Asymptomatic Severe Aortic Stenosis with Normal Ejection Fraction: when the Early/Elective Surgery Might be the Choice?

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Abstract
Aortic valve replacement (AVR) therapy is clear in symptomatic AS patients, because it improves symptoms, LV function and survival. However, the indications for AVR in asymptomatic patients with severe AS are vague and the subject of ongoing debate. There are observational data that early AVR leads to favorable outcome compared to late (after symptom onset) surgery. Having in mind that operative risk for isolated AVR is low in experienced centers, there is growing and reasonable interest in identifying the subsets of asymptomatic patients which may benefit from early AVR.

ABBREVIATIONS
AS: Aortic Stenosis; AVR: Aortic Valve Replacement; LV EF: Left Ventricular Ejection Fraction

INTRODUCTION
Aortic stenosis (AS) is a common and important cause of cardiovascular morbidity and mortality [1]. Not only is AS most common valvular heart disease, but it is also the third most common heart disease after coronary heart disease and hypertension [2]. The prognosis for isolated AS is the worst of all isolated heart defects left untreated or treated with medications [3]. In the case of severe AS [aortic valve area (AVA) < 1cm²; mean pressure gradient (Pmean) > 40mmHg] [4] chronic pressure overload and outflow obstruction lead to left ventricular (LV) hypertrophy and subsequent myocardial fibrosis, often resulting in LV systolic and diastolic dysfunction and even impaired coronary flow reserve [5] which, ultimately, causes the symptoms of dyspnea, angina or syncope.

Aortic valve replacement (AVR) therapy is clear in symptomatic AS patients, because it improves symptoms, LV function and survival [6]. However, the indications for AVR in asymptomatic patients with severe AS are vague and the subject of ongoing debate [7-10]. The most recent guidelines [11] do not have class I indication for AVR in asymptomatic severe AS patients with normal LV ejection fraction (EF). There are observational data [7,8] that early AVR leads to favorable outcome compared to late (after symptom onset) surgery. Having in mind that operative risk for isolated AVR is low in experienced centers [7,12], there is growing and reasonable interest in identifying the subsets of asymptomatic patients which may benefit from early AVR.

Risk factors in AS and potential arguments in favor of early surgery
It is well recognized that the, sudden death is the major risk of "waiting for symptoms to develop strategy" in the patient with severe AS. The risk of sudden death in asymptomatic AS patients seems to be higher than 1%, as was assumed in the past, with most studies reporting up to 3%, but as high as 13% in retrospective study by Pai et al. (however the study did not report a number of patients who developed symptoms but refused to undergo AVR, which could have decreased the percent of reported sudden death) [13]. Furthermore, at a death rate of 2% per month once symptoms occur, some patients may die soon after symptom onset [14]. Even if patients are followed up every 6 months, which usually is the case for patients with asymptomatic severe AS, there is still a substantial window of time for symptoms to develop (and for death to occur) between visits to the physician. There is an option to alert patient to refer to his/her physician as soon as AS symptoms begin, but such a strategy may be unreliable, simply because patient may not recognize symptoms, or may even deny it.

In recent years, substantial assistance in decision-making
process with the detection of latent AS symptoms comes from exercise testing [15-18]. There are different criteria used for assessing the test as a positive one (including occurrence of symptoms, exercise intolerance, increase in Pmean > 18mmHg, failure to achieve a rise in blood pressure, etc...) [9], but with a positive stress-test patients are likely to develop symptoms and need AVR within a year [15,16]. It seems logical that in these patients early-elective AVR should be the choice, rather than to wait for the disease to take its natural course.

Another strong predictor of future adverse events in those asymptomatic AS patients with normal LV EF is the degree of aortic valve calcification [19]. In addition, AS progression is more rapid in more severely calcified valves [19]. The more calcified the valve, the sooner the patient will progress to symptoms. Patients who have a peak jet velocity > 4 m/s will most probably require an AVR within 2 years and patients with a jet velocity > 5 m/s within 1 year [20,21]. Obviously, for these two years a patient will only get older, and assuming that there are no significant comorbidities, the risk of surgery will increase. The Society of Thoracic Surgeons risk calculator [22] for cardiac surgery projects that as age increases, for example from 73 to 75 years, absolute operative mortality risk increases by 0.1% and combined mortality and serious morbidity increases by 0.5%. This raises the argument that surgery should be performed more safely immediately than 2 years later; thus, little may be gained by waiting for symptoms to occur.

Another significant fact is that most patients with severe AS develop significant concentric LV hypertrophy as a compensatory mechanism to neutralize high afterload and to preserve LV pump function [23,24]. The presence of LV hypertrophy in AS, as well as in other cardiac diseases, is associated with increased mortality and increased risk of heart failure, especially in the presence of coronary artery disease [25-27]. The same holds true for inappropriately high LV mass (>110% of that expected for body size, gender and wall stress) [28]. Therefore, waiting for symptoms to develop also allows time for excessive LV hypertrophy to develop and for heart to increase its mass, which again leads to the conclusion that early surgery might be associated with a better outcome.

Biochemical markers, in particular Brain natriuretic peptide (BNP) and its precursor, NT-proBNP, have been studied as potential symptom surrogates in AS [29,30]. The study by Bergler-Klein and associates [30] proposed a BNP value > 130pg/ml as a prognostic marker in asymptomatic AS patients, as these patients had substantially lower symptom-free survival during follow-up compared to those with BNP < 130pg/ml. Similarly, the prognostic significance of coronary flow reserve and microvascular function in asymptomatic AS patients with normal LV EF and nonobstructed coronary arteries have been shown [31]. However, the clinical usefulness of above mentioned parameters in the context of early AVR and risk stratification are still to be confirmed.

There are several retrospective, observational studies that demonstrated the potential usefulness of early AVR in asymptomatic AS patients with normal LV EF [7-9,13,19]. The data from Kang and associates [7] are most persuasive because they seem to be the closest to the randomized controlled trial design. The other studies compared the outcome of patients who underwent AVR just after became symptomatic with patients who did not undergo AVR, mainly because they stayed asymptomatic. The results from these observational studies suggest that severe asymptomatic AS patients who undergo AVR after they develop symptoms have a better prognosis than those who remain asymptomatic and do not have AVR. However, the observational studies have many confounding factors that might influence results, such as the lack of understanding how serious co morbidities these patients have and how much they might influence patient’s activity or symptomatic status.

So, which asymptomatic patient may benefit from AVR?

Obviously, to refer asymptomatic patient to an open heart surgery is not an easy decision, especially in younger population (below 65 years). The potential benefit of early surgery must be carefully weighed against the risk of the AVR, which is predicted both on the risk factors presented by the patient and on the skill and experience of the cardiovascular team performing the surgery. Also, the postoperative course is very important, especially in terms of avoiding intrahospital infection, which sometimes might be a problem. However, with all the advances in the field of anaesthesia, better myocardial preservation, advanced surgical techniques and advances in medical equipment in general, the long-standing fear from operative mortality should be decreased. One center recently reported 190 consecutive AVRs without a death [12], and the Society of Thoracic Surgeons risk calculator projects a mortality risk for 70-years old man of just 0.8% with a combined mortality and serious morbidity rate of 8.2%. Although reliable, this risk calculator may often overestimate the risk seen in actual practice [22,32], so that actual risk may be even less. Thus, the operation in experienced hands is quite safe, and operative risk appears to be less than the risk of sudden death in asymptomatic patients. This is even more accentuated in patients less than 65 years old. In that context, age must be considered in the decision to recommend AVR to the asymptomatic AS patient with normal LV EF, and desired lifestyle also must be taken into account. A recommendation for AVR in the asymptomatic 55-year-old whose passion is to play tennis seems much more reasonable than to recommend AVR to the sedentary 80-year-old who is happy with his current lifestyle.

In addition to operative risk, the risk of postoperative valve-related complications must be considered. These include structural valve deterioration in bioprosthetic valves and thromboembolic/hemorrhagic complications in mechanical valves. However, as vast majority of these patients would eventually undergo AVR, these risks should be calculated for only the (relatively short) period in between.

CONCLUSION

It would be reasonable to assume that the majority of cardiologist are reluctant to send their asymptomatic AS patient with normal LV EF to AVR, because in their opinion the risk of early surgery exceeded its benefit. However, in recent years we have become capable of recognizing asymptomatic patients at higher than average risk for whom early AVR appears reasonable, whereas the risk of both AVR and of postoperative valve-related

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complications have decreased. These high risk patients may include those with positive stress-test, very severe AS (AVA <0.6cm², max jet velocity > 5m/s) heavy valve calcifications with fast progression of the disease (> 0.3m/s per year) [33], pronounced LV hypertrophy, high BNP and decreased coronary flow reserve (diminished microvascular circulation).

Ultimately a randomized trial could give us an ultimate answer whether early AVR is beneficial, but until such a trial is performed all we can do is make decisions according to existing non-randomized studies and our clinical experience; which in real world translates to decisions on patient-to-patient basis.

REFERENCES


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