Effect of Progression of Left Ventricular Hypertrophy on Coronary Artery Dimensions in Aortic Valve Disease

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Objectives. The effect of progression of left ventricular hypertrophy on coronary artery dimensions was studied in patients with aortic valve disease.

Methods. Cross-sectional area of the left and right coronary arteries was determined by quantitative coronary arteriography in 12 control subjects and in 10 patients with aortic valve disease at baseline and after a follow-up period of 66 months.

Results. The cross-sectional area of the left coronary artery was larger in patients with aortic valve disease than in control subjects (left anterior descending artery 13 vs. 8 mm²; p < 0.001; left circumflex artery 13 vs. 6 mm², p < 0.001). At the follow-up examination, cross-sectional area of the left coronary artery increased (left anterior descending artery 15 mm²; p < 0.01 vs. baseline; left circumflex artery 15 mm²; p < 0.01 vs. baseline). The cross-sectional area of the right coronary artery was different in patients with aortic valve disease from that in control subjects. Left ventricular muscle mass was larger in patients with aortic valve disease both at baseline (269 g, p < 0.001) and after follow-up examination (339 g, p < 0.001) than in control subjects (136 g). The appropriateness of coronary artery size with respect to muscle mass was evaluated by normalizing cross-sectional area of the left coronary artery (left anterior descending plus left circumflex artery) per 100 g of left ventricular muscle mass (mm²/100 g). This index was 10.9 mm²/100 g in control subjects, and decreased in subjects with aortic valve disease from 10.3 mm²/100 g at baseline to 8.6 mm²/100 g at the follow-up measurement (p < 0.05 vs. control values).

Conclusions. In patients with aortic valve disease, the progression of left ventricular hypertrophy is associated with an increase in left anterior descending and left circumflex coronary artery dimensions, whereas the size of the right coronary artery remains unchanged. Despite the enlargement of the left coronary artery, the cross-sectional area of the left coronary artery per 100 g of left ventricular muscle mass decreased. Hence, the increase in coronary artery size appears to be inadequate when the severity of left ventricular hypertrophy increases.

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Several observations suggest that in the hypertrophied left ventricle there is increased vulnerability to ischemia (1,2). Although in the overloaded left ventricle coronary blood flow at rest is within normal limits (3), relative subendocardial hypoperfusion may develop during exercise or rapid cardiac pacing (1,2,4–6). It has been reported (7) that in patients with aortic valve disease and massive hypertrophy, left coronary artery size was enlarged preoperatively but decreased after valve replacement at an equal rate with the regression of left ventricular muscle mass. The purpose of the present study was to evaluate changes in coronary artery dimensions after progression of left ventricular hypertrophy in patients with aortic valve disease who were not yet surgical candidates at the baseline cardiac catheterization.

Methods

Ten patients (mean age 51 ± 9 years, range 35 to 79) with aortic valve disease and normal coronary arteries were studied at baseline and after a follow-up period of 66 ± 36 months (range 24 to 122) (mean age 56 ± 11 years, range 46 to 85). Three patients had a bicuspid aortic valve. Twelve normal subjects (mean age 52 ± 8 years, range 38 to 65) evaluated for atypical chest pain served as control subjects. No control subject had a bicuspid valve. Body surface area did not differ between control subjects (1.85 ± 0.22 m²) and patients with aortic valve disease either at baseline (1.81 ± 0.18 m²) or at follow-up study (1.82 ± 0.19 m²). Physical working capacity was determined by upright bicycle exercise testing at baseline and after the follow-up period. The maximal work load, which was achieved under steady state conditions (3-min steps), was expressed in percent of the age-, gender- and height-corrected normal value (8).

Cardiac catheterization. Informed consent was obtained from all patients. The study protocol required selective coronary arteriography.
coronary arteriograms of high quality. These were obtained during diagnostic arteriography without any further examination for scientific purposes. Premedication consisted of 10 mg of chlordiazepoxide given orally 1 h before cardiac catheterization. Vasoactive substances were withheld for 24 h before catheterization. Left ventricular pressure was measured transseptally with use of an 8.5F Brockenbrough catheter, whereas aortic pressure was determined through an 8F pigtail catheter introduced retrogradely from the right femoral artery. Pulmonary artery pressure was measured with a 7F Courmand catheter. Mean coronary perfusion pressure was calculated as mean aortic pressure minus mean right atrial pressure. Mean systolic pressure gradient and aortic valve area were calculated according to standard formula. Aortic regurgitation was assessed by thermodilution technique.

Left ventricular angiograms were recorded simultaneously in the right and left anterior oblique projections at a filming rate of 50 frames/s. Left ventricular volumes and ejection fraction were calculated with the area-length method (9). Left ventricular muscle mass was determined according to the method of Rackley et al. (10).

Selective left and right coronary arteriography was carried out from the right femoral artery (Judkins technique, 8F catheters) with multiple views for optimal visualization of the coronary arteries. Only patients with normal coronary arteries were included in the present analysis.

Quantitative coronary arteriography. Quantitative evaluation of coronary angiograms was performed with a semiautomatic computer system (7,11,12). The system is based on a 35-mm film projector (Tagarno 35 CX), a slow-scan CCD-camera for image digitation and a computer work station (Apollo DN 3000) for image storage and processing. Contour detection was carried out with use of a geometric-densitometric edge detection algorithm (12-14) (Fig. 1). The method of computerized analysis of coronary angiograms has been described elsewhere (7,11-17).

The proximal cross-sectional area of the three major coronary vessels (left anterior descending, left circumflex and right coronary arteries) was measured from one to three end-diastolic cine frames. The proximal cross-sectional area of the left anterior descending and left circumflex arteries was defined as the vessel segment immediately beyond the bifurcation of the left main coronary artery over a length of approximately 1 cm. The computer traced this segment automatically and calculated the mean area over this segment. A circular lumen was assumed because only patients with normal coronary arteries were included (Fig. 1). The proximal cross-sectional area of the right coronary artery was defined as the vessel segment 1 to 2 cm distal to the coronary ostium. A vessel segment over a length of approximately 1 cm was analyzed, and the mean cross-sectional area was calculated as for the left coronary artery. For each vessel segment, three measurements in different projections were obtained and averaged to correct for biologic variations in coronary artery dimensions (11,17,18). Calibration was performed automatically by using the proximal part of the 8F Judkins catheter as a scaling device (7,19). Left or right coronary artery dominance was evaluated according to standard criteria (20). No correlation between left dominance and bicuspid valve was observed. As an index of the enlargement of the coronary arteries with respect to muscle mass, the cross-sectional area of the left coronary artery (left anterior descending plus left circumflex artery) per 100 g of left ventricular angiographic mass was calculated (7,21).

Statistics. Statistical comparisons of hemodynamic and angiographic data among control subjects and baseline and follow-up measurements in patients with aortic valve disease were carried out by a one-way analysis of variance. When the analysis was significant, the Scheffé procedure was applied. The paired Student t test was used to compare baseline and follow-up data in patients with aortic valve disease. The chi-square test was used to compare the type of coronary dominance between control subjects and patients with aortic valve disease.
Table 1. Hemodynamic and Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 12)</th>
<th>Patients With AVD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70 ± 13</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>114 ± 20</td>
<td>163 ± 21†</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9 ± 3</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>15 ± 3</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>MCPP (mm Hg)</td>
<td>86 ± 8</td>
<td>102 ± 33</td>
</tr>
<tr>
<td>EF (%)</td>
<td>65 ± 4</td>
<td>63 ± 8</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>137 ± 28</td>
<td>223 ± 75†</td>
</tr>
<tr>
<td>LMM (g)</td>
<td>136 ± 30</td>
<td>209 ± 60§</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01, §§ p < 0.001 versus control values. 

Results

Five patients had pure or predominant aortic stenosis (mean systolic pressure gradient 41 mm Hg [range 25 to 61]; aortic valve area 1.08 cm² [range 0.9 to 1.5]) and five had pure or predominant aortic regurgitation (regurgitant fraction 29%, range 21% to 37%). In patients with aortic stenosis, mean systolic pressure gradient was 69 mm Hg (range 30 to 90) (p < 0.01 vs. baseline) and aortic valve area was 0.6 cm² (range 0.45 to 0.98) (p < 0.01 vs. baseline) at the follow-up examination, whereas regurgitant fraction was minimal. In patients with aortic regurgitation, mean regurgitant fraction was 54% (35% to 65%) (p < 0.01 vs. baseline) at the follow-up examination. Functional classification according to the New York Heart Association was significantly higher at the follow-up evaluation than at baseline (2.43 vs. 1.25, respectively, p < 0.001) in both aortic stenosis and regurgitation. Physical working capacity was comparable to control values (97 ± 15%) in patients with aortic valve disease at baseline (82 ± 18%) but was decreased (p < 0.01) at the follow-up evaluation (56 ± 22%).

Hemodynamic and angiographic data (Table 1). All patients were in sinus rhythm. Heart rate was similar in all three groups. Left ventricular peak systolic pressure was significantly higher in patients with aortic valve disease than in control subjects both at baseline and at follow-up examination. Left ventricular end-diastolic pressure was significantly higher in patients with aortic valve disease at follow-up than at baseline or than in control subjects, whereas mean pulmonary artery pressure was higher in patients with aortic valve disease at follow-up than in control subjects. Mean coronary perfusion pressure was similar in control subjects and in patients with aortic valve disease both at baseline and follow-up. Ejection fraction was comparable in control subjects and in patients with aortic valve disease at baseline; however, it decreased significantly at the follow-up examination when compared with both baseline evaluation or with control values. Left ventricular mass was significantly increased in patients with aortic valve disease with respect to control values; a further increase in left ventricular mass occurred at the follow-up examination.

Coronary artery dimensions (Table 2, Fig. 2). In seven subjects in the control group, the right coronary artery was dominant, whereas the left coronary artery was dominant in three and a balanced type of distribution was present in two. Of the patients with aortic valve disease, right coronary dominance was present in four patients, left dominance in another four and a balanced distribution in two. These types of coronary dominance did not differ between the control group and patients with aortic valve disease.

At baseline the proximal cross-sectional area of the left anterior descending and the left circumflex artery was significantly larger in patients with aortic valve disease than in control subjects; however, after the follow-up period the dimensions of the left anterior descending and circumflex arteries were similar in control subjects and patients with aortic valve disease.

Table 2. Quantitative Coronary Arteriographic Data

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 12)</th>
<th>Patients With AVD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>CSA_LAD (mm²)</td>
<td>7.8 ± 3.6</td>
<td>13.3 ± 2.5‡</td>
</tr>
<tr>
<td>CSA_LCX (mm²)</td>
<td>6.3 ± 3.4</td>
<td>12.9 ± 5.3‡</td>
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<tr>
<td>CSA_RCA (mm²)</td>
<td>9.0 ± 4.7</td>
<td>10.4 ± 5.3</td>
</tr>
<tr>
<td>f (mm²/100 g)</td>
<td>10.9 ± 3.2</td>
<td>10.3 ± 2.3</td>
</tr>
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</table>

*p < 0.05, †p < 0.01, §§ p < 0.001 versus control values. 

Figure 2. Coronary artery dimensions in control subjects and in patients with aortic valve disease (AVD) at baseline (B) and follow-up (F-U) evaluation. The cross-sectional area of the left anterior descending (LAD) and the left circumflex (LCX) coronary artery of the patients was increased significantly at baseline when compared with values in control subjects; both dimensions increased further at follow-up evaluation. The size of the right coronary artery (RCA) did not change.
Table 3. Correlations Between Coronary Artery Dimensions and Hemodynamic Variables

<table>
<thead>
<tr>
<th>Cross-Sectional Area (mm²)</th>
<th>Left Coronary Artery (n = 32)</th>
<th>Right Coronary Artery (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p*</td>
</tr>
<tr>
<td>vs. LVSP (mm Hg)</td>
<td>0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vs. LVEDP (mm Hg)</td>
<td>0.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>vs. MPAP (mm Hg)</td>
<td>0.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>vs. EF (%)</td>
<td>-0.48</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>vs. LVEDV (ml)</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vs. LMM (g)</td>
<td>0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vs. MCPP (mm Hg)</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>vs. PWC (%)</td>
<td>0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

*By linear regression analysis. LVEDV = left ventricular end-diastolic volume; PWC = physical working capacity; other abbreviations as in Table 1.

arteries increased significantly with respect to baseline. The proximal cross-sectional area of the right coronary artery did not differ from control values at baseline or at follow-up.

The index of the appropriateness of left coronary artery size per 100 g of left ventricular muscle mass was comparable in patients with aortic valve disease at baseline and in control subjects (10.3 vs. 10.9 mm²/100 g) but decreased significantly at the follow-up examination in the patients with valve disease (8.6 mm²/100 g).

Correlations (Table 3). Correlations were calculated from all available data (n = 32) from control subjects as well as those from patients with aortic valve disease at baseline and at follow-up examination. There was a significant correlation between cross-sectional area of the left coronary artery and left ventricular peak systolic and end-diastolic pressure, mean pulmonary artery pressure, left ventricular end-diastolic volume and left ventricular muscle mass (Fig. 3). Left coronary cross-sectional area was inversely related to ejection fraction (r = -0.48, p < 0.01) but did not correlate with mean coronary perfusion pressure or maximal work load in percent of the age-, gender- and height-corrected normal value. Cross-sectional area of the right coronary artery was correlated significantly only with mean pulmonary artery pressure (r = 0.47, p < 0.01). A close inverse relation was present between the cross-sectional area of the left coronary artery per 100 g of left ventricular mass and the duration of the follow-up period (r = -0.65, p < 0.05, Fig. 4).

Figure 3. Correlation between left coronary artery cross-sectional area and left ventricular muscle mass (n = 32). The dashed lines represent the 95% confidence limits. Abbreviations as in Figure 2.

Discussion

Coronary artery enlargement consequent to left ventricular hypertrophy has been shown to represent an adaptive mechanism to maintain blood flow and shear stress constant (22,23). Because coronary blood flow velocity is approximately the same in normal and hypertrophied ventricles (22), the relation between coronary artery dimension and left ventricular muscle mass should also be constant. The data of the present study suggest that in the presence of moderate left ventricular hypertrophy the increase in coronary artery dimensions is proportionate to the increase in left ventricular mass in that cross-sectional area of the left coronary artery per 100 g of left ventricular muscle mass is comparable to that in control subjects (7,21,24,25). A further increase in left ventricular mass is accompanied by a further enlargement of coronary artery size; however, this increase is not proportionate to the increase in mass.

Progression of left ventricular hypertrophy and coronary artery size. Marcus et al. (26) have demonstrated in dogs that the duration of left ventricular hypertrophy does not influence the severity of the decrease in coronary vasodilator reserve. However, in the same experimental study left ventricular mass was comparable at baseline and follow-up evaluation. In the present study the severity of aortic valve disease was mild to moderate, and ejection fraction was preserved at the time of the baseline evaluation. Ng et al.
(27) have demonstrated that, among patients with aortic valve stenosis, those with absent or mild left ventricular functional impairment are more likely to have progression of valve disease. In the present study all patients with aortic stenosis had a reduction in aortic valve area of >20% and an increase in the mean systolic pressure gradient of >40%. In patients with aortic regurgitation, the regurgitant fraction increased by >55% of the baseline value at follow-up evaluation. Thus, the severity of aortic valve disease increased in all patients in our study. The persistence and the increased severity of the overload condition led to a significant increase in left ventricular mass and a decrease in systolic ejection performance. The inverse relation between these two variables has been previously described by Murakami et al. (28).

In preoperative patients with aortic valve disease and left ventricular hypertrophy, it was shown that the dimensions of the left anterior descending and left circumflex arteries, but not of the right coronary artery, are increased. The present study confirms these findings in patients with mild to moderate aortic valve disease who were not yet candidates for surgery at baseline examination. After a follow-up period of approximately 6 years, a significant increase in the severity of aortic valve disease was accompanied by a significant increase in left ventricular mass and a further increase in left coronary artery dimensions, whereas those of the right coronary artery did not change. Nevertheless, at follow-up evaluation the enlargement of the left coronary artery was not adequate to match the increased left ventricular mass; thus, the cross-sectional area per 100 g of left ventricular mass decreased significantly. This inadequate growth of the cross-sectional area was mainly due to the lower percent increase in left coronary artery dimensions with respect to the percent increase in left ventricular mass (21% vs. 27%, respectively, Fig. 5).

Murray and Vatner (29) have demonstrated in dogs with severe right ventricular hypertrophy that the increase in right ventricular mass was not accompanied by a proportionate increase of the total cross-sectional area of the coronary vasculature supplying the hypertrophied right ventricle. Several other studies (7,21,24,25) reported a reduction of cross-sectional area per 100 g of left ventricular mass in the hypertrophied left ventricle. Our findings suggest that the main determinant for the increase in coronary size is left ventricular hypertrophy. A previous report from our laboratory (7) has shown that in preoperative patients with aortic valve disease (360 g) the cross-sectional area of the left coronary artery per 100 g of left ventricular mass was reduced. After valve replacement and regression of left ventricular hypertrophy, the residually hypertrophied myocardium (250 g) was supplied by a coronary artery that was enlarged but adequately sized with respect to left ventricular muscle mass (7). In the present study we observed the same pattern of variations; that is, coronary cross-sectional area per 100 g was normal in the presence of moderate left ventricular hypertrophy (left ventricular mass 269 g), whereas the increase in coronary artery dimensions was inappropriate when left ventricular hypertrophy was severe (left ventricular mass 339 g).

Determinants of coronary artery size. The stimulating factor for increasing coronary cross-sectional area is not known. Several mechanisms are possible, such as coronary flow, myocardial hypertrophy or changes in microvasculature.

Coronary blood flow. Certainly coronary blood flow plays a major role. The continuous release of vasoactive substances, such as the endothelium-derived relaxing factor, increases with an increase in coronary blood flow and thus might stimulate the growth of coronary artery size. It is unknown if flow at rest or maximal flow is the stimulating factor for the increase in coronary artery size; flow at rest is increased in patients with myocardial hypertrophy, whereas maximal flow is normal and thus coronary flow reserve (maximal flow divided by resting flow) is decreased (3).

If flow at rest is the stimulating factor for the increase in coronary artery size, the growth of coronary arteries in patients with myocardial hypertrophy could be easily explained by the increase in flow at rest. However, the inadequate growth of the coronary arteries in patients with severe hypertrophy (decrease in coronary cross-sectional area per 100 g of muscle mass, Table 2) is difficult to explain but could be due to the relative decrease in coronary flow per 100 g mass that has been observed in patients with severe aortic valve disease (30,31).

If maximal flow is the stimulating factor for the increase in coronary artery size, then the reduction in coronary flow reserve in patients with severe myocardial hypertrophy...
could explain the inadequate growth of the coronary arteries because maximal blood flow does not increase in proportion to left ventricular muscle mass (3) but remains more or less unchanged. The occurrence of myocardial ischemia with redistribution of coronary blood flow from the subendocardium to the subepicardium (32-34) also could influence the growth of the coronary arteries by decreasing maximal flow to the subendocardium during exercise (32,33).

Myocardial hypertrophy. Left ventricular hypertrophy plays an important role in the regulation of coronary blood flow and thus coronary artery size. The increase in cross-sectional area of the coronary arteries in patients with severe aortic valve disease can be explained by the increase in coronary blood flow associated with myocardial hypertrophy. However, humoral (growth factors) or mechanical (stretch) stimuli could be responsible for the growth of the vascular smooth muscle; in other words, the growth factors causing left ventricular hypertrophy may also cause the increase in coronary artery size. An increase in the size of the epicardial coronary arteries was observed in postmortem hearts of patients with left ventricular hypertrophy (35,36). The relation between total heart weight and the diameters of the coronary arteries was found to be linear only up to a heart weight of 500 g (35).

Microvasculature. Changes in the microvasculature (5,37) could lead to a decrease in coronary flow reserve and thus could be associated with an inadequate growth of the epicardial coronary arteries. However, it has been shown in patients with aortic valve disease (3) that coronary flow reserve tends to normalize after successful valve replacement, suggesting that the microvasculature is not altered but that hypertrophy is not associated with an appropriate increase in the cross-sectional area of the microvascular bed.

Angiogenesis has been observed in dogs (38) during long-term left ventricular hypertrophy that is sufficient to increase the cross-sectional area of the resistance vessels in proportion to the increase in left ventricular mass. However, in contrast to experimental studies in animals, no evidence exists that significant angiogenesis occurs in humans with left ventricular hypertrophy (39).

Limitations of the study. It is important to consider other determinants of coronary artery size, such as physical working capacity, vessel dominance and coronary vasomotor tone.

Physical working capacity has been reported to have a direct influence on coronary artery size (7). However, at the follow-up measurements there was an increase in cross-sectional area of the left coronary artery and a decrease in physical working capacity. Thus, it is unlikely that the enlargement in coronary artery size was mediated by the physical working capacity.

It is well known that a close relation exists between myocardial territory size and proximal coronary artery diameter (40,41). However, in the present study coronary dominance was the same in control subjects and patients with aortic valve disease. Moreover, as in a previous study (7), after subgrouping the patients according to left or right coronary artery dominance, the same patterns of variations in the left and right coronary artery dimensions were observed.

Coronary vasomotor tone is another important factor that influences coronary artery dimensions. We did not evaluate coronary vasomotor tone, but it can be assumed that "overall" autonomic activity was similar because heart rate was the same in control subjects and patients with aortic valve disease (Table 1). However, we recognize that both humoral and endothelium-derived vasoactive factors may have varied among our patients.

Conclusions. In patients with aortic valve disease, the progression of left ventricular hypertrophy is associated with an increase in left anterior descending and left circumflex dimensions, whereas the size of the right coronary artery remains unchanged. Despite the enlargement of the left coronary artery dimension, the cross-sectional area of the left coronary artery per 100 g of left ventricular muscle mass decreases with progression of left ventricular hypertrophy. Hence, the increase in left coronary artery size appears to be inadequate to match the severity of left ventricular hypertrophy.

References

13. Krickeide RL, Gould KL, Pasci JL. Assessment of coronary stenoses by...


