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±1076 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. In industrialized countries, aortic valve stenosis is most frequently caused by progressive calcification and degeneration of the aortic cusps. The disease shows a progressive course, especially after the threshold to mild aortic stenosis has been crossed. 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. Several studies have identified the degree of aortic valve calcification as a strong predictor both for the progression and outcome of aortic stenosis. 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. Electron beam tomography (EBT) is a cross-sectional imaging technique with high temporal resolution. It has so far mainly been used to sensitively detect and quantify coronary calcifications; 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. Some studies suggested the use of EBT or computed tomography to detect and quantify aortic valve calcification. A weak correlation between the extent of calcification and the severity of aortic valve stenosis has been described. 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.
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

|                          | 546.8±932    | 632.9±1180                            | 455.5±554                             | NS   |
| Volume score, initial scan | 665.1±1085  | 705.5±1278                            | 620.2±834                             | NS   |
| Volume score, follow-up scan | 27.3±37    | 16.2±23                               | 39.7±46                               | <0.001|

Aortic valve calcifications

|                          | 324.8±796    | 239.9±356                            | 427.6±1116                            | NS   |
| Volume score, initial scan | 404.1±1076  | 272.8±409                            | 563.5±1530                            | NS   |
| Volume score, follow-up scan | 24.5±38    | 9.1±22                                | 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,39 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 and coronary artery 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 cardiovascular risk factors (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 mm³ for the first and 386.6 mm³ 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 mm³) were 14.3±11% and 11.9%, whereas the mean and median variabilities in the upper tercile of aortic valve calcification (score >1531.7 mm³) 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 mm³ in the initial scan to 404±1076 mm³ 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 mm³), the mean progression was 39.2±57% (median 18.8%), whereas in the upper tercile (score >274 mm³), the mean progression was 14.7±11% (median 14.7, P=0.18).

The mean coronary artery calcification score increased from 546±932 mm³ to 665±1085 mm³ 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 both of aortic valve and coronary
Figure 3. A, Scatterplot of LDL cholesterol level in mmol/L (x-axis) and the percent annualized progression of aortic valve calcifications (y-axis). Bold line indicates regression line; thin lines, 95% CI. The corresponding correlation coefficient was \( r=0.35 \) \((P<0.001)\). Associated estimate of the regression coefficient was \( b=10.55 \) (95% CI 5.09 to 16.02, \( P<0.001\)). B, Scatterplot of LDL cholesterol level in mmol/L (x-axis) and the percent annualized progression of coronary calcifications (y-axis). Bold line indicates regression line; thin lines, 95% CI. Corresponding correlation coefficient was \( r=0.25 \) \((P=0.01)\). Associated estimate of the regression coefficient was \( b=8.49 \) (95% CI 1.87 to 15.12, \( P=0.01\)).

Patients were divided according to their LDL cholesterol level, using a predefined value of 3.36 mmol/L (130 mg/dL) as an arbitrarily chosen cut point. In patients with a LDL cholesterol level \( \leq 3.36 \) mmol/L (group 1, \( n=57\)), the mean annual progression of aortic valve calcification was \( 9.1\pm22\% \), whereas in patients with LDL cholesterol levels >3.36 mmol/L (group 2, \( n=47\)), the mean annual progression was \( 43.2\pm44\% \) \((P<0.001)\). Correspondingly, the mean annual coronary calcium progression was \( 16.1\pm22\% \) (group 1) and \( 39.7\pm46\% \) (group 2), respectively (\( P<0.001\), Figure 4). We found no influence of smoking, hypertension, diabetes, or patient age on the rate of progression, possibly because of the small size of the respective subgroups.

The use of cholesterol-lowering medication by itself had no significant influence on the progression of aortic valve calcification. Fifty four patients were treated with HMG-CoA reductase inhibitors during the follow-up interval; their mean LDL cholesterol level was \( 2.97\pm0.83 \) mmol/L (114.7±32 mg/dL). The mean annual progression of aortic valve calcification in these 54 patients was \( 21.5\pm44\% \). The mean LDL cholesterol level in the 50 patients not treated with HMG-CoA inhibitors was \( 3.96\pm1.16 \) mmol/L (153.2±45 mg/dL), and these patients displayed a mean annual progression of \( 27.8\pm31\% \) \((P=0.4)\). If, however, the 54 patients treated with statins were divided according to their LDL cholesterol level (\( \leq 3.36 \) mmol/L, 39 patients; >3.36 mmol/L, 15 patients), a statistically significant difference of annualized aortic valve calcium progression was found (10.1±26% and 51.1±65%, \( P=0.002\)).

Multiple Regression Analysis
Stepwise multiple regression analysis was performed for two reasons: to identify predictors of the progression of aortic valve and coronary calcifications and to verify an independent association between the degree of progression of coronary calcifications and the progression of aortic valve calcification. For entry into calculation, a univariate probability value of 0.10 was set for all parameters. LDL cholesterol levels and age were entered as continuous variables, whereas hypertension, diabetes, and smoking were entered as categorical variables.

The serum LDL level could be identified as a parameter with an independent influence both on the progression of aortic valve (slope 0.29; 95% CI 0.13 to 0.46; \( P=0.001\)) and coronary calcifications (slope 0.22; 95% CI 0.05 to 0.39; \( P=0.01\)). The overall data fit of the model was \( R^2=0.11\) for the progression of aortic valve calcifications and \( R^2=0.06\) for the influence on progression of coronary calcifications.

When the annualized relative progression of coronary artery calcification was added to the regression analysis, it could be identified as an independent predictor of the progression of aortic valve calcification (slope 0.37; 95% CI 0.18 to 0.57; \( P<0.001\)) along with the LDL cholesterol level (slope 0.19; 95% CI 0.03 to 0.36; \( P=0.02\)). The overall data fit of this model was \( R^2=0.22\).

Discussion
The degree of aortic valve calcification is of high predictive value concerning the progression and clinical outcome of aortic valve stenosis\(^10\) 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 plaque.27 These results strongly add to the findings of previous investigations, which have suggested a similar nature of calcified aortic valve stenosis and 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 stenosis5,28,29 or by demonstrating that aortic valves affected by degenerative stenosis contain higher amounts of oxidized LDL cholesterol and show increased expression of metalloproteinases compared with healthy valves.30–32 Observations that are also made in coronary atherosclerotic plaque.33,34 Even though it therefore seems possible that risk factor modifications that have proven to beneficially influence the progression and outcome of coronary artery disease, such as the reduction of LDL cholesterol, may also be able to slow the progression of calcified aortic valve stenosis, this remains to be proven in intervention studies, especially because aortic valve stenosis may be a multifactorial disease and nonatherosclerotic risk factors for disease progression have also been identified.29

Our study, intended as a first investigation to analyze a possible association between the progression of aortic valve and coronary artery calcification, has several limitations. It is a retrospective analysis in patients who had been referred for coronary calcium scanning and is therefore subjected to selection bias, because patients with cardiovascular risk factors are overrepresented. Even though a significant influence of LDL cholesterol levels on the progression of aortic valve calcification could be demonstrated, the sample size was too small to reliably analyze the effect of other risk factors, such as diabetes, which was only present in a very small subgroup of our patients. Apart from the determination of reproducibility in our study and a small, previously published group of 19 patients,25 no other validations of EBT for the quantification of aortic valve calcification have been performed. However, it is reasonable to assume that the close association that has been found for EBT and histological measurements of coronary artery calcium also should hold true for the aortic valve.36 Most importantly, we only assessed aortic valve calcification, and no measurements concerning the functional status of the aortic valve were performed. Patients with symptoms suggestive of severe aortic valve stenosis were excluded from our investigation. However, echocardiographic data were not available in all subjects and, therefore, our patients may have been an inhomogeneous group, consisting of patients with aortic sclerosis without obstruction and patients with asymptomatic, calcified valvular stenosis. Even though other authors have described a weak correlation between the extent of aortic valve calcification and the degree of aortic stenosis,22 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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