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Repeated Intravascular Ultrasound Imaging in Cardiac Transplant Recipients Does Not Accelerate Transplant Coronary Artery Disease

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OBJECTIVES This study was designed to examine the impact of repeated intravascular ultrasound (IVUS) examinations on transplant coronary artery disease (CAD).

BACKGROUND Serial IVUS is the most accurate method for early detection and surveillance of transplant CAD. However, the long-term safety of serial IVUS exams is not well described. Accordingly, we examined the impact of repeated IVUS examinations on transplant CAD.

METHODS We examined 226 transplant recipients who underwent one or more IVUS examinations and coronary angiography at least one year after the last IVUS exam. The coronary angiograms were analyzed using quantitative coronary angiography. Vessel diameters, frequency, and severity of stenoses in IVUS-imaged and nonimaged coronary arteries were compared. In a subgroup analysis of 31 patients, angiographic lumen diameters were measured at baseline (within eight weeks of transplantation) and during follow-up (after two, three, or four IVUS studies).

RESULTS In the 226 patients, 548 coronary arteries were previously imaged by IVUS and 130 arteries were not imaged by IVUS. On subsequent angiograms, stenoses were observed in 16.2% (21/130) of nonimaged arteries and 19.5% (107/548) of imaged arteries ($p = 0.38$). The arterial diameters of nonimaged and imaged arteries were not significantly different ($p = 0.07$), regardless of the number of IVUS exams and duration of follow-up. Subgroup analysis revealed a significant decrease in vessel lumen diameter over time in nonimaged as well as imaged arteries. The magnitude of the diameter decrease was not significantly different between the two groups.

CONCLUSIONS Repeated IVUS examinations following heart transplantation do not result in angiographically evident acceleration of transplant CAD. Therefore, serial IVUS imaging is a safe method for the detection and surveillance of transplant CAD. (J Am Coll Cardiol 2003;41: 1739–43) © 2003 by the American College of Cardiology Foundation

Intravascular ultrasound (IVUS) is a complementary technique to coronary angiography for assessing the presence, extent, and progression of coronary atherosclerosis. The value of IVUS in the early detection and surveillance of transplant coronary artery disease (CAD) has been shown by numerous studies (1–5). On the basis of these studies, many transplant centers have performed serial IVUS examinations to assess the progression of transplant CAD. More recently, serial IVUS analysis of plaque burden has been utilized as an end point in pharmacologic atherosclerosis regression and progression studies (6).

However, there is concern that repeated intracoronary instrumentation itself might accelerate CAD by causing endothelial injury. Data demonstrating the long-term safety of repeated IVUS imaging are limited. In this study, we sought to assess the effect of repeated IVUS examinations on the progression of coronary lesions in cardiac transplant patients.

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METHODS

The study group consisted of all patients who underwent cardiac transplantation at our institution between 1992 and 2001. Patients who were not eligible for cardiac catheterization, who died during hospitalization, or who could not provide informed consent were excluded. The study protocol was approved by our Institutional Review Board. In this study, we included all patients who underwent at least one IVUS study and had follow-up coronary angiography within two years after the last IVUS exam. The coronary angiograms of these patients were analyzed by quantitative coronary angiography (QCA).

IVUS protocol. Intravascular ultrasound was performed at baseline (within eight weeks of transplantation) and at the time of the annual surveillance coronary angiography following standard protocols (7). After administration of heparin and intracoronary nitroglycerin, a 30-MHz, 3.5F monorail ultrasound catheter (Boston Scientific, Maple Grove, Minnesota) interfaced with a dedicated scanner (Hewlett-Packard, Andover, Massachusetts) was introduced over a 0.014-inch angioplasty guide wire. The transducer was advanced to a distal site in the coronary artery

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Abbreviations and Acronyms

CAD = coronary artery disease
CASS = Coronary Artery Surgery Study
IVUS = intravascular ultrasound
LAD = left anterior descending artery
LCX = left circumflex artery
QCA = quantitative coronary angiography
RCA = right coronary artery

large enough to avoid flow interruption, and the location was documented by cineangiography. During a slow distal to proximal pullback, ultrasound images were recorded on a SVHS tape.

Coronary angiography. Using standard technique, a 6F or 7F sheath was placed in the femoral artery and selective cine left and right coronary angiography was performed using manual injections of contrast. Standard projections of the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) were obtained.

QCA. Quantitative coronary angiography was performed on digitized coronary angiograms obtained within two years after the last IVUS exam and evaluated using the CAAS II software (Cardiovascular Angiographic Analysis System version 5vl. x, 1996; Pie Medical Imaging, Maastricht, Netherlands). For each artery, the best single-plane angiographic projection was selected. Vessel lumen diameters and stenosis severity were measured for all three epicardial arteries.

For the assessment of the arterial lumen diameter, each artery was divided into proximal, middle, and distal Coronary Artery Surgery Study (CASS) segments (8). After calibration of the angiography catheter, a line was tracked through the center of the entire length of the vessel segment. The CAAS software then calculated the lumen diameters using the edge detection system. For each segment the maximum and minimum diameter in an angiographically normal site was recorded and an average diameter calculated (9).

For the assessment of stenosis severity, all angiographically visible lesions were included. To quantify the severity of the lesion, the minimal lumen diameter and the diameter in an uninvolved reference site were measured and the percent stenosis calculated. The vessel lumen diameters and stenosis severity of arteries subjected to IVUS interrogation were compared with vessels never imaged by IVUS.

Comparison between baseline and follow-up coronary angiograms. In a subset of patients, the largest proximal and smallest distal vessel lumen diameters were compared at baseline and follow-up. The baseline angiogram was performed within eight weeks of transplantation and the follow-up angiograms after two, three, or four IVUS studies. The diameter measurements at baseline and follow-up were performed at the same coronary artery measurement sites in matched projection planes. Baseline and follow-up diameter measurements were compared to identify any change over time. Changes were further compared among arteries subjected to IVUS imaging and those that were never imaged by IVUS.

Table 1. Number of Arteries (LAD, LCX, and RCA) That Underwent 0 to 6 IVUS Exams

Number of IVUS Exams	LAD	LCX	RCA	Total
0	14	48	68	130
1	57	49	43	149
2	55	50	43	148
3	43	43	33	119
4	32	19	21	72
5	18	13	13	44
6	7	4	5	16

IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Statistical analysis. Statistical analysis was performed using SAS software (SAS Institute Inc., release 8.2, Cary, North Carolina). Analysis of the lumen diameter and stenoses measurements was performed using mixed models for spatial repeated measures. This method takes into account the measurement of the same parameters at different spatial sites. The stenoses data were rank-transformed before analysis, because the stenoses were not normally distributed. The chi-square test was used to evaluate the stenosis frequency. Levels of significance were determined, and differences were considered significant if $p < 0.05$.

RESULTS

At our institution, 380 patients underwent at least one IVUS exam following cardiac transplantation. Of these, 102 patients did not follow up at our institution, had expired, or had a recent cardiac transplantation and, thus, had not yet received a follow-up angiogram. Of the remaining 278 patients, angiograms suitable for QCA were available in 226 patients.

Of these 226 patients, 81% were men and 19% women. A total of 678 vessels were analyzed. Of these, 548 vessels underwent one to six IVUS exams and 130 vessels were never imaged with IVUS. The number of arteries that underwent one to six IVUS exams is displayed in Table 1. Among the arteries imaged by IVUS, 39% were LAD, 32% were LCX, and 29% were RCA.

Stenoses frequency and severity. Regardless of severity, stenoses were observed in 16.2% (21/130) of nonimaged arteries and 19.5% (107/548) of arteries previously imaged with IVUS ($p = 0.38$). There was no correlation between the frequency of stenoses and the number of previous IVUS exams performed. The vast majority of lesions in the IVUS-imaged arteries (98.7%) and nonimaged arteries (98.5%) were <50% severe ($p = 0.82$).

The stenosis severity of nonimaged and imaged arteries was not statistically different ($F_{7,171} = 1.05$, $p = 0.4$). Comparing the subgroups of arteries that underwent one or two versus three to six IVUS examinations, the difference in stenosis severity between nonimaged and imaged vessels was not significant ($p = 0.61$ and $p = 0.25$, respectively).

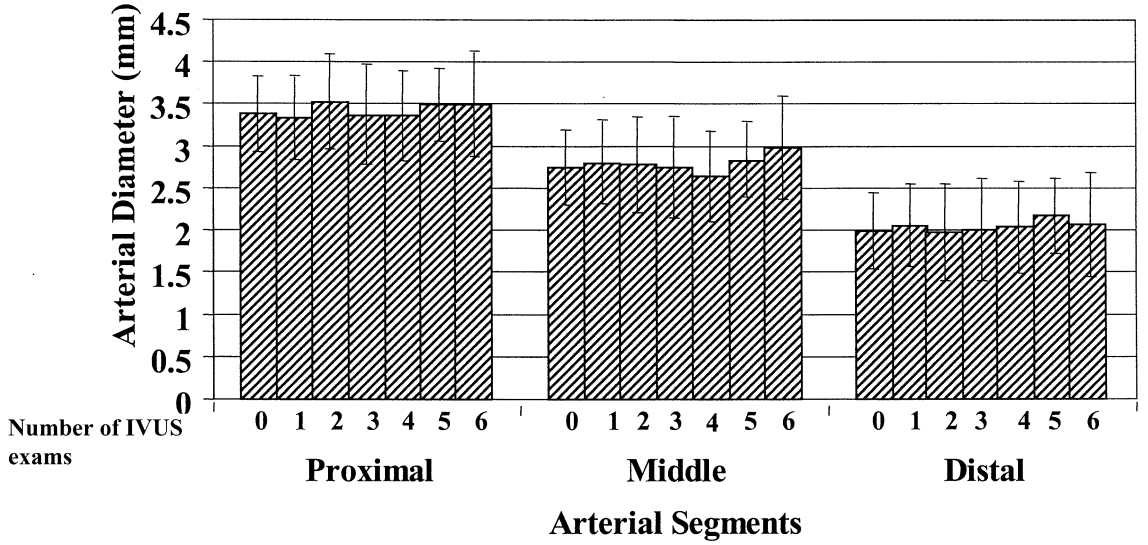

Figure 1. Arterial diameter of the left anterior descending artery displayed by the Coronary Artery Surgery Study segment and the number of intravascular ultrasound (IVUS) exams. No significant difference was found among the diameters of arteries that had no IVUS exam versus those that underwent 1 to 6 exams.

Arterial lumen diameter measurements. The arterial lumen diameter of nonimaged and imaged vessels was not statistically different ($F_{7,167} = 1.91$, $p = 0.07$), even after adjusting for type of epicardial artery, CASS segment, number of IVUS exams, and years after transplantation. Nonimaged vessels were nonsignificantly smaller in diameter than the imaged vessels. Furthermore, mixed models statistical analysis with spatial repeated measures showed no significant decrease in vessel lumen diameter with increasing number of IVUS exams. Figures 1 to 3 display the mean arterial lumen diameters for the LAD, LCX, and RCA by arterial segments and number of IVUS exams.

QCA measurements at baseline versus follow-up coronary angiograms. In a subgroup analysis of 31 patients, matched diameter measurements were performed at baseline and one year after two, three, or four IVUS studies. There were a total of 33 nonimaged arteries and 60 imaged arteries. Compared with baseline, a significant decrease in vessel diameters was seen in follow-up angiograms in both nonimaged and imaged vessels (Fig. 4). This decrease in diameter, however, was not significantly different in previously imaged versus nonimaged vessels. These findings were consistent regardless of the number of IVUS exams.

DISCUSSION

The results of our study indicate that serial IVUS examinations after transplantation do not lead to accelerated vasculopathy. Neither the comparison among imaged and nonimaged vessels nor the comparison among vessels imaged one to six times showed significant differences in vessel

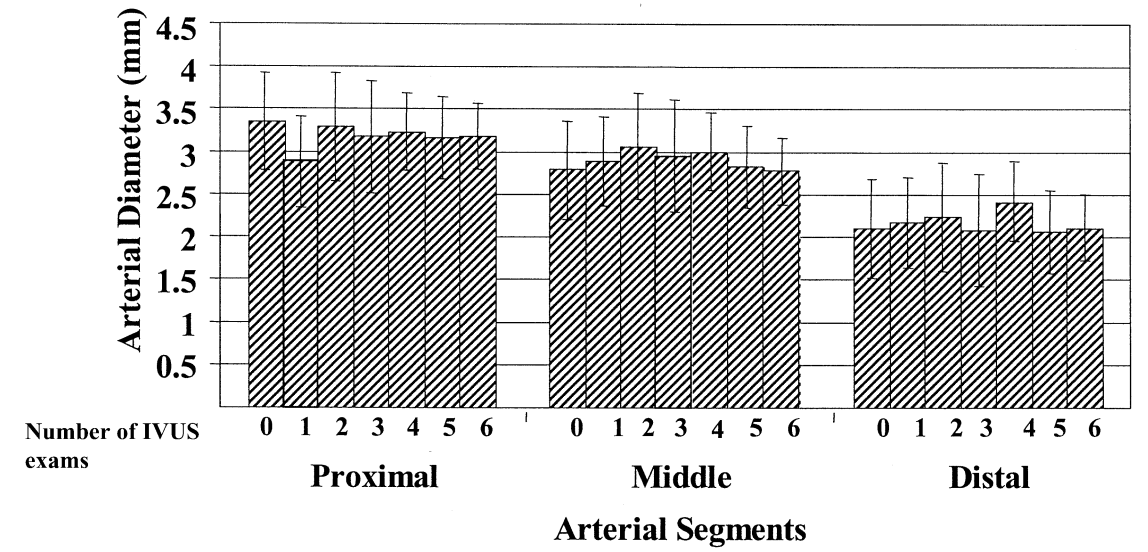

Figure 2. Arterial diameter of the left circumflex artery displayed by the Coronary Artery Surgery Study segment and the number of intravascular ultrasound (IVUS) exams. No significant difference was found among the diameters of arteries that had no IVUS exam versus those that underwent 1 to 6 exams.

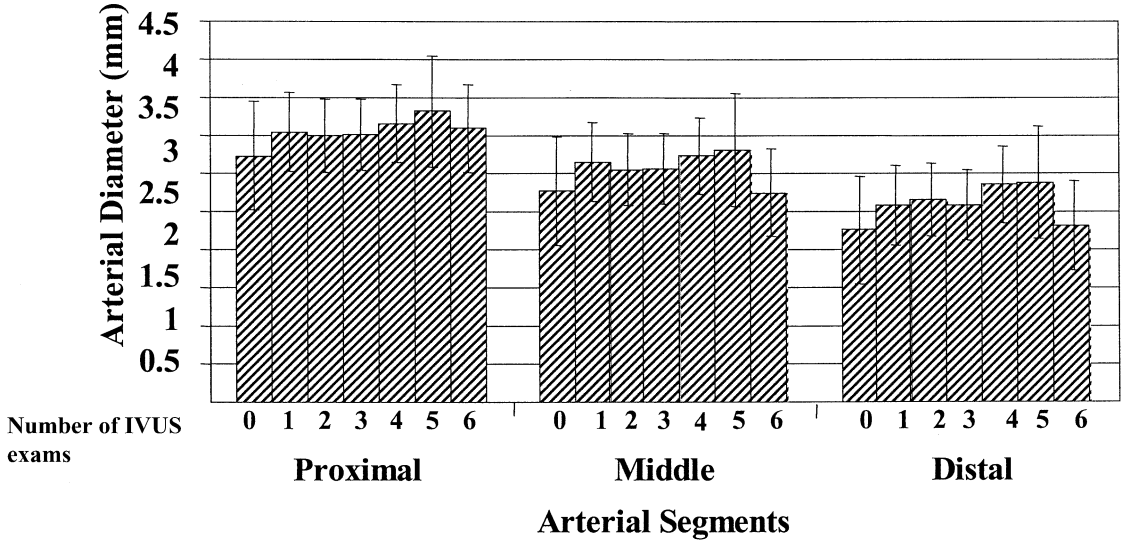

Figure 3. Arterial diameter of the right coronary artery displayed by the Coronary Artery Surgery Study segment and the number of intravascular ultrasound (IVUS) exams. No significant difference was found among the diameters of arteries that had no IVUS exam versus those that underwent 1 to 6 exams.

diameters or stenoses frequency. These results are important, because serial IVUS assessment of plaque volume has become an end point in studies examining transplant vasculopathy in cardiac transplant recipients and in assessing the progression and regression of native coronary atherosclerosis in nontransplant patients.

As applications for repeated IVUS examinations emerge, legitimate concerns over long-term deleterious effects of repeated intravascular manipulation arise. Animal studies have demonstrated that foreign body-induced endothelial injury can lead to the development of atherosclerosis. Moore et al. (10) demonstrated that placement of a catheter in a rabbit aorta resulted in intimal thickening and atherosclerotic plaque formation in areas of repeated wall contact. Lee et al. (11) observed in animals various forms of arterial wall injury resulting from instrumentation of arteries with a fiber-optic scope. The risk of endothelial injury was associated with large diameter of the scope, rigidity of the scope, and frequency of the interventions (11). However, human in-vivo data examining the effect of diagnostic intravascular catheters on intimal injury and progression of atherosclerosis are limited.

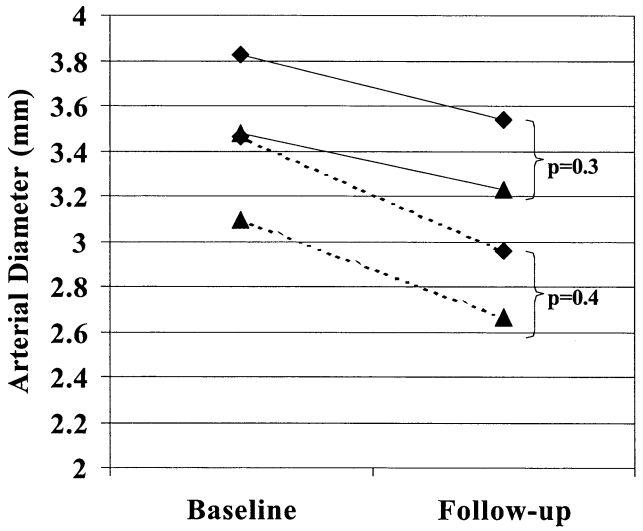

Figure 4. Baseline and follow-up quantitative coronary angiography measurements (up to four years after cardiac transplantation) of proximal and distal diameters in arteries with previous intravascular ultrasound (IVUS) exams (n = 60) and without previous IVUS exams (n = 33). A significant decrease in proximal and distal vessel diameters could be demonstrated in the nonimaged and imaged arteries. However, the change in diameter between baseline and follow-up exams in nonimaged as well as imaged arteries was not statistically different (see p value). **Diamond/solid line** = imaged proximal; **triangle/solid line** = nonimaged proximal; **diamond/dashed line** = imaged distal; **triangle/dashed line** = nonimaged distal.

The type and frequency of immediate complications of IVUS have been well described. These include vessel spasm, dissections, and guidewire complications (12–16). However, there is little data demonstrating the long-term safety of repeated IVUS exams and its effect on the progression of transplant CAD. So far, two publications have evaluated the long-term safety of IVUS. These studies describe results after a maximum of two previous IVUS exams. Pinto et al. (12) evaluated CAD progression in 38 cardiac transplant recipients one year after the initial IVUS examination. No significant difference in vessel lumen diameter was noted between the 49 imaged and 61 nonimaged vessels (12). Son et al. (17) evaluated annual QCAs of 86 heart transplant recipients over a period of two years post-transplantation. There was no significant difference in lumen diameters between imaged and nonimaged arteries after a maximum of two IVUS exams in 26 patients (17).

To our knowledge, this is the largest and the longest study evaluating the effect of repeated IVUS examinations on vessel lumen diameter and stenosis severity as assessed by QCA. Vessel diameter was measured in the three CASS segments of each epicardial artery in order to account for the diffuse nature of allograft vasculopathy. Discrete stenoses

were also evaluated in order to capture possible focal points of injury by the IVUS catheter that could progress to atherosclerotic lesions. We did not find any significant difference in the vessel lumen diameters and stenosis severity between imaged and nonimaged arteries, indicating no deleterious effect of repeated IVUS imaging. Data analysis revealed a statistically insignificant trend towards smaller diameters in nonimaged vessels. This can be attributed to the basis for selection of imaged arteries. Although our institutional protocol advocates multivessel imaging, safety is paramount (18). Operators have the discretion to forego imaging any artery with a potential increased risk of complication, such as smaller size, tortuous course, or unusual takeoff.

In a subset of patients, matched analysis was performed in which each artery (with and without IVUS exam) was evaluated with QCA of matched angiograms at baseline and follow-up after two, three, or four IVUS exams. There was a significant decrease in vessel diameter from baseline to follow-up QCA measurements in imaged as well as nonimaged vessels. However, when the change in diameter between baseline and follow-up was compared, no significant difference could be found in the nonimaged or imaged arteries. These results imply an overall progression of transplant vasculopathy with time regardless of previous IVUS exams. Similarly, Tsutsui et al. (19) demonstrated progressive lumen loss by serial IVUS measurements over a five-year period post-transplant.

Study limitations. Several limitations of our study warrant further discussion. First, patients with advanced vasculopathy did not undergo repeated IVUS examinations. Therefore, these findings pertain to patients with less severe disease. Second, arteries with smaller diameters were not imaged for safety considerations, thereby possibly affecting the lumen diameter measurements. Because our results are based on angiographic end points, atherosclerotic changes that do not result in luminal changes could not be analyzed. In a subset of patients, diameter measurements were performed at the same arterial site at baseline and follow-up. The required matching results in an unblinded comparison. However, the use of QCA should have minimized the bias from unblinding. Furthermore, this study was limited to cardiac transplant recipients, and, thus, the results may not be generalizable to nontransplant patients.

Transplant CAD is the most important cause for long-term mortality in heart transplant patients, and it is difficult to detect by angiography or noninvasive studies. Intravascular ultrasound allows early detection and monitoring of transplant CAD. However, IVUS is not widely used because of its invasive nature and lack of convincing safety data. Our study demonstrates that repeated IVUS imaging for the surveillance of allograft vasculopathy appears to be safe and does not accelerate transplant CAD. The results of this study can be used as a reference for safety in nontransplant patients who undergo serial IVUS studies until similar data specific to this patient population are available.

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REFERENCES

1. Miller LW. Role of intracoronary ultrasound for the diagnosis of cardiac allograft vasculopathy. Transplant Proc 1989;27:1989–92.
2. Waller BF, Pinkerton CA, Slack JD. Intravascular ultrasound: a histological study of vessels during life: the new "gold standard" for vascular imaging. Circulation 1992;85:2305–10.
3. Ventura HO, White CJ, Jain SP, et al. Assessment of intracoronary morphology in cardiac transplant recipients by angioscopy and intravascular ultrasound. Am J Cardiol 1993;72:805–9.
4. Klauss V, Rieber J, Uberfuhr P, Theisen K, Mudra H. Qualitative and quantitative assessment of cardiac allograft vasculopathy by intravascular ultrasound. Transplant Proc 1995;27:1975–6.
5. Kobashigawa JA. Coronary artery disease in the transplanted heart: why does it happen and what can we do about it? Cardiol Rev 1996;4:216–25.
6. Nissen SE. Rationale for a postintervention continuum of care: insights from intravascular ultrasound. Am J Cardiol 2000;86:12H–7H.
7. Ziada KM, Kapadia SR, Tuzcu EM, Nissen SE. The current status of intravascular ultrasound imaging. Curr Probl Cardiol 1999;24:541–66.
8. The Principal Investigators of CASS and Their Associates. The National Heart Lung, and Blood Institute Coronary Artery Surgery Study (CASS). Circulation 1981;63 Suppl 1:I1–81.
9. Hermiller JB, Cusma JT, Spero LA, Fortin DF, Harding MB, Bashore TM. Quantitative and qualitative coronary angiographic analysis: review of methods, utility, and limitations. Cathet Cardiovasc Diagn 1992;25:110–31.
10. Moore S. Thromboatherosclerosis in normolipemic rabbits. A result of continued endothelial damage. Lab Invest 1973;29:478–87.
11. Lee G, Beerline D, Lee MH, et al. Hazards of angioscopic examination: documentation of damage to the arterial intima. Am Heart J 1988;116:1530–6.
12. Pinto FJ, St. Goar FG, Gao SZ, et al. Immediate and one-year safety of intracoronary ultrasonic imaging. Evaluation with serial quantitative angiography. Circulation 1993;88:1709–14.
13. Batkoff BW, Linker DT. Safety of intracoronary ultrasound: data from a multicenter European registry. Cathet Cardiovasc Diagn 1996;38:238–41.
14. Hausmann D, Erbel R, Alibelli-Chemarin MJ, et al. The safety of intracoronary ultrasound. A multicenter survey of 2207 examinations. .Circulation 1995;91:623–30.
15. Alfonso F, Flores A, Escaned J, et al. Pressure wire kinking, entanglement, and entrapment during intravascular ultrasound studies: a potentially dangerous complication. Cathet Cardiovasc Intervent 2000;50:221–5.
16. Tobis JM, Mallery J, Mahon D, et al. Intravascular ultrasound imaging of human coronary arteries in vivo. Analysis of tissue characterizations with comparison to in vitro histological specimens. Circulation 1991;83:913–26.
17. Son R, Tobis JM, Yeatman LA, Johnson JA, Wener LS, Kobashigawa JA. Does use of intravascular ultrasound accelerate arteriopathy in heart transplant recipients? Am Heart J 1999;138:358–63.
18. Kapadia SR, Ziada KM, L' Allier PL, et al. Intravascular ultrasound imaging after cardiac transplantation: advantage of multi-vessel imaging. J Heart Lung Transplant 2000;19:167–72.
19. Tsutsui H, Ziada KM, Schoenhagen P, et al. Lumen loss in transplant coronary artery disease is a biphasic process involving early intimal thickening and late constrictive remodeling. Results from a 5-year serial intravascular ultrasound study. Circulation 2001;104:653–7.