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Clinical research

Mild and moderate aortic stenosis

Natural history and risk stratification by echocardiography

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KEYWORDS
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Aims To define the natural history and predictors of outcome in mild and moderate aortic stenosis (AS).
Methods and results One hundred and seventy-six consecutive asymptomatic patients (73 women, age 58±19 years) with mild to moderate AS (jet velocity 2.5 to 3.9 m/s) were followed for 48±19 months. Haemodynamic progression and clinical outcome was analysed. Event-free survival with end-points defined as death (n=34) or aortic valve surgery (n=33), was 95±2%, 75±3% and 60±5% at 1, 3 and 5 years, respectively. Both, cardiac and non-cardiac mortality were significantly increased, resulting in a 1.8 times higher mortality than expected (P<0.005). By multivariate analysis, moderate to severe aortic valve calcification, coronary artery disease (CAD) and peak jet velocity were independent predictors of outcome. Event-free survival for patients with moderate or severe valve calcification was 92±4%, 61±7% and 42±7% at 1, 3 and 5 years versus 100%, 90±4% and 82±5% for patients with no or mild calcification. Patients with calcified aortic valves, CAD or with an event had a significantly faster haemodynamic progression. Of 129 patients with a follow-up echocardiographic exam, 59 (46%) developed severe stenosis during follow-up.
Conclusion Outcome of mild and moderate AS is worse than commonly assumed. Rapid progression and excess mortality have to be considered. Significant valve calcification, CAD and rapid progression of aortic jet velocity indicate poor outcome. Patients with these characteristics may require closer follow-up than generally assumed.

Introduction

Symptomatic patients with severe aortic stenosis (AS) have a very poor prognosis,[1] whereas outcome is relatively favourable as long as patients remain free of symptoms.[2–4] Nevertheless, a considerable number of these patients develop symptoms and require surgery within a short time period. Recently, we were able to demonstrate that the degree of aortic valve calcification and the haemodynamic progression at serial Doppler-echocardiography studies allow identification of high risk patients who require special care.[2] Furthermore, the presence of aortic sclerosis has, recently, been reported to be associated with a significantly increased mortality.[5]

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Table 1 Patient characteristics

Variable	All patients	Patients with event	Patients without event
n	176	109	67
Gender (female)	41%	36%	45%
Age (years)	58±19	67±11	54±21
Age ≥50 years	76%	94%	64%
Aortic valve jet velocity (m/s)	3.13±0.39	3.25±0.37	3.06±0.38
Aortic valve jet velocity ≥3 m/s	68%	79%	61%
Aortic valve peak gradient (mmHg)	40.0±9.7	42.9±9.6	37.9±9.4
Aortic valve mean gradient (mmHg)	25.3±7.4	27.5±7.3	23.5±7.2
Moderate or severe aortic valve calcification	46%	73%	31%
Coronary artery disease	33%	52%	23%
Hypertension	41%	49%	37%
Diabetes mellitus	21%	22%	20%
Hypercholesteraemia	34%	36%	33%

In contrast, the natural history of mild and moderate AS remains poorly defined.

Although a number of studies have reported on the haemodynamic progression[4,6–12] and the clinical outcome[13–17] of mild and moderate AS, they have the limitations of small patient numbers and/or potential selection bias since many of these studies date back to the era when only cardiac catheterization was available to evaluate this disorder. Despite the lack of solid data, mild and moderate AS have been considered a benign disease by many physicians and current guidelines recommend relatively long time intervals for follow-up visits. Nevertheless, patients with rapid progression and poor outcome have been observed. However, no data have, so far, been available to provide risk stratification and appropriate individual patient management.

We, therefore, followed a large cohort of consecutive patients with mild and moderate AS in order to study the natural history of this disease and to identify clinically helpful predictors of outcome.

Methods

Patient population

In 1994, we initiated a prospective study on the outcome of asymptomatic, haemodynamically severe AS.[2] The results of this investigation stimulated the present study on mild to moderate AS. As a consequence, all patients who were studied in our echocardiography laboratory between 1 January and 31 December 1994 and who were found to have a stenotic native aortic valve with a peak aortic jet velocity between 2.5 m/s and 3.9 m/s in the presence of normal left ventricular systolic function as defined by a left ventricular ejection fraction >50%, were identified and included into this retrospective study when they had no additional haemodynamically significant valve lesion (moderate to severe or severe) and presented without symptoms. According to these criteria, 176 patients (age, 58±19 years; 73 female; aortic valve peak velocity, 3.13±0.39 m/s) were identified (Table 1).

The presence of hypercholesteraemia (total cholesterol >220 mg/dl or patient on lipid lowering therapy), diabetes mellitus (as listed in patient chart), arterial hypertension (blood pressure ⩾140/90 mmHg based on the average of repeated readings) and coronary artery disease (documented previous myocardial infarction or angiographically documented coronary artery stenosis) was recorded.

Echocardiography

Echocardiography was performed with commercially available ultrasound systems. All patients underwent a comprehensive examination including M-mode, two-dimensional echocardiography, continuous wave, pulsed and color Doppler by an experienced echocardiographer.

Video recordings were reviewed to score the degree of aortic valve calcification according to previously described echocardiographic criteria.[2] The degree of calcification of the aortic valve was scored according to the following criteria: 1—no calcification, 2—mildly calcified (isolated, small spots), 3—moderately calcified (multiple bigger spots), 4—heavily calcified (extensive thickening/calcification of all cusps).

For all patients who had two or more echocardiographic studies separated by at least 6 months (*n*=129), mean progression of aortic jet velocity in m/s/year was calculated.

Follow-up

The follow-up information was obtained from interviews with the patients, their relatives and their physicians. Particular care was taken to obtain information regarding the development of cardiac symptoms, eventual aortic valve replacement and death.

For the assessment of outcome, end points were defined as death or aortic valve replacement.

Statistical analysis

Continuous variables are expressed as mean±standard deviation. Mean values were compared using the unpaired Student *t*-test. The chi-square test was used for evaluation of differences between proportions. Probabilities of event-free survival were obtained by Kaplan—Meier estimates (including standard errors) for the levels of various prognostic factors (age, gender, hypercholesteraemia, diabetes mellitus, arterial hypertension, coronary artery disease, aortic valve jet velocity at entry and degree of aortic valve calcification). The effects of these prognostic factors on survival were assessed by means of simple and multiple Cox models. No selection of prognostic factors for the multiple model was done by means of univariate analyses. No

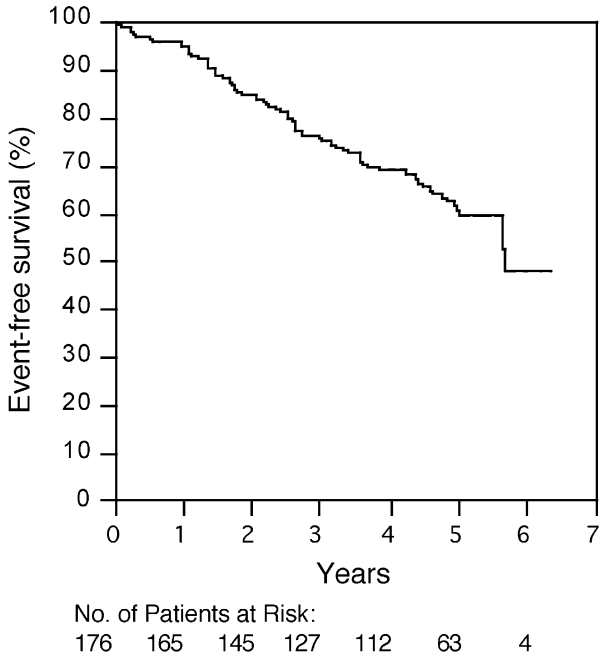

Fig. 1 Kaplan–Meier event-free survival (events: aortic valve replacement *n*=33, death *n*=34).

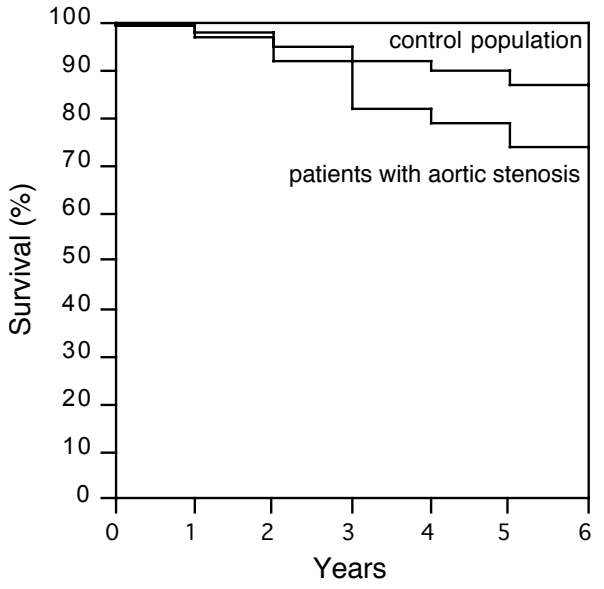

Fig. 2 Kaplan–Meier overall survival of patients compared with survival for age- and gender-matched control subjects (*P*=0.004). This analysis includes perioperative and postoperative deaths for those patients who required valve replacement during follow-up. The data were taken from the Austrian life tables of 1992 that are provided by the Austrian Statistical Institute and represent the survival of the general Austrian population.

other model building procedures were used. The assumption of proportion hazards was assessed by adding interactions of all prognostic factors with log of time, which never turned out to be significant.

A *P*-value <0.05 was considered to indicate statistical significance.

Overall survival (taking into account perioperative deaths and postoperative follow-up for those patients who required surgery) was also quantified and related to the survival of age- and gender-matched 'control subjects', resulting in relative survival functions. The 'control subjects' who represent the survival of the general Austrian population are taken from the Austrian life tables of 1992, which are provided by the Austrian Statistical Office. An approximate chi-square test was used to separately compare the cardiac and the non-cardiac mortality to that of the general population.

Results

Follow-up information was complete for 171 patients (97%).

Event-free survival

During a median follow-up of 55 months (range 1–76 months), 67 end-points were observed including 33 aortic valve replacements and 34 deaths. Estimated event-free survival was 95±2% at 1 year, 75±3% at 3 years, and 60±4% at 5 years (Fig. 1).

Surgery

In the 33 patients who had valve replacement, the reason for surgery was development of severe symptomatic AS in 30 patients while three patients underwent coronary artery bypass grafting and had their aortic valve replaced at the same time because of moderate AS. All three patients had a peak aortic jet velocity greater than 3.5 m/s at the time of surgery.

Deaths

Of 34 deaths, 15 were definitely of cardiac origin. All but one of these 15 patients had developed symptoms before death. Severe AS had been documented prior to death in only seven of these 15 patients. Aortic valve replacement was not performed in these patients for the following reasons: death on the waiting list (two), patient's refusal (two), advanced age and comorbidity (two), unknown reasons (one). One patient died of an ischaemic cardiomyopathy, one had endocarditis. Remarkably, five patients who died had had no follow-up echocardiogram performed although they had developed cardiac symptoms or signs of congestive heart failure before death. Finally, there was one sudden cardiac death that was not preceded by symptoms.

Seventeen non-cardiac deaths involved renal failure (three), respiratory failure (one), hepatic failure (three), cancer (four), perioperative mortality at non-cardiac surgery (four), suicide (one) and Parkinson disease (one). The exact reasons of death remained unknown in two patients.

Overall survival

The overall survival censored at the end of the study including perioperative and late deaths after aortic valve

Table 2 Univariate and multivariate analysis of clinical and echocardiographic predictors of outcome

Variable	Univariate		Multivariate	
	P	Risk ratio	*P*	Risk Ratio
Age ≥50 years	0.0001	2.6 (1.7–4.8)	0.69	1.1 (0.6–2.3)
Gender (female)	0.28	0.9 (0.7–1.1)	0.77	1.1 (0.7–1.5)
Coronary artery disease	0.0002	1.7 (1.3–2.2)	0.0060	1.7 (1.2–2.7)
Hypertension	0.18	1.2 (0.9–1.6)	0.052	0.7 (0.5–1.0)
Diabetes	0.52	1.1 (0.8–1.5)	0.16	0.7 (0.5–1.1)
Hypercholesteraemia	0.75	1.0 (0.8–1.4)	0.66	1.1 (0.8–1.6)
Aortic valve peak velocity ≥3 m/s	0.0079	1.5 (1.1–2.0)	0.034	1.6 (1.04–2.8)
Aortic valve calcification (score 3 or 4)	0.0001	2.1 (1.5–3.0)	0.0012	2.0 (1.3–3.3)

surgery was assessed. The actuarial probability of survival was 96±1% at 1 year, 92±2% at 2 years, 84±3% at 3 years, and 75±3% at 5 years (Fig. 2). Survival of patients with mild and moderate AS was significantly worse than that predicted for age- and gender-matched control subjects with an overall mortality that was 80% higher than that of the general population (*P*=0.004). Both, cardiac (*P*=0.001) as well as non-cardiac mortality (*P*=0.001) were significantly increased.

Predictors of outcome

The degree of aortic valve calcification turned out to be the most powerful predictor of outcome (Table 2). Estimated event-free survival for patients with moderate to severe calcification of their aortic valve was 92±4% at 1 year, 73±6% at 2 years, 61±7% at 3 years and 42±7% at 5 years as compared to 100% at 1 year, 95±3% at 2 years, 90±4% at 3 years and 82±5% at 5 years for patients with no or mild calcification of their aortic valve (*P*=0.0001, Fig. 3A). Outcome was almost identical for patients with moderate and for those with severe calcification.

Patients with higher aortic jet velocities at study entry also had a significantly higher event-rate. Estimated event-free survival for patients with an aortic jet velocity =3 m/s at study entry was 94±2% at 1 year, 70±4% at 3 years and 55±5% at 5 years as compared to 98±2% at 1 year, 89±4% at 3 years and 70±7% at 5 years for patients with aortic jet velocities <3 m/s (*P*=0.008; Fig. 3B). Peak aortic jet velocity remained a significant independent predictor of outcome by multivariate analysis (*P*=0.034).

Of the clinical variables tested, coronary artery disease was the only independent predictor of outcome (*P*=0.006 by multivariate analysis). Patients without coronary artery disease had an estimated event-free survival of 98±1% at 1 year, 86±3% at 3 years and 74±4% at 5 years, as compared to 94±3%, 63±7% and 40±8%, respectively for those with coronary artery disease (*P*=0.0002).

The mean age of the patients who had an event was 67±11 years compared with 54±21 years for patients without event (*P*=0.0001). Mean age of patients who died was also significantly higher (68±10 years) than that of patients alive at the end of the follow-up (55±20 years; *P*=0.0002). In particular, none of the patients younger than 47 years died. Nevertheless, age was a predictor of outcome only by univariate but not by multivariate analysis. Gender, hypercholesteraemia, diabetes mellitus and arterial hypertension were not found to be significant predictors of outcome.

Haemodynamic progression

For the entire patient group with multiple echocardiograms, the average increase in aortic jet velocity was 0.24±0.30 m/s/year (Fig. 4). Mean time interval between the exams was 46±19 months.

A significantly faster haemodynamic progression was present in patients with an event during follow-up compared with those without event (0.45±0.38 vs 0.14±0.18 m/s/year; *P*=0.0001). Furthermore, patients with moderate to severe calcification of their aortic valve had a significantly faster increase in aortic jet velocity than those with no or only mild calcification (0.35±0.31 vs 0.16±0.19 m/s/year; *P*=0.0004). Progression was also significantly faster for patients with coronary artery disease (0.34±0.42 vs 0.18±0.19 m/s/year; *P*=0.004) and in patients older than 50 years (0.30±0.33 vs 0.10±0.14 m/s/year; *P*=0.0005).

Diabetes, arterial hypertension, hypercholesteraemia, gender and aortic jet velocity at entry were not found to significantly affect the haemodynamic progression of AS.

A progression to severe AS, defined as an aortic valve jet velocity $\geqslant$4 m/s in the presence of normal left ventricular function, was observed in 60 out of 129 (47%) patients who had repeated echocardiographic exams during follow-up. All patients had normal left ventricular function at study entry. Only three had developed moderately to severely reduced left ventricular systolic function and 1 patient had mildly impaired function at last follow-up. These patients had developed severe AS by both definitions, aortic jet velocity $\geqslant$4 m/s as well as AVA $\leqslant$1.0 cm^2 (0.6 to 0.7 cm^2). The effective orifice area was also $\leqslant$1.0 cm^2 in all other patients who had progressed to severe AS as defined by a peak aortic jet velocity $\geqslant$4 m/s. Mean effective orifice area for all patients who developed severe AS was 0.73±0.18 cm^2 with a range of 0.4 to 1.0 cm^2. Mean effective orifice area adjusted to BSA in this group was 0.40±0.09 cm^2/m^2 (range 0.25 to 0.60 cm^2/m^2). Aortic jet velocity at study

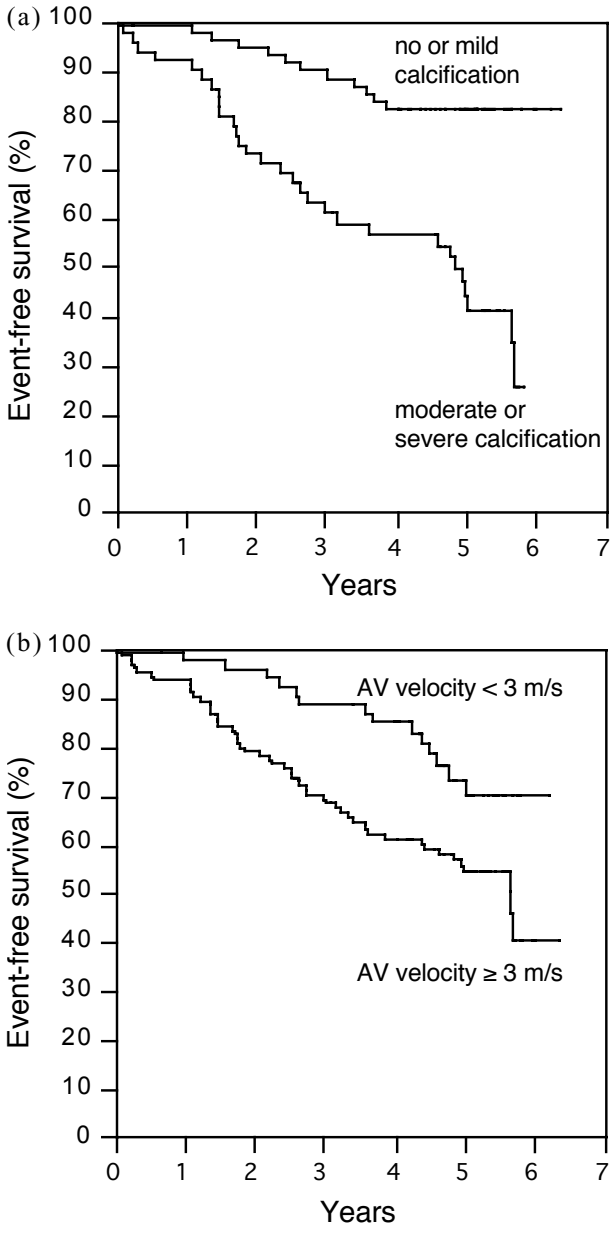

Fig. 3 (a) Kaplan–Meier event-free survival for patients with no or mild calcification compared with patients having moderate or severe aortic valve calcification (P=0.0001). (b) Kaplan–Meier event-free survival for patients with an aortic jet velocity <3 m/s compared with patients having a jet velocity =3 m/s at study entry (P=0.008).

entry ranged from 2.5 to 3.0 m/s in 15, from 3.0 to 3.5 m/s in 27 and from 3.5 to 3.9 m/s in 18 of these patients. Thus, rapid progression to severe AS during follow-up was observed for moderate as well as for mild AS.

Discussion

Current practice guidelines recommend follow-up visits for patients with mild and moderate AS in wide intervals.[18] The results of the present study however, emphasize that even mild and moderate AS must be viewed with more caution than currently thought and that management guidelines may require re-evaluation. Mortality in such patients was 1.8 times higher than that of an age and gender-matched control population and 67 of 171 patients had valve surgery or died within a mean follow-up of 51 months. Rapid progression of moderate and even mild stenosis to haemodynamically severe stenosis is common and was observed in 46% of patients in the present study. Although several previous studies have addressed the outcome of patients with mild and moderate AS, their findings remain controversial. While Horstkotte et al.[16] and Turina et al.[4] describe a relatively benign course of moderate AS with event-free survival rates of 86% and of 80%, respectively at 4 years, Otto and coworkers reported a worse outcome with an event rate of 38% at 3 years.[17] Our study, including a large number of consecutive patients, thus confirms Otto's findings.

Mortality

Otto and coworkers recently reported that the presence of aortic sclerosis is associated with an approximately 50% increase in the risk of cardiovascular death.[5] Similarly, abdominal aortic calcific deposits have been found to be associated with increased vascular morbidity and mortality.[19] These studies indicate that calcific degenerative processes, which are also present in many patients with mild and moderate AS, are associated with an increased mortality. Thus, excess mortality in patients with mild to moderate AS may not be surprising. Mortality in the present study, was, however markedly higher than commonly assumed. Although their study was limited by a small patient number, selection of patients at cardiac catheterization and inclusion of 82% symptomatic patients, Kennedy et al. have previously reported a poor outcome of moderate AS with 14 deaths attributed to AS among 66 patients followed for 35 months.[15] Furthermore, the significantly increased non-cardiac mortality in the present study identifies mild and moderate AS as a marker of poor prognosis due to additional comorbidity. However, as our department is a tertiary referral centre, part of the comorbidity might also be attributed to negative patient selection.

Finally, it may be surprising that mortality of patients with severe but asymptomatic AS in our own previous report was slightly but not significantly higher than that of the general population.[2] This difference may again partly be explained by negative patient selection in the present study. In addition, some of the patients may have developed severe AS during follow-up, which remained undiagnosed because patients and their physicians are less aware of the potential hazards when a recent echocardiogram shows non-severe AS. Appropriate follow-up and treatment is then delayed.

Progression of aortic valve disease

The mean rate of progression of 0.24±0.30 m/s/year in the current study is comparable to the rate of progression observed in previous studies.[2,17] However, in individual patients, rapid progression of mild or moderate to severe

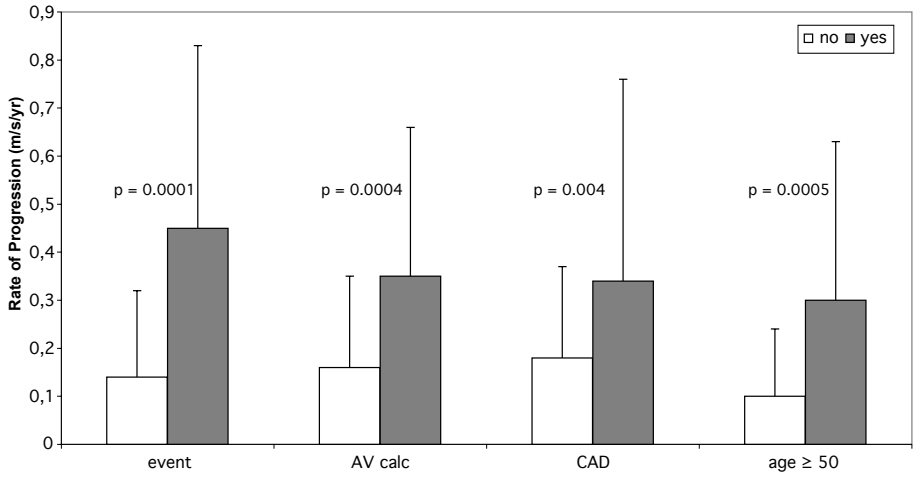

Fig. 4 Rate of progression for patients with absence (white bars) or presence (shaded bars) of the following factors, respectively: occurrence of an event, aortic valve calcification, coronary artery disease and age of 50 or older.

AS may occur within a short time period. We have previously defined rapid haemodynamic progression by an increase in aortic jet velocity of 0.3 m/s/year or greater.[2] In a cohort of asymptomatic patients with severe aortic stenosis, such rapid progression was a significant predictor of poor outcome.[2] In the present study, more rapid progression was also associated with a higher event-rate: patients with an event during follow-up had a rate of progression of 0.45±0.38 m/s/year compared to 0.14±0.18 m/s/year for those without event. Patient-subgroups with higher rates of progression have been identified: patients with moderate to severe calcification of their aortic valve, patients older than 50 years and those with coronary artery disease.

These results confirm previous studies limited by smaller patient numbers and the use of catheter techniques only.[6,7,9–12]

Predictors of outcome

Since outcome varies widely in mild and moderate AS ranging from rapid development of symptomatic severe AS to stable, event-free survival for many years, a general recommendation to closely follow patients with this disease would logistically and economically be problematic. Thus, predictors of outcome that allow risk assessment and more individual assignment of follow-up intervals and management strategies would be desirable. The relation of peak aortic jet velocity at entry to outcome in the present study confirms Otto's findings.[17] However, the presence of moderate to severe aortic valve calcification appears to be the most powerful predictor of outcome in mild and moderate AS and should, therefore, be determined in all patients.

In addition, coronary artery disease indicates a worse prognosis. Age by itself does not appear to be an important risk factor but is rather associated with a higher likelihood of moderate to severe valve calcification.

Valve replacement in patients undergoing coronary bypass surgery

Controversy remains whether aortic valve replacement should be performed in patients with mild or moderate AS at the time of coronary artery bypass surgery or other cardiac surgery.[18] The risk of later aortic valve replacement has to be weighed against the increased risk of prophylactic valve replacement at the time of initial bypass surgery. Although frequently recommended, Rahimtoola calculated an excess mortality for the latter approach when generally performed.[20] Thus, risk stratification may again be helpful for proper management decision. In particular, patients with calcified aortic valves and those with rapid haemodynamic progression are more likely to benefit from valve surgery at the time of bypass surgery.

Limitations

One limitation of this study is its retrospective nature. However, it has to be emphasized that all consecutive patients who fulfilled the entry criteria and were seen in the Echolab within one year were included without any selection and that follow-up was complete in 97%.

Events were defined as aortic valve replacement indicated by the development of symptoms and death. An alternative approach would have been to define the onset of symptoms as an event by itself. However, in a retrospective study this would have been a weak end-point. Since not all patients who developed symptoms eventually underwent surgery, the number of events would have been even greater when using onset of symptoms as an end-point. Thus, there should not be a relevant bias, and in particular, the conclusions would not be different.

Another limitation is that not all patients had a follow-up echo study. This may have affected the analysis of haemodynamic progression. Nevertheless, the progression rate of these patients was very similar to previous reports.

Clinical implications

Mild and moderate AS are associated with substantial mortality, which in part is due to non-cardiac causes. Rapid progression from mild and moderate AS to severe AS is not uncommon.

Patients with mild or moderate AS should therefore be carefully instructed to recognize symptoms of severe AS. Both, patients and their physicians should be aware that the stenosis may have progressed to a severe stage when such symptoms occur, even if a relatively recent echocardiogram may have shown it to be of a lesser degree.

Patients at particularly high risk for such rapid progression are those who on echocardiographic examination have been found to have moderately or severely calcified aortic valves, those in whom serial studies reveal a rapid increase in aortic jet velocity, and those with associated coronary artery disease.

These findings imply that patients with these characteristics may require closer follow-up than generally assumed.

Future research efforts should concentrate on delaying the progression of degenerative aortic valve disease. In the meantime we must focus on avoiding the risks of unnecessary delays in early recognition and appropriate treatment of patients who progress to have haemodynamically significant aortic stenosis.

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