Determinants of Coronary Remodeling in Transplant Coronary Disease
A Simultaneous Intravascular Ultrasound and Doppler Flow Study

Severin P. Schwarzacher, MD; Neal G. Uren, MD; Michael R. Ward, MBBS, PhD; Anne Schwarzkopf, BA; Nadia Giannetti, MD; Sharon Hunt, MD; Peter J. Fitzgerald, MD, PhD; Stephen N. Oesterle, MD; Alan C. Yeung, MD

Background—Coronary remodeling plays a significant role in lumen loss in transplant allograft vasculopathy (TxCAD), but the determinants of remodeling are unknown. We assessed the relationship between remodeling and plaque topography, coronary compliance, and blood flow in TxCAD.

Methods and Results—One artery in each of 27 transplant patients was investigated with simultaneous intravascular ultrasound and coronary flow measurements (basal and hyperemic by Doppler flow wire). At 4 to 8 different cross sections (mean 5.1 ± 1.2), plaque topography (concentric or eccentric) was determined, and total vessel area, lumen area, and intimal/medial area (IMA) were measured. Mean remodeling ratio (vessel area/IMA) in eccentric lesions (E, n = 28) was significantly larger than that in concentric lesions (C, n = 70) (E 3.89 ± 0.93 versus C 3.58 ± 0.62; P < 0.001), despite similar IMA (E 3.89 ± 0.68 versus C 3.90 ± 0.41; P = NS) and distribution of imaged segments. Remodeling ratio was consistently larger in eccentric lesions in all 3 vessel segments when analyzed separately, and mean remodeling ratio for each artery was larger in vessels with predominantly eccentric lesions. Coronary compliance ([Δ lumen area/diastolic lumen area/Δ mean arterial pressure]×10^3) was also significantly greater in eccentric lesions versus concentric lesions (proximal 1.00 ± 0.39 versus 0.22 ± 0.04; mid 0.71 ± 0.17 versus 0.21 ± 0.10; distal 0.43 ± 0.13 versus 0.01 ± 0.08; all P < 0.01). Coronary flow reserve was also significantly higher in coronary arteries with primarily eccentric lesions (E 2.49 ± 0.64 versus C 1.87 ± 0.28; P < 0.01).

Conclusions—Vessel remodeling in transplant vasculopathy is significantly greater in eccentric lesions than in concentric lesions, possibly due to greater coronary compliance and resistive vessel function. (Circulation. 2000;101:1384-1389.)

Key Words: transplantation □ remodeling □ plaque □ blood flow

Transplant coronary artery disease (TxCAD), which significantly increases morbidity and mortality after heart transplantation, has been traditionally attributed to accelerated intimal thickening. However, recent studies in TxCAD have shown that impaired coronary remodeling may also play a major role in the progressive loss of luminal caliber. Lim et al showed that 51% of coronary segments with TxCAD have inadequate remodeling in relation to the degree of intimal thickening in these segments, while Pethig et al have shown that remodeling is the chief determinant of lumen loss at sites of maximal lumen stenosis. However, little is known about the determinants of vascular remodeling in TxCAD. Coronary flow and increased plaque load have been shown to have significant influence on the remodeling process in native atherosclerosis. Studies in animals have shown that increased blood flow via exercise leads to progressive vessel enlargement in atherosclerotic segments. Glagov et al showed that plaque load is the major determinant of the remodeling process, because vessels with >40% plaque area have significantly reduced remodeling capabilities. Preliminary studies have also shown that site-specific determinants, such as topography of the intimal thickening (eg, eccentricity), may also play a role in governing the ability of the vessel to remodel. In these studies, coronary segments with eccentrically distributed plaque had a larger vessel area than segments with concentrically distributed plaque, which suggests that eccentric plaques have greater ability to remodel and preserve luminal area. Accentuated remodeling in eccentric lesions could be related to the compliance of the vessel or the ability to sense changes in blood flow (endothelial function). The purpose of the present study was to determine whether factors such as plaque topography, compliance, and coronary blood flow influence the remodeling process in cardiac transplant recipients.

Methods

Patients
Twenty-seven transplant patients were investigated during their annual angiographic follow-up. The study was approved by the...
institutional review board of Stanford University School of Medicine, and an informed consent was obtained from each patient before any study was performed. Patients were selected on the basis of the following criteria: minimal or no epicardial coronary disease on angiography, creatinine <1.5 mg/dL, and no concurrent rejection. Imaging was performed on vessel segments with a minimum angiographic diameter of 2 mm: 1 artery was selected from each patient that would give the axially longest section for analysis (25 left anterior descending coronaries and 2 circumflex coronaries). All immunosuppressive and antihypertensive medications were maintained throughout the investigation.

Information on the following baseline characteristics was collected for all patients: age, sex, body size (body surface area [BSA]), and interventricular septal end-diastolic dimension (as a marker of left ventricular hypertrophy) as determinants of arterial size; and donor age, months since transplant, fasting lipids (serum total cholesterol, LDL, and triglyceride levels), rejection history, left ventricular function (mild/moderate/severe systolic dysfunction), cytomegalovirus (CMV) status (of recipient), and therapy with HMG-CoA reductase inhibitors or calcium channel blockers as determinants of TxCAD.

Study Protocol
Sublingual (0.4 mg) and intracoronary (200 μg) nitroglycerin were given before intravascular imaging was performed. The intravascular ultrasound (IVUS) catheter (3.2F/30 MHz; CVIS/Boston Scientific) was advanced to the distal vessel over a 0.014-in Doppler flow wire (Cardiometrics). The short monorail design of the 3.2F IVUS catheter allows simultaneous IVUS imaging and measurement of coronary flow velocity via the flow wire while maintaining stable catheter/guidewire positions. This setup also allows intracoronary drugs to be injected via the flush port of the IVUS catheter (Figure 1).

Ultrasound Imaging Procedure and Measurements
The ultrasound core was then pulled back to 4 to 8 (mean 5.1±1.2) positions separated by equal distances (see Figure 1). Segments at or adjacent to side branches were excluded, leaving 98 segments for analysis. The catheter was kept at each position for 60 seconds for offline compliance measurements. All images were gated to the cardiac cycle by use of an ECG-signal on the video screen. Images were stored on Super VHS tape for further analysis.

IVUS Measurements
Measurements of the IVUS images were performed offline with a commercially available image analysis system (Tape Measure, In-
clinical and transplant history data relevant to the study for all patients and for the patients with predominantly concentric and eccentric lesions. Comparisons of major clinical variables showed no significant differences between patients with predominantly concentric and eccentric lesions.

Vessel Measurements and Remodeling Ratio
A total of 98 coronary segments were measured with IVUS in 25 left anterior descending arteries and 2 circumflex coronary arteries. The coronary segments were then divided according to plaque topography (28 eccentric and 70 concentric segments). Total VA and IMA were 15.83±1.13 versus 15.22±0.75 mm² (P<0.05) and 3.89±0.68 versus 3.90±0.41 mm² for eccentric and concentric segments, respectively.

Irrespective of the segmental position (proximal versus mid versus distal), eccentric segments had a larger VA and LA. The remodeling ratios were also significantly higher in eccentric segments in the mid and distal vessels. Table 2 summarizes these results.

To determine the differences in remodeling ratio between eccentric and concentric segments without being confounded by the differences of IMA, the remodeling ratios of segments with an IMA <5 mm² were compared. When this threshold was applied, IMA was not significantly different between eccentric and concentric plaque (eccentric 1.71±0.08 versus concentric 1.95±0.11 mm²); however, the remodeling ratio

FIGURE 2. Relationship between remodeling ratio and coronary compliance. Cross sections with higher remodeling ratios (higher values) also exhibited increased compliance.

TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>All Patients (n=27)</th>
<th>Concentric (n=16)</th>
<th>Eccentric (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.3±2.1</td>
<td>50.9±11.5</td>
<td>51.9±10.8</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>22/5</td>
<td>14/2</td>
<td>8/3</td>
</tr>
<tr>
<td>Donor age, y</td>
<td>30.2±11.1</td>
<td>28.9±10.6</td>
<td>32.0±12.2</td>
</tr>
<tr>
<td>Months after HTx</td>
<td>55.6±27.8</td>
<td>54.5±29.0</td>
<td>57.3±27.0</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Chol</td>
<td>222.0±29.8</td>
<td>227.8±33.5</td>
<td>213.6±22.5</td>
</tr>
<tr>
<td>LDL Chol</td>
<td>138.6±30.1</td>
<td>145.4±32.5</td>
<td>128.8±24.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>178.4±87.7</td>
<td>165.8±79.7</td>
<td>196.8±99.2</td>
</tr>
<tr>
<td>BSA</td>
<td>2.01±0.21</td>
<td>2.02±0.22</td>
<td>2.00±0.21</td>
</tr>
<tr>
<td>Rejection* (nil/mild)</td>
<td>16/11</td>
<td>9/7</td>
<td>7/4</td>
</tr>
<tr>
<td>LV fn (1/2/3/4)</td>
<td>16/7/2/1</td>
<td>9/4/2/1</td>
<td>7/3/0/0</td>
</tr>
<tr>
<td>IVS EDD, cm</td>
<td>1.25±0.19</td>
<td>1.21±0.15</td>
<td>1.32±0.23</td>
</tr>
<tr>
<td>CMV status, +/−</td>
<td>19/8</td>
<td>13/3</td>
<td>6/5</td>
</tr>
<tr>
<td>CCB therapy, +/−</td>
<td>20/7</td>
<td>10/6</td>
<td>10/1</td>
</tr>
<tr>
<td>Statin therapy, +/−</td>
<td>8/19</td>
<td>3/13</td>
<td>5/6</td>
</tr>
<tr>
<td>BSA</td>
<td>2.01±0.21</td>
<td>2.02±0.22</td>
<td>2.00±0.21</td>
</tr>
<tr>
<td>Rejection* (nil/mild)</td>
<td>16/11</td>
<td>9/7</td>
<td>7/4</td>
</tr>
<tr>
<td>LV fn (1/2/3/4)</td>
<td>16/7/2/1</td>
<td>9/4/2/1</td>
<td>7/3/0/0</td>
</tr>
<tr>
<td>IVS EDD, cm</td>
<td>1.25±0.19</td>
<td>1.21±0.15</td>
<td>1.32±0.23</td>
</tr>
<tr>
<td>CMV status, +/−</td>
<td>19/8</td>
<td>13/3</td>
<td>6/5</td>
</tr>
<tr>
<td>CCB therapy, +/−</td>
<td>20/7</td>
<td>10/6</td>
<td>10/1</td>
</tr>
<tr>
<td>Statin therapy, +/−</td>
<td>8/19</td>
<td>3/13</td>
<td>5/6</td>
</tr>
</tbody>
</table>

HTx indicates heart transplantation; Chol, serum cholesterol; BSA, body surface area; LV fn, left ventricular function on echocardiography; estimated ejection fraction 1 >60%, 2 40–59%, 3 25–39%, 4 <25%; IVS EDD, interventricular septal end-diastolic dimension; CMV status, recipient antibody status at transplantation; and CCB, calcium channel blocker.

*Rejection is based on biopsy grade.

All numerical data are listed as mean±SD. All P>0.05.

18 µg of adenosine was injected through the flush port of the IVUS catheter. Hyperemic velocity responses after the injections were then recorded, and CBF was calculated based on the blood flow velocity and IVUS LA (time velocity integral×diastolic lumen area). These measurements were repeated 3 to 4 times until consistent flow measurements were obtained. Coronary flow reserve (CFR) was defined as CBFhyperemic/CBFbasal.

Statistical Analysis
Data are presented as mean±SD. An unpaired Student’s t test with Bonferroni correction for multiple comparisons was used to compare the data. A simple regression model was used to assess relationships between variables selected. P<0.05 was assumed to be statistically significant.

Results
Patients
All patients were free of angiographically significant coronary disease and had minimal rejection at biopsy. Table 1 compares the clinical and transplant history data relevant to the study for all patients and for the patients with predominantly concentric and eccentric lesions. Comparisons of major clinical variables showed no significant differences between patients with predominantly concentric and eccentric lesions.

Vessel Measurements and Remodeling Ratio
A total of 98 coronary segments were measured with IVUS in 25 left anterior descending arteries and 2 circumflex coronary arteries. The coronary segments were then divided according to plaque topography (28 eccentric and 70 concentric segments). Total VA and IMA were 15.83±1.13 versus 15.22±0.75 mm² (P<0.05) and 3.89±0.68 versus 3.90±0.41 mm² for eccentric and concentric segments, respectively.

Irrespective of the segmental position (proximal versus mid versus distal), eccentric segments had a larger VA and LA. The remodeling ratios were also significantly higher in eccentric segments in the mid and distal vessels. Table 2 summarizes these results.

To determine the differences in remodeling ratio between eccentric and concentric segments without being confounded by the differences of IMA, the remodeling ratios of segments with an IMA <5 mm² were compared. When this threshold was applied, IMA was not significantly different between eccentric and concentric plaque (eccentric 1.71±0.08 versus concentric 1.95±0.11 mm²); however, the remodeling ratio
The vascular remodeling ratio also showed a relationship with the remodeling ratio. Vessel segments with greater compliance also showed a higher remodeling ratio \((R=0.47, P=0.001)\) (Figure 2).

**Coronary Flow Reserve**

CFR data were obtained in 20 of the 24 patients. Basal coronary flow was 134±63 mL/min, and maximum coronary flow was 286±137 mL/min. Minimum CFR was 1.45, and maximum CFR was 3.06. CFR was influenced by the percentage of eccentric plaque in the respective vessel, as shown in Figure 3A. Vessels with a high proportion of eccentric segments had higher CFR values. The vascular remodeling ratio also showed a relationship with CFR (Figure 3B), indicating greater remodeling in vessels with higher CFR values. Within each group of lesions (eccentric or concentric), higher CFR values were associated with greater remodeling.

**Discussion**

In this study, we have demonstrated the following in TxCAD: (1) segments with concentric plaque have impaired remodeling compared with eccentric lesions; (2) concentric plaque distribution in the vessels is also associated with markedly reduced compliance and impaired CFR; and (3) impaired remodeling is strongly associated with reduced compliance at the site of the lesion and weakly associated with reduced CFR. These associations may be related to the coassociation with plaque topography.

Remodeling is known to play a pivotal role in determining lumen size in transplant vasculopathy, a major determinant of survival after heart transplantation. In previous longitudinal studies, we and others have shown that despite progressive intimal thickening, vessel size may reduce with time from transplant and contributes increasingly to lumen loss.\(^6\) However, the determinants of remodeling in transplant vasculopathy are poorly understood. Whereas many factors have been shown to affect angiographic lumen loss after transplant (such as CMV status and diltiazem\(^8\) and/or statin therapy\(^9\)), it is uncertain whether these factors specifically affect remodeling.

**Remodeling and Eccentricity**

Although factors such as blood flow and lesion eccentricity can influence remodeling in atherosclerotic coronary disease,\(^4,6\) their importance in transplant vasculopathy, which is pathologically distinct, has not been determined. In the present study, we have shown that plaque topography may significantly influence the remodeling response. The remodeling ratio \((VA/IMA)\) for eccentric lesions was significantly greater than that observed in concentric lesions, resulting in better preservation of lumen size. Larger lumen size and remodeling ratio were due both to larger vessel size, despite adjustment for position within the vessel, and to less plaque. Studies by Glagov et al\(^5\) and Pasterkamp et al\(^10\) have also demonstrated that the remodeling response may become impaired in atherosclerosis as plaque burden increases. However, we found that the remodeling index in eccentric lesions was higher than that in concentric lesions with equal amounts of plaque. In addition, studies examining the early (up to 1 year) course of transplant vasculopathy have noted that eccentric lesions are more likely to represent donor atherosclerosis than TxCAD,\(^11\) which could affect remodeling patterns. However, donor disease is likely a less significant contributor to eccentric lesions at a mean of just under 5 years after transplant, especially when the imaged segments are randomly selected. In previous IVUS studies in atherosclerosis, the remodeling responses in eccentric plaques appeared dependent on the length of disease-free arc,\(^6\) suggesting that this may relate to either preservation of vessel compliance or its ability to sense and respond to flow. Indeed, we found that lesions with eccentrically distributed plaque were significantly more compliant than concentric lesions and that compliance in the vessels with eccentric lesions was proportional to the length of disease-free arc. This has previously...
been demonstrated in atherosclerotic lesions, but such large heterogeneous plaques, with variable amounts of calcium and lipid, may have quite different distensibility characteristics from early transplant vasculopathy. Although impaired vascular compliance has also been demonstrated by IVUS in coronary vessels with wall thickening that were angiographically disease free, suggesting that loss of vascular compliance may be an early event in many types of vascular disease, the relationship between eccentricity and compliance has not been demonstrated in such early lesions.

Remodeling and Compliance

Interestingly, the remodeling ratio also showed a clear relationship with the degree of vascular compliance. There are some theoretical reasons why compliance may affect remodeling. By definition, more compliant vessels undergo more pulsatile stretch. Stretch increases the activity of matrix metalloproteases 1 (interstitial collagenase) and 9 (gelatinase B), which degrade the matrix skeleton of the vessel wall and permit remodeling. Stretch-mediated induction of angiotensin II may mediate apoptosis or proliferation of smooth muscle cells depending on the receptors present, thus permitting changes in the cellular content of the vessel wall.

Alternatively, compliance may be merely a marker of preserved endothelial function, because vascular compliance is dependent on smooth muscle cell relaxation mediated by release of nitric oxide from the endothelium, allowing the transfer of stretch into elastin fibers rather than smooth muscle cells, which are inelastic. In eccentric lesions, therefore, compliance may be merely a marker of intact endothelial function in the disease-free arc and its ability to appropriately release nitric oxide, which is critical for flow-dependent remodeling.

Remodeling and Flow Reserve

Data in this study show that resistive vessel function is preserved to a higher degree in vessels with primarily eccentric lesions than in vessels with predominantly circumferential disease. Interestingly, the remodeling ratio also showed a similar relationship with CFR (resistive vessel function), although with a wider scattering of the data. More remodeling could be appropriate owing to higher flow, better endothelial sensing of flow, or both. Flow-dependent remodeling depends on the integrity of endothelial function at the site of the lesion, not in the microvasculature. However, impaired resistive vessel endothelial function may be a marker for endothelial dysfunction at the site of the lesion.

Yet, endothelial function in the conduit vessels correlates poorly with microvascular endothelial function in transplant vasculopathy, and this may explain why the correlation between CFR and remodeling was weaker than that between compliance and remodeling. Alternatively, accentuated remodeling in the eccentric lesions could be due to higher flow. It is unclear whether basal or hyperemic (exercise-induced) flow is more important in flow-dependent remodeling, although studies in which flow-dependent remodeling was induced in atherosclerotic animals with only 3 hours of exercise per week would suggest that hyperemic responses are more important. Our data would support this concept, because the basal blood flow in vessels with eccentric and concentric lesions was similar, whereas hyperemic flow was higher in vessels with eccentric lesions. It would be interesting to determine whether flow rates and plaque topography are additive in their influence over remodeling; however, our study was not powered to elucidate such a relationship.

Study Limitations

This study has used a new method to evaluate remodeling in an attempt to overcome specific difficulties in the evaluation of remodeling in TxCAD. In the past, arterial remodeling has largely been measured by the use of a reference: either the same site at an earlier time point or by comparison with a “disease-free” site within the same vessel segment. Recent evidence has shown that both of these approaches may be less than ideal, especially in the study of transplant vasculopathy and particularly for the hypotheses being assessed in the present study. The reliability of sequential evaluation of change in VA at the same site over time is critically dependent on axial reproducibility in sampling. Accurate axial orientation has relied on the presence of a focal lesion, which frequently does not exist in transplant vasculopathy, or on proximity to side branches. In the present study, a random sampling technique was used to avoid selection bias and to obtain an impression of remodeling within the vessel as a whole, while side branches were avoided. Others have tried to overcome these difficulties by serial volumetric analysis of remodeling in TxCAD, but to relate this to variable plaque topography within each volumetric segment would be difficult. In addition, remodeling after transplantation is a temporally heterogeneous process, which creates difficulty when progression between arteries at different times after transplant is being compared. Furthermore, it is quite possible that eccentric lesions may eventually become concentric but almost never vice versa. Hence, any sequential study may have difficulty in adequately discriminating between these 2 groups. Additionally, such longitudinal studies are time-consuming and costly, making them increasingly difficult to fund. The other commonly used reference-based method to define remodeling is to compare lesion site with a disease-free reference site. In transplant vasculopathy, a diffuse process with insidious onset and progression, disease-free sites frequently do not exist; in the present study of angiographically normal vessels in which the sample sites were chosen at regular intervals rather than by IVUS criteria, neither do lesion sites.

In an effort to overcome these problems, we compared VA and LA at sites from the same vessel segment. Axial reduction in vessel size (tapering) in normal vessels occurs predominantly because of branching. Angiographic studies have shown that vessel size within a specific segment is fairly consistent once factors such as sex, left ventricular hypertrophy, and age have been taken into account. These factors were similar in the 2 groups in the present study, and therefore baseline vessel size within each segment is likely to have been similar. In addition, we compared remodeling ratio, or the ratio of VA and plaque area, to try to compensate for any differences between the 2 groups in plaque burden. This ratio may potentially be misleading if sites that were
originally different sizes are compared (because equal amounts of compensatory enlargement for the same amount of plaque would result in a larger remodeling ratio in larger vessels) or if vessels with vastly different plaque burdens are compared. However, in comparisons of sites within the same segment and with similar plaque burden, the remodeling ratio was larger in eccentric than in concentric lesions.

Intuitively, assessment of the effect of compliance and resistive vessel function on remodeling would be best examined by measuring these parameters at baseline and examining remodeling at follow-up. However, evidence suggests that conduit vessel endothelial function is maximally impaired soon after transplant, with variable recovery. In addition, although resistive vessel function is progressively impaired, this may be significantly reduced by some of the newer immunomodulatory drugs. Thus, measurements of such parameters at follow-up are probably equally accurate estimates of their mean over time as measurements at baseline.

Conclusions
Remodeling in TxCAD is significantly associated with plaque eccentricity and vessel compliance, which themselves are interrelated. In addition to these site-specific parameters, remodeling is also impaired in the presence of small-vessel dysfunction in TxCAD. Additional studies are warranted to determine whether interventions that reduce lumen loss in TxCAD do so by affecting remodeling through their known beneficial effects on endothelial function.

References
Determinants of Coronary Remodeling in Transplant Coronary Disease: A Simultaneous Intravascular Ultrasound and Doppler Flow Study
Severin P. Schwarzacher, Neal G. Uren, Michael R. Ward, Anne Schwarzkopf, Nadia Giannetti, Sharon Hunt, Peter J. Fitzgerald, Stephen N. Oesterle and Alan C. Yeung

_Circulation_. 2000;101:1384-1389
doi: 10.1161/01.CIR.101.12.1384

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/12/1384

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/