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Does use of intravascular ultrasound accelerate arteriopathy in heart transplant recipients?

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Background Intravascular ultrasound (IVUS) is a sensitive method for assessing allograft vasculopathy in heart transplant recipients, but it is not known whether this instrumentation traumatizes the transplanted arteries and affects progression of arteriopathy.

Methods and Results Yearly coronary angiograms were obtained in 86 patients who underwent heart transplantation between January 1991 and May 1995. Patients were divided into 3 groups: (1) no IVUS performed after transplantation (group 1, n = 47); (2) IVUS of the left anterior descending artery (LAD) performed only at year 1 (group 2, n = 13); and (3) IVUS of the LAD performed at both baseline (within 2 months after transplantation) and year 1 after transplantation (group 3, n = 26). Coronary angiography measurements of lumen diameter were performed at 5 segments along the length of the LAD and left circumflex artery (LCX) from baseline through the second-year studies except in group 2, which did not receive a baseline angiogram; IVUS measurements were obtained at 10 cross sections from each artery. At baseline, there was no significant difference in vessel diameter for either the LAD or the LCX artery between the IVUS (group 3) and no IVUS (group 1) groups. Within each group, the lumen of both the LAD and LCX narrowed from baseline to year 1 (group 1: 3.3 ± 0.6 mm to 2.8 ± 0.5 mm in LAD, $P = .001$; 3.3 ± 0.6 mm to 3.0 ± 0.5 mm in LCX, $P = .006$; group 3: 3.5 ± 0.7 mm to 3.1 ± 0.6 mm in LAD, $P = .01$; 3.1 ± 0.6 mm to 2.8 ± 0.5 mm in LCX, $P = 0.07$), but there were no significant differences between the instrumented artery (LAD) and control artery (LCX) or further changes observed at year 2. There were also no significant differences in the percent reductions at year 1 and year 2 between arteries or between groups. By IVUS, from baseline to year 1 in group 3, the plaque cross-sectional area (CSA) increased (1.6 ± 1.9 to 2.3 ± 1.7 mm^2, $P < .0001$), the lumen CSA decreased (12.7 ± 3.7 to 11.7 ± 3.3 mm^2, $P = .04$), and the maximum lumen diameter decreased (4.2 ± 0.6 to 4.0 ± 0.6 mm, $P = .04$).

Conclusions The use of IVUS is not associated with acceleration of arteriopathy in heart transplantation recipients. Luminal narrowing occurs predominantly during the first year after transplantation. There was no significant change in lumen dimensions during the second year. (Am Heart J 1999;138:358-63.)

Accelerated coronary atherosclerosis is the leading cause of long-term morbidity and mortality in heart transplant recipients.[1-6] Annual coronary angiography, which can detect severe transplantation coronary artery disease (TCAD) as early as 1 to 2 years after heart transplantation, has been used for diagnostic and surveillance purposes because patients may remain asymptomatic until myocardial infarction, congestive heart failure, cardiac arrhythmia, or sudden death develop.[3,7] Angiography is relatively insensitive for detecting early or less severe TCAD because of its diffuse nature and because the early phases of intimal hyperplasia may be associated with vessel wall expansion (positive remodeling) and minimal luminal narrowing.[8,9]

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The development of intravascular ultrasound (IVUS) has allowed more accurate and sensitive detection of coronary artery disease (CAD).[10-12] IVUS is also more sensitive in assessing allograft vasculopathy in patients who receive heart transplantation before angiographic changes have occurred.[13,14] The accuracy, reproducibility, and immediate safety of IVUS has been documented in both transplant recipients and in patients who have not undergone transplantation.[10,11,14] However, it is not known whether instrumentation of transplanted arteries affects progression of arteriopathy over several years. The purpose of this study was to examine if there was a correlation between performing IVUS examinations and the acceleration of TCAD.

Methods

Patient population

The study population consisted of 95 patients who underwent heart transplantation at the University of California Los Angeles Medical Center between January 1991 and May 1995. Nine patients were excluded because of insufficient informa-

Table I. Clinical characteristics of study patients at baseline

	Group 1	Group 2	Group 3	*P* value
No. of patients	47	13	26	
Recipient age (y)	54.1 ± 12.7	60.0 ± 11.6	59.0 ± 6.2	.09
Donor age (y)	30.1 ± 10.8	31.7 ± 12.4	32.7 ± 13.3	.65
Recipient sex (male)	36 (76.6%)	11 (84.6%)	20 (76.9%)	.81
Donor sex (male)	39 (83.0%)	9 (69.2%)	18 (69.2%)	.33
Pretransplantation CAD	24 (51.1%)	9 (69.2%)	15 (57.5%)	.50
Donor ischemic time (min)	166.7 ± 45.6	180.1 ± 30.2	177.2 ± 42.0	.46
Time after transplantation to first angiography (d)	51 ± 17	–*	46 ± 13	.19

Values are mean ± SD.
*Group 2 did not receive baseline angiogram until 1 year after transplantation.

tion. Of the remaining 86 patients, there were 67 men and 19 women, with a mean age of 56.5 years. Routine surveillance coronary angiography was obtained annually after transplantation from baseline (year 0) through year 2 (within 2 months, 1 and 2 years after transplantation). Baseline angiograms were not available in some patients who received heart transplantation in 1991 to 1992 because this documentation angiogram was not performed routinely during that time period. These patients received an angiogram and IVUS study at year 1 and therefore constituted the second group of patients (IVUS at year 1 only) mentioned below. IVUS was performed in the left anterior descending artery (LAD). The use of IVUS was not assigned in a random manner but varied according to the clinical protocol that was in use. The patient groups were not treated differently in terms of tissue preservation techniques or medical treatment. Patients were divided into 3 groups according to the performance of IVUS: (1) no IVUS performed after transplantation (group 1, n = 47); (2) IVUS to LAD performed at year 1 only (group 2, n = 13); (3) IVUS to LAD performed at both baseline and year 1 after transplantation (group 3, n = 26).

Coronary angiography

Coronary angiography was performed in a routine manner from the femoral artery with a 7F or 8F catheter. Multiple projections of both right and left coronary systems were obtained. Angiograms performed in serial studies after transplantation were obtained in identical projections to the baseline study. For each patient, technically suitable single-plane angiographic images were selected for serial analysis from both the LAD and left circumflex (LCX) arteries. Most of the LAD images were selected from the left anterior oblique (LAO) cranial or right anterior oblique (RAO) cranial view, whereas images of the LCX were selected from the RAO caudal view. All selected images were digitized with a Macintosh Quadra 840 computer (Apple Corp, Cupertino, Calif) with video frame-grabbing boards and software by Media 100 (Data Translation, Inc, Marlboro, Mass).

Intravascular ultrasound

After coronary angiography was performed, a 0.014-inch coronary guide wire was positioned in the LAD under fluoroscopic guidance. The IVUS imaging catheter was then passed over the guide wire into the LAD. Sublingual (400 μg) or intracoronary nitroglycerin (100 to 200 μg) was given before insertion of the catheter. The imaging system consisted of a 30-MHz transducer enclosed within an acoustic housing at the tip of a 4.3F or 2.9F catheter (CVIS/SCIMED Inc, Sunnyvale, Calif). The imaging catheter was advanced approximately two thirds down the length of the LAD or until the lumen was a diameter of 2 mm. Contrast cineangiography was used to record the IVUS catheter position. The LAD was imaged with IVUS during a continuous, manual pullback from the distal site to the origin of the LAD at a speed of approximately 1 mm/s. The study was recorded on a VHS (before March 1994) or S-VHS (after April 1994) format at 30 frames per second.

Quantitative coronary angiography analysis

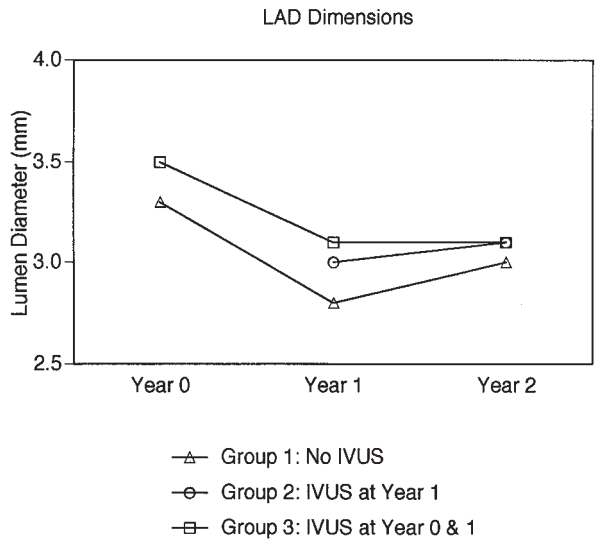
The LAD was divided into 5 equal segments from the ostium of the LAD to the distal site. The distal site was defined as the farthest site that the IVUS catheter tip reached. In the patients who had received a prior IVUS examination, the distal site was matched carefully in the same view taken during the previous annual diagnostic coronary angiogram. The other 4 sites were also matched visually from the angiograms. In the patients who did not undergo IVUS studies, a distribution was chosen of measurement sites that were comparable to those used for the patients who had IVUS studies. For the LCX measurements, 5 equidistant sites were chosen and marked in the same manner as had been done in the LAD. The positions where the measurements were made were annotated and stored as separate files on the computer for reference with the other serial studies.

Lumen measurements were made with the use of an operator-assisted edge detection method with public-domain software, NIH Image (Internet: by anonymous file transfer protocol, http://zippy.nimh.nih.gov/pub/nih-image). The angiography catheter diameter was used to calibrate the images. The lumen diameter (D) was measured at site 1 (D_1), site 2 (D_2), site 3 (D_3), site 4 (D_4), and site 5 (D_5) of the LAD and LCX in each patient from the baseline angiogram through the study at year 2. The average (Avg) of every set of the 5 sites [AvgD =(D_2 + D_3 + D_4 + D_5)/5] and the percent change from baseline to year (Yr) 1 [% change(Yr0 to Yr1) = (Yr0 AvgD – Yr1 AvgD)/Yr0 AvgD], from year 1 to year 2 [% change(Yr1 to Yr2) = (Yr1 AvgD – Yr2 AvgD)/Yr1 AvgD], and from baseline to year 2 [% change(Yr0 to Yr2) = (Yr0 AvgD – Yr2 AvgD)/Yr0 AvgD] were then calculated.

IVUS measurements

The videotape of the pullback was divided into 10 equal time intervals. An IVUS image was chosen for analysis at each

Figure 1



LAD lumen diameter changes from year 0 through year 2.

time interval when there were no branches interrupting the lumen and the cardiac cycle was at end diastole. Each image was digitized with a Macintosh Power PC 7500 (Apple Corp, Cupertino, Calif).

Measurements were made with the use of computerized planimetry with public-domain software (NIH Image). Vessel cross-sectional area (CSA), lumen CSA, vessel diameter (maximum and minimum), and lumen diameter (maximum and minimum) were measured, and plaque CSA was then calculated from the measurements Plaque CSA = Vessel CSA – Lumen CSA.

For each variable, the average value of the 10 cross sections was calculated.

Statistical analysis

Statistical analysis was performed on a Power Macintosh 8500 with commercially available software programs (Statview 4.5, Abacus Concepts Inc, Berkeley, Calif, and JMP 3.1, SAS Institute Inc, Cary, NC). All values were expressed as mean ± SD. Differences in mean values of the 3 groups were evaluated by 1-way analysis of variance, and those for different arteries in different groups were explored with a 2-way multiple analysis of variance. For significant *F* ratios, group mean values were compared by use of the Bonferroni/Dunn procedure as a post hoc test. When only 2 groups were available, the unpaired *t* test was used. To evaluate the IVUS measurement changes in group 3, a paired *t* test was used. A level of statistical significance was set at $P < .05$. Multiple analysis of variance was used to compare mean value differences and percent changes.

Results

Clinical characteristics

The mean age of the 86 study patients at the time of transplantation was 56.5 ± 11.2 years (range 23 to 74) and the mean donor age was 31.1 ± 11.8 years (range 12 to 59). There were 67 (77.9%) men and 19 (22.1%) women in the recipients and 66 (76.7%) men and 20 (23.3%) women in the donors. The pretransplantation diagnosis was CAD in 48 (55.8%) of the patients and nonischemic cardiomyopathy in 38 (44.2%). The mean donor ischemic time was 172 ± 43 minutes (range 72 to 286). Baseline clinical characteristics of the 3 study groups are listed in Table I. There were no significant differences in mean age and sex of either recipient or donor between the 3 groups. There were also no differences in pretransplantation diagnosis and donor ischemic time in the 3 groups. Except for group 2, which did not receive a baseline angiogram, there were no differences in time after transplantation to first angiography between group 1 and group 3.

Table II. Vessel diameter changes from year 0 through year 2

	Year 0	Year 1	Year 2	*P* value
LAD				
Group 1	3.3 ± 0.6	2.8 ± 0.5	3.0 ± 0.6*	.006
Group 2	–	3.0 ± 0.4	3.1 ± 0.5	.56
Group 3	3.5 ± 0.7	3.1 ± 0.6	3.1 ± 0.6	.02
LCX				
Group 1	3.3 ± 0.6	3.0 ± 0.5	2.9 ± 0.5†	.003
Group 2	–	2.8 ± 0.7	2.8 ± 0.6	.10
Group 3	3.1 ± 0.6	2.8 ± 0.5	2.9 ± 0.7	.17

Group 2 did not receive baseline angiogram until 1 year after transplantation.
*$P = .17$ vs year 1; †$P = .52$ vs year 1.

Comparison of vessel diameter changes in LAD

As shown in Table II, the measurements from baseline through the second year after transplantation were obtained except for group 2 (LAD instrumented with IVUS only at year 1), which did not receive a baseline angiogram. There was no significant difference in LAD vessel diameter among group 1, group 2, and group 3 at baseline (3.3 ± 0.6 mm in group 1 vs 3.5 ± 0.7 mm in group 3, $P = .13$), year 1 ($P = .15$), or year 2 ($P = .72$) (Figure 1). Compared with the baseline measurements, the lumen diameters of both group 1 and group 3 became significantly smaller at year 1 (group 1: 3.3 ± 0.6 mm vs 2.8 ± 0.5 mm, $P = .001$; group 3: 3.5 ± 0.7 mm vs 3.1 ± 0.6 mm, $P = .01$) and remained narrower at year 2 compared with baseline (group 1: 3.3 ± 0.6 mm vs 3.0 ± 0.6 mm, $P = .04$; group 3: 3.5 ± 0.7 mm vs 3.1 ± 0.6 mm, $P = .01$). However, there were no differences between year 1 and year 2 in each group ($P = .17$ in group 1; $P = .50$ in group 2; $P = .95$ in group 3).

Comparison of vessel diameter changes in LCX

Because group 2 did not receive a baseline angiogram, the LCX analysis was performed without baseline measurements in that group. Similar to the results of the LAD analysis, there was no significant difference in the

Table III. Comparison of percent reduction between no IVUS and IVUS groups

	Group 1	Group 3	*P* value
LAD diameter percent reduction (%)			
Year 0 to year 1	16 ± 14	11 ± 22*	.27
Year 1 to year 2	−7 ± 16	−2 ± 22	.34
Year 0 to year 2	16 ± 12	12 ± 17†	.32
LCX diameter percent reduction (%)			
Year 0 to year 1	12 ± 12	9 ± 10	.38
Year 1 to year 2	2 ± 11	−2 ± 11	.17
Year 0 to year 2	12 ± 11	8 ± 12	.16

*P = .81 vs value in LCX; †P = .34 vs value in LCX.

Table IV. IVUS measurement changes in group 3 (IVUS group)

	Year 0	Year 1	*P* value
Vessel CSA (mm^2)	14.3 ± 3.9	14.0 ± 3.4	.58
Vessel diameter, maximum (mm)	4.4 ± 0.6	4.4 ± 0.5	.46
Vessel diameter, minimum (mm)	4.0 ± 0.6	4.0 ± 0.5	.81
Lumen CSA (mm^2)	12.7 ± 3.7	11.7 ± 3.3	.04
Lumen diameter, maximum (mm)	4.2 ± 0.6	4.0 ± 0.6	.04
Lumen diameter, minimum (mm)	3.7 ± 0.6	3.6 ± 0.5	.09
Plaque CSA (mm^2)	1.6 ± 1.9	2.3 ± 1.7	<.0001

LCX diameter between group 1, group 2, and group 3 at baseline (3.3 ± 0.6 mm in group 1 vs 3.1 ± 0.6 mm in group 3, P = .13), year 1 (P = .40), or year 2 (P = .82) (Table II and Figure 2). Compared with the baseline study, the LCX artery in group 1 became significantly smaller at year 1 (3.3 ± 0.6 mm vs 3.0 ± 0.5 mm, P = .006), but there were no further changes at year 2 (3.0 ± 0.5 mm vs 2.9 ± 0.5 mm, P = .52). Neither group 2 nor group 3 showed a significant difference at year 1 (3.1 ± 0.6 mm vs 2.8 ± 0.5 mm in group 3, P = .07) or year 2.

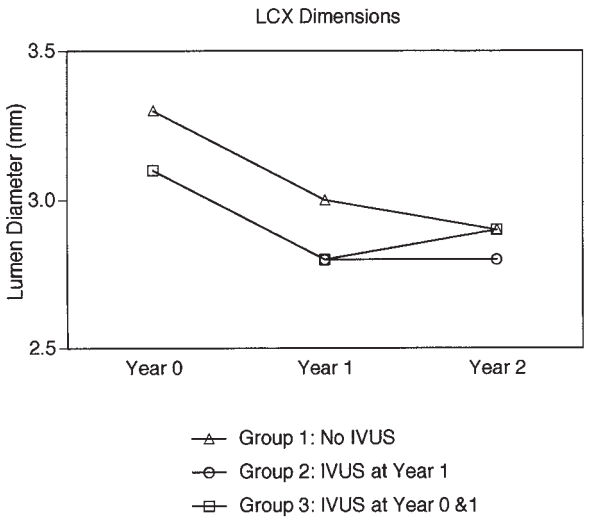
Comparison of percent reduction between no IVUS and IVUS groups

LAD and LCX diameter percent reduction of both the no IVUS (group 1) and IVUS (group 3) groups are shown in Table III. Although the percent reduction in luminal narrowing in the no IVUS group was slightly higher, there was no significant difference between these 2 groups.

Comparison of LAD and LCX diameter changes within IVUS group

Within group 3, in which IVUS was performed both at year 0 and year 1, the LAD diameter was bigger than the LCX at baseline (3.5 ± 0.7 mm vs 3.1 ± 0.6 mm, P = .01). However, the diameter change from year 0 to year 1 in the LAD did not differ from that in the LCX (3.5 ± 0.7 mm to 3.1 ± 0.6 mm in LAD vs 3.1 ± 0.6 mm to 2.8 ± 0.5 mm in LCX, P = .38). Therefore the LAD diameter

Figure 2



LCX lumen diameter changes from year 0 through year 2.

remained bigger than the LCX at year 1 (3.1 ± 0.6 mm vs 2.8 ± 0.5 mm, P = .08), and there were no further changes at year 2 (3.1 ± 0.6 mm vs 2.9 ± 0.7 mm, P = .25) (Table II). In the comparison of percent reduction as shown in Table III, the reduction in LAD lumen size did not differ from that of the LCX at both year 1 (11% ± 22% vs 9% ± 10%, P = .81) and year 2 (12% ± 17% vs 8% ± 12%, P = .34).

IVUS measurement changes from baseline to year 1

As shown in Table IV, the lumen CSA (12.7 ± 3.7 mm^2 to 11.7 ± 3.3 mm^2, P = .04) and lumen maximum diameter (4.2 ± 0.6 mm to 4.0 ± 0.6 mm, P = .04) was smaller at the year 1 study compared with baseline. The plaque CSA increased commensurately at year 1 (1.6 ± 1.9 mm^2 to 2.3 ± 1.7 mm^2, P < .0001). There were no significant changes in vessel measurements (ie, no negative remodeling) or in minimum lumen diameter (Table IV).

Discussion

Allograft arteriosclerosis begins early after transplantation and is insidious and progressive.[15] As the survival rate after heart transplantation improves because of successful management of allograft rejection and infectious complications, accelerated allograft arteriopathy becomes the major limitation to long-term survival for heart transplantation recipients.[3,15,16] Serial angiographic studies in heart transplantation recipients have demonstrated an increased prevalence of coronary abnormalities associated with longer graft survival.[6] By 5 years after transplantation, 40% to 50% of patients have angiographic evidence of disease.[6,17]

Comprehensive pathologic examinations of coronary arteries from transplantation recipients have demonstrated a broad spectrum of abnormalities.[18] The early stage is characterized by a diffuse, homogeneous, and concentric intimal proliferation of smooth muscle cells and collagen. Focal, complex atherosclerotic plaques that bear a close resemblance to native atherosclerosis occur in more advanced stages of the disease.[18] Because of the concentric and diffuse nature of TCAD, it may be difficult to detect early changes by angiography.

IVUS imaging may demonstrate intimal proliferation and atheroma formation before there is angiographic evidence of CAD.[13,14] Because IVUS is more sensitive than coronary angiography, IVUS is used as a diagnostic tool in heart transplantation recipients. However, there is concern that instrumentation of transplanted coronary arteries, especially in the milieu of multiple antirejection medications, may have deleterious effects on the intima and cause acceleration of the arteriopathy. Pinto et al[19] reported that IVUS imaging could be performed safely in transplanted hearts and that there was no significant difference between the instrumented and noninstrumented vessels 1 year after the initial IVUS study. In a self-reporting registry, Hausmann et al[12] described the complications associated with IVUS imaging. In patients without transplantation, the risk of spasm was 3.2% (21 of 656), and complications occurred in 0.6% (1 acute occlusion, 1 thrombus, 1 arrhythmia, 1 emergency coronary artery bypass graft, n = 656). When IVUS was used during diagnostic procedures in transplantation recipients, the incidence of spasm was 3.0%, but no other major or acute procedural complications occurred. We have reported a higher incidence of intense spasm (16.9%) in our transplantation population[20] that heightens our concern for the long-term outcome of IVUS studies in these patients.

The purpose of the current study was to assess the long-term safety of IVUS imaging in transplanted coronary arteries by determining whether instrumentation by IVUS accelerates arteriopathy. The current angiographic study revealed that lumen diameter changes occur mainly in the first year after heart transplantation, but the incidence and magnitude of the lumen narrowing were similar in arteries with or without IVUS instrumentation. There was also no relation between progression of arteriopathy and the time IVUS was initially performed after transplantation. In the first year after transplantation, there was significant luminal narrowing; however, this longitudinal study demonstrated that the rate of lumen narrowing stabilized in the second year. Other IVUS studies of lumen and plaque CSA in heart transplantations demonstrate that there is compensatory enlargement by the second year.[21] The media enlarges to accommodate the increase in intimal hyperplasia, and this permits the lumen CSA to be preserved or increased.[21]

Study limitations

This was a retrospective, nonrandomized study, but there were no baseline differences between the patients in the 3 groups. Patients were excluded who were involved in other drug intervention research protocols that may affect TCAD. In addition, patients were selected from our transplantation population who survived the first 3 years and had angiographic studies. Some patients who received heart transplantation in 1991 to 1992 did not have a baseline angiogram because this was not performed routinely during that time. IVUS studies were only performed in the LAD in our patient population. The use of IVUS was not assigned in a random manner but varied according to the clinical protocol that was in use.

Although histologic studies have shown that in TCAD the distal artery has more advanced disease, measurements of the distal one third of the artery were not obtained in the current study. In the patients in this study, only the proximal two thirds of the LAD was examined by IVUS, and the angiographic measurements were performed only along the segments where the IVUS catheter was placed.

The IVUS examinations were performed with a manual pullback instead of a more uniform motorized pullback. This should not affect our estimation of the average values of lumen and vessel size because previous morphometric studies have shown that no more than 8 to 10 random sites are necessary to reproducibly determine the mean severity of TCAD.[22] If these sites are approximately spaced uniformly throughout the length of the artery, it does not matter whether the pullback is manual or mechanical.

Conclusions

The use of IVUS imaging is not associated with acceleration of arteriopathy in heart transplantation recipients. There is no difference in progression of disease in the instrumented LAD artery versus the noninstrumented circumflex or noninstrumented LAD arteries. Luminal narrowing in this population of transplanted hearts occurred to a mild degree (9% to 16%) during the first year after heart transplantation. There was no significant change in lumen diameter during the second year.

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