

Natural history of aortic stenosis

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Summary

Background: Management of patients with aortic stenosis is challenging since only few data exists indicating the rate of progression and the correlation to relevant determinants. We investigated whether analysis of the long-term progression, etiology and vascular risk factors could help to define optimal control intervals.

Methods: We included 77 patients (age 51.1 ± 14.3 years) in one referral centre with an echocardiography-proven aortic stenosis (mean gradient >12 mm Hg) and a long-term follow-up of three echocardiographic examinations. Missing clinical data were supplemented by a questionnaire to the general practitioner. Two retrospective examination time intervals were defined as a second interval of <2 years (1.3 ± 0.4) and a first interval of >2 years (6.0 ± 2.4) dating back to the initial examination (maximum of 10.6 years prior to the last examination).

Results: During 6.0 ± 2.4 years, the mean pressure gradient increased from 24.2 ± 13.6 to 38.1 ± 20.4 mm Hg ($p < 0.0001$); respectively 2.1 ± 3.0 mm Hg/year in the first time period and 4.2 ± 8.2 mm Hg/year in the second time period ($p = 0.049$), for the entire population. According to severity, patients with mild or moderate aortic stenosis showed an increase from 2.0 ± 2.7 to 4.0 ± 6.6 mm Hg/year ($p = 0.04$) or from 2.2 ± 3.2 to 3.5 ± 10.9 mm Hg/year respectively ($p = 0.66$). The group with severe aortic stenosis had an increase of 9.6 ± 12.0 mm Hg/year (group too small for statistical analysis).

During the total examination period, left ventricular mass index increased from 149 ± 60 g/m² to 168 ± 63 g/m² ($p < 0.0001$), which corresponds to an increase of 3.2 to 7.8 g/m² per annum ($p = 0.52$), and the relative wall thickness increased from 40.0 ± 8.5 to $43.0 \pm 9.8\%$ ($p = 0.002$). Ejection fraction remained stable and we found no correlation between etiology, vascular risk factors and progression of the disease.

Conclusions: Progression of the mean pressure gradient in patients with aortic stenosis went from 2 mm Hg/year for mild stenosis, to 4 mm Hg/year for moderate stenosis. We found no correlation to conventional vascular risk factors. In patients with mild aortic stenosis and preserved left ventric-

ular ejection fraction, echocardiographic follow-up every 3 to 5 years, until a mean transvalvular pressure gradient of 30 mm Hg is reached, might be a safe and cost-effective follow-up strategy. In patients with more severe aortic stenosis, follow-up has to be more frequent.

Introduction

The most frequent cause of aortic stenosis is the degeneration of the aortic valve, which leads from an aortic sclerosis to an aortic stenosis (AS) in one out of six patients [1]. Although there is a lot of evidence available regarding the natural history and progression of AS, the data concerning the development of the pressure gradient over time are inconsistent. Potential risk factors are still in debate and there is a discussion about clinical and genetic factors, and cellular and molecular reactions due to early inflammatory lesions [14, 15]. Therefore progression seems not to be simply a consequence of atherosclerosis and degeneration of the aortic valve, but also to be influenced by mechanical stress and various other factors. Better knowledge of potential risk factors and rate of pressure rise should be helpful when searching for an effective therapy to avoid calcification of the aortic valve. The aim of this study was to analyse the long-term progression of AS in relation to the etiology, as well as to co-existing vascular risk factors, and to investigate the rate of progression in order to define clinically meaningful as well as cost-effective follow-up strategies.

Methods

Study population

220 patients were eligible for inclusion into our study based on the leading diagnosis of an AS, after checking the clinical database of the echocardiography laboratory at the Hospital of the University of Zurich. 74 patients had to be excluded be-

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cause of incomplete echocardiographic examinations and 69 due to incomplete follow-up data. Thus, 77 patients were included in the study. Only patients with an echocardiography-proven aortic stenosis (mean pressure gradient [Pmean] of at least 12 mm Hg) and a long-term follow-up of at least three echocardiographic examinations were included. Patients with severe aortic regurgitation were excluded. The progression of aortic stenosis was analysed in relation to different determinants, such as gender, etiology (congenital, post-rheumatic, degenerative), severity, obesity, vascular risk factors (hypertension, history of smoking, diabetes mellitus) and intake of statines or ACE inhibitors.

Follow-up protocol

The echocardiographic examinations were analysed retrospectively. Based on the last examination of native valve, two retrospective time intervals were defined: a second interval from 0.25–2 years (1.3 ± 0.4 years) and a first interval from 2 years dating back to the first and oldest echocardiographic examination (6.0 ± 2.4 years up to a maximum of 10.6 years). Clinical data were collected from the clinical database and completed by a questionnaire sent out to general practitioners (rate of return 77%).

Echocardiography

The severity of the aortic stenosis was classified according to the guidelines of the European Society of Cardiology [18]. Thus severity of aortic stenosis was classified upon mean pressure gradient measurements of mild (Pmean <30 mm Hg), moderate (Pmean 30–50 mm Hg) and severe (Pmean >50 mm Hg).

Measurements of the left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF), relative wall thickness (RWT) and fractional shortening (FS) were performed according to the guidelines of the American Society of Echocardiography [19].

Furthermore, development of left ventricular (LV) mass indexed to body surface area (LVMI), RWT, LVEF as well as FS of the left ventricle were analysed. Changes of Pmean and LVMI over time between the two examinations were divided by the time period (delta Pmean respectively delta LVMI).

Table 1

Baseline characteristics of patients with aortic stenosis.

	All (n = 77)	Mild AS (n = 54)	Moderate AS (n = 19)	Severe AS (n = 4)
Mean age (years)	51.1	53.5	47.4	36.3
Women (%)	36	39	32	25
Etiology of AS (%)				
Degenerative/post-rheumatic	61	68	42	50
Congenital	39	32	58	50
Arterial Hypertension (%)	36	40	29	25
Diabetes mellitus (%)	7	6	0	50
Hypercholesteremia (%)	45	40	63	25
History of smoking (%)	39	34	50	50
Obesity (%)	10	9	16	0
ACE-Inhibitors (%)	45	47	44	33
Statins (%)	29	26	47	0

Statistical analysis

For statistical analysis, the programme StatView (SAS Institute Inc., San Francisco, CA, USA) was used. The numerical data was shown as mean with standard deviation and the categorical variables as percentage. For the comparison within one group, a paired t-test and between different groups an unpaired t-test were applied. Comparisons of groups was accomplished by ANOVA or a chi-square test. The limit for significance was defined as p-value below 0.05.

Results

At the time of the first examination, the mean age of the 77 included patients was 51.1 ± 14.3 years (ranging from 24.4 to 77.9 years). Baseline characteristics are given in table 1. Classification according to the etiology only showed a younger age in patients with congenital AS than in the other groups (44.0 ± 13.7 vs 55.7 ± 12.9 years ($p = 0.0003$)).

Pressure gradient

For the entire population during the study period, Pmean increased from 24.2 ± 13.6 to 38.1 ± 20.4 mm Hg ($p < 0.0001$). Progression showed an increase of 2.1 ± 3.0 mm Hg/year in the first time period and 4.2 ± 8.2 mm Hg/year in the second time period ($p = 0.0499$).

In patients with a mild aortic stenosis at baseline, we found an increase of Pmean from 16.9 ± 5.8 mm Hg to 31.3 ± 17.8 mm Hg ($p < 0.0001$), whereas in those with a moderate or severe stenosis at baseline, the mean pressure gradient increased from 35.2 ± 3.4 mm Hg to 48.1 ± 10 mm Hg ($p < 0.0001$) and from 63.3 ± 10.9 to 80.8 ± 20.3 mm Hg ($p = 0.14$), respectively.

According to the severity of AS, delta Pmean increased from 2.0 ± 2.7 to 4.0 ± 6.6 mm Hg/year ($p = 0.04$) in mild AS, and from 2.2 ± 3.2 to 3.5 ± 10.9 mm Hg/year ($p = 0.66$) in moderate AS.

Left ventricular mass index and function

For the whole study population, LVMI increased from 149 ± 60 g/m² to 168 ± 63 g/m² ($p < 0.0001$) with an increase of delta LVMI from 3.2 ± 9.9 g/m²/year to 7.8 ± 40.7 g/m²/year ($p = 0.52$) between the first and the second time period.

In patients with mild AS, LVMI changed from 142 ± 55 g/m² to 161 ± 56 g/m² ($p = 0.002$) and in patients with moderate stenosis from 150 ± 54 g/m² to 165 ± 58 g/m² ($p = 0.053$).

During examination, RWT increased from $40.0 \pm 8.5\%$ to $43.0 \pm 9.8\%$ ($p = 0.002$) for the entire population. Classification according to the severity of AS showed an in-

crease of RWT from $38.5 \pm 8.1\%$ to $42.0 \pm 9.9\%$ ($p = 0.01$) for mild, from $42.6 \pm 8.9\%$ to $43.9 \pm 8.8\%$ ($p = 0.09$) for moderate and from $48.0 \pm 5.3\%$ to $52.9 \pm 9.3\%$ ($p = 0.27$) for severe AS.

During follow-up, LVEF did not change significantly in the entire population or in the different groups (table 2–4).

Further classifications

Categorisation of gender, history of smoking, hypertension, hyperlipidemia, obesity, intake of ACE inhibitors or statines did not show any correlation for progression of the aortic mean pressure gradient. The influence of diabetes mellitus could not be evaluated (only 4 patients). Patients with a history of smoking or hyperlipidemia were significantly younger (44.0 ± 11.9 vs 56.8 ± 13.1 years ($p = 0.0001$) and 45.9 ± 13.1 vs 58.4 ± 11.9 years ($p < 0.0001$), respectively at study entry, which had no impact on the progression of AS.

Discussion

Although there is a lot of evidence available regarding the natural history and progression of AS, the data concerning the development of the mean as well as the maximal pressure gradient over time are inconsistent.

We could establish a nonlinear progression of delta Pmean in AS, accelerating from 2 mm Hg/year during the first study interval to 4 mm Hg/year during a later study interval. In patients with severe stenosis, we found a steeper increase of 9 mm Hg/year, but we did no further analysis. However our results imply a nonlinear increase of Pmean, which contrasts to other studies [3–5] describing a linear increase of delta Pmean between 5 and 9 mm Hg/year. Although only Doppler flow velocity and ejection fraction were independent predictors of subsequent cardiac events from all clinical and echocardiographic variables in the study of Pellikka et al. [6], we found no significant dif-

Table 2

Results for all patients (77 patients).

	Age (year)	Pmean (mm Hg)	LVMI (g/m ²)	RWT (%)	LVEF (%)	FS (%)
Exam 1	51.1 ± 14.3	24.2 ± 13.6	149 ± 60	40.0 ± 8.5	75.7 ± 9.0	38.4 ± 7.3
Δ/Δt		2.1 ± 3.0 ^a	3.2 ± 9.6 ^b			
Exam 2	2 55.9 ± 14.4	32.3 ± 16.8	163 ± 60	42.9 ± 9.5	74.6 ± 9.9	37.7 ± 8.0
Δ/Δt		4.2 ± 8.2 ^a	7.8 ± 40.7 ^b			
Exam 3	57.2 ± 14.4	38.1 ± 20.4	168 ± 63	43.0 ± 9.8	73.5 ± 12.7	37.3 ± 10.1

Pmean = mean pressure gradient; LVMI = left ventricular mass index; RWT = relative wall thickness; LVEF = left ventricular ejection fraction; FS = fractional shortening.
^a mm Hg/year; ^b g/m²/year .

Table 3

Results for all patients with mild aortic stenosis (54 patients).

	Age (year)	Pmean (mm Hg)	LVMI (g/m ²)	RWT (%)	LVEF (%)	FS (%)
Exam 1	53.5 ± 13.4	16.9 ± 5.8	142 ± 55	38.5 ± 8.1	74.3 ± 9.7	37.3 ± 7.6
Δ/Δt		2.0 ± 2.7	1.6 ± 8.2			
Exam 2	58.6 ± 13.5	25.5 ± 13.5	155 ± 51	41.4 ± 9.9	73.1 ± 10.6	36.5 ± 8.3
Δ/Δt		4.0 ± 6.6	10.4 ± 42.8			
Exam 3	59.9 ± 13.5	31.3 ± 17.8	161 ± 56	42.0 ± 9.9	73.8 ± 13.9	37.9 ± 11.1

Table 4

Results for all patients with moderate aortic stenosis (19 patients).

	Age (year)	Pmean (mm Hg)	LVMI (g/m ²)	RWT (%)	LVEF (%)	FS (%)
Exam1	47.4 ± 15.1	35.2 ± 3.4	150 ± 54	42.6 ± 8.9	79.2 ± 6.4	41.4 ± 6.2
Δ/Δt		2.2 ± 3.2	5.4 ± 12.9			
Exam 2	51.6 ± 14.5	44.1 ± 9.3	168 ± 56	46.2 ± 8.1	78.3 ± 7.1	40.6 ± 6.8
Δ/Δt		3.5 ± 10.9	-3.6 ± 33.8			
Exam 3	52.7 ± 14.6	48.1 ± 10.0	165 ± 58	43.9 ± 8.8	72.4 ± 10.4	35.8 ± 8.2

ferences or factors influencing LVEF or FS, but a significant increase of LVMI for mild AS and a trend for moderate AS ($p = 0.053$).

Influence of the etiology on the progression of aortic stenosis

In our study classification according to the etiology of AS, we found significant differences only for age. As expected, patients with congenital AS were significantly younger. In accordance to other studies, although some were very small, we could find no significant differences between the group of degenerative and post-rheumatic etiology nor an impact of the etiology on the progression of AS [3, 5, 7, 8]. Therefore we combined them as one group for further analysis. However we found no results supporting that the etiology has any impact on the natural history of AS.

Influence of severity on the progression of aortic stenosis

The current study showed that prediction of the progression of the pressure gradient should rely on the severity of stenosis at baseline. This is consistent to the study of Otto et al. [3] who concluded that the degree of severity at baseline is the strongest predictor for the progression of AS, but other studies [5, 6, 9] found no significant influence.

Other factors

In our study, neither a correlation of pressure increase to vascular risk factors nor a positive effect of the intake of ACE inhibitors or statins on the progression of AS could be detected [2–8]. Davies et al. [5] found a correlation of both the age of the patient and the degree of calcification with progression of the pressure gradient.

However, this was not examined in our study because quantification of calcification based on morphological criteria alone is inaccurate.

Limitations of this study

Of the 146 patient included in our study, 69 had to be excluded due to missing data. Therefore some groups were too small for statistical analysis. However, progression of aortic stenosis could be evaluated for the most important confounding factors. Unfortunately we could only include four patients with severe aortic stenosis.

Conclusions

In patients with aortic stenosis, the progression of mean pressure gradient was 2 mm Hg/year for mild stenosis to 4 mm Hg/year for moderate stenosis. We found no correlation to conventional vascular risk factors. In patients with mild aortic stenosis and preserved left ventricular ejection fraction, echocardiographic follow-up every 3 to 5 years until a mean transvalvular pressure gradient of 30 mm Hg is reached might be a safe and cost-effective follow-up strategy. In patients with more severe aortic stenosis, follow-up has to be more frequent.

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