ORIGINAL ARTICLES

Distribution and Morphologic Features of Coronary Artery Disease in Cardiac Allografts: An Intracoronary Ultrasound Study

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The longitudinal distribution and circumferential pattern of coronary intimal proliferation were studied with intravascular ultrasonography in 135 patients after heart transplantation. Eighty-seven (64%) of 135 patients had significant intimal thickening, with most lesions (63%) concentric and free of fibrosis or calcification. Both diffuse and nonuniform longitudinal patterns of intimal thickening were found. (J Am Soc Echocardiogr 1995;8:1-8.)

Coronary artery disease presents a difficult challenge in the long-term management of patients after heart transplantation. It is a major factor limiting survival and accounts for 23% of all deaths, most instances of graft failure beyond the first year after surgery, and more than 50% of retransplantation procedures.[1-4] Although its pathogenic mechanisms are not completely understood, an immunologic insult seems to play an important role. This may or may not be related directly to rejection.[5-7] Most knowledge of coronary artery disease in heart transplant recipients is based on either angiographic or pathologic data. However, both angiographic and pathologic studies reflect the coronary disease as it appears in its more advanced and most apparent stages. Intracoronary ultrasonography is an accepted method to study the coronary vessels because its diagnostic value and safety in transplant recipients have recently been established by our group.[8,9] The ability of this method to detect early stages of intimal thickening before any changes are noted by angiography also has been demonstrated.[8,10] It is of interest to know whether intimal thickening within the coronary arteries of allografts is a uniform process with respect to both the length and circumference of these vessels. This has implications for potential understanding of mechanisms of intimal thickening; however, analyses of the clinical and laboratory data potentially correlating with this process are beyond the scope of this study.

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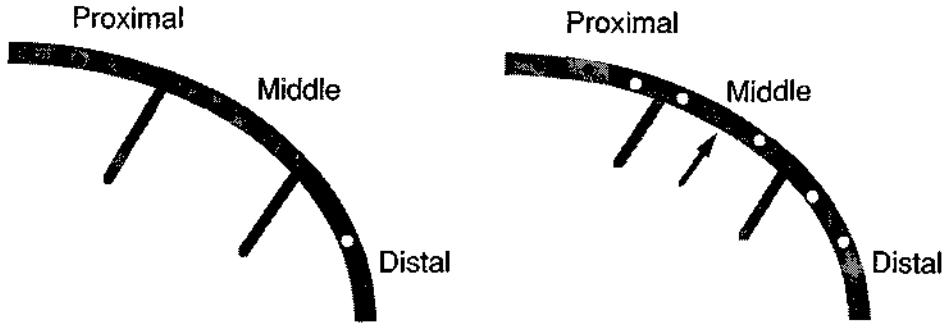
METHODS

Population

Annual follow-up examinations, including right ventricular endomyocardial biopsy, right-sided heart catheterization, and coronary angiography, are routinely performed at Stanford University Medical Center in patients after heart transplantation. Since July 1990, intracoronary ultrasonography also has been performed routinely in these patients after completion of the coronary angiography if the serum creatinine level is below 2.5 mg/dl. All the patients have given informed consent to the ultrasound study protocol that was approved by the Committee for the Protection of Human Subjects in Research at Stanford University. From July 1990 until May



Diffuse intimal thickening:

Class III-IV IT at minimum one site in each segment

Non-uniform intimal thickening:

Class III-IV IT absent from all sites in some segments.

Figure 1 Schematic drawing shows convention used to assess longitudinal distribution of intimal thickening *(IT)*. Each vessel was divided into three segments. Each vessel segment was analyzed with intracoronary ultrasonography at one to three sites and defined as having significant or insignificant intimal thickening according to most severely diseased site. *Black dots* represent sites with class III-IV intimal thickening; *white dots* represent sites with less severe intimal thickening. *Arrow* indicate subcategory of focal intimal thickening in which significantly diseased site is bracketed by sites without significant disease.

1993, 193 patients were studied by intracoronary ultrasonography. For the purpose of this report, we retrospectively reviewed the intracoronary images obtained in patients studied more than 12 months after transplantation and in whom at least two segments of one coronary artery (left main, left anterior descending, left circumflex, or right coronary artery) were visualized by intracoronary ultrasonography. One hundred thirty-five patients (mean age 48 ± 11 years; males/females 109/26) fulfilled these criteria 3.8 ± 3 years after transplantation (median 3 years; range 1 to 16 years), and the findings in this group are reported here. Some of these patients also are included in other reports from this laboratory.[8-11]

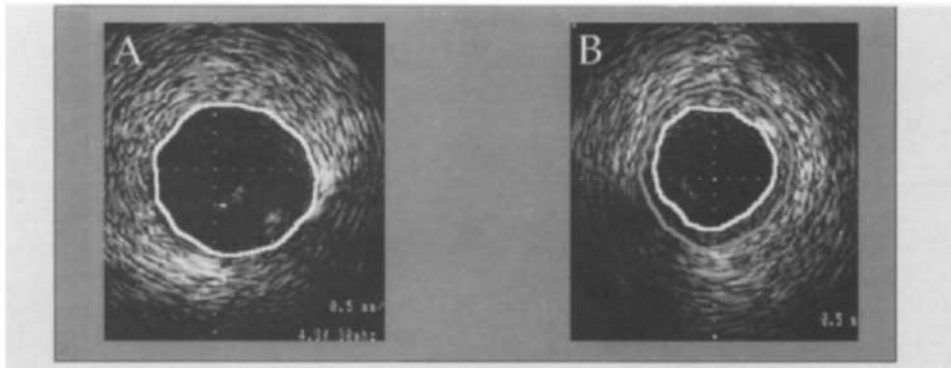
Ultrasound Imaging Procedure

Heparin, 10,000 units administered intravenously, and nitroglycerin, 0.4 mg administered sublingually, were given at the beginning of the study. After the completion of the standard coronary angiography, intracoronary imaging was performed with a 30 MHz single-element transducer positioned at the tip of either a 5F or 4.3F monorail, 135 cm length catheter (CVIS Inc., Sunnyvale, Calif.). The characteristics of the catheter have been reported previously in detail.[8] With this imaging system, the ultrasound beam is reflected against an angulated mirror that is rotated by a flexible drive cable at 1800 rpm.

Ultrasound imaging was performed after coronary angiography by advancing the imaging catheter, under fluoroscopic control, from the guiding catheter in the ostium of the left main coronary artery into the left anterior descending coronary artery or left circumflex coronary artery until the vessel diameter was noted to be 2 mm by ultrasonography and then slowly pulling the imaging catheter back into the guiding catheter. A number of distinct sites, separated by at least 1 cm within each vessel segment, were chosen for subsequent measurements. Site locations were documented angiographically and the timing and sequence of imaging for each site were recorded. The entire study was recorded continuously on a ½-inch S-VHS videotape.

Data Analysis

The angiographic studies were reviewed and the imaged vessels were divided into more proximal, middle, and more distal segments. The first major septal branch and the second diagonal branch were used as anatomic landmarks for the left anterior descending artery.[12] If these anatomic landmarks were not suitable for this purpose, or when other coronary arteries were studied, each vessel was divided into thirds by consensus of two observers (A.C. and F.P.). The location of sites within each segment imaged by ultrasonography was documented and the sites were classified as more proximal, middle, and more distal within each segment (Figure 1). The left main cor-



CLASS	I (minimal)	II (mild)	I I I (moderate)	IV (severe)
Intimal Thickness	< 0.3 mm	< 0.3 mm	0.3-0.5 mm	>1 mm
Circumference	< 180 °	> 180 °	> 0.5 mm/< 180 °	> 0.5 mm/> 180 °

Figure 2 Quantification of intimal thickening. **A,** Tracing of luminal area in vessel without intimal thickening. **B,** Tracing of luminal area (*white line;* i.e., leading edge of lumen-intima interface) and intimal plus luminal area (*gray line;* i.e., leading edge of intima-media interface) in vessel with severe intimal thickening. Definition of four classes of intimal thickening according to maximum intimal thickness and circumferential involvement is also given.

onary artery was analyzed in 44 patients, the left anterior descending artery in 124 patients, the left circumflex artery in 22 patients, and the right coronary artery in one patient. In 82 patients one of these four vessels was imaged, in 49 patients two vessels were imaged, and in four patients three vessels were imaged.

Ultrasound Analysis

The ultrasound studies were reviewed off-line and analyzed for lesion severity, eccentricity, and fibrosis or calcification according to methods described previously by our group.[8] Briefly, the largest lumen available in a cardiac cycle just before the injection of contrast material was used for analysis of each site. If intimal thickening was appreciated visually, both the luminal area and the total cross-sectional area of the vessel lumen were planimetered (Figure 2). The values were entered into a customized computer database that provided a mean intimal thickness and an intimal index (intimal index = total cross-sectional area − luminal area/total cross-sectional area).[8] The intimal thickness and the visually assessed subtended angle of vessel circumference involved were used to define four classes of severity of intimal thickening as reported previously[8] (Figure 2). Intimal thickening of more than 0.3 mm (classes III and IV) was considered significant, based on reported values of intimal thickness in a normal population.[13] A lesion was considered concentric if the intimal thickening involved more than 180 degrees of the vessel circumference. Fibrosis was defined as the presence of areas of intense echogenicity in a region of intimal thickening without acoustic shadowing and calcification was identified as an area of intense echogenicity associated with acoustic shadowing.

Definitions

Vessel segments were considered to have insignificant intimal thickening (class II or less) or significant intimal thickening (class III or IV), according to the most severe site within a segment (Figure 1). The presence of significant intimal thickening in all the segments visualized defined a longitudinally diffuse intimal thickening pattern. Significant intimal thickening in only some of the visualized segments defined a longitudinally nonuniform intimal thickening pattern. Focal intimal thickening was a variant of longitudinally nonuniform thickening defined as the presence of class III-IV–bracketed sites without significant intimal thickening (Figure 1).

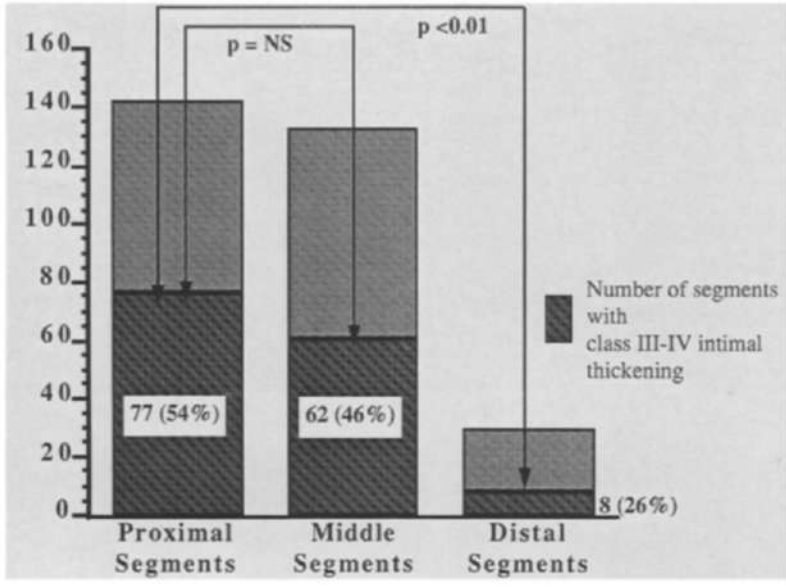


Figure 3 Longitudinal distribution of intimal thickening in each vessel segment. Class III-IV intimal thickening was significantly less frequent in more distal segments compared with more proximal and middle segments.

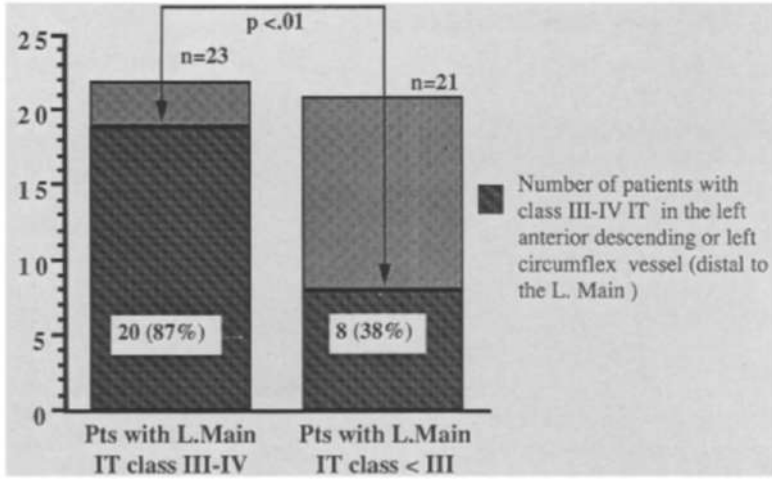


Figure 4 Comparison of more distal disease with left main *(L.Main)* disease in 44 patients with appropriate imaging sites for analysis. *Left bar* shows intracoronary ultrasound findings in more distal vessels in 23 patients with significant intimal thickening *(IT)* in left main coronary artery. *Right bar* shows incidence of finding more distal in 21 patients without significant intimal thickening in left main vessel.

Statistics

Results were expressed as absolute numbers and percentages of sites and segments with significant intimal thickening. The χ^2 test was used to compare the prevalence of significant intimal thickening in proximal versus middle and distal segments. Statistical significance was assigned to p values <0.05.

RESULTS

Prevalence and Longitudinal Vessel Distribution of Intimal Thickening

Significant intimal thickening in at least one vessel segment was present in 87 (64%) of the 135 patients. Significant intimal thickening was found in 23 (52%)

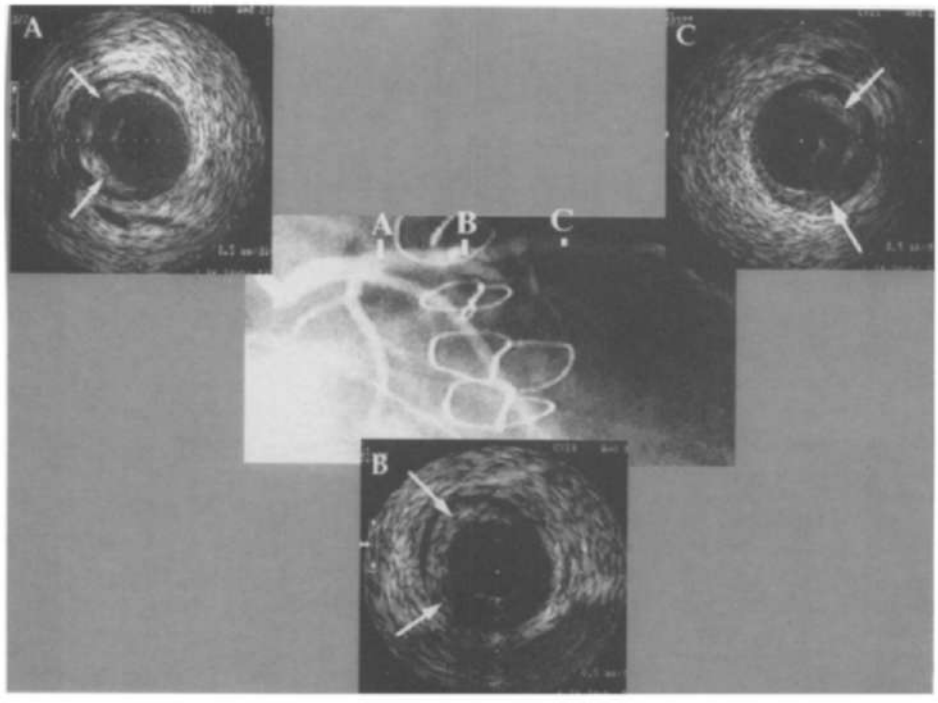


Figure 5 Example of diffuse longitudinal pattern of intimal thickening. Intracoronary ultrasound images *(lettered, small panels)* from three segments indicated on contrast coronary angiogram *(corresponding letters, central large panel)*. *Black circle* in center *(calibration dots* at intervals of 0.5 mm) of each ultrasound image is imaging catheter. Circular lumen is slightly less black. *Soft gray shadow* of intimal thickening *(small arrows)* is outlined by *darker stripe* of more echolucent medial layer. Intimal thickening is severe (Figure 2) in all three segments and is classified as having diffuse longitudinal pattern. Note radiodense imaging unit in ultrasound catheter just below *B* on angiogram. Also note sternal wires on angiogram in patients after transplantation surgery. **A,** Site in more proximal segment; **B,** site in middle segment; **C,** site in more distal segment.

of 44 left main vessels studied, in 81 (65%) of 124 left anterior descending vessels studied, and in nine (40%) of 22 left circumflex vessels studied. A significant sparing of the more distal segments by the intimal proliferation process was noted, with involvement of 77 (53%) of the 143 most proximal segments versus 62 (46%) of the 134 middle segments and eight (26%) of the 30 more distal segments (Figure 3). In the 53 patients in whom two or more vessels were imaged there was a concordant pattern of presence or absence of intimal thickening in 39 patients (73%) and a discordant pattern in the other 14 patients (27%). The presence or absence of intimal thickening in the left main coronary artery was a good predictor of the findings in the more distal vessels (Figure 4).

Pattern of Distribution of Intimal Thickening

Of the 87 patients with class III or IV intimal thickening, in 77 two or more segments were visualized per vessel. In the other 10 patients only one segment was visualized per vessel but two vessels were imaged. Diffuse longitudinal intimal thickening (Figures 1 and 5) was noted in 43 (55%) of the 77 patients. In the remaining 34 patients (45%), nonuniform longitudinal intimal thickening was noted and was limited to the proximal segment in 18 (52%) of these 34 patients (Figures 1 and 6). Focal involvement (i.e., the presence of diseased sites bracketed by sites that were free of disease) was noted in eight patients.

Lesion Characteristics

Lesion characteristics were analyzed at the 207 sites imaged with class III-IV intimal thickening (Figure 7). Circumferential eccentricity was found in 37% of these 207 sites, with concentric intimal thickening found in the remaining 63%. Either fibrosis or calcification of the intimal lesions was present at 11% of these sites, so 89% of the lesions were "soft."

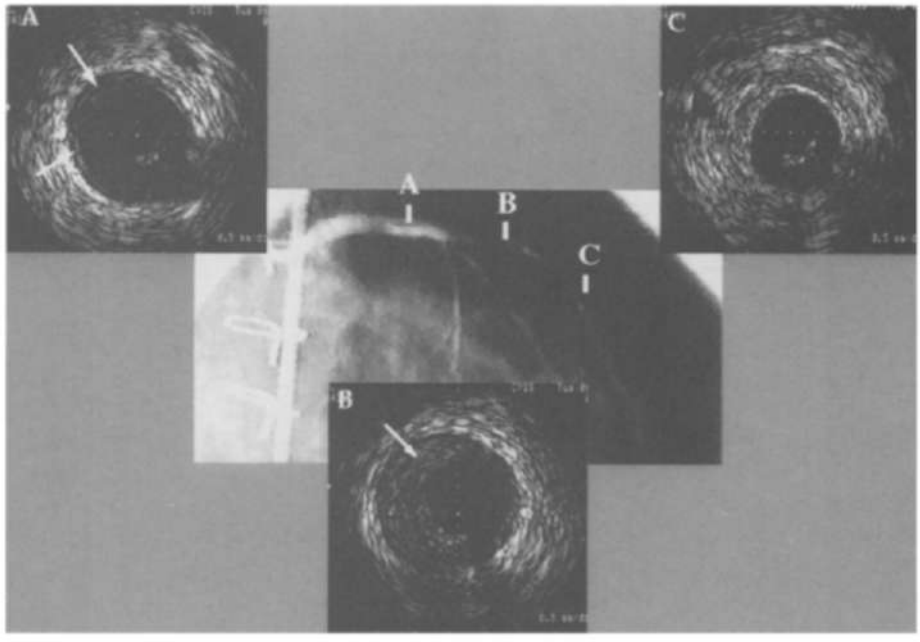


Figure 6 Longitudinally nonuniform pattern of intimal thickening. Intracoronary ultrasound images *(lettered, small panels)* from three segments indicated on contrast coronary angiogram *(corresponding letters, central large panel: A,* site in more proximal segment; *B,* site in middle segment; *C,* site in more distal segment). *Black circle* in *center* (*calibration dots* at intervals of 0.5 mm) of each ultrasound image is imaging catheter. Circular lumen is slightly less black. *Soft gray shadow* of intimal thickening *(small arrows)* is outlined by *darker stripe* of more echolucent medial layer in panels *A* and *B*. Intimal thickening is severe (Figure 2) in segments *A* and *B*, but there is little or no thickening of intima in vessel segment in *C*. This is classified as longitudinally nonuniform pattern of intimal thickening.

DISCUSSION

Heart transplantation is used widely in the treatment of patients with severe symptoms of end-stage heart disease. However, graft atherosclerosis is a major problem that still is not fully understood after more than 25 years of transplantation. Most information on the characteristics of this process comes from either angiographic or pathologic studies that are inherently biased toward recognizing the more advanced forms of disease. Intracoronary ultrasonography has emerged recently as a method shown to be more sensitive than angiography in both detecting early stages of intimal proliferation and monitoring its progression in these patients.[10]

This study found significant ultrasound-detected coronary disease in 64% of the patients. This figure is similar to those of previous reports of intracoronary ultrasonography in smaller patient populations.[8] The reported angiographic disease prevalence of 40% to 50% 5 years after transplantation is less than that found here.[14]

The main findings of this study are the high prevalence (45%) of a nonuniform longitudinal pattern of disease and the preferential involvement of the more proximal and middle segments of the vessels, with relative sparing of the distal segments. This is surprising in view of the emphasis, by some authors, on the diffuse character of intimal thickening associated with this form of coronary arteriopathy.[15] However, although a diffuse pattern is said to be characteristic of coronary disease in heart transplant recipients, it is by no means the only form of the manifestation of this process.[16] Gao et al.[17] used qualitative angiography in 132 patients after heart transplantation and 32 patients with native coronary artery disease. They found an angiographically diffuse pattern of lesions present only in the group after transplantation, with more discrete localized lesions present in both the group with native disease and in a large proportion (74%) of the transplant recipients. Quantitative angiographic data showed that the absolute decrease in luminal diameter during the follow-up period was more striking in the large vessel

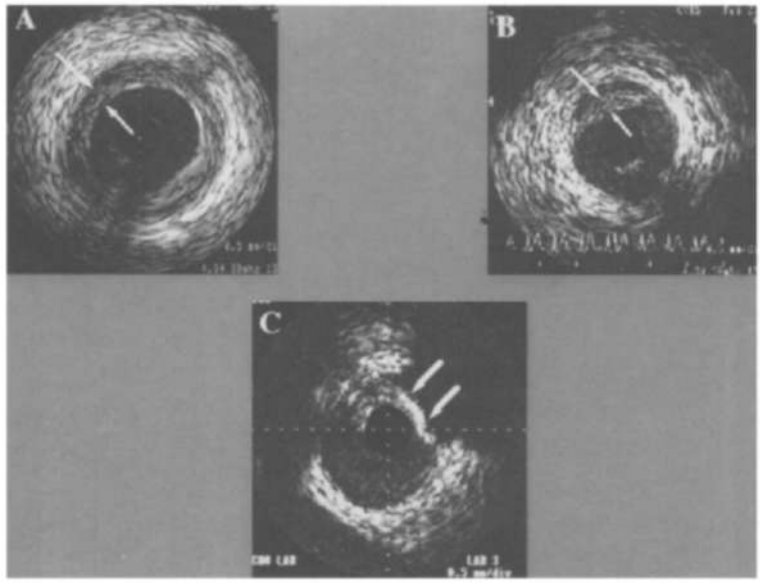


Figure 7 Intracoronary ultrasound images show characteristics of intimal thickening in transplant coronary artery disease definable by this method. *Black circle* in *center* (*calibration dots* at intervals of 0.5 mm) of each ultrasound image is imaging catheter. Circular lumen is slightly less black. Circumferentially nonuniform *soft gray shadow* of intimal thickening *(small arrows)* is outlined by *darker stripe* of more echolucent medial layer in panels *A* and *B*. **A,** Concentric severe lesion; **B,** eccentric severe lesion; **C,** eccentric and calcified lesion. *Large arrows* indicate eccentric area with bright echoes from intima associated with acoustic shadowing beyond plaque. Acoustic shadowing is characteristic of calcium within lesion. *White streak* near catheter with fuzziness beyond shown in panels *A* (7 o'clock), *B* (5 o'clock) and *C* (10 o'clock) is due to structure of imaging catheter.

segments, suggesting that the intimal proliferation process was more active in the proximal segments.[18,19] Johnson et al.[20] reported pathology studies in 60 patients who died at intervals ranging from 1 day to 12 years after heart transplantation. The most common lesion (49%) in their series was intimal hyperplasia confined to the large and medium-size segments of the epicardial coronary arteries. Diffuse longitudinal intimal thickening involving both large and small epicardial vessels was observed in only 15% of cases. Similar findings are reported by Carrier et al.[21] in seven patients with the diagnosis of accelerated coronary disease by either angiography or autopsy. Diffuse involvement of distal coronary arteries was found in three patients whereas four patients exhibited only segmental stenoses.

These findings allow for a comparison with what is known from angiographic and pathologic studies of native atherosclerotic disease. Although native coronary disease generally consists of widely spread foci of lesions with near-normal areas often present between diseased segments,[22] transplant coronary disease seems to spare the distal segments of the major epicardial trunks and was found to be focal in only 9% of the patients studied in this series. Circumferential lesion eccentricity and calcification or fibrosis of the intimal lesions were not prominent findings in this study (37% and 11%, respectively). This is in contrast to the 70% prevalence of plaque eccentricity reported in autopsy studies of native coronary disease.[22] Finally, involvement of the left main coronary artery was relatively frequent in this transplantation series (52%) compared with the low prevalence reported (16%) in the setting of native coronary disease.[22]

Limitations

The large more proximal and middle segments were visualized predominantly in our patients because of the decision to avoid segments less than 2 mm in diameter. Thus the pattern of intimal thickening is reported without knowledge of the findings in the smaller, truly distal, and nonimaged segments. However, this bias would only cause an underestimation of the prevalence of the nonuniform longitudinal pattern of intimal thickening. In the 20 patients in

whom all three segments were visualized within a single diseased vessel, the prevalence of a longitudinal nonuniform process was 60%. However, these 20 patients represent a select group in which the larger luminal areas of the more distal segments allowed the operator to advance the imaging catheter more distally. The findings in this subgroup underscore the probability that the overall prevalence of 45% for longitudinally nonuniform intimal thickening reported here is a conservative estimate. Gao et al.[18] reported that the diffuse forms of this disease are present mainly in the branches of the primary epicardial vessels by angiography. Only main trunks were visualized in this study.

The basic differences between methods should be kept in mind when comparing data. Both angiographic and pathologic studies provide information on the entire coronary tree, whereas intracoronary ultrasonography as performed in this study is limited to larger vessels. On the other hand, intracoronary ultrasonography helps recognize the presence of intimal thickening alone and will not mask the remodeling process or be affected by changes in the vascular tone.[23]

The findings of this study are interesting, especially with regard to the presumed immunologic mediation of allograft arteriopathy, because one would assume diffuse exposure of the intima to these factors. However, analysis of laboratory and clinical parameters in these patients is beyond the scope of this study.

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