REVIEW ARTICLE

The role of stress echocardiography in cardiovascular disorders

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ABSTRACT
Stress echocardiography is a safe, low-cost, widely available, radiation-free versatile imaging modality that is becoming increasingly recognized as a valuable tool in the assessment of coronary heart disease. In recent years, there has also been an increasing use of stress echocardiography in the assessment of nonischemic cardiac disease given its unique ability for simultaneous assessment of both functional performance and exercise-related noninvasive hemodynamic changes, which can help guide treatment and inform about the prognosis of the patients. Today, in the echocardiography laboratory, we can not only detect wall motion abnormalities resulting from coronary artery stenosis, but also detect alterations to the coronary microvessels, left ventricular systolic and diastolic parameters, heart valves, pulmonary circulation, alveolar-capillary barrier, and right ventricle. The role of stress echo has been well established in several pathologies, such as aortic stenosis and hypertrophic cardiomyopathy; however, other indications, namely the results of diastolic stress testing and pulmonary hypertension, need additional data and research. This paper presents the current evidence for the role of stress testing in mitral regurgitation, aortic stenosis, hypertrophic cardiomyopathy, heart failure with preserved ejection fraction, and pulmonary hypertension.

Introduction Stress echocardiography (SE) has an established essential role in evidence-based guidelines as a diagnostic tool in daily cardiology practice. It is not only a valid and useful method for the diagnostic and prognostic stratification of patients with coronary artery disease (CAD)[1] but it also shows an emerging value in the assessment of cardiac function in other cardiovascular conditions.[2-4] Unfortunately, apart from CAD, the application is still somewhat marginal in the routine cardiology practice. Stress echocardiography provides the opportunity to identify the function of the microvasculature and heart valves, detect possible pulmonary hypertension (PH), lung congestion, and also evaluate the systolic and diastolic reaction and mechanics of the left or right ventricle (LV/RV) in response to load. For this reason, SE permits recognition of many causes of cardiac symptoms in addition to ischemic heart disease, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, PH, heart failure with preserved ejection fraction (HFpEF), and valvular heart disease.[5] From a simple method such as wall motion analysis by 2-dimensional echocardiography, M-Mode, pulsatile and continuous color, and tissue Doppler, we have now moved on to the next-generation laboratory, employing a variety of up-to-date technologies such us deformation imaging, lung ultrasound, and 3-dimensional echocardiography.[4] The parameters measured during the stress test combined with exercise capacity, blood pressure, and heart response will provide a comprehensive, low-cost, noninvasive assessment of cardiovascular pathologies.

Stress echocardiography for noncoronary indications focuses on the following: 1) assessment of the true functional class of the patient when a discrepancy is observed between the reported lack of symptoms and the objective assessment of pathology as severe; 2) establishing a correlation between exertional symptoms and

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the hemodynamic changes derived from echocardiography and signs unmasked by stress test; 3) assessment of LV contractile reserve in patients who are considered surgical candidates.[6]

The purpose of this paper is to review the present status of SE in conditions other than CAD, focusing on mitral regurgitation (MR), aortic stenosis (AS), HCM, HFpEF, and PH.

Mitral regurgitation MR results from several pathological conditions. Primary MR is defined as regurgitation resulting from organic valvular pathology such as prolapse, rheumatic lesions, chordal rupture, collagen vascular disease, or damage from endocarditis. Secondary MR results from ischemic or myopathic alternations (ischemic, dilated, or HCM) to the LV leading to incomplete closure of the mitral leaflets.[7] Risk stratification using SE, particularly in patients without symptoms, becomes important not only in the exact diagnosis and characterization of the etiology of MR but also in guiding therapy.

Severe primary mitral regurgitation without symptoms In patients with primary MR, SE may provoke symptoms during the exercise. During daily activities, the patients might limit their physical activity and therefore not develop symptoms. Diagnosis and follow-up in these patients are very important because conservatively managed asymptomatic severe MR and an effective regurgitant orifice area of more than 40 mm^2 have an excess risk of death and cardiac events.[8]

To assess MR changes during SE, a semi-supine bicycle is the best choice. Since MR is severe at rest, there is no need to assess MR severity during stress. For this reason, imaging should first focus on acquiring LV views for the assessment of regional and global LV systolic function and to calculate global longitudinal strain. Continuous-wave Doppler measurement of tricuspid regurgitation jet for estimation of pulmonary artery systolic pressure (PASP) is essential. The development of symptoms at low workload and severe MR with ejection fraction (EF) of more than 30% is class I, level of confidence B, indication for surgery.[9] Besides the development of symptoms, there are several other indices that indicate poor prognosis in patients with severe MR. These include exercise-induced increase in PASP of 60 mm Hg or more,[10,11] absence of LV contractile reserve,[1,12] and limited RV contractile recruitment (defined as peak-exertion tricuspid annular plane systolic excursion <19 mm).[13] Ejection fraction is traditionally used as the measure to assess contractile reserve, with a rise in left ventricular ejection fraction (LVEF) on exertion of less than 4% indicating the absence of contractile reserve. An absolute increase in global longitudinal strain of less than 2% indicates lack of contractile reserve.[1]

Nonsevere mitral regurgitation with symptoms In patients with complaints in whom there is suspicion of severe MR but it is not evident on resting echocardiogram, SE demonstrating progression of MR helps to correlate the pathology with the patient's symptoms. However, as stress tests may worsen any MR, concomitant increase in PASP supports MR as the cause of symptoms. The dataset in symptomatic patients should include color flow Doppler (to allow offline quantification of severity by proximal isovelocity surface area method and vena contracta of the regurgitant jet), MR continuous wave Doppler to quantify the severity by the proximal isovelocity surface area method, tricuspid regurgitation continuous wave Doppler to estimate the PASP, and LV views to assess global and regional systolic function (FIGURE 1).[1] The therapeutic implications of exercise-induced severe MR are not clearly defined. The European Society of Cardiology (ESC) guidelines do not specifically address this issue even though they recommend SE for evaluation of exercise-induced changes in MR severity.[9]

Secondary mitral regurgitation In secondary MR, lower thresholds have been proposed because, compared with the primary MR, the adverse outcomes are associated with a smaller calculated effective regurgitant orifice area.[9]

In patients with secondary MR, exercise SE is recommended in the following settings: 1) presence of exertional symptoms which cannot be explained with LV systolic dysfunction or MR severity at rest; 2) recurrent and unexplained acute pulmonary edema; 3) nonsevere MR at rest in patients scheduled for coronary artery bypass surgery (CABG) to identify those who may benefit from combined revascularization and mitral valve repair.

The management of chronic secondary MR is less clear. As secondary MR is just one part of the disease in LV dysfunction, restoration of mitral valve competence is not by itself curative. Therefore, the indication for surgery in secondary MR and the choice of intervention (repair versus replacement) remain debatable. Surgery is indicated in patients with severe secondary MR at rest and LVEF of more than 30% undergoing CABG (ESC/European Association for Cardio-Thoracic Surgery guidelines class I, level of evidence C).[9] At the same time, the management of moderate MR, or dynamic MR at the time of CABG, and moderate or severe MR in patients not requiring revascularization remains highly controversial. Current European guidelines note that echocardiographic quantification of MR during exercise may provide prognostic information of dynamic characteristics of MR; however, there is no suggestion about the impact of the stress test on treatment.[9]

Aortic stenosis According to the latest ESC guidelines, both the diagnostic workup and

the therapeutic approach to AS is based on echocardiographic assessment.[9] Surgical repair or transcatheter aortic valve implantation is recommended in patients with severe AS with otherwise not explained symptoms and/or LV systolic dysfunction (class I).[9] The criteria for severe AS are: peak transvalvular velocity of 4 m/s or higher or the mean transvalvular pressure gradient of 40 mm Hg or higher without a high flow state present and aortic valve area (AVA) of less than 1 cm^2.[14] However, these criteria are fulfilled only in the case of the high-gradient AS. In several other clinical settings, when the valve morphology is suspicious of AS, the guidelines recommend SE to assess the severity of AS and to guide the therapeutic decision through risk stratification. Low-dose dobutamine SE is the chosen method if the assessment of the contractile or flow reserve is the aim. In the case of asymptomatic patients with severe AS, exercise SE is recommended.

The recommended types of SE along with the minimum acquired dataset and most important findings depending on indication are listed in TABLE 1.

Asymptomatic severe aortic stenosis In patients with severe AS in whom symptoms have not developed yet, exercise SE is recommended to unmask symptoms or pathologic blood pressure responses.[1] It also has remarkable prognostic value: an elevation of 18 to 20 mm Hg or higher in the mean aortic pressure gradient, or a decrease/no change in LVEF and induced PH (≥60 mm Hg) are markers of poor prognosis.[15-18]

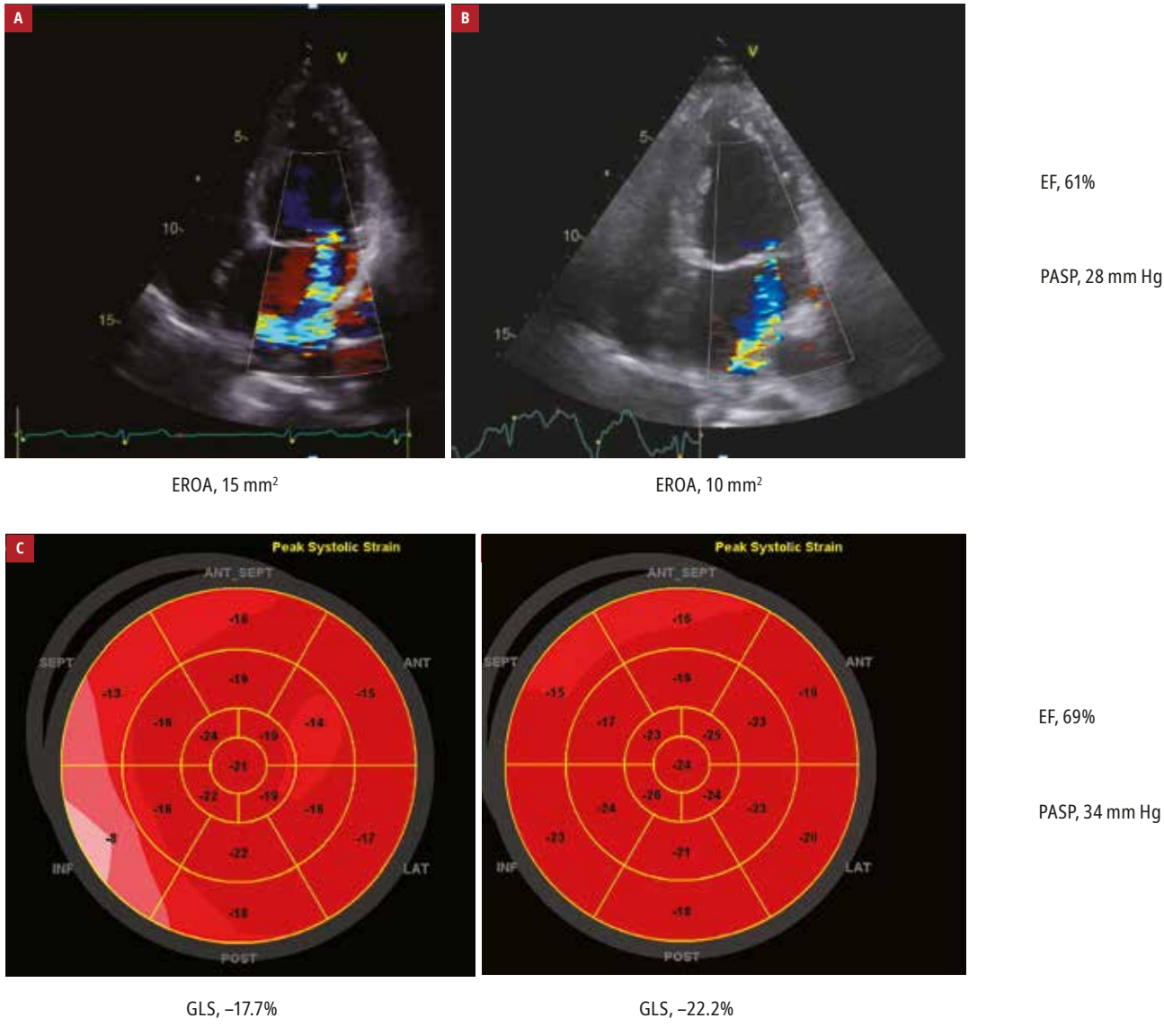

FIGURE 1 Stress echocardiography of a 56-year-old woman with mitral valve prolapse and uncertain symptoms. The mitral regurgitation severity did not increase during the exercise and preserved contractile reserve was observed (elevation in the left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS]). The estimated pulmonary artery systolic pressure (PASP) did not increase significantly. During a 4-year follow-up, cardiac disease (along with mitral regurgitation and LVEF) did not progress.

Abbreviations: EF, ejection fraction; EROA, effective regurgitant orifice area

TABLE 1 The recommended types of stress echocardiography with the minimum acquired dataset and most important findings depending on indication. Adapted from Lancellotti et al.[1]

Indication	Type of SE	Minimum acquired dataset					Results determining AVR	Additional findings with mainly prognostic importance
		LV views	LVOT PW Doppler	AV CW Doppler	MR color Doppler	TR CW Doppler		
Severe AS without symptoms	Exercise	✓	✓	✓	✓	✓	Symptoms; fall of blood pressure	Pulmonary hypertension; dynamic MR; no contractile reserve; inducible ischemia; GLS
Nonsevere AS with symptoms	Exercise	✓	✓	✓	✓		Gradient increase; no / min AVA increase; LVEF drop; no increase	Pulmonary hypertension; dynamic MR; no contractile reserve; inducible ischemia; GLS
	Low-dose dobutamine	✓	✓	✓				
Low-flow, low-gradient AS	Low-dose dobutamine	✓	✓	✓			Symptoms; fall of blood pressure below baseline; gradient increase; no / min AVA increase; flow or contractile reserve	No flow; contractile reserve; GLS
	Exercise- low workload	✓	✓	✓				
Aortic valve prosthesis stenosis or PPM	Exercise	✓	✓	✓	✓	✓	Symptoms; gradient increase	PASP elevation (>60 mm Hg)
	Low-dose dobutamine	✓	✓	✓				

Abbreviations: AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; AVR, aortic valve repair; CW, continuous-wave; GLS, global longitudinal strain; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; PPM, patient-prosthesis mismatch; PW, pulsed-wave; TR, tricuspid regurgitation

Classic low-flow, low-gradient aortic stenosis

In patients with low-flow, low-gradient aortic stenosis (LFLG AS) with reduced systolic function (stroke volume [SV] index <35 ml/m^2, AVA <1 cm^2, aortic velocity <4 m/s, MG <40 mm Hg, and LVEF <50%) low-dose dobutamine SE is recommended to assess the stress-induced symptoms, blood pressure change, change in pressure gradients or AVA, and to determine the flow (defined as SV increase ≥20%) and contractile reserve. Typically, in true severe AS, a marked increase in gradients can be observed with no or minimal increase in AVA. AVR is indicated in symptomatic patients with true severe AS (class I, level of evidence B) or in case of symptomatic patients, whose gradients did not elevate but the AVA remained smaller than 1 cm^2 and the presence of flow / contractile reserve has been proved (class I, level of evidence C).[9] If the symptomatic patient's AVA and gradient measurements have not changed during the SE and there is no contractile / flow reserve (which suggests an operative mortality of 30%–50%, the therapeutic decision making is possible only after CT calcium scoring of the aortic valve.[9]

Paradoxical low-flow, low-gradient aortic stenosis

Paradoxical LFLG AS is present if LVEF is 50% or higher, SV index is 35 ml/m^2 or less, AVA is less than 1 cm^2, indexed AVA is less than 0.6 cm^2/m^2, and the mean gradient is less than 40 mm Hg at rest. It is considered the most challenging group. The diagnostic workup recommended by the guidelines is the same as described with the classical LFLG type. According to the guidelines, in these patients, AVR is recommended if symptoms are present and severe AS has been confirmed (class IIa, level of evidence C).[9]

Hypertrophic cardiomyopathy Sufficient data have now been collected showing that exercise testing is not only safe but also that it is a key element in the comprehensive evaluation of patients with HCM.[19] Exercise-related symptoms in patients with HCM are due to a number of factors including increased LV outflow tract (LVOT) gradients, MR, diastolic dysfunction, and myocardial ischemia in the absence of epicardial CAD. The recent ESC guidelines assign a IB class of recommendation to perform exercise SE in symptomatic patients without a resting LVOT obstruction (if bedside maneuvers fail to induce LVOT gradient ≥50 mm Hg) to detect exercise-induced LVOT obstruction and MR.[19] LVOT obstruction developing rapidly at lower levels of exercise is associated with greater impairment in functional capacity compared with

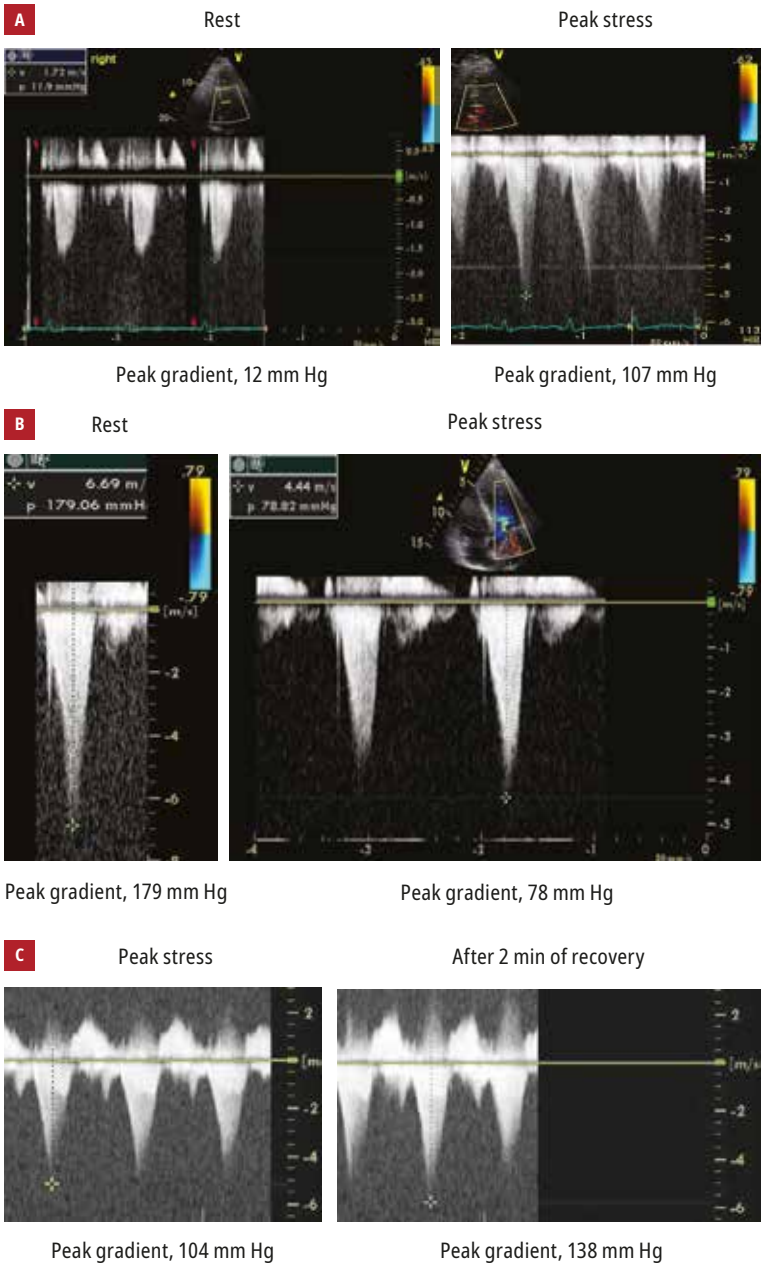

FIGURE 2 Continuous-wave Doppler echocardiography of 3 patients. **A** – in the first patient, obstruction of the left ventricular outflow tract (LVOT) was developed during exercise (12–107 mm Hg). **B** – in the second patient, the high peak gradient with the dagger shaped envelope measured in the LVOT decreased during exercise (179–78 mm Hg). **C** – in the third patient, the high LVOT gradient reached its peak not at peak stress, but 2 minutes after terminating the exercise (104–138 mm Hg).

later onset of the gradient.[20] Posteriorly directed MR is a secondary consequence of systolic anterior motion. The MR jet may overlap and contaminate the LV outflow jet, potentially resulting in an erroneous overestimation of the subaortic gradient. Doppler systolic flow shape typical of LV outflow gradients characteristically demonstrates a gradual increase in velocity in early systole with mid-systolic acceleration and peaking ("dagger-shaped") (FIGURE 2A). Whereas the MR signal begins suddenly at the onset of systole and rapidly establishes markedly increased velocity which then persists throughout systole ("bell-shaped").[21] Key findings of worse prognosis are: limited exercise capacity, an abnormal blood pressure response (hypotensive or blunted response), significant ST-depression, inducible wall motion abnormalities, blunted coronary flow reserve, LVOT obstruction (more than 50 mm Hg), and blunted systolic function. Interestingly, some patients can show a paradoxical decrease in LVOT obstruction during exercise, which is associated with a more favorable outcome and suggests alternative reasons for symptoms (FIGURE 2B). Another paradoxical phenomenon can be also observed when the LVOT gradient starts to elevate after the stress test (FIGURE 2C). The potential explanation is that in the recovery phase the preload and afterload rapidly drop down, and therefore the left ventricular volumes and dimensions decrease as well, which contributes to the LVOT obstruction (FIGURE 2C).

Heart failure with preserved ejection fraction SE has been extensively validated in patients with heart failure with reduced ejection fraction.[22-24] Left ventricular contractile reserve is associated with a greater chance of response to the cardiac resynchronization therapy.[23,25] Shortness of breath, exertional fatigue, or poor exercise capacity has been increasingly recognized as the consequence of diastolic dysfunction and considered to be the main cause in approximately 40% of patients presenting with heart failure. HFpEF is a complex pathophysiological entity. Echocardiographic parameters provide a key tool for the diagnosis of the disease, as indicated in the new ESC guidelines.[26] HFpEF is defined as the presence of heart failure symptoms and signs with normal or preserved left ventricular EF and normal or small LV volumes. Structural heart disease can be also observed, which most often means LV hypertrophy or left atrial enlargement. Furthermore, evidence of diastolic dysfunction (abnormal E/e' ratio [averaged ≥13] and abnormal e' <9 cm/s) can support the diagnosis too.[26] A strong correlation between E/e' and physical activity has been demonstrated in HFpEF.[27] E/e' has been compared to an invasive hemodynamic measurement during exercise and the correlation was in an acceptable range.[28] However, it is not infrequent for patients with HFpEF to fall within a "grey zone" of E/e' value.[26] In the case of SE, multiparametric approach is considered (FIGURE 3). During the stress test, PASP should be measured. Stroke volume and its change during exercise should also be assessed.[29] With diastolic heart failure during stress, lung ultrasound may show B-lines or ultrasound lung comets, which is a simple, direct, semiquantitative sign of extravascular lung water accumulation.[30] The absence of increased cardiac output during exercise, average E/e' ratio higher than 14, the septal e' velocity smaller

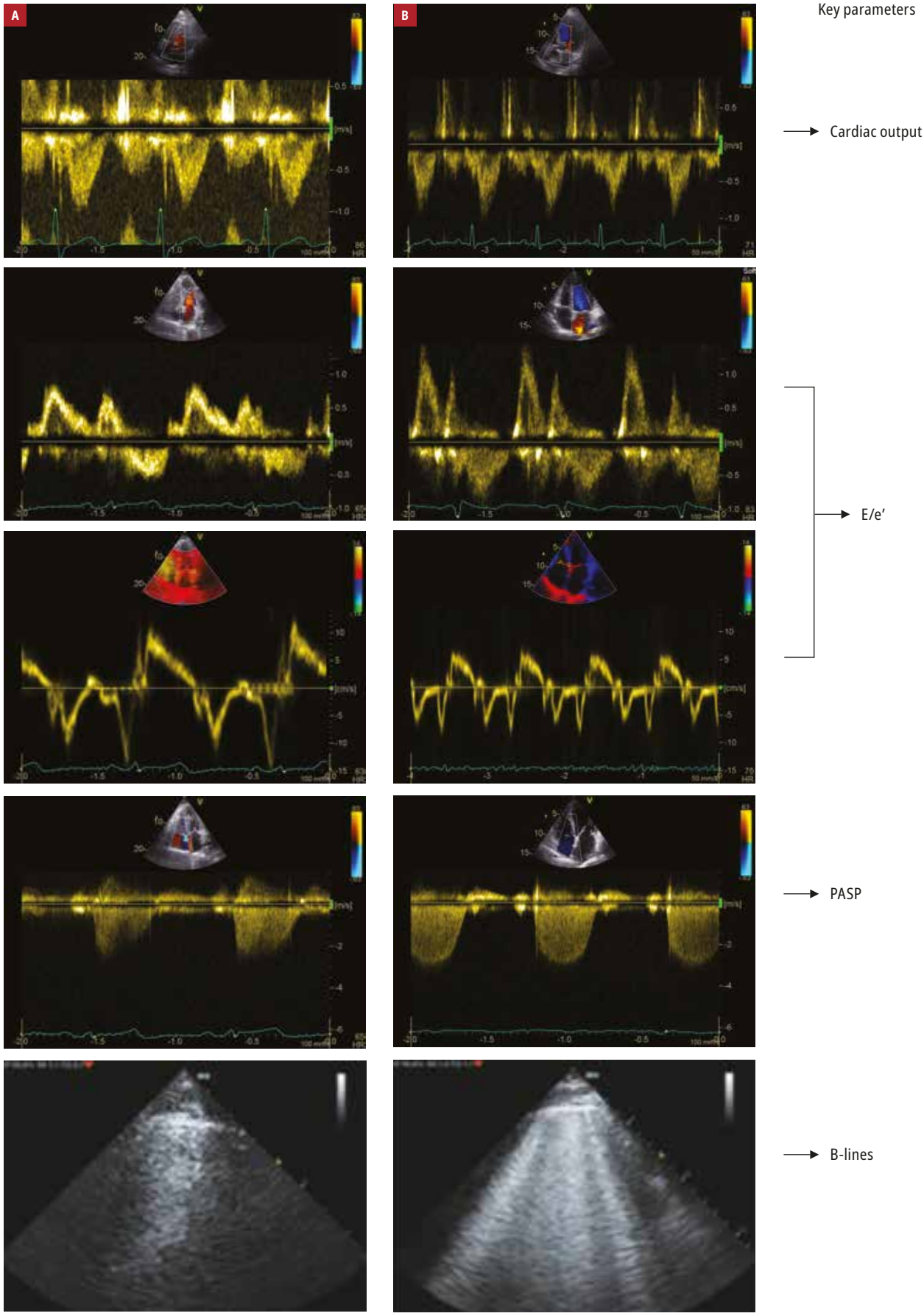

FIGURE 3 Assessment of right ventricular pressure, left ventricular filling, left ventricular output, and extravascular lung water in patients with unexplained dyspnea and suspected heart failure with preserved ejection fraction

Abbreviations: E/e', ratio of early mitral inflow velocity to mitral annular early diastolic velocity; others, see FIGURE 1

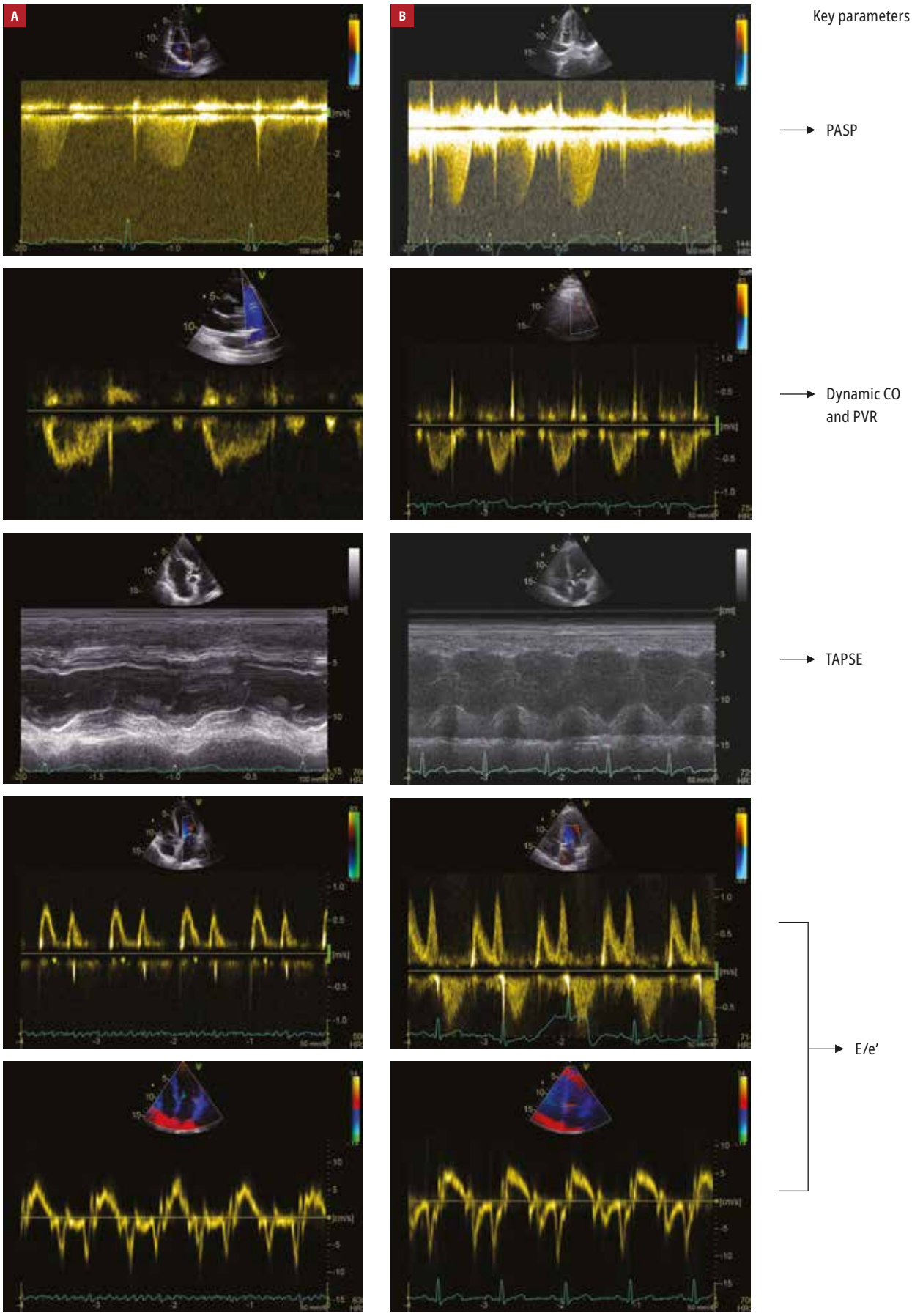

FIGURE 4 Assessment of right ventricular pressure, noninvasively measured dynamic pulmonary vascular resistance (PVR), tricuspid annular plane systolic excursion (TAPSE), and left ventricular filling pressure in patients at risk of pulmonary hypertension

Abbreviations: CO, cardiac output; others, see FIGURES 1 and 3

than 7 cm/s at baseline, peak tricuspid regurgitation velocity higher than 2.8 m/s with exercise usually indicate an abnormal stress test.[1,31]

Pulmonary hypertension Patients with certain types of pathologies are at significantly increased risk for pulmonary arterial hypertension (PAH). Annual screening with rest echocardiography has been proposed for these patients (systemic sclerosis, heritable form of PAH, first degree relatives of a patient with heritable PAH, portal hypertension, HIV infection, sickle cell disease). The stimulating concept of exercise-induced PH (as a possible transitional phase anticipating resting PH) has been developed in several pathologies including systemic sclerosis. Several studies report significant percentages of patients with normal pulmonary pressure at rest but abnormal hemodynamic response during stress.[32-34] This high percentage of exercise-induced increase in pressure at SE clearly overestimates the subset of patients who will develop PAH.

Stress echocardiography should be performed on a semirecumbent cycle ergometer with an incremental workload of 25 every 2 minutes up to the symptom-limited maximal tolerated workload.[35] The minimum acquired dataset includes tricuspid regurgitant velocity and RV size and systolic function (tricuspid annular plane systolic excursion), lateral annular tissue Doppler, and RV free wall systolic strain, cardiac output, and depending on the referral indication, LV size and systolic, diastolic function (FIGURE 4). Doppler recordings should be obtained within 1 to 2 minutes of test completion.[1] Postexercise imaging is less reliable since PASP is known to return to baseline very quickly.

During the examination, focusing on PASP with exercise is not enough. Studies have suggested that an assessment of pulmonary vascular resistance is more sensitive.[36] A steeper slope of the dynamic pulmonary vascular resistance curve suggests a cohort at increased risk for the development of PAH.[36] The inability to augment PASP with exercise, likely an indirect surrogate of impaired contractile reserve, is associated with worse outcome.[37]

Conclusion Stress echocardiography is an effective, noninvasive, cost-efficient, radiation-free, and easily reproducible method, which plays an important role in the diagnostic and prognostic evaluation of nonischemic heart diseases. While the benefit of SE in the evaluation of several heart diseases (for example HCM and CAD) is well established, its role in other diseases, such as mitral valve pathologies, HFpEF, or PH, has been for now more limited to the assessment of the prognosis. In these pathologies, the importance of SE in therapeutic decision making is not undoubtedly proven. Further multicenter studies are needed to clarify the uncertainty.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Picano E. Stress echocardiography. From pathophysiological toy to diagnostic tool. Circulation. 1992; 85: 1604-1612.

2 Lancellotti P, Pellikka PA, Budts W, et al. The clinical use of stress echocardiography in non-ischemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2016; 17: 1191-1229.

3 Płońska-Gościniak E, Kasprzak JD, Olędzki S, et al. Polish Stress Echocardiography Registry (Pol-STRESS registry) - a multicentre study. Stress echocardiography in Poland: numbers, settings, results, and complications. Kardiol Pol. 2017; 75: 922-930.

4 Picano E, Ciampi Q, Citro R, et al. Stress echo 2020: the international stress echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound. 2017; 15: 3.

5 Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. Eur Heart J. 2014; 35: 1033-1040.

6 Chenzbraun A. Non-ischemic cardiac conditions: role of stress echocardiography. Echo Res Pract. 2014; 1: R1-R7.

7 Yared K, Lam KM, Hung J. The use of exercise echocardiography in the evaluation of mitral regurgitation. Curr Cardiol Rev. 2009; 5: 312-322.

8 Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. 2005; 352: 875-883.

9 Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38: 2739-2791.

10 Magne J, Pibarot P, Sengupta PP, et al. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. JACC Cardiovasc Imaging. 2015; 8: 83-99.

11 Magne J, Donal E, Mahjoub H, et al. Impact of exercise pulmonary hypertension on postoperative outcome in primary mitral regurgitation. Heart. 2015; 101: 391-396.

12 Lancellotti P, Cosyns B, Zacharakis D, et al. Importance of left ventricular longitudinal function and functional reserve in patients with degenerative mitral regurgitation: assessment by two-dimensional speckle tracking. J Am Soc Echocardiogr. 2008; 21: 1331-1336.

13 Kusunose K, Popović ZB, Motoki H, Marwick TH. Prognostic significance of exercise-induced right ventricular dysfunction in asymptomatic degenerative mitral regurgitation. Circ Cardiovasc Imaging. 2013; 6: 167-176.

14 Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003; 24: 1231-1243.

15 Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation. 2005; 112 (suppl 9): I377-I382.

16 Maréchaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J. 2010; 31: 1390-1397.

17 Maréchaux S, Ennezat PV, LeJemtel TH, et al. Left ventricular response to exercise in aortic stenosis: an exercise echocardiographic study. Echocardiography. 2007; 24: 955-959.

18 Lancellotti P, Magne J, Donal E, et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation. 2012; 126: 851-859.

19 Task Force members; Elliott PM, Anastasakis A, Borger MA et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35: 2733-2779.

20 Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2017; 10: 1374-1386.

21 Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006; 114: 2232-2239.

22 Stępniewski J, Kopeć G, Magoń W, Podolec P. Ischemic aetiology predicts exercise dyssynchrony in patients with heart failure with reduced ejection fraction. Kardiol Pol. 2018; 76: 1450-1457.

23 Gilewski W, Błażejewski J, Karasek D, et al. Are changes in heart rate, observed during dobutamine stress echocardiography, associated with a response

to cardiac resynchronisation therapy in patients with severe heart failure? Results of a multicentre ViaCRT study. Kardiol Pol. 2018; 76: 611-617.

24 Pratali L, Otasevic P, Neskovic A, et al. Prognostic value of pharmacologic stress echocardiography in patients with idiopathic dilated cardiomyopathy: a prospective, head-to-head comparison between dipyridamole and dobutamine test. J Card Fail. 2007; 13: 836-842.

25 Ciampi Q, Carpeggiani C, Michelassi C, et al. Left ventricular contractile reserve by stress echocardiography as a predictor of response to cardiac resynchronization therapy in heart failure: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2017; 17: 223.

26 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18: 891-975.

27 Erdei T, Aakhus S, Marino P, et al. Pathophysiological rationale and diagnostic targets for diastolic stress testing. Heart. 2015; 101: 1355-1360.

28 Donal E. The value of exercise echocardiography in heart failure with preserved ejection fraction. J Ultrason. 2019; 19: 43-44.

29 Obokata M, Kane GC, Reddy YN, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation. 2017; 135: 825-838.

30 Picano E, Frassi F, Agricola E, et al. Ultrasound lung comets: a clinically useful sign of extravascular lung water. J Am Soc Echocardiogr. 2006; 19: 356-363.

31 Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol. 2006; 47: 1891-1900.

32 Collins N, Bastian B, Quiqueree L, et al. Abnormal pulmonary vascular responses in patients registered with a systemic autoimmunity database: Pulmonary Hypertension Assessment and Screening Evaluation using stress echocardiography (PHASE-I). Eur J Echocardiogr. 2006; 7: 439-446.

33 Alkotob ML, Soltani P, Sheatt MA, et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients with scleroderma. Chest. 2006; 130: 176-181.

34 Callejas-Rubio JL, Moreno-Escobar E, de la Fuente PM, et al. Prevalence of exercise pulmonary arterial hypertension in scleroderma. J Rheumatol. 2008; 35: 1812-1816.

35 Ferrara F, Gargani L, Armstrong WF, et al. The Right Heart International Network (RIGHT-NET): rationale, objectives, methodology, and clinical implications. Heart Fail Clin. 2018; 14: 443-465.

36 Gabriels C, Lancellotti P, Van De Bruaene A, et al. Clinical significance of dynamic pulmonary vascular resistance in two populations at risk of pulmonary arterial hypertension. Eur Heart J Cardiovasc Imaging. 2015; 16: 564-570.

37 Grünig E, Tiede H, Enyimayew EO, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. Circulation. 2013; 128: 2005-2015.