ORIGINAL INVESTIGATION

The Risk of the Development of Aortic Stenosis in Patients With "Benign" Aortic Valve Thickening

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Background: Aortic valve thickening (AVT) without aortic stenosis (AS) is common and was often considered benign. However, it has recently been found to be associated with increased morbidity and mortality. It is unknown whether patients with AVT are at risk for the development of AS.

Methods: Our echocardiography database from 1987 to 1993 was searched for cases of AVT with at least 1 year of echocardiographic follow-up. The risk of the development of AS was compared in patients with and without AVT.

Results: There were 2131 patients with AVT and at least 1 year of echocardiographic follow-up. Aortic stenosis developed in 338 patients (15.9%) (mild, 10.5%; moderate, 2.9%; and severe, 2.5%). Multivariate analysis, including age, left ventricular hypertrophy, and mitral annular calcification, revealed that only mitral annular calcification was independently and significantly associated with progression to AS.

Conclusions: Aortic valve thickening without stenosis is common, and it may progress to significant AS. It is possible that this development of AS may be responsible for some of the increased morbidity and mortality in patients with AVT.

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AORTIC VALVE thickening (AVT) without aortic stenosis (AS) is a common echocardiographic finding. Its prevalence is 26% in adults older than 65 years[1] and up to 40% in those older than 75 years.[2] In an echocardiographic study of nonagenarians, only 10% had a normal aortic valve.[3] The fact that the majority of elderly people do not have AVT implies that risk factors other than age play a role in its pathogenesis.

Although AVT is often considered benign, it is known that patients with AVT have risk factors for the development of cardiac disease.[4] Moreover, an association between AVT and an increased risk of cardiovascular morbidity and mortality has been demonstrated.[5] However, to our knowledge, there has been no systematic evaluation of the risk of AS developing in patients with AVT to date. The present study was undertaken to investigate the possible progression of AVT to AS in a large cohort of patients.

METHODS

We searched our echocardiography database from 1987 to 1993 for patients with AVT and at least 1 year of echocardiographic follow-up. They had been referred for a variety of clinical indications. Aortic valve thickening was defined as focal or diffuse leaflet thickening or calcification, normal valve excursion, and peak Doppler flow velocity of less than 2 m/s. Follow-up echocardiograms were evaluated for the development of AS. Mild AS was defined as a peak gradient between 16 and 36 mm Hg or a mean gradient of less than 25 mm Hg. Moderate AS was defined as a peak gradient between 36 and 63 mm Hg or a mean gradient between 25 and 44 mm Hg. Severe AS was defined as a peak gradient of 64 mm Hg or more or a mean gradient of 45 mm Hg or more. For the purposes of this study, left ventricular function was not taken into account. Persons who developed significant (moderate or severe) AS (*patients*) were matched for time of follow-up to those with AVT who did not develop any AS (*controls*). We excluded those who had moderate or severe aortic regurgitation.

The patients were compared with the controls with respect to predictors associated with the progression of established AS, ie, age, sex, and the echocardiographic variables of mitral annular calcification (MAC), left ventricular hypertrophy (LVH) (wall thickness ≥12 mm), left ventricular function (decreased ejection fraction [<50%]), and mitral regurgitation. Also, 100 subjects with normal aortic valves (no AVT) were matched for age and time of echocardiography follow-up to those with AVT, and evaluated for the development of AS.

Continuous variables were analyzed using a *t* test. Discontinuous variables were analyzed using χ^2 analysis. Any variables with a *P* value of .10 or less on univariate analysis were entered into a model for multivariate analysis (stepwise logistic regression) (SPSS Software, Version 10; SPSS Inc, Chicago, Ill). A *P* value of .05 or less was considered statistically significant.

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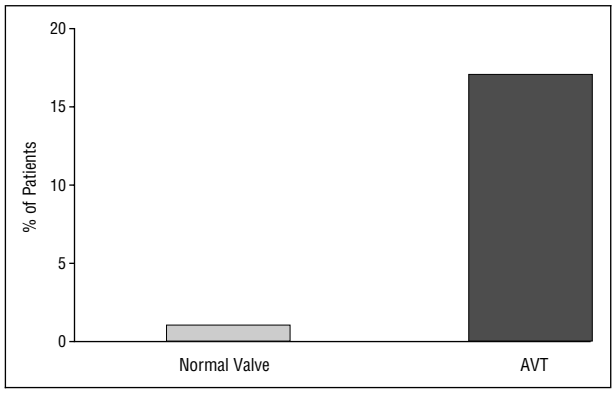

Figure 1. The development of aortic stenosis. AVT indicates aortic valve thickening.

Comparison Between Patients With AVT Who Progressed to Significant AS and Controls With AVT Who Did Not*

	Patients (n = 115)	Controls (n = 115)	*P* Value
Age, mean ± SD, y	70.8 ± 7.8	68.6 ± 10.9	.07
Male sex	66 (57.0}	70 (61.0)	.59
MAC	42 (36.5)	22 (19.1)	.003
LVH	40 (34.8)	24 (20.9)	.02
MR	16 (13.9)	18 (15.6)	.71
Low EF	10 (8.7)	8 (6.9)	.62

*AVT indicates aortic valve thickening; AS, aortic stenosis; MAC, mitral annular calcification; LVH, left ventricular hypertrophy; MR, mitral regurgitation; and EF, ejection fraction. Values other than age are given as number (percentage).

RESULTS

Over the 6-year period from 1987 to 1993, we found 2131 patients with AVT and at least 1 year of echocardiographic follow-up. These patients made up the study group. Aortic stenosis of any degree developed in 338 patients (15.9%) with AVT. This was a significantly higher incidence of AS than we found in the subjects with normal valves (without AVT), among whom just 1 patient (1%; $P < .001$) developed only mild AS (**Figure 1**). These 2 groups were matched for age (69.3 years vs 69.7 years) and time of follow-up (7.3 years vs 7.4 years).

Mild AS developed in 223 patients (10.5%) with AVT; moderate AS developed in 61 patients (2.9%); and severe AS developed in 54 patients (2.5%). The mean±SD time to follow-up of the 115 patients with AVT who developed moderate or severe AS was 7.4±2.4 years, and this follow-up time was matched to that of the patients with AVT who did not develop any AS (7.4±2.3 years, $P = .84$). The 2 groups were compared and the findings are presented in the **Table**. The years at which moderate and severe AS developed are shown in **Figure 2** and **Figure 3**. The largest number of patients who developed moderate AS were observed to do so at 6 years; severe AS was observed most often with 2 more years of follow-up (ie, at 8 years).

There was no significant difference in sex between the 115 patients and the 115 controls: 66 (57%) male vs 70 (61%) male ($P = .60$). There was a trend toward older age in the patients compared with the controls (70.8±7.8 [mean±SD] years vs 68.6±10.9 years), but it was not statistically significant ($P = .08$). Mitral annular calcification was found in significantly more patients (those with AVT who developed AS) than controls (AVT with no development of AS): 42 (36.5%) vs 22 (19.1%) ($P = .003$). Left ventricular hypertrophy was also found in significantly more patients than controls: 40 (34.8%) vs 24 (20.9%) ($P = .02$). Moderate or severe mitral regurgitation was found in 16 patients (13.9%) and 18 controls (15.6%) ($P = .71$). Decreased left ventricular function was found in 10 patients (8.7%) and 8 controls (6.9%) ($P = .62$).

Multivariate analysis using a model that included age, MAC, and LVH revealed that only MAC ($P = .02$) was significantly and independently associated with a progression from AVT to significant AS when age and LVH were controlled for. Age ($P = .44$) and LVH ($P = 0.10$) were not independently associated with progression of AVT to AS.

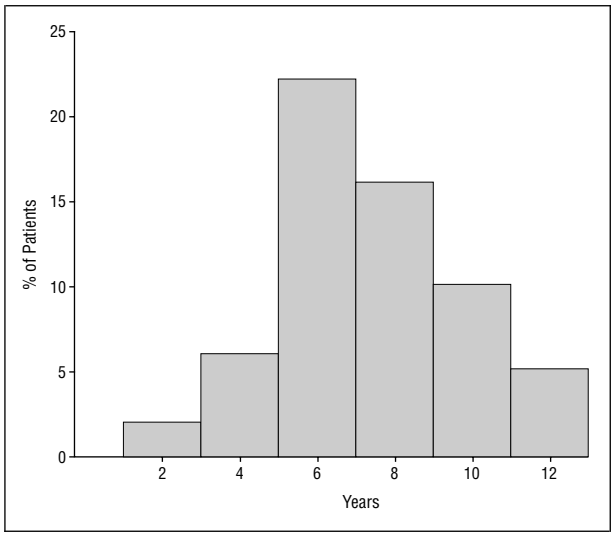

Figure 2. The number of years from aortic valve thickening to moderate aortic stenosis.

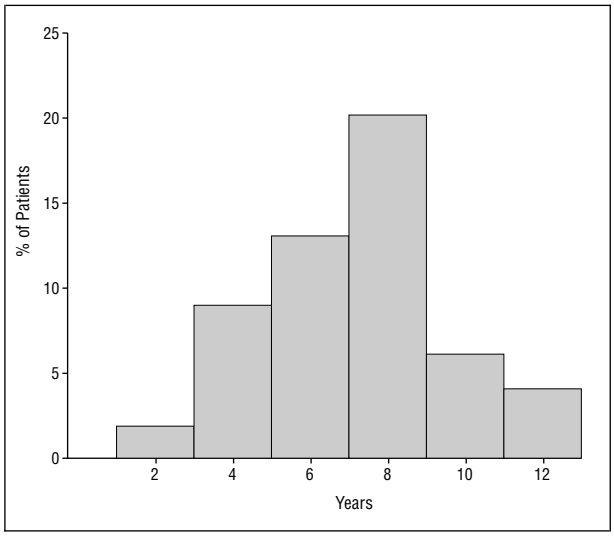

Figure 3. The number of years from aortic valve thickening to severe aortic stenosis.

COMMENT

Although usually thought of as a common, benign valvular condition, AVT has been shown by 3 independent

investigations to be associated with increased morbidity and mortality.[5-7] In a study by Otto et al,[5] there was a 50% increase in the risk of cardiovascular mortality and myocardial infarction in patients with AVT.

Exactly how AVT influences cardiovascular morbidity and mortality has not been determined. Aortic valve thickening has been associated with risk factors for cardiovascular disease, such as increasing age, male sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, increased levels of lipoprotein(a), and reduced levels of high-density lipoprotein.[1,8,9] These associations may partially explain the increased risk for cardiovascular disease in patients with AVT.

We have found that AS may develop in a significant number of patients with AVT. Although we did not have natural history data available, it is possible that the development of AS may also be an important element in the increased cardiovascular morbidity and mortality. Aortic stenosis and AVT appear to represent different stages in a continuum of aortic valve disease.

Predictors of the progression of established AS have been identified: age, coronary artery disease, left ventricular dysfunction, left ventricular wall thickness, valvular calcification, mitral regurgitation, and worsening symptoms.[10,11] However, the factors that may predict the progression of AVT to AS are unknown. We analyzed some of the factors that are known to predict the progression of established AS to determine whether they may also serve to predict the progression of AVT to AS. On univariate analysis, the development of AS from AVT was associated with LVH and MAC, and there was a trend for an association with age. A similar association was not demonstrated for left ventricular dysfunction or mitral regurgitation. However, our multivariate analysis model revealed only MAC, not age or LVH, as independently predictive of progression to AS.

The process of aortic valve calcification has similarities to that of atherosclerosis.[12] Therefore, calcification of the aortic valve and coronary arteries as well as of the mitral annulus may represent a unified process of inflammation and/or degeneration,[13] and the association of the progression of AVT to AS with MAC may be a manifestation of this process. Although further investigation is needed to firmly link the pathogenesis of these entities, the presence of a common pathway of tissue injury leading to sclerosis and calcification would imply that calcific aortic valve disease is an active process that might be modified by treating associated risk factors.[12]

The major limitation of this study was its retrospective nature. Because all of our patients were referred to the echocardiography laboratory for various indications, this is a source of bias. Furthermore, we were limited to the examination of available follow-up echocardiograms, and therefore could not identify the exact time at which AS developed. There is also selection bias in the referral of patients for echocardiographic follow-up, and patients who developed AS may have been more likely to have been referred for echocardiographic follow-up. However, the large size of the population studied would tend to offset some of these limitations.

Gradient, rather than valve area, was used to grade the severity of AS. Therefore, some patients may have developed more or less severe AS than the degree reported. However, the low prevalence of left ventricular dysfunction and the large number of patients both offset this limitation.

We do not have other clinical information about these patients, such as their history of risk factors for, or clinical manifestations of, atherosclerosis. We also do not have information about subsequent morbidity and mortality, which have been previously evaluated by others.

CONCLUSIONS

Aortic valve thickening is a common echocardiographic finding, and it may progress to hemodynamically significant AS. The presence of MAC may serve to predict which patients with AVT are at risk of developing AS. A prospective study of the progression of AVT to AS would be important.

It remains to be seen whether or not the development of AS is responsible for part of the increase in complications seen in patients with AVT. Further investigation may focus on the duration of time between the appearance of AVT and the development of AS. Finally, the possible impact of risk factor modification (to reduce the risk of AS) on the large numbers of patients with AVT is a question for future study.

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