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# Influence of Preexistent Donor Coronary Artery Disease on the Progression of Transplant Vasculopathy

An Intravascular Ultrasound Study

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Javier Botas, Fausto J. Pinto, Adrian Chenzbraun, David Liang, John S. Schroeder, Stephen N. Oesterle, Edwin L. Alderman, Richard L. Popp, and Alan C. Yeung

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**ABSTRACT:** *Background* Transplant vasculopathy (TxCAD) limits long-term survival of allograft recipients. The possibility that preexistent donor coronary disease (PEDD) might accelerate this process is of concern. The serial progression of sites with and without PEDD as assessed by intravascular ultrasonic imaging is explored in this study. *Methods and Results* Thirty patients with baseline intravascular imaging within 3 weeks of cardiac transplantation who had at least one annual follow-up study were included in this study. Vessel luminal area (LA), total area (TA), intimal index ( $II=TA-LA/TA$ ), mean intimal thickness (MIT), and Stanford classification were expressed for each image site and for each patient at each study. Progression of sites and of patients with and without PEDD on the baseline study was compared. Patients with PEDD ( $n=9$ ) still had significantly more intimal disease than those

without PEDD (n=21) at the first follow-up study (MIT=0.35±0.13 versus 0.13±0.11 mm; II=0.29±0.11 versus 0.11±0.1; class=3.7±0.5 versus 2.2±0.94;  $P<.001$  for all comparisons). However, the increase in intimal thickness during the 1- year interval was not significantly different between the two groups. In 4 patients in whom both types of sites were present, no difference in progression was found. Data were similar for patients and sites studied over >1 year. *Conclusions* PEDD does not accelerate the progression of TxCAD within the first few years after cardiac transplantation. The pathophysiology of TxCAD is most likely immune mediated and does not seem to be accelerated by native coronary artery disease.

**Key Words:** transplantation ■ coronary disease ■ ultrasonics

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**C**ardiac allograft vasculopathy is a unique form of coronary artery disease that is now the primary factor limiting long-term survival of heart transplant recipients.<sup>1 2 3 4 5</sup> The pathogenesis of this vasculopathy is not fully understood, but the presence of “disease” by angiography and intravascular ultrasound has been associated with hyperlipidemia, obesity, hypertension, and donor age.<sup>6 7 8 9 10 11 12</sup> The pathogenic relation between donor age and subsequent development of graft vasculopathy is unclear, but it might be expected to be associated with preexisting coronary artery disease in the older donor. Because of the shortage of organ donors compared with the number of patients awaiting transplantation, the question of accepting older donors with possible native coronary disease is an important issue.

Cardiac transplant recipients undergo a baseline coronary angiogram before hospital discharge and return annually for follow-up studies for surveillance for coronary vasculopathy at Stanford University and many other institutions. Since 1990, we have included intracoronary ultrasound (ICUS) as part of this surveillance. This technique is more sensitive than angiography for observation of early allograft vasculopathy,<sup>13</sup> and it has suggested a prevalence of approximately 20% for preexistent coronary artery lesions among donors<sup>14</sup> (Fig 1). The objective of this study was to examine the effect of preexistent coronary artery lesions in the donor heart on the subsequent progression of cardiac allograft vasculopathy as assessed annually by intravascular ultrasound and angiography.

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## **METHODS**

### **Patient Population**

ICUS data were obtained usually within 3 weeks of transplantation and before initial hospital discharge in 66 patients. At least one follow-up ICUS imaging study was available in 35 of these patients. This study includes 30 of the 35 patients who underwent at least one annual serial follow-up study and had at least one coronary imaging site correctly replicated in both studies (see below). The left anterior descending artery was studied in all 30 cases; the circumflex artery also was imaged in 2 cases.

The Table summarizes the clinical data of transplant recipients and donors. The recipient population included 24 men and 6 women with a mean age of  $52.2 \pm 9.4$  years at the time of the baseline study. Patients received a triple maintenance regimen for immunosuppression combining cyclosporine, azathioprine, and prednisone. Information regarding donor hearts was obtained through

a review of charts and data provided by our transplant registry. Donors typically were young and died of unanticipated causes. The mean age of the donor heart was  $29.2 \pm 9.2$  years (22 men, 8 women).

The study protocol was approved by the Committee for the Protection of Human Subjects in Research at Stanford University Medical Center, and written informed consent was obtained from all subjects before inclusion in this study.

### **Ultrasound Imaging Procedure and Analysis**

Intravascular ultrasound imaging was done with a 30-MHz ultrasound transducer and rotating mirror system enclosed within an acoustic housing at the tip of either a 5F or a 4.3F rapid exchange catheter (Cardiovascular Imaging Systems Inc). Intracoronary nitroglycerin (200  $\mu$ g) or sublingual nitroglycerin (0.4 mg) was given before ultrasound imaging to prevent vasospasm and to minimize variations in the vessel tone. After the patients were anticoagulated with heparin, the imaging catheter was introduced through a guiding catheter over a 0.014-in coronary guide wire. The left main coronary artery, proximal and middle portions of the left anterior descending artery, or the circumflex artery was imaged. Coronary segments  $< 2$  mm in diameter were avoided. During the baseline study, several distinct arterial sites per patient were selected for precise ultrasound measurements (Fig 1). If intimal thickening was detected in the artery, the most severe thickening within that segment was selected for measurement. Several other nondiseased segments that were an equal distance apart also were recorded for measurements. If no disease was detected in the artery, three to four segments that were an equal distance apart were selected. Both ICUS and concomitant angiography of these sites were obtained on sequential annual studies.

The technique for replication of the imaging sites was reviewed in detail recently.<sup>15</sup> In brief, the projection that best showed the artery to be studied with the least foreshortening and vessel overlap was chosen at the time of the first study. The height of the image intensifier and the C-arm angles were noted in the patient record so that this angulation could be duplicated in subsequent studies. A drawing and a video hard copy of the angiogram in this specific projection were obtained. The position of the radiopaque transducer in relation to the side branches visualized at the time of concomitant angiography was then filmed and marked in the drawing and hard copy for future reference. Imaging of the same sites on subsequent examinations was done according to the notes, drawing, and photos obtained in the initial examination and a review of the cineangiogram. Each coronary site was again imaged simultaneously with ultrasound and contrast angiography on each follow-up study. Accuracy of matching of the imaging sites was then determined off-line for each site with side-by-side comparison of the follow-up and baseline angiograms. One to four sites were studied per patient, but only sites that matched in subsequent evaluations were analyzed.

Ultrasound studies were recorded on 0.5-in videotape and analyzed off-line. Gain settings were adjusted for optimal visualization of the vessel-lumen interface, and the images were digitized. The frame with the largest lumen from the cardiac cycle immediately before the contrast injection was selected for measurement. Measurements included the luminal cross-sectional area (LA) and, if intimal thickening was present, the total cross-sectional area (TA) or area within the media layer (Fig 2). The values were entered into a customized database that calculated a mean intimal thickness (MIT) from the difference between TA and LA. Also, an intimal index, a measure of plaque area, was calculated ( $II=TA-LA/TA$ ). We

previously showed good reproducibility and low interobserver and intraobserver variabilities for the above-mentioned intravascular parameters.<sup>16</sup>

To further categorize the degree of coronary disease, all segments studied were classified according to both the severity of intimal thickening and the degree of circumferential involvement as previously described<sup>13</sup> (Fig 2). The following definitions were applied: class 0 (none), no evidence of an intimal layer by ultrasound and a homogeneous wall; class 1 (minimal), intimal layer <300 µm thick involving <180° of the vessel circumference; class 2 (mild), intimal layer <300 µm thick involving >180° of the vessel circumference; class 3 (moderate), intimal layer 300 to 500 µm thick but involving <180° of the vessel circumference or >500 µm thick at any point of the vessel cross section; and class 4 (severe), intimal layer >500 µm thick involving >180° of the vessel circumference or >1 mm at any point of the vessel cross section.

For the purpose of this analysis and according to previous pathological studies, class 3 or 4 coronary intimal thickening was considered significant<sup>17 18</sup> and was considered to represent preexistent donor disease if encountered in the baseline posttransplantation study.

## **Coronary Angiography**

Coronary angiography was performed with the percutaneous femoral approach and standard angiographic techniques. Multiple projections of both the right and left coronary systems were obtained after nitroglycerin premedication and duplicated in the follow-up studies. Interpretation of serial cinefilms was based on side-by-side comparisons with two projectors. Coronary artery disease was classified as mild (<30% luminal stenosis), moderate (31% to 69%

luminal stenosis), or severe (>70% luminal stenosis or diffuse pruning of distal vessels).

## **Statistical Analysis**

All data are expressed as mean±SD for continuous variables and as percentages for discrete variables. Comparisons between groups were determined by the  $\chi^2$  test for differences in proportions and by Student's *t* test or ANOVA for differences in means. A two-sided value of  $P<.05$  was considered statistically significant.

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## **RESULTS**

High-resolution ultrasound images were obtained without complication in all patients. Thirty patients had two studies separated by 1 year, 17 patients had three, and 4 patients had four in which at least one coronary site was correctly matched in each study. The results of intimal thickening progression as evaluated by intravascular ultrasound are presented per individual site and per patient. For individual patient analysis, the quantitative ultrasound parameters of all sites for that patient were averaged, but the semiquantitative classification representative of the most severe site was recorded.

## **Prevalence and Clinical Correlates of Donor Coronary Artery Disease**

Significant intimal thickening (class 3 or 4) by intravascular ultrasound was present in 19 of the 66 patients (28.8%) constituting the full cohort of patients studied early after transplantation. Of the 30 patients with serial studies, 9 (29%) had at least one coronary site with class 3 or 4 intimal thickening in the baseline study (29%) (see the Table). These 30 patients yielded 77 intracoronary sites (2.6 sites

per patient) for image analysis. Of these 77 sites, 15 (19.5%) had significant disease by intravascular ultrasound.

At the baseline study, 28 of the 30 patients had completely normal angiograms. Two patients (patients 19 and 24 in the Table) had mild disease (<30% diameter stenosis), although the left anterior descending artery was affected in only 1 patient. Both patients had significant intimal thickening by intravascular ultrasound.

Information regarding donor hearts was obtained by a review of charts and data provided by the Stanford transplant registry. Several differences were noted between donors with and without coronary artery disease detectable by intravascular ultrasound (the Table). Allografts with coronary artery disease came from older donors. The mean donor age of the nine allografts with preexistent disease was  $37.4 \pm 6.2$  versus  $25.6 \pm 8$  years for the 21 allografts without baseline disease ( $P < .001$ ). All allografts with preexistent disease came from patients >29 years of age (the Table). Of the 9 allografts with preexistent coronary disease, 8 came from male donors. The prevalence of coronary disease in allografts from male and female donors was 36% (8 of 22) and 12.5% (1 of 8), respectively ( $P = \text{NS}$ ).

There was a significant association between the presence of known risk factors for coronary disease in the donors and the existence of coronary lesions. Smoking, arterial hypertension, or family history of coronary heart disease was present in 7 of the 9 donors (77%) whose hearts had ultrasound evidence of preexistent disease. The process was present in only 4 of the 21 donors (19%) without risk factors ( $P < .01$ ).

No differences were found in the duration of ischemia time during transplantation of allografts with and without preexistent coronary disease ( $160 \pm 21$  versus  $165 \pm 50$  minutes, respectively,  $P = \text{NS}$ ). The age of the recipients at the time of transplantation also was not



different in the two groups ( $55.2\pm 8$  versus  $50.9\pm 9.8$  years for recipients of allografts with and without preexistent coronary disease, respectively,  $P=NS$ ).

## **Intravascular Ultrasound Measurements**

***Patients and Sites With One Follow-up Evaluation*** MIT and II were calculated per patient, taking the average of the measurements of all lesions in each patient. At baseline for the total cohort of 30 patients, MIT was  $0.10\pm 0.12$  mm, II was  $0.09\pm 0.10$ , and class was  $1.6\pm 1.1$ . Nine patients (29%) had donor disease and, by definition, a higher MIT, II, and Stanford class than the 21 patients without donor disease (Fig 3). At the 1-year follow-up study, the intimal thickening increased in both groups. Patients with donor disease still had significantly more severe disease than patients without donor disease as measured by MIT, II, and Stanford class (all  $P<.001$ , Fig 3). Although the intima was thicker at the follow-up study in patients with preexistent donor disease, the increase in intimal thickness over this 1-year interval was not significantly different between groups (Fig 4).

The per-site analysis yielded similar findings. Seventy-seven coronary sites were studied twice in this group of 30 patients (2.6 sites per patient). Fifteen sites (19.5%) were considered to have donor disease. At baseline examination, by definition, they had a higher MIT ( $0.33\pm 0.09$  versus  $0.04\pm 0.06$  mm), II ( $0.28\pm 0.09$  versus  $0.04\pm 0.06$ ), and class ( $3.1\pm 0.3$  versus  $0.7\pm 0.7$ ) than the 62 sites without donor disease (all  $P<.001$ ). At the 1-year follow-up study, sites with donor disease still had significantly more disease than sites without donor disease. For sites with and without donor disease, MIT was  $0.38\pm 0.20$  versus  $0.14\pm 0.13$  mm, II was  $0.31\pm 0.16$  versus  $0.12\pm 0.11$ , and class was  $3.3\pm 0.96$  versus  $1.8\pm 0.10$  (all  $P<.001$ ), respectively. However, although ultrasound parameters were still

more severe at the follow-up study in sites with preexistent donor disease, the increase ( $\Delta$ ) in MIT and II was not significantly different between groups. For sites with and without donor disease,  $\Delta$ MIT was  $0.05\pm 0.18$  versus  $0.09\pm 0.14$  mm ( $P=NS$ ),  $\Delta$ II was  $0.04\pm 0.14$  versus  $0.08\pm 0.12$  ( $P=NS$ ), and  $\Delta$ class was  $0.2\pm 0.9$  versus  $1.0\pm 1.2$  ( $P<.05$ ), respectively.

### ***Patients and Sites With Two or More Follow-up Evaluations***

Seventeen patients underwent three evaluations. At the time of the initial study, the average MIT was  $0.11\pm 0.14$  mm, II was  $0.10\pm 0.12$ , and class was  $1.4\pm 1.2$ . Over the 2-year period, there was a significant increase in each ultrasound parameter of intimal thickening ( $P<.01$ ). On the second and third evaluations, the average MIT increased to  $0.18\pm 0.18$  and  $0.24\pm 0.2$  mm, the II to  $0.15\pm 0.15$  and  $0.18\pm 0.14$ , and class to  $2.2\pm 1.3$  and  $2.5\pm 1.5$ , respectively.

Of these 17 patients, 5 (29%) had donor disease. Accordingly, they had at baseline a higher MIT ( $0.31\pm 0.06$  versus  $0.03\pm 0.05$  mm), II ( $0.26\pm 0.05$  versus  $0.03\pm 0.04$ ), and class ( $3\pm 0$  versus  $0.7\pm 0.7$ ) than the 12 patients without donor disease (all  $P<.001$ ). At the time of the third evaluation, 2 years after the baseline study, patients with donor disease still had significantly more disease than patients without donor disease ( $P=.05$ , Fig 5). Although the disease was more severe at the 2-year follow-up study in patients with preexistent donor disease, the interval increase in intimal thickness was not significantly different between groups (Fig 4).

Coronary artery disease progression was also analyzed on a per-site basis. Of the 36 sites studied three times in this group of 17 patients (2.1 sites per patient), 8 (22%) were considered to have donor disease. By definition, at baseline examination they had a higher MIT ( $0.37\pm 0.08$  versus  $0.05\pm 0.07$  mm), II ( $0.31\pm 0.08$  versus  $0.05\pm 0.06$ ), and class ( $3\pm 0$  versus  $0.7\pm 0.8$ ) than the 28 sites without

donor disease (all  $P<.001$ ). Two years later, sites with donor disease still had significantly more disease than patients without donor disease. For sites with and without donor disease, MIT was  $0.43\pm0.26$  versus  $0.21\pm0.22$  mm, II was  $0.31\pm0.15$  versus  $0.15\pm0.15$ , and class was  $3.5\pm0.53$  versus  $2.0\pm1.4$  (all  $P<.05$ ), respectively. Again, although the disease was more severe at the end of follow-up study in sites with preexistent donor disease, the increase in intimal thickness over this 2-year period was not significantly different between groups. For sites with and without donor disease,  $\Delta$ MIT was  $0.06\pm0.26$  versus  $0.16\pm0.23$  mm,  $\Delta$ II was  $0.01\pm0.16$  versus  $0.11\pm0.16$ , and  $\Delta$ class  $0.5\pm0.53$  versus  $1.3\pm1.7$  ( $P=NS$ ), respectively.

### **Follow-up Angiography**

At the time of the last intravascular ultrasound and angiographic evaluation, only 3 patients (patients 10, 19, and 24 in the Table) had angiographic evidence of coronary artery disease. Two patients (patients 19 and 24) already had evidence of mild coronary disease when evaluated immediately after transplantation. In 2 patients (patients 10 and 19), only mild lesions (<30%) were noted, and in 1 patient (patient 10), the lesions involved the left anterior descending artery (the vessel evaluated by ultrasound). One patient (patient 24) developed moderate disease in the right coronary artery, but the left anterior descending artery had only mild disease by angiographic assessment.

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## **DISCUSSION**

The purpose of this study was to analyze the prevalence and clinical precursors of preexistent donor coronary artery disease and, most importantly, to assess the influence of preexistent donor coronary disease on the subsequent development and progression of transplant coronary vasculopathy. Although several studies showed a

relation between older donor age and the subsequent development of allograft vasculopathy, the mechanism of this association remains unclear.<sup>6 7 11 19</sup> Although intuitively one might suspect preexistent coronary disease to be responsible for this association, no data support or refute this hypothesis. We previously reported that a substantial proportion (20%) of a small series of transplant recipients studied with intravascular ultrasound soon after transplantation had focal intimal thickening and that this finding seems related to the presence of coronary risk factors in the donor.<sup>14</sup> Those 25 patients previously reported are included in the 66 patients whose baseline studies are included here.

The present study demonstrates that allografts from older donors and donors with recognized cardiac risk factors have evidence of early coronary atherosclerosis. The presence of the disease is not detectable by contrast angiography but is evident by the more sensitive intravascular ultrasound technique.<sup>13</sup> This study demonstrates that patients receiving allografts with preexistent donor disease had more intimal thickening 1 and 2 years after the operation than patients who received grafts that were normal by ultrasound examination. This was by virtue of the preexistent disease. Preexistent donor coronary artery disease, however, is not a trigger for the accelerated development of coronary vasculopathy subsequently. The progression of intimal thickening at specific sites within the coronary arteries was not statistically significant between the two groups of patients. Four patients had sites with and sites without significant disease in the same vessel at the baseline study. No significant difference was noted for the change of intimal thickness over the 1-year period between sites with and without donor disease. Therefore, the data suggest that preexisting donor coronary disease

does not provide the nidus for or potentiate transplant vasculopathy by any method of analysis.

Numerous advances in cardiac surgery, immunology, and antimicrobial therapy have permitted both long-term patient survival after cardiac transplantation and the widespread use of this procedure. Cardiac allograft vasculopathy is a unique form of coronary artery disease that is now the primary factor limiting long-term patient survival and the main reason for retransplantation.<sup>1 2 3 4 5</sup> Our group and others reported that up to 50% of patients have evidence of vascular disease on coronary angiography by 5 years after transplantation.<sup>6 20 21</sup> Importantly, the presence of angiographically detectable disease is associated with both graft failure and poor prognosis.<sup>20 22 23</sup> Little is known about the etiology of transplant coronary disease. It is believed to be an immune-mediated process primarily because the disease is limited to the vascular bed of the allograft and the vessels are diffusely affected.<sup>20 24 25 26</sup> However, clinical studies assessing the relation of cellular rejection and transplant coronary disease yielded conflicting, usually negative, results.<sup>2 6 7 20 27 28 29 30 31 32</sup> Moreover, different immunosuppressive protocols were shown not to decrease the incidence or severity of transplant coronary artery disease.<sup>20 21 30</sup> Some conventional risk factors for native coronary artery disease also were associated with the development of allograft vasculopathy. In particular, hyperlipidemia, obesity, and older donor age have been related to transplant coronary artery disease.<sup>6 7 8 9 10 11 18</sup>

Previous studies demonstrated intravascular ultrasound is more sensitive than contrast angiography for diagnosis of the early stages of coronary disease.<sup>13 14</sup> Although coronary angiograms may be normal immediately after transplantation,<sup>20 22</sup> our study has demonstrated that transplanted preexistent coronary artery disease

is common. The incidence of preexisting transplant coronary diseases varies from 30% to 50%,<sup>33</sup> depending on the ultrasound criteria. These baseline studies were performed within a few weeks after transplantation, as soon as the patient was stable enough to undergo cardiac catheterization; therefore, it is unlikely that significant vasculopathy developed in the postoperative period. Because there is a striking association between older donor age and the presence of coronary risk factors and the existence of intimal thickening on the pre-discharge examination by ultrasound, these data strongly suggest that the areas of focal intimal thickening observed in the baseline examination indeed represent transplanted preexistent disease.

The mechanism by which an older donor age predisposes to the subsequent development of transplant coronary disease, as shown by previous angiographic studies, is unclear.<sup>6 7 11 12</sup> This study shows that, 2 years after transplantation, the degree of intimal thickening in allografts with preexistent donor disease is higher than in allografts without donor disease (Fig 5). However, progression of the disease was not accelerated by the presence of donor disease (Fig 4). Whether the data were analyzed per patient to provide more meaningful information from a clinical point of view or per site to provide more pathophysiological information on the influence of focal donor disease, the results were not different. Patients with preexistent donor disease have a higher degree of intimal thickening 2 years after transplantation not because they progress more but because they started at a higher level.

These data suggest that preexistent early native coronary artery lesions in the donor heart do not trigger the development of transplant vasculopathy. However, because sites with donor disease still are more heavily diseased 2 years after transplantation than sites without donor disease, the long-term clinical implications are uncertain.

Interestingly, all patients with angiographically detectable coronary disease at the end of the follow-up had evidence of donor disease at the baseline examination as detected by intravascular ultrasound.

## **Study Limitations**

This study concentrated only on the effect of preexistent coronary artery disease in the donor heart as a predictor of progressive disease and did not analyze all the other factors potentially affecting the process of vasculopathy in these patients. Patients have not been treated differently at this institution on the basis of the presence or absence of donor coronary artery disease. These data were analyzed for each patient on the assumption that clinical and laboratory factors in a given patient might affect all lesions in the heart. Thus, data were averaged from all sites for a given patient. However, the specific question of whether sites with preexistent lesions progressed more rapidly led to expression of the data for all sites as well. Although the sites may not be data points independent of each other, the results seem the same whether analyzed by patient or by site.

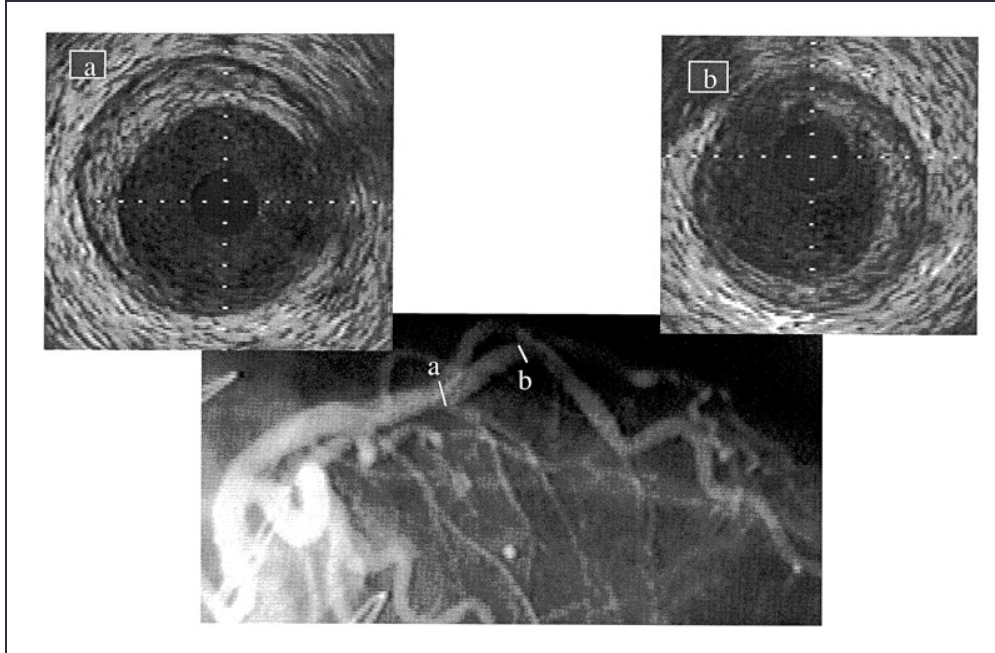
The potential limitation of correct location of the same site on serial studies of this type has been a concern of this research group and has been investigated. A rigorous procedure for duplication of angiographic projection, vessel segment studied, and imaging sites studied within the vessel was used in this study.<sup>15 34</sup> Our reproducibility studies showed that, if the sites are not matched by ultrasound and angiography, the SD of the difference is approximately 12%. If the sites are well matched, the SD of the difference is only 6%. The matching process requires meticulous review of the reference ultrasound tapes and angiograms before the follow-up studies, followed by verification of the positions after the procedure.

About 20% to 30% of the sites are discarded after this matching analysis. The difference in absolute measurements between the groups with or without preexisting donor disease in this study greatly exceeds the SD of the difference and therefore should not affect the conclusions drawn.

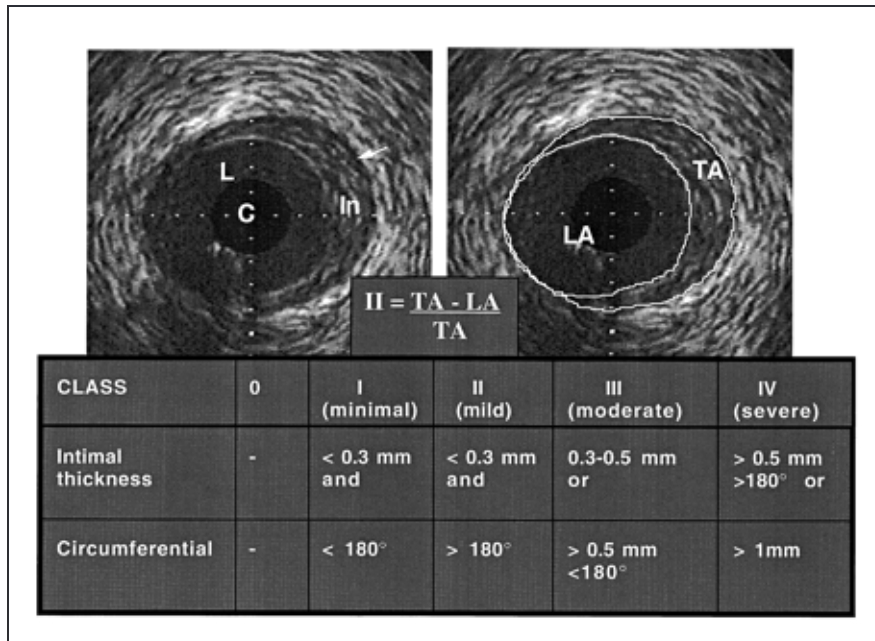
However, given that the progression in intimal thickness is not different between the two groups, ie, a negative finding, the power of these analyses needs to be addressed. The power of these analyses varies from 0.5 to 0.9, depending on the parameters (MIT, II, or class) used. The group without preexisting disease tends to progress even more at year 2 (Fig 4). Therefore, the conclusion that patients or sites with preexisting donor disease do not progress more is probably valid. However, a larger sample size (on the order of hundreds of patients) is needed to validate this conclusion.<sup>35</sup>

The detection of early intimal thickening and coronary atheroma formation is limited by the resolution of the imaging method used to enable visual appreciation of the process. Prior studies suggested that the intracoronary ultrasonic imaging system used in this study shows a pattern definable as intimal thickening when the intima is  $\geq 178 \mu\text{m}$  thick.<sup>17</sup> In the current series, the visible lesions on the baseline studies did not progress more than those areas without visible lesions. It is possible that sites without baseline lesions actually progressed more than those sites with visible donor disease, but we could not tell this because of the resolution on the imaging system. Nevertheless, the conclusions reached from the current data, namely that donor disease does not predispose to more rapid progression of transplant vasculopathy, would not be altered by that finding.

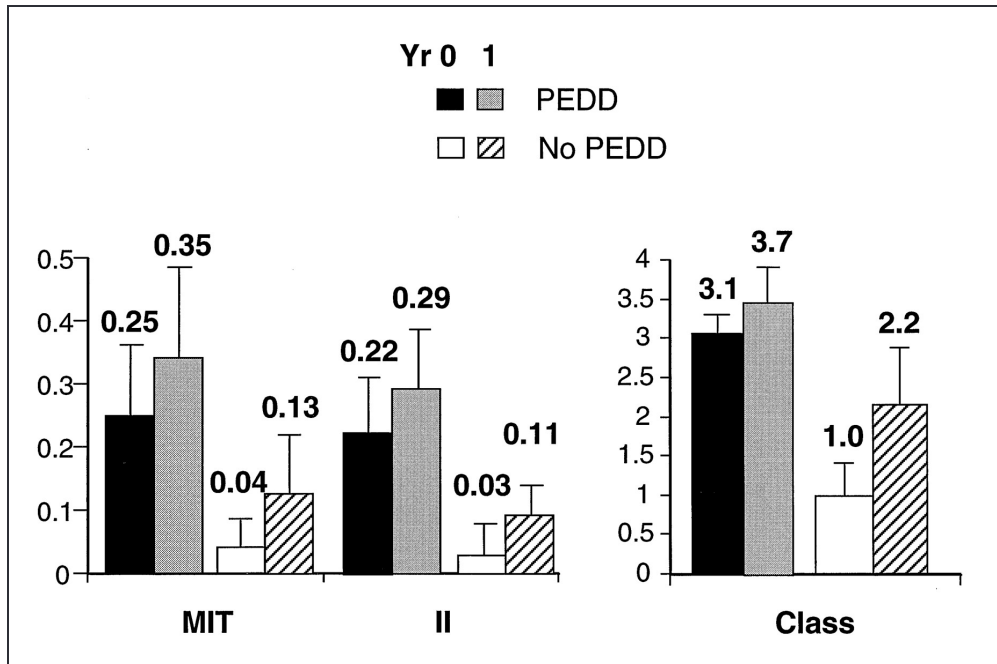




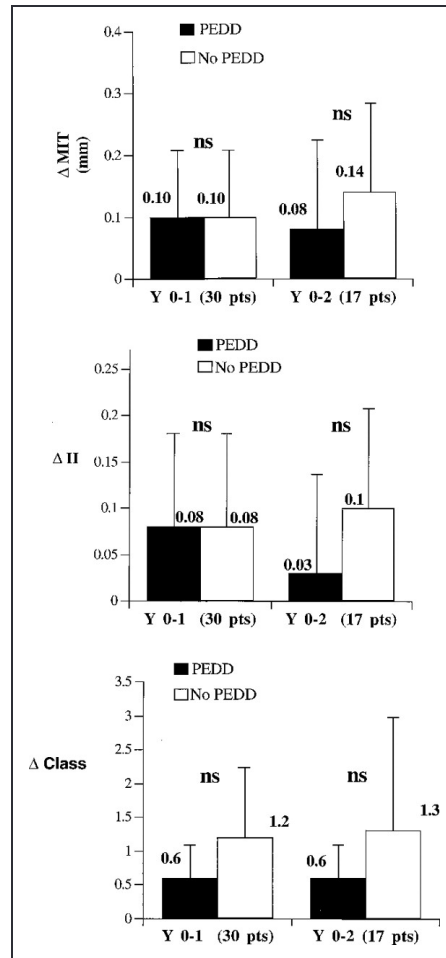
**Figure 1.** Intracoronary ultrasound images (top) and contrast coronary arteriogram (bottom) of the left anterior descending vessel at sites (a and b) in a cardiac allograft studied within 3 weeks of cardiac transplantation. The arteriogram shows apparently normal vessels. In the ultrasound images, the black circle at the intersection of the calibration grid (0.5 mm per division) represents the imaging catheter. The dark gray, nearly circular area 0.5 to 2.5 mm beyond the catheter represents the blood-filled lumen of the vessel. The eccentric lighter gray area bordering the lumen, from 8 to 2 o'clock (a) and from 11 to 8 o'clock (b), represents thickening of the intimal layer of the vessel wall. The boundary of the medial layer is represented by the nearly black ring just beyond the intima. This is considered preexistent disease in the donor heart.



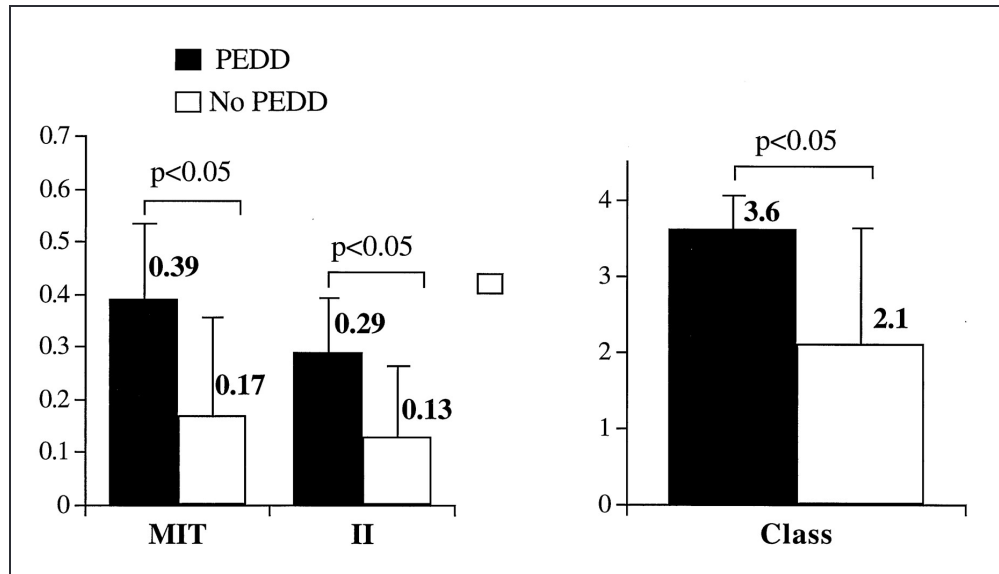
**Figure 2.** Classification of coronary artery disease by intracoronary ultrasound images. The black circle at the intersection of the calibration grid (0.5 mm per division) represents the imaging catheter (C, left). The dark gray, nearly circular area (L, left; inner white circular line, right) 1.0 to 2.0 mm beyond the catheter represents the blood-filled lumen of the vessel or luminal area (LA). The lighter gray area between the irregular white circles (right) represents the eccentric thickening of the intimal layer of the vessel wall (In, left). The boundary of the medial layer is represented by the nearly black ring (arrow, left). The formula illustrates the method for measuring the index of intimal thickening (II) obtained by dividing the difference of the total area (TA=LA+intimal areas) minus luminal area (LA) by the total area. Each site was classified according to the intimal thickness and circumferential extent of thickening (see text for details).



**Figure 3.** Bar graphs showing intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the baseline predischarge and 1-year studies in the patients with (n=9) and without (n=21) preexistent donor disease (PEDD) as defined in the text. Those with PEDD had significantly more intimal thickening than those without at both predischarge and 1-year studies.



**Figure 4.** Bar graphs showing the change ( $\Delta$ ) in intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the study 1 year (Y 0-1) and 2 years (Y 0-2) after transplantation in the patients (pts) with (solid bars) and without (open bars) preexistent donor disease (PEDD). Patients transplanted with allografts having preexistent coronary artery lesions did not develop more, or accelerated, intimal vasculopathy compared with those patients without preexistent disease.



**Figure 5.** Bar graphs showing intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the study 2 years after transplantation in patients with (solid bars, n=5) and without (open bars, n=12) preexistent donor disease (PEDD) as defined in the text. Those with preexistent donor disease still had significantly more intimal thickening than those without preexistent disease.

**Table 1.** Clinical and Intravascular Ultrasound Baseline Data ([Table view](#))

Patient	Donor Age, y	Donor Sex	Recipient Age, y	Recipient Sex	Cardiac Risks Factors	Vessel Studied	Ischemic Time, s	Mean Intimal Thickness, mm	Me Int Inc
1	32	M	60	M		LAD	194	0.09	0.1
2	17	M	58	M		LAD	265	NM	NM
3	17	M	55	M		LAD	155	0.09	0.0
4	32	F	51	F		LAD	122	NM	NM
5	23	M	24	M		LAD	132	NM	NM
6	46	M	61	M	Tob	LAD	177	0.14	0.1
7	23	M	44	M	Tob	LAD	157	0.11	0.1
8	34	M	47	F		LAD	123	0.02	0.0
9	25	M	48	M		Cx	198	0.12	0.1
10	43	M	42	M	Tob	LAD	145	0.37	0.3
11	19	F	40	M	Tob	LAD	194	NM	NM
12	21	M	60	M		LAD	135	NM	NM
13	18	M	54	M		LAD	87	NM	NM

Patient	Donor Age, y	Donor Sex	Recipient Age, y	Recipient Sex	Cardiac Risks Factors	Vessel Studied	Ischemic Time, s	Mean Intimal Thickness, mm	Me Int Inc
14	32	M	61	F		LAD	117	NM	NM
15	38	M	52	M	HTN	LAD	172	0.18	0.2
16	35	F	44	M		LAD	185	0.14	0.0
17	28	F	50	M		LAD	142	NM	NM
18	17	M	36	M		LAD	161	NM	NM
19	43	M	55	M	FHx	Cx	158	0.37	0.3
20	20	M	47	M	Tob	LAD	268	0.08	0.0
21	15	F	53	F		LAD	204	0.08	0.0
22	39	M	54	M		LAD	147	NM	NM
23	35	M	70	M	Tob	LAD	131	0.27	0.2
24	29	M	49	M	Tob	LAD	132	0.30	0.2
25	19	F	56	F		LAD	88	NM	NM
26	30	F	64	M	Tob	LAD	194	0.11	0.1
27	30	F	51	F	HTN	LAD	164	0.23	0.2
28	41	M	57	M		LAD	168	0.10	0.0
29	40	M	66	M		LAD	220	NM	NM
30	34	M	57	M		LAD	172	NM	NM

Ischemic time indicates the period of ischemia during transplantation; LAD, left anterior descending artery; NM, not measured; Tob, history of smoking; Cx, circumflex artery; HTN, history of hypertension; and FHx, family history of coronary disease.

## ARTICLE INFORMATION

accepted 6 March 1995; Received 15 December 1994; revision received 2 March 1995.

## Correspondence

Correspondence to Alan C. Yeung, MD, Stanford University Medical Center, Division of Cardiovascular Medicine, 300 Pasteur Dr, Stanford, CA 94305.

## Affiliations

From the Division of Cardiovascular Medicine, Stanford (Calif) University School of Medicine.

## Acknowledgments

Dr Botas was supported in part by grant 92/5228 from the Fondo de Investigaciones Cientificas de la Seguridad Social and a grant from the Fundacion MAPFRE Medicina, Madrid, Spain. Dr

Pinto is the recipient of a Fellowship Award from the Fundação Calouste Gulbenkian (Lisbon, Portugal). Dr Chenzbraun was supported in part by the Israeli Heiden Fellowship, Jerusalem; by the American Physicians Fellowship, Brookline, Mass; and by the Mervin and Roslyn Morris Fellowship, Stanford, Calif. Dr Yeung is supported by NIH CIDA grant K08-HL-02787. This work was supported by the Butterway Fund, Stanford, Calif. We wish to thank Dr S.Z. Gao and Ann Schwartzkopf for angiographic data on these patients and Marcia Schreck for preparation of the manuscript.

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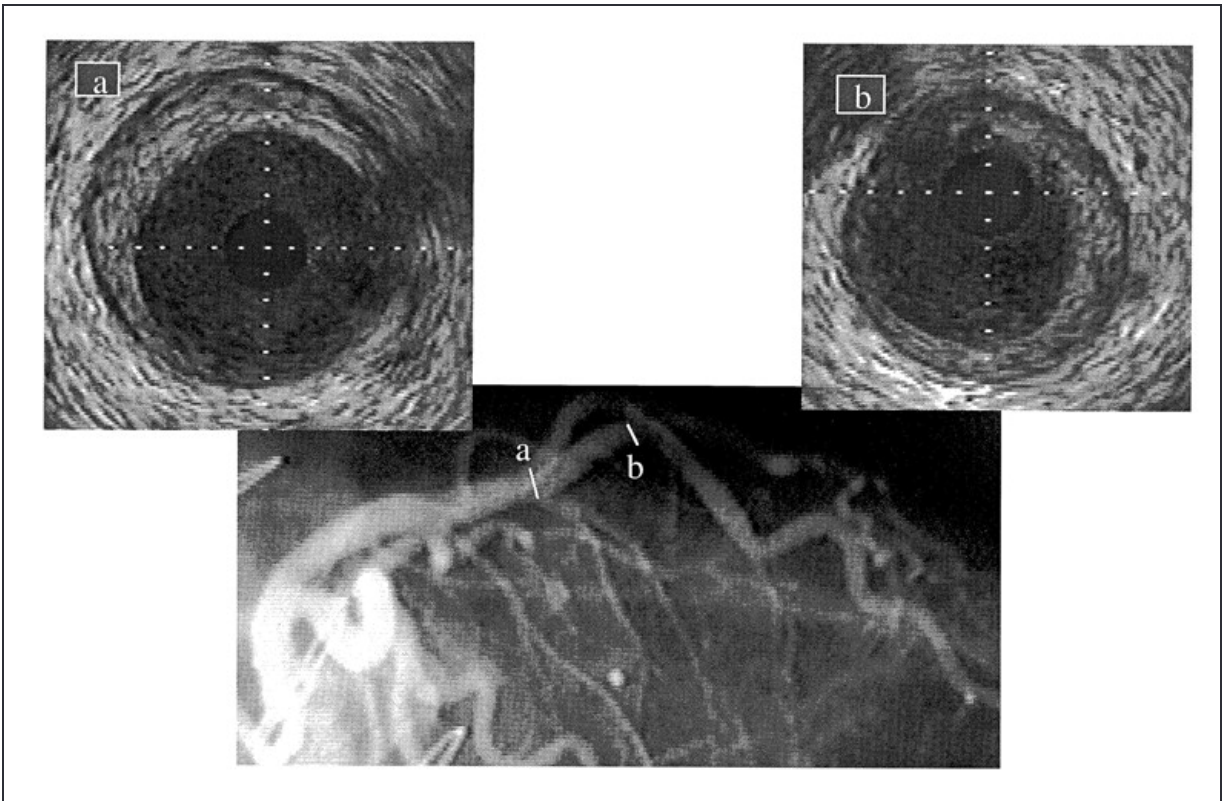
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# Sections

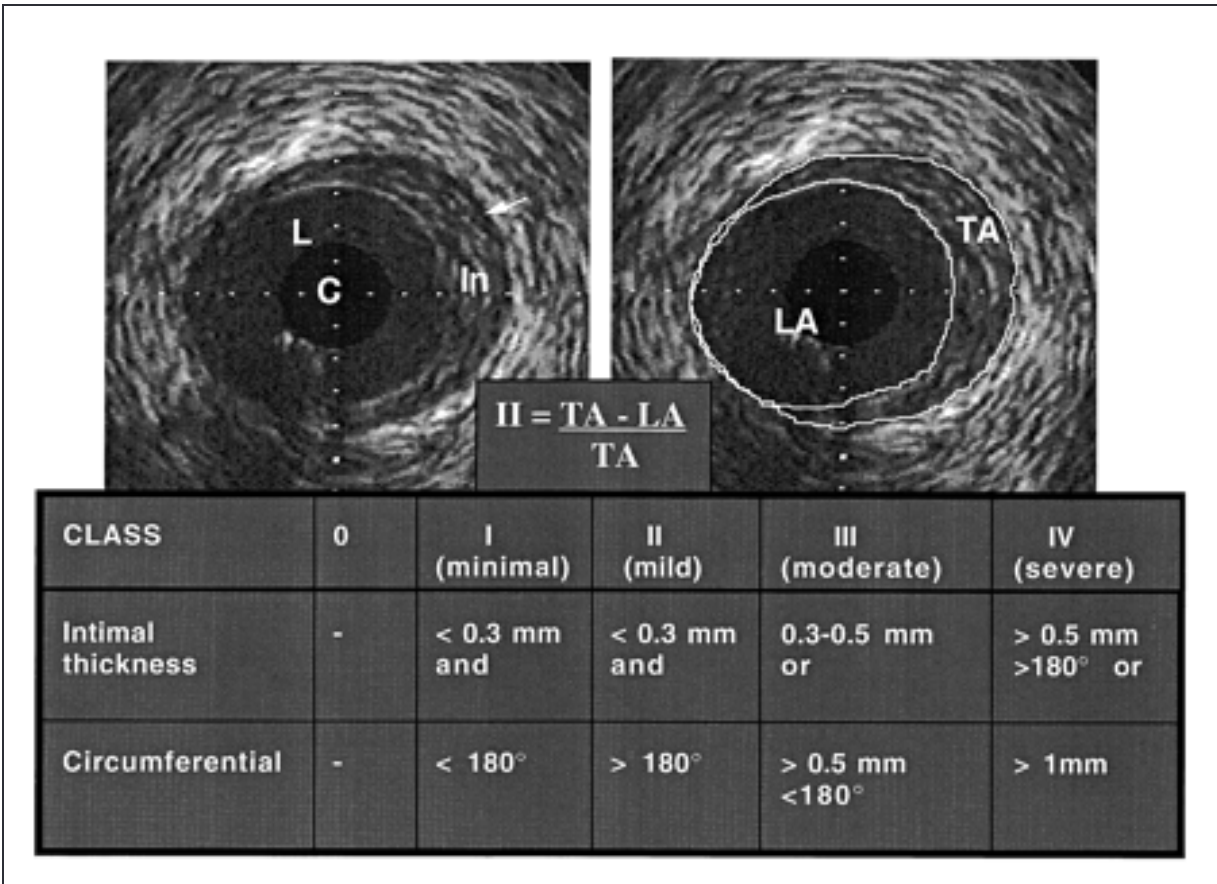
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3. Results
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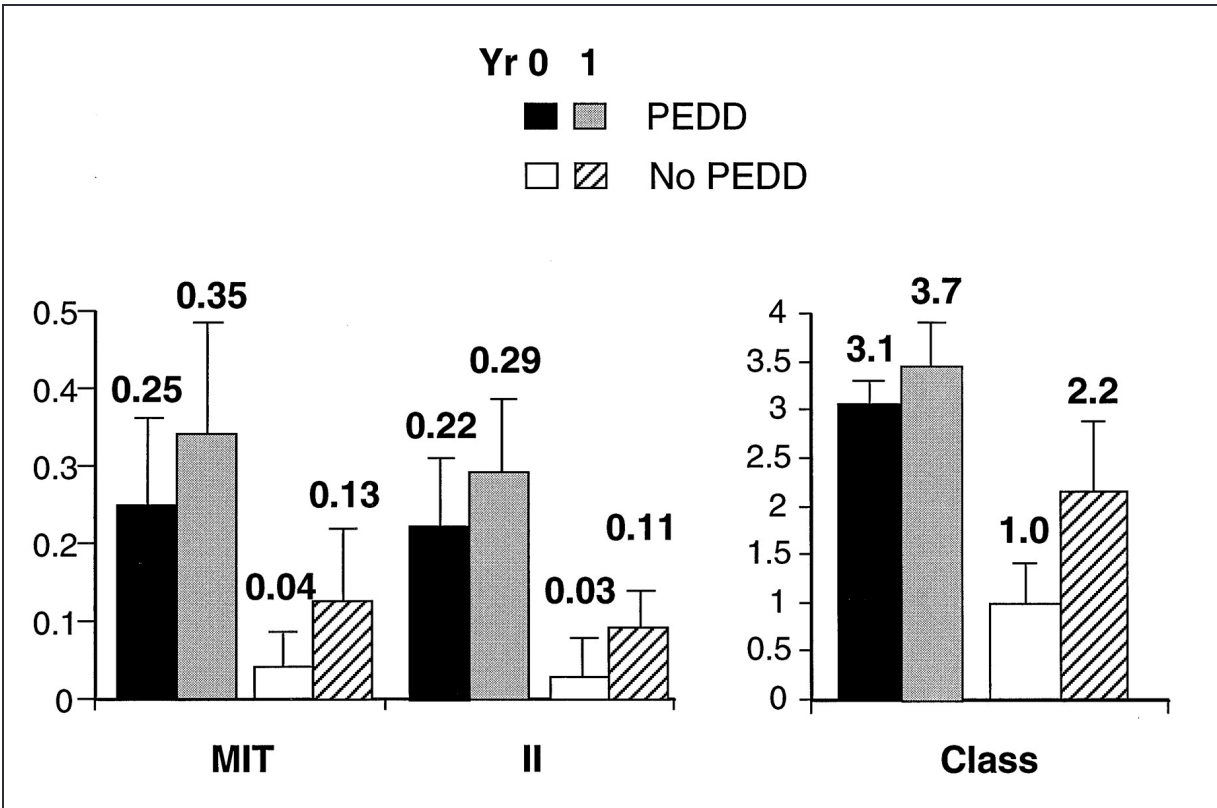
1. Figure 1.
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4. Figure 4.
5. Figure 5.



**Figure 1.** Intracoronary ultrasound images (top) and contrast coronary arteriogram (bottom) of the left anterior descending vessel at sites (a and b) in a cardiac allograft studied within 3 weeks of cardiac transplantation. The arteriogram shows apparently normal vessels. In the ultrasound images, the black circle at the intersection of the calibration grid (0.5 mm per division) represents the imaging catheter. The dark gray, nearly circular area 0.5 to 2.5 mm beyond the catheter represents the blood-filled lumen of the vessel. The eccentric lighter gray area bordering the lumen, from 8 to 2 o'clock (a) and from 11 to 8 o'clock (b), represents thickening of the intimal layer of the vessel wall. The boundary of the medial layer is represented by the nearly black ring just beyond the intima. This is considered preexistent disease in the donor heart.

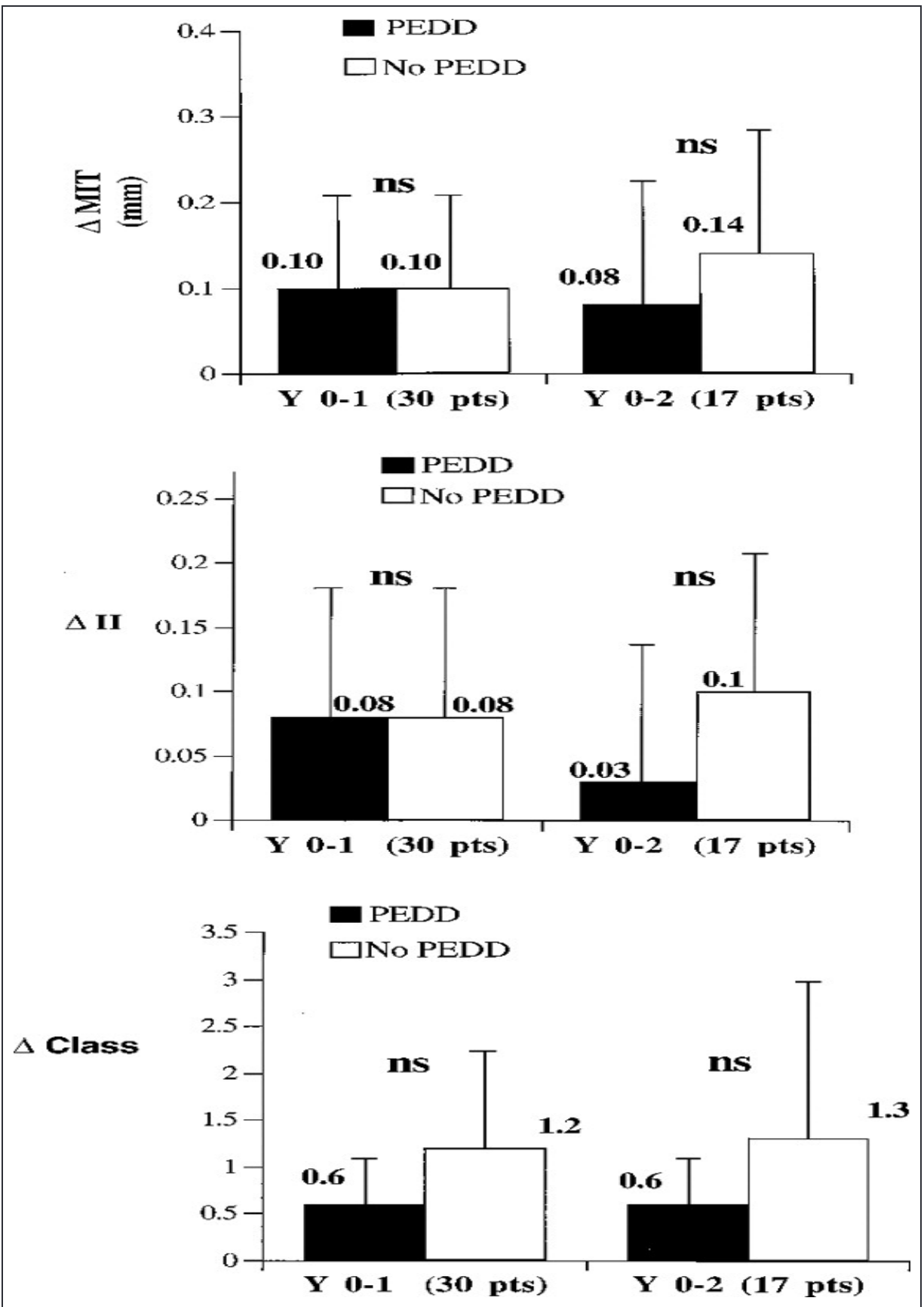


**Figure 2.** Classification of coronary artery disease by intracoronary ultrasound images. The black circle at the intersection of the calibration grid (0.5 mm per division) represents the imaging catheter (C, left). The dark gray, nearly circular area (L, left; inner white circular line, right) 1.0 to 2.0 mm beyond the catheter represents the blood-filled lumen of the vessel or luminal area (LA). The lighter gray area between the irregular white circles (right) represents the eccentric thickening of the intimal layer of the vessel wall (In, left). The boundary of the medial layer is represented by the nearly black ring (arrow, left). The formula illustrates the method for measuring the index of intimal thickening (II) obtained by dividing the difference of the total area (TA=LA+intimal areas) minus luminal area (LA) by the total area. Each site was classified according to the intimal thickness and circumferential extent of thickening (see text for details).



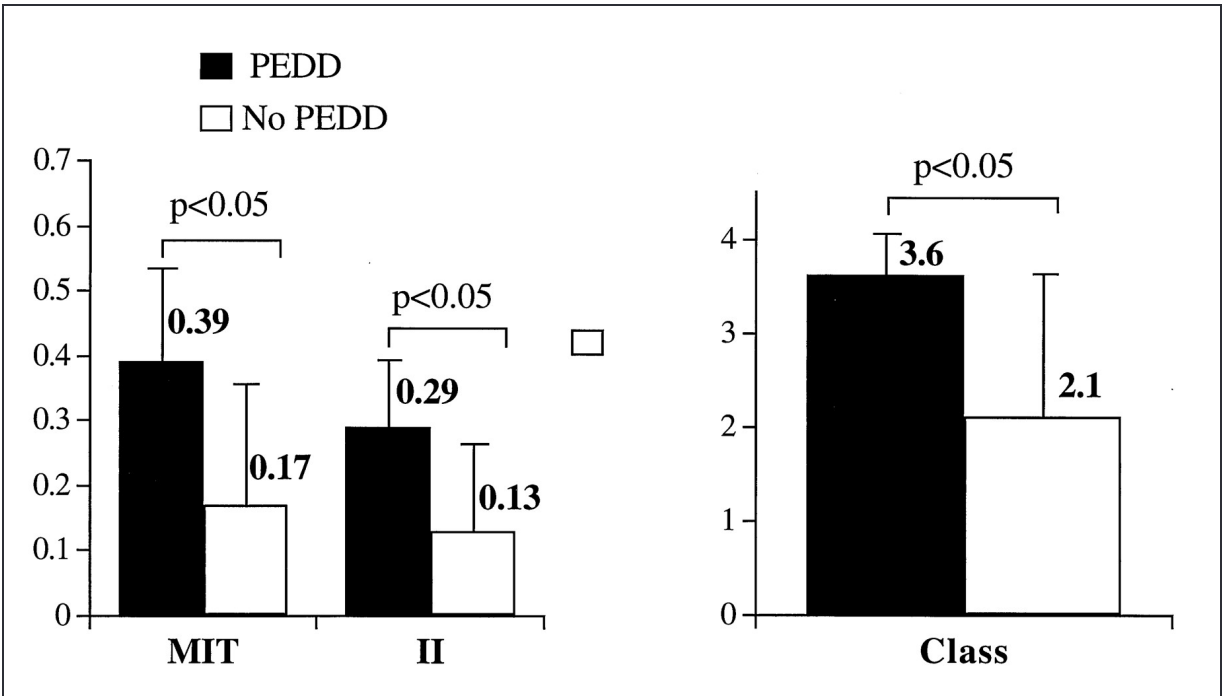
**Figure 3.** Bar graphs showing intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the baseline predischarge and 1-year studies in the patients with (n=9) and without (n=21) preexistent donor disease (PEDD) as defined in the text. Those with PEDD had significantly more intimal thickening than those without at both predischarge and 1-year studies.







**Figure 4.** Bar graphs showing the change ( $\Delta$ ) in intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the study 1 year (Y 0-1) and 2 years (Y 0-2) after transplantation in the patients (pts) with (solid bars) and without (open bars) preexistent donor disease (PEDD). Patients transplanted with allografts having preexistent coronary artery lesions did not develop more, or accelerated, intimal vasculopathy compared with those patients without preexistent disease.



**Figure 5.** Bar graphs showing intracoronary ultrasound parameters of mean intimal thickness (MIT), intimal index (II), and Stanford class at the study 2 years after transplantation in patients with (solid bars, n=5) and without (open bars, n=12) preexistent donor disease (PEDD) as defined in the text. Those with preexistent donor disease still had significantly more intimal thickening than those without preexistent disease.

**Table 1.** Clinical and Intravascular Ultrasound Baseline Data

Patient	Donor Age, y	Donor Sex	Recipient Age, y	Recipient Sex	Cardiac Risks Factors	Vessel Studied	Ischemic Time, s	Mean Intimal Thickness, mm	Me Int Inc
1	32	M	60	M		LAD	194	0.09	0.1
2	17	M	58	M		LAD	265	NM	NM
3	17	M	55	M		LAD	155	0.09	0.0
4	32	F	51	F		LAD	122	NM	NM
5	23	M	24	M		LAD	132	NM	NM
6	46	M	61	M	Tob	LAD	177	0.14	0.1
7	23	M	44	M	Tob	LAD	157	0.11	0.1
8	34	M	47	F		LAD	123	0.02	0.0
9	25	M	48	M		Cx	198	0.12	0.1
10	43	M	42	M	Tob	LAD	145	0.37	0.3
11	19	F	40	M	Tob	LAD	194	NM	NM
12	21	M	60	M		LAD	135	NM	NM
13	18	M	54	M		LAD	87	NM	NM
14	32	M	61	F		LAD	117	NM	NM
15	38	M	52	M	HTN	LAD	172	0.18	0.2
16	35	F	44	M		LAD	185	0.14	0.0
17	28	F	50	M		LAD	142	NM	NM
18	17	M	36	M		LAD	161	NM	NM
19	43	M	55	M	FHx	Cx	158	0.37	0.3
20	20	M	47	M	Tob	LAD	268	0.08	0.0
21	15	F	53	F		LAD	204	0.08	0.0
22	39	M	54	M		LAD	147	NM	NM
23	35	M	70	M	Tob	LAD	131	0.27	0.2
24	29	M	49	M	Tob	LAD	132	0.30	0.2
25	19	F	56	F		LAD	88	NM	NM
26	30	F	64	M	Tob	LAD	194	0.11	0.1
27	30	F	51	F	HTN	LAD	164	0.23	0.2
28	41	M	57	M		LAD	168	0.10	0.0
29	40	M	66	M		LAD	220	NM	NM

Patient	Donor Age, y	Donor Sex	Recipient Age, y	Recipient Sex	Cardiac Risks Factors	Vessel Studied	Ischemic Time, s	Mean Intimal Thickness, mm	Me Int
30	34	M	57	M		LAD	172	NM	NM

Ischemic time indicates the period of ischemia during transplantation; LAD, left anterior descending artery; NM, not measured; Tob, history of smoking; Cx, circumflex artery; HTN, history of hypertension; and FHx, family history of coronary disease.