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Longitudinal Study of Vascular Remodeling in Coronary Arteries after Heart Transplantation

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Background: Cross-sectional studies by intravascular ultrasound (IVUS) in heart transplant recipients have suggested that vascular remodeling occurs in coronary arteries years after transplant. However, no reports describe vascular remodeling in the same cohort of patients studied prospectively using morphometric analysis (10 evenly spaced images obtained from a slow pullback from the left anterior descending coronary artery). Morphometric analysis better reflects total vessel anatomy compared with previously reported site (2 to 3 images) analysis.

Methods: We reviewed 20 patients studied by IVUS at 2 months, 1 year, 2 years, and 3 years after heart transplant.

Results: Over time, the coronary artery luminal area decreased from baseline level of 12.0 mm^2 to a 3-year mark of 9.7 mm^2 ($p = 0.02$). Vessel shrinkage was seen in 16/20 patients. After an initial rise in intimal parameters (maximal intimal thickness, intimal index, and plaque area) from baseline to 1 year, we found a significant decrease in intimal parameters between Year 1 and Year 3 after transplant. For example, plaque area decreased from 2.05 mm^2 at 1 year post-transplant to 1.48 mm^2 by 3 years post-transplant ($p = 0.05$).

Conclusion: In a majority of heart transplant patients, early intimal thickening in the first year post-transplant is accompanied by constrictive remodeling. Over the subsequent 2 years, further constrictive remodeling is seen despite a decrease in intimal area. J Heart Lung Transplant 2000;19:546–550.

The coronary arteries in the donor heart after heart transplantation are known to develop an accelerated form of atherosclerosis. The precise mechanisms have not been established; however, many immune and non-immune factors appear to contribute to this long-term complication.[1] All factors are associated with coronary artery endothelial cell damage, which may lead to vascular remodeling of the transplanted coronary arteries.

Glagov et al[2] originally proposed that in native coronary atherosclerosis, coronary arteries may enlarge as the plaque area increases to a certain amount of stenosis. When the coronary artery cross-sectional narrowing approaches 40%, the lumen area decreases markedly as the stenosis continues to increase. This initial enlargement of the vessel may even overcompensate for the amount of plaque area and dilation of the vessel that occurs. Other authors including Zarins et al[3] have found that the distal left anterior descending coronary artery segments demonstrated a greater propensity to enlarge in response to expanding plaque than the proximal segments. This author postulated that smaller coronary arteries may

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have more smooth muscle and fewer elastic and collagen fibers than larger ones.

The use of intravascular ultrasound (IVUS) is a more sensitive technique to measure lumen area and intimal thickness compared with coronary angiography. An IVUS study by Gerber et al[4] confirmed the initial report by Glagov. Gerber found that in patients with left main coronary artery cross-sectional narrowing of less than 40%, the lumen area was not significantly different from that in patients without left main coronary artery plaque. However, the lumen area decreased sharply in arteries with ≥40% stenosis. Thus, compensatory remodeling preserves lumen size in early lesions, but when the plaque expands to occupy >40% of the cross sectional area of the vessel, this protective mechanism fails to compensate for further increases in plaque mass and the lumen area decreases.

Several studies have used IVUS to look at remodeling of coronary arteries after heart transplantation. A study by Lim et al[5] demonstrated in matched coronary artery sites over time that compensatory dilatation occurs despite increase in intimal thickness. In contrast, a study by Ziada et al[6] demonstrated in matched site analysis that in diseased segments, the increase in plaque area correlated to the decrease in lumen area over time. The use of matched sites in heart transplant patients may not represent true vascular remodeling in the entire coronary artery, as much heterogeneity may exist in diseased vessels of heart transplant recipients. Klauss et al[7] and Tuzcu et al[8] have demonstrated that more intimal thickness appears to occur in proximal segments than in more distal segments. With heterogenous disease, one may find compensatory dilatation and constriction in the same artery because of differences in intimal thickness. Therefore, to assess the true vascular remodeling of the transplanted coronary artery with atherosclerosis, morphometric analysis has been used. Morphometric analysis is a simple method of determining the average severity of coronary artery disease in an artery segment.[9] It involves measuring 10 evenly spaced sites along a selected artery. In this manner, one can avoid selection bias and can precisely determine with known confidence intervals the average lumen area and disease severity (or total plaque burden) of the selected artery.

Therefore, we undertook a study of heart transplant patients who were serially measured with IVUS using morphometric analysis to assess vascular remodeling in the coronary arteries of their transplanted donor hearts.

METHODS

Between July 1992 and October 1993, 20 heart transplant patients had serial IVUSs performed at baseline (4 to 6 weeks after transplant) and yearly for 3 years. After administration of 100 to 300 μg of intracoronary nitroglycerin, IVUS was performed in the left anterior descending coronary artery with 30 MHz probes (4.3 French, CVIS; Sunnyvale, CA; or 3.5 French, Hewlett-Packard; Palo Alto, CA). Intravascular ultrasound imaging of the most distal position was documented with cineangiography and contrast injection, and a continuous 30-second, slow, manual pullback was performed. Recorded videotape images were analyzed at the imaging laboratory by morphometric analysis,[9] using 10 evenly spaced positions from the IVUS pullback. All measurements were recorded during diastole on Super-VHS video and analyzed by computerized planimetry. The following measurements (mean of the 10 positions) were obtained: (1) maximal intimal thickness; (2) intimal area; (3) intimal index: intimal area ÷ (lumen area + intimal area); and (4) lumen area. Changes in intimal thickness indices, and lumen dimensions were assessed with each patient serving as his/her own control. All patients were treated with triple drug immunosuppression (cyclosporine, prednisone, and azathioprine) and did not have rejection at the time of their studies.

RESULTS

The study population had a mean age of 54 ± 7 years, mean donor age of 30 ± 13 years, and 35% were female. In the first year after transplant, 60% of patients were free of rejection. The IVUS revealed that the average intimal area, maximal intimal thickness, and intimal index increased from baseline to 1 year (Table I). From Year 1 to Year 3 post–heart transplant, the intimal area decreased significantly. Luminal area significantly decreased from baseline to Year 3 with an overall 19% reduction in luminal area. From baseline to 1 year, the amount of increase in intimal area was more than the amount of decrease in luminal area, and therefore inadequate compensatory dilation appears to have occurred (Figure 1). From Year 1 to Year 3 post-transplant, the amount of intimal area decreased yet the amount of luminal area decreased (Figure 2). This is consistent with constrictive remodeling. Among the 20 patients assessed, we found variation in coronary artery intimal area and luminal size. In the baseline to 1 year data, 19 of 20 (95%) patients had increased intimal area. Of these pa-

TABLE Intimal thickness measurements of the 20 heart transplant patients studied serially from baseline (4 to 6 weeks after transplant) to 3 years after transplant

		Years after Transplant		
	Baseline	1	2	3
IA (mm^2)	1.21	2.05	1.88	1.48*
MIT (mm)	0.20	0.34	0.34	0.28
II	0.07	0.14	0.13	0.12
LA (mm^2)	12.0	11.4	10.2	9.7†

IA, intimal area; MIT, maximal intimal thickness; II, intimal index; LA, lumen area.
†p = 0.02 for measurements between baseline to Year 1 after transplant.
*p = 0.05 for measurements between Year 1 to Year 3 after transplant.

tients, 7 of 19 (37%) had some compensatory dilation. From 1 year to 3 years post-transplant, 13 of 20 (65%) patients had decreases in intimal area and 16 of 20 (80%) patients demonstrated decreases in lumen area.

DISCUSSION

The original work by Glagov suggested that the early stages of atherosclerotic lesion development may be associated with compensatory enlargement that maintains lumen area despite the development of atherosclerotic plaque. However, at some point (greater than 40% lumen stenosis), the artery no longer enlarges at a rate sufficient to counterbalance the expansion of the atherosclerotic plaque, and the lumen narrows. Subsequent studies using IVUS in native coronary atherosclerosis have confirmed Glagov's concepts of vascular remodeling.[4,10,11]

Reports from studies using IVUS describe vascular remodeling of coronary arteries after heart transplant. A study by Lim and colleagues evaluated 75 heart transplant patients at various years after transplant using matched site analysis with 1- to 3-year intervals between studies. They found that compensatory dilation occurs with increasing intimal thickness in 49% of patients. Pethig et al[12] studied 35 heart transplant patients at various years after transplant, identified target lesions, and compared them with proximal and distal reference sites in the same coronary artery. They found that inadequate com-

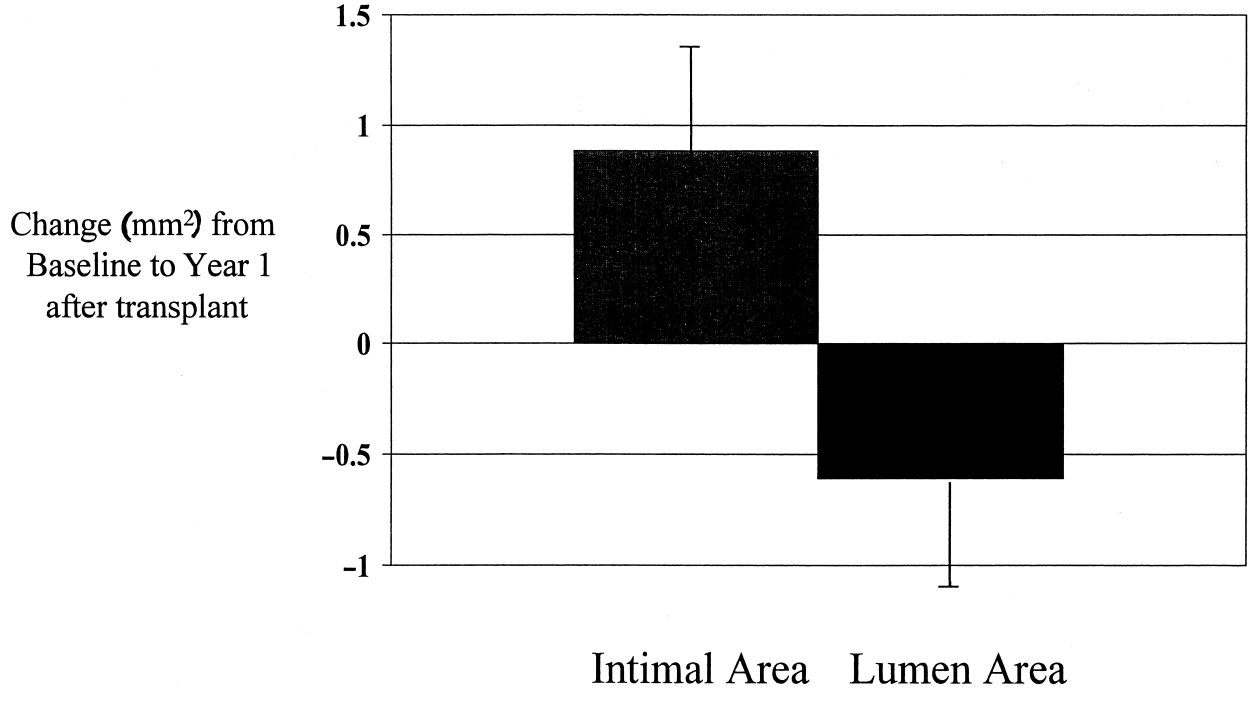

FIGURE 1 In the 20 heart transplant patients studied serially at baseline to 1 year after transplant, the amount of increase in intimal area was more than the amount of decrease in luminal area, indicating inadequate compensatory dilation.

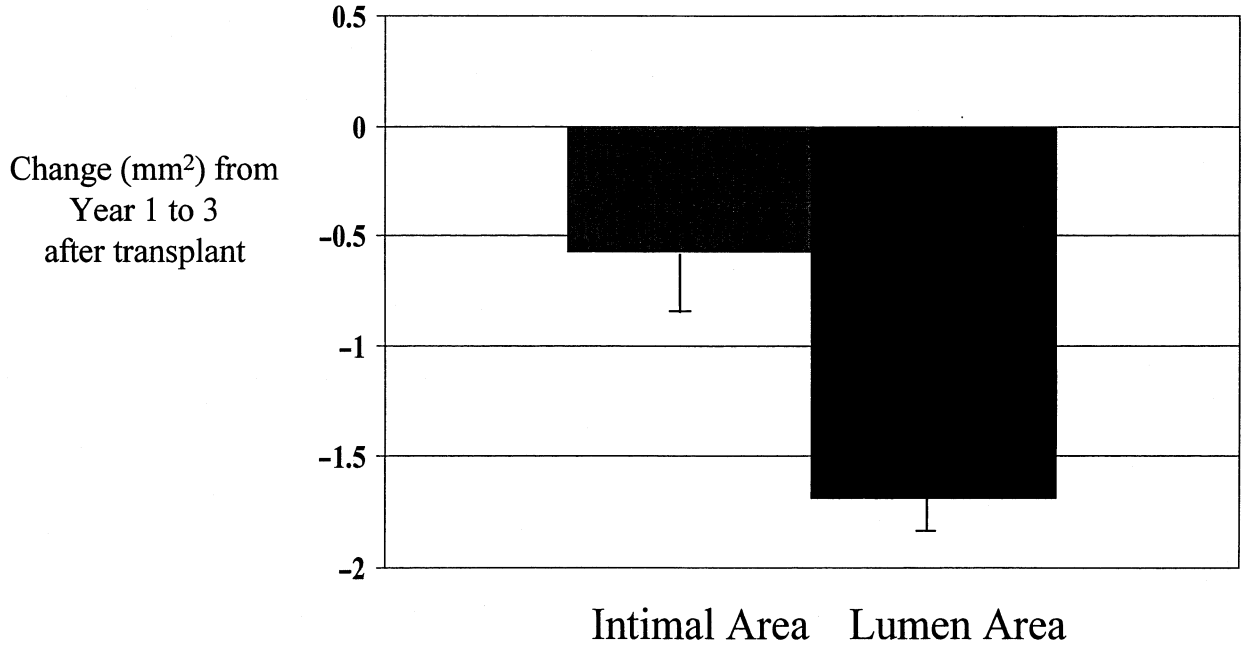

FIGURE 2 The 20 heart transplant patients from Year 1 to Year 3 after transplant demonstrated a decrease in lumen area despite a decrease in intimal area, suggesting a constrictive remodeling.

pensatory dilation rather than an increase in intimal thickness predicts decrease in luminal area. Rieber et al[13] studied 60 heart transplant patients between 1 and 5 years after transplant using matched site analysis and found an increase over time in lumen area despite increase in intimal area. Finally, Zaida studied 32 patients using matched site analysis from baseline to 3 years and found that in disease segments, increase in plaque area correlated over time to decrease in luminal area. These studies all used 2 to 3 matched sites for analysis, which represents vascular remodeling over time of only that selected site of the coronary artery. Because transplant coronary artery disease is heterogenous, different or less prominent areas of vascular remodeling may occur in various areas of the coronary artery. Therefore, the measurement of 2 to 3 selected coronary artery sites over time may not reflect the true vascular remodeling of that coronary artery. The use of morphometric analysis of IVUS images better assesses vascular remodeling of the coronary artery under examination because it averages the measurements of 10 evenly spaced sites.

In the present study using morphometric analysis of IVUS, we observed that luminal area decreased over time. However, in the first year after transplant (comparison of baseline to 1 year studies), we saw some compensatory dilation as luminal area decreased far less than expected with the amount of increase in intimal area. From Year 1 to Year 3 post-transplant, intimal area actually decreased as luminal area continued to decrease, consistent with constrictive remodeling. These findings of vascular remodeling may be due to effects specific to heart transplantation.

Vascular remodeling in the coronary arteries of heart transplant recipients may be a response to injury in the vessels, especially to the endothelial cells. Many immune and non-immune factors affect the donor heart before and after transplant that contribute to endothelial cell injury and the subsequent development of transplant coronary artery disease.[1] These processes appear very active in the first year after transplant and result in a significant increase in intimal area. This appears to cause most coronary arteries to compensate with less luminal narrowing than one would expect with the amount of increase in intimal area. These compensatory mechanisms however do not continue to be effective between Year 1 and Year 3 post-transplant. Luminal area continues to decrease with an observed decrease in intimal area. These observations may be explained by contraction of the atherosclerotic plaque or by adventitial inflammation and subse-

quent fibrosis, which may lead to contraction of the vessel.[14] This is seen in balloon angioplasty studies in non-transplant patients where restenosis may be due to adventitial fibrosis. Adventitial damage caused by stretch and tears from balloon dilation may trigger inflammation, a proliferative reaction with subsequent contraction of the adventitial scar that may cause late lumen narrowing. Vascular remodeling in the donor heart may also be due to episodes of recurrent rejection.[15] Vasoactive mediators and proinflammatory cytokines have been correlated to endothelial cell dysfunction and subsequent decreased nitric oxide production. Increase in rejection, based on a scale of average biopsy score, correlates to a lower coronary flow reserve by Doppler wire, indicating endothelial cell dysfunction. Other factors that may lead to decrease in intimal area over time may include increased fibrosis in the maturing atherosclerotic plaque due to apoptosis and diminution of lipid content, which may result in plaque retraction. With more advanced lesions, when vascular narrowing is severe, the reduction in wall tension due to the Venturi effect may also contribute to constriction of the vessel wall.

In conclusion, the coronary arteries in heart transplant recipients appear to narrow over time. Initial inadequate coronary dilation appears to be a compensatory mechanism to an increase in intimal area, which causes less reduction in luminal area than expected (for the increase in intimal area). One year to 3 years after transplant, intimal area appears to decrease and the luminal area continues to decrease, consistent with constrictive remodeling. Mechanisms for this are still speculative. In heart transplant recipients, vascular remodeling includes early inadequate compensatory dilation with late (> 1 year) constrictive remodeling that appears to be independent of intimal area.

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