Review

Challenges in the management of severe asymptomatic aortic stenosis

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Summary

It is well established that the treatment of symptomatic aortic stenosis is timely aortic valve replacement. By contrast, the optimum treatment of severe asymptomatic aortic stenosis is not clear. There are no randomised controlled trials on which to base management. Current guidelines recommend a watch-and-see approach, with surgery deferred until symptoms develop, unless certain criteria, for example, severe left-ventricular hypertrophy or an abnormal exercise test, are met. This strategy is based on the observation that asymptomatic patients have a low risk of sudden death. It ignores, however, the long-term consequences of irreversible left-ventricular remodelling resulting from a high afterload, which could potentially adversely affect perioperative and long-term outcomes. Observational studies suggest that early aortic valve replacement provides long-term outcomes superior to deferred surgery. We suggest that clinicians should consider this approach when planning how best to manage patients with severe asymptomatic aortic stenosis.

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1. Introduction

The timing of aortic valve replacement (AVR) in asymptomatic patients with severe aortic stenosis (AS) with peak velocity >4.0 m s⁻¹ and normal ejection fraction presents a difficult clinical problem. There are no randomised controlled trials to inform the management of these patients. Contemporary practice embodied in guidelines [1,2] is generally to delay operation until or if symptoms develop. The European Society of Cardiology (ESC) Guidelines of 2008 [1] suggest AVR for asymptomatic patients with an abnormal response to exercise (chest pain, undue breathlessness, failure to increase blood pressure, complex ventricular arrhythmias or ischaemic changes), a rate of progression of >0.3 m s⁻¹ year⁻¹ or excessive left-ventricular (LV) hypertrophy (>1.5 cm). The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines of 2006 [2] suggest AVR for asymptomatic patients with severe AS with an abnormal response to exercise, if there is a high likelihood of rapid disease progression or very severe disease (peak velocity >5.0 m s⁻¹) and the expected operative mortality <1.0%. Patients not in any of these categories should be observed rather than proceeding to AVR. The recommendations from both sets of guidelines are all of level of evidence C. The rationale for this approach is that the risk of death without the previous development of symptoms is low and that surgery can be safely delayed until the development of symptoms. Further support for this approach is based on the concept that many elderly patients will never develop symptoms and will die with the disease rather than because of it, and would therefore never require surgery. They would thereby avoid the morbidity and mortality associated with what is considered an unnecessary procedure [3]. Even in younger patients in whom an operation is likely to be required at some stage, delaying surgery means that the 1% or 2% of patients, who would die as a result, will gain extra years of life, while not compromising the outcome of the vast majority, who would survive surgery. Furthermore, the presence of an aortic valve substitute (whether mechanical or biological) carries its own risks: for example, valve degeneration or failure, increased risk of endocarditis and risks associated with anticoagulation.

What is the evidence that these concepts actually translate into clinical practice? In the absence of randomised clinical trials, we have to consider observational studies. Table 1 summarises some of the larger studies of severe asymptomatic AS. Event-free survival refers to survival without AVR. Amato et al. [4] studied patients with a relatively high event rate. Conversely, Pellikka et al. [5]...
appear to have studied patients with a particularly low event rate. These differences presumably relate to patient selection for the particular studies. Event-free survival in the other studies was similar. Overall, for patients in their late 50s—70s, about two-thirds can expect to remain event free during the subsequent year. The risk of sudden death is generally low (documented in different ways in these reports) and appears to be approximately 1% per year [6,7].

These data thus appear to support a policy of postponing surgery until symptoms develop. The risk of sudden death is low and similar to the operative mortality, and the majority of patients will remain asymptomatic in each successive year. This interpretation, however, does not address the clinically relevant question of whether early surgery results in a better long-term outcome compared with a wait-and-see strategy. Specifically, does delaying surgery until the development of symptoms adversely affect outcome? Alternatively and equivalently, does early AVR improve long-term outcome? Kang et al. [8] report an observational study of patients with severe asymptomatic AS, some of whom underwent AVR while asymptomatic and others, who were managed according to the wait-and-see strategy. The two groups had similar baseline characteristics with a mean age of 63 (SD 11) years and a mean peak aortic valve velocity of 5 m s\(^{-1}\). The 6-year all-cause mortality rates were 2% (SD 1) and 32% (SD 6) for the early surgery and wait-and-see groups, respectively. A subgroup of propensity-matched pairs had a hazard ratio of 0.14 (95% confidence interval (CI), 0.03—0.6) for all-cause mortality in favour of an early AVR approach, that is, a risk reduction of 85%.

These findings are suggestive, but are not conclusive, of an indication that an early surgical approach in asymptomatic patients with severe AS can substantially improve outcome compared with the contemporary approach of wait and see. Despite this evidence, it must be noted that these results are based on relatively young patients and, therefore, do not guide the best management strategy for septuagenarians and octogenarians. Such patients will have less years of life left for the potentially beneficial effects of early AVR to outweigh the likely higher operative mortality. A randomised controlled trial is needed to avoid any potential bias.

Long-standing severe AS (whether or not symptomatic) results in LV hypertrophy, increased wall stress, compromised subendocardial myocardial perfusion and, eventually, raised diastolic pressures. As the myocardium becomes stiff, left-atrial pressure rises, which will be complicated by secondary pulmonary hypertension. While this development could be useful to bring the patient to the attention of the medical profession, it may increase the surgical risk [9]. In addition, the raised left-atrial pressure causes left-atrial remodelling with the associated risk of the development of atrial fibrillation. The QRS duration is commonly prolonged in these patients, which will also disrupt systolic and diastolic LV function. Finally, it should be remembered that AS, irrespective of its severity, is often associated with some degree of mitral regurgitation. LV systolic and diastolic dysfunction add to the severity and abnormal time relations of mitral regurgitation, which itself is another mechanism for symptoms and perpetual cardiac dysfunction. These changes will impact on perioperative outcomes and may not be reversible. It has been reported [10] that many of these abnormalities will recover by 6 months, following AVR. LV function, however, does not completely recover, septal long-axis amplitude remains depressed, myocardial hypertrophy does not completely regress and QRS duration may remain prolonged. An established stiff myocardium, probably fibrosed, will leave the patient with irreversibly raised left-trial pressure and limiting breathlessness. These persisting abnormalities will continue to adversely affect LV function and may impact on exercise capacity and long-term survival. Perioperative mortality and long-term survival after AVR are impaired in patients with worse preoperative symptoms and higher aortic velocity [5,11]. These physiological considerations would suggest improved outcomes with early operation, in support of the observational findings [8]. Ironically, therefore, by delaying AVR, we appear to be inadvertently adversely affecting short- and long-term outcomes. Other associated complications of AS, for example, anaemia, may contribute to the unsatisfactory outcome of those patients [12].

Table 1. Summary of reports examining prognosis in asymptomatic patients with aortic stenosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>AS severity (peak velocity m s(^{-1}))</th>
<th>Age (years)</th>
<th>One year event rate</th>
<th>Sudden deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenhek et al. [3]</td>
<td>128</td>
<td>5.0 (0.6)</td>
<td>60 (18)</td>
<td>67 (5)</td>
<td></td>
</tr>
<tr>
<td>Amato et al. [4]</td>
<td>66</td>
<td>Mean 4.3</td>
<td>44 (14)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Pellikka et al. [5]</td>
<td>622</td>
<td>&gt;4.0</td>
<td>72 (11)</td>
<td>80</td>
<td>1%/year</td>
</tr>
<tr>
<td>Rosenhek et al. [6]</td>
<td>116</td>
<td>&gt;=5.0</td>
<td>67 (16)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Lancellotti et al. [7]</td>
<td>163</td>
<td>4.2 (0.6)</td>
<td>70 (10)</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

The foregoing suggests that the wait-and-see approach for asymptomatic patients with severe AS, which, of note, is not evidence based, may not be the most appropriate management strategy for many patients. Physicians should acknowledge to themselves and their patients that a wait-and-see approach may not be the best strategy. Patients should be offered an early operation while asymptomatic, after an explanation of the risks and benefits. An exercise test (for those patients capable of exercising) may help inform this decision. For those who are unable to perform a traditional treadmill or bicycle test, a 6-min walk test with ambulatory monitoring may be helpful. Patients, who have a normal exercise test, have a much higher event-free survival than those with a positive test, 85% and 19%, respectively, at 24 months [4]. Nevertheless, it is important not to rely too much on the exercise test. It is clearly good at predicting event-free survival, but does not give information on whether patients with a negative test have an, at least, as good an outcome with a wait-and-see approach compared with early surgery. Another means for predicting long-term outcome of asymptomatic AS is the STS (Society of Thoracic Surgeons) score [13].
When a wait-and-see approach is adopted, it is most important that surgery is undertaken in a timely fashion once symptoms develop. This means within weeks rather than months. In countries where there is a wait of many months for surgery, patients should be put on the 'waiting list' while asymptomatic so they can have a timely operation once symptoms develop. Great care should be taken to determine whether the patient is truly asymptomatic. Patients may subtly reduce their physical activity to avoid symptoms and thereby maintain their asymptomatic status. Sequential exercise tests may be helpful to determine if exercise capacity is declining. Patient education is very important to ensure that when symptoms do occur, the patient seeks medical attention promptly. It has been suggested that patients may not always do this [3]. Finally, early examination and thorough investigations may guide towards optimum management of severe but asymptomatic coronary artery disease in patients, who do not exercise.

A common co-morbidity with AS, which needs optimum management, is systemic hypertension. Being a form of afterload, hypertension has its direct effects on myocardial function, irrespective of the severity of AS [14]. Patients with isolated hypertension present with significant degree of subendocardial dysfunction, and are well known to develop stiff LV and raised left-atrial pressure and atrial fibrillation later on in life. In a patient with normal blood pressure and moderate AS (gradient of 40 mmHg), the LV myocyte faces a consistent systolic pressure of 160 mmHg, which is not less than significant hypertension, according to the guidelines, which recommend treatment. Common cardiology practice dismisses these patients for 12 months' follow-up appointments, considering them as cold cases. A hypertensive patient with systolic pressure of 160 mmHg usually has these values fluctuating over the course of the day, but, in the presence of additional moderate AS, the outflow tract resistance is consistently high at 200 mmHg. The 80-mmHg accumulative extra pressure as a result of the two moderate diseases, by simple mathematics, would have a serious effect on the myocardial function. Guidelines towards optimum management of such commonly seen patients is lacking, particularly in an era where most anti-hypertensive medications have a peripheral vasodilator effect and, hence, are discouraged to be used in AS. The combination of poorly controlled hypertension and even moderate AS may prove a sufficient indication for AVR to preserve LV function.

It seems, therefore, that there is a strong case for early intervention for significant AS, irrespective of symptoms, which when they develop, reflect LV disease [15], which may be irreversible. Missed cases and those with serious co-morbidities that stand a high surgical risk can now be offered trans-catheter aortic valve implantation (TAVI procedure) [16,17], with satisfactory early results. However, the long-term outcome of this approach remains unknown. Furthermore, patients unsuitable for TAVI, according to the current recommendations, will be left with no hope but a courageous surgeon to reinstitute them on the surgical list.

References


