Feasibility of Serial Intracoronary Ultrasound Imaging for Assessment of Progression of Intimal Proliferation in Cardiac Transplant Recipients

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Background Serial quantitative coronary angiography is used to assess progression of coronary disease; however, pathology studies have demonstrated angiographic insensitivity for determining atheroma. Intracoronary ultrasound (ICUS) can define and measure the components of the arterial wall and offers the potential for precise quantitative assessment of disease progression on serial examinations. The present study was done to test the feasibility of serially assessing intimal proliferation at the same coronary site with ICUS imaging in cardiac transplant recipients.

Methods and Results ICUS imaging was done with a 30-MHz, 5F or 4.3F ultrasound imaging catheter at the time of angiography in 70 cardiac allografts (3.8 sites per patient) initially and 1 year later. Mean intimal thickness (IT), luminal area (LA), and total area (TA) of lumen plus intima and an index of intimal thickness (II=TA−LA/TA) were measured at each site. Additionally, vessels were graded using a scale incorporating criteria of intimal thickness and circumferential involvement. Side-by-side comparisons of paired angiograms were performed both to verify the similarity of ICUS imaging site and to detect new angiographic abnormalities. At least one site could be assessed serially by ICUS in 100% of patients, but only 189 of the original 263 coronary sites (72%) (2.7 sites per patient) could be matched satisfactorily on the second study.

Thirty-nine patients (56%) had mild IT and 31 patients (44%) had moderate or severe IT on the initial study. Both groups showed the same IT progression the following year (Δ= 0.05±0.13 versus 0.07±0.15 mm; *P*=NS). Twenty-seven of the 70 patients (39%) showed progression by ICUS. The 23 patients with ICUS progression and angiographically normal vessels had the same progression in intimal thickening as the 4 patients with ICUS progression but showing angiographic disease (Δ=0.17±0.13 versus 0.22±0.10 mm; *P*=NS).

Conclusions Replication of the intracoronary imaging site by judgment of two observers at an initial study and at a second study 1 year later was possible in at least one vessel site in 100% of the 70 patients and in 72% (189 of 263) of the original imaging sites (2.7 sites per patient). Serial ICUS demonstrates progression of intimal thickening at specific sites in only some cardiac transplant patients. Progression of intimal proliferation can occur in individuals in the presence or absence of initially increased intimal thickening or of angiographic disease at the time of the initial studies. Angiography is insensitive for recognizing early intimal thickening of the coronary vessels. (*Circulation*. 1994;90:2348-2355.)

Key Words • intravascular ultrasound • transplantation • coronary artery disease

The development of diffuse occlusive intimal hyperplasia of the coronary arteries is a major problem for patients surviving beyond 1 year after cardiac transplantation.[1-4] Transplant patients with angiographically detectable coronary artery disease are at increased risk for development of graft failure and are the focus of studies to improve prognosis.[5] However, angiography is an insensitive technique for defining the early stages of coronary artery disease, when subintimal atheroma development may be accompanied by compensatory vascular dilation and enlargement of the medial and adventitial vascular layers.[6] This shortcoming is particularly manifest in cardiac transplant recipients, who frequently present with a diffuse and concentric form of coronary disease.[7-9] Intravascular ultrasound is a new imaging modality, able to define the components of the arterial wall and measure wall thickness and luminal diameter.[10-15] We have shown its ability to detect the presence of intimal proliferation in angiographically normal vessels, demonstrating the insensitivity of angiography for detection of coronary artery disease.[16,17] Intravascular ultrasound provides a unique opportunity to study the atherosclerotic process at early stages of development, before it can be detected by angiography. The purpose of the present study was to test the feasibility of serially assessing intimal proliferation at the same coronary site with intracoronary ultrasound imaging in cardiac transplant recipients.

Methods

Patient Population

The study group consisted of 70 cardiac transplant recipients with mean donor age of 25±8 years (range, 14 to 46 years), studied twice by angiography and intracoronary ultrasonic imaging, at an interval of 1 year during routine annual

coronary arteriograms. There were 54 men and 16 women. The mean age was 47 ± 12 years at the time of their baseline study (range, 20 to 66 years); mean time after transplantation was 3.1 ± 3.5 years (range, 1 week to 15 years.) Twenty-one of the 70 patients were studied within the first month after transplantation and again at their first annual reexamination. The other 49 patients also were studied twice at a 1-year interval, but the time after transplantation of the initial study was distributed as follows: 10 patients, 1 year; 7 patients, 2 years; 5 patients, 3 years; 12 patients, 4 years; 4 patients, 5 years; 1 patient, 6 years; 1 patient, 7 years; 3 patients, 8 years; 1 patient each at 9 and 11 years; and 1 patient each at 13 and 15 years. All subjects gave informed written consent to the protocol approved by the Committee for the Protection of Human Subjects at the Stanford University Medical Center.

Intracoronary Imaging Procedure

The intracoronary imaging system consists of a high-frequency, 30-MHz, single mechanical transducer and rotating mirror enclosed within an acoustic housing at the tip of a 5F or 4.3F, flexible, 135-cm long, rapid exchange catheter (Cardiovascular Imaging Systems Inc). The catheter characteristics have been reported previously in detail.[12,16] Nitroglycerin was given before all ultrasound imaging. Heart rate and blood pressure were monitored during the procedure. After anticoagulation with heparin, the catheter was introduced through a high-flow 8F guiding catheter (internal diameter, 0.082 in.) over a 0.014-in. coronary guide wire from the ostium of the left main coronary artery to the midportion of the left anterior descending and/or left circumflex artery. This technique allows for manipulation of the ultrasound catheter in a coronary artery similar to coronary balloon angioplasty systems. Vessel segments less than 2 mm in diameter were avoided. Both intracoronary ultrasound and concomitant angiography were obtained on the sequential annual studies.

The projection that best showed the vessel to be studied, with least foreshortening and vessel overlap, was chosen at the time of the original study. Replication of the imaging sites was facilitated by notation, made in the patient record, of the angulation of the image intensifier tube with respect to the fixed patient table so this angulation could be duplicated for subsequent procedures. The goal of replicating both angiographic projections (coronary anatomy) and locations of the intracoronary imaging catheter-transducer within the coronary vessel was facilitated by using a drawing and either a video hard copy or photo of the initial angiogram, indicating the location of the radioopaque catheter tip for each imaging site. Replication of the imaging sites was aided by noting the location of the imaging transducer within a segment defined by side branches established as landmarks. Matching of sites on the second annual examination was done visually by first observing the similarity of the coronary anatomy to that shown on the hard copy of the prior study in the same projection regarding minor changes in the angulation of the image intensifier tube. Finally, the location of the imaging transducer within a coronary segment was noted, relative to the side branches and the sites indicated on the drawing of the prior study, and those loci were used for image collection on the second study.

Each coronary segment was imaged simultaneously with ultrasound and contrast cineangiography to aid in verification of reproduced catheter placement within the vessel on serial studies. Accuracy of location was then determined off-line for each site with side-by-side comparison of the serial angiograms (see below). Ultrasonic imaging sites judged by consensus of two of the authors (F.P. and A.C.) as not accurately matched visually within one guiding catheter diameter distance (≈2.6 mm) on the side-by-side images of the serial studies were excluded from analysis. Transducer position relative to the very small branch vessels also was a criterion for exclusion. If the transducer was on the opposite sides of the origin of any
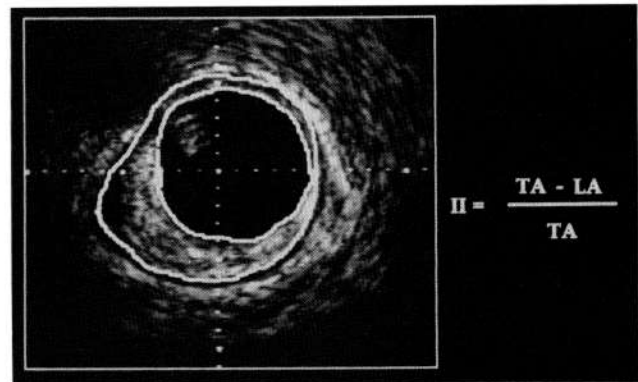

FIG 1. In vivo intracoronary ultrasound image of a cardiac allograft 7 years after transplantation. Black circle at the intersection of the calibration grid (0.5 mm per division) represents the imaging catheter. Dark gray, nearly circular area (inner white circular line) 1.0 to 2.5 mm beyond the catheter represents the blood-filled lumen of the vessel or luminal area (LA). Light gray area between the irregular white lines represents the eccentric thickening of the intimal layer of the vessel wall. Medial layer is represented by the nearly black (transsonic) ring just beyond the outer white line. Formula on the right illustrates the method for measuring the index of intimal thickening (II), obtained by dividing the difference of the total (luminal plus intimal) area (TA) minus luminal area (LA) by the total area.

small branch vessel on the two studies, the site was excluded from analysis even if the location was within one catheter diameter in absolute distance. One to four sites were imaged per coronary segment in each patient. Paired ultrasonic images in sequential studies were compared for analysis of intimal thickness and circumferential extent of intimal thickening.

Intravascular Ultrasound Measurements

All ultrasound studies were recorded on half-inch videotape for subsequent measurement from single-frame images. Gain settings were adjusted for optimal visualization of the vessel-lumen interface. Representative sequential frames were digitized on a $512\times512\times8$-bit matrix in 34-frame sequences using an image processing computer dedicated to echocardiographic analysis (Dextra Medical Inc). All patients had heart rates above 60 beats per minute (mean, 85 ± 13), permitting at least one full cardiac cycle to be digitized for each analysis sequence (30 frames per second). Software algorithms for smoothing and contrast enhancement resident in the image processing computer were used to optimize visualization of vessel wall layers. The frames with the largest luminal area from a cardiac cycle were selected for measurement. The ultrasound parameters included vessel lumen cross-sectional area, measured by tracing the inner boundary (leading edge) of the coronary artery lumen-wall interface from a single frame, and mean vessel diameter, derived mathematically from the area. In addition, the combined area of lumen plus intima (total area) was measured. Mean intimal thickness was calculated from the difference of the luminal and total areas. An index of intimal thickness was calculated as (total area minus intimal area) divided by total area (Fig 1). We previously have shown good reproducibility and low interobserver and intraobserver variability for the above-mentioned intravascular measurements.[11] Progression of intimal thickening from the first to the second study was defined as an increase in the intimal index of >10% of the value on the initial study or new development of class 3 or 4 lesions (see below).

Classification of Transplant Coronary Artery Disease

All intracoronary ultrasound studies were reviewed by two of the authors (F.P. and A.C.) and classified according to the
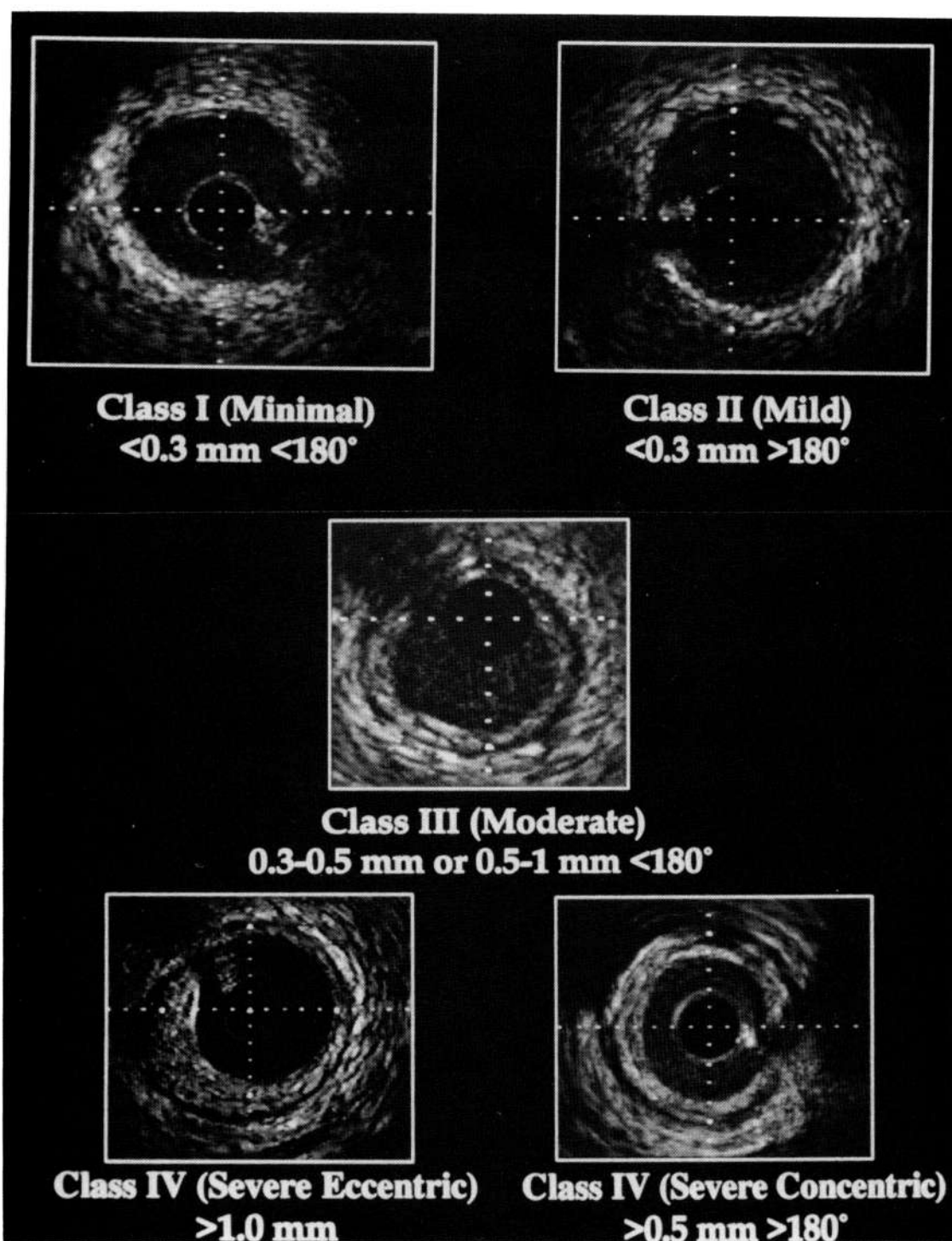
FIG 2.   Classification of coronary artery disease by intracoronary ultrasound. Each site was graded according to the intimal thickness and circumferential extent of thickening (see text for details).

degree and extent of intimal thickening, as previously described.[16] The following grades were defined: (1) none: no evidence of intimal layer, homogeneous wall, (2) minimal: intimal layer <300-μm thick measurable in <180° of the vessel circumference, (3) mild: intimal layer <300-μm thick measurable in >180° of the vessel circumference, (4) moderate: intimal layer 300- to 500-μm thick or an intima >500-μm thick involving <180° of the vessel circumference, and (5) severe: intimal layer >500 μm involving >180° of the vessel circumference or an intimal layer >1 mm in any area of the vessel cross section. The classification representative of the most

severe site was recorded for each patient at each study. Each site was also analyzed for areas of fibrosis or calcification according to the acoustic properties of the vessel wall. Calcification was recognized as a discrete echo-dense area with acoustic shadowing beyond it. An example of each grade is shown in Fig 2.

Coronary Arteriography

All patients underwent left and right heart catheterization and selective coronary arteriography. After nitroglycerin premedication, multiple projections of both right and left coro-
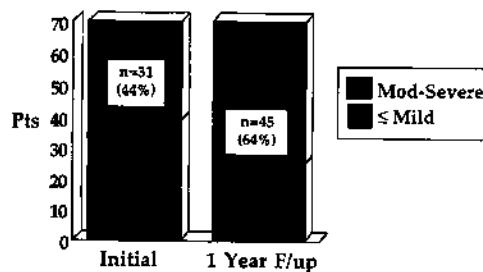
Fɪɢ 3. Bar graph: Distribution of intimal thickening by intracoronary ultrasound at the time of the initial study and follow-up (F/up) 1 year later in the 70 patients (Pts) studied using the classes defined in Fig 2. Forty-four percent of the patients had moderate or severe intimal thickening on the initial study and 64% had moderate or severe intimal thickening 1 year later.

nary systems were obtained. Projections were replicated on serial studies in an individual as described above. Arteriograms were reviewed with side-by-side comparisons of projected cineangiograms both to verify the similarity of imaging and to detect new lumen irregularities in order to define angiographic progression of disease anywhere within the coronary tree. Final interpretation of the coronary vessels was based on consensus reached by two experienced angiographers blinded to the ultrasound data. Evidence of angiographic disease anywhere within the coronary artery system categorized patients as normal or abnormal, and progression of disease was defined by comparison of abnormalities on serial studies.[1,18,19] Quantitative coronary angiographic methods were not used in this study.

Data Analysis

Values are expressed as mean±1 SD. Comparisons between groups were determined by χ^2 test and Student's t test for differences in proportions and means, respectively. Differences between stages were analyzed by two-way ANOVA. For significant F ratios, group mean values were compared using Fisher's test. A P value of <.05 was considered statistically significant.

Results

Yield of Matched Intravascular Imaging Sites

A total of 263 coronary sites (3.8 sites per patient) was imaged by ultrasound on the initial study. Replication of the intracoronary ultrasound imaging during a second study was possible in at least one vessel site in 100% of the 70 patients. Of the 263 potential sites for serial assessment, 189 (72%) were judged to be correctly matched on the two studies separated by an interval of 1 year. This provided 2.7 matched coronary sites per patient for comparison of interval changes in intimal characteristics. The left anterior descending vessel alone was studied in 63 patients, the left circumflex vessel alone was studied in 5 patients, and both the left anterior descending and the left circumflex vessels were studied in the remaining 2 patients.

Intravascular Ultrasound Measurements

A mean intimal thickness and a mean intimal index were determined for each patient, taking the average of the measurements of all lesions in each patient. At the time of the initial study, a mean intimal thickness of 0.22±0.19 mm and a mean intimal index of 0.18±0.14 were obtained from the 189 sites eventually matched on serial studies in the 70 patients. Thirty-nine patients (56%) comprised a group with no,

minimal, or mild grades of intimal thickening on the initial study; and 31 patients (44%) comprised a second group with moderate or severe thickening on the initial study (Fig 3). The measured increase of intimal thickening from the initial to the second study was similar in both groups (Δ=0.05±0.13 versus 0.07±0.15 mm, respectively; P=NS).

Twenty-seven of the 70 patients (39%) showed some progression of intimal thickening in one or more locations by ultrasound. Fourteen of these 27 patients initially had no, minimal, or mild intimal thickening, and 13 patients initially had moderate or severe intimal thickening. This difference was not statistically significant (14 of 39, 36%, versus 13 of 31, 42%; P=NS) (Figs 4 and 5).

Seven of the 70 patients had abnormal angiograms at the time of the initial study. By the time of the second study, 3 additional patients, or 10 patients in total, had abnormal arteriograms. Only 4 of these 10 patients showed progression by ultrasound: 1 with an abnormal angiogram at the initial study and 3 with new angiographic abnormalities only on the second study. The other 6 of these 10 patients had both angiographic disease and intimal thickening by ultrasound on their initial study but failed to demonstrate progression by either method.

These 10 patients with angiographically notable abnormalities on the second study had more intimal thickening initially compared with the initial values in the other 60 patients without eventual angiographic disease (0.43±0.15 versus 0.19±0.18 mm; P=.0001). However, the progression of thickening by ultrasound in these 10 patients with angiographically detected lesions was not significantly different compared with the 60 patients without angiographically detectable disease (Δ=0.11±0.13 versus 0.05±0.14 mm; P=.25). Of the 27 patients with progression of disease by ultrasound, the 23 patients who had angiographically normal vessels on the second study showed the same progression of intimal thickening as the 4 patients with angiographic lesions on the second study (Δ=0.17±0.13 versus 0.22±0.10 mm; P=NS) (Fig 6).

Discussion

Accelerated graft coronary artery disease is the major cause of death or retransplantation in patients surviving beyond the first year after transplantation.[2,3,20] Up to 50% of patients have angiographically detectable coronary artery disease 5 years after transplantation, and 50% of those patients will develop graft failure.[1,5] Histopathology studies suggest that many short-term and virtually all long-term survivors have significant coronary artery disease.[9,19,21] Annual quantitative angiography is performed at Stanford University and many other cardiac transplantation centers both to study and to monitor progression of coronary artery disease in this patient population. However, even quantitative angiography is unable to define the earliest stages of graft coronary disease when intimal atheroma development presumably is accompanied by compensatory vascular dilation and enlargement of the medial and adventitial layers.[6] Transplant coronary artery disease is often diffuse, which may partially explain the failure of arteriography to accurately show the severity of vascular disease in these patients.[19] A better monitoring method, sensitive to the earliest stages of the disease, is
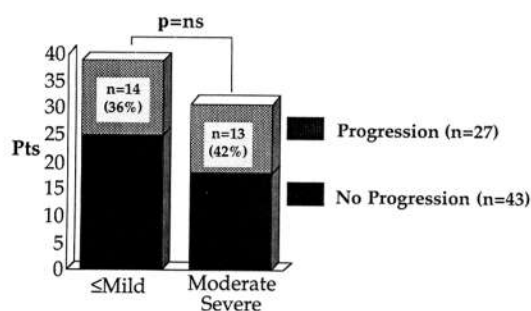
FIG 4. Bar graph: Relation of the progression of intimal thickening to the class of intimal thickening on the initial study. Twenty-seven of the 70 patients (Pts) (39%) showed progression of intimal thickening by ultrasound. Fourteen patients had no, minimal, or mild intimal thickening at the time of the initial study (≤Mild), and 13 patients had moderate or severe intimal thickening at the time of the initial study. This difference was not significant (14 of 39, 36%, vs 13 of 31, 42%; *P*=NS).

essential to study the early evolution of transplant coronary artery disease and to better assess therapeutic interventions.

Intravascular ultrasound has the ability to define the components of the arterial wall and measure wall thickness as well as luminal diameter, potentially providing a unique tool to quantify changes in intimal proliferation before they are detectable angiographically.[22,23] Several studies have verified the accuracy of interpretation of ultrasonic appearance of vessel wall morphology compared with in vitro pathology.[10,15,24] A recent study in vivo, with confirmation in vitro, showed that intravascular ultrasound is more sensitive than angiography for demonstrating the presence and extent

of arterial calcification as well as atherosclerosis.[25] The advantages of intracoronary ultrasonic imaging compared with angiography have been reported from this laboratory in cross-sectional studies.[11,16] The present investigation was undertaken to assess the feasibility of intravascular ultrasound for monitoring the progression of intimal proliferation serially in individual patients. The more complex analysis of factors related to progression of intimal hyperplasia awaits the results of this feasibility study.

In the present series, intracoronary ultrasonic imaging was performed at multiple sites within proximal segments of one or more vessels in each patient (mean, 3.8 sites per patient). Replication of the intracoronary imaging site, by judgment of two observers at an initial study and at a second study 1 year later, was possible in at least one vessel in 100% of the 70 patients and in 72% (189 of 263) of the original imaging sites (2.7 sites per patient). Despite the care taken to reproduce the angiographic anatomy for site verification, slight changes in patient position, different angiographic rooms and equipment, and variations in catheter tip positioning during the time constraints of such a catheter-based study apparently caused sufficient alterations of anatomy to prevent perfect site replication on these serial annual studies when judged later by scrutiny of the two studies placed side by side. Data from sites not meeting our criteria were not analyzed.

Changes in intimal thickness were noted by ultrasound imaging in some patients and not found in others. Only 39% (27 of 70) of the patients showed progression of intimal thickening by ultrasound over the 1-year interval. A group of 39 patients (56%) initially had no, minimal, or mild grades of intimal thickening, and
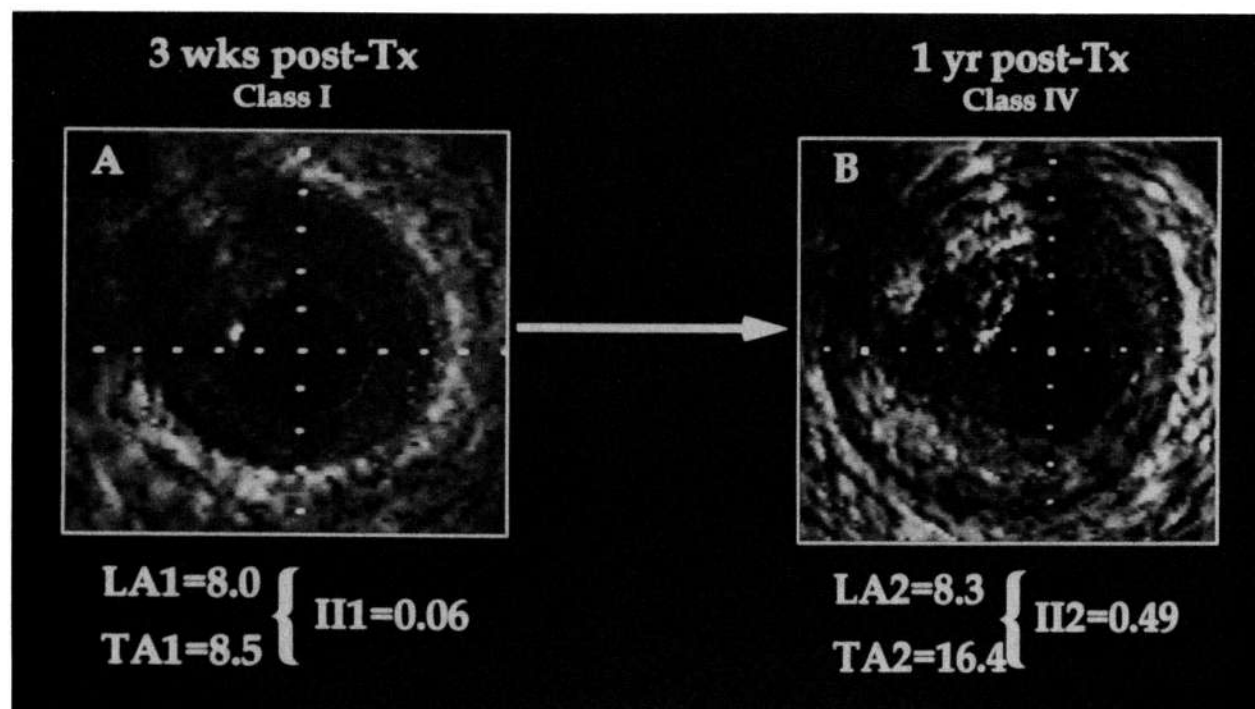

FIG 5. Intracoronary ultrasonic images 3 weeks after cardiac transplantation (A) and on the serial study 1 year later (B), at the same left anterior descending coronary artery site from a 29-year-old donor heart (57-year-old patient). There is minimal intimal thickening on the initial study (soft, thin echoes inside the brighter white adventitia from the 2 o'clock to 4 o'clock positions and no visible media, a normal finding) in A and severe concentric intimal thickening (see Fig 1) 1 year later. No significant change was observed in luminal area (LA) on serial studies, but the intimal index (II) increased markedly (II1 vs II2). TA indicates total area (see Fig 1).
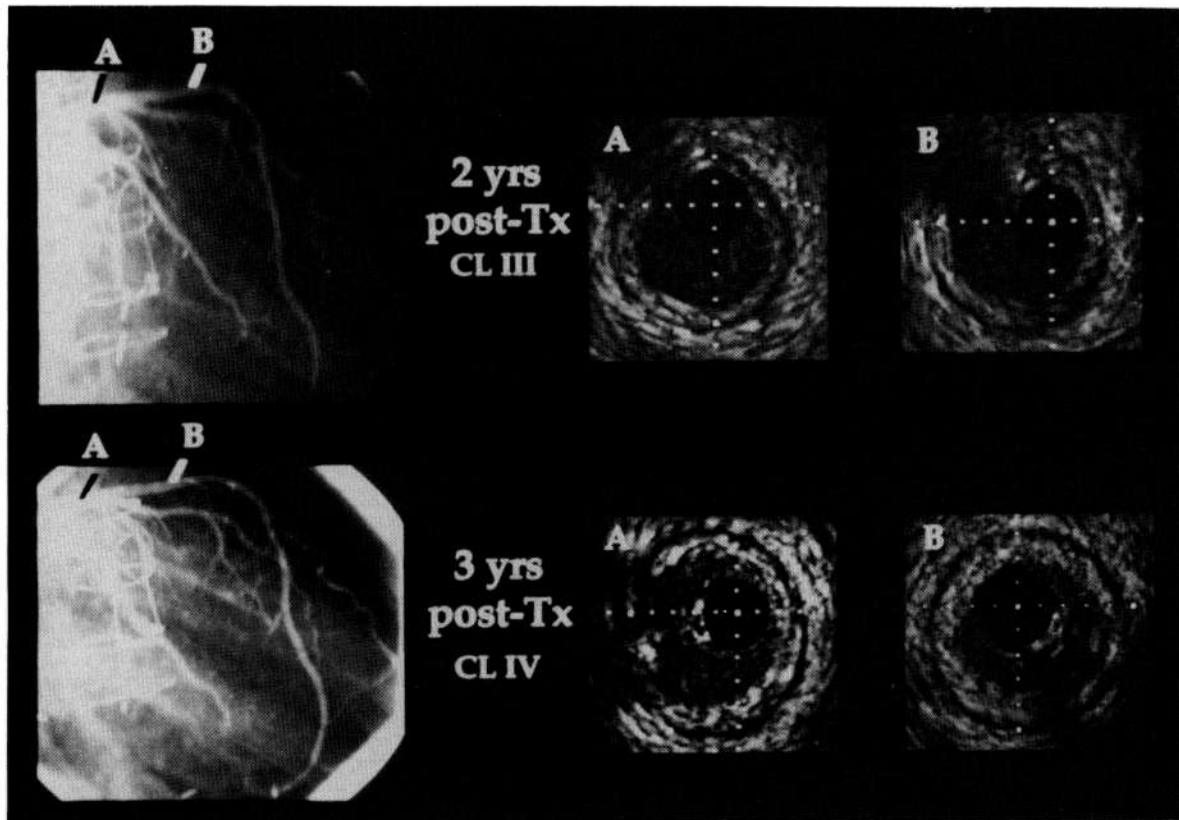
FIG 6.   Coronary angiograms (left panels) and intracoronary ultrasonic images (right panels) from the initial study (upper panels) 2 years after transplantation and the second study (lower panels) 1 year later (3 yrs post-Tx) from a 56-year-old patient with a 28-year-old donor heart, showing moderate diffuse concentric intimal thickening in the proximal (A) and middle segments of the left anterior descending vessel (B). The lower panel shows progression of concentric intimal thickening compared with the earlier images. (Note: Vertical and horizontal calibration grids indicate 0.5 mm per division.)

another group of 31 patients (44%) initially had moderate or severe intimal thickening (Fig 3). Fourteen of the 27 patients showing progression were in the first group, and the other 13 patients were in the second group. This was not a statistically significant difference (14 of 39, 36%, versus 13 of 31, 42%; P=NS) (Figs 4 and 5). Therefore, a minority of the group had progressive intimal thickening over this period, and this minority was not predicted by the initial degree or class of intimal thickness. Similar progression of intimal thickening also was found by quantitative analysis of those patients with and those without moderate or severe intimal thickening on the initial study (Δ=0.05±0.13 versus 0.07±0.15 mm, respectively; P=NS).

Angiography did not show as much coronary artery disease in these patients as was demonstrated by intravascular ultrasound imaging. Although 31 patients had moderate or severe intimal thickening by ultrasonic imaging on the initial study, only 7 of these patients were considered abnormal by angiogram at that time. This is consistent with prior studies.[16,17,22] At the time of the second study, angiograms were read as abnormal in 3 additional patients (total of 10 patients). These 10 patients initially did have more intimal thickening compared with the other 60 patients without eventual angiographic disease (0.43±0.15 versus 0.19±0.18 mm; P=.0001). However, the progression of intimal thickening over the same time period in these patients was not significantly different from that in the total group without eventual angiographic disease (Δ=0.11±0.13 versus 0.05±0.14 mm; P=.25). Specifically, the 23 patients who had progression by ultrasonic imaging but apparently normal vessels on the second angiogram showed the same quantitative progression in intimal thickening as the 4 patients who had progression but showed angiographically defined abnormalities on the second study 1 year later (Δ=0.17±0.13 versus 0.22±0.10 mm; P=NS) (Fig 6). This suggests that there may be something about the eccentricity or nonuniformity of individual coronary intimal lesions that makes them more recognizable on the angiogram. Such detailed analysis of this issue is beyond the scope of this study.

While the primary goal of this investigation was to test the feasibility of observing specific coronary sites on repeated imaging, another new observation is that progression of intimal proliferation can occur in individuals in the presence or absence of initially increased intimal thickening or of angiographic disease at the time of the initial studies. These findings add to the body of evidence suggesting that the stimuli for intimal proliferation are not constant. They also support anecdotal observations of transplant patients with angiographically apparent but stable coronary disease.

Recent data from our institution suggests that diltiazem prevents or slows the progressive decline in the mean coronary diameter by quantitative angiography during the first year after transplantation.[26] The present study shows that it is possible to do serial ultrasonic

imaging studies to assess changes in intimal thickening at specific sites within the coronary vasculature. Ongoing studies using intravascular ultrasound will address to what degree an apparent decline in the mean coronary artery diameter by quantitative angiography is due to prevention of progression of intimal proliferation rather than changes in vascular diameter due to alterations in tone. The prognostic implications of the intracoronary ultrasound findings in these and other patients remain to be determined by long-term longitudinal studies. Observations in a limited number of patients suggest that instrumentation of the proximal coronary arteries with the intracoronary catheters used in this study is safe regarding acceleration of intimal proliferation.[27] A preliminary report of a larger multicenter study also suggests that there are very few acute significant complications of the procedure beyond reversible spasm of the instrumented vessel.[28]

Study Limitations

Only the proximal segments (two thirds) of the left anterior descending or left circumflex coronary artery were examined by intracoronary ultrasound, and measurements were performed on a finite number of sites in this study. Thus, the identification of the extent of coronary artery disease, the measurements of intimal thickness, and the intimal index reflect the process in a limited number of coronary sites in each patient (2.7 sites per patient). However, the primary purpose of this study was to test our ability to image the same site twice at an interval of 1 year in order to gauge the stability or progression of intimal proliferation at that site and not to completely characterize the coronary tree. Transplant coronary disease is considered a relatively diffuse process by pathologists who may see the most advanced cases by selection bias. In vivo studies in this regard will be facilitated by further reduction in imaging catheter size below the current 4.3F size. The resolution of the ultrasonic imaging system used in this study is approximately 0.15 mm, so intimal thickness less than this value is not detectable with this device.[24]

In the present study, a laborious technique was used to carefully document catheter position and angiographic projection during the initial study to enable duplication of ultrasonic imaging sites. This investigation was limited by using only visual assessment criteria of site reproduction. Nevertheless, at least one site was reproduced serially in 100% of the 70 patients, and 72% of the initial sites (189 of 263) were reproduced on the second study. Future refinements in methods of catheter location, as well as better documentation of the relation of imaged sites in three-dimensional space, should improve the ability of operators to accurately monitor the state of intimal lesions on longitudinal studies.[29] Continuous recording of the images during catheter pullback was not helpful to us at the time of this study because the picture-in-picture recording of both fluoroscopic and ultrasound images on the same videotape, for later analysis, was not available. Such data still require that one determine the accuracy of duplication of the site of the beginning and end of the pullback on serial studies. Also, one still must select individual sites for analysis even if the most severe site in a segment is chosen for measurement. Uniform mechanical pullback, when combined with three-dimen-

sional reconstructuion of a complete segment defined by side branches, may be helpful for understanding of intimal changes between serial studies.[30]

Classification of coronary disease severity by ultrasonic imaging, as used in this study, allows grouping of patients by the degree of vessel wall involvement but does not reflect the continuum of the disease process. However, the use of a classification system has the advantage of providing a simplified working definition of the severity of the patient's disease to supplement quantitative measurements for serial studies. Quantitative coronary arteriography was not used for comparison with the quantitative ultrasonic imaging because the matching of imaging sites was the primary goal.

Acknowledgments

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