Exercise echocardiography in aortic stenosis: one more piece in the puzzle

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Aortic valve replacement (AVR) is the current standard treatment for severe aortic stenosis (AS) with symptoms or left ventricle (LV) systolic dysfunction. However, controversy remains regarding the best treatment for asymptomatic patients with severe AS and preserved LV systolic function and also for those with moderate AS. Improved life expectancy has led to an increasing number of elderly patients with these conditions, in whom the symptoms are harder to evaluate. Many patients may reduce their level of physical activity to avoid or minimize symptoms and be unaware of subtle changes in effort tolerance. The accurate determination of symptoms is crucial, considering the risk of sudden death and the dismal prognosis once symptoms begin. Thus, the exercise test in ‘asymptomatic’ patients with severe AS has already established its role. The ESC guidelines recommend AVR whenever patients present symptoms (class I) or develop asymptomatic hypotension (class IIa) or asymptomatic ventricular arrhythmias (class IIb) during the exercise test. In contrast, the ACC/AHA guidelines recommend AVR if symptoms or hypotension appear during the exercise test (class IIb). The divergent strengths of these recommendations can be explained by the lack of definitive evidence from prospective clinical trials and subsequent different interpretation by the two groups.

Conversely, exercise test echocardiography is not even recommended in the guidelines and remains an issue of debate. Lancellotti et al. presented the first study to demonstrate that quantitative Doppler echocardiography has prognostic importance and provides additional information in patients with asymptomatic severe AS. Their results showed that 69 patients with an increase in mean pressure gradient $\geq 18$ mmHg, during exercise test echocardiography, had a worse outcome in a 15 month follow-up period, independent of the severity of resting stenosis and of exercise-induced electrocardiographic changes.

Maréchaux et al. have presented a larger multicentre study with consonant convincing results. They included 135 ‘truly asymptomatic’ patients with moderate to severe AS defined by aortic valve area $<1.5$ cm$^2$ and indexed aortic valve area $<0.9$ cm$^2$/m$^2$. These patients performed a symptom-limited graded maximum bicycle exercise test in the semi-supine position, which confirmed the absence of symptoms, and echocardiographic data were acquired at rest and at peak exercise. Exercise exercise is recommended for echocardiographic valvular evaluation instead of a treadmill, due to the possibility of obtaining Doppler information during the different stages of exercise, which was not achieved in this study. It is also clearly preferred over pharmacological stress, due to the better evaluation of exertional symptoms and blood pressure responses. The patients’ characteristics are consistent with those of the typical patient with AS, the mean age was $64 \pm 15$ years, the majority (64%) were men, and risk factors for atherosclerosis were common. Fifty-three per cent had severe AS defined by aortic valve area $<1.0$ cm$^2$, and the remainder had moderate AS. A criticism might be levelled at the authors for not restricting the population to patients with severe AS, but moderate AS is not a benign disease and the outcome is worse than generally assumed. This last entity represents a highly heterogeneous group of patients, in which individual prediction is not possible, but rapid progression of aortic jet velocity and significant valve calcification are associated with a poor outcome. The ACC/AHA guidelines recommend echocardiography re-evaluation every 1–2 years, but it is debated whether closer follow-up might be needed.

A complete follow-up was achieved for all patients and, during the mean follow-up of $20 \pm 14$ months, 67 (50%) patients reached the first composite endpoint of cardiovascular death or need for AVR, due to symptom development or LV systolic dysfunction. The authors performed a separate multivariate analysis including variables in continuous and dichotomous format. Not surprisingly, older age, diabetes, and higher resting mean gradient were independent predictors of events in both analyses, and LV hypertrophy was an independent predictor when considered in...
dichotomous format. However, the strength of the study comes from a larger exercise-induced increase in mean gradient as an independent predictor of events. It was significant as a continuous variable, and also when considering the cut-off of the exercise-induced increase in mean gradient \( \geq 20 \text{ mmHg} \), which is close to the cut-off value \( \geq 18 \text{ mmHg} \) proposed by Lancellotti et al.\(^6\) Therefore, an increase in mean gradient \( \geq 20 \text{ mmHg} \) during exercise was independently associated with a 3.8-fold increase in the risk of events, after adjusting for other risk factors. Moreover, the increase in mean gradient during exercise did not correlate with the rest gradient or with any other rest echocardiographic data. Nevertheless, the patients with a mean rest gradient \( \leq 35 \text{ mmHg} \) and an increase in gradient \( > 20 \text{ mmHg} \) did not display a significant increase in event risk, but the low number of patients in this condition limits interpretation of the data.

The authors discussed potential mechanisms underlying the exercise-induced increase in gradient. Naturally, a larger increase in gradient during exercise may reflect a more severe stenosis; however, it remained a powerful predictor of outcome, even after adjusting for the resting gradient, suggesting the implication of other mechanisms, such as differences in intrinsic valve compliance. This is according to the belief that severe calcification implies a faster haemodynamic progression of the disease and a higher risk for the rapid progression to symptoms and events.\(^1^1\) Unfortunately, there are no data presenting the calcification score, making further considerations impossible.

The stroke volume behaviour during the course of the exercise test is also debated in this study. Larger increases in stroke volume and heart rate during exercise were the independent determinants of a larger exercise-induced increase in gradient; however, after adjustment in the multivariate model for the prediction of event risk, the hazard ratio of the exercise-induced increase in gradient remained similar. Speculations regarding the kinetics of the gradient increase during the exercise test are presented, which might become an interesting theme for future studies. There was no clarification of the potential usefulness of peak exercise LV ejection fraction for risk stratification in patients with asymptomatic AS. Maréchaux et al. have previously presented evidence suggesting that patients with limited LV functional reserve are at increased risk for events,\(^1^2\) though in the present study this factor had a trend for an association between reduced peak exercise LV ejection fraction and risk of events, but it was not found to be a predictor of outcome. There is still a place for further studies on this topic.

There is one last consideration regarding the presented outcomes. Among the 67 patients who reached an endpoint during follow-up, 59 underwent AVR and one was waiting for surgery, but four developed severe symptoms and did not undergo AVR because they were considered at prohibitive surgical risk, and three died from cardiovascular causes, one of them also being refused surgery and the other two not even being presented for surgery because of severe co-morbidities. This brings us to the dismal prognosis of this entity, to the severe co-morbidities frequently associated with it, and to the consequent denial of surgery.\(^1^3\) These patients are now being given new hope with transcatheter aortic valve prosthesis.\(^1^3\) This novel approach is presenting confident results at medium term follow-up and might change our conventional treatment of these patients and eventually of the asymptomatic patients with severe AS, for whom the risk/benefit might gain a different weight.\(^1^4\)

In conclusion, this study notably improves current understanding of the characteristics of asymptomatic moderate or severe AS with

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**Figure 1** Moderate and severe asymptomatic aortic stenosis approach according to ESC guidelines adapted to S. Maréchaux et al. exercise echocardiography results. AS, aortic stenosis; AVR, aortic valve replacement; ESC, European Society of Cardiology.
preserved ejection fraction and may help to modify and improve the management of this disease. The use of an exercise test is widespread since it was proved to be safe in asymptomatic patients;\textsuperscript{5,15} even so the measures of maximum exercise capacity may fail to identify patients at higher risk for rapid disease progression. Stress echocardiography is a widely available and low cost technique, that has already established its role in patients with low-flow, low-gradient AS.\textsuperscript{1,2} The additional value of exercise echocardiography for ‘truly asymptomatic’ patients was convincingly demonstrated in this study, showing that a large increase in gradient during exercise may help to recognize patients who are at higher risk for rapid progression to symptoms and cardiovascular events, for whom a closer follow-up might be highly beneficial.

Conflict of interest: none declared.

References