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Immediate and One-Year Safety of Intracoronary Ultrasonic Imaging

Evaluation With Serial Quantitative Angiography

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Background. **Intracoronary ultrasound (ICUS) has the ability to quantitatively evaluate vessel wall morphology and is well suited for serial studies of coronary artery disease regression and progression. However, the potential risk for catheter-induced endothelial damage and accelerated atherosclerosis in instrumented vessels is a concern. The acute effects as well as the 1-year safety of ICUS regarding its impact on the atherosclerotic process were assessed.**

Methods and Results. **The acute studies include 240 intracoronary studies performed in 170 cardiac transplant recipients. Patients were systematically heparinized. Only vessels ≥2 mm in diameter were visualized. Coronary arteries of 38 patients were measured by quantitative coronary angiography in matched angiograms at an interval of 1 year after the initial ICUS examination was performed to assess long-term effects. The angiographic measurements in the previously instrumented and noninstrumented vessels were compared. Forty-nine vessels that had been imaged (IM) in these 38 patients with a 5F ICUS catheter were compared with 61 vessels not previously imaged (NIM) in the same patients. Absolute and percentage change in angiographically measured mean vessel diameters in the ICUS imaged and nonimaged segments were compared. Despite pretreatment with nitroglycerin, 20 patients (8.3%) had angiographically evident coronary spasm. In all cases, this was reversed by giving nitroglycerin. One year after the original imaging study, no difference was noted between imaged and nonimaged vessels in change in absolute vessel diameter (IM, −0.11±0.28 mm vs NIM, −0.07±0.22 mm; $P=.49$) or in percentage change in diameter (IM, −5±11% vs NIM, −3±7%; $P=.32$).**

Conclusions. **Intracoronary ultrasound in cardiac transplant recipients was associated with no clinical morbidity and a low incidence of vessel spasm in large and medium-size coronary arteries. It does not accelerate progression of angiographically quantifiable coronary artery disease. This study suggests that ICUS can be safely used even in coronary arteries not undergoing interventions. (*Circulation*. 1993;88[part 1]: 1709-1714.)**

KEY WORDS • **ultrasound** • **angiography** • **coronary artery disease**

Intravascular ultrasound is a new imaging technique with the unique ability to study vessel wall morphology in vivo.[1-5] In vitro and in vivo studies have demonstrated the accuracy and reproducibility of the method to measure vessel lumen dimensions and delineate wall morphology.[5-7] Other studies have shown the ability of intravascular imaging to assess vascular responses to pharmacological stimuli[8] and to evaluate the acute success of mechanical interventions such as balloon angioplasty, stent placement, and atherectomy.[9-11] Intracoronary ultrasound detects measurable intimal proliferation and atheroma formation before angiographic evidence of coronary artery disease.[12] Therefore, it may be a powerful and sensitive method for serially evaluating and quantifying progression and/or regression of coronary artery disease. However, concern has been raised regarding catheter-induced endothelial damage leading to acceleration of the atherosclerotic process in instrumented vessels. The safety of the method must be demonstrated before this invasive imaging technique can be used routinely to serially follow patients who do not undergo therapeutic coronary interventions.

Cardiac transplant recipients at Stanford University undergo annual coronary angiography as part of an ongoing program monitoring for otherwise silent coronary disease.[13] Intracoronary ultrasound has been performed in these patients, with informed consent, at the time of the annual angiograms since July 1990.[12] The purpose of the present study was to assess both the immediate effects and safety of intracoronary ultrasound and the effect, if any, of coronary instrumentation on acceleration of atherosclerosis as determined by quantitative coronary angiography. The acute effects are reported in all patients. The yearly return of these

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Two of the authors of this paper (F.G.S., R.L.P.) are consultants to and hold stock options with CVIS, Inc, manufacturer of the imaging system used.

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patients also provided the opportunity to perform serial measurements using quantitative coronary angiography to compare progression of disease in the previously instrumented and noninstrumented coronary arteries.

Methods

Patient Population

Two hundred forty intracoronary ultrasound studies were performed in 170 cardiac transplant recipients from July 1990 to May 1992. Thirty-eight of these cardiac transplant recipients undergoing standard yearly screening coronary angiography had two serial matched angiograms, allowing comparison of quantitative coronary angiographic measurements during and at 1 year after their initial intracoronary ultrasound study. The mean age of the patients was 47±12 years. There were 27 men and 11 women. Time from transplantation at the first study ranged from 3 weeks to 13 years (mean, 3.5 years). This protocol was approved by the Committee for Protection of Human Subjects in Research of the Stanford University Medical Center, and each patient gave written informed consent for the study of their coronary vessels by intravascular ultrasound.

Intravascular Ultrasound

At the time of their angiogram, all patients were also examined with a previously described 5F (1.7 mm) (85 patients) or 4.3F (1.4 mm) (85 patients), 30-MHz, flexible, 135-cm-long, over-the-wire ultrasound catheter system (Cardiovascular Imaging Systems, Inc, Sunnyvale, Calif).[14] The ultrasound beam is reflected against an angulated mirror rotating at 1800 rpm, creating a 360° imaging plane perpendicular to the catheter. A flexible drive cable through the length of the catheter is connected to a motor at the distal end, which drives the mirror. The imaging catheter has a lumen that accommodates a 0.014-in. coronary guide wire that exits the catheter centrally, distal to the transducer via a flexible, tapered tip. This allows manipulation of the ultrasound catheter in coronary arteries similar to large diameter coronary balloon angioplasty systems. An 8F superflow coronary guiding catheter (internal diameter, 0.082 in.) (Schneider, Inc, Minneapolis, Minn) was used to deliver the ultrasound catheter for all studies.

All patients received 0.4 mg of sublingual nitroglycerin before the ultrasound study as part of a standard angiographic protocol. After anticoagulation with 10 000 units of intravenous heparin to achieve an ACT >300, coronary vessels were continuously scanned with the ultrasound catheter from the ostium of the left main coronary artery to the midportion of the left anterior descending and/or left circumflex arteries. In the group of 38 patients with two serial angiograms, the left anterior descending artery alone was studied in 24 patients, the left circumflex artery was studied in 3 patients, and 11 patients had studies of both the left anterior descending and left circumflex arteries. Other patients with all three vessels imaged could not be used for this study. The ultrasound catheter was not advanced into any vessel smaller than 2.0 mm diameter. The average imaging time with the ultrasound catheter inside the coronary vessels was 8 minutes, ranging from 3 to 20 minutes.

Cardiac Catheterization

All 38 patients in the long-term study had a baseline coronary angiogram performed at the time of the initial intracoronary ultrasound study, and a second coronary angiography was repeated 1 year after by the percutaneous femoral approach. All angiograms were performed using 5- to 7-in. intensifier modes and were considered as suitable for analysis by quantitative coronary arteriography. Catheters containing metallic cylindrical markers of known diameter were used for calibration.[15] Multiple projections including cranial and caudal angulated views were obtained for all 38 patients in the long-term study at baseline angiography and were replicated at 1 year. In each case, maximum vessel dilatation was obtained before angiography with sublingual nitroglycerin 0.4 mg to minimize the effect of varying vascular tone and to enhance visualization of the vascular detail. Diltiazem and all other vasodilators were withheld for 24 hours before each procedure. All patients had an intracoronary contrast injection after the intracoronary ultrasound was performed to look for vessel spasm, thrombus, or other angiographically visible potential complications of intracoronary ultrasound imaging.

Quantitative Coronary Arteriography

Quantitative angiography was performed in matched projections from the initial and 1-year follow-up coronary angiograms.[16] Matched coronary segments from the proximal two thirds of the left anterior descending coronary artery, circumflex artery, and right coronary artery were measured at baseline and 1 year after intracoronary ultrasound. Only coronary segments that were clearly visualized were quantitated and used for analysis. Projections were selected that best displayed the segment in profile. Segments were excluded from analysis if they were too short or overlapping with other vessels.

Coronary cineangiographic films were analyzed by computer-assisted edge detection using a 35-mm cinefilm transport mechanism mounted on a movable stage (Vanguard Instruments, Melville, NY).[17] Single end-diastolic cineframes, identified by an ECG-triggered mark on the frames and selected for optimal coronary vessel opacification, were optically focused and magnified (×3.5). Coronary segments were centered in the image field, and the image was digitized with a video processor (model 5524, De Anza Systems, Fremont, Calif) controlled by a Hewlett-Packard 2100 computer (Andover, Mass). The digitized image was displayed on a graphic computer terminal linked to a light pen. Coronary segments were identified from study to study by anatomic landmarks and fixed segment lengths. The margins of either the catheter or coronary segment were traced manually using the light pen. Using these lines as initial search locations, the automated edge-detection algorithm drew and smoothed the vessel edges, defined as the peak of the first derivative of the gray scale density gradient, perpendicular to the long axis of the catheter or vessel as estimated from the initial manual tracings. When the computer algorithm was unable to resolve vessel boundaries in areas of noise or vessel crossings, manual editing of short segments of boundary with the light pen was used to correct the computer-

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Change in Instrumented Versus Noninstrumented Vessel Diameter by Quantitative Coronary Angiography

	% DiameterΔ	P	Absolute DiameterΔ, mm	P
Instrumented vs noninstrumented vessel (n=38)	−5±11% vs −3±7%	.3	−0.11±0.28 vs −0.07±0.22	.5
LAD (I) vs RCA (NI) (n=31)	−2±10% vs −2±7%	.9	−0.04±0.27 vs −0.3±0.22	.8
LAD (I) vs LCx (NI) (n=24)	−7±12% vs −4±8%	.2	−0.15±0.31 vs −0.12±0.25	.6

I indicated instrumented; NI, noninstrumented; LAD, left anterior descending coronary artery; RCA, right coronary artery; and LCx, left circumflex coronary artery.

generated boundary. At no time did the length of a manually entered margin exceed 20% of the total length of the quantitated segment. After the light pen indicated the segment fiducial (starting) and end points, the mean diameter of the segment was computed from perpendiculars constructed through the length of a computer-generated center line. The mean diameter of the segment was then used for analysis. The quantitation system has been shown to measure coronary dimensions from different end-diastolic cineframes with an average standard deviation of the measurement differences of ±0.033 mm.[16] A threshold for a significant difference was arbitrarily defined at 0.2 mm.[16] Imaged and nonimaged segments were matched for size. Imaged segment diameters averaged 2.89±0.38 mm and nonimaged segments, 3.13±0.52 mm. Measurements were obtained by one investigator (S.Z.G.) blinded to the ultrasound procedure, including which vessels were instrumented.

Data Analysis

Data are presented as mean±SD. Forty-nine vessels that had been imaged with the ultrasound catheter were compared with 61 vessels not previously imaged. Each patient served as his/her own control. Imaged and nonimaged segments each were averaged, and absolute and percentage change in angiographically measured mean vessel diameters were compared between the two groups of vessels within the same patient using a two-tailed paired *t* test. A value of $P<.05$ was considered significant.

Results

Procedural Observations and Acute Complications

The 240 intracoronary ultrasound studies were performed in 170 patients without any significant clinical or angiographic acute complications. Twenty patients had angiographically evident coronary spasm. In all of these cases, the spasm was shown angiographically as an area of sudden luminal narrowing, successfully reversed with intracoronary nitroglycerin. In no case was flow totally occluded by the spasm. In 2 of these 20 patients, the spasm was associated with ST-segment elevation during intracoronary ultrasound imaging. In 1 of these 2 patients, the procedure was stopped before imaging was completed, with immediate return of the ST-segment to baseline as soon as the imaging catheter was pulled out of the coronary artery, and no other complications were noted. In the other patient, the ST-segment returned to baseline after nitroglycerin, and the study was completed without incident. Ten of these 20 patients were studied within 1 month after transplantation, and all had evidence of intimal thickening by ultrasound. The other 10 patients with spasm, studied more remotely from transplantation, all had increased intimal thickening by ultrasound, and 2 also had coronary artery disease by angiography. No other complications were noted; specifically, there were no instances of coronary dissection noted by angiography or intracoronary ultrasound.

One-Year Assessment

The change in absolute diameter in the 49 imaged vessels was −0.11±0.28 mm versus a change of −0.07±0.22 mm in the 61 nonimaged vessels ($P=.49$). The percentage change in diameter of the imaged vessels was −5±11% versus −3±7% in the nonimaged vessels ($P=.32$). Three patients had angiographic evidence of transplant coronary artery disease on their initial angiogram represented by either distal small vessel disease or proximal discrete lesions.[16] These three patients did not demonstrate accelerated angiographic narrowing of their imaged vessels when compared with their nonimaged vessels on their follow-up study (−0.21 mm vs −0.23 mm and −11% vs −9%). Seven patients had greater than 500 μm of mean circumferential intimal thickness measured by intravascular ultrasound in their proximal left anterior descending or left circumflex coronary arteries on their initial ultrasound study but no angiographically evident coronary artery disease, ie, angiographically silent intimal thickening. This subgroup of patients also had no increased narrowing of their imaged arteries compared with their nonimaged vessels (−0.16±0.3 mm vs −0.8±0.17 mm, $P=.6$, and −6±12% vs −2±5%, $P=.5$). See Table and Figure. The results of serial intravascular ultrasound evaluating progression of intimal proliferation will be reported separately.

Discussion

Serial computer-assisted quantitative angiography is presently the most accessible, well-validated technique that can readily survey the entire coronary vascular system and allow quantification of coronary artery disease progression and regression. Intracoronary ultrasound has the ability to detect intimal proliferation before angiographic evidence of disease and therefore offers a unique potential to study atheromatous coronary artery disease progression and regression. However, the safety of this imaging technique must be validated before it will be readily accepted for use in vessels not undergoing coronary interventions. In particular, these issues need to be resolved if intracoronary ultrasound is to be used as a tool to assess progression or regression of coronary artery disease.

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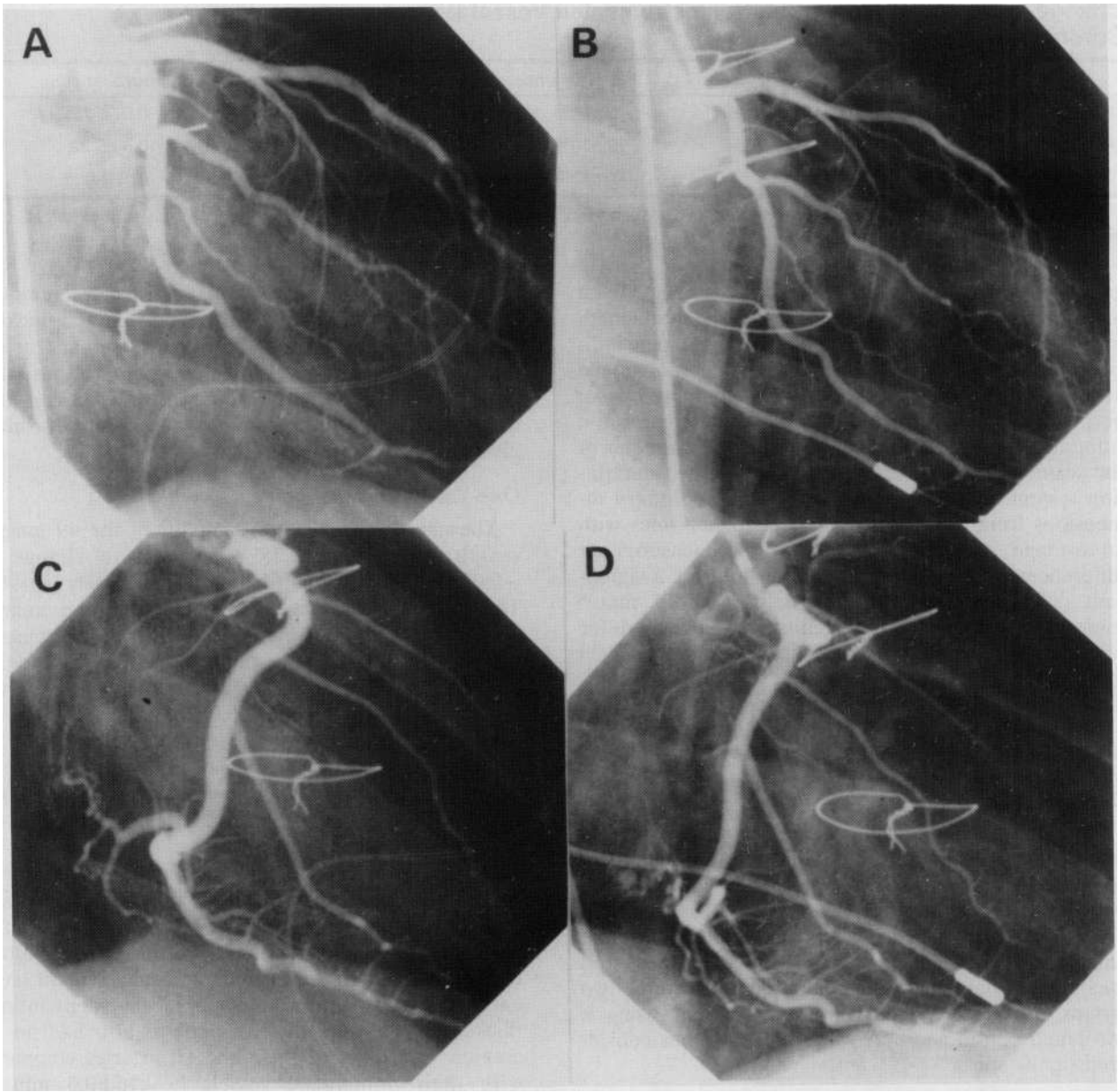

Cardiac transplant recipient studied at 3 weeks (A, C) and 1 year after transplantation (B, D). There is a diffuse decrease in luminal size involving the three major epicardial vessels. The left anterior descending artery (upper right, A and B) was the vessel instrumented for intracoronary ultrasound imaging.

The acute clinical safety of intracoronary ultrasound has been demonstrated in a previous publication describing intracoronary studies performed in 80 cardiac transplant recipients without any significant complications.[12] This is further supported in the present study. Although 20 patients had angiographic evidence of coronary spasm, despite pretreatment with nitroglycerin, this was easily reversed by intracoronary nitroglycerin. Only one study had to be interrupted because of ST-segment elevation. In this case, there was immediate return of the ST-segment to baseline after withdrawal of the catheter without clinical sequelae. In fact, most of the examples of vessel spasm were first recognized on the intracoronary ultrasound image and were confirmed by angiography. Thus, it is unlikely that unrecognized spasm occurred at other times in other patients. This incidence (8.3%) of vascular spasm is notable but was associated with other evidence of physiological significance by ECG criteria in only two cases (0.8%).

Graft coronary artery disease represents the major cause of death or retransplantation in cardiac transplant recipients surviving beyond 1 year after transplantation.[18-20] Therefore, annual screening coronary angiography has been performed at Stanford since shortly after the transplant program was started.[13] More recently, intracoronary ultrasound imaging of these patients was begun to attempt better understanding of transplant coronary artery disease.[21,22] Repeated high-resolution imaging of the disease process could serve to monitor the effects of interventions to retard or reverse this clinically important process in this patient population. However, the consequences of intracoronary manipulations with the potential for mechanically induced injury and possible intimal disruption could represent a

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significant risk for accelerated atherogenesis. Thus, the demonstration of long-term safety and the impact on progression of angiographically measurable coronary atherosclerosis is clinically important.

The present study shows no significant difference between the instrumented and noninstrumented vessels regarding angiographically detectable luminal narrowing. It also shows a lack of significant impact of the intervention, both in subgroups of patients who initially had angiographic evidence of coronary disease and in those with ultrasound evidence of intimal thickening but without angiographic evidence of coronary disease at the time of their first study.

It is possible the instrumentation of the coronary arteries did have some negative effect on the intima. Catheter abrasion of vessels is an established method for stimulating local atherogenesis.[23,24] However, these results suggest the acceleration of the atherosclerotic process in this group of patients is mild and not discernable beyond the variability of the process within patients. This should reassure the patients and physicians participating in studies assessing this technique for various purposes, as it implies a negligible effect from the procedure itself. On the other hand, the fact that the disease process may have obscured effects of lumen instrumentation should be considered. These patients served as their own control, thus minimizing this possibility. The trend suggesting a reduction in luminal size in the imaged vessels is slight in this study, so very large numbers of vessels might be needed to establish a statistical difference between instrumented and noninstrumented vessels (ie, type II error). In the present study, only one type of ultrasound catheter was used, consisting of a single mechanically driven acoustic mirror and transducer. Other studies will be needed to evaluate complication rates among patients studied with different catheter configurations.

Intracoronary ultrasonic imaging is increasingly recognized for its ability to accurately display the details of vessel structure,[25] but quantitative angiography is still used as the gold standard for monitoring progression of coronary artery disease. The coronary angiogram represents only a projectional image of the vessel lumen. Several comparative studies of angiography and pathology have demonstrated the shortcomings of angiography for estimation of atheromatous plaque.[26-29] Understanding the limitations of angiography, it was obvious from the outset that angiography is an imperfect tool to answer the question of long-term safety addressed in this study. However, current technologies do not allow imaging or measurement of atheroma by other methods usable for this study. The limitations of angiography were minimized by using the patient as his/her own control and by routinely administering nitroglycerin to mitigate the effects of variable vascular tone. The present study does not address the question of possibly altered endothelial function after coronary instrumentation. However, absence of coronary artery diameter change is a reasonable and time-honored marker for coronary disease.

The potential overriding effect of the rate of acceleration of disease in this group of patients can only be addressed by comparison with a similar study in patients with native coronary artery disease. We are not aware of any such study so far. In the present study, all patients were systematically heparinized to achieve ACT >300. Whether this degree of heparinization is necessary or not is uncertain. The present study shows that intravascular ultrasound is safe when used in large and medium-size coronary arteries, since we did not advance into vessels smaller than 2 mm because of the ultrasound catheter size.

These data suggest that intracoronary ultrasound is a safe and feasible imaging technique for the serial study of coronary artery disease in patients who are not undergoing therapeutic coronary interventional procedures.

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