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Valve Stress Echocardiography

A Practical Guide for Referral, Procedure, Reporting, and Clinical Implementation of Results From the HAVEC Group

Madalina Garbi, MD, MA,* John Chambers, MD,† Mani A. Vannan, MBBS,‡ Patrizio Lancellotti, MD, PhD§‖

ABSTRACT

Valve stress echocardiography (VSE) is increasingly used both within specialist valve clinics and within dedicated VSE services, mandating practical guidance for referral, procedure, reporting, and clinical implementation of results. Therefore, a didactic VSE guide was compiled based on current European Society of Cardiology and American College of Cardiology/American Heart Association valve disease management guidelines, review of existing evidence, and the authors' extensive experience with VSE. The VSE indications were grouped into 3 categories: symptoms despite nonsevere valve disease, asymptomatic severe valve disease, and valve disease with reduced left ventricular systolic function. The aim of the test, the type of stress to be used, the sequence of image acquisition, the information to be included in the report, and the implication of the VSE results for clinical management were described for every indication and summarized in user-friendly tables. (J Am Coll Cardiol Img 2015;8:724–36) © 2015 by the American College of Cardiology Foundation.

In patients who have asymptomatic severe valve disease, exercise testing is an established practice to detect occult symptoms (1–5). However, additional diagnostic and prognostic information can be obtained by adding echocardiographic imaging to exercise testing or to dobutamine infusion, in a wider range of indications (1–3,6). Valve stress echocardiography (VSE) is being increasingly used, both within the specialist valve clinics and within dedicated VSE services receiving referrals from cardiologists and cardiac surgeons outside the boundaries of the specialist valve clinic. To aid in this evolving clinical practice, and mirroring routine in the authors' own departments, the current paper presents a didactic guide for VSE procedures and reporting and also for VSE referral and interpretation of results; the information is based on guidelines, recommendations, referenced current evidence, and the authors' experience. The HAVEC (Heart Valve Clinic International Database) group recognized the need for concerted efforts to enhance the VSE evidence base before the update of current valve disease management guidelines to reflect expert practice trends.

REFERRAL GUIDE

The VSE indications can be classified into 3 categories: symptoms despite nonsevere valve disease, asymptomatic severe valve disease, and valve disease with reduced left ventricular (LV) systolic function. Throughout the text, the references associated with each indication denote whether the indication is well established and generally accepted, being consequently included in current European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (1,2) and recommendations (7), or is not well established but supported by some more recent evidence. Comments lacking a reference represent the opinion of the authors. The VSE indications' acceptance status and evidence have been summarized (**Table 1**) to highlight the gap between current trends and

From the *King's Health Partners, King's College Hospital NHS Foundation Trust, London, United Kingdom; †Cardiothoracic Centre, Guy's and St. Thomas' Hospital, London, United Kingdom; ‡Marcus Heart Valve Center, Piedmont Heart Institute, Atlanta, Georgia; §University of Liège Hospital, GIGA Cardiovascular Sciences, Departments of Cardiology, Heart Valve Clinic, CHU Sart Tilman, Liège, Belgium; and ‖GVM Care and Research, Lugo (RA), Italy. The HAVEC group is composed of volunteers (not sponsored) who have put together a collection of prospectively collected data on valvular heart disease. Centers involved in HAVEC have facilities to diagnose and regularly monitor patients with valvular heart disease. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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guidelines. The goal of the test depends on the VSE indication (**Table 2**).

SYMPTOMS DESPITE NONSEVERE VALVE DISEASE. Exertional breathlessness, chest pain, or unexplained acute pulmonary edema requires revaluation of valve disease severity based on flow-dependent changes or on its dynamic component (1,2).

Mitral regurgitation. Secondary mitral regurgitation (MR) as a result of ischemic heart disease is likely to worsen on exertion, but this outcome can occur for any MR etiology (1,2,8,9). In patients with unexplained acute pulmonary edema (1,8), stress may induce myocardial ischemia with associated dynamic ischemic MR.

Mild MR is an indication for exercise VSE before coronary artery bypass grafting (CABG), as suggested by evidence from the RIME (Randomized Ischemic Mitral Evaluation) trial (10). This trial found that mitral annuloplasty at the time of CABG in patients with moderate ischemic MR at rest or developed on exertion might improve functional capacity, LV reverse remodeling, MR severity, and B-type natriuretic peptide levels. The ESC guidelines (1) recommend mitral valve surgery at the time of CABG in patients with moderate MR and use of VSE to assess symptoms and exertion-induced MR severity and systolic pulmonary arterial pressure (SPAP) increases.

Mitral stenosis. A noncompliant mitral valve may be moderately stenotic at rest but hemodynamically severely stenotic during stress, as it fails to open further to accommodate the increase in flow (1,2,6,11–15). In addition, because indexed valve area thresholds are not defined, VSE may be useful for grading mitral stenosis (MS) in patients with a large body surface area (13). Gradient thresholds (1,2,11,16–19) for severe MS have been established as >15 mm Hg on exertion or >18 mm Hg during dobutamine infusion. In addition, SPAP >60 mm Hg on exertion (1,2,11,18) suggests severe MS. Proof of hemodynamic significance may help clinical decision-making in cases of valve morphology not suitable for balloon valvotomy and those of high surgical risk. Furthermore, even in cases of valve morphology suitable for balloon valvotomy, proof of increases in mean gradient and increases in SPAP to >60 mm Hg during VSE strengthens the decision to proceed if the MS is only moderate at rest.

Aortic regurgitation. Aortic regurgitation (AR) is reduced at high heart rates as diastole shortens even if the systemic pressure rises. Consequently, although exercise testing is recommended to confirm equivocal symptoms (2), echocardiographic imaging can only be added with the goal of revealing inducible myocardial ischemia but not with the goal of re-grading AR severity.

Aortic stenosis. As with MS, a noncompliant aortic valve may be moderately stenotic at rest but severely stenotic during stress (20,21) because the valve fails to open further. Consequently, gradient increase and calculated functional valve area failure to increase during VSE suggest severe aortic stenosis (AS) (5,8,11,13,20,21). VSE is indicated (1,2) to regrade AS severity in symptomatic patients. Furthermore, because coexistence of coronary artery disease is common in calcific AS, the VSE may also detect inducible ischemia.

VSE may help grade AS severity in paradoxical low-flow AS (22,23). Dobutamine should be used with caution and could be potentially contraindicated if (as is common in paradoxical low-flow AS) the LV has severe hypertrophy, especially of the basal interventricular septum and small cavity, because of the high likelihood of dobutamine-induced left ventricular outflow tract (LVOT) obstruction and drop in blood pressure during the test.

Prosthetic valves. A VSE is recommended to help diagnose an obstructive prosthetic valve (7). A significant mean gradient rise (for both aortic and mitral prosthetic valves) (16,24) and a calculated functional valve area failure to rise (for aortic prosthetic valves)

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

AR = aortic regurgitation

AS = aortic stenosis

CABG = coronary artery bypass grafting

ESC = European Society of Cardiology

LV = left ventricular

MR = mitral regurgitation

MS = mitral stenosis

SPAP = systolic pulmonary arterial pressure

VSE = valve stress echocardiography

TABLE 1 VSE Indications' Acceptance Status and Supportive Evidence

VSE Indication	ESC	ACC/AHA	Evidence (Ref. #)	Expert Practice
Symptomatic patient				
Nonsevere MR	Yes	Yes	(6,8,9,11)	Yes
Pulmonary edema	Yes	No	(8)	Yes
Mild MR before CABG	Yes	No	(10)	Yes
Nonsevere MS	Yes	Yes	(6,8,11,13–19)	Yes
Nonsevere AR	No	Yes*	No	Yes†
Nonsevere AS	Yes	Yes	(8,11,13,20,21,41)	Yes
Paradoxical low-flow AS	Yes	Yes	(8,11,22,23)	Yes
Equivocal AV PPM/stenosis	Yes	Yes	(7,8,11,24)	Yes
Equivocal MV PPM/stenosis	Yes	Yes	(7,8,11)	Yes
Asymptomatic patient				
Severe MR	Yes	Yes	(6,8,11,25–28)	Yes
Significant MS	Yes	Yes	(6,8,11,13–19)	Yes
Severe AR	No	Yes*	(29,30)	Yes
Severe AS	Yes	Yes	(3–5,8,11,13,20,21,31–37,39)	Yes
Low LVEF				
Low-flow AS	Yes	Yes	(8,11,23,38–45,47,48)	Yes
Low-flow AV prosthesis	No	No	No	Yes

*Exercise test only. †Exercise echocardiogram to assess existence of inducible ischemia.

ACC = American College of Cardiology; AHA = American Heart Association; AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CABG = coronary artery bypass grafting; ESC = European Society of Cardiology; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; PPM = patient-prosthesis mismatch; VSE = valve stress echocardiography.

TABLE 2 VSE Aim According to Indication

	Aim of the Test
Symptomatic patient	
Nonsevere MR	Query exertion induced MR severity rise ± SPAP rise >60 mm Hg ± LVEF failure to rise by at least 4% to explain symptoms
Pulmonary edema	Query inducible ischemia and dynamic ischemic MR
Mild MR before CABG	Query exertion-induced MR severity rise ± SPAP rise >60 mm Hg
Nonsevere MS	Query exertion-induced mean gradient >15 mm Hg ± SPAP >60 mm Hg ± rise in MR severity or dobutamine-induced mean gradient >18 mm Hg to explain symptoms
Nonsevere AR	Query coexistent abnormalities (e.g., inducible ischemia), LVEF failure to rise, and/or SPAP rise to >60 mm Hg on exertion
Nonsevere AS	Query coexistent abnormalities (e.g., inducible ischemia) and mean gradient rise and calculated AV area failure to increase with flow to explain symptoms
Paradoxical low-flow AS	Query severe AS assessing transvalvular gradient and calculated AV area changes with increase in flow
Equivocal AV PPM/stenosis	Query severe PPM/stenosis assessing transvalvular gradient and calculated valve area changes with increase in flow
Equivocal MV PPM/stenosis	Query severe PPM/stenosis assessing transvalvular gradient and calculated valve area changes with increase in flow
Asymptomatic patient	
Severe MR	Query exercise tolerance and symptoms ± SPAP rise >60 mm Hg, LVEF failure to rise by at least 4% ± global longitudinal strain failure to rise by -2%
Significant MS	Query exercise tolerance and symptoms ± mean gradient rise >15 mm Hg ± SPAP rise >60 mm Hg
Severe AR	Query exercise tolerance and symptoms ± contractile reserve
Severe AS	Query exercise tolerance and symptoms ± SBP drop or failure to rise by 20 mm Hg, ST-segment depression, RWMA, contractile reserve, LV longitudinal function, SPAP rise >60 mm Hg, mean gradient rise >18–20 mm Hg
Low LVEF	
Low-flow AS	Query LV flow reserve and gradient + calculated AV area changes with increase in flow
Low-flow AV prosthesis	Query LV flow reserve and gradient + calculated valve area changes with flow

LV = left ventricular; RWMA = regional wall motion abnormality; SBP = systolic blood pressure; SPAP = systolic pulmonary arterial pressure; other abbreviations as in Table 1.

with associated reproduction of symptoms during VSE suggest that an obstructive valve is the cause of symptoms (patient-prosthesis mismatch or prosthesis stenosis). A mean gradient rise is significant if it is at least >20 mm Hg for prosthetic aortic valves and at least >12 mm Hg for prosthetic mitral valves (11). In cases of an obstructive prosthetic aortic valve, the VSE may also reveal inducible ischemia or significant exertion-induced MR (7). In cases of an obstructive prosthetic mitral valve, the VSE may also reveal an exertion-induced SPAP increase to >60 mm Hg.

ASYMPTOMATIC SIGNIFICANT VALVE DISEASE. The main goal of VSE is to detect occult symptoms because they are an indication for surgery, as with spontaneously reported symptoms (1,2). The test can be performed with treadmill or bicycle exercise. The addition of echocardiography to exercise test data may add diagnostic and prognostic benefit.

Severe primary MR. In patients with repairable valves at low surgical risk, symptoms (1,2) and/or SPAP >60 mm Hg (1) during exercise testing (6,25) strengthen the argument for surgery. There is also evidence that the exercise VSE-demonstrated lack of contractile reserve (failure to increase the left ventricular ejection fraction [LVEF] by >4% [26] or the global longitudinal strain by -2% [27,28]) confers poor prognosis.

Significant MS. In MS with a valve area <1.5 cm^2 but >1 cm^2 (defined as moderate but significant in the ESC guidelines and defined as severe in the ACC/AHA guidelines), VSE is indicated before major noncardiac surgery or pregnancy planning (1,8). During routine surveillance, VSE can be considered (6,14–16) in MS with a valve area <1.5 cm^2 but >1 cm^2 if the valve is suitable for balloon valvotomy (2) or in MS with a valve area <1 cm^2 (defined as severe in the ESC guidelines) if the valve is unsuitable for valvotomy (1,2).

Severe AR. Exercise testing is indicated to uncover symptoms (2) because of the high mortality implied. Exercise VSE allows for assessment of LV contractile reserve, the lack of which predicts the development of LV systolic dysfunction at follow-up or postoperatively (8,29). Longitudinal function at rest and on exertion may also aid in the detection of early LV systolic dysfunction (8,30).

Severe AS. Exercise testing is recommended in these patients with severe AS (1,2). Ventricular arrhythmia, systolic blood pressure drop or failure to rise by 20 mm Hg, ST-segment depression, induced regional wall motion abnormalities, reduced contractile

reserve, impaired rest or exertion LV longitudinal function (31), SPAP >60 mm Hg (32), and development of angina, breathlessness, pre-syncope, or syncope characterize an abnormal exercise response (8,33–35). Mean gradient increases >18 to 20 mm Hg suggest a poor prognosis (1,36,37). Caution regarding exercise testing is recommended in cases of AS with peak velocity >5 m/s or mean gradient >60 mm Hg, which in cases of low surgical risk represent a Class IIa surgical indication in both the ACC/AHA (1) and the ESC (2) guidelines; the ESC guidelines allow for a higher peak velocity (5.5 m/s).

VALVE DISEASE WITH REDUCED LV SYSTOLIC FUNCTION. Low-flow, low-gradient AS. VSE is recommended for grading of AS severity and for assessment of flow reserve when the LVEF is <50% (1,2). Mean gradient increase and calculated functional valve area failure to increase during VSE suggest severe AS. The existence of flow reserve is diagnosed when there is an increase in stroke volume or LVOT velocity time integral by >20% (8,20,23,38–44).

Low-flow aortic valve prosthesis. As for low-flow, low-gradient AS, VSE may be used for prosthesis dysfunction grading in symptomatic patients.

Although VSE indications are continuously evolving and there is still need for further evidence in many aspects of the test, there is no indication or there is even contraindication for VSE in some clinical scenarios. VSE is contraindicated in symptomatic patients with severe disease, both because these clinical scenarios indicate intervention and because of the risk associated with the test, particularly for those with severe AS (1,2). There is no indication for VSE, due to futility, in patients unsuitable for intervention. There is also no indication for VSE in asymptomatic patients with mild or moderate disease in whom the test results would not affect clinical management.

PROCEDURE GUIDE

There is limited information in the published data regarding practical aspects of the VSE procedure. Therefore, this procedure guide is mainly based on the experience of the authors.

TYPE OF STRESS. Depending on clinical indication, the VSE is performed with exercise or dobutamine (Table 3).

Exercise VSE. Exercise is physiological and can be used to assess symptoms and exercise tolerance, and it is the stressor of choice in asymptomatic severe valve disease. Although dobutamine has been used in asymptomatic severe AS to assess the valve compliance to flow (16), it is usually contraindicated in severe AS because it can precipitate life-threatening hypotension and pulmonary edema in case the valve area is fixed, limiting the increase in forward flow. Consequently, exercise remains the stressor of choice when severe AS is diagnosed at rest (1,2,8,31–37). In addition, only exercise VSE provides information regarding dynamic SPAP changes (1,2,11,18). Furthermore, due to complex interference of dobutamine effects with MR mechanisms, only exercise VSE can be used for MR assessment (1,2,8–10).

Dobutamine VSE. Dobutamine-induced inotropic recruitment is currently the only VSE method recommended for assessment of low-flow, low-gradient AS (1,2,8,20,23,38–44). This sole recommendation is because of concerns that symptoms or a low exercise tolerance in asymptomatic sedentary patients can limit the exercise-induced contractile recruitment, consequently preventing the correct assessment of both stenosis severity and flow reserve. Nevertheless, some patients, particularly asymptomatic, physically active patients with incidental low-flow, low-gradient AS, might potentially achieve the target workload (20% increase in LVOT-derived stroke volume), which allows for a correct diagnosis (8,20,23,38–44). An exertion-induced increase in stroke volume, demonstrating the existence of flow reserve with an associated rise in calculated functional AV area, suggests target workload and test endpoint achievement. It is the opinion of the current writing group that a dobutamine test can be avoided in this case. However, if the achieved workload is low, with an apparent lack of flow reserve, the test should be repeated with dobutamine.

STRESS PROTOCOL. Exercise. Treadmill exercise testing can be used for VSE. Nevertheless, the authors favor supine bicycle exercise testing for VSE because treadmill exercise has the major disadvantage of allowing only pre- and post-stress image acquisition. Consequently, because changes in recorded parameters are transient, immediately decreasing with cessation of exercise and being short-lasting, consequences of exercise can be underestimated or even missed. Furthermore, post-treadmill image acquisition does not allow for timing of events, appreciation of sequence of events, or acquisition of images at low workload, thus potentially concealing important information. For example, although SPAP increases often on exertion, an early rise at low workload is more specific for a pathological response. Regarding sequence of events, whereas low LV systolic function at peak (or post-peak) exercise may signify a lack of contractile reserve, an

TABLE 3 Type of Stress Used According to VSE Indication

Exercise Only	Exercise or Dobutamine	Dobutamine Only
Symptomatic patient	Symptomatic patient	Symptomatic patient
Nonsevere MR	Pulmonary edema	
Mild MR before CABG	Nonsevere MS	
Nonsevere AR	Paradoxical low-flow AS	
	Nonsevere AS	
	Equivocal AV PPM/stenosis	
	Equivocal MV PPM/stenosis	
Asymptomatic patient	Asymptomatic patient	Asymptomatic patient
Severe MR	Moderate MS	
Severe MS		
Severe AR		
Severe AS		
Low LVEF	Low LVEF	Low LVEF
		Low-flow, low-gradient AS
		Low-flow AV prosthesis

Abbreviations as in Table 1.

initial increase in LV systolic function at low workload followed by a drop at high workload suggests the existence of inducible ischemia rather than a lack of contractile reserve (45). Treadmill exercise excludes image acquisition at low workload, when contractility recruitment is achieved but the heart rate remains below forbidden levels (100 to 110 beats/min) for some modalities (i.e., 3-dimensional echocardiography for LV contractile reserve).

Supine bicycle exercise allows image acquisition at any stage during the VSE. Exercise protocols can be designed and programmed on an electronic bicycle, or they can be manually adjusted for each patient's needs. The workload should be initially low (0, 25, or 50 W depending on patient's age, expected exercise tolerance, and pathology) and then increased in steps, usually by 25 W every 2 min. A more gradual increase in workload can be used for assessment of exercise tolerance or contractile reserve; nevertheless, a higher workload rather than a longer exertion time more likely reveals severity of pathology, particularly MR and SPAP increases.

The predicted maximum workload for healthy subjects is 2.5 W/kg in women and 3.0 W/kg in men between 21 and 30 years of age, minus 10% for each added decade. The workload achieved depends not only on severity of valve disease but also on the patient's exercise habits and familiarity with the test. Prolonging the test by starting with a too-low workload for a certain patient may result in a lower achieved maximum workload. Starting with a too-high workload may discourage the patient from completing the test.

Dobutamine. A low-dose dobutamine infusion protocol is used for grading of AS severity, with 5-min stages and incremental doses of 5, 10, 15, and 20 μg/kg/min. The test is terminated when the target increase in flow (20% increase in LVOT-derived stroke volume) is achieved (8,20,23,38-44); a dobutamine dose of 10 μg/kg/min is usually sufficient.

A high-dose dobutamine infusion protocol is used in patients with a history of unexplained pulmonary edema in the absence of severe AS, with 3-min stages and incremental doses of 5, 10, 20, 30, and 40 μg/kg/min. The same protocol is used for grading of MS severity (6,8,11,14-19), with the test being terminated if a mean gradient suggestive of severe stenosis develops.

PRE-TEST REQUIREMENTS. Heart rate-limiting drugs with inotropic negative effects are stopped before VSE to assess contractile reserve, flow reserve, parameters depending on enhanced contractility (e.g., aortic valve gradients), or exercise tolerance. To avoid excessive increases in heart rate, exceptions can be made for patients in chronic atrial fibrillation. Heart rate-limiting drugs are not stopped before VSE when the goal is to assess exertion-induced changes in mitral valve Doppler flow parameters.

For exercise VSE, patients are asked not to eat for 2 h and not to drink for 1 h before the test; this is because supine exercise is more comfortable on an empty stomach. Height and weight are measured before the test to calculate body surface area for indexed measurements, the predicted workload, or the dose of dobutamine.

IMAGE ACQUISITION PROTOCOL. Dedicated image acquisition protocol templates can be created on the echocardiography machines for every indication, to act as a reminder, and to reproduce rest settings during exercise. Nevertheless, templates may be restrictive during the test in cases of unexpected developments that dictate off-protocol imaging. Free image acquisition is usually preferred.

The sequence of image acquisition depends on the VSE indication; it should always commence with images essential for diagnosis to ensure that these images at a minimum have been acquired in case the test is suddenly terminated because the patient stops cycling or a complication occurs. For example, in the case of severe MR, the tricuspid regurgitation continuous Doppler for SPAP estimation and the LV images are first acquired because decision-making depends on SPAP rise and LV contractile reserve. Conversely, in cases of mild or moderate MR suspected to increase on exertion, color and continuous wave Doppler flow images will be acquired first.

The sequence of image acquisition for a minimum dataset according to VSE indication is displayed in Table 4.

Images should be acquired at least at baseline, low workload, and peak during exercise VSE and at the end of every stage during dobutamine VSE. For both stress modalities, we advise almost continuous live imaging if transient changes are likely. For example, in the case of low-flow AS, an initial contractile recruitment-related rise in LVOT and transvalvular velocities can be transient and followed by an ischemia-related reduction in systolic function, with a consequent drop in velocities.

At low workload, the main parameters to be assessed are SPAP and LV systolic function, with particular significance for some VSE indications. For example, in the case of nonsevere MS with symptoms, a significant SPAP increase at this stage strengthens a diagnosis of severe MS in case of significant mitral valve gradient rise at peak. In the case of severe MR without symptoms, LV systolic function assessment to estimate existence of contractile reserve is performed at this stage.

IMAGE OPTIMIZATION. Contrast administration is usually avoided because of Doppler aliasing and noise. An exception can be made if decision-making depends mainly on accurate assessment of LVEF.

To allow LV systolic function assessment, either with 3-dimensional LVEF or speckle tracking–derived global longitudinal strain, low workload images should be acquired at a heart rate <100 to 110 beats/min. The higher the heart rate, the higher the optimal frame rate (or volume rate) for image acquisition. Optimization is obtained by reducing the depth of acquisition to include the LV only, minimizing the sector width, and, for 3-dimensional imaging, using multicycle acquisition.

A suboptimal frame rate can also limit the quality of color flow Doppler images; therefore, a narrow sector and lower possible depth acquisition is recommended with zoom images being used for measurements (e.g., proximal isovelocity surface area radius in MR) to minimize errors. For proximal isovelocity surface area measurements, color flow Doppler images need a baseline shift, which may have to be performed before acquisition if not feasible offline with the echocardiographic machine used.

To minimize measurement errors, spectral Doppler traces should be acquired at maximum speed and minimum scale, which allows good trace definition without aliasing. To avoid missing the peak, the scale has to be increased on exertion in expectation of higher velocities. Heart translation with accelerated respiration and movement of the chest wall during exertion make image acquisition challenging, and it is rare to obtain a complete series of Doppler traces throughout the respiratory cycles. Doppler traces from the parasternal window are affected to a larger extent, making them unreliable during exertion. For example, even if at rest the maximum tricuspid

TABLE 4 Sequence of Image Acquisition According to VSE Indication

	Image Acquisition Sequence
Symptomatic patient	
Nonsevere MR	Color flow Doppler (to assess MR PISA, vena contracta, regurgitant jet), MR CW Doppler for PISA, TR CW Doppler for SPAP, LV views
Pulmonary edema	LV views, color flow Doppler to detect MR
Mild MR before CABG	Color flow Doppler (to assess MR PISA, vena contracta, regurgitant jet), MR CW Doppler for PISA, TR CW Doppler for SPAP, LV views
Nonsevere MS	TR CW Doppler for SPAP, MS CW Doppler for gradient
Nonsevere AR	LV views, TR CW Doppler for SPAP, color flow Doppler to detect MR
Nonsevere/paradoxical low-flow AS	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)
Equivocal AV PPM/stenosis	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only), color flow Doppler to detect MR
Equivocal MV PPM/stenosis	TR CW Doppler for SPAP, MS CW Doppler for gradient
Asymptomatic patient	
Severe MR	TR CW Doppler for SPAP, LV views
Significant MS	TR CW Doppler for SPAP, MS CW Doppler for gradient
Severe AR	LV views, TR CW Doppler for SPAP, color flow Doppler to detect MR
Severe AS	LV views, TR CW Doppler for SPAP, AV CW Doppler, LVOT PW Doppler, color flow Doppler to detect MR
Low LVEF	
Low-flow AS	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)
Low-flow AV prosthesis	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)

CW = continuous wave; LVOT = left ventricular outflow tract; PISA = proximal isovelocity surface area; PW = pulsed wave; TR = tricuspid regurgitation; other abbreviations as in Tables 1 and 2.

regurgitation velocity may be obtained from the parasternal short-axis or right ventricular inflow view, only velocities from apical 4-chamber views are usually accessible on exertion.

QUANTIFICATION. The amplitude of Doppler velocities depends on flow alignment, which varies significantly on exertion from beat to beat. The highest velocities, with better alignment, should be used for measurements in sinus rhythm. An average of 5 to 6 cardiac cycles can be used in atrial fibrillation, for example, to estimate SPAP or mean mitral valve gradient in MS. Nevertheless, it is challenging to match averaged cycles between AV and LVOT velocities for the use of continuity equation in AS.

LV assessment. LVEF can be estimated or calculated by using 2-dimensional biplane or 3-dimensional methods. 3D echocardiography can be used only at baseline and at low workload when the heart rate is still <100 to 110 beats/min and breath-holding for multicycle acquisition might still be feasible. The volume rate may be satisfactory with 1 cycle acquisition when the left ventricle is small, fitting within a narrow sector width in all imaging planes.

Mitral valve assessment. The mean gradient is used to assess MS severity, and MR quantification is based on the proximal isovelocity surface area method and on the vena contracta width. The feasibility and reproducibility of the proximal isovelocity surface area method-based MR quantification during exercise VSE (9) was demonstrated in the laboratory of 1 of the study authors (P.L.). The semiquantitative MR severity assessment based on the MR jet area, not reliable at rest, is even more misleading on exertion; it underestimates MR severity in conditions of higher left atrial pressure and fast heart rate for the frame rate achieved.

AV assessment. Gradients (peak and mean) and calculated functional valve area should be quantified, both at baseline and at peak in AS, because severity grading is based on gradient rise with concomitant valve area failure to increase during the test. Only the apical window can be reliably used during exercise VSE; therefore, if the highest AV velocities at rest are obtained from the right parasternal window, a low-dose dobutamine VSE is more appropriate because it allows the use of this window throughout the test.

REPORTING GUIDE

In the absence of relative information in the existing published data, the reporting guide describes the clinical practice of the authors. A nonprescriptive guide of minimum information to be included in the report according to VSE indication is provided in Table 5.

The exercise VSE report includes information regarding achieved workload as an absolute value and as a percentage of the maximum predicted workload. The exercise tolerance of the patient is graded considering not only the achieved workload but also the usual level of activity (sedentary patients are

TABLE 5 Minimum Report Content According to VSE Indication

	Reporting Guide
Symptomatic patient	Report relationship of symptoms with observed VSE-induced changes
Nonsevere MR	Increase or not in MR severity, maximum MR severity and SPAP, contractile reserve, presence or absence of inducible ischemia
Pulmonary edema	Presence or absence of inducible ischemia and ischemic MR
Nonsevere MS	Findings-based MS severity ± pulmonary hypertension grading, gradient, exertion SPAP
Nonsevere AR	Contractile reserve, SPAP, inducible MR
Nonsevere/paradoxical low-flow AS	AS severity, contractile reserve, presence or absence of inducible ischemia
Equivocal AV PPM/stenosis	AV PPM/stenosis severity, contractile reserve, presence or absence of inducible ischemia, presence or absence of inducible MR, exertion SPAP
Equivocal MV PPM/stenosis	Findings-based MS severity ± pulmonary hypertension grading, gradient, exertion SPAP
Asymptomatic patient	Report observed symptomatic status
Severe MR	SPAP, contractile reserve
Mild MR before CABG	Increase or not in MR severity, maximum MR severity and SPAP, contractile reserve, presence or absence of inducible ischemia
Significant MS	Findings-based MS severity ± pulmonary hypertension grading, gradient, exertion SPAP
Severe AR	Contractile reserve, SPAP, inducible MR
Severe AS	Contractile reserve, presence or absence of inducible ischemia, presence or absence of inducible MR, SPAP
Low LVEF	
Low-flow AS	AS severity, flow reserve, presence or absence of inducible ischemia
Low-flow AV prosthesis	AS severity, flow reserve, presence or absence of inducible ischemia

Abbreviations as in Tables 1 and 2.

expected to perform less) and the type of disease. Developed symptoms and the reason for termination of the test are reported.

The dobutamine VSE report includes information regarding dose and duration of dobutamine infusion, developed symptoms, potential complications (e.g., arrhythmia, vaso-vagal), and the reason for termination of the test.

The description of findings is difficult to standardize, and the characterization of disease is challenging, particularly in cases of >1 valve disease. In self-declared "asymptomatic" patients, the observed symptomatic status is reported. In self-declared "symptomatic" patients, the relationship of symptoms with the observed VSE-induced changes is reported, stating whether it is believed that the symptoms are due to the valve disease. Grading of valve disease severity based on VSE findings is also reported.

CLINICAL IMPLEMENTATION OF RESULTS

Clinical management is tailored according to VSE-diagnosed valve disease severity and symptomatic status, as described in **Table 6**. Both ESC (dated 2012) and ACC/AHA (dated 2014) guidelines (1,2) acknowledge the VSE response as an indication for intervention in a series of clinical scenarios.

SYMPTOMS DESPITE NONSEVERE VALVE DISEASE. Symptomatic patients with VSE displaying only mild to moderate disease should remain under surveillance and their symptoms should be investigated as noncardiac. Their follow-up should be performed at time intervals defined by the ESC (1) or ACC/AHA (2) guidelines. In cases in which the symptoms persist and a noncardiac cause was not found, it may be reasonable to repeat the VSE at follow-up instead of limiting the assessment to echocardiography at rest.

Symptomatic patients with VSE displaying severe disease are referred for intervention. Although both the ESC and ACC/AHA guidelines recommend VSE in symptomatic, nonsevere primary MR, only the ACC/AHA guidelines (2) (published 2 years after the ESC guidelines) clearly state that MR severity increases on exertion to levels that explain the symptoms is an indication for surgery. Nevertheless, for secondary MR, the ESC guidelines (1) recommend mitral valve surgery at the time of CABG, in case of shortness of breath during exercise VSE with associated increase in MR severity, and pulmonary hypertension.

Both the ESC and ACC/AHA guidelines (1,2) recommend VSE for assessment of hemodynamic significance of MS in symptomatic patients, and in both guidelines symptomatic severe MS is a Class I indication for intervention. Consequently, symptomatic patients with VSE-demonstrated severe MS should be referred for intervention according to the morphological characteristics of the valve. A valve area <1.5 cm^2 is the generally accepted anatomic severity threshold for surgery (1,2); however, a valve area >1.5 cm^2 is an indication for intervention in the ACC/AHA guidelines (2) in case of suitability for percutaneous balloon valvotomy.

In symptomatic patients with moderate AR, VSE-demonstrated LV contractile reserve, and lack of inducible ischemia, induced MR or pathologic SPAP increases are reassuring. Although further evidence is needed, in the authors' clinical practice, an abnormal VSE response prompts case discussion by the heart valve team. VSE-demonstrated severe AS in symptomatic patients with paradoxical low-flow AS is a Class IIa indication for surgery in both guidelines (1,2).

In the case of prosthetic valves, the clinical implementation mirrors the management of the respective valve. Symptomatic patients with VSE-demonstrated severe prosthetic valve dysfunction and hemodynamic consequences require reintervention. Considering the higher surgical risk at reintervention, the limited evidence, and the existing controversy, it is appropriate, in the authors' experience, to use a case-by-case approach with discussion by the heart valve team.

ASYMPTOMATIC SIGNIFICANT VALVE DISEASE. Symptomatic severe MR is a Class I indication for surgery in both the ESC and ACC/AHA guidelines (1,2); therefore, demonstration of symptoms during exercise VSE in self-declared "asymptomatic" patients with severe MR is a robust surgical indication. The ESC guidelines (1) recognize exertion-induced SPAP increase to >60 mm Hg as a Class IIb indication for surgery in asymptomatic severe MR, in cases of high likelihood of durable repair and low surgical risk. No recommendation based on an exercise-induced SPAP increase exists in the current ACC/AHA guidelines (2). There is evidence that the lack of LV contractile reserve during VSE predicts a drop in LVEF at follow-up, which is associated with functional capacity deterioration in conservatively treated patients (26,27) and post-operative LV systolic dysfunction and lower event-free survival in surgically treated patients (28). LV systolic dysfunction is a Class I surgical indication in asymptomatic patients with severe MR; although VSE is recommended in these patients by the ESC guidelines (1), thus acknowledging the role of contractile reserve and speckle tracking global longitudinal strain in early detection of LV systolic dysfunction, no clear

TABLE 6 Clinical Implementation of Results According to VSE Indication

	VSE Result	Clinical Implementation of Results (Ref. #)
Symptomatic patient		
Nonsevere MR	Nonsevere MR	Medical management
	Severe MR	Surgical indication (2)
Pulmonary edema	Inducible ischemia ± MR	Revascularization ± MV repair
Mild MR before CABG	No dynamic MR	CABG only
	Dynamic MR + SPAP rise	CABG + MV repair (1)
Nonsevere MS	Nonsevere MS	Medical management
	Severe MS	Intervention, class I indication (1,2)
Nonsevere AR	Normal response	Medical management
	Abnormal response	Case discussion by the heart valve team
Nonsevere AS	Nonsevere AS	Investigate symptoms as noncardiac
	Severe AS	Intervention, class I indication (1,2)
Paradoxical low-flow AS	Nonsevere AS	Medical management
	Severe AS	Intervention, class IIa indication (1,2)
Equivocal PPM/stenosis	Nonsevere PPM/stenosis	Medical management
	Severe PPM/stenosis	Case discussion by the heart valve team considering intervention
Asymptomatic patient		
Severe MR	Symptoms	Surgery, class I indication (1,2)
	No symptoms + normal VSE	Review at 6 months
	No symptoms + SPAP >60 mm Hg	Repair if durable low-risk, class IIb indication (1)
	No symptoms + no LV CR	Case discussion by the heart valve team considering intervention
Significant MS	Symptoms	Intervention, class I indication (1,2)
	No symptoms	Hemodynamically significant MS may need intervention before noncardiac surgery or pregnancy planning
Severe AR	Symptoms	Surgery, class I indication (2)
	No symptoms	Review at 6 months
	No symptoms + no LV CR	Close surveillance
Severe AS	Symptoms	Intervention, class I indication (1,2)
	No symptoms + normal VSE	Review at 6 months
	No symptoms + blood pressure drop	Intervention, class IIa indication (1,2)
	No symptoms + mean gradient rise >20 mm Hg	Intervention, class IIb indication (1)
Low LVEF		
Low-flow AS	Nonsevere AS	Medical management
	Severe AS + flow reserve	Intervention, class IIa indication (1,2)
	Severe AS + no flow reserve	Intervention, class IIb indication (1)/class IIa indication (2)

CR = contractile reserve; other abbreviations as in Tables 1 and 2.

indication for surgery is stated based on the results. In the authors' clinical practice, however, a lack of LV contractile reserve triggers a case discussion by the heart valve team, taking into consideration the suitability of valve morphology for repair, surgical risk, local repair success rate, and surgical mortality rate. Wait times for intervention are also considered because of the high probability of hemodynamic decompensation within 6 months (26,27).

Severe MS with demonstrated symptoms and limited exercise tolerance is a Class I indication for intervention in both the ESC and ACC/AHA guidelines (1,2); the type of intervention selected is based on the morphological characteristics of the valve. Although symptomatic severe AR is a Class I indication for surgery in both ESC and ACC/AHA guidelines, demonstration of symptoms during VSE in asymptomatic patients may be an indication for surgery (as recommended by the ACC/AHA guidelines). In patients with preserved exercise tolerance, in the authors' practices, VSE-demonstrated lack of LV contractile reserve prompts close clinical surveillance.

Both the ESC and the ACC/AHA guidelines (1,2) clearly state that demonstration of symptoms during exercise VSE is a Class I indication for intervention in severe AS. Furthermore, in both guidelines, blood pressure drop on exertion is a Class IIa surgical indication. Although both guidelines recognize the prognostic value of a VSE-demonstrated >20 mm Hg mean gradient rise, only the ESC guidelines (1) state that this is a Class IIb surgical indication.

CENTRAL ILLUSTRATION **Valvular Stress Echocardiography Guide For Referral, Procedure, Reporting, and Clinical Implementation of Results**

VALVULAR STRESS ECHOCARDIOGRAPHY (VSE) GUIDE FOR REFERRAL, PROCEDURE, REPORTING AND CLINICAL IMPLEMENTATION						
VSE Indication	**VSE Queries**	**Type of Stress**	**Sequence of Image Acquisition**	**Minimum Report Content**	**VSE Result**	**Clinical Implementation**
Symptomatic patient				Report symptoms relationship with changes		
Non-severe MR	MR severity rise +/- SPAP rise >60mmHg +/- LVEF failure to rise by 4%	Exercise	Color Doppler (MR PISA, VC, jet), MR CW Doppler (PISA), TR CW Doppler (SPAP), LV views	MR severity increase, max MR severity and SPAP, CR, inducible ischemia	Non-severe MR Severe MR	Medical management Surgical indication (2)
Pulmonary edema	Inducible ischemia +/- ischemic MR	Exercise	LV views, color Doppler to detect MR	Inducible ischemia and ischemic MR	Ischemia +/- MR	Revascularisation +/- MV repair
	Inducible ischemia	Dobutamine				
Mild MR before CABG	MR severity rise +/- SPAP rise >60mmHg	Exercise	Color Doppler (MR PISA, VC, jet), MR CW Doppler (PISA), TR CW Doppler (SPAP), LV views	MR severity increase, max MR severity and SPAP, inducible ischemia	No dynamic MR Dynamic MR + SPAP rise	CABG only CABG + MV repair (1)
Non-severe MS	Mean grd >15mmHg +/- SPAP >60mmHg +/- MR severity rise	Exercise	TR CW Doppler (SPAP), MS CW Doppler (mean grd)	MS severity grading, exertion mean grd, exertion SPAP	Non-severe MS Severe MS	Medical management Intervention (class I - 1, 2)
	Mean grd >18mmHg	Dobutamine				
Non-severe AR	Co-existent abnormalities (e.g. ischemia), LVEF failure to rise +/- SPAP >60mmHg	Exercise	MS CW Doppler (mean grd) only LV views, TR CW Doppler for SPAP, color Doppler to detect MR	Contractile reserve, SPAP, inducible MR	Normal response Abnormal response	Medical management Heart Valve Team decision
Non-severe AS	Co-existent abnormalities (e.g. ischemia), and mean grd rise with calculated AV area failure to increase with flow	Exercise / Dobutamine	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)	AS severity, contractile reserve, inducible ischemia	Non-severe AS Severe AS	Assess non-cardiac causes Intervention (class I - 1, 2)
Paradoxical low flow AS	Severe AS assessing grd and calculated AV area change with increase in flow	Exercise / Dobutamine	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)	AS severity, contractile and flow reserve, inducible ischemia	Non-severe AS Severe AS	Medical management Intervention (class IIa - 1, 2)
Equivocal AV PPM / stenosis	Severe PPM/stenosis assessing grd and valve area change with increase in flow	Exercise / Dobutamine	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only), color Doppler (to detect MR)	AV PPM / stenosis severity, CR, inducible ischemia, inducible MR, exertion SPAP	Not severe PPM/ stenosis Severe PPM/ stenosis	Medical management Heart Valve Team decision
Equivocal MV PPM / stenosis	Severe PPM/stenosis assessing grd and SPAP	Exercise	TR CW Doppler (SPAP), MS CW Doppler (mean grd)	MV PPM / stenosis severity, mean grd, exertion SPAP	Not severe PPM/ stenosis Severe PPM/stenosis	Medical management Heart Valve Team decision
	Severe PPM/stenosis assessing grd	Dobutamine				
Asymptomatic patient				Report observed symptomatic status		
Severe MR	Symptoms +/- SPAP rise >60mmHg, LVEF failure to rise by 4% +/- GLS failure to rise by -2%	Exercise	TR CW Doppler (SPAP), LV views	SPAP, CR	Symptoms No symptoms + normal VSE No symptoms + SPAP >60mmHg No symptoms + no LV CR	Surgery (class I - 1, 2) Review at 6 months Repair if durable low risk (class IIb - 1) Heart Valve Team decision
Significant MS	Symptoms +/- mean grd >15mmHg +/- SPAP >60mmHg	Exercise	TR CW Doppler (SPAP), MS CW Doppler (mean grd)	MS severity grading, exertion mean grd, exertion SPAP	Symptoms No symptoms	Intervention (class I - 1, 2) Hemodynamically significant MS may need intervention before major surgery / pregnancy planning
Severe AR	Symptoms +/- CR	Exercise	LV views, TR CW Doppler (SPAP), color Doppler (to detect MR)	CR, SPAP, inducible MR	Symptoms No symptoms No symptoms + no LV CR	Surgery (class I - 2) Review at 6 months Close surveillance
Severe AS	Symptoms +/- SBP drop or failure to rise by 20mmHg, ST depression, RWMA, CR, LV longitudinal function, SPAP>60mmHg, mean grd >18-20mmHg	Exercise	LV views, TR CW Doppler (SPAP), AV CW Doppler, LVOT PW Doppler, color Doppler (to detect MR)	CR, inducible ischemia, inducible MR, SPAP	Symptoms No symptoms + normal VSE No symptoms + SBP drop No symptoms + mean grd >20mmHg	Intervention (class I - 1, 2) Review at 6 months Intervention (class IIa - 1, 2) Intervention (class IIb - 1)
Low LVEF						
Low flow AS	LV flow reserve and grd + calculated AV area changes with increase in flow	Dobutamine	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)	AS severity, flow reserve, inducible ischemia	Non-severe AS Severe AS + flow reserve Severe AS + no flow reserve	Medical management Intervention (class IIa - 1, 2) Intervention (class IIb – 1; class IIa - 2)
Low flow AV prosthesis	LV flow reserve and grd + calculated valve area changes with flow	Dobutamine	AV CW Doppler, LVOT PW Doppler, LV views, LVOT view (baseline only)	AS severity, flow reserve, inducible ischemia	Non-severe stenosis Severe stenosis	Medical management Heart Valve Team decision

Garbi, M. et al. J Am Coll Cardiol Img. 2015; 8(6):724-36.

This table combines the essential information from the VSE guide tables. It can be printed and used as a poster guide in echocardiography laboratories and valve clinics.

VALVE DISEASE WITH REDUCED LV SYSTOLIC FUNCTION. VSE-demonstrated severe AS in patients with low-flow, low-gradient AS is an indication for intervention in both guidelines (1,2). The ACC/AHA guidelines state this as a Class IIa indication (2). The ESC guidelines differentiate the indication into Class IIa in the presence of flow reserve and Class IIb in its absence (1).

GUIDELINES, EVIDENCE, AND FURTHER RESEARCH NEEDS

Agreement between the current ESC and ACC/AHA valve disease management guidelines reveals the VSE indications supported by robust evidence at the time of the publication of these guidelines, while disagreement reveals the VSE indications in need for either further research or appraisal of the later acquired evidence.

SYMPTOMS DESPITE NONSEVERE VALVE DISEASE. Both the ESC and the ACC/AHA valve disease management guidelines (1,2) recommend VSE and intervention in VSE-demonstrated severe valve disease in MS (Online Figures 1 to 7) and AS. The guidelines differ in MR and AR.

In primary MR, both guidelines (1,2) recommend VSE, but only the ACC/AHA guidelines (2) recommend intervention in cases of severe MR. MR quantification is known to be challenging, particularly when the MR jet is eccentric. Quantification becomes even more challenging on exertion and the evidence regarding quantification of MR severity changes during VSE in primary MR is limited (9). Further evidence is necessary in primary MR to corroborate MR quantitative changes during VSE with catheterization findings on exertion and the clinical outcome of patients with and without demonstrated severe MR.

In unexplained pulmonary edema, only the ESC guidelines (1) recommend VSE. Despite the lack of evidence, this seems a reasonable VSE indication (8) to exclude ischemia and ischemic MR. Nevertheless, evidence is needed regarding the incidence of VSE-demonstrated MR (or other hemodynamic changes) in this setting.

Before CABG, only the ESC guidelines (1) recommend MR assessment with VSE to inform decision-making regarding concomitant mitral valve repair. As described earlier in the Mitral Regurgitation section, the RIME trial (10) provides evidence on this topic. This trial reported mitral valve repair benefit at the time of CABG in patients with at least moderate MR at rest or on exertion but did not specifically address the role of VSE. For this assessment, a similar study would be needed, randomizing patients with at least moderate MR on exertion only.

In AR, the ACC/AHA guidelines (2) recommend exercise testing. There is no role for echocardiography to regrade AR severity during exertion, because, as described in the Aortic Regurgitation section, AR is reduced with increases in heart rate.

ASYMPTOMATIC SIGNIFICANT VALVE DISEASE. Both the ESC and the ACC/AHA valve disease management guidelines (1,2) recommend exercise testing and intervention in cases of demonstrated symptoms of MR, MS, and AS.

In MR, only the ESC guidelines (1) recommend intervention (Class IIb indication) when SPAP is >60 mm Hg during VSE. Although there is evidence that SPAP increases with exertion (25) can predict the development of symptoms within 2 years, clinical follow-up of patients with severe MR is performed at shorter intervals. To a greater extent, SPAP >60 mm Hg on exertion is not unusual with age even in the absence of MR (46). Consequently, further evidence is needed to refine this indication considering age-related exertional SPAP and exertional SPAP change at follow-up for the same patient.

Although there is evidence (26–28) that the lack of LV contractile reserve predicts poor prognosis, no relative indication for intervention exists. This mirrors skepticism regarding the ability of echocardiography to accurately determine a small change in LVEF (4%) and the limited data regarding global longitudinal strain. Current evidence suggests at least the need for further research regarding LV contractile reserve in asymptomatic severe MR (27). The role of 3-dimensional echocardiography must also be investigated, considering its higher accuracy and reproducibility in LVEF assessments.

In AS, both guidelines (1,2) also recommend intervention in cases of blood pressure drop on exertion. Nevertheless, only the ESC guidelines recommend intervention (Class IIb) in cases of mean gradient rise >20 mm Hg during VSE. There is evidence (36,37) that this mean gradient rise confers poor prognosis within 18 to 24 months, although clinical follow-up of patients with severe AS is performed at shorter intervals. Because samples used in the aforementioned studies were small, further evidence is needed.

In AR, exercise testing to reveal symptoms is recommended only by the ACC/AHA guidelines (2), and VSE is not recommended. The role of VSE in predicting LV systolic dysfunction has limited evidence (29,30); considering the clinical implications of LV systolic dysfunction in severe AR, it seems worthwhile to further investigate this VSE indication and its impact on clinical outcomes.

VALVE DISEASE WITH REDUCED LV SYSTOLIC FUNCTION. Both the ESC and the ACC/AHA valve disease management guidelines (1,2) recommend VSE and intervention in cases of demonstrated severe AS in low-flow, low-gradient AS with reduced LV systolic function (Online Figures 8 to 13). The indication is Class IIa in the ACC/AHA guidelines regardless of flow reserve status but Class IIb in the ESC guidelines in cases of lack of demonstrated flow reserve. In support of the ACC/AHA guidelines, there is evidence that the VSE-demonstrated lack of flow reserve does not predict lack of LVEF recovery (47), and, furthermore, there is evidence that clinical outcome is improved by aortic valve replacement in patients with VSE-demonstrated lack of flow reserve (48). Larger clinical outcome studies may shed more light on this topic.

CONCLUSIONS

VSE is an important clinical tool in the assessment and management planning of patients with valve disease. The technique is being perfected in high-volume centers, and the applications are continuously evolving (**Central Illustration**). Nevertheless, further evidence is needed with regard to many VSE indications and the outcome-based clinical implementation of results.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Patrizio Lancellotti, Department of Cardiology, University Hospital, Université de Liège, CHU du Sart Tilman, 4000 Liège, Belgium. E-mail: plancellotti@chu.ulg.ac.be.

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KEY WORDS dobutamine, exercise, guidelines, stress echocardiography, valvular heart disease

APPENDIX For supplemental images and their legends, as well as a list of the HAVEC study group members, please see the online version of this article.