Heart Transplant

Volumetric Remodeling of the Proximal Left Coronary Artery: Early Versus Late After Heart Transplantation
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OBJECTIVES
The aim of this study was to characterize progression of cardiac allograft vasculopathy (CAV) with special respect to coronary artery geometry.

BACKGROUND
As previously shown by intravascular ultrasound (IVUS), CAV is characterized by a multifocal intimal hyperplasia. Little is known, however, about vascular remodeling processes influencing vessel geometry and luminal narrowing.

METHODS
In 30 heart transplant recipients serial IVUS studies were performed at baseline (BL) and after a mean follow-up period of 12.5 ± 2.5 months. Changes in plaque, lumen and vessel volume were assessed in the proximal left anterior descending artery. Pattern of remodeling was analyzed in patients "early" (n = 15, BL study 1.4 ± 0.7 months after heart transplantation [HTX]) compared with "late" after HTX (n = 15, BL 46.1 ± 29.1 months).

RESULTS
Plaque volume was found to increase by a mean of 23.8 ± 25.9 mm³, not significantly different within and beyond the 1st year after HTX. Significant differences, however, were observed in changes in vessel volume with a mean decrease of -252.8 ± 70.9 mm³ in the early group, whereas late follow-up group presented with an enlargement of 32.3 ± 46.0 mm³. Based on these changes, lumen volume decreased by -73.2 ± 69.8 mm³ early, in contrast to a slight increase of 5.2 ± 32.6 mm³ in the late group.

CONCLUSIONS
Progression of CAV is a complex process, modified by changes in the vascular geometry. Especially within the 1st year after HTX, luminal loss is influenced not only by an increase in plaque area but by a decrease in total vessel volume as well. (J Am Coll Cardiol 1999;34:197–203) © 1999 by the American College of Cardiology

Cardiac allograft vascular disease is characterized by a multifocal myointimal hyperplasia, resulting in a continuous luminal loss of coronary arteries within the graft (1–3). It represents one of the most accelerated progressing coronary syndromes in the human heart (4). Chronic inflammatory reactions to immunologic and nonimmunologic injury are considered to be involved in the pathogenesis (5). However, beyond intimal hyperplasia, histopathologic examination demonstrates inflammation in the media and adventitia of coronary vessels as well (6,7). Development of adventitial fibrosis can be regarded as part of this syndrome and raises the question of influences on vascular geometry in terms of coronary artery remodeling (8). To analyze these changes under clinical conditions, in the form of longitudinal studies within the vessel as well as studies of time-dependent changes of matched sites, intravascular ultrasound (IVUS) can be considered to be the imaging procedure of choice. All major vascular structures, such as lumen, plaque and total vessel area, can be visualized and analyzed quantitatively (9,10).

Few studies are focused on questions of coronary artery remodeling in heart transplant recipients as yet. They have been able to demonstrate the presence of changes in vascular geometry within the transplanted heart (11–13). As in native coronary artery disease (14), not only plaque-induced compensatory enlargement (positive remodeling) but vascular constriction (negative remodeling) could be shown to influence luminal obstruction (12) as well. However, little is known about the time course and contribution of remodeling processes in progressive cardiac allograft vasculopathy. Therefore, we analyzed serial intravascular ultrasound studies in a consecutive series of 30 patients. To exclude a potential bias by analyzing not exactly identical sites, a volumetric approach was chosen, as suggested in the past (15), quantitating multiple images in a well defined region of the proximal left anterior descending artery (LAD). The aim of this study was 1) to analyze changes in plaque and total vessel volume contributing to a luminal loss over time;
and 2) to assess whether there are differences in changes of vascular geometry early versus late after heart transplantation (HTX).

METHODS

Patients. After obtaining written informed consent, 30 consecutive heart transplant recipients underwent an IVUS study of the LAD in addition to their routine surveillance angiography. In 15 patients, baseline examination was performed 1.4 ± 0.7 months after transplantation (“early” group); the other 15 were examined 46.1 ± 29.1 months after HTX (between 2 and 9 years, “late” group). Progression of disease was assessed in both groups by a follow-up study at a mean interval of 12.6 ± 1.7 months (early group) and 12.4 ± 3.1 months (late group).

There were 28 male and two female patients; mean age at transplantation was 50.6 ± 9.7 years. Immunosuppression was performed by a triple therapy using cyclosporine, azathioprine and prednisolone. Further demographic data and transplant characteristics are detailed in Table 1.

Catheterization procedure. Initially, all patients were evaluated by left heart catheterization including left ventricular cineangiography as well as selective coronary arteriography using a percutaneous transfemoral approach. Before intravascular placement of a 0.014-in. (0.036 cm) coronary guide wire (GWF-wire, Biotronik, Berlin, Germany), 10,000 IU of heparin and 100 mg of intracoronary nitroglycerin were administered into the left coronary artery to achieve anticoagulation and optimal vasodilation, and to avoid spasm. After placement of the IVUS catheter (monorail 3.5 F, 30 MHz, Sonicath, Boston Scientific, Natick, Massachusetts) under fluoroscopic guidance to the periphery of the LAD (avoiding lumen diameters of less than 2.0 mm), quality of IVUS images (Hewlett-Packard Sonos Intravascular, Andover, Massachusetts) was optimized using standardized settings for the gain. During a subsequent pullback maneuver (1 mm/s motorized device) images were documented on an SVHS videotape for further analysis.

Ultrasound image analysis and volumetric assessment by planimetry. Image analysis was performed off-line from the videotape. Frames were digitized and lumen, plaque as well as vessel area were analyzed by planimetry with a conventional image analysis system (Tape Measure, Indec Systems, San Francisco, California). Lumen was defined as the area within the intimal border, the total vessel as the area within the media/adventitia boundary (characterized by the external border of the echolucent zone) (10,16,17) and plaque as the space between vessel and lumen area. As the motorized pullback with a constant speed of 1 mm/s allows for equidistant spacing of adjacent images, additional information about longitudinal plaque distribution can be achieved. Starting with the first complete vascular ring distal to the bifurcation with the left circumflex artery, manual planimetry was performed over a distance of 30 mm. Serial cross-sectional images with the largest lumen area during cardiac cycle were chosen every 2 mm toward the periphery of the LAD (Fig. 1). Localization of small side branches or other significant vascular markers were used to compare for identity of vascular segments at baseline and follow-up examination. Vascular sites with major side branches and calcifications, occupying a vessel circumference of more than 30%, were excluded from quantification. Based on up to 16 cross-sectional measurements, plaque, lumen and total vessel volume (in mm³) were calculated as follows: mean cross-sectional area (in mm²) multiplied by the assessed distance of 30 mm. A volume index was calculated as: (plaque volume/vessel volume) × 100.

Reproducibility of measurements. In a pilot study reproducibility of volumetric assessment was analyzed in 10 patients. Two subsequent pullback maneuvers were performed in identical vascular segments. A close correlation between vessel, lumen and plaque volume (vessel: \( r = 0.96; \)

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 30)</th>
<th>( \leq 1 ) Year (n = 15)</th>
<th>&gt;1 Year (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.6 ± 9.7</td>
<td>53.0 ± 9.5</td>
<td>48.6 ± 9.8</td>
<td>0.22</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>28/2</td>
<td>14/1</td>
<td>14/1</td>
<td>1.0</td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>36.7 ± 10.2</td>
<td>34.9 ± 11.2</td>
<td>38.5 ± 9.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Underlying disease (CAD/other)</td>
<td>13/17</td>
<td>6/9</td>
<td>7/8</td>
<td>0.71</td>
</tr>
<tr>
<td>Ischemia (min)</td>
<td>168.7 ± 37.6</td>
<td>167.5 ± 47.8</td>
<td>170.1 ± 25.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Time post HTX (mo)</td>
<td>23.7 ± 30.4</td>
<td>1.4 ± 0.7</td>
<td>46.1 ± 29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interval between studies (mo)</td>
<td>12.5 ± 2.5</td>
<td>12.6 ± 1.7</td>
<td>12.4 ± 3.1</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Demographic data of the study population, overall and differentiated for patients within versus beyond the 1st year after heart transplantation (HTX). Except for time after transplantation, there were no significant differences between these subgroups.

CAD = coronary artery disease.
lumen: $r = 0.99$; plaque: $r = 0.99$) could be shown, demonstrating adequate reliability of measurements (Fig. 2).

**Analysis of data.** Statistical analysis was performed with the SPSS (Cary, North Carolina) software package (version 6.1.3). Continuous data are presented as mean ± 1 standard deviation. Univariate analysis to compare for different demographic data between the early and late groups (Table 1) was performed using the Student $t$ test (for continuous data) and the chi-square test (for noncontinuous data). Further on the Student $t$ test was used to test for progression of plaque lumen as well as vessel volume and for differences between the volumetric progression in early versus late follow-up. A $p$ value $<0.05$ was considered to be statistically significant.

**RESULTS**

In total 910 vascular cross-sectional sites were analyzed (mean 30.3 per patient).

**Changes in plaque, lumen and vessel volume.** Analyzing the whole patient group, plaque volume increased from a mean of $105.3 \pm 55.2$ $\text{mm}^3$ (range 31.8 to 240.0 $\text{mm}^3$) at baseline to $129.1 \pm 64.0$ $\text{mm}^3$ (range 30.6 to 259.2 $\text{mm}^3$) at follow-up examination by $23.8 \pm 25.9$ $\text{mm}^3$ or 22.6% ($p < 0.001$). Total vessel volume could be shown to be constant over time. From a mean of $450.9 \pm 96.9$ $\text{mm}^3$ (range 274.8 to 719.4 $\text{mm}^3$) at baseline to $440.7 \pm 96.3$ $\text{mm}^3$ (range 300.0 to 723.6 $\text{mm}^3$) at follow-up only a small and not significant reduction in vessel volume was observed ($p = 0.5$). These changes resulted in a significant decrease in lumen volume from $345.6 \pm 92.7$ $\text{mm}^3$ (range 203.1 to 566.1 $\text{mm}^3$) to $311.6 \pm 84.9$ $\text{mm}^3$ (range 147.3 to 496.2 $\text{mm}^3$) by $34.0 \pm 66.7$ $\text{mm}^3$ or 9.8% ($p = 0.009$). For details see Table 2.

**Volumetric changes early versus late after transplantation.** Increase in plaque volume did not differ significantly in patients within versus beyond the first year after transplantation (Table 3). However, changes in vessel lumen presented to be strongly time dependent. A plot of the individual changes (Fig. 3) demonstrates that the majority of patients within the first year after transplantation experienced a decrease in vessel volume, whereas changes in the late group are predominated by increasing volumes. These differences in the early compared with the late group were statistically highly significant ($p = 0.001$, see Table 3). Based on these findings, a large volume loss (increase in plaque volume augmented by a decrease in vessel volume) was observed in patients within the first year after transplantation, contrasting with a slight lumen gain in the late group. Therefore loss in vessel volume was the most
Table 2. Volumetric Progression—Overview

<table>
<thead>
<tr>
<th>Change in</th>
<th>Overall</th>
<th>≤1 year</th>
<th>&gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
</tr>
<tr>
<td>Plaque volume (mm$^3$)</td>
<td>105.3 ± 55.2</td>
<td>129.1 ± 64.0</td>
<td>73.2 ± 41.5</td>
</tr>
<tr>
<td>Lumen volume (mm$^3$)</td>
<td>345.6 ± 92.7</td>
<td>311.6 ± 84.9</td>
<td>405.1 ± 76.4</td>
</tr>
<tr>
<td>Vessel volume (mm$^3$)</td>
<td>450.9 ± 96.3</td>
<td>440.7 ± 96.3</td>
<td>480.0 ± 94.5</td>
</tr>
<tr>
<td>Volume index (%)</td>
<td>23.6 ± 11.8</td>
<td>29.0 ± 13.3</td>
<td>14.9 ± 7.3</td>
</tr>
</tbody>
</table>

Absolute values for plaque, lumen and vessel volume as well as the volume index at baseline and at follow-up examination (overall and differentiated for patients "early" vs. "late" after transplantation).

DISCUSSION

Our study shows that progression of allograft vascular disease represents a complex process. Although plaque volume was found to increase continuously over time, total vessel volume decreased significantly within the first year after heart transplantation as compared with a compensatory enlargement in the late group of follow-up. The resulting luminal loss, predominantly due to a negative vascular remodeling, was maximal within the first year, followed by a slight increase in lumen later on. To our knowledge, these are the first volumetric observations of vascular remodeling processes in heart transplant recipients so far.

Coronary artery remodeling within the graft. Since the first description of a compensatory vascular enlargement of coronary arteries by Glagov in 1987 (18), vascular remodeling has become more recognized to be of major importance in influencing vessel geometry and luminal obstruction (19,20). However, as in native coronary artery disease, not only compensatory enlargement but local vascular constriction was identified as a second pattern of remodeling and identified to be present in heart transplant recipients as well (12–14). Volumetric data in this study demonstrate that in the overall study group about 50% of luminal loss is due to a decrease in vessel volume; an increase in plaque burden contributes to about 60% of lumen volume reduction. Differentiated over time, however, there are significant differences in patients early (within the first year) versus late (3.8 ± 2.4 years) after heart transplantation. While in the 1st year a severe decrease in vessel volume (negative remodeling) contributes to more than 70% of luminal narrowing, later on changes in vascular geometry are characterized by an increase in vessel dimensions, even overcompensating the increase in plaque burden (Fig. 5). Using this volumetric approach, our data confirm previous observations in circumscript stenosis (12), that an inadequate coronary artery remodeling is an important mechanism in diffuse luminal obstruction as well. The time-dependent differences, however, with an inadequate remodeling predominantly early after HTX, are in contrast to findings by the Stanford group (13). Focused on the temporal aspect of remodeling in heart transplant recipients, Lim et al. (13) observed inadequate vessel enlargement predominantly in patients late after transplantation, whereas the early follow-up was characterized by a compensatory increase in vessel area. Although not directly comparable (volumetric approach versus matched pairs of single vascular sites), these discrepancies have to be addressed in future studies focusing on these important questions of coronary artery remodeling.

Pathophysiologic background. Currently, there is only limited knowledge about pathophysiologic mechanisms underlying coronary artery remodeling processes. An increase in plaque-induced shear forces may represent a stimulus for dilation of the vascular wall, resulting in compensatory vessel enlargement as a general principle in atherosclerotic disease (19,21). Especially patients beyond the first year after HTX presented with this type of vascular adaptation. The underlying mechanism of inadequate vascular remodeling, however, remains speculative. An inflammatory reaction, as present in native coronary artery as well as in allograft vascular disease (6,22), might be related to constrictive remodeling processes (8). Because transplanted hearts present with the highest immunologic activity within

Table 3. Volumetric Progression—Changes Over Time

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 30)</th>
<th>≤1 Year (n = 15)</th>
<th>&gt;1 Year (n = 15)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque volume (mm$^3$)</td>
<td>23.8 ± 25.9</td>
<td>22.3 ± 29.8</td>
<td>25.3 ± 22.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Lumen volume (mm$^3$)</td>
<td>−34.0 ± 66.7</td>
<td>−73.2 ± 69.8</td>
<td>5.2 ± 32.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Vessel volume (mm$^3$)</td>
<td>−10.3 ± 72.9</td>
<td>−52.8 ± 70.9</td>
<td>32.3 ± 46.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Volume index (%)</td>
<td>5.5 ± 6.8</td>
<td>7.5 ± 8.9</td>
<td>3.4 ± 2.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Changes in plaque, lumen and vessel volume as well as in the volume index.
the first year after transplantation (23), antigen-dependent immunologic injury can be considered to be one of the most important inflammatory stimuli, resulting in endothelial dysfunction (24) as well as structural changes in vascular geometry predominantly early after transplantation (8).

Implications for diagnostic approaches. Regardless of the pathophysiologic background, these observations should have considerable impact on future diagnostic approaches. Using quantitative angiography, a progressive luminal narrowing in graft coronary arteries has been known for several years (25,26). However, data on vascular remodeling demonstrate that an increase in plaque mass represents only one aspect of disease. Regarding luminal obstruction, a decrease in vessel area or vascular volume, respectively, might be of even greater importance, especially within the first year after transplantation. To define the natural course of disease, and to form a basis for future prognostic interpretations as well as a follow-up after preventive or therapeutic interventions, remodeling processes have to be taken into consideration. Beneath differentiated changes in plaque, lumen and vessel volume, the use of a volume index as a derived measure of plaque and vessel volume might be helpful and more representative than plaque volume alone.

Implications on therapy. Observations about vascular remodeling over the last years support the increasing evidence that cardiac allograft vasculopathy is a process not limited to the intima of coronary arteries. Beyond therapeutical approaches focusing on intimal hyperplasia (like calcium antagonists or lipid-lowering drugs [27–29]) an anti-inflammatory therapy addressing all vascular structures might be more successful in prevention of disease. Especially in the early period after transplantation an intensified immunosuppressive therapy or antagonists against proinflammatory cytokines (30) should be discussed as a perspective for the future.

Limitations. Data for this study were obtained from a limited vascular region only. The proximal LAD was chosen because of the usually linear vessel course of the proximal left coronary artery with a low rate of artifacts. Although volume calculations (based on a formula for a straight tube) can only give an estimate of the “true” vascular geometry, not absolute numbers but changes in vessel, lumen and plaque volume are analyzed under the aspect of vascular remodeling. Demonstrating the good reproducibility of measurements at each time point (Fig. 2), this procedure might be the most appropriate method available today.

These data represent first observations on volumetric remodeling; they do not claim to be representative for the entire coronary vascular bed. Especially peripheral vascular structures and intramuscular coronary arteries might have a completely different pattern of intimal hyperplasia and vascular remodeling (31).

Although IVUS can be regarded as the most sensitive imaging procedure, an in vivo study cannot differentiate functional changes (in terms of a primary endothelial dysfunction resulting in inadequate dilation) from structural processes (in terms of changes of the extracellular matrix or fibrosing processes in the adventitia). Principally, histopathologic observations demonstrate the presence of growth factors (7) as well as severe perivascular fibrosis in transplanted hearts (8), suggesting inadequate remodeling to be caused by structural changes in the whole vessel.

Finally the question of the heterogeneous patient population should be addressed. Especially patients in the late group were followed at different time points after HTX.
Further studies in larger patient cohorts are required to clarify the time dependency of remodeling processes after HTX.

**Conclusions.** Volumetric progression of cardiac allograft vasculopathy represents a complex process. Beyond intimal hyperplasia, remodeling processes are of major importance in influencing vascular geometry and luminal obstruction. Especially within the first year after HTX, luminal loss is influenced not only by an increase in plaque area but to a large extent by a decrease in total vessel volume, whereas changes later on are characterized predominantly by a vascular enlargement.

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**Figure 4.** Cross-sectional examples of identical vascular sites in the left anterior descending artery 3.5 and 4.5 years after heart transplantation. Note compensatory enlargement of vascular cross-sectional area (characterized by the echolucent zone of the lamina elastica externa) maintaining a constant vessel lumen despite an increase in plaque mass.

**Figure 5.** Bar graph demonstrating the significant decrease in mean vessel area, which is the most important factor responsible for the considerable luminal loss “early” after transplantation. In contrast changes “late” after heart transplantation are shown to be characterized by a mean increase in vessel volume, resulting in a slight increase in lumen volume. **White bars** = plaque volume; **black bars** = lumen volume; **shaded bars** = vessel volume. **pp** = 0.001.
REFERENCES


