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Clinical Utility of Negative Contrast Intravascular Ultrasound to Evaluate Plaque Morphology Before and After Coronary Interventions

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Although intravascular ultrasound (IVUS) is used for evaluation of plaque volume and lumen size as well as detection of vessel wall structures after catheter-based interventions, differentiation between the lumen and plaque structures can be difficult. This study attempted to evaluate the efficacy of negative contrast IVUS imaging for assessment of vessel wall morphology after coronary interventions. IVUS studies were performed in 67 lesions in 66 patients before and after coronary interventions. After the baseline ultrasound imaging run, warm 5% glucose solution was injected manually through the guiding catheter into the coronary artery to washout blood from the lumen to avoid speckled reflections from red blood cells (negative contrast). Quantitative measurements were obtained and plaque morphology was assessed for the presence and extent of medial dissections and intimal flaps. There was no difference in each quantitative parameter between baseline images and negative contrast images. The vessel wall boundary was clearly delineated from the lumen, which was defined as effective negative contrast in 51 of 67 lesions (76%). The baseline images revealed plaque dissection in 9 lesions (18%) and an intimal flap in 13 lesions (25%). In addition, 4 dissections (8%) and 16 intimal flaps (31%) were visualized during the infusion of negative contrast. Additional treatment was performed in 4 lesions (8%) based on the images with negative contrast. Negative contrast IVUS was more sensitive in demonstrating a plaque fracture than were baseline images. This method is useful for enhancing the diagnostic capability of IVUS imaging and may influence the decision-making process during interventional procedures. ©1999 by Excerpta Medica, Inc.

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Echogenic contrast agents have been used to delineate the vessel wall boundary during intravascular ultrasound (IVUS) studies in dogs.[1] An echogenic contrast agent like sonicated ioxaglate is safe and effective for myocardial contrast echocardiography.[2] Although contrast agents may detect a dissection plane or an ulcerated plaque that is connected to the lumen,[1] subtle morphologic changes of the luminal surface may be missed due to backscatter from blood cells. To overcome these technical difficulties, we injected 5% glucose solution into the coronary artery during IVUS imaging to provide a negative contrast agent that avoids backscatter from red blood cells. This study evaluates whether negative contrast IVUS imaging is clinically useful in assessing luminal morphology of the coronary artery after catheter-based coronary interventions.

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METHODS

Patient group: We studied 67 target lesions in 66 consecutive patients by IVUS and coronary angiography before and after coronary interventions (Table I). Balloon angioplasty was performed in 8 lesions, directional coronary atherectomy (DCA; Devices for Vascular Intervention, Inc. Redwood City, California) in 12, cutting balloon angioplasty (InterVentional Technologies Europe, Ltd., Donegal, Republic of Ireland) in 18, and Palmaz-Schatz stent implantation (Johnson & Johnson Interventional Systems, Warran, New Jersey) in 29. Informed consent for coronary interventions and the adjunctive IVUS studies was obtained from all patients ≥24 hours before the procedure. During catheterization, all patients received isosorbide dinitrate intravenously (5 mg/hour) after a bolus injection of 7,500 IU of heparin, followed by a continuous infusion of 1,200 IU/hour throughout the procedure. A 12-lead surface electrocardiogram was continuously monitored during the entire procedure.

IVUS imaging: IVUS imaging was performed with either a mechanical 3.2Fr, 30-MHz short monorail catheter (Boston Scientific Corporation, Boston, Massachusetts) in 60 patients, or a 3.5Fr, 30-MHz short monorail catheter (Boston Scientific Corporation) in the other 6 patients. Before the intervention, the IVUS catheter was placed over an 0.014-inch guidewire to a

TABLE I Patient Characteristics (n = 66)

Age (yr)	58 ± 7
Men/women	49/17
Coronary artery treated	67
Left anterior descending	38 (57%)
Right coronary	25 (37%)
Left circumflex	4 (6%)
Device selection	
Directional coronary atherectomy	12 (18%)
Palmaz-Schatz stent	29 (43%)
Cutting balloon	18 (27%)
Balloon angioplasty	8 (12%)

TABLE II Negative Contrast Effect Among Target Coronary Arteries

	Good	Poor
Left anterior descending coronary artery	25 (63%)	13 (34%)
Right coronary artery	25 (100%)	0
Left circumflex coronary artery	1 (25%)	3 (75%)

TABLE III Comparison of Plaque Morphology After Interventions Between Baseline and Negative Contrast Images (n = 51)

	Baseline	Negative Contrast
Dissection	9 (18%)	13 (25%)
Intimal Flap	13 (25%)	29 (57%)

position distal to the target lesion. The time gain control settings were adjusted to provide an optimal dynamic range. An automatic pullback imaging run was performed at 0.5 mm/s from the distal to the treated lesion to the guiding catheter. Then the IVUS catheter was again introduced to the treated segment. Warm (37°C) 5% glucose solution was injected manually through the guiding catheter into the coronary artery at about 5 ml/s to washout blood from the lumen and thereby avoid speckled reflections from red blood cells (negative contrast). The maneuver was repeated several times at each region of interest. After the coronary intervention, the IVUS catheter was reinserted distal to the lesion and the automatic pullback was repeated, followed by manual placement of the catheter at select locations during flushes of 5% glucose. IVUS studies were recorded on 1/2-inch high-resolution super VHS tape (Sony, Tokyo, Japan) for off-line analysis. In 3 patients, a pressure wire (RADI Medical Systems, Uppsala, Sweden) was inserted distal to the lesion during IVUS imaging to measure the changes in distal coronary artery pressure simultaneously during injection of the 5% glucose solution. In 8 patients, the target lesion was evaluated by coronary angioscopy after intervention. Angioscopy was performed with a 4.5Fr angioscope (Baxter Healthcare Corporation, Irvine, California).

IVUS analysis: The ability of the 5% glucose flushes to produce negative contrast was defined as effective if the reflections from the red blood cells completely disappeared during injection. If >10% of the lumen still had reflections from red blood cells, then the procedure was designated as ineffective. Quantitative measurements were obtained off-line from the videotape. Lumen cross-sectional area was defined as the area within the leading-edge echo; the external elastic membrane cross-sectional area was determined as the area within the media-adventitia boundary; plaque plus media cross-sectional area was calculated as the external elastic membrane cross-sectional area minus the lumen area; and the percent cross-sectional narrowing was defined as the plaque plus media cross-sectional area divided by external elastic membrane cross-sectional area. Each parameter was measured and compared between baseline images and the images obtained during negative contrast injection. Qualitative assessment of the IVUS images was performed by 2 blinded independent observers. Plaque morphology was assessed for the presence and extent of medial dissections and intimal flaps.

Statistical analysis: Statistical analysis was performed by use of StatView 4.11 software (Abacus Concepts Inc. Berkeley, California). All quantitative data are presented as mean ± SD. The paired Student *t* test was used to detect differences between continuous variables. Differences were considered statistically significant when the p value was <0.05.

RESULTS

There were no complications during the IVUS study with injection of 5% glucose solution into the coronary artery. There were no patients who developed arrhythmias, ST-T changes, or hemodynamic compromise during or after the procedure.

Qualitative contrast effects: An effective negative contrast was obtained in 51 of 67 lesions (76%) (Table II). In these lesions, the vessel wall boundary was clearly delineated from the lumen. Both observers' findings coincided except that 1 observer missed an intimal flap in 1 case on plain IVUS. There was a difference in the contrast effectiveness among coronary arteries (Table II). There were 51 lesions for which effective negative contrast studies were obtained to permit a comparison with baseline studies. The baseline images revealed plaque dissection in 9 of 51 lesions (18%) and an intimal flap in 13 of 51 lesions (26%). During the infusion of negative contrast, all of the dissections and intimal flaps that were seen at baseline were also recognized. In addition, there were 4 dissections (8%) and 16 intimal flaps (31%) that were visualized during injection of negative contrast that were not seen during baseline imaging (Table III). Of 51 lesions with effective negative contrast, there were 8 lesions after DCA, 23 lesions after Palmaz-Schatz stent implantation, 5 lesions after balloon angioplasty, and 14 lesions after cutting balloon angioplasty. Minor flaps within the surface of the plaque were visualized in all 8 lesions after DCA (Figure 1). Intimal flaps wavering through the stent

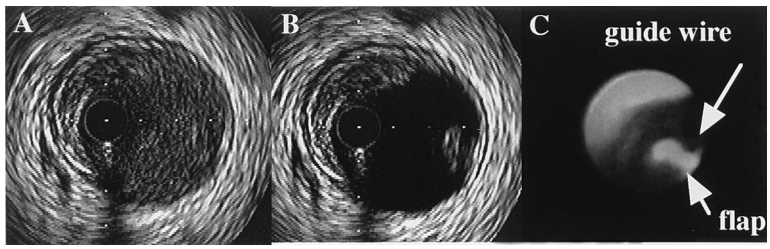

FIGURE 1. Intravascular ultrasound cross-sectional images and a coronary angioscopic picture of a representative case after directional coronary atherectomy. *A,* a plain ultrasound image showed a wide lumen with a small amount of residual plaque; *B,* a negative contrast image revealed a bulky flap at 3 to 4 o'clock, which was wavering. The border between the lumen and the plaque was also clearly demonstrated; *C,* coronary angioscopy comfirmed this flap.

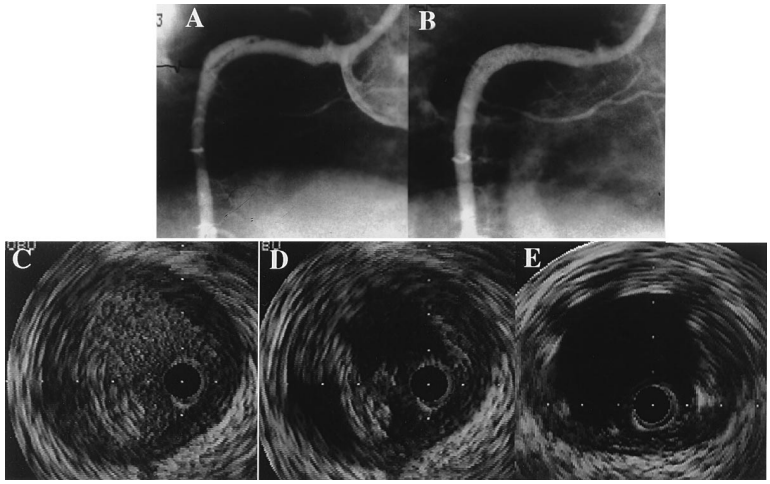

FIGURE 2. A representative case in which the negative contrast images influenced additional treatment. *A,* coronary angiogram after directional atherectomy revealed a dissection at the proximal right coronary artery; *B,* a plain intravascular ultrasound image demonstrated the wide lumen with a suspect of intimal flap at 6 o'clock; however, it was not clear because of reflections from red blood cells; *C,* a negative contrast image documented a large bulky flap which straddled the lumen; *D,* based on these findings, a Wiktor stent was subsequently implanted; *E,* intravascular ultrasound image after Wiktor stent implantation demonstrated that the flap was completely relieved with stent struts.

struts were demonstrated in 8 lesions (16%). Coronary angioscopy also confirmed that small intimal flaps were wavering within the stent struts in these lesions.

Additional treatment was performed in 4 lesions (8%) based on the images with negative contrast. A large intimal flap was documented with negative contrast imaging in a proximal right coronary artery after DCA (Figure 2). Based on this observation, a Wiktor stent was implanted. A bulky flap was demonstrated in 2 lesions for which repeat atherectomy cuts were performed. A medial dissection and intimal flap were revealed at the proximal site of a Palmaz-Schatz stent implantation. This was subsequently treated with an additional 9-mm Palmaz-Schatz stent implant (Figure 3).

Quantitative ultrasound measurements: There was no difference in the external elastic membrane area between baseline images and negative contrast images (20.3 ± 5.7 vs 20.7 ± 5.9 mm^2; $p = 0.057$). The lumen cross-sectional area did not change significantly during negative contrast injection (9.1 ± 3.2 vs 9.3 ± 3.2 mm^2; $p = 0.157$). Coronary artery pressure distal to the lesion increased significantly from 125 ± 14 to 158 ± 13 mm Hg ($p \leq 0.001$) during 5% glucose injection; however, it returned immediately to baseline level after the injection.

DISCUSSION

Enhanced diagnostic capability of negative contrast IVUS: In this study, the interfering reflections from red blood cells were removed in 75% of the lesions studied. This negative contrast effect was successful in all of the right coronary arteries studied, because the right coronary artery has fewer large branches than the left coronary artery. However, this technique was less effective in circumflex arteries (25%), because it is frequently not coaxial to the guiding catheter.

Detection of medial dissection and intimal flaps was more sensitive in images with negative contrast than in plain images. Baseline IVUS images revealed medial dissection in 18% and intimal flaps in 26% of the lesions after intervention. Negative contrast images demonstrated medial dissection in 26% and intimal flaps in 58% of the lesions. After Palmaz-Schatz stent implantation, angioscopy occasionally reveals intimal flaps protruding into the lumen through the stent struts.[3] In this study, an intimal flap wavering through the stent struts during contrast injection was revealed in 21% of the stented lesions. It is likely that angioscopy is superior to IVUS imaging in evaluating morphology of the luminal surface compared with plain images. Although this study does not provide an extensive comparison with angioscopic findings, negative contrast IVUS images provide better sensitivity for detecting dissections and intimal flaps than standard IVUS imaging.

Safety of the negative contrast IVUS: Distal coronary artery pressure significantly increased during injection, because bolus injection was performed manually. However, no major complication, hemodynamic compromise, or ST-T changes occurred during or after the procedure. In this study, 5% glucose solution was used as the contrast agent during IVUS imaging because that is the flush solution used routinely during catheterization, except in diabetic patients. Normal saline solution may also be used as a negative contrast agent. There was no difference in the visual contrast effect when we used either saline or 5% glucose solution for the same lesions in 10 patients.

Clinical implications: Accurate evaluation of complex vessel wall structures after transcatheter coronary interventions is clinically important. It has been re-

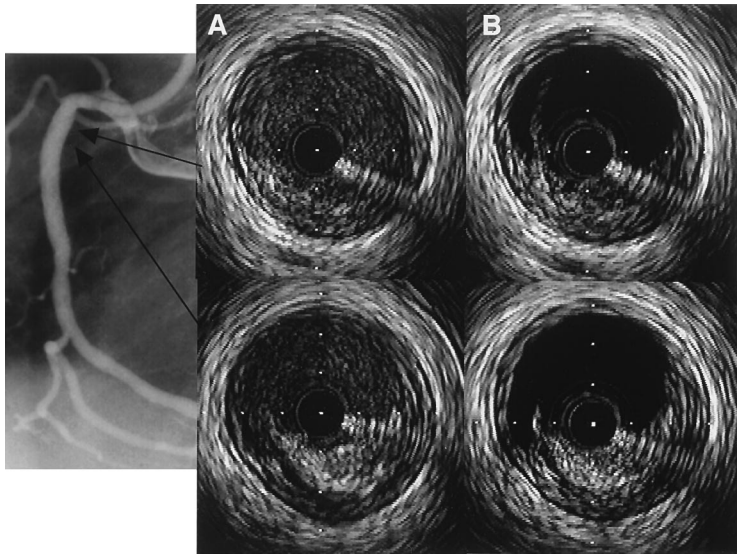

FIGURE 3. A case of an intimal flap that occurred at the proximal edge of the Palmaz-Schatz stent after high-pressure inflation. Coronary angiography showed a good result without dissections. *A,* a plain intravascular ultrasound image of the proximal edge of the Palmaz-Schatz stent is shown; *B,* a negative contrast image clearly revealed an intimal flap that may be a cause of an adverse event. This flap was successfully covered after additional Palmaz-Schats stent implantation.

ported that dissection after balloon angioplasty or DCA may cause adverse events.[4] In this study, in 4 of 67 lesions (6%) another intervention was performed because of the observations uncovered by the negative contrast study. It has been reported that restenosis of Palmaz-Schatz stents may occur at the edge of the implanted stent.[5] It is thought that dissection at the edge of the stent may be caused by high-pressure inflation, which in turn may be a stimulus for intimal hyperplasia. Negative contrast IVUS imaging may be useful in demonstrating an unsuspected edge tear or dissection after high-pressure stent implantation.

This method is also useful in training our eyes for interpreting standard IVUS images. The plain IVUS images should be reviewed after negative contrast IVUS studies reveal dissections and flaps. This feedback enhances our reading skills for evaluation of IVUS findings.

Study limitations: Volume overload may be a problem when the patient's cardiac function is poor. In patients with low left ventricular ejection fraction or history of congestive heart failure, the injection volume should be minimized. The 5% glucose solution should be warm (37°C), because cold solutions could generate arrhythmias. Because the 5% glucose solution was manually injected as a bolus, only 1 beat of adequate negative contrast is usually obtained at a specific cross section of the lesion. Repeat injections are necessary when the lesion is long. Occasionally the imaging element moves a bit longitudinally during the injection of 5% glucose solution. To minimize this phenomenon, one operator keeps the IVUS catheter in place and the other regulates the speed and volume of the injection.

In conclusion, negative contrast IVUS enhances the visualization of plaque surface morphology. This may be especially useful when using IVUS catheters with higher frequencies, because they usually have more reflections from red blood cells.

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