Current concepts and evidence

Stress echocardiography for assessment of native valvular heart disease

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Introduction

Stress echocardiography (SE) plays an important role along with resting transthoracic (TTE) and transesophageal echocardiography (TEE) with respect to evaluation and management of valvular heart disease.

It can be mainly used when there is a discrepancy between the clinical manifestation and the severity of the valvular disease at rest in the following settings:

(A) Severe asymptomatic valvular disease.

(B) Symptomatic non-severe valvular disease.

(C) Low-Flow-Low-Gradient Status in severe aortic stenosis (LF-LG-AS) with reduced ejection fraction (LVEF).

Thus, a quantitative prognostic assessment can be achieved, which helps in the decision-making with regards to the need of an intervention or surgery.

Accordingly, SE is recommended in specific situations as an adjunct to assessment of valvular heart disease by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) [1–3]. In this review we will summarize the current concepts and evidence for stress echocardiography in the most common clinical situations encountered in patients with heart valve disease. For a summary of the current recommendations please refer to the table.

Methods for stress echocardiography in valve disease

The underlying principle for stress echocardiography in valve disease is an increase in cardiac output. This can be achieved either by exercise using **(a)** supine-bicycle exercise **(b)** treadmill exercise or by pharmacological stress with **(c)** low-dose dobutamine.

A disadvantage of the exercise stress test conducted on a treadmill compared to supine-cycling is that the image acquisition can only be obtained shortly after the peak-stress is reached, not during it. This delay leads to loss of the exact moment of the maximum exertion and may lead to an underestimation of the findings. In addition, low level exercise assessment is impossible on a treadmill. Therefore, the supine-bicycle stress is preferred for SE studies when available.

Physical exercise is physiological and should ideally be pursued if possible. It can be used to evaluate not only the physical performance but also the pulmonary pressure (sPAP) during stress. On the other hand, non-cardiac limiting factors (i.e skeletomuscular system related) leading to reduced physical performance and early termination of the test is disadvantageous in exercise SE and affects the validity of the test negatively.

List of abbreviations

A-fib	Atrial fibrillation
AS	Aortic stenosis
AR	Aortic regurgitation
AVPG	Aortic valve pressure Gradient
DSE	Dobutamine stress echocardiography
EROA	Effective regurgitation orifice area
ESC	European society of cardiology
GLS	Global longitudinal Strain
HF	Heart failure
LF	Low flow
LG	Low gradient
LV	Left ventricle
LVEF	Left ventricular ejection Fraction
MR	Mitral Regurgitation
MS	Mitral Stenosis
MVPG	Mitral valve pressure gradient
MVR	Mitral valve replacement
PMBC	Percutaneous mitral balloon commissurotomy
RV	Right Ventricle
SAVR	Surgical aortic valve replacement
SE	Stress echocardiography
sPAP	Systolic pulmonary arterial Pressure
TAVR	Transcatheter aortic valve replacement
TDI	Tissue Doppler imaging
TEE	transesophageal echocardiography
TVPG	Transvalvular pressure Gradient
TTE	Transthoracic echocardiography

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Pharmacological stress with the inotropic agent dobutamine is an alternative when exertion with sufficient physical stress is not possible. This is classically done in the case of LF-LG-AS with reduced LVEF. Because of the vasodilatory effect of dobutamine and its influence on hemodynamics, assessment of sPAP or mitral regurgitation (MR) during this stress modality is not recommended [1].

Before any stress test is conducted for assessment of valvular heart disease, a comprehensive resting transthoracic echocardiography is performed, including evaluation of function and volumes of both ventricles, pulmonary pressure, and with an additional focus on the specific measurements of the valve disease under investigation. This is followed by measurements at different levels of stress, allowing for evaluation of the valve function during physiological stress, its effect on biventricular volumes and function, as well as the hemodynamic changes of the transvalvular pressure gradients (TVPG) and sPAP.

Furthermore, additional aspects such as symptoms, blood pressure reaction and the functional capacity are assessed. These aspects can provide additional information about the severity and physiological limitations of a valvular disease, which can be helpful in making decisions about further management [1–3].

Aortic Stenosis (AS)

A severe symptomatic AS is an indication for aortic valve replacement (TAVR/SAVR). Stress testing is contraindicated in symptomatic patients [2, 3].

Asymptomatic severe Aortic Stenosis

In asymptomatic patients with **(a)** manifest LV systolic dysfunction in TTE (EF <50% class I and EF <55% class IIa) or with **(b)** a normal EF and evidence of very severe aortic valve stenosis, such as Vmax >5m/s, dp mean >60 mmHg, rapid progression of the valve disease or elevated BNP (class IIa), an interventional or surgical

Table 1

Valvular disease	SE-Protocol	Monitored Parameters	Indicators of significant valvular disease
Asymptomatic severe Aortic Stenosis	Exercise or dobutamine	Symptoms	Development of symptoms
		BP reaction	Pathological BP response
		Mean AVPG	Increase in mean gradient >18 mm Hg
		sPAP	sPAP >60 mm Hg
			pathological contractile reserve or GLS reaction
Symptomatic non-severe Aortic Stenosis	Exercise or dobutamine	Mean AVPG	Increase in mean AVPG >20 mm Hg
			Mean resting AVPG >35 mm Hg and a stress-induced increase >20 mm Hg
Low-Flow-Low-Gradient Aortic Stenosis with reduced LVEF	Low dose dobutamine (up to 20 mg/kg/min)	SV	SV >20% increase
		AVA	AVA <1.2 cm^2
		mean AVPG	Mean gradient
			>30 mm Hg
Aortic Regurgitation	Exercise	Symptoms	Development of symptoms
		Functional capacity	Reduced functional capacity
Mitral Stenosis	Exercise or dobutamine	Symptomsfunctional capacity-mean MVPG,sPAP	Development of symptoms
			Reduced functional capacity
			mean MVPG >15 mm Hg during Exercise,
			mean MVPG >18 mm Hg during dobutamine
			sPAP >60 mm Hg
Chronic primary mitral Regurgitation	Exercise or dobutamine	Symptoms	Development of symptoms
		functional capacity	reduced functional capacity,
		EF	sPAP >60 mm Hg
		sPAP,	increase in Regurgitation volume
		coaptation distance,	Reduced TAPSE
		severity of MR	
Chronic Secondary Mitral Regurgitation	Exercise or dobutamine	Symptoms	EROA >13 mm^2
		EROA	large increase of sPAP
		sPAP	

SE = stress echocardiography, BP = blood pressure, AVPG = aortic valve pressure gradient, sPAP = systolic pulmonary artery pressure, SV = stroke volume, AVA = aortic valve area, MVPG = mitral valve pressure gradient, TAPSE = tricuspid anular plane systolic excursion, EROA = effective regurgitant orifice area

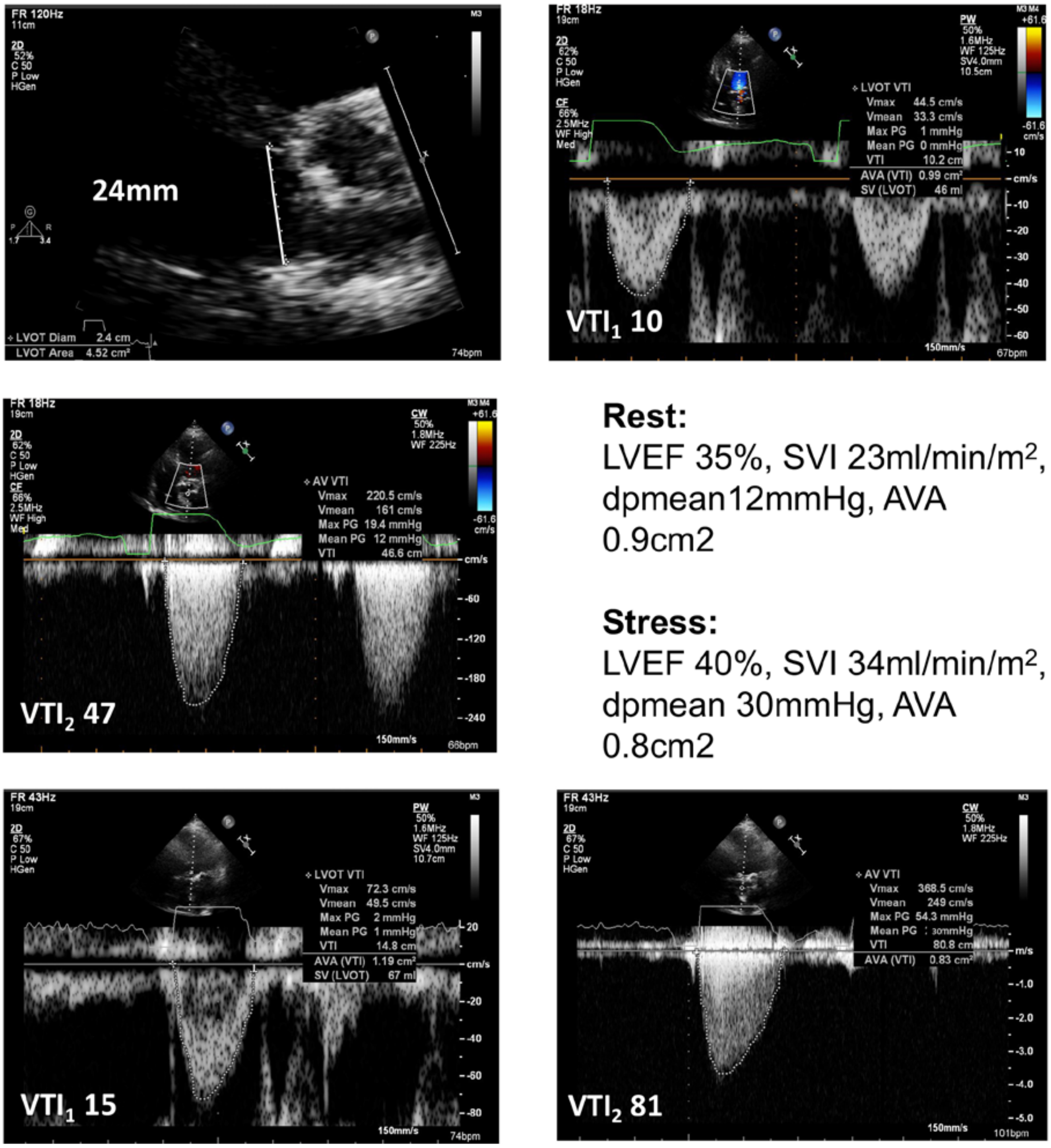

Figure 1: Illustration of findings in true severe low-flow low-gradient aortic sternosis during low-dose dobutamine stress echocardiography. Top and middle row – findings at rest. Bottom row – findings during low dose dobutamine stress (20µg/kg/min). Findings indicate contractile reserve and severe stenosis.

treatment (TAVR/SAVR) is recommended according to the AHA and ESC guidelines. [2, 3].

In asymptomatic patients not fulfilling the above criteria, SE can help to identify a specific patient population that may benefit from aortic valve replacement [4]. In asymptomatic aortic valve stenosis, SE may unmask symptoms [5]. Asymptomatic patients who become symptomatic during stress testing are more likely to develop symptoms within 12 months [6].

An increase in the mean transvalvular pressure gradient (AVPG) during exercise may suggest a severe, hemodynamically relevant AS or a rigid aortic valve. Prospective cohort studies and meta-analyses have shown that an increase in mean AVPG (>18–20 mmHg) or sPAP (>60 mmHg) during stress-testing in asymptomatic patients can serve as predictive parameters for adverse cardiac outcomes such as occurrence of symptoms, decompensated heart failure, hospitalisation, or AVR dictated by symptoms during follow-up [7–9]. However, according to the available evidence, the importance of these parameters with respect to long-term mortality is still debatable [7]. Thus, there are no strong recommendations in the current American and European Guidelines concerning the value of these measurements in the decision making with regards to valve replacement [2, 3]. These measurements may however be an indicator for the necessity of a close follow-up. In addition, the decrease or minimal increase in LVEF during exercise is an abnormal response and prognostically worse compared to patients with normal LV systolic response [10].Donal E et al. have shown that a relevant AS has a negative impact on longitudinal myocardial function (GLS) evaluated by TDI (Tissue Doppler imaging) despite normal EF. Moreover the GLS is more severely impaired in populations with a relevant AS and a positive SE [11]. This could be due to subclinical microvascular ischemia. In addition, a meta-analysis by Magne J. et al. and a study by Klaeboe LG et al. have shown that a pathological GLS reaction during exercise is associated with increased mortality [12, 13]. Therefore, asymptomatic patients with a pathological EF or pathological GLS reaction induced by a stress test may benefit from early therapy [13].

Accordingly, the American and European guidelines recommend an aortic valve replacement (SAVR/TAVR) in asymptomatic patients with severe AS who demonstrate symptoms (class I) or a pathological drop in blood pressure or reduced functional capacity in a stress test.

Prospective studies have shown that an abnormal ergometry with regard to symptoms, pathological ST-segment changes, ventricular arrhythmias, or an abnormal systolic blood pressure response (<10mmHg exercise induced rise or >20mmHg drop compared to baseline) is associated with a poor prognosis in terms of the development of symptoms or sudden cardiac death [14, 15]. Accordingly, the American and European guidelines recommend an aortic valve replacement (SAVR/TAVR) in asymptomatic patients with severe AS who demonstrate symptoms (class I) or a pathological drop in blood pressure (AHA >10 mmHg, ESC >20 mmHg, class IIa) or reduced functional capacity in a stress test [2, 3].

Symptomatic non-severe Aortic Stenosis

SAVR is recommended in this group of patients undergoing cardiac surgery for any other reason (ESC class IIa, AHA/ACC IIb), otherwise follow-up with TTE is recommended [2, 3].

There are several studies that have investigated the value of SE in this patient group. According to these studies, an increase in mean AVPG >20 mmHg during stress-testing is associated with a more rapid progression of moderate AS, similar to asymptomatic severe AS [16]. In a prospective cohort study, Maréchaux S et al. showed that a mean resting gradient >35 mmHg and a stress-induced increase >20 mmHg of the mean AVPG were associated with high cardiovascular mortality during a 24-months follow-up. Consequently, a subgroup of patients at high risk could be identified with the help of these measurements, who may benefit from close monitoring and therefore improved timing of an invasive treatment [17].

Low-Flow-Low-Gradient Aortic Stenosis (LF-LG-AS) with reduced LVEF (<50%)

LF-LG-AS with reduced LVEF is defined by an aortic valve area (AVA) <1 cm^2, a maximal flow velocity (Vmax) <4 m/s, and a mean AVPG <40 mmHg in case of a reduced left ventricular systolic function. This can be due to a true severe AS, or due to a pseudo-severe AS in which the reduced opening of the AV is due to the reduced transvalvular blood flow [18]. Low-dose dobutamine SE is an indispensable test for differentiating between the two forms and is therefore recommended in the current guidelines [2, 3]. If a contractile reserve (increase in stroke volume >20%) is present, in the case of true severe AS, the blood flow (Vmax>4 m/s) or the mean AVPG (>30 mmHg) will increase during stress without an increase in the AVA (figure), whereas in the case of pseudo-severe AS, the AVA increases (>1 cm^2) with a concomitant minimal increase in the mean AVPG [19]. In the case of limited flow reserve, the severity of the AS can be estimated by the projected AVA estimated hypothetically at normal transvalvular flow rate (250 mL/min) and calculated with the following formula.

$$AVAProj = AVARest + \frac{AVAPeak - AVARest}{QPeak - QRest} x(250 - QRest)$$

Annabi M.S. et al. showed that the projected AVA performs better to define a true severe LF-LG-AS in comparison to the classical Guidelines criteria (AVA<1 cm^2 or mean AVPG >40 mmHg) and is the best predictor of mortality in patients receiving conservative medical treatment [20].

In the absence of contractile reserve, computed tomography (CT) serves as an additional diagnostic tool to evaluate the severity of AS [21]. In addition, it has been shown that the absence of contractile reserve is associated with higher perioperative mortality [22].

Low-Flow-Low-Gradient Aortic Stenosis (LF-LG-AS) with normal LVEF (>50%)

In this group with a normal ejection fraction, the calculated AVA is <1 cm^2 while the mean AVPG is <40 mmHg. A LF-LG-AS with normal LVEF is often found in elderly patients with a diagnosis of arterial hypertension and a hypertrophic LV, where the small volume of the LV may result in reduced tansvalvular flow [23]. However, this diagnosis should only be made with caution and after exclusion of measurement errors, especially when Vmax <3m/s and mean AVPG <20 mmHg [19]. SE does not play a role in this group [19]. The severity of calcification assessed by calcium score can be helpful in this situation [21].

Aortic Regurgitation (AR)

SAVR is indicated, according to current American and European guidelines, in **(a)** symptomatic severe AR, **(b)** asymptomatic AR with reduced LVEF <50% (class I), or **(c)** patients with asymptomatic moderate (class IIa) to severe (class I) AR undergoing cardiac surgery for any other reason. In addition, in normal LVEF with LV dilatation (LVESD >50 mm, indexed LVESD >25 mm/m^2, or LVEDD >70 mm), SAVR should be considered (class IIa according to ESC) and could be performed in severe AR with normal LVEF and increasing LV dilatation (LVEDD >65 mm) (class IIb AHA/ACC) [2, 3].

In asymptomatic AR with normal LV function and dimensions, an exercise test is considered reasonable to provoke symptoms because of the remarkably high mortality in case of delayed treatment [2, 3, 24, 25].

Thus, there are no strong recommendations in the current American and European Guidelines concerning the value of these measurements in the decision making with regards to valve replacement.

In addition, stress echocardiography may unmask subclinical LV dysfunction in terms of a decrease or less than expected increase in LVEF (lack of contractile reserve) or pathological GLS during stress [1]. The decrease in LVEF during stress occurs because of hemodynamic changes due to volume overload and increased left ventricular afterload. The absence of contractile reserve, in contrast to resting parameters, is an important predictive factor for the development of LV systolic dysfunction during follow-up [26]. Reduced longitudinal contraction during stress in longitudinal function evaluation by TDI could indicate latent LV dysfunction [27]. The aim of these parameters is to avoid irreversible LV dysfunction as a consequence of severe AR by choosing the right timing for surgical treatment. However, there is not yet sufficient evidence for a recommendation concerning these criteria in the current guidelines [2, 3].

Stress echocardiography plays no role in the graduation of AR, as tachycardia with subsequent shortening of diastole leads to a decrease in the severity of AR during exercise [1].

Mitral Stenosis (MS)

Percutaneous mitral balloon commissurotomy (PMC) or mitral valve replacement (MVR) are recommended in current guidelines for patients with symptomatic moderate to severe MS (MVA<1.5 cm2) (Class I). In asymptomatic patients with high thromboembolic risk (Atrial fibrillation, history of thromboembolism) or high risk of hemodynamic decompensation (sPAP >50 mmHg, prior to major non-cardiac surgery, pregnancy desire), PMBC should be considered for an MVA<1.5 cm2 with favorable anatomy [2, 3].

SE is an established investigation in the evaluation of relevant MS and plays a significant role in patients with discrepancies between symptoms and severity of MS. It is particularly useful in: **(a)** asymptomatic MS with MVA<1 cm2 **(b)** asymptomatic MS with MVA1-1.5 cm2 suitable for PMBC or prior to planned major surgery/pregnancy [1]. This involves assessment of symptoms, exercise capacity, and the hemodynamic effects of MS, represented by a relevant increase in mean MVPG and pulmonary pressure during exercise (Class I ACC/AHA) [2, 28]. While exercising, the cardiac output and HF increase and diastole shortens, leading to an exponential increase in MV gradients and pulmonary pressure. This reflects why the relevance of MS cannot be comprehensively evaluated by echocardiography at rest. Brochet E. et al. showed in their study that symptoms could be provoked in 46% of asymptomatic patients with relevant MS during SE, especially in the case of rheumatic MS [29]. Some data show that **(a)** an increase in mean MVPG >15 mmHg with exercise SE or >18 mmHg with Dobutamine SE or **(b)** increase of sPAP >60 mmHg in exercise SE are high-risk features and suggest a hemodynamically relevant MS [30–32]. In

Prognostically, an increase in EROA >13 mm^2 or sPAP (28 vs. 18 mmHg) is indicative of increased morbidity and mortality. On the other hand, a decrease in MR in DCM with a preserved contractile reserve may indicate a better prognosis.

symptomatic patients with an MVA >1.5 cm2, PMC may be considered in the presence of these high risk findings during stress (Class IIb) [2, 3].

In principle, exercise SE is recommended to evaluate the mean MVPG and sPAP during stress. If exercise is not possible, MVPG can be evaluated by Dobutamine SE. In this case, the sPAP should not be assessed [1].

Mitral Regurgitation (MR)

Chronic primary mitral Regurgitation

MVR is recommended for **(a)** symptomatic severe MR (class I), **(b)** asymptomatic severe MR with an LVEF <60% or a LVESD >40 mm (class I), and **(c)** asymptomatic severe MR with an LVEF >60%, a LVESD <40 mm, and either A-fib. secondary to the MR, a severely dilated LA (LAVI >60 ml/m2), or a sPAP >50 mmHg at rest (class IIa, ESC) [2, 3].

Similar to MS, SE can be informative in cases of discrepancy between symptoms and severity of MR (asymptomatic severe MR or symptomatic non-severe MR), as well as for risk stratification [2, 3]. Some studies have shown that a reduced exercise capacity in asymptomatic patients with severe MR is associated with a worse prognosis and increased mortality during follow-up [33, 34]. An increase in severity, an increase in sPAP >60 mmHg, absence of contractile reserve, or deterioration in RV function all indicate a poor prognosis and are associated with worse outcomes [35–38]. However, the available evidence is not sufficient for recommendations regarding these findings in the latest American and European guidelines [2, 3].

Chronic Secondary Mitral Regurgitation

Chronic secondary MR usually develops in ischemic or nonischemic cardiomyopathy. Primary drug therapy is recommended for secondary chronic MR in the current guidelines. If CABG surgery is planned, severe MR should be treated surgically at the same time (class I ESC, IIa ACC/AHA) [2, 3].

An increase in the severity of MR during exercise may also be of utility in cases of unclear symptoms (e.g., dyspnea or recurrent unclear events of cardiac decompensation) if the severity of MR or the systolic dysfunction at rest do not provide a sufficient explanation for the symptoms [1]. Prognostically, an increase in EROA >13 mm^2 or sPAP (28 vs. 18 mmHg) is indicative of increased morbidity and mortality [39]. On the other hand, a decrease in MR in DCM with a preserved contractile reserve may indicate a better prognosis [40].

Conclusion

SE provides important additional information in valvular heart disease and is thus helpful for assessment of prognosis and optimal planning of therapy. Physical stress allows for the assessment of symptomatic limitations and hemodynamic effects, while pharmacological stress informs about hemodynamic effects of valvular heart disease by echocardiography; both stress modalities deliver prognostic information. However, the evidence is currently still insufficient in many areas for corresponding recommendations in the current guidelines.

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Take home messages

- Stress echocardiography is a valuable diagnostic method in (a) severe asymptomatic valvular disease, in (b) symptomatic non-severe valvular disease and in (c) Low-Flow-Low-Gradient Status in severe aortic stenosis (LF-LG-AS) with reduced ejection fraction (LVEF).
- Physical stress, preferably with supine-bicycle exercise should be employed except for LF-LG-AS.
- In patients with asymptomatic severe aortic stenosis, symptoms or a pathological drop in blood pressure during a stress test, valve replacement should be considered.
- Gradients across stenotic valves, increase in severity of regurgitation, left ventricular systolic dysfunction, and systolic pulmonary artery pressure give prognostic information and may be accounted for when managing patients with non-symptomatic or on-severe valve disease.

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References
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