical practice implications (Table 1):

- in symptomatic severe LFLG (< 40 mm Hg) AS and reduced LVEF, AVR is recommended/should be considered after the demonstration of truly severe AS with evidence of flow (contractile) reserve using low dose DSE (ESC/EACTS IC; ACC/AHA IIaB) [2, 3];
- in symptomatic LFLG AS and reduced LVEF without flow (contractile) reserve during low dose DSE, AVR should be considered, particularly when CT calcium scoring confirms severe AS (ESC/EACTS IIaC) [2].

Severe asymptomatic aortic regurgitation (AR)

Symptomatic patients with severe AR have a markedly increased mortality rate [29], and they benefit from AVR

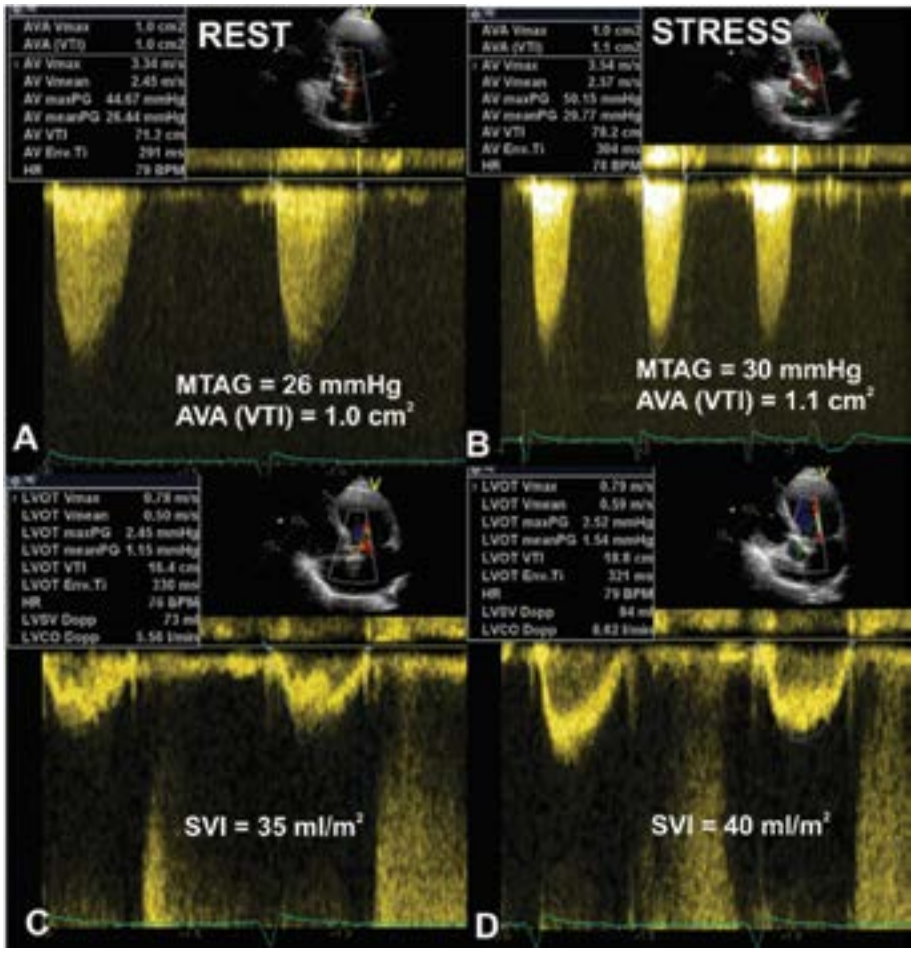

Figure 3A–D. Doppler findings obtained while performing DSE in symptomatic male patient with LFLG AS. At rest (**left panels**) there is low-flow situation with SVI of about 35 mL/m^2 (**C**) and low gradient with an MTAG of 26 mm Hg (**A**). At peak low dose DSE (**left panels**) the absence of LV flow reserve (15% increase in SV) (**D**) and indeterminate severity of AS (MTAG = 30 mm Hg, AVA – 1.1 cm^2) (**B**) was observed. After the assessment of calcium score by CT (1000 Agatston units) it was decided to treat patient conservatively. Abbreviations are the same as in Figure 1

[2, 3]. According to ACC/AHA guidelines, exercise testing can be used to prove the presence of symptoms and to assess functional capacity in patients with AR [3]. The use of EE on routine basis in patients with severe asymptomatic AR is not recommended. If the decision to perform EE is taken, the main goal of EE should be to unmask the symptoms and subclinical LV dysfunction using standard LVEF measurement or LV longitudinal function assessment [9]. In our laboratory, we perform EE in selected AR patients, mostly when there are discrepancies between resting echocardiographic data and symptoms.

Clinical practice implications — see Table 1.

— As the additional value of exercise testing or EE is still not clear, both guidelines highlight, that the key examination procedure in AR still remains rest echocardiography [2, 3]. ESC/EACTS guidelines says, that in patients not reaching the thresholds for surgery, close follow-up is needed and exercise testing should be performed to identify borderline symptomatic patients [2].

Mitral stenosis (MS)

Echocardiography is the main method for the assessment of the MS severity and consequences. Discrepancies between symptom status and severity of MS are frequent. Therefore, an exercise test, and particularly EE should be considered for objective assessment of functional capacity and unmasking symptoms in patients, who deny symptoms or have doubtful symptoms. Semi-supine EE is now preferred technique, as it allows assessing the trans-mitral gradient and SPAP at each step of increasing workload. Haemodynamic changes at effort are highly variable for a given degree of stenosis. Although DSE has been shown to have prognostic value in patients with MS [30], but in

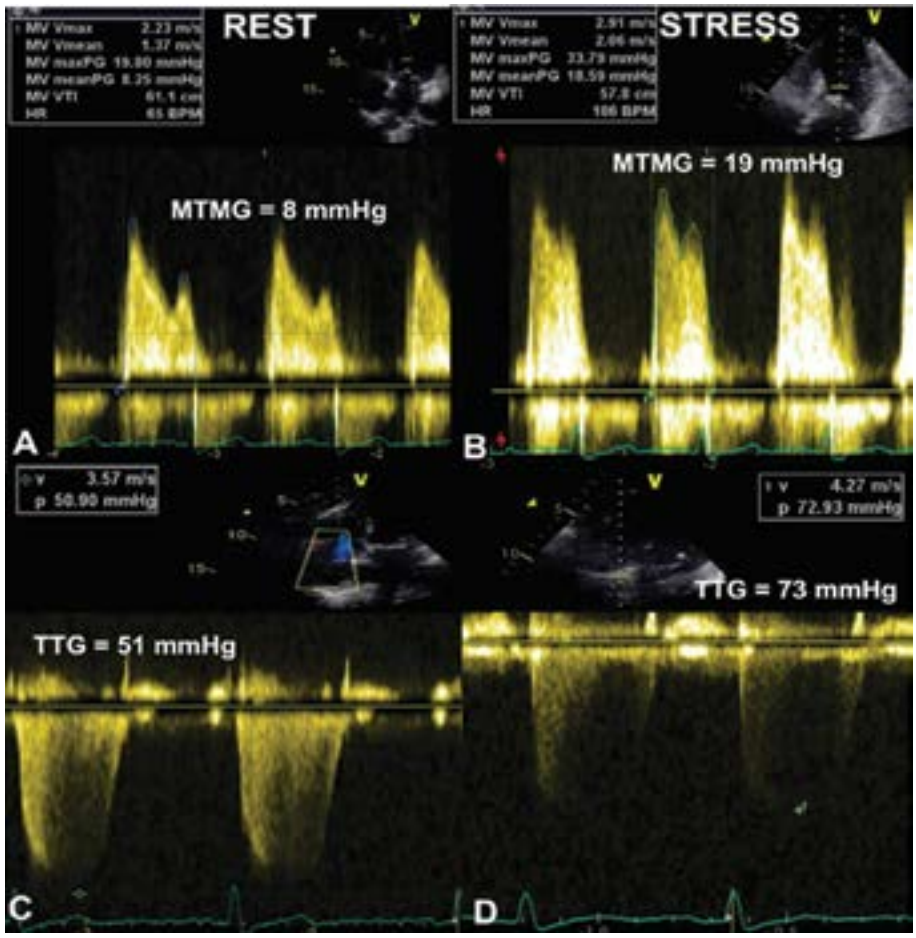

Figure 4A–D. Doppler findings obtained by performing EE in an asymptomatic patient with moderate rheumatic MS (MVA 1.3 cm^2) at rest (**left panels**). The increase in MTMG during exercise was significant (MTMG increased up to 19 mm Hg) (**A** and **B**) with a significant increase in TTG up to 73 mm Hg (**C** and **D**) and exercise-induced dyspnoea. The patient underwent PMC; HR — heart rate; maxPG — maximal pressure gradient; meanPG — mean pressure gradient; MTMG — mean trans-mitral gradient; MV — mitral valve; MVA — mitral valve area; TTG — trans--tricuspid gradient; Vmax — maximal velocity; Vmean — mean velocity; VTI — velocity time integral

general is a less physiological approach than EE and in our centre is not used for this purpose.

By performing EE, it is possible to assess patient's functional capacity, exercise-induced symptoms, mean trans-mitral gradient (MTMG) and SPAP during exercise (Figure 4). The dynamic assessment, according to the recent study, is essential to define the real severity of MS [31]. In the earlier ACC/AHA guidelines, an increase in MTMG to ≥ 15 mm Hg or SPAP to ≥ 60 mm Hg was considered a class IIb indication for percutaneous mitral balloon commissurotomy (PMC) [32]. However, cut-off values for interpreting the results of the test in MS remain arbitrary, based on expert consensus agreement and not supported by outcome data from large randomised clinical trials [11, 33, 34]. Therefore, further clinical research evaluating the impact of exercise Doppler data on outcome is still needed.

Clinical practice implications (Table 1):

- EE is recommended in ACC/AHA guidelines in patients, who present a discrepancy between resting Doppler echocardiographic findings and clinical symptoms or signs (ACC/AHA IC) [3]. According to ESC/EACTS guidelines, stress testing is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of MS. EE may provide additional objective information by assessing changes in MTMG and SPAP [2]. Truly asymptomatic patients, as assessed using stress testing, are usually not candidates for the PMC, except in cases, where there is increased risk of systemic embolism or haemodynamic decompensation [2];
- PMC may be considered in symptomatic patients with mitral valve area > 1.5 cm^2 if there is evidence of haemodynamically significant MS based on increase in MTMG to > 15 mm Hg during exercise (ACC/AHA IIbC) [3].

Mitral regurgitation (MR)

The importance of SE for evaluating patients with regurgitant VHD is becoming more significant and its clinical value has been extensively demonstrated in patients with MR[8]. Assessing the patients with chronic MR, there is a need to divide this VHD according to the mechanism of MR into two groups: primary and secondary MR [3].

Degenerative (primary) MR

Primary MR covers all aetiologies, in which intrinsic lesions affect one or several components of the mitral valve apparatus [2]. It is a primary disease of the valve, but not left ventricle. In general, surgery is recommended in patients who have symptoms due to chronic primary MR, but no contraindications to surgery.

The main method to assess the severity of asymptomatic primary MR is resting echocardiography. In general, the effective regurgitant orifice area (EROA) ≥ 40 mm^2 and regurgitant volume (RVol) ≥ 60 mL defines severe primary MR. However, primary MR is a dynamic process and exercise testing might identify patients with unrecognised symptoms or clarify symptoms that are out of proportion with resting MR severity [9]. For more than one third of the patients with primary MR, moderate MR may develop during exercise into severe MR [8]. In such cases, EE is used to evaluate exercise capacity, subclinical LV dysfunction, unrecognised symptoms, and to determine patients that may benefit from early surgery [1]. Patients with worsening of MR severity, a marked increase in SPAP (> 60 mm Hg), decreased exercise capacity and the occurrence of symptoms during EE are those patients, that likely will benefit from early surgery [11]. In chronic asymptomatic moderate to severe primary MR, a marked increase in MR severity (increase of EROA ≥ 10 mm^2 and RVol ≥ 15 mL) with exercise well correlated with exercise-induced pulmonary hypertension [34]. The main detrimental consequence of dynamic MR is the occurrence of pulmonary hypertension during exercise, which is associated with a markedly reduced two-year symptom-free survival and is a more accurate predictor of progression to symptoms compared with resting SPAP [9]. EE is useful to unmask subclinical LV dysfunction associated with MR, especially in cases with borderline LVEF (60–65%) or LV end-systolic diameter (near 40 mm or 22 mm/m^2) [35]. Absence of contractile reserve (i.e. the inability to increase LVEF by > 4% with exercise) has been associated with LV dysfunction after mitral valve surgery, and progressive decrease in LV function without surgery [36]. Moreover, the absence of LV contractile reserve measured using LV GLS (increase < 2% with exercise) has been associated with the higher risk of cardiac complications [37].

For the management of patients with chronic primary MR, three different exercise tests can be used — EE, exercise ECG and cardiopulmonary exercise testing. EE in a semi-supine position should be used to evaluate chronic primary MR. Importantly, the assessment of haemodynamic component (especially EROA) of primary MR during exercise particularly requires experience and the learning curve of the EE performing physician should be taken into account. DSE is not useful because of the haemodynamic effects leading to decreases of preload and afterload. Additional information about a cardiac or non-cardiac limitation can be obtained while performing cardiopulmonary exercise test.

According to ACC/AHA guidelines [3], EE should be considered in symptomatic patients with chronic primary MR in case there is a disagreement between the symptoms and the severity of MR at rest (IIaB). In the latter cases, the increase in severity of MR and/or SPAP helps to explain exercise-induced symptoms and indicates the early mitral surgery (Figure 5). Additionally, exercise testing can be useful for unmasking the symptom status and for evaluation of exercise tolerance (IIaC) [3]. ESC/EACTS guidelines [2] express similar opinion by stating, that EE is useful to quantify changes in MR, SPAP and LV function during exercise, especially in patients with symptoms and uncertainty about the severity of MR based on measurements at rest. Additionally, determination of functional capacity while performing cardiopulmonary exercise testing, may give useful information regarding symptoms status [38]. Moreover, new parameters, such as exercise-induced changes in LV volumes, LVEF and GLS may predict LV dysfunction after valve surgery [39]. The use of GLS is still limited by inconsistent algorithms used by different commercially available echocardiographic systems [2].

Clinical practice implications (Table 1):

- EE should be considered in symptomatic patients with chronic primary MR in case there is a discrepancy between symptoms and the severity of MR at rest (ACC/AHA IIaB) [3];
- However, haemodynamic criteria provided by EE that may indicate surgery have not been sufficiently well defined to be included in the current recommendations [2, 3].

Ischaemic (secondary) MR

Secondary MR is not the primary disease of the valve as primary MR, but it is caused by the geometrical distortion of the subvalvular apparatus, secondary due to LV enlargement and remodelling due to idiopathic dilative cardiomyopathy or CHD [2].

The indications for isolated mitral valve surgery in symptomatic patients with severe secondary MR (EROA ≥ 20 mm^2 and RVol ≥ 30 mL) and severe systolic LV dysfunction with no option for revascularisation are questionable. Repair may be considered in selected patients with low comorbidity, in order to avoid or postpone heart transplantation. In the other patients, the optimal contemporary heart failure treatment (including heart resynchronisation

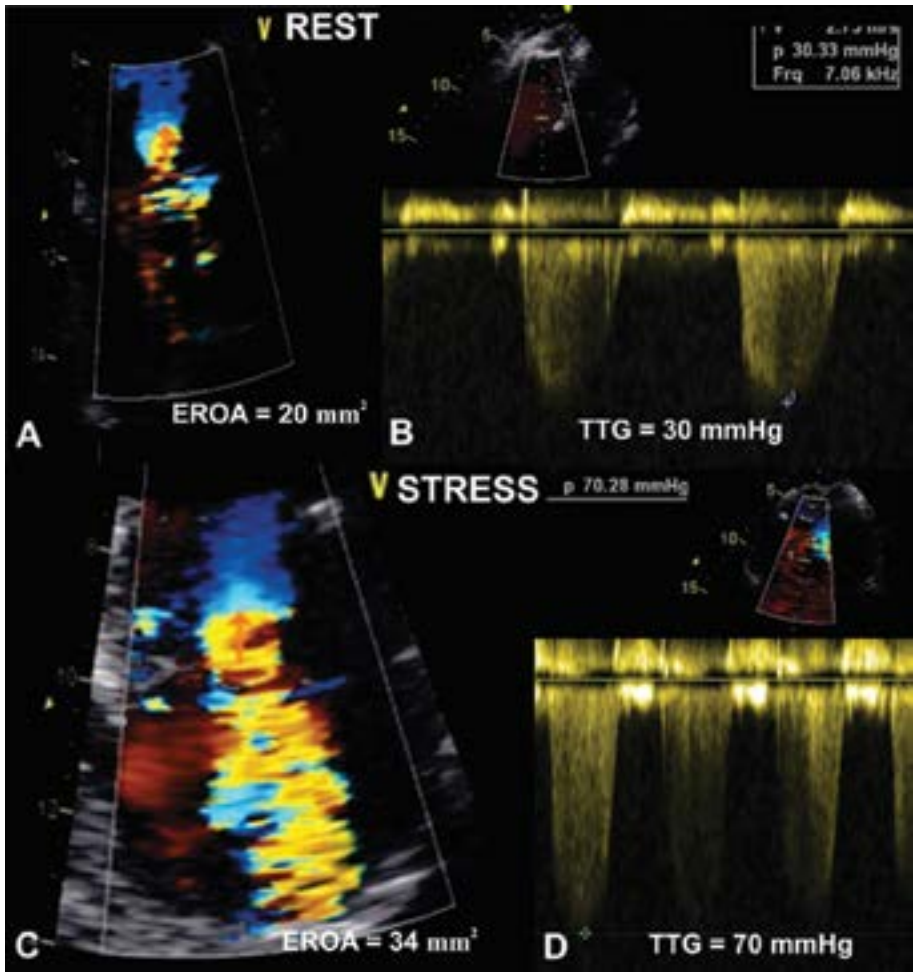

Figure 5A–D. Doppler findings in a symptomatic patient with moderate primary MR and borderline SPAP at rest (**upper panels**). During EE, a marked increase in MR associated with pulmonary hypertension (**lower panels**) and exercise-induced symptoms was observed. The patient underwent MV repair; EROA — effective regurgitant orifice area; TTG — trans-tricuspid gradient

therapy) is currently the best option [2]. There is a continuing debate regarding the need for surgical correction of moderate ischaemic MR in patients undergoing coronary artery bypass grafting (CABG). Mitral valve surgery is more likely to be considered in patients with low LVEF, if substantial amount of viable myocardium is present and if comorbidity is low.

As ischaemic MR is a highly dynamic condition and can manifest clinically as intermittent pulmonary oedema or dyspnoea. Therefore, according to ESC/EACTS guidelines, EE may provide prognostic information of dynamic characteristics of secondary MR [2]. An increase of EROA $\geq$ 13 mm^2 during exercise is associated with a significant increase in the relative risk of death and hospitalisation due to heart failure [40]. The prognostic value of dynamic MR has not been validated in non-ischaemic cardiomyopathy. EE remains the best modality to evaluate the dynamic component of secondary MR, because DSE leads to confounding effects caused by reduction in loading conditions [9]. EE can provide useful information in patients with LV dysfunction and: 1) exertional dyspnoea, which is out of proportion to the MR severity or LV dysfunction at rest; 2) acute pulmonary oedema without a clear cause; 3) moderate MR before surgical revascularisation [41]. EE is useful for risk stratification of mortality and heart failure [42]. Cut-off values of significant exercise-induced increase in MR should undergo validation in a large prospective randomised trial. Importantly, the assessment of haemodynamic component of secondary MR during EE particularly requires experience, and the learning curve of the EE performing physician should be taken into account. Exercise-induced dyspnoea, marked increase in MR severity and exercise-induced pulmonary hypertension favour combined surgery — CABG together with surgical MV correction (preferably repair). The prognostic value of exercise test for predicting the results of surgical treatment still requires evaluation.

Additionally, in patients with ischaemic MR, DSE may be used to assess the viable myocardium and predict the

response to revascularisation [1]. ACC/AHA guidelines [3] recommend to perform non-invasive imaging (nuclear modalities, cardiovascular magnetic resonance (CMR), or SE), cardiac CT angiography, or cardiac catheterisation, including coronary arteriography, for establishing the aetiology of chronic secondary MR and/or to assess viable myocardium (IC). ESC/EACTS guidelines says, that the myocardial viability testing may be useful in patients with ischaemic secondary MR, who are candidates for revascularisation [2]. There is no clear place for quantitative assessment of secondary MR using EE in the ACC/AHA guidelines.

Clinical practice implications (Table 1):

- in patients with moderate to severe secondary MR and LV dysfunction, CHD and myocardial viability should be assessed (ACC/AHA IC) [3];
- severe secondary MR according to ESC/EACTS (IC, in case LVEF >30%) and ACC/AHA (IIaC) guidelines, should be addressed during CABG [2, 3];
- management of patients having moderate MR is controversial. ESC/EACTS guidelines recommend considering EE in patients capable of exercising to assess exercise-induced dyspnoea, increase in MR severity and SPAP during exercise [2]. According to ESC/EACTS guidelines, combined surgery is more likely to be considered if myocardial viability is present and if comorbidity is low [2]. According to recent ACC/AHA guidelines update in patients with chronic, moderate, ischaemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain (IIbB-R) [42].

Conclusions

Although the surgical treatment of VHD continue to be based on symptoms and resting LV morphology and function, the growing evidence have confirmed the additive prognostic value of the assessment of exercise-induced symptoms and exercise capacity, and evaluation of the haemodynamic components of VHD using SE, particularly EE. SE can be useful for risk stratification and timing of surgery in VHD. The incremental prognostic value of EE has been shown in the setting of AS and MR. DSE has its strong in patients with LFLG AS for assessing aortic stenosis severity and for operative risk stratification. Further randomised clinical trials are required to confirm the impact of clinical decisions making based on stress imaging data on outcome in VHD patients. More data are still needed regarding the value of new parameters obtained by 3D EE, tissue Doppler EE and exercise strain imaging. Despite the lacking evidence, EE is useful modality in selected VHD patients and experienced hands, and its broader use is warranted.

Streszczenie

Autorzy analizują znaczenie elektrokardiografii wysiłkowej i elektrokardiografii obciążeniowej u osób z chorobą zastawkową serca (*valvular heart diseases*, VHD) na podstawie najnowszych danych naukowych oraz zaleceń zawartych w wytycznych *European Society of Cardiology/European Association of Cardio-Thoracic Surgery* (ESC/EACTS) i *American College of Cardiology/American Heart Association* (ACC/AHA) dotyczących diagnozowania i leczenia VHD. W obu wytycznych podkreśla się rolę elektrografii wysiłkowej w ujawnianiu w obiektywnym badaniu występowania objawów u chorych, którzy żadnych objawów nie zgłaszają lub mają objawy budzące wątpliwości, jednak kwestionuje się znaczenie echokardiografii obciążeniowej w ocenie hemodynamicznej komponenty VHD i wykrywaniu bezobjawowej dysfunkcji miokardium. Powyższe wytyczne zdecydowanie zalecają, aby podejmować decyzję dotyczące chirurgicznego leczenia choroby zastawkowej na podstawie występowania objawów oraz parametrów morfologicznych i funkcjonalnych lewej komory ocenianych w spoczynku. Echokardiografia obciążeniowa może być przydatna u wybranych chorych z VHD do ustalenia rokowania, wyjaśniania przyczyny objawów i podejmowania decyzji dotyczących terminu zabiegu chirurgicznego. Mimo że istnieją dane naukowe na temat obrazowania obciążeniowego, potrzebne są randomizowane badania kliniczne oceniające ich znaczenie w podejmowaniu decyzji w codziennej praktyce klinicznej.

Słowa kluczowe; elektrokardiografia wysiłkowa, elektrokardiografia obciążeniowa, próba dobutaminowa, obrazowanie obciążeniowe, choroba zastawkowa serca

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