Prevalence of Atherosclerosis of the Coronary and Extracranial Cerebral Arteries in Patients Undergoing Aortic Valve Replacement for Calcified Stenosis

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Background and aim of the study: **The study aim was to investigate the coexistence of various atherosclerotic changes in patients with non-rheumatic calcific aortic valve stenosis (AS), since calcific AS shares various clinical risk factors with atherosclerosis.**
Methods: **In 282 consecutive patients with severe calcific stenosis of a tricuspid aortic valve scheduled for aortic valve replacement, the prevalence of atherosclerotic changes of the coronary and extracranial cerebral arteries were assessed using coronary angiography and Doppler sonography, respectively.**
Results: **The severities of coronary and extracranial cerebral artery atherosclerosis were significantly associated (p = 0.005). The prevalence and severity of both coronary and extracranial cerebral artery atherosclerosis were age-dependent. Coronary or extracranial cerebral artery stenosis was present in 59% and 16% of patients, respectively, while 91% of the study population and all patients aged >80 years showed atherosclerosis of the coronary and/or extracranial cerebral arteries.**
Conclusion: **The data obtained indicated a very high prevalence of atherosclerotic changes in patients with calcific AS, suggesting pathogenetic similarities of both disorders. Routine screening of the extracranial cerebral arteries is warranted in all patients with calcific AS and scheduled for valve replacement.**

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Non-rheumatic, calcific aortic valve stenosis is the most prevalent heart valve disease, and the most common cause for heart valve replacement in the elderly (1). Both, non-obstructive aortic valve sclerosis and calcific aortic valve stenosis share various clinical risk factors with atherosclerosis (2). Whilst both disorders have been shown to be associated with an increased prevalence of carotid, peripheral and coronary atherosclerosis (3-7), few data are available on the coexistence of atherosclerotic changes in patients with calcific aortic valve stenosis. It is thought that only 50% of patients with aortic valve stenosis have stenotic coronary artery disease (8). However, the absence of stenotic coronary artery disease does not mean an absence of atherosclerosis. Because calcific aortic valve stenosis and atherosclerosis share many pathogenetic similarities, the present study was initiated to assess the coincidence of atherosclerotic diseases and calcific aortic valve stenosis.

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Clinical material and methods

Patients

A total of 282 consecutive patients in two centers (Aachen and Mannheim) (163 males, 119 females; mean age 71 ± 8 years) with severe calcific stenosis (valve area <1 cm^2) of a tricuspid aortic valve who were scheduled for aortic valve replacement, was included in the study. Written informed consent was obtained from each patient as applicable for all procedures performed. Patients with a known history of rheumatic heart disease or other valvular disorders were excluded. Hypercholesterolemia was considered present if the total fasting serum cholesterol was >200 mg/dl, or if the patient was receiving cholesterol-lowering medication. Since cholesterol data were not accessible in all patients, it cannot be fully excluded that some patients might have taken statins for reasons other than hyperlipidemia. Arterial hypertension was considered present if the resting blood pressure was >140/90 mmHg, and diabetes mellitus was considered present if the fasting serum glucose concentration was >126 mg/dl, or if the patient was taking anti-diabetic medication.

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Cardiac catheterization

Left heart catheterization (including coronary angiography) was performed in all patients. For each study, at least two projections of the right and four projections of the left coronary artery were recorded digitally. Coronary angiograms were graded for the presence of coronary atherosclerosis by an experienced cardiologist blinded to the results of Doppler sonography, using the following categories: 0 = no coronary atherosclerosis; 1 = non-obstructive coronary atherosclerosis with a luminal narrowing <50%; and 2 = obstructive coronary atherosclerosis with a luminal narrowing ≥50%.

Doppler sonography

All patients underwent comprehensive Doppler sonographic evaluation of the extracranial cerebral arteries (common, internal and external carotid, vertebral and subclavian arteries) according to current guidelines. For the present study, the Doppler sonographic recordings were assessed for the presence of atherosclerosis by an experienced angiologist or neurologist, respectively, using the following categories: 0 = no carotid atherosclerosis; 1 = non-high-grade carotid atherosclerosis with a luminal narrowing <70% and without direct or indirect criteria of stenosis (flow acceleration, pulsatility changes or signs for collateral blood flow); and 2 = high-grade atherosclerosis (≥70%).

Statistical analysis

Statistical analysis was performed with the commercially available statistics software package SPSS (Version 11.0, SPSS Inc., Chicago, USA). Continuous data were expressed as mean ± SD. A chi-square analysis was used to assess the distribution of categoric variables within groups. A p-value <0.05 was considered to be statistically significant.

Results

Arterial hypertension was present in 189 patients (67%), hyperlipidemia in 149 patients (53%), and diabetes mellitus in 84 patients (30%). The prevalence of atherosclerotic changes in the study group is detailed in Table I. The severity of coronary and extracranial cerebral artery atherosclerosis showed a significant statistical association ($\chi^2 = 14.8$, $p = 0.005$). The prevalence and severity of both coronary and extracranial cerebral artery atherosclerosis were age-dependent (Fig. 1). Coronary or extracranial cerebral artery stenosis was present in 59% and 16% of patients, respectively, while 91% of the study population and all patients aged over 80 years showed atherosclerosis of the coronary and/or brain-supplying arteries.

Table I: Prevalence of coronary and carotid atherosclerosis in 282 patients with severe calcific aortic valve stenosis.

Condition	No. of patients
Normal coronary arteries	61 (22)
Non-obstructive coronary atherosclerosis	54 (19)
Obstructive coronary atherosclerosis	167 (59)
Normal brain-supplying arteries	91 (32)
Non-high-grade atherosclerosis of brain-supplying arteries	145 (51)
High-grade atherosclerosis of brain-supplying arteries	46 (16)
Any atherosclerosis	256 (91)

Values in parentheses are percentages.

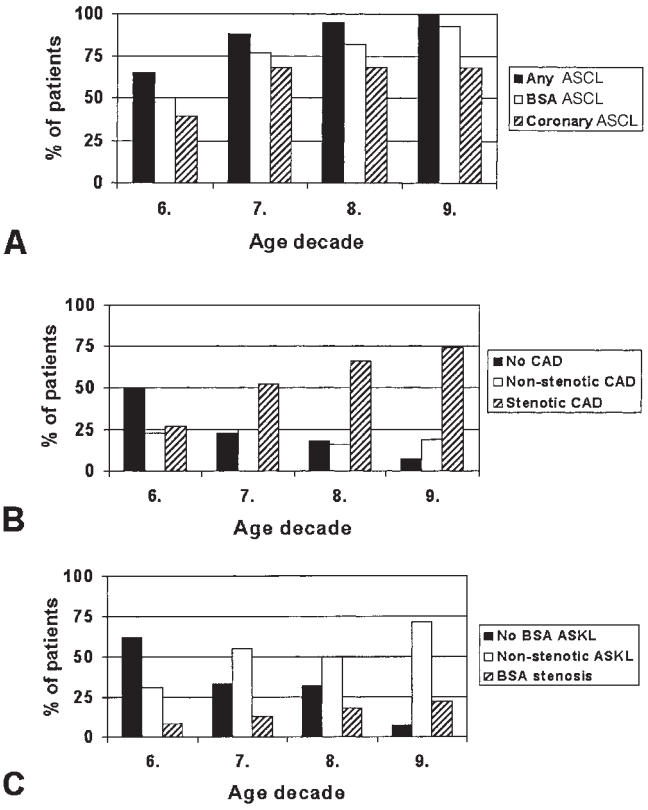

Figure 1: Distribution of atherosclerosis (ASCL) in patients with severe calcific aortic valve stenosis according to age decades. A) Age-dependent increase in the prevalence of coronary and extracranial cerebral artery atherosclerosis, or both ($\chi^2 = 26.1$, $p < 0.001$). B) Age-dependent increase in the severity of coronary atherosclerosis ($\chi^2 = 22.8$, $p = 0.001$). C) Age-dependent increase in the severity of atherosclerosis of the brain-supplying arteries (BSA) ($\chi^2 = 19.0$, $p = 0.004$). CAD: Coronary artery disease. Numbers of patients: 6th decade: n = 26; 7th decade: n = 77; 8th decade: n = 152; 9th decade: n = 27; total: n = 282.

Discussion

Data obtained from 282 consecutive patients with calcific aortic valve stenosis showed that atherosclerotic changes are highly prevalent in this type of patient. A variety of studies have focused on the association of calcific aortic valve stenosis and atherosclerosis. The prevalence of coronary artery disease is high in patients with aortic valve stenosis (9) and exceeds the prevalence in elderly persons without aortic valve stenosis (7). An association of aortic valve sclerosis and aortic atherosclerosis has been demonstrated in older men and in a population-based study using transesophageal echocardiography (10,11). Comparable results were shown by spiral computed tomography demonstrating that aortic valve calcium was associated with aortic calcification in elderly hypertensive patients (12). Peripheral artery disease was also associated with aortic valve stenosis of any grade in an elderly population aged about 80 years (5). Moreover, carotid artery atherosclerosis was associated with the prevalence of both, a calcified, but non-stenotic aortic valve and with calcific aortic valve stenosis of all grades (3,13). It is difficult to separate exactly the factors involved in the pathogenesis of aortic valve stenosis. First, the traditional cardiovascular risk factors are highly prevalent in patients with aortic stenosis (2). Second, cardiovascular risk factors are associated with the severity of coronary atherosclerosis (14) but not with the prevalence of aortic valve stenosis. Considering the fact that there are many patients with atherosclerosis, but without aortic valve stenosis, it is interesting to know whether, in contrast, there are any patients with degenerative aortic valve stenosis, but without atherosclerosis.

Among the present group of patients with severe degenerative aortic valve stenosis there were almost no patients without signs of systemic atherosclerosis. This high coincidence of atherosclerosis and calcific aortic valve stenosis is of special interest because the detection methods used in the present study were rather insensitive in detecting early atherosclerotic changes. It could therefore be speculated that using more sensitive methods such as intravascular ultrasound, multislice computed tomography or magnetic resonance tomography, an even higher extent of atherosclerotic burden would have been detected. Moreover, by focusing on coronary and carotid disease, other important regions of atherosclerosis such as the abdominal aorta and peripheral arteries were not included. Based on these facts, it could be proposed that the real prevalence of 'systemic' atherosclerosis might be up to 100% in patients with calcific aortic valve stenosis. Although these data may support the hypothesis that atherosclerosis is the basis of calcific aortic valve stenosis, a causal relationship cannot be deduced from the findings of the present study. It is also possible that atherosclerosis and calcific aortic stenosis, whilst possessing similar risk factors, are different processes and may occur concurrently. Some authors have proposed that stiffening of the aortic wall due to old age fibrosis and/or atherosclerosis may lead to increased hemodynamic stress on the aortic valve stenosis which, in turn, may initiate the process of aortic valvular thickening and calcification (15). In addition, genetic variants have been identified previously which are associated with calcific aortic valve stenosis (16). Further investigations are needed to address the important issue of the basic pathogenetic mechanisms of calcific aortic valve stenosis.

In conclusion, the results of the present study demonstrate a close association of atherosclerosis and calcific aortic valve stenosis. These data strongly emphasize the need for cerebral artery screening in all patients who are to undergo surgery for aortic stenosis, even if they are asymptomatic.

References

1. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-1243
2. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol 1997;29:630-634
3. Adler Y, Levinger U, Koren A, et al. Relation of nonobstructive aortic valve calcium to carotid arterial atherosclerosis. Am J Cardiol 2000;86:1102-1105
4. Aronow WS, Ahn C, Shirani J, et al. Comparison of frequency of new coronary events in older persons with mild, moderate, and severe valvular aortic valve stenosis with those without aortic valve stenosis. Am J Cardiol 1998;81:647-649
5. Aronow WS, Ahn C, Kronzon I. Association of valvular aortic valve stenosis with symptomatic peripheral arterial disease in older persons. Am J Cardiol 2001;88:1046-1047
6. Chandra HR, Goldstein JA, Choudhary N, et al. Adverse outcome in aortic sclerosis is associated with coronary artery disease and inflammation. J Am Coll Cardiol 2004;43:169-175
7. Mautner GC, Roberts WC. Reported frequency of coronary arterial narrowing by angiogram in patients with valvular aortic valve stenosis. Am J Cardiol 1992;70:539-540
8. Otto CM, O'Brien KD. Why there is discordance between calcific aortic stenosis and coronary artery disease? Heart 2001;85:601-602

9. Vandeplas A, Willems JL, Piessens J, et al. Frequency of angina pectoris and coronary artery disease in severe isolated valvular aortic valve stenosis. Am J Cardiol 1988;62:117-120
10. Tolstrup K, Roldan CA, Qualls CR, et al. Aortic valve sclerosis, mitral annular calcium, and aortic root sclerosis as markers of atherosclerosis in men. Am J Cardiol 2002;89:1030-1034
11. Agmon Y, Khandheria BK, Meissner I, et al. Aortic valve sclerosis and aortic atherosclerosis: Different manifestations of the same disease? Insights from a population-based study. J Am Coll Cardiol 2001;38:827-834
12. Adler Y, Shemesh J, Tenenbaum A, et al. Aortic valve calcium on spiral computed tomography (dual slice mode) is associated with advanced coronary calcium in hypertensive patients. Coronary Artery Dis 2002;13:209-213
13. Aronow WS, Kronzon I, Schoenfeld MR. Prevalence of extracranial carotid arterial disease and of valvular aortic valve stenosis and their association in the elderly. Am J Cardiol 1995;75:304-305
14. Ortlepp JR, Schmitz F, Bozoglu T, et al. Cardiovascular risk factors in patients with aortic stenosis predict prevalence of coronary artery disease, but not the prevalence of aortic stenosis. An angiographic pair matched case-control study. Heart 2003;89:1019-1022
15. Robicsek F, Thubrikar MJ. Etiology of degenerative disease of the tri-leaflet aortic valve: A simple explanation for a complex problem. Z Kardiol 2001;90:35-38
16. Ortlepp JR, Hoffmann R, Ohme F, et al. The vitamin D receptor genotype predisposes to the development of calcific aortic valve stenosis. Heart 2001;85:635-638