JACC: CARDIOVASCULAR IMAGING VOL. 7, NO. 2, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2013.08.011

CME

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STATE-OF-THE-ART PAPER

Exercise Testing in Asymptomatic Severe Aortic Stenosis

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JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragavendra R. Baliga, MD

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CME Objective for This Article: At the end of this activity, the reader should be able to: 1) evaluate the usefulness and clinical implication of exercise stress echocardiography in asymptomatic patients with severe aortic stenosis; and 2) analyze the exercise echocardiographic findings identifying patients at higher risk of reduced event-free survival.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosure: All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval:
Issue Date: February 2014
Expiration Date: January 31, 2015

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Manuscript received March 8, 2013; revised manuscript received July 26, 2013, accepted July 26, 2013.

Exercise Testing in Asymptomatic Severe Aortic Stenosis

The management and the clinical decision making in asymptomatic patients with aortic stenosis are challenging. An "aggressive" management, including early aortic valve replacement, is debated in these patients. However, the optimal timing for surgery remains controversial due to the lack of prospective data on the determinants of aortic stenosis progression, multicenter studies on risk stratification, and randomized studies on patient management. Exercise stress testing with or without imaging is strictly contraindicated in symptomatic patients with severe aortic stenosis. Exercise stress test is now recommended by current guidelines in asymptomatic patients and may provide incremental prognostic value. Indeed, the development of symptoms during exercise or an abnormal blood pressure response are associated with poor outcome and should be considered as an indication for surgery, as suggested by the most recently updated European Society of Cardiology 2012 guidelines. Exercise stress echocardiography may also improve the risk stratification and identify asymptomatic patients at higher risk of a cardiac event. When the test is combined with imaging, echocardiography during exercise should be recommended rather than post-exercise echocardiography. During exercise, an increase >18 to 20 mm Hg in mean pressure gradient, absence of improvement in left ventricular ejection fraction (i.e., absence of contractile reserve), and/or a systolic pulmonary arterial pressure >60 mm Hg (i.e., exercise pulmonary hypertension) are suggestive signs of advanced stages of the disease and impaired prognosis. Hence, exercise stress test may identify resting asymptomatic patients who develop exercise abnormalities and in whom surgery is recommended according to current guidelines. Exercise stress echocardiography may further unmask a subset of asymptomatic patients (i.e., without exercise stress test abnormalities) who are at high risk of reduced cardiac event free survival. In these patients, early surgery could be beneficial, whereas regular follow-up seems more appropriate in patients without echocardiographic abnormalities during exercise. (J Am Coll Cardiol Img 2014;7:188–99)

Aortic stenosis (AS) is the most common valvular disease and the third most prevalent form of cardiovascular disease in the Western world. Its prevalence increases with population aging and is present in 3% to 7% of patients over 65 years of age (1). The diagnosis of AS is classically based on echocardiography and may be supplemented by other cardiovascular imaging modalities. The majority of AS patients are asymptomatic but have an increased risk of untoward events such as ventricular dysfunction, symptomatic deterioration, heart failure, and even death in a significant proportion of them. In 2 recent studies including asymptomatic patients with at least moderate AS, a mean rate of cardiovascular death and of sudden death of 3.7% and 1.55% respectively, were reported during a median follow-up of 16 to 18 months (2,3). In this regard, "aggressive" management, including early aortic valve replacement (AVR), is debated in asymptomatic patients. The optimal timing for AVR remains controversial due to the lack of prospective data on the determinants of AS progression, multicenter studies on risk stratification, and randomized studies on patient management. In the recently updated European Society of Cardiology (ESC) guidelines and in the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines (4), based on a consensus of experts, the only class I indication for performing an AVR in patients with severe AS is the presence of symptoms at rest or during an exercise test and/or the presence of left ventricular (LV) systolic dysfunction, defined as LV ejection fraction <50%. Initial symptoms experienced by patients with AS are often subtle or insidious and can be difficult to identify purely on clinical grounds. Many patients either fail to acknowledge their symptoms or do not report their symptoms promptly. The development of symptoms signifies a dramatic change in the natural history of the condition with a reported average survival of <2 years. Moreover, patients who become symptomatic are at significant risk of developing adverse cardiac events while waiting for surgery, and perioperative risk increases significantly with the severity of symptoms. Of note, women seem to be less likely than men to be referred for surgery despite symptoms and severe AS. This adverse

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clinical outcome has recently raised the question of whether performing early elective surgery could be a more beneficial strategy in reducing long-term risk. However, there is reluctance to perform surgery earlier than necessary because of a mortality rate for AVR of approximately up to 3% to 5%, even in patients younger than 70 years of age, followed by long-term prosthetic valve-related morbidity.

The ESC and the ACC/AHA have placed renewed emphasis on the role of exercise testing to provide objective evidence of exercise capacity and symptom status in patients with valvular heart disease (4,5). Exercise testing represents the first choice over pharmacological stress for risk stratification in asymptomatic patients with AS (6,7). When combined with echocardiography, although post-exercise echocardiography using treadmill or bicycle exercise may be used, supine bicycle exercise is the recommended technique. Semisupine exercise echocardiography offers the advantage that Doppler information, in addition to the assessment of regional wall motion, can be evaluated at peak exercise but also continuously throughout the test (8). However, exercise test is strictly contraindicated in symptomatic patients with AS.

ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

AS = aortic stenosis

AVR = aortic valve replacement

ESC = European Society of Cardiology

LV = left ventricular

PHT = pulmonary hypertension

SPAP = systolic pulmonary arterial pressure

Indications for Exercise Stress Test

AS is a prevalent condition and a progressive disease (2). When symptoms appear, usually after a long asymptomatic period, prompt surgical replacement of the aortic valve is warranted (4,9). The risk of sudden death is usually considered as low in asymptomatic patients, even with severe AS. It may, nevertheless, occur soon after the onset of symptoms or if the waiting period for surgery is too long. Moreover, symptomatic status can be difficult to establish, especially in elderly patients, who may ignore their symptoms or may reduce their level of physical activity to avoid or minimize symptoms. Thus, exercise testing could be useful to unmask symptoms in patients with severe AS who claim to be asymptomatic or who have equivocal symptoms. A recent meta-analysis confirmed that symptom-limited stress testing is safe and has an important prognostic value (10). Of interest, among the 7 studies comprising approximately 500 patients, none of the patients with normal exercise stress test experienced sudden cardiac death. Exercise testing is strongly advocated in the ESC guidelines (5), whereas it is a Class IIb recommendation in the ACC/AHA guidelines (4). In asymptomatic AS, the clinical value of exercise echocardiography as well as its place in the recent guidelines is still limited. It may, however, refine the risk stratification of asymptomatic AS patients. In this regard, exercise stress test could be recommended in patients with at least moderate AS in which symptom status is unclear. Furthermore, exercise stress echocardiography could be helpful for the management of patients with asymptomatic moderate to severe AS and preserved LV function.

Recommended Exercise Protocol

The following section is mainly based on our experience. These recommendations arise from more than 10 years of practice and from confrontation and discussion with other groups in Europe and North America.

A symptom-limited graded exercise test is recommended, and at least 80% of the age-predicted heart rate should be reached in the absence of symptoms. The test should be adapted to the clinical condition and should be performed under supervision of experienced person.

When the test is not combined with imaging, treadmill exercise is the most commonly used test in the United Kingdom and in the United States, while the upright bicycle test is the preferred approach in the rest of Europe. The exercise stress test is performed according the ACC/AHA practice guidelines using a Bruce modified protocol (11). In contrast, when combined with imaging during exercise, the test is performed on a dedicated tilted bicycle (Fig. 1).

Classically, the initial workload of 25 W is maintained for 2 min and the workload is increased every 2 min by 25 W. An increase by 10 W seems to be more appropriate in elderly patients with AS or in patients with low level of physical activities. Blood pressure and a 12-lead electrocardiogram are recorded at rest and at each step of the test. The patient should be frequently questioned for symptoms. Exercise test is interrupted promptly when the target heart rate is reached or in case of typical chest pain, limiting breathlessness, dizziness, muscular exhaustion, hypotension (drop in systolic blood pressure ≥20 mm Hg), or significant ventricular arrhythmias. To note, isolated abnormalities in the ST-segment (>2 mm ST-segment depression, horizontal, or down-sloping) are rarely a reason to stop the stress examination in patients with AS. The test is considered abnormal if the patient presents with ≥1 of the following criteria:

angina, evidence of dyspnea, dizziness, syncope or near-syncope, ≥2 mm ST-segment depression in comparison to baseline level, fall in systolic blood pressure ≥20 mm Hg or below baseline value, and complex ventricular arrhythmias (ventricular tachycardia, more than 3 premature ventricular complexes in a row) (12). The following contraindications should be strictly respected: 1) truly symptomatic AS (exertional shortness of breath, angina, dizziness, or syncope); 2) physical or mental disability to adequately perform an exercise stress test; 3) clear indication for surgery; 4) high blood pressure (systolic arterial pressure >200 mm Hg or diastolic arterial pressure >110 mm Hg); 5) uncontrolled or symptomatic arrhythmias; and 6) systemic illness.

Exercise Echocardiography

Exercise echocardiography (i.e., imaging performed during exercise) requires training and experience and the use of an adequate stress table. The images acquisition will focus on parameters related to the valve (including hemodynamics), to the LV and to the systolic pulmonary arterial pressure (SPAP). As some valve-related exercise changes are evanescent, peak exercise imaging is mandatory. Change in the LV filling pressure estimation (i.e., E/e′ ratio) should be obtained at low level of exercise (usually around 100 beats/min) in order to avoid E and A waves fusion and to ensure good tissue Doppler imaging quality; all other parameters should be obtained throughout the test. The dynamic changes in aortic mean pressure gradient and in transtricuspid pressure gradient need to be assessed throughout the test, from rest to low, intermediate, and peak levels of exercise (13,14). Due to frequent LV and aortic valve biphasic hemodynamic and mechanical responses during exercise, the imaging acquisition throughout the test may help to unmask this phenomenon (15). A rapid increase in pressure gradients or in SPAP can indicate a more severe disease process or an absence of pulmonary vascular function adaptation, low pulmonary compliance, and markedly increased pulmonary resistance.

The assessment of exercise-induced changes in LV systolic function is also very useful. Worsening in wall motion from baseline classically indicates an ischemic insult. The use of wall motion score may help to quantify such abnormalities that do not necessarily indicate the presence of significant coronary artery disease. The absence of LV contractile reserve is generally characterized by the absence or only small increase in LV ejection fraction or in long-axis function (derived from tissue Doppler imaging or 2-dimensional [2D] speckle tracking) (12,15–17). In a series of 50 asymptomatic patients with AS and normal resting LV ejection fraction (>50%), 40% of patients did not have LV contractile reserve and showed a significant exercise-induced decrease in LV ejection fraction (from 64 ± 10% to 53 ± 12%), suggesting that around one-half of them exhibited overt LV dysfunction during exercise. Furthermore, these patients with abnormal LV function adaptation during exercise more frequently developed symptoms during exercise and had lower event-free survival (18).

Recently, Donal et al. (17) reported that the quantification of LV myocardial longitudinal function using 2D speckle tracking during submaximal exercise may identify subclinical LV dysfunction. In addition, compared with LV ejection fraction, exercise LV longitudinal function appears to more accurately detect early and latent LV dysfunction, and an improvement <−1.4% in LV global longitudinal strain has been shown to be associated with a high risk of exercise abnormal response (17).

Figure 1. Exercise Stress Echocardiography Laboratory

Example of setting currently used to performed exercise stress echocardiography including 12-lead electrocardiogram and sphygmomanometer.

Clinical and Prognostic Value of Exercise Test

There are more studies published in the literature promoting the use of exercise stress test (i.e.,

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without imaging) than supporting exercise stress echocardiography.

Changes in clinical and electrocardiographic parameters during treadmill exercise test have been recently proven to influence the prognosis and subsequent clinical decision making in asymptomatic AS patients (Table 1). Approximately one-third of patients who claim to be asymptomatic may develop symptoms on exercise (14,18–22). The occurrence of exercise-limiting symptoms (dizziness, dyspnea at low workload, angina, or syncope), although nonspecific, predicts the rapid development of symptoms in daily life, cardiac death (including sudden death) and need for AVR (19–22), particularly in patients who are <70 years of age and physically active (21). Dizziness during a treadmill test had a higher positive predictive value than other criteria for the development of symptoms during the next year (21). The occurrence of rapidly reversible dyspnea at high workload (close to the age-sex predicted maximum workload) is considered to be normal. Abnormal blood pressure response (<20 mm Hg increase in systolic blood pressure) and ST-segment depression (>2 mm, horizontal or down-sloping) during exercise do not seem to improve the accuracy of the test (21).

In the meta-analysis published by Rafique et al. (10), it was shown that an abnormal exercise test in asymptomatic patients with AS leads to an 8-fold increase in risk of cardiac event during the follow-up. More importantly, the risk of sudden death was increased 5.5-fold.

During exercise stress test, appraisal of the respiratory gas-exchange and the measurement of peak maximal oxygen uptake (VO_2) may be of interest. In a recent bicentric study, we have shown that asymptomatic patients with AS might have reduced maximal exercise capacity, even in the absence of LV dysfunction or abnormal exercise response (in terms of symptoms, blood pressure, or electric changes) (23). Indeed, close to one-half of our patients had markedly reduced (<84%) age- and sex-predicted peak VO_2, according to the American Thoracic Society/American College of Chest Physicians recommendations (24). Furthermore, the main determinant of impaired maximal exercise capacity was elevated global LV hemodynamic afterload (i.e., valvuloarterial compliance, a surrogate of both valvular and arterial overload burden faced by the LV). Consequently, the measurement of peak VO_2 may provide an objective parameter allowing a better assessment of the symptomatic status and unmasking patients who deny symptoms or adapt their life-style to their condition. In the follow-up of these patients, regular (yearly) maximal exercise capacity evaluation could be of clinical interest and may

Table 1. Impact of Exercise Testing on Outcome and Clinical Decision Making in Patients With Asymptomatic AS

Stress Data	Parameters	Impact on Outcome	Ref. #	Impact on Clinical Decision (AVR): ESC Guidelines	Impact on Clinical Decision (AVR): ACC/AHA Guidelines
Clinical	Symptoms (dizziness, dyspnea at low workload, angina, syncope)	Onset of symptoms, cardiac-related death, AVR dictated by symptoms	(19,21,45)	Class I (level of evidence: C)	Class IIb (level of evidence: C)
	Abnormal blood pressure response (fall in blood pressure)			Class IIa (level of evidence: C)	Class IIb (level of evidence: C)
Electrocardiographic	Ventricular arrhythmias ST-segment depression (≥2 mm)	Onset of symptoms, cardiac-related death, AVR dictated by symptoms	(19,21,45)	—	Class IIb (level of evidence: C)
Echocardiographic	Increase in mean aortic pressure gradient: >18 or 20 mm Hg	Spontaneous symptoms, cardiac-related death, AVR dictated by symptoms, hospitalization for heart failure	(14,22)	Class IIb (level of evidence: C)	—
	Decrease/small increase in LV ejection fraction	Spontaneous symptoms, cardiac-related death, abnormal exercise test	(18)	—	—
	Exercise PHT	Reduced cardiac event-free survival, high rate of cardiac death	(13)	—	—

ACC/AHA = American College of Cardiology/American Heart Association; AS = aortic stenosis; AVR = aortic valve replacement; ESC = European Society of Cardiology; LV = left ventricular; PHT = pulmonary arterial hypertension.

improve the timing of surgery. Nonetheless, the relationship between decreased maximal exercise capacity in asymptomatic AS patients and outcome requires clarification and further studies.

Clinical and Prognostic Value of Exercise Echocardiography

Exercise-induced changes in mean pressure gradient. In asymptomatic moderate or severe AS (valve area <1.2 cm^2), exercise-induced changes in LV function or AS indexes are predictive of the outcome. Whatever the results of the exercise test, an increase in mean aortic pressure gradient by ≥18 to 20 mm Hg during exercise (Fig. 2) is associated with an increased risk of cardiac-related events (14,22). Two studies have reported similar results regarding the prognostic value of exercise-induced changes in mean aortic pressure gradient in asymptomatic AS. Our group has reported the results of a series including 69 consecutive patients with asymptomatic severe AS and normal LV function in whom exercise stress echocardiography was performed. Although patients who experienced an event during the follow-up had no significant difference in mean aortic pressure gradient at rest, as compared to those without event (41 ± 12 mm Hg vs. 38 ± 9 mm Hg), they exhibited a significant higher exercise-induced increase in mean gradient (+23 ± 8 mm Hg vs. +12 ± 7 mm Hg). Consequently, patients with marked exercise-induced increase in mean aortic pressure gradient also have significantly worse cardiac event-free survival (around 80% of events at 2-year follow-up). Furthermore, this parameter seems to provide incremental prognostic value over resting echocardiographic data and exercise electrocardiogram (22).

In 2010, a multicenter study confirmed our results (14). They have reported the resting and exercise echocardiographic data of 186 "truly" asymptomatic patients (i.e., without abnormality during an exercise test) with at least moderate AS. The cutoff value of an exercise-induced increase in mean aortic pressure gradient >+20 mm Hg was identified as a powerful predictor of poor outcome and was independently associated with a 3.8-fold increase in risk of cardiac event, regardless of age, exercise LV ejection fraction, or resting mean aortic

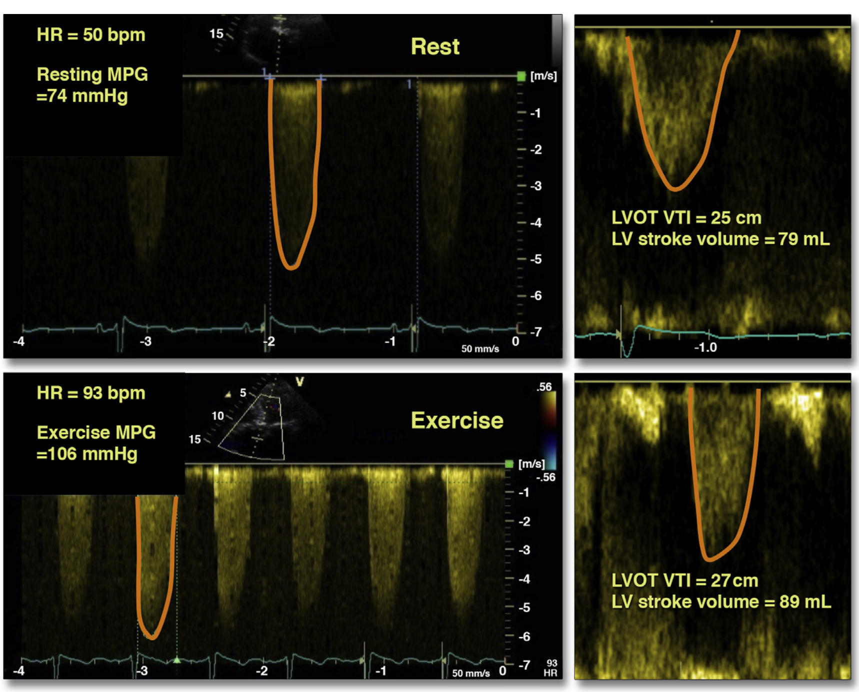

Figure 2. Example of an Asymptomatic Patient With Severe Aortic Stenosis and Exercise-Induced Increase in MPG, Despite Only Mild Increase in LV Stroke Volume

bpm = beats per minute; HR = heart rate; LV = left ventricular; LVOT = left ventricular outflow tract; MPG = mean aortic pressure gradient; VTI = velocity-time integral.

pressure gradient. Interestingly, these 2 studies reported a rate of marked (i.e., >18 to 20 mm Hg) increase in mean gradient during exercise of 35% and 21%, respectively.

The increase in pressure gradient reflects the presence of either a more severe AS (the more severe the stenosis at rest, the higher the increase in gradient for a given flow rate during exercise) and/or a noncompliant and rigid aortic valve (no or minimal improvement of aortic valve orifice area during test) (25). The latter phenomenon could be related to the presence of highly calcified aortic valve, which is, in turn, considered as an important marker of outcome (26–28).

The exercise-induced changes in aortic mean pressure gradient should, however, be analyzed in the light of the exercise-induced changes in LV stroke volume. Indeed, a marked increase in LV stroke volume in response to exercise may directly affect the aortic mean pressure gradient, even in the presence of aortic valve opening reserve. In contrast, in highly calcified aortic stenosis, without improvement in aortic valve area during exercise, mild increase in LV stroke volume may produce significant changes in mean aortic pressure gradient.

Exercise-induced changes in LV function and contractile reserve. The assessment of the adaptation of LV function during exercise is of clinical interest. Patients with a decrease or a small increase in LV ejection fraction during exercise are more likely to exhibit an abnormal response to exercise and cardiac-related events during follow-up (17,18). In the study by Marechaux et al. (18), LV contractile reserve was defined as an exercise-induced increase in LV ejection fraction, and its absence was associated with more frequent abnormalities and development of symptoms during exercise (Fig. 3) and with markedly reduced midterm cardiac event-free survival (around 40% at 2-year follow-up). Furthermore, abnormal response to exercise (i.e., excessive symptoms, fall or <20 mm Hg increase in systolic blood pressure, and ≥2 mm ST-segment depression) was associated with a maladaptation of the LV ejection fraction during exercise (decrease or only mild increase) (12). Using tissue Doppler imaging, Van Pelt et al. (29) suggested that an exercise-induced increase in S′-wave velocity >5 cm/s could be a good cutoff value to determine the presence of LV contractile reserve. Similarly, 2D speckle tracking analysis was used by Donal et al. (17), who report a threshold of −1.4% in exercise-induced changes in LV global longitudinal strain as accurate marker of LV contractile reserve. Nonetheless, it should be noted that these studies are based on relatively small sample sizes and did not validate their cutoff values against patients' outcome.

During exercise, the increase in LV stroke volume, cardiac output, and cardiac index is mandatory to adequately respond to the peripheral demands. In the absence of substantial increase in systolic blood pressure, the peripheral demands may rapidly exceed the rise in cardiac output. This phenomenon may explain, at least in part, the occurrence of symptoms, such as chest pain, angina pectoris, or leg discomfort (25,30,31). Similarly, reduced LV compliance and relaxation may participate in the increase in LV filling pressure (E/e′ ratio), which also contributes to limited exercise capacity and symptoms (mainly dyspnea) in patients with severe AS (32). Furthermore, using 2D speckle tracking echocardiography, the assessment of myocardial longitudinal function with the quantification of global longitudinal strain may identify subtle, latent, and early LV dysfunction in asymptomatic patients with preserved LV ejection fraction (Fig. 3).

Exercise-induced changes in SPAP. Elevated SPAP and the presence of pulmonary hypertension (PHT) (SPAP >50 mm Hg in patients with severe AS) (Fig. 4) seem to be associated with a poor prognosis (33,34) and a higher mortality rate after valve replacement (35), and they represent an independent predictor of hospital mortality and post-operative major adverse cardiovascular and cerebrovascular events (36). In patients receiving transcatheter aortic valve implantation, PHT was a strong independent predictor of poor outcome, doubling the risk of late mortality (37). However, when present, PHT is often associated with symptoms, which limits its usefulness for clinical decision making. In contrast, exercise PHT is generally considered as a predictor of occurrence of resting PHT during the follow-up, development of symptoms, and/or outcome in various cardiac diseases (38–40), including valvular heart disease (41–43). We have reported the prospective results of 105 "truly" asymptomatic patients with severe AS in whom exercise echocardiography was performed purposely to identify the changes in SPAP during exercise. Whereas only 6% of the population exhibited resting PHT (SPAP >50 mm Hg), 55% of patients developed exercise PHT (SPAP >60 mm Hg). Exercise PHT was mainly determined by resting SPAP and male sex, but also by exercise parameters of diastolic dysfunction burden (exercise indexed LV end-diastolic volume, exercise e′-wave velocity and exercise-induced changes in indexed left atrial area). Moreover, exercise PHT was

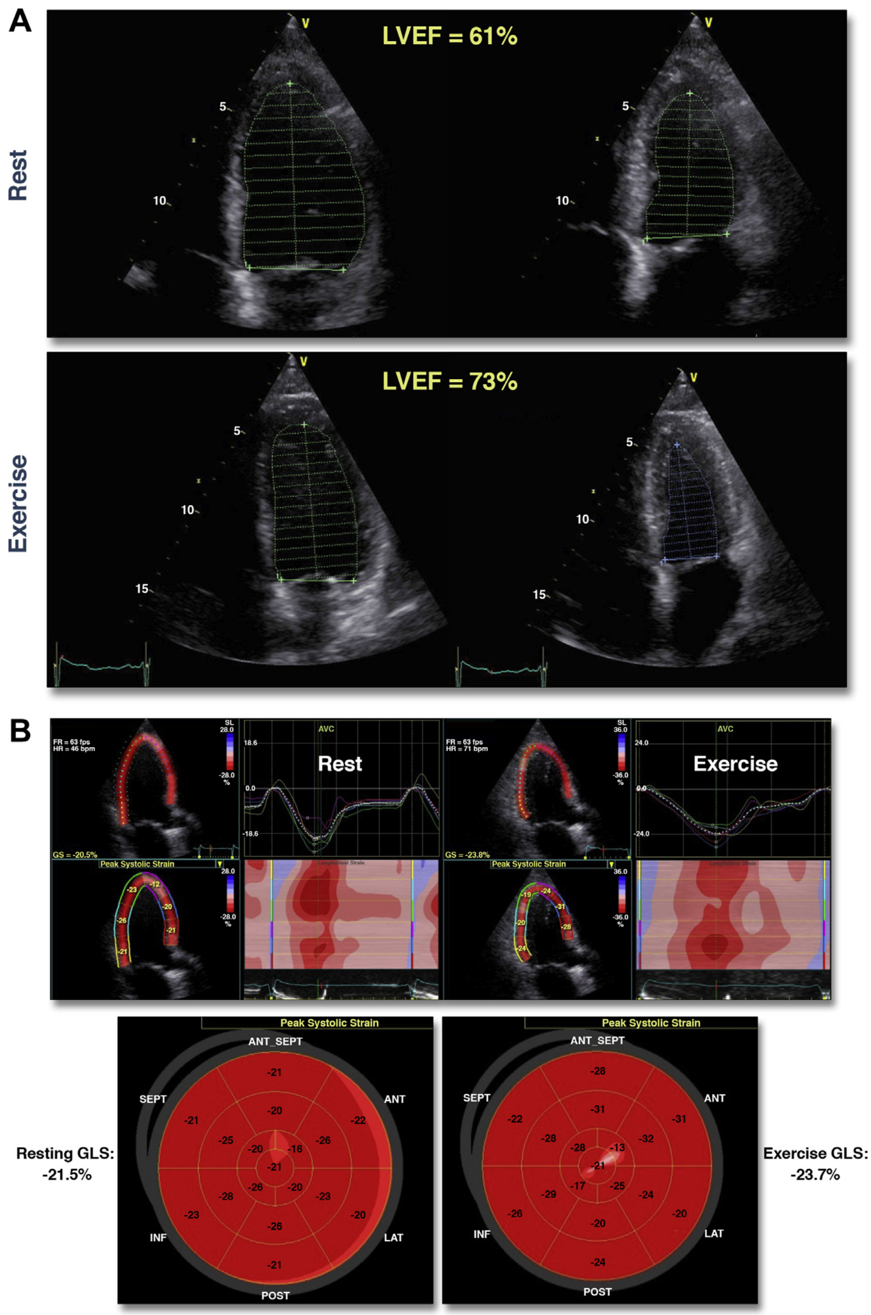

Figure 3. Example of the Presence of LV Contractile Reserve in an Asymptomatic Patient With Severe Aortic Stenosis Using LVEF and GLS (Using 2D Speckle Tracking)

(A) Shows an apical 2-dimensionnal (2D) 4-chamber view and **(B)** shows measurement of left ventricular (LV) myocardial longitudinal strain. ANT = anterior; GLS = global longitudinal strain; INF = inferior; LAT = lateral; LVEF = left ventricular ejection fraction; POST = posterior; SEPT = septal.

independently associated with a 2-fold increase in risk of cardiac event at 3-year follow-up. Interestingly, 7 cardiovascular deaths (3 sudden deaths and 4 deaths following heart failure requiring hospitalization) were reported in this series, and all of these fatal events occurred in the group of patients with exercise PHT, whereas only 1 patient died who had resting PHT.

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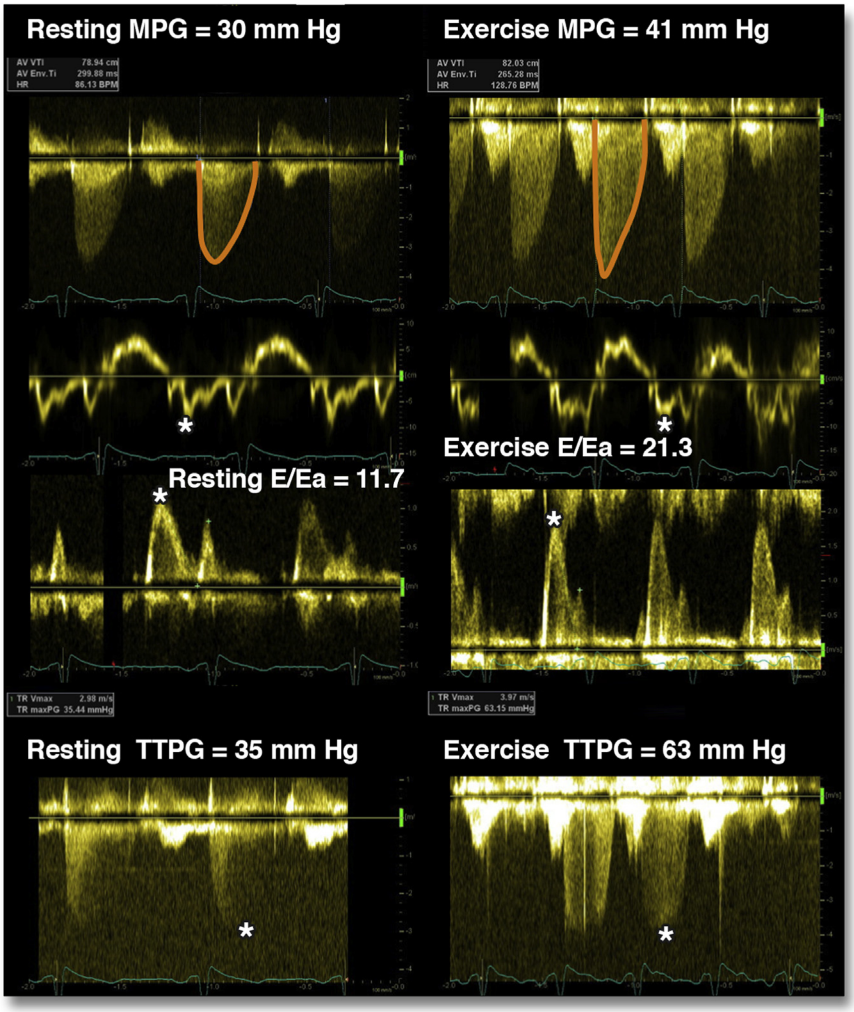

Figure 4. Example of Development of Exercise Pulmonary Hypertension (Systolic Pulmonary Arterial Pressure >60 mm Hg) in an Asymptomatic Patient With Aortic Stenosis

Red lines refer to Doppler envelope and **asterisks** to the peak measurements of waves. MPG = mean aortic pressure gradient; TTPG = transtricuspid pressure gradient.

Practically, the measurement of SPAP throughout the exercise could provide useful additive information. However, the dynamic changes in SPAP and the occurrence of exercise PHT should be cautiously interpreted and analyzed in light of age, exercise load, and changes in systemic blood pressure and in cardiac output.

Impact on Clinical Decision Making

In the most recent ESC guidelines, AVR is now indicated in asymptomatic severe AS, if the exercise test is abnormal, particularly in case of symptom development (Class I, Level of Evidence: C) or asymptomatic hypotension (Class IIa, Level of Evidence: C) (5). Conversely, ACC/AHA 2006 guidelines only recommend performing AVR as Class IIb in patients with severe AS and equivocal symptoms depicting exercise-induced symptoms or fall in blood pressure (4). Consequently, regarding the most recent expert consensus, it seems reasonable to perform AVR in asymptomatic severe AS patients with preserved LV function but in the presence of exercise abnormalities. Actually, these recommendations emphasize that such abnormalities may identify asymptomatic patients in whom AVR could be beneficial. Nevertheless, in patients without exercise abnormalities, exercise stress

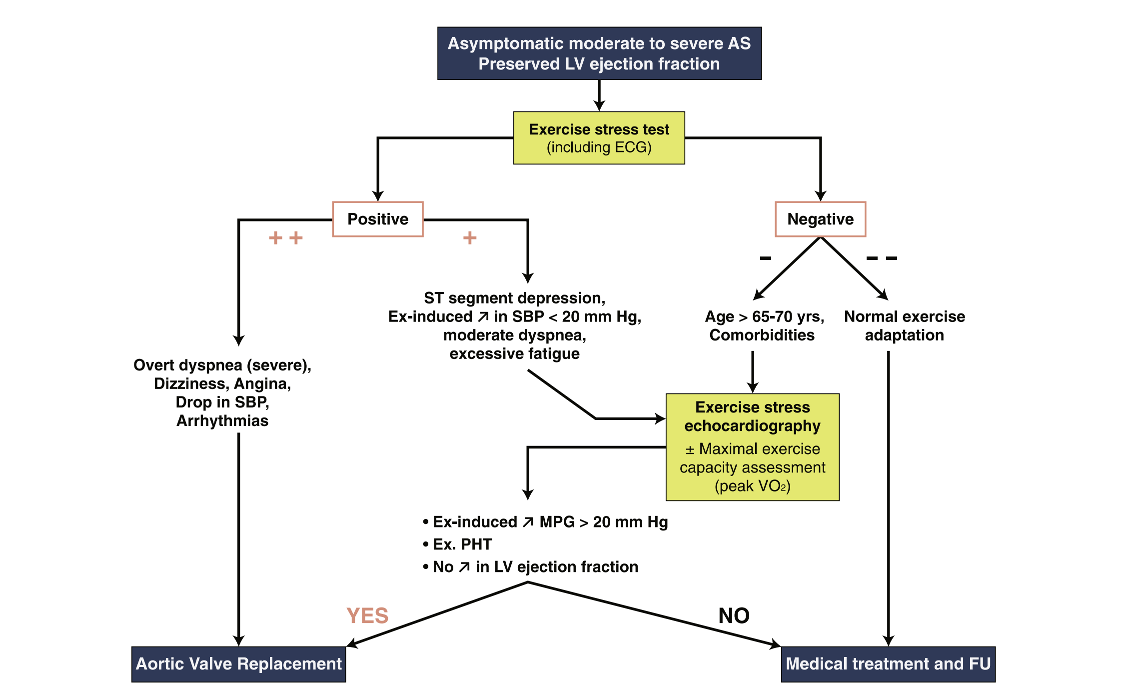

Figure 5. Decisional Algorithm for the Management of Asymptomatic Patients With Preserved LV Ejection Fraction (>50%)

AS = aortic stenosis; ECG = electrocardiogram; FU = follow-up; LV = left ventricular; MPG = mean aortic pressure gradient; PHT = pulmonary hypertension; SBP = systolic blood pressure; VO_2 = maximal oxygen uptake.

echocardiography may be very useful. Indeed, in the light of our experience, patients with inconclusive or negative exercise test but with comorbidities and patients over 65 to 70 years of age may have some hemodynamic or LV function alterations that can be revealed by a comprehensive exercise echocardiographic test (Fig. 5). As underlined previously, exercise-induced changes in mean aortic pressure gradient, LV ejection fraction, LV longitudinal strain, and SPAP may identify a subset of patients with early and subtle, sometimes latent, harmful consequences of the increased LV afterload generated by the AS. The current ESC guidelines indicate that AVR may be considered in asymptomatic patients with severe AS, normal LV ejection fraction, and increase of mean pressure gradient during exercise by >20 mm Hg (Class IIb, Level of Evidence: C). In addition, and despite no clear recommendations, the ESC guidelines state that exercise stress echocardiography may provide prognostic information in asymptomatic severe AS by assessing the changes in LV function. In addition to these recommendations and in light of our experience, it appears that elevated exercise SPAP and the presence of exercise PHT may be considered as a trigger for surgery in asymptomatic patients, mainly due to the unexpected high rate of cardiac event and death reported in these patients (13). Indeed, early surgery could be beneficial in these patients. At least, referral to dedicated valvular heart disease clinic (44) and close follow-up (3- to 6-month follow-up) could be indicated. At the time of the visit, careful evaluation of symptoms is mandatory. The measurement of peak VO_2 could be promoted to objectivize the symptomatic status, and the visit may be completed by exercise stress echocardiography.

On the other hand, patients with appropriate exercise echocardiographic adaptation (i.e., increase in mean aortic pressure gradient <18 to 20 mm Hg, increase in LV ejection fraction, absence of exercise PHT) may be safely followed up every year.

Obviously, confirmatory data are needed to support incorporating this technique in the daily management of asymptomatic patients with AS.

Conclusions

In asymptomatic patients with severe AS, exercise stress test and exercise stress echocardiography may provide incremental clinical and prognostic value, in addition to physical examination and resting echocardiography. Exercise stress test may identify resting asymptomatic patients who develop exercise abnormalities and in whom surgery may be recommended according to current guidelines. Exercise stress echocardiography may further unmask a subset of asymptomatic patients (i.e., without exercise stress test abnormalities) who are at high risk of reduced cardiac event free survival. In these patients, early surgery may be beneficial, whereas regular follow-up seems more appropriate in patients without echocardiographic abnormalities during exercise.

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REFERENCES

1. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol 1997;29:630–4.
2. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364–71.
3. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging 2012;5:719–25.
4. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol 2006;48:e1–148.
5. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012;33:2451–96.
6. Pierard LA, Lancellotti P. Stress testing in valve disease. Heart 2007;93:766–72.
7. Picano E, Pibarot P, Lancellotti P, Monin JL, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. J Am Coll Cardiol 2009;54:2251–60.
8. Rosca M, Lancellotti P, Magne J, Pierard LA. Stress testing in valvular heart disease: clinical benefit of echocardiographic imaging. Expert Rev Cardiovasc Ther 2011;9:81–92.
9. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230–68.
10. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol 2009;104:972–7.
11. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30:260–311.
12. Lancellotti P, Karsera D, Tumminello G, Lebois F, Pierard LA. Determinants of an abnormal response to exercise in patients with asymptomatic valvular aortic stenosis. Eur J Echocardiogr 2008;9:338–43.
13. Lancellotti P, Magne J, Donal E, et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation 2012;126:851–9.
14. Marechaux 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;31:1390–7.
15. Lancellotti P, Moonen M, Garweg C, Pierard LA. Image. Afterload mismatch revealed by an exercise biphasic response in aortic stenosis. Arch Cardiovasc Dis 2009;102:593–4.
16. Magne J, Lancellotti P, O'Connor K, Van de Heyning CM, Szymanski C, Pierard LA. Prediction of exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. J Am Soc Echocardiogr 2011;24:1004–12.
17. Donal E, Thebault C, O'Connor K, et al. Impact of aortic stenosis on longitudinal myocardial deformation during exercise. Eur J Echocardiogr 2011;12:235–41.
18. Marechaux S, Ennezat PV, LeJemtel TH, et al. Left ventricular response to exercise in aortic stenosis: an exercise echocardiographic study. Echocardiography 2007;24:955–9.
19. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. Heart 2001;86:381–6.
20. Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. J Heart Valve Dis 2002;11:204–9.
21. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J 2005;26:1309–13.
22. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005;112:I377–82.
23. Dulgheru R, Magne J, Capoulade R, et al. Impact of global hemodynamic load on exercise capacity in aortic stenosis. Int J Cardiol 2013;168:2272–7.
24. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211–77.
25. Leurent G, Donal E, de Place C, et al. Argument for a Doppler echocardiography during exercise in assessing asymptomatic patients with severe aortic stenosis. Eur J Echocardiogr 2009;10:69–73.
26. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7.
27. Messika-Zeitoun D, Aubry MC, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation 2004;110:356–62.
28. Messika-Zeitoun D, Bielak LF, Peyser PA, et al. Aortic valve calcification: determinants and progression in

the population. Arterioscler Thromb Vasc Biol 2007;27:642–8.

29. Van Pelt NC, Stewart RA, Legget ME, et al. Longitudinal left ventricular contractile dysfunction after exercise in aortic stenosis. Heart 2007;93:732–8.
30. Laskey WK, Kussmaul WG III, Noordergraaf A. Systemic arterial response to exercise in patients with aortic valve stenosis. Circulation 2009;119:996–1004.
31. Weisenberg D, Shapira Y, Vaturi M, et al. Does exercise echocardiography have an added value over exercise testing alone in asymptomatic patients with severe aortic stenosis? J Heart Valve Dis 2008;17:376–80.
32. Dalsgaard M, Kjaergaard J, Pecini R, et al. Left ventricular filling pressure estimation at rest and during exercise in patients with severe aortic valve stenosis: comparison of echocardiographic and invasive measurements. J Am Soc Echocardiogr 2009;22:343–9.
33. Cooper R, Ghali J, Simmons BE, Castaner A. Elevated pulmonary artery pressure. An independent predictor of mortality. Chest 1991;99:112–20.
34. McHenry MM, Rice J, Matlof HJ, Flamm MD Jr. Pulmonary hypertension and sudden death in aortic stenosis. Br Heart J 1979;41:463–7.
35. Copeland JG, Griepp RB, Stinson EB, Shumway NE. Long-term follow-up after isolated aortic valve replacement. J Thorac Cardiovasc Surg 1977;74:875–89.
36. Carnero-Alcazar M, Reguillo-Lacruz F, Alswies A, Villagran-Medinilla E, Maroto-Castellanos LC, Rodriguez-Hernandez J. Short- and mid-term results for aortic valve replacement in octogenarians. Interact Cardiovasc Thorac Surg 2010;10:549–54.
37. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080–90.
38. Kessler R, Faller M, Weitzenblum E, et al. "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. Am J Respir Crit Care Med 2001;164:219–24.
39. Van De Bruaene A, La GA, Prior DL, Voigt JU, Delcroix M, Budts W. Pulmonary vascular resistance as assessed by bicycle stress echocardiography in patients with atrial septal defect type secundum. Circ Cardiovasc Imaging 2011;4:237–45.
40. Shim CY, Kim SA, Choi D, et al. Clinical outcomes of exercise-induced pulmonary hypertension in subjects with preserved left ventricular ejection fraction: implication of an increase in left ventricular filling pressure during exercise. Heart 2011;97:1417–24.
41. Magne J, Lancellotti P, Pierard LA. Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol 2010;56:300–9.
42. Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. Circulation 2010;122:33–41.
43. Brochet E, Detaint D, Fondard O, et al. Early hemodynamic changes versus peak values: what is more useful to predict occurrence of dyspnea during stress echocardiography in patients with asymptomatic mitral stenosis? J Am Soc Echocardiogr 2011;24:392–8.
44. Lancellotti P, Rosenhek R, Pibarot P, et al. ESC Working Group on Valvular Heart Disease Position paper—heart valve clinics: organization, structure, and experiences. Eur Heart J 2013;34:1597–606.
45. Das P, Rimington H, Smeeton N, Chambers J. Determinants of symptoms and exercise capacity in aortic stenosis: a comparison of resting haemodynamics and valve compliance during dobutamine stress. Eur Heart J 2003;24:1254–63.

Key Words: aortic stenosis ■ exercise ■ stress test.

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