JACC Vol. 27, No. 4
March 15, 1996:839–46

Dichotomous Pattern of Coronary Atherosclerosis 1 to 9 Years After Transplantation: Insights From Systematic Intravascular Ultrasound Imaging

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Objective. **The aim of this study was to evaluate the extent and distribution of coronary atherosclerosis after transplantation.**

Background. **Transplant coronary artery disease is an important cause of death after cardiac transplantation. Unlike coronary angiography, intravascular ultrasound is a sensitive tool for detection and quantitation of this disease.**

Methods. **We performed intravascular ultrasound imaging in 132 (106 men, 50 ± 10 years) patients, 1 to 9 years after transplantation using a 30-MHz ultrasound catheter.**

Results. **All three coronary arteries were visualized in 49, two in 62 and one in 21 patients. Of the 1,188 coronary artery segments, 706 were imaged (74% proximal, 64% mid- and 40% distal). At least one site with atherosclerosis (intimal thickness ≥ 0.5 mm) was found in 83% of patients. Atherosclerosis was noted in 64% of proximal, 43% of mid- and 26% of distal segments. Disease was diffuse in 48% and focal in 52%, circumferential in 66% and noncircumferential in 34%. Focal atherosclerosis was more common in proximal (59%) than mid- (48%) and distal segments (27%) ($p \approx 0.001$). Noncircumferential plaques were more common in the proximal (42%) than mid- (28%) and distal segments (12%) ($p \approx 0.001$). This pattern of focal and noncircumferential disease proximally, diffuse and circumferential disease distally, was observed irrespective of the time from transplantation.**

Conclusions. **Atherosclerosis was detected in more than 80% of patients, with proximal segments most frequently involved. Diffuse and circumferential atherosclerosis was more common in mid- and distal segments. However, focal and noncircumferential involvement was more frequent proximally, a similar pattern to native atherosclerosis. These findings suggest that transplant coronary artery disease has a dual etiology based on the dichotomous pattern of atherosclerosis seen by intravascular ultrasound.**

(J Am Coll Cardiol 1996;27:839–46)

Cardiac transplantation has been an important step in the treatment of patients with end-stage heart failure (1,2), but long-term survival is limited by transplant coronary artery disease (3,4). Traditional diagnostic methods have a low sensitivity in the early detection of this disease (5). Annual screening coronary angiograms often fail to detect atherosclerosis before a clinical event (6–9).

Necropsy studies have demonstrated that angiography underestimates transplant coronary artery disease (8,10). Accordingly, intravascular ultrasound has been increasingly utilized for the early detection and quantitation of transplant coronary artery disease (9,11–14). Intravascular ultrasound provides detailed cross-sectional images of both the vessel wall and the lumen, thereby identifying the initial stages of atherosclerosis (15–17). In early studies, large catheter size and poor handling characteristics limited most examinations to the proximal segment of a single coronary artery (11–13,18–20).

Recent developments in ultrasound imaging technology have yielded devices suitable for comprehensive examination of the coronary tree. In addition, major improvements in ultrasound image quality have enabled more precise and detailed examination of the morphologic patterns of atherosclerotic disease. Using this advanced technology, we demonstrated a high prevalence of donor-transmitted atherosclerosis in 50 recent transplant recipients (14). However, the impact of donor atherosclerosis on the development of transplant coronary artery disease remains uncertain. In this study, we evaluated the extent and distribution of atherosclerosis in multiple vessels and segments 1 to 9 years after transplantation. We sought to determine the different patterns and distribution of atherosclerosis and to explore whether these differences suggest more than one potential mechanism in the development of transplant coronary artery disease.

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Manuscript received June 23, 1995; revised manuscript received October 31, 1995, accepted November 10, 1995.

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0735-1097/96/$15.00
0735-1097(95)00564-1

JACC Vol. 27, No. 4
March 15, 1996:839–46

Methods

Patients. Between 1984 and 1992, 244 patients underwent cardiac transplantation at our institution; 174 were alive in January 1993. Exclusion criteria eliminated the patients not followed at our institution (8), those ineligible for cardiac catheterization (3) and patients with angiographically documented severe coronary artery disease, defined as ≥50% diameter stenosis by visual estimate (10). We also excluded patients who were unable or unwilling to give informed consent (3). Images from seven patients were not adequate for interpretation. Intravascular ultrasound imaging was not performed in 12 patients because of scheduling difficulties. The study protocol was approved by our Institutional Review Board. The remaining 128 patients plus 4 patients who underwent transplantation at other institutions constituted our study cohort.

The number of surviving transplant recipients during each calendar year (annual cohorts) over the 9-year period varied from 1 in 1984 to 60 in 1992. Because of the relatively small number of patients in some annual groups, we combined several cohorts to generate three distinct subgroups for data analysis. These were defined as patients who underwent transplantation 1 year, 2 to 3 years and 4 years or more before the ultrasound examination.

Coronary intravascular ultrasound. Cardiac catheterization with coronary arteriography has been performed annually since 1985 in all transplant recipients. The procedure consisted of right heart catheterization followed by endomyocardial biopsy. Subsequently, 100 to 200 μg intracoronary nitroglycerin was administered, and coronary arteriography was performed using 7F coronary guiding catheters. Beginning in 1992, intravascular ultrasound imaging was performed systematically as part of the annual catheterization.

After completion of coronary angiography, 3,000 to 7,000 IU of heparin was administered intravenously, and intraluminal imaging was performed. The operator placed a 0.014-in. (0.36-mm) high-torque angioplasty guide wire at a distal location in the target vessel. The ultrasound catheter was passed over the guide wire to the most distal site in the coronary artery to which it could be safely advanced. Ultrasound images were recorded continuously while the ultrasound catheter was gradually withdrawn. At sites of evident atherosclerosis and adjacent normal segments, the operator paused to enable identification of the site via contrast injection and to obtain several cardiac cycles of imaging data. The left anterior descending, left circumflex and right coronary arteries were all targeted for intravascular imaging. For each vessel, all three segments of the major epicardial arteries (proximal, middle and distal) were targeted for imaging. An independent observer examined the angiograms to determine the segments that were imaged by intravascular ultrasound (Fig. 1). The Coronary Artery Surgery Study (CASS) segment classification system was employed to identify the most distal site imaged by ultrasound (21).

Intravascular ultrasound imaging was performed using a 3.5F catheter (Boston Scientific Corp.), and images were reconstructed using a dedicated scanner (Hewlett-Packard). The ultrasound catheter was 135 cm long, contained a 15-mm long monorail guide wire lumen at the distal end and a transducer located 20 mm from the catheter tip. A drive shaft cable rotated the 30-MHz transducer at 1,800 rpm to generate a 360° imaging plane angulated 15° forward from perpendicular to the long axis of the catheter. Axial resolution of this imaging system averages 80 to 100 μm.

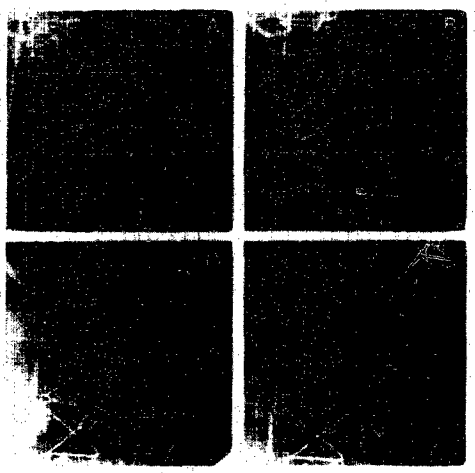

Figure 1. A, Left coronary arteriogram in the right anterior oblique projection. Ultrasound catheter is located in the (B) distal, (C) mid or (D) proximal segment of left anterior descending coronary artery. Arrows indicate the site of the transducer. The distal marker is located at the tip of the catheter.

Ultrasound analysis. The intravascular ultrasound images were analyzed in a dedicated core laboratory by an experienced technician who was unaware of patients' clinical characteristics. For each examined site, a short time sequence (10 to 20 s) of videotape was digitized at 30 frames per second into a 640 × 480-pixel matrix image with a 8-bit gray scale. For each site, the full-motion sequences were examined frame by frame to select the image with the greatest extent of atherosclerosis.

From selected frames, the following measurements were obtained: 1) maximal intimal thickness, defined as the greatest distance from the intimal leading edge to the leading edge of the adventitia border; 2) minimal intimal thickness, defined as the shortest distance from the intimal leading edge to adventitia leading edge; 3) mean intimal thickness, defined as the average of maximal and minimal intimal thickness; 4) minimal lumen diameter, defined as the shortest distance between opposing intimal leading edges; 5) lumen area, defined as the area within the boundaries of the intimal leading edge; 6) vessel area, defined as the area within the adventitia leading edge; 7) plaque cross-sectional area, defined as the difference between vessel and lumen areas; 8) percent area stenosis, (lumen area/vessel area) × 100 (Fig. 2).

Atherosclerosis was diagnosed when a patient had at least

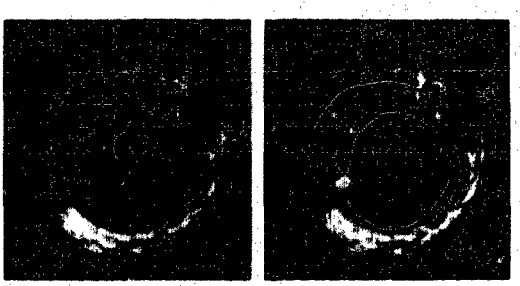

Figure 2. Intravascular image of an atherosclerotic coronary artery. The area within the media–adventitia border (**gray arrow**) represents the vessel area; the area within the intimal leading edge (**black arrow**) represents the lumen; the difference between the two areas is the plaque area. Maximal intimal thickness is shown by the **double-headed arrow**. The atherosclerotic plaque is noncircumferential, involving more than half of the vessel circumference between 7 and 3 o'clock; the remaining arc of the wall appears normal.

one site with ≥0.5-mm maximal intimal thickness at any site examined. The distribution pattern of atherosclerosis was assessed in two ways: 1) longitudinally (diffuseness) and 2) circumferentially. The diffuseness of atherosclerosis was determined by examining vessels on a segment-by-segment basis. Diffuse disease was defined as intimal thickening extending the entire length of a segment (within proximal, middle or distal segment), whereas focal disease consisted of intimal thickening occurring at isolated sites (Fig. 3). A plaque was considered circumferential if the entire vessel circumference had intimal thickening (≥0.5 mm) (Fig. 3) and noncircumferential if any arc of vessel wall showed an intimal thickness <0.5 mm (Fig. 2).

Statistical analysis. Normally distributed data were reported as mean value ± SD. Chi-square or the Fisher exact test was used to test for a significant association between categoric variables. An unpaired Student *t* test was used to examine differences between the mean values for continuous variables. A p value ≤0.05 was considered statistically significant.

Results

Patients. The study included 132 patients who underwent transplantation between 1984 and 1992, 128 at our institution and 4 at other institutions. More than 70% of surviving patients from each annual cohort were examined by ultrasound. There were 106 men and 26 women with a mean age at the time of transplantation of 50 ± 10 years. Of the 132 patients, 51 had ultrasound imaging 1 year after transplantation, 43 were examined after 2 to 3 years, and 38 had ultrasound imaging 4 years or more after transplantation. We have previously reported our observations in 50 patients who underwent imaging 4.6 ± 2.6 weeks after cardiac transplantation (14).

Extent of intravascular imaging. Of the 396 arteries in 132 patients, 292 (74%) or 2.2 arteries per patient were successfully imaged. All three major epicardial arteries were examined in 49 (37%) patients, two arteries in 62 (47%), and only one artery was imaged in 21 (16%) patients. The number of arteries imaged was similar in all three groups. The left anterior descending coronary artery was examined in 123 (93%), left circumflex in 90 (68%) and right coronary in 79 patients (60%). The imaging ratios of the coronary arteries were similar in the three groups. One hundred four arteries were not examined for a variety of technical reasons, including severe proximal tortuosity, small caliber vessel, nondominant right coronary artery, coronary spasm or equipment difficulties.

A total of 1,188 segments (396 each from proximal, mid and distal segments) were targeted for imaging; 709 (60%) were actually imaged (Table 1). Among the segments of the 292 arteries that were successfully entered with an imaging catheter, 81% of 876 segments were examined. Similar proportions

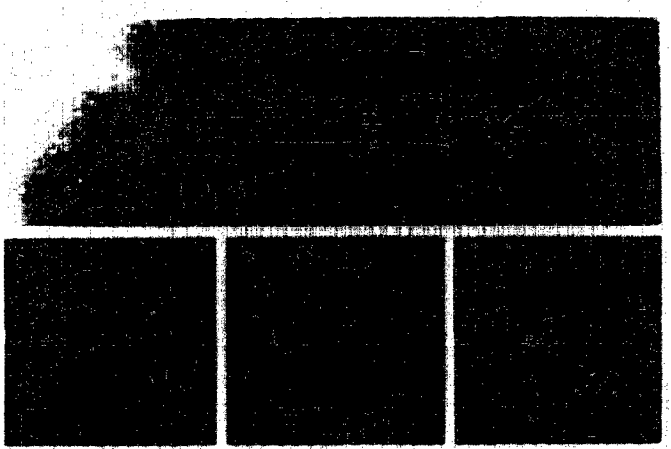

Figure 3. Left coronary arteriogram in the cranial projection. The ultrasound images from the three sites in the midsegment of the left anterior descending artery (**A, B** and **C**) show circumferential atherosclerosis of various degrees. This is an example of diffuse and circumferential atherosclerosis. The midsegment appears to be free of atherosclerosis on the angiogram despite a large plaque burden demonstrated by ultrasound.

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Table 1. Proximal, Mid and Distal Segments Imaged by Intravascular Ultrasound in the Three Groups

	1 Yr Post-Tx (n = 51)	2–3 Yr Post-Tx (n = 43)	>4 Yr Post-Tx (n = 38)	Total (n = 132)
Segments	267/459 (58)	244/387 (67)	197/342 (58)	706/1,188 (59)
Proximal	111/153 (73)	100/129 (78)	81/114 (71)	292/396 (74)
Mid	96/153 (63)	88/129 (68)	71/114 (62)	255/396 (64)
Distal	60/153 (39)	55/129 (43)	44/114 (39)	159/396 (40)

Data presented are number (%) of imaged/targeted segments. Post-Tx = after transplantation.

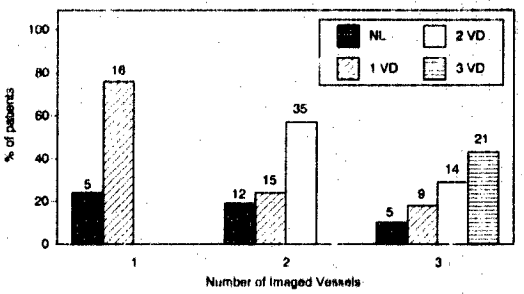


Figure 4. Percentage of one-vessel, two-vessel and three-vessel coronary artery disease in patients who had one, two and three coronary arteries imaged by ultrasound. **Numbers over bars** = absolute number of patients in that category. NL = normal; VD = vessel disease.

of patients in each of the three groups had proximal, mid and distal segment imaging.

Complications. There were no cases of coronary artery dissection, thrombus formation, embolization, myocardial infarction, need for emergency angioplasty or cardiac surgery or peripheral vascular complications requiring surgery or transfusions. Coronary spasm, which resolved promptly with intracoronary nitroglycerin, occurred in 5% of the patients.

Prevalence of atherosclerosis. Of the 132 patients, 110 (83%) had at least one site with atherosclerosis detected by ultrasound (maximal intimal thickness ≥0.5 mm). Atherosclerosis was found in 41 patients (80%) in the first year, 43 (79%) in the second and third years and 35 (92%) in the fourth through ninth years after transplantation. There were no statistically significant differences among the three groups.

There was no significant difference among the three groups in regard to minimal lumen diameter, minimal intimal thickness, the area of the vessel, plaque and lumen or percent area stenosis (Table 2). There was a trend toward a greater maximal intimal thickness ($p = 0.08$) and mean intimal thickness ($p = 0.06$) in patients imaged 4 years or more after transplantation.

Multivessel versus single-vessel disease. The prevalence of single-, double- and triple-vessel disease in patients who had imaging of one, two and three coronary arteries is shown in Figure 4. If all three arteries were imaged, at least one site with abnormal intimal thickening was detected in 44 (90%) of 49 patients. If two vessels were studied, atherosclerosis was evident in 50 (81%) of 62 patients. In patients with single-vessel imaging, 16 (76%) of 21 had atherosclerosis. Patients in whom all three vessels were imaged showed a trend toward greater incidence of abnormal intimal thickening in comparison with patients in whom only a single vessel was imaged ($p = 0.14$).

Distribution of atherosclerosis. *Proximal, mid and distal segments.* The longitudinal extent of disease was evaluated by comparing the prevalence of atherosclerosis in proximal, mid- and distal segments in early, intermediate and late posttransplant groups. The proximal coronary segments had the highest prevalence of disease. For the entire cohort, abnormal intimal thickening was detected in 190 (65%) of 292 proximal, 110 (43%) of 255 mid and 41 (26%) of 159 distal segments that were imaged ($p = 0.001$). For groups stratified by time from transplantation, a similar pattern of distribution was observed (Fig. 5). Thus, greater involvement of proximal segments was evident irrespective of time from transplantation.

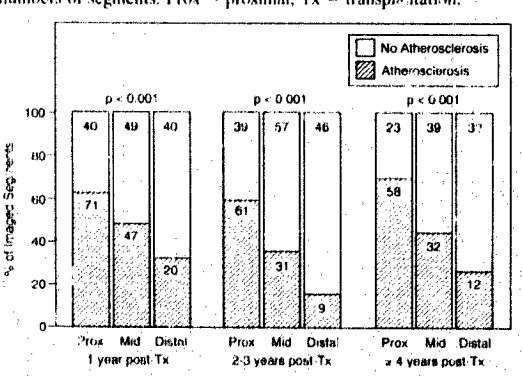
Diffuse versus focal. Of the 341 segments with ≥0.5 mm intimal thickening, diffuse disease involving the entire segment

Table 2. Ultrasound Measurements From Sites With Greatest Intimal Thickness in the Three Groups

	1 Yr Post-Tx (n = 51)	2–3 Yr Post-Tx (n = 43)	>4 Yr Post-Tx (n = 38)
Minimal lumen diameter (mm)	3.29 ± 0.88	3.46 ± 0.60	3.37 ± 0.75
Minimal intimal thickness (mm)	0.18 ± 0.12	0.18 ± 0.12	0.27 ± 0.46*
Maximal intimal thickness (mm)	1.02 ± 0.49	0.93 ± 0.45	1.27 ± 0.65
Mean intimal thickness (mm)	0.60 ± 0.26	0.57 ± 0.25	0.78 ± 0.47†
Lumen area (mm^2)	11.21 ± 5.73	11.83 ± 3.51	11.26 ± 4.73
Vessel area (mm^2)	16.49 ± 6.00	17.37 ± 4.40	18.00 ± 6.89
Plaque area (mm^2)	5.28 ± 2.69	5.53 ± 3.46	6.73 ± 3.97
Area stenosis (%)	33.8 ± 14.8	31.0 ± 15.59	36.95 ± 16.69

*$p = 0.08$, †$p = 0.06$. Data presented are mean value ± SD. Post-Tx = after transplantation.

Figure 5. Atherosclerosis in proximal, mid and distal imaged coronary segments in the three groups. **Numbers within bars** = absolute numbers of segments. Prox = proximal; Tx = transplantation.



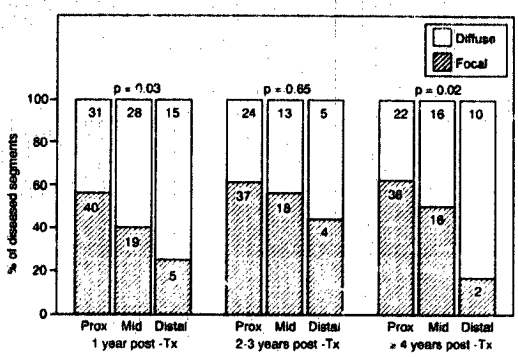


Figure 6. Percentage of focal versus diffuse involvement in the proximal, mid and distal coronary segments with atherosclerosis in the three groups. **Numbers within bars** = absolute numbers of segments. Prox = proximal; Tx = transplantation.

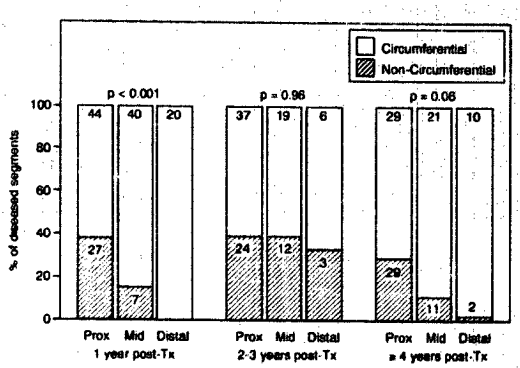


Figure 7. Percentage of circumferential versus noncircumferential involvement in the proximal, mid- and distal coronary segments with atherosclerosis in the three groups. **Numbers within bars** = absolute numbers of segments. Prox = proximal.

was found in 164 (48%) segments, whereas 177 (52%) segments had only focal atherosclerosis. The likelihood of focal atherosclerosis was dependent on the location of the segment. In the proximal segments, focal atheroma was observed more frequently (59%) than in mid (48%) and distal (27%) segments ($p = 0.001$). This striking pattern of more focal disease in proximal segments and more diffuse disease in distal segments was comparable irrespective of the time from transplantation (Fig. 6).

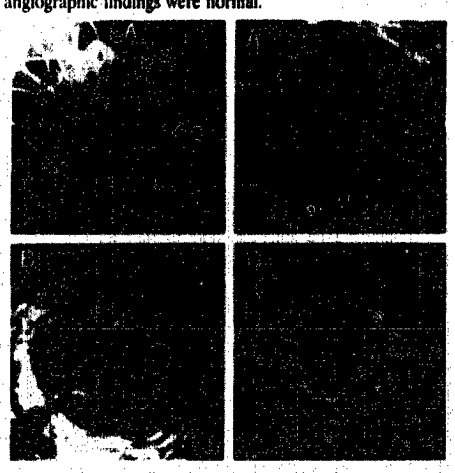
Circumferential versus noncircumferential. In the 341 segments, the dominant pattern of distribution was circumferential in 226 (66%) segments, whereas 177 (52%) segments had noncircumferential atherosclerosis. The likelihood of circumferential involvement was significantly influenced by the longitudinal location of the segment. The noncircumferential pattern was more frequently observed in proximal segments (42%) than mid and distal segments, 28% and 12%, respectively ($p < 0.001$). Noncircumferential atherosclerosis was observed more frequently in proximal than distal segments in all three groups (Fig. 7).

The distribution of atherosclerosis was diverse in individual patients. In 110 patients with atherosclerosis, both diffuse and focal atherosclerosis patterns were detected in 26 (24%) patients. Similarly, we observed both circumferential and noncircumferential disease in 34 (31%) patients (Fig. 8).

Discussion

Transplant coronary artery disease is the leading cause of death beyond the first year after cardiac transplantation (3,4). The prevalence, morphologic patterns and distribution of transplant vasculopathy have been difficult to characterize, relying, until recently, on angiographic and necropsy studies. The reported incidence ranges from 15% to 20% per year (22,23). Recent investigations have employed intravascular ultrasound to detect and quantify transplant vasculopathy and reported a much higher incidence of disease (13,14,19,20). However, most prior ultrasound studies used relatively large and inflexible catheters, limiting examination to proximal sites in a single coronary artery (11,12,18–20). A major goal of the current investigation was comprehensive examination of all three coronary arteries, including proximal, mid and distal segments. Although complete imaging was not always feasible, we successfully examined 74% of the major epicardial vessels and 60% of all possible segments. This extent of examination significantly surpasses previous reports and provides additional

Figure 8. Coronary arteriogram 7 years after transplantation in the right anterior oblique projection. **A,** Ultrasound image from the left main coronary artery reveals diffuse circumferential atherosclerosis. **B,** Cross section from the proximal segment of the left anterior descending artery shows a focal atheroma with noncircumferential distribution. **C,** In the midsegment, ultrasound shows normal vessel wall. Despite a large eccentric plaque in the proximal left anterior descending coronary artery and circumferential plaque in the left main coronary artery, the angiographic findings were normal.



insights into the various patterns of disease occurring within different segments of the coronary tree.

The most salient finding derived from more complete interrogation of the coronary arteries is a very high prevalence of atherosclerosis with a distinctly heterogeneous pattern of longitudinal and circumferential involvement. Overall, abnormal intimal thickening was evident in 80% of patients at 1 year and more than 92% of patients studied 4 years or more after transplantation. These data may underestimate the true prevalence because of the rigorous definition of abnormal intimal thickening employed in this investigation. Necropsy studies in subjects without known atherosclerosis show that average intimal thickness increases with age, yielding normal values ranging from 0.10 mm to 0.35 mm for ages 20 to 40 (24). Intravascular ultrasound studies have reported intimal thickness in normal people ranging from 0.18 mm to 0.24 mm (15,25). We used a conservative threshold (0.50 mm) as abnormal to ensure that the reported prevalence rates represented unequivocal atherosclerosis.

Extent of imaging. Our study population represented a cross section of transplant recipients studied at various time intervals after transplantation. In order to minimize selection bias, we imaged nearly all surviving patients 1 to 9 years after transplantation. For the entire cohort of 150 patients who were free from severe angiographic disease or comorbidities, 84% underwent intravascular ultrasound examination. For the subgroups stratified into annual cohorts, the percentage of patients successfully imaged ranged from 78% to 100%. Multivessel and multisegment imaging was performed to increase the probability of detecting atherosclerosis and to characterize the pattern and distribution of this disease. More than one major epicardial artery was successfully imaged in 84% of patients.

Although we attempted to image all three major epicardial coronary arteries, success was partially dependent on the size and configuration of each vessel. In some patients, safety considerations precluded complete imaging, typically for vessels less than 2 mm in diameter at their origin. Acute angulation of the vessel origin and proximal tortuosity were also important obstacles to instrumentation. The left anterior descending coronary artery, which is generally large and free of proximal tortuosity, was successfully imaged in almost all patients (93%). The left circumflex coronary artery was more difficult to cannulate, yielding a success rate of 68%. The right coronary artery was also more challenging (60% success), limited by factors including sharp angulation at the origin, a proximal "Shepherd's crook" or nondominant distribution. In the current study, multisegment imaging was considered essential to understanding the longitudinal distribution of atherosclerosis in transplant recipients. Overall, 60% of the 1,188 targeted segments were successfully imaged by intravascular ultrasound. For arteries not excluded for small size or proximal tortuosity, 77% of attempted segments were actually imaged.

Prevalence of atherosclerosis. The precise time course and rate of progression of transplant vasculopathy have remained elusive. Prior necropsy and intravascular ultrasound studies have demonstrated that many recipients have evidence of abnormal intimal thickening by the end of the first year of transplantation (10,13,19,20). In a large ultrasound study involving 174 heart transplant recipients, moderate or severe intimal thickening was observed in 26% of the patients at baseline, in 55% at 1 year after transplantation and in 83% by 5 years (19). Our observations revealed a higher prevalence of early disease (1 year after transplantation), with 80% of patients having at least one abnormal site, increasing to 92% in the group examined 4 years or later. The difference in prevalence of atherosclerosis between the two studies is probably multifactorial and related to differences in measurements of intimal thickness, patient characteristic, clinical factors and extent of imaging. We found that the likelihood of detecting atherosclerosis increased with imaging of a larger number of vessels, although this increment was not statistically significant. In patients who underwent single-vessel imaging, 24% were free of atherosclerosis, whereas only 10% of patients with three-vessel imaging were normal.

Intravascular ultrasound examination demonstrates a higher prevalence of transplant vasculopathy than angiographic studies because of major differences in orientation and perspective of these two imaging modalities (9,11,14). Angiography depicts arteries in a two-dimensional silhouette of the vessel lumen. It detects atherosclerosis inferentially by comparing abnormal sites with "normal" reference segments. In contrast, intravascular ultrasound directly images the vessel wall, enabling identification and quantification of the subtle intimal thickening characteristic of early transplant vasculopathy (11,14). The differences between these two imaging modalities are particularly relevant in the presence of diffuse, concentric intimal thickening. Angiographers may misinterpret diffusely diseased arteries as normal, although perhaps somewhat smaller in diameter.

Our findings and studies performed by others demonstrate that the prevalence of vasculopathy increased markedly during the first year of transplantation but less steeply in the ensuing years (14,19). The severity of atherosclerosis assessed by maximal intimal thickness also progresses more slowly after the first year of surgery. In our study, there was a trend ($p = 0.06$) toward greater intimal thickness in patients examined at 4 years or more compared with those imaged 1 year following transplantation. However, this apparent slow progression after the first year of transplantation could represent a selection bias resulting from examining only surviving patients who do not have angiographically significant disease. Ongoing studies with serial examinations will conclusively elucidate the pace of progression of transplant coronary artery disease.

A dichotomy of atherosclerosis. The current investigation provides the opportunity to better understand the distribution of transplant coronary disease. Angiographic and necropsy studies have suggested that diffuse, severe atherosclerosis in transplanted hearts frequently involves distal coronary segments and small arterial branches (26–28). However, such studies have relied on either angiography, which lacks sensitivity, or necropsy, which examines only recipients who died. A

recently published necropsy study examined perfusion-fixed left anterior descending arteries from 25 human cardiac allografts (28). The severity of intimal thickening was greater proximally than distally, although the percent area stenosis was similar at both sites. The mean thickness of intima and media was 0.6 mm (range 0.2 to 1.2 mm) proximally, and 0.3 mm (range 0.2 to 0.8 mm) distally.

In our study, atherosclerosis was also observed more commonly in the proximal third of the artery compared with the mid- and distal segments. Although disease was observed less frequently distally, atherosclerosis, if present, was more likely to be diffuse and circumferential distally than proximally. These findings only partially support the concept widely described in the literature that allograft vasculopathy is often diffuse and concentric in nature (29). In the present study, the frequent observation of both focal and noncircumferential plaques, particularly in proximal segments, raises doubts regarding the commonly accepted morphologic pattern of diffuse concentric atherosclerosis. Strikingly, we found that the pattern of atherosclerosis in many proximal segments appeared similar to conventional atherosclerosis with eccentric focal plaques at proximal sites, often located near branching points (30).

The precise patterns and genesis of proximal and distal transplant coronary disease are controversial. A necropsy study of 10 explanted cardiac allografts reported two different types of plaques (10). Atheromatous lesions in proximal segments were focal and appeared similar to native coronary atherosclerosis, while diffuse fibrous thickening, typical of allograft vasculopathy, was frequently noted in the mid and distal segments. The authors suggested that atheromatous plaques, indistinguishable from spontaneous atherosclerosis, represent the advanced stage of immunologically mediated allograft vasculopathy.

Etiology of disease. The findings of the current study must be interpreted in the context of previously published data on coronary artery disease in recent transplant recipients. In a separate report, we described unequivocal atherosclerosis in 56% of recipients studied within 1 month after transplantation (14). Disease detected within a few weeks after transplantation almost certainly represents donor-transmitted atherosclerosis. The results of the current investigation, combined with our prior observations, suggest a dual etiology of transplant coronary artery disease. We believe that intimal abnormalities in transplant recipients represent a heterogeneous process in which many early, focal, noncircumferential plaques in proximal segments are donor transmitted (14). The diffuse, concentric pattern observed in distal segments likely represents the results of immune-mediated vessel injury. Thus, at any given time after transplantation, examination may show the coexistence of both types of disease. The high prevalence of disease 1 year or more after transplantation most likely represents a mixture of donor-transmitted and acquired vasculopathy.

Study limitations. This study has several limitations. This is not a serial but a cross-sectional study. Findings cannot be interpreted as those of a natural history study. Our observations should be confirmed by serial examinations in a single patient cohort. Some transplant recipients were excluded. In addition to patients who died, we excluded recipients with angiographically severe coronary artery disease and those followed at other institutions. This practice may have introduced a selection bias probably resulting in underestimation of the prevalence and severity of atherosclerosis. It is also important to note that distal segments were not completely examined. The ultrasound transducer is located 15 to 20 mm proximal to the tip of the catheter, which precluded imaging within 2 to 3 cm of the terminal portion of the coronary artery, even in cases where the catheter was advanced to the distal tip of the coronary artery. Imaging was not attempted in small-caliber segments because of the size of the ultrasound catheter. In some of these vessels, the small caliber may have resulted from diffuse atherosclerosis rather than a small lumen size. The morphologic aspects of transplant coronary artery disease constituted the focus of this study. Thus, we have not included the patient characteristics and clinical factors in this report.

Implications. The collective findings of intravascular ultrasound studies of transplant patients have redefined our understanding of this disease process. The dichotomous pattern of coronary atherosclerosis observed in this study demonstrated that the role of donor-transmitted disease must be considered in future intervention trials. The high prevalence of disease by 1 year suggests that for maximal effectiveness, new treatments may need to be initiated in the early posttransplantation period. The high sensitivity of ultrasound will likely enable investigators to detect a treatment effect more quickly and reliably than previously available methods. To further improve sensitivity of detection and quantitation of the effects of these interventions, comprehensive multivessel imaging may be preferable. But the trend favoring multivessel imaging needs further studies in a larger patient population. We remain optimistic that the improved detection of disease provided by ultrasound will ultimately enable longer survival after cardiac transplantation.

We thank Eric J. Topol, MD for review of the manuscript and Karen L. Howell for valuable assistance in manuscript preparation.

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