Prognosis of Aortic Valve Sclerosis in Cardiovascular Mortality of Patients Seen at the Cardiology Institute of Rio Grande do Sul

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Summary

Objective: To evaluate the prognostic effect of aortic valve sclerosis in mortality and cardiac death of patients assisted at the Cardiology Institute of the Brazilian state of Rio Grande do Sul from 1996 to 2000.

Methods: A historical cohort study using information from both the database of the Echocardiography Laboratory of the Cardiology Hospital and the Death Registry of Rio Grande do Sul Health Department. The evaluation was carried out from 1996 to 2000. Study endpoints were death and cardiac death.

Results: A total of 8585 patients were analyzed, 2154 (25%) of whom had aortic valve sclerosis. Mean follow-up was 41 ± 6 months, and death and cardiac death were 299 (3.5%) and 95 (1.1%), respectively. The group of patients with aortic valve sclerosis had more segmental cardiomyopathy, ventricular dysfunction, ventricular enlargement, and ventricular hypertrophy; yet, they did not show higher risk for death or cardiac death in the multivariate analysis.

Conclusion: The presence of aortic valve sclerosis was not associated with increased risk for death and cardiac death in the population studied.

Key words: Heart valve diseases / prevention / mortality; echocardiography.

Introduction

The etiological factors underlying the development of coronary atherosclerosis may also cause aortic valve leaflet thickening[1,2]. Among them, diabetes mellitus, hypertension, smoking, and dyslipidemia are thought to play a leading role[1-4,7]. The structural and physiological similarities shared by the coronary intimal-medial layer and the tissues overlying aortic valve leaflets explain, in part, their susceptibility to common etiological factors[2,4-11]. Aortic valve sclerosis (AVS) may be associated with coronary atherosclerosis and greater risk for myocardial infarction or cardiovascular death[3, 7,12,15].

The greater risk for cardiovascular death in AVS patients may be related to a progressive loss of aortic leaflet mobility and the development of aortic stenosis[3]. The association with coronary atherosclerosis may be also implicated[3,12,13].

Otto and colleagues have demonstrated increased all-cause and cardiovascular mortality in a subgroup of patients with sclerotic aortic valves. The relative risk of cardiovascular death found in these patients was 1.52 (1.12 to 2.05)[8]. Nevertheless, later reports called these results into question, suggesting that methodological aspects would justify these findings[9-11].

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Aortic valve sclerosis was regarded as a change brought on by normal aging, with no other connotation. Currently, it is considered a disease, and alternative treatments are being sought[7]. Angiotensin-converting-enzyme inhibitors and hydroxymethylglutaryl-coenzyme A reductase inhibitors were used experimentally to reduce the risk of cardiovascular death of patients with aortic valve sclerosis. Thus far, only small and contradictory studies exist[10,11,16-20].

This study was meant to evaluate the effect of aortic valve sclerosis on all-cause and cardiovascular mortality of patients seen at the Cardiology Institute of Rio Grande do Sul (IC-FUC).

Methods

A cohort study comprising patients seen at the IC/FUC from January 1996 to December 2000. Inclusion criteria were patients older than 50 living in the state of Rio Grande do Sul who underwent echocardiography at the IC-FUC from January 1996 to December 2000. Exclusion criteria were mitral or aortic valve prosthesis, moderate to severe mitral or aortic regurgitation, rheumatic heart disease, congenital heart disease, heart valve surgery, ongoing hemodialysis treatment, hypertrophic cardiomyopathy (asymmetric septal hypertrophy), aortic stenosis, or the presence of diseases that reduce life expectancy to less than six months.

Patients were selected from the database of the IC-FUC Echocardiography Division, according to the inclusion and

exclusion criteria, and from the Death Registry of Rio Grande do Sul Health Department. Central to this study was the presence of aortic valve sclerosis. Study endpoints were all-cause or cardiovascular death. Cardiovascular death was considered with the death certificate reported acute myocardial infarction, angina pectoris, ischemic cardiomyopathy, cardiogenic shock, or sudden death.

The following variables were analyzed: gender, age, ventricular dysfunction, segmental cardiomyopathy, left ventricular hypertrophy, and ventricular enlargement.

Qualified echocardiographers, who were also medical doctors, performed one- and two-dimensional transthoracic echocardiograms, pulsed and continuous wave Doppler, and color Doppler flow mapping. The following devices were used: Sonus 1000, ATL HDI 5000 CV, Philips Medical Systems 25000 and 5500, equipped with 2.5 MHz mechanical and electronic transducers.

Aortic valve sclerosis was diagnosed by the thickening of one of the valve cusps on its border, without increase in the left ventricular-aortic gradient. Segmental cardiomyopathy was determined in the presence of segmental akinesia, dyskinesia or hypokinesia on the echocardiogram. Rheumatic heart disease was diagnosed according to echocardiographic criteria. The diagnosis of left ventricular hypertrophy was made when LV septal or free wall thickness exceeded 11 mm. Ventricular enlargement was defined as systolic diameter > 36 mm or diastolic diameter > 55 mm. Ventricular dysfunction was defined as ejection fraction < 45%, using the Teichholz method.

Statistical analysis was performed using SPSS statistical software. The following tests were applied: relative risk, confidence intervals, Cox multivariate analysis, and Kaplan-Meier curve.

Results

Between 1996 and 2000, 8585 patients were assessed, of whom 2154 (25%) had aortic valve sclerosis. Mean age of patients was 56, and mean follow-up period was 41 months. Two hundred and ninety-nine patients died (3.5%), 95 (1.1%) of them from cardiovascular cause. The other variables, namely, gender, segmental cardiomyopathy, ventricular dysfunction, and ventricular enlargement, are described in table 1.

Table 2 shows the distribution of the following variables, according to the presence of aortic valve sclerosis: age, gender, segmental cardiomyopathy, ventricular dysfunction, ventricular enlargement, left ventricular hypertrophy, normal examination, mean follow-up, and number of all-cause and cardiovascular deaths. AVS patients showed higher rates of segmental cardiomyopathy (16.2% vs. 7.5%, p<0.001), ventricular dysfunction (17.2% vs. 10.4%, p<0.001), and ventricular hypertrophy (23.1% vs. 10.9%, p<0.001) than non-AVS controls. In addition, patients in the AVS group were found to be older (67.87 ± 10.43 vs. 50.72 ± 15.16, p<0.001) and to have a higher mortality rate (6% vs. 2.6%, p<0.001) than the control group.

In table 3 comparisons are made between patients who died and those who survived by the end of the follow-up period. In the group of patients who died, the presence of aortic valve sclerosis (49.4% vs. 24.3%, p<0.001), male gender (52.9% vs. 41.8%, p<0.001), mean age (6.44 ± 14.63 vs. 54.62 ± 15.52 in years, p<0.001), segmental cardiomyopathy (20.9% vs. 9.3%, p<0.001), ventricular dysfunction (30.8% vs. 11.4%, p<0.001), ventricular enlargement (15.6% vs. 5.7%, p<0.001), and ventricular hypertrophy (24% vs. 13.5%, p<0.001) was more frequent than in the survivor group. Follow-up period was lower (18.72 ± 13.56 vs. 42.54 ± 3.34 in months, p<0.001), and normal echocardiographic examination (8% vs. 29.3%) was less frequent in patients who died than in those who survived, respectively. When the analysis is repeated for cardiovascular death (Tab. 4), these variables showed the same behavior.

Aortic valve sclerosis has no prognostic effect on all-cause (RR 1.04, CI 0.78-1.38) and cardiovascular (RR 1.38, CI 0.85-2.24) mortality by the Cox multivariate analysis (Tabs. 5 and 6, Figs. 1 and 2). The following variables were associated with higher mortality rate: age, ischemic cardiomyopathy, ventricular dysfunction, ventricular enlargement, and ventricular hypertrophy. Male sex was statistically significant when tested for death (Tabs. 5 and 6).

Discussion

In our study, the presence of aortic valve sclerosis was not associated with increased risk for all-cause and cardiovascular mortality, which contradicts the results of some published studies[3, 4, 6, 15, 21-28].

Literature data on the association of aortic valve sclerosis with coronary artery disease or coronary ischemic events are controversial, ranging from reports suggesting a 50% increase in cardiovascular mortality to those demonstrating an association with coronary artery disease to recommendations for secondary prevention with statins or angiotensin-converting

Characteristics	Values	
Patients, n	8585	
Male, n (%)	3607	(42.7)
Mean age, years (SD)	56	± 16
Segmental cardiomyopathy, n (%)	833	(9.7)
Ventricular dysfunction, n (%)	1041	(12.1)
Ventricular enlargement, n (%)	523	(6.1)
Ventricular hypertrophy, n (%)	1200	(14)
Normal examination, n (%)	2470	(28.8)
Aortic valve sclerosis, n (%)	2154	(25)
Mean follow-up, months (SD)	41.68	± 6.12
Death, n (%)	299	(3.5)
Cardiovascular death, n (%)	95	(1.1)

n: number; (%): percentage; months: mean of months; SD: standard deviation.

Table 1 - Distribution of sample variables

enzymes in AVS patients[29-47]. At the other extreme, Chandra and colleagues found no association between aortic valve sclerosis and the all-cause or cardiovascular mortality endpoint[48], and Tolstrup et al found no association between aortic valve sclerosis and coronary artery disease[49]. In our study, there was evidence of association between aortic valve sclerosis and segmental cardiomyopathy, but no independent association with death was observed. Coronary atherosclerosis and aortic valve sclerosis share common etiopathogenic features, but we have not grasped how to associate the presence of aortic valve sclerosis with the development of coronary endothelial instability.

The study by Otto et al represents a reference regarding the prognostic effect of aortic valve sclerosis on overall and cardiovascular mortality. In this study, aortic valve sclerosis did not influence patients' prognosis, with the exception of a subgroup of patients with no ischemic heart disease[1]. Our findings are consistent with those of Otto et al, because our sample comprised patients with and without segmental cardiomyopathy, which explains the lack of a prognostic effect. Therefore, we suppose that if a study were carried out to evaluate primarily the prognostic effect of aortic valve sclerosis in patients with no ischemic heart disease, it is likely that positive results would be obtained.

The disproportionate occurrence of segmental cardiomyopathy, hypertensive cardiomyopathy, ventricular dysfunction, and ventricular enlargement presented in table 2 is not due to any selection bias. The large number of cases included in our study allows hypothesizing that this disproportion is not accidental, but rather that an association exists between aortic valve sclerosis and hypertensive cardiomyopathy, ventricular dysfunction, and ventricular enlargement, as with ischemic heart disease.

The major non-measured factors that could limit our findings are the fact that the time elapsed since AVS onset was not defined at study entry; the method used to infer the

	Aortic valve sclerosis	No aortic valve sclerosis	P
Patients, n	2154	6431	
Male, n (%)	888 (41.2)	2719 (42.2)	0.268
Mean age, years (SD)	67.87± 10.43	50.72± 15.16	0.001
Segmental cardiomyopathy, n (%)	350 (16.2)	483 (7.5)	0.001
Ventricular dysfunction, n (%)	371 (17.2)	670 (10.4)	0.001
Ventricular enlargement, n (%)	139 (6.5)	384 (6)	0.369
Ventricular hypertrophy, n (%)	498 (23.1)	702 (10.9)	0.001
Normal examination, n (%)	5 (0.2)	2465 (38.3)	0.001
Mean follow-up, months (SD)	40.85 ± 6,97	41.96 ± 5.79	0.001
Death, n (%)	130 (6)	169 (2.6)	0.001
Cardiovascular death, n (%)	58 (2.6)	37 (0.6)	0.001

n: number; %: percentage; SD: standard deviation.

Table 2 - Distribution of variables for aortic valve sclerosis

	Death	No death	p
Patients, n	263	8305	
Male, n (%)	139 (52.9)	3468 (41.8)	0.001
Mean age, years (SD)	66.44 ± 14.63	54.62 ± 15.52	0.001
Segmental cardiomyopathy, n (%)	55 (20.9)	775 (9.3)	0.001
Ventricular dysfunction, n (%)	81 (30.8)	946 (11.4)	0.001
Ventricular enlargement, n (%)	41 (15.6)	476 (5.7)	0.001
Ventricular hypertrophy, n (%)	63 (24)	1125 (13.5)	0.001
Normal examination, n (%)	21 (8)	2435 (29,3)	0.001
Mean follow-up, months (SD)	18.72 ±13.56	42.54 ± 3.34	0.001
Aortic valve sclerosis, n (%)	130 (49.4)	2015 (24.3)	0.001

n: number; %: percentage; SD: standard deviation.

Table 3 - Distribution of exposure and risk factors for death

	Cardiovascular death	No death	p
Patients, n	95	8409	
Male, n (%)	52 (54.7)	3555 (42)	0.013
Mean age, years (SD)	68.35 ± 11.17	55.53 ± 15.86	0.001
Segmental cardiomyopathy, n (%)	27 (28.4)	803 (9.5)	0.001
Ventricular dysfunction, n (%)	32 (33.7)	995 (11.7)	0.001
Ventricular enlargement, n (%)	15 (15.8)	502 (5.9)	0.001
Ventricular hypertrophy, n (%)	25 (26.3)	1163 (13.7)	0.01
Normal examination, n (%)	5 (5.3)	2451 (28.9)	0.001
Aortic valve sclerosis, n (%)	58 (61.1)	2087 (24.6)	0.001
Mean follow-up, months (SD)	18.42 ± 12.59	42.06 ± 5.08	0.001

n: number; %: percentage; SD: standard deviation.

Table 4 - Distribution of exposure and risk factors for cardiovascular death

	RR	CI	P
Male	1.3	1-1.69	0.047
Age	1.04	1.03-1.06	0.0001
Segmental cardiomyopathy	1.73	1.23-2.42	0.001
Ventricular dysfunction	2.01	1.42-2.84	0.0001
Ventricular enlargement	1.72	1.12-2.62	0.012
Ventricular hypertrophy	1.59	1.18-2.15	0.002
Normal examination	0.73	0.42-1.26	0.26
Aortic valve sclerosis	1.04	0.78-1.38	0.76

RR: relative risk; CI: confidence interval; p 0.05.

Table 5 - Multivariate analysis of all-cause death

	RR	CI	P
Male	1.40	0.9-2.18	0.130
Age	1.05	1.03-1.07	0.0001
Segmental cardiomyopathy	2.55	1.52-4.30	0.0001
Ventricular dysfunction	1.91	1.10-3.32	0.020
Ventricular enlargement	2.16	1.08-4-34	0.029
Ventricular hypertrophy	1.86	1.14-3.03	0.012
Normal examination	0.78	0.26-2.32	0.66
Aortic valve sclerosis	1.38	0.85-2.24	0.18

RR: relative risk; CI: confidence interval; p 0.05.

Table 6 - Multivariate analysis of cardiovascular death

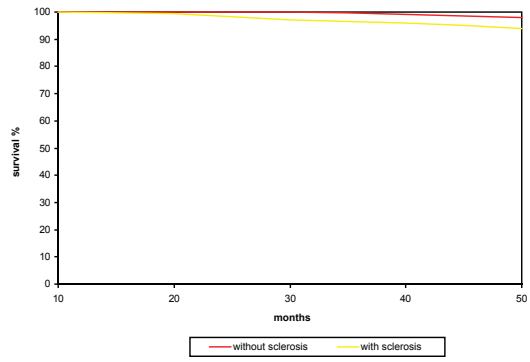

Fig. 1 - *Kaplan-Meier curve comparing the survival of patients with and without aortic valve sclerosis.*

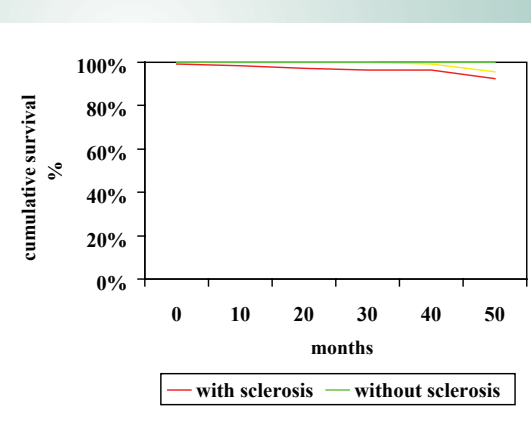

Fig. 2 - *Kaplan-Meier curve comparing the survival of patients with and without aortic valve sclerosis in cardiac death.*

diagnosis of heart disease, that is, restricted to the presence of segmental cardiomyopathy on the echocardiogram; the method used to consider patients as survivors at study

conclusion, that is, the fact that they were not included in the death registry of the Health Department; and the reliability of information abstracted from death certificates. Another potential source of bias is the lack of information in the database regarding the use of drugs such as vastatin and ACE inhibitors, which could eventually influence the results.

In conclusion, our findings indicate that, in this study, AVS patients did not face higher risk of all-cause or cardiovascular mortality; yet, further studies are warranted to replicate these data.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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