Indian Heart Journal 68 (2016) 576–580

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

C3 – Core Curriculum in Cardiology

Asymptomatic severe aortic stenosis with normal left ventricular function – A review

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ARTICLE INFO

Article history:
Received 25 July 2015
Accepted 9 May 2016
Available online 21 May 2016

Keywords:
Asymptomatic aortic stenosis
Aortic valve replacement surgery
Aortic stenosis with normal LV function

ABSTRACT

Aortic stenosis (AS) is one of the commonest forms of acquired valvular heart disease. Aortic valve replacement (AVR) is the treatment of choice for symptomatic severe AS. Conservative management is usually advocated for asymptomatic severe AS. But there are data on predictors to identify subsets of asymptomatic AS patients at high risk of cardiac events in whom early surgical intervention is warranted. Non-invasive tests like exercise stress test, exercise echocardiography will help us to identify those who are at high risk of developing early symptoms due to LV dysfunction and also those at high risk of sudden death. In this article, an attempt is made to review the literature on this subset of asymptomatic severe AS to help clinicians to decide regarding the need for early aortic valve replacement in them.

1. Introduction

Patients of severe valvular aortic stenosis (AS) with symptoms such as syncope, angina or heart failure carry grave prognosis.[1] Aortic valve replacement (AVR) is known to improve survival and quality of life in them.[2] Patients of asymptomatic AS with normal left ventricular (LV) function are a heterogeneous group with very few of them being at a high risk of sudden death and some of them at risk of developing early symptoms due to progressive myocardial dysfunction. The optimal timing of surgery in this subset of patients is debatable. Asymptomatic subjects need to be examined for denial or downplay of symptoms and also some of them may restrict activities to avoid occurrence of symptoms. The risk vs. benefit of AVR needs to be assessed in asymptomatic individuals keeping in mind the operative risk, morbidity related to valve prosthesis and the risk related to the use of oral anticoagulants.

The risk of AVR in cases of uncomplicated AS is 1–2% at high volume centres[3] and 3–4% at low volume surgical centres.[4] The reported incidence of thromboembolism and bleeding risk related to anticoagulation in the setting of mechanical valve in aortic position is 1.1 and 4.6/100 patient-years respectively.[5] The bleeding risk increases significantly in the elderly (age ≥75 yrs). The incidence of infective endocarditis has been reported to be 0.27% per patient-year in western countries.[6]

The risk of development of complete heart block with need for pacemaker implantation is high in patients who have left bundle branch block (LBBB) and calcification extending into the interventricular septum. Surgical expertise is required to enlarge annular size for those with small aortic annulus which will add to the surgical risk. Another important factor to consider is management of anticoagulation status. Surgical expertise and proper monitoring of anticoagulation status may not be readily available in many rural and semiurban towns in developing countries. These are the issues which raise the question whether we should operate on asymptomatic patients with severe AS as they have less than 1% risk of sudden death.

Early AVR however is expected to result in regression of LV mass. The chances of developing LV dysfunction with AVR are less which may result in improved long-term survival.[7] Certain variables identified as markers of sudden death are LBBB, associated coronary artery disease (CAD), non-sustained ventricular tachycardia by Holter monitoring and densely calcified aortic valve (AV). In severe AS certain factors such as age above 50 years, dense calcification of AV, associated risk factors like hypertension, dyslipidemia and CAD[8] were shown to result in rapid progression of symptoms.

2. Natural history of asymptomatic AS

Natural history of patients with asymptomatic severe AS is shown in Table 1. Various studies differed in their design, inclusion

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http://dx.doi.org/10.1016/j.ihj.2016.05.006

criteria and duration of follow-up. It has been found that approximately one third of patients become symptomatic within 2 years[9] and two-thirds of them were reported to have had either AVR or sudden cardiac death within 5 years.[8,11,12] Survival in asymptomatic unoperated patients was reported to be 99%, 98% and 93% at the end of 1, 2 and 5 years respectively.[11] It is interesting to note that survival in these patients was noted to be similar to age and sex matched healthy population.[11] Long-term prognosis however worsens with the onset of symptoms.

Risk of sudden death in asymptomatic severe AS observed in various prospective and retrospective studies is shown in Table 2. Sudden death rate per year ranged between 0.2% and 3.1%. Pellikka et al.[11] reported sudden death of 1% per year during 5 years follow-up in 622 cases of asymptomatic AS with a peak AV velocity of ≥4 m/s.

Symptoms occur in patients with AS and normal LV systolic function when the stenosis is severe (valve area is <1.0 cm^2, the jet velocity is over 4.0 m/s, and the mean transvalvular gradient ≥40 mmHg). However, some patients may become symptomatic when the stenosis is even moderately severe, particularly if there is coexisting aortic regurgitation. In Rosenhek's study,[18] some patients showed increase in mean gradients as much as 15–19 mmHg per year without progression of symptoms. Similarly, some patients had little or no progression in symptoms though the average rate of decline in valve area observed was 0.1 cm^2/yr.[18]

Taniguchi et al.[19] reported 5-year outcomes of CURRENT AS (Contemporary Outcomes after Surgery and Medical Treatment in Patients with Severe Aortic Stenosis) registry involving 1808 patients of asymptomatic severe AS who were initially treated either conservatively (n = 1517) or with AVR (n = 291). The authors found a higher rate of mortality (26.4% vs. 15.4%; p = 0.009) and hospitalizations for heart failure (19.9% vs. 3.8%; $p < 0.001$) at 5 years of follow-up in patients who were managed conservatively compared to those who underwent AVR. These data seemingly conflict with recommendations of watchful waiting for the development of symptoms.

Table 3
Exercise testing in asymptomatic severe AS.

Positive if patient develops
• Symptoms
• Complex ventricular arrhythmias
• BP failed to rise by 20 mmHg
• Fall in systolic BP
• > 1 mm horizontal/downsloping ST ↓
2 yrs event free survival 19% if test is positive
85% if test is negative
(Amato et al.[13])

3. Role of non-invasive testing

3.1. Electrocardiography (ECG)

In a multivariate analysis, left ventricular hypertrophy (LVH) as per Romhilt and Estes criteria was found to be an independent predictor of early development of symptoms.[20] However, the sensitivity of detecting LVH by ECG was found to be as low as 40%. Recently, by 24 h continuous ECG monitoring, it was shown that Tp-e interval, Tp-e/QT and Tp-e/QTc ratio can be novel indicators for prediction of ventricular arrhythmias and mortality. It was shown that Tp-e/QTc ratio had significant positive correlation with mean aortic gradient.[21]

3.2. Exercise testing

The development of symptoms and abnormal BP response to exercise were associated with poor outcomes. The appearance of symptoms, complex ventricular arrhythmias, fall in systolic BP or failure of BP to rise by 20 mmHg during exercise and ≥1 mm ST depression during exercise were found to have 2 year event free survival of only 19% as reported by Amato et al.[13] (Table 3). The 2-year survival was 85% when the exercise test was negative. Symptoms appearing during stress test predicted development of symptoms in 57% of asymptomatic patients during 1-year follow-up. However, the value of stress ECG was noted to be limited in

Table 1
Natural history of asymptomatic severe AS.

	Symptom definition	Cardiac event (or) end point definition	Symptom-free survival (%)			Event-free survival (%)				
			1 yr	2 yrs	5 yrs	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Pellika et al.[9]	Ang, Dys, syncope	AVR, cardiac death sec to AS	86 ± 3	62 ± 6		93 ± 2				
Otto et al.[10]	Ang, HF, sync, near syn	AVR, cardiac death				93 ± 5		67 ± 10		34 ± 15
Rosenhek et al.[8]	NA	AVR, cardiac death and non-cardiac death				67 ± 5	56 ± 5		33 ± 5	
Pellika et al.[11]	Ang, Dys, syncope	Symptom development, AVR, cardiac death	82	67	33	80	63			25

HF-Heart failure

Table 2
Risk of sudden death in asymptomatic severe AS.

Study	Design	No. of pts	Mean FU ± SD (months)	Events AVR	Death without preceding symptoms	Sudden death rate per year
Rosenhek et al.[8]	P	128	22 ± 18	59	1	0.43%
Amato et al.[13]	P	66	23.6 ± 12.5	N/A	4	3.1%
Lancellotti et al.[14]	P	69	15 ± 7	12	2	2.3%
Pellikka et al.[11]	R	622	64.8 ± 48	352	11	0.33%
Pai et al.[15]	R	338	42	99	N/A	13.3%
Lancellotti et al.[16]	P	163	20 ± 19	57	3	1.1%
Cioffi et al.[17]	P	209	22 ± 13	72	2	0.52%
Rosenhek et al.[18]	P	116	41 (26–63)	90	1	0.2%

P, prospective; R, retrospective.