Progression of Aortic Valve Calcification
Association With Coronary Atherosclerosis and Cardiovascular Risk Factors

Karsten Pohle, MD; Ralph Mäffert, MD; Dieter Ropers, MD; Werner Moshage, MD; Nicolaos Stilianakis, PhD; Werner G. Daniel, MD; Stephan Achenbach, MD

Background—Recent studies demonstrated an influence of atherosclerotic risk factors on the progression of aortic valve stenosis. The extent of aortic valve calcification (AVC) was also found to be a strong predictor of stenosis progression. We investigated the influence of the LDL cholesterol level (LDL), other standard cardiovascular risk factors, and the extent of coronary calcification (CC) on the progression of AVC quantified by electron beam tomography (EBT).

Methods and Results—In 104 patients (64.7±8 years, 89 male) with an EBT scan positive for AVC, CC and AVC were quantified using a volumetric score. EBT was repeated at a mean interval of 15 months (10 to 36 months), and the progression of AVC and CC was determined. Patients were divided into 2 groups according to LDL: group 1, LDL≤3.36 mmol/L (130 mg/dL), 57 patients; group 2, LDL>3.36 mmol/L (130 mg/dL), 47 patients. Mean values for CC were 546±932 mm³ in scan 1 and 665±1085 mm³ in scan 2 for AVC 324±796 mm³ and 404±1076 mm³, respectively. The mean progression of CC was 27±37% (group 1, 16±22%; group 2, 39±46%, P<0.001) and of AVC was 25±38% (group 1, 9±22%; group 2, 43±44%, P<0.001).

Conclusions—Quantification of AVC by EBT permits new insights into the progression of aortic valve sclerosis. We observed a strong influence of LDL cholesterol level on the progression of AVC and CC, suggesting that lipid-lowering therapy may decrease the progression of aortic valve calcification. (Circulation. 2001;104:1927-1932.)

Key Words: imaging ▪ heart diseases ▪ lipids ▪ risk factors ▪ atherosclerosis

Aortic valve stenosis has a prevalence of 2% to 7% in the population above 65 years of age.¹ In industrialized countries, aortic valve stenosis is most frequently caused by progressive calcification and degeneration of the aortic cusps.²³ The disease shows a progressive course, especially after the threshold to mild aortic stenosis has been crossed.⁴ Common pathomechanisms of aortic valve stenosis and atherosclerosis have been discussed, and several studies have demonstrated an influence of cardiovascular risk factors on the progression and outcome of aortic valve stenosis, but results have been inhomogeneous as to the relative importance of specific risk factors.⁵⁻⁹ Several studies have identified the degree of aortic valve calcification as a strong predictor both for the progression and outcome of aortic stenosis.¹⁰⁻¹¹ Presently, there are no accurate methods to quantify the extent of aortic valve calcification; most studies rely on categorical scoring systems derived from echocardiographic valve morphology.¹¹⁻¹²

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Electron beam tomography (EBT) is a cross-sectional imaging technique with high temporal resolution.¹³⁻¹⁴ It has so far mainly been used to sensitively detect and quantify coronary calcifications;¹⁵⁻¹⁷ several studies used EBT to follow the progression of coronary calcification. An influence of cardiovascular risk factors, especially the LDL cholesterol level, on the degree of coronary calcium progression could be demonstrated.¹⁸⁻²² Some studies suggested the use of EBT or computed tomography to detect and quantify aortic valve calcification.²³⁻²⁵ A weak correlation between the extent of calcification and the severity of aortic valve stenosis has been described.²⁵ We therefore used EBT in a group of 104 patients to quantify the extent of aortic valve calcification, to determine the rate of progression, and to analyze the influence of cardiovascular risk factors on the course of aortic valve calcification. In addition, we investigated the relationship between the progression of aortic valve calcification and the extent and progression of coronary atherosclerosis, expressed through the amount of coronary calcification. We hypothesized that adults with aortic sclerosis and low levels of LDL cholesterol would have a lower increase in aortic valve and coronary calcification, as measured by EBT, compared with those with higher LDL cholesterol levels.
Methods

Patients
One hundred four patients (89 men and 15 women, mean age 64.7 ± 8 years) with aortic valve calcification in EBT were included in the study in a retrospective fashion. The patients were recruited by reviewing 2124 EBT studies that had been obtained for detection of coronary artery calcification on an outpatient basis in our center between 1997 and 2000. Two hundred seventy two individuals with aortic valve calcification in the EBT scan (volume score > 10 mm³) were identified and invited for a follow-up EBT investigation to assess the progression of coronary and aortic valve calcification. One hundred sixty eight patients with aortic calcification had to be excluded because they refused return for follow-up or for other reasons that did not permit inclusion in the investigation (established diagnosis or symptoms suggestive of coronary artery disease or aortic valve stenosis at the baseline scan, arrhythmias, possible pregnancy, history of renal disease or renal failure [elevated serum creatinine concentrations], or change of lipid-lowering medications within the observation interval). All participating patients gave written informed consent to the investigation, and the study protocol was approved by the institutional ethics committee.

Assessment of Cardiovascular Risk Factors
Cardiovascular risk factors were determined by interviewing the patients at the time of the follow-up scan. The following risk factors were assessed: patient age (≥55 years), present smoking, hypertension (antihypertensive medication or known and untreated hypertension), and diabetes (use of insulin or oral hypoglycemic agents). In addition, fasting blood samples were taken from all patients, and the serum levels of LDL cholesterol and total cholesterol were measured.

Image Acquisition and Evaluation
Imaging was performed with an Imatron C-150 XP EBT scanner (Imatron Inc). Patients were scanned in supine position. After determination of the heart position, 40 axial cross-sections of the heart were acquired during inspiratory breathhold. Imaging was performed using the high-resolution single slice mode of the scanner with 100-ms exposure time, 3-mm slice thickness, and 3-mm table feed between consecutive slices. Image acquisition was triggered to the patient’s ECG at 40% of the cardiac cycle. Cross-sectional images were reconstructed with a 26-cm field of view using the scanner’s sharp kernel. To assess the interscan variability of aortic valve calcification measurements by EBT, a second scan was performed in 50 patients at the time of the follow-up investigation. After repositioning the patient, the EBT scan was repeated with identical parameters as the first scan, but only 12 images were acquired to selectively cover the region of the aortic valve.

Clinical Characteristics of the Patients and Results of Coronary and Aortic Valve Calcification Measurements

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Group 1, LDL Cholesterol ≤3.36 mmol/L</th>
<th>Group 2, LDL Cholesterol &gt;3.36 mmol/L</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>104</td>
<td>57</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Men/women</td>
<td>89/15</td>
<td>49/8</td>
<td>40/7</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.7 ± 8</td>
<td>65.8 ± 7</td>
<td>63.4 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>44.2</td>
<td>40.4</td>
<td>48.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.0</td>
<td>50.9</td>
<td>51.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.5</td>
<td>12.3</td>
<td>10.6</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.4 ± 1.1</td>
<td>2.6 ± 0.6</td>
<td>4.4 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Coronary calcification
- Volume score, initial scan: 546.8 ± 932 vs. 632.9 ± 1180 vs. 455.5 ± 554 NS
- Volume score, follow-up scan: 665.1 ± 1085 vs. 705.5 ± 1278 vs. 620.2 ± 834 NS
- Percent annualized increase: 27.3 ± 37 vs. 16.2 ± 23 vs. 39.7 ± 46 <0.001

Aortic valve calcifications
- Volume score, initial scan: 324.8 ± 796 vs. 239.9 ± 356 vs. 427.6 ± 1116 NS
- Volume score, follow-up scan: 404.1 ± 1076 vs. 272.8 ± 409 vs. 563.5 ± 1530 NS
- Percent annualized increase: 24.5 ± 38 vs. 9.1 ± 22 vs. 43.2 ± 44 <0.001

Continuous variables are expressed as mean ± SD.
Acquired images were transferred to an offline workstation (NetraMD, Scimage). Coronary and aortic valve calcifications were defined as areas of at least 2 contiguous pixels (area ≥0.51 mm²) with a density of 130 HU or more (see Figure 1). Using an interpolated volume score, the total volumes of coronary and aortic valve calcification were determined. Calcifications of the aortic wall that were immediately connected to calcifications of aortic valve cusps were included in the aortic valve calcification score.

To determine interscan variability, the absolute difference of the two aortic valve calcification scores was divided by the mean score and expressed as percent value. To determine the change of aortic valve calcification over time, the initial score was subtracted from the follow-up score and the difference was divided by the initial score and expressed as percent value. This value was divided by the actual number of days between the initial and follow-up scan and multiplied by 365 to obtain the annualized percent change in aortic valve and coronary calcification.

Statistical Analysis
Statistical analysis was performed using a PC-based computer program (SPSS version 10.0). To compare the influence of LDL cholesterol levels on the progression of coronary and aortic valve calcification, patients were divided into two groups using an arbitrary threshold. In group 1, the LDL cholesterol level was ≤3.36 mmol/L (130 mg/dL); in group 2, the LDL cholesterol level was >3.36 mmol/L (130 mg/dL). Comparisons between groups were performed using the t test for unpaired samples. The relationship between the progression of coronary and aortic valve calcification was analyzed by bivariate correlation using the Pearson coefficient. In addition, stepwise multiple regression analysis was performed to identify independent predictors of the progression of aortic valve and coronary calcification. P≤0.05 was considered to indicate a significant difference.

Results
Baseline Patient Characteristics
The mean interval between the initial and follow-up EBT scan was 15.3±5 months (range, 10 to 36 months). There were no significant differences concerning age, sex, and cardiovascular risk factors between the two patient groups divided according to LDL cholesterol levels. Fifty four patients (39 in group 1 and 15 in group 2) were treated with HMG-CoA reductase inhibitors. The Table shows the patient characteristics in all patients as well as in the subgroups. The mean initial aortic valve calcification score in all 104 patients was 324±796 mm². The baseline amount of aortic valve calcification was not significantly different in the 2 patient groups, and it was not associated with any of the other tested variables (age, P=0.46; diabetes, P=0.22; hypertension, P=0.52; smoking, P=0.33). All patients had coronary calcifications in the baseline scan (mean score, 541±929 mm²). No significant correlation was found between the amount of coronary and aortic valve calcification in the initial EBT investigation (r=0.04, P=0.7).

Variability of Aortic Valve Calcification Measurements
In 50 patients, measurement of aortic valve calcification was repeated at the follow-up investigation to determine interscan variability. The mean aortic valve calcification score was 410.5 mm² for the first and 386.6 mm² for the second measurement (P=0.9), resulting in a mean variability of 8.2±9% and a median variability of 6.9%. There was a significant influence of the total amount of aortic valve calcification on interscan variability: Mean and median variabilities in the lowest tercile of aortic valve calcification (score <96.8 mm²) were 14.3±11% and 11.9%, whereas the mean and median variabilities in the upper tercile of aortic valve calcification (score >1531.7 mm²) were 4.8±6% and 5.9±5%, respectively (P=0.05).

Progression of Aortic Valve and Coronary Calcification
The mean aortic valve calcification score of all 104 patients increased from 324±796 mm² in the initial scan to 404±1076 mm² in the follow-up scan, corresponding to a mean annualized progression of 24.5±38%. Eighty five patients (82%) showed progression, whereas 19 patients (18%) showed regression in the amount of aortic valve calcification. There was no significant influence of the amount of aortic valve calcification in the initial scan on the rate of progression. In the lowest tercile (score <34 mm²), the mean progression was 39.2±57% (median 18.8), whereas in the upper tercile (score >274 mm²), the mean progression was 14.7±11% (median 14.7, P=0.18).

The mean coronary artery calcification score increased from 546±932 mm² to 665±1085 mm² during the study period. The mean annualized progression was 27.3±37%. There was a significant correlation between the annualized progression of coronary and aortic valve calcification (r=0.42, P<0.001, Figure 2). In the upper tercile of annualized coronary calcium progression (annual progression >33.8%), the mean annual increase of aortic valve calcification was 47.3±33% (median 38.6), whereas in the lowest tercile of coronary calcium progression (<8.3%), the mean annual increase of aortic valve calcium was only 9.5±22% (median 6.5, P<0.001).

Influence of Cardiovascular Risk Factors on the Progression of Aortic Valve Calcification
There was a significant influence of serum LDL cholesterol levels on the progression of both aortic valve and coronary...

Figure 2. Scatterplot of percent annualized progression of coronary calcifications (x-axis) and aortic valve calcifications (y-axis). Bold line indicates regression line; thin lines, 95% CI. Corresponding correlation coefficient was r=0.42 (P<0.001). Associated estimate of the regression coefficient was b=0.44 (95% CI 0.27 to 0.59, P<0.001).
The degree of aortic valve calcification is of high predictive value concerning the progression and clinical outcome of aortic valve stenosis and has also been identified as a predictor of cardiovascular mortality, echocardiographic evidence of aortic valve sclerosis being associated with a 50%
increase in the risk of death from cardiovascular causes. Clinical and histopathological data suggest that aortic valve sclerosis and stenosis represent different stages of the same disease.\(^{12}\)

In our study, we could demonstrate that electron beam tomography permits the quantification of aortic valve calcification with high interscan reproducibility. It was demonstrated that aortic valve calcification, even in asymptomatic patients, is progressive, with a mean increase of 24.5% per year. In addition, we could show that the degree of progression of aortic valve calcification is influenced by the LDL cholesterol level, and that, independent from risk factors, the progression of aortic valve calcification is more rapid in patients with a rapid progression of coronary artery calcification, a surrogate marker for the amount of coronary atherosclerotic risk factors or the presence of coronary artery disease, for example by establishing an association between atherosclerotic risk factors or the presence of coronary artery disease and the progression of aortic stenosis.\(^{5,28,29}\)

In addition, there is a significant, independent correlation between the progression of aortic valve calcification and the degree of aortic stenosis,\(^{25}\) the data we obtained as to the progression of valve calcification cannot be directly extrapolated to the progression of aortic valve stenosis.

Despite these limitations, our study demonstrates that electron beam tomography permits new insights into the progression of aortic valve disease by quantification of aortic valve calcification. We could show that the LDL cholesterol level influences the progression of aortic valve calcification and that there is a significant, independent correlation between the progression of calcifications in the coronary arteries and the aortic valve, suggesting similar mechanisms of disease and possible benefits of risk factor modification on the clinical course of calcified aortic valve stenosis.

References


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