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INTRAVASCULAR ULTRASOUND

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Intravascular ultrasound has the unique advantage to study vessel wall morphology and pathology under the endothelial surface (32, 45). Although earlier prototypes have been described and tested in the seventies (2), the major impetus for its development into a practical tool was a consequence of the introduction of catheter-based interventions for treatment of atherosclerotic disease both in coronary and peripheral arteries. Knowledge of the characteristics of the atherosclerotic plaque (eccentricity, composition, effect of initial dilatation or ablation) would help in correct planning of the procedure, guidance during the intervention, assessment of results and diagnosis of complications. It would appear that detailed information on arterial wall morphology offers great research potential as well.

INSTRUMENTATION

Two approaches are currently applied to obtain cross-sectional images of the vessel wall. One approach is based on mechanical rotation of a single crystal (single element mechanical system) while in the other, several crystals are mounted around the tip of the catheter and used in sequence to scan around the circumference (multielement electronic system) (Fig. 1). Advantages and disadvantages of the two systems can be summarized as follows:

Single element mechanical systems: Mechanical rotation of the ultrasound element permits to circumferentially scan the vessel wall perpendicular to the long axis of the catheter. Rotating an acoustic reflector in front of a fixed transducer is an alternative approach. The principle is simple but realizing a driving mechanism while keeping the catheter fully flexible and steerable as well as its miniaturization are challenging problems. Distortion of the image because of an unequal rotation of the element/mirror at the catheter tip is a limitation of these systems. Their advantages are images with high resolution and without the presence of near-field artifact.

Multi-element electronic systems: Sixty-four transducer elements are mounted around the circumference of the tip of a catheter which is as thin as an angioplasty intracoronary catheter. The signal is processed and multiplexed via ultra-miniaturized integrated circuits contained in the tip of the catheter. Each transducer element transmits and receives independently. Thus, this dynamic aperture array differs from phased array technology in which elements are activated in concert. Advantages of the system are: the catheter shaft, containing conductive wires only, is very flexible; a central lumen is available for guidewire insertion; no distortion of the image due to inhomogeneous mechanical rotation is present; the system has the potential for further miniaturization (3.5 F catheters are available). The disadvantages are a

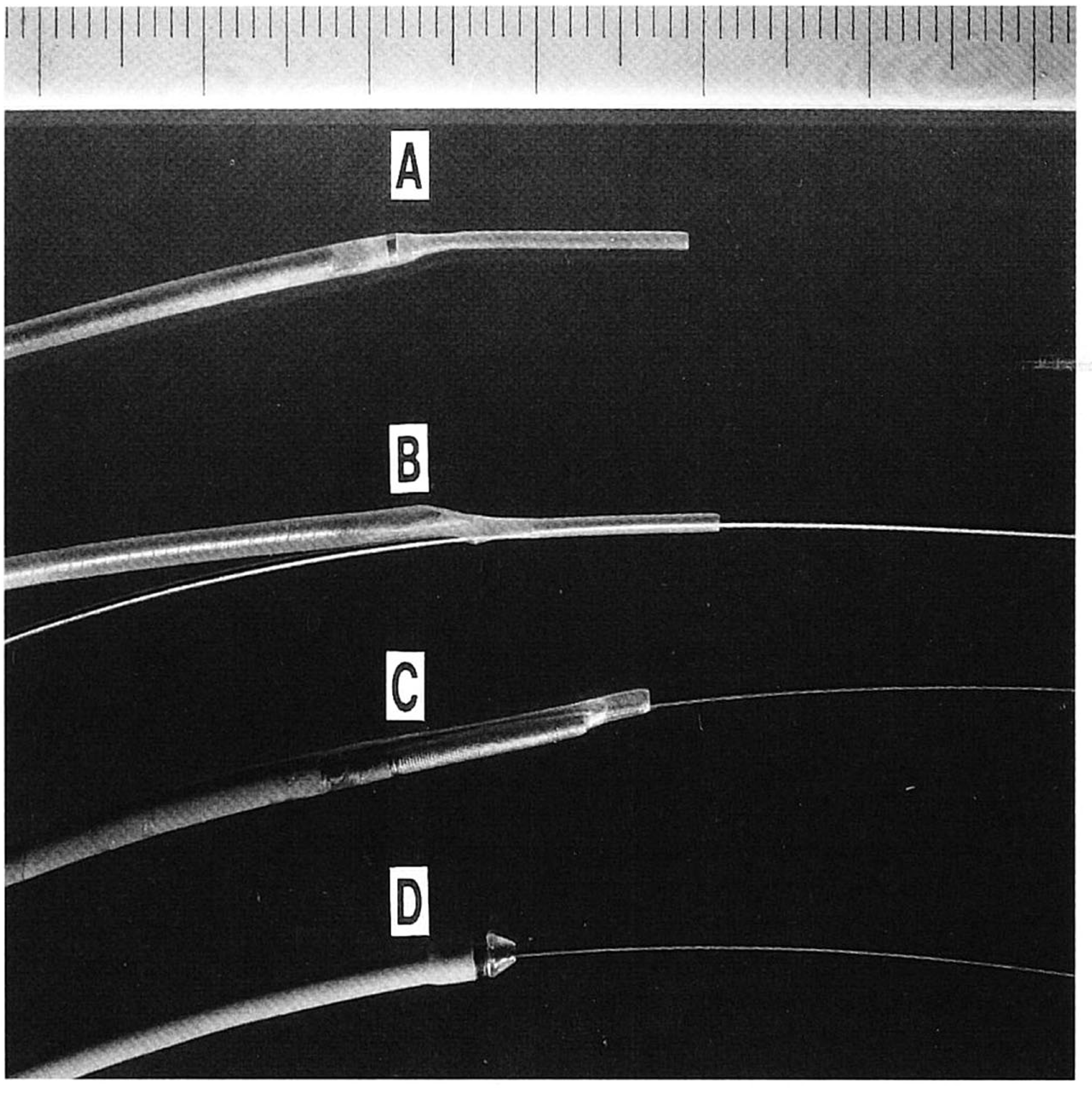

Fig. 1. Magnified image of the tip of four intravascular ultrasound catheters. A millimetric ruler is shown for comparison.
A) Intertherapy intracoronary catheter: a flexible driving shaft can be moved independently in an external plastic sheath;
B) Mechanical rotating element system (Cvis, Sunnyvale, CA); the presence of an inner lumen in the last 30 cm allows the use of a guidewire (Monorail system);
C) Multielement electronic system (Endosonics, Pleasanton, CA): a central free lumen for catheter insertion is available along the entire length of the catheter;
D) rotating element mechanical system (DuMed, Rotterdam, The Netherlands).

near-field artifact around the tip of the catheter, so that structures close to the catheter tip are not imaged, and the limited resolution and dynamic range of the system.

IMAGE INTERPRETATION

CHARACTERISTICS OF THE NORMAL WALL

In vitro and *in vivo* studies (10) have shown that it is possible to distinguish among different types of arteries. On the basis of the echographic appearance two distinct types of artery morphologies can be distinguished. Muscular arteries have a hypoechoic smooth muscle component in the media which results in a three-layered appearance (Fig. 2). Elastic arteries and veins have a more homogeneous appearance of their walls. Intimal atheroma and calcification may induce diffuse attenuation or shadowing and prevent the evaluation of the underlying media. Furthermore, fibrous degeneration of the muscular component of the media results in a homogeneous appearance in one fifth of the histologically muscular arteries (21). When a three-layered appearance is present the middle hypoechoic layer is used as a landmark for both the detection and quantitation of intimal and medial changes (41). A possible application of intravascular ultrasound can be the assessment of the changes in medial thickness induced by the presence of systemic arterial hypertension and the evaluation of the effects of long-term anti-hypertensive treatment.

STUDY OF THE ATHEROSCLEROTIC PLAQUES

Pathology studies have shown that coronary arteries undergo a progressive enlargement in relation with increases in plaque area, so that a reduction of lumen area is delayed until the atherosclerotic lesion occupies more than 40 % of the area circumscribed by the internal elastic lamina (9). These findings explain why angiographically normal arterial segments may show an extensive atherosclerotic involvement at autopsy, by direct surgical inspection and on intraoperative epicardial high-frequency echograms. When only segments with per cent area stenosis < 30 % were examined with intravascular ultrasound, an excellent correlation was observed between the area inside the internal elastic lamina and the plaque area. An increase of 2.7 mm^2 of the area circumscribed by the internal elastic lamina per each mm^2 of increase of the plaque area was observed, suggesting that arterial enlargement may overcompensate for early atherosclerotic changes. Lumen area was not correlated to per cent area stenosis for lesions with < 30 % area stenosis while with > 30 % area stenosis a significant inverse correlation between lumen and plaque area was observed (14). Angiography depicts only a silhouette of the vessel lumen, so that the extent of luminal narrowing can be misinterpreted in complex and eccentric lesions. Intravascular ultrasound has the potential of detecting atherosclerotic changes in the prestenotic phase and it allows the measurement of lumen and plaque area and the evaluation of plaque characteristics and complications. Dietary and pharmacologic interventions are likely to induce a regression of the vascular changes in the prestenotic rather than in the more advanced phases of atherosclerotic disease. Intravascular ultrasound has the potential capability of a direct analysis of these wall abnormalities and offers additional information since it differentiates lipid plaques potentially amenable to regression after intervention, from fibro-calcific plaques, less likely to respond to such an intervention.

In vitro experience: In vitro studies have shown that two types of atherosclerotic plaques can be distinguished (10, 21). "Hard" plaques are seen as bright lesions composed of dense fibrous tissue, with shadowing and duplicate echoes in the presence of calcific deposition. Soft plaques consist of fibromuscular tissue, loose collagen or of markedly hypoechoic areas of lipid deposition or intraplaque necrotic degeneration.

Trombi, plaque rupture and dissection after an intervention can be detected with great detail.

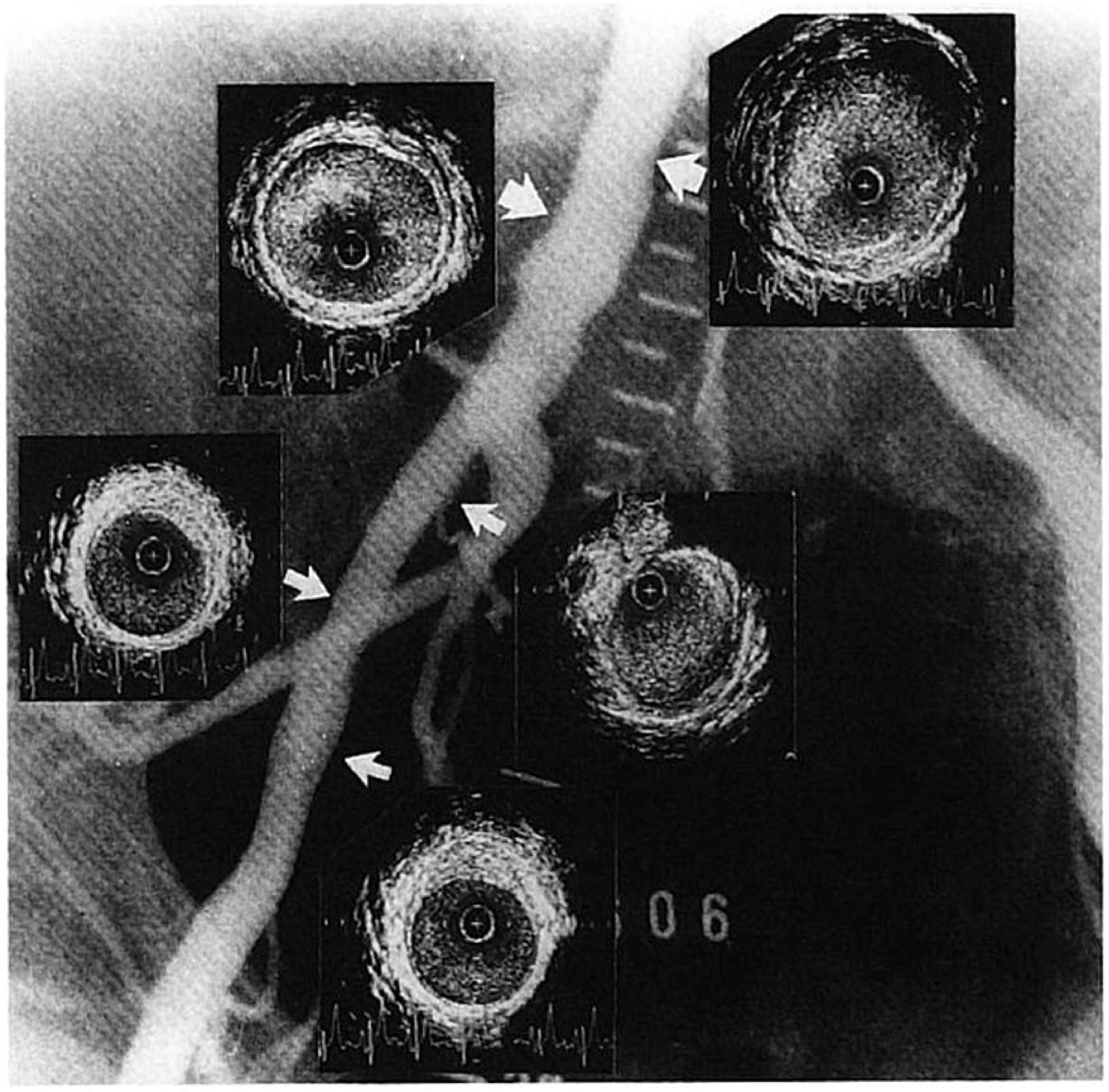

Fig. 2. Digital angiogram of the right iliac artery showing multiple edge irregularities and mild stenosis. Note the superimposition of the contour automatically traced by a computer assisted quantitative angiographic system (DCI, Philips, Best, the Netherlands). The arrowheads indicate the position of the ultrasound transducer during the acquisition of the displayed arterial cross-sectional images. Note the relatively concentric bright ring of intimal thickening in the upper image, corresponding to an apparently normal circular lumen at angiography. In the following two cross-sections an eccentric, fibrocalcific plaque is shown in a segment of moderate lumen diameter stenosis with quantitative angiography. Note the two lowest ultrasonic cross-sections, corresponding to a normal segment at angiography but showing a semilunar bright eccentric atherosclerotic plaque not protruding inside the regular circular lumen with ultrasound. Calibration: 1 mm.

Clinical experience: Imaging of the aorta, iliac and femoral arteries can be obtained safely using a retrograde introduction of the ultrasound catheter through an arterial femoral sheath (25). Severity of stenosis, type and extent of atherosclerotic plaque and involvement of the medial layer (11) can be assessed (Fig. 2). Quantitative analysis of lumen and plaque area shows a close correlation with

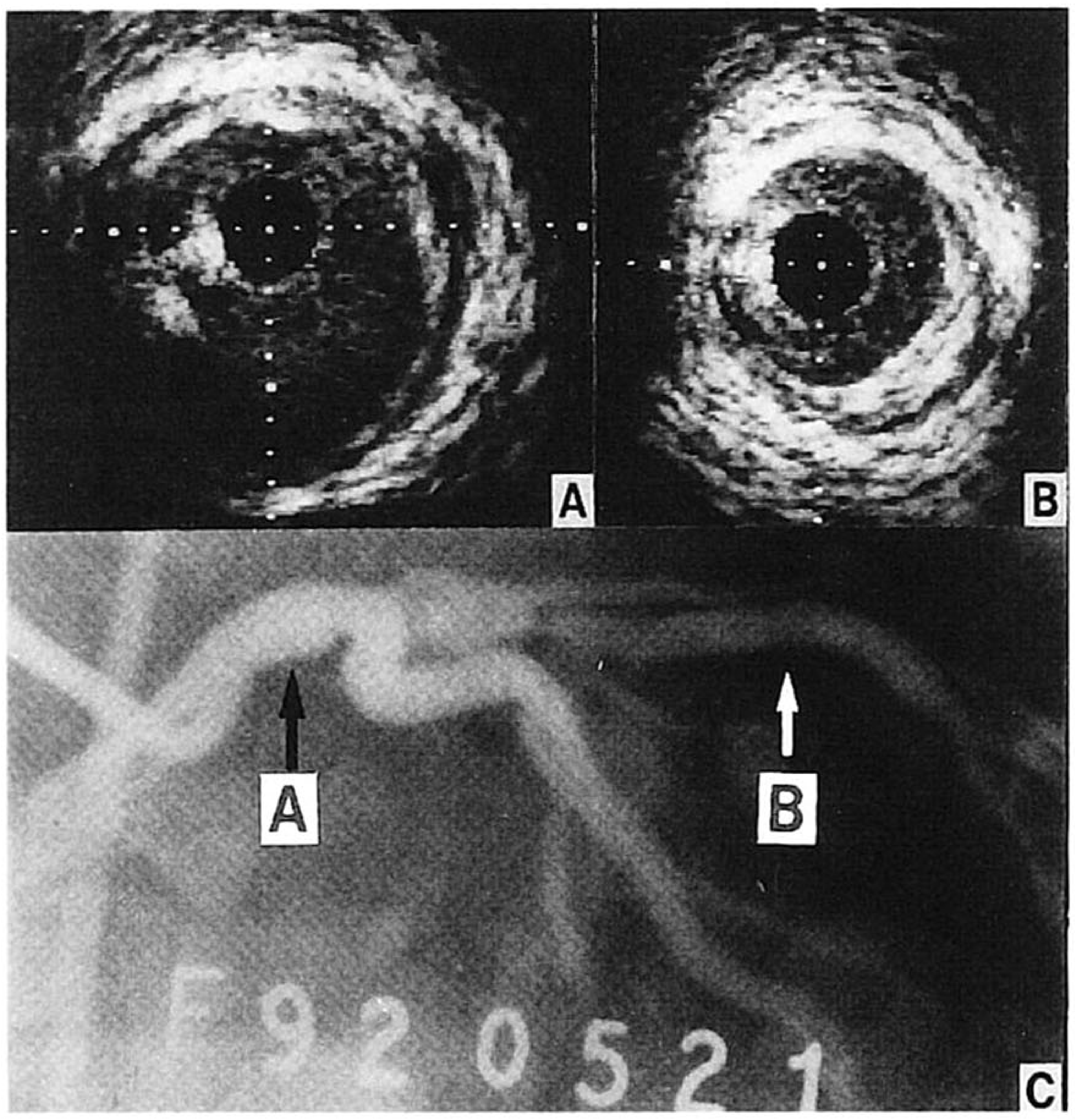

Fig. 3. A) The presence of a hypoechoic middle layer allows the delineation of a diffuse area of intimal thickening in an apparently normal segment of the left main coronary artery;
B) Despite a smooth angiographic contour intravascular ultrasound shows an eccentric plaque also in the middle segment of the left anterior descending coronary artery. Calibration: 0.5 mm.

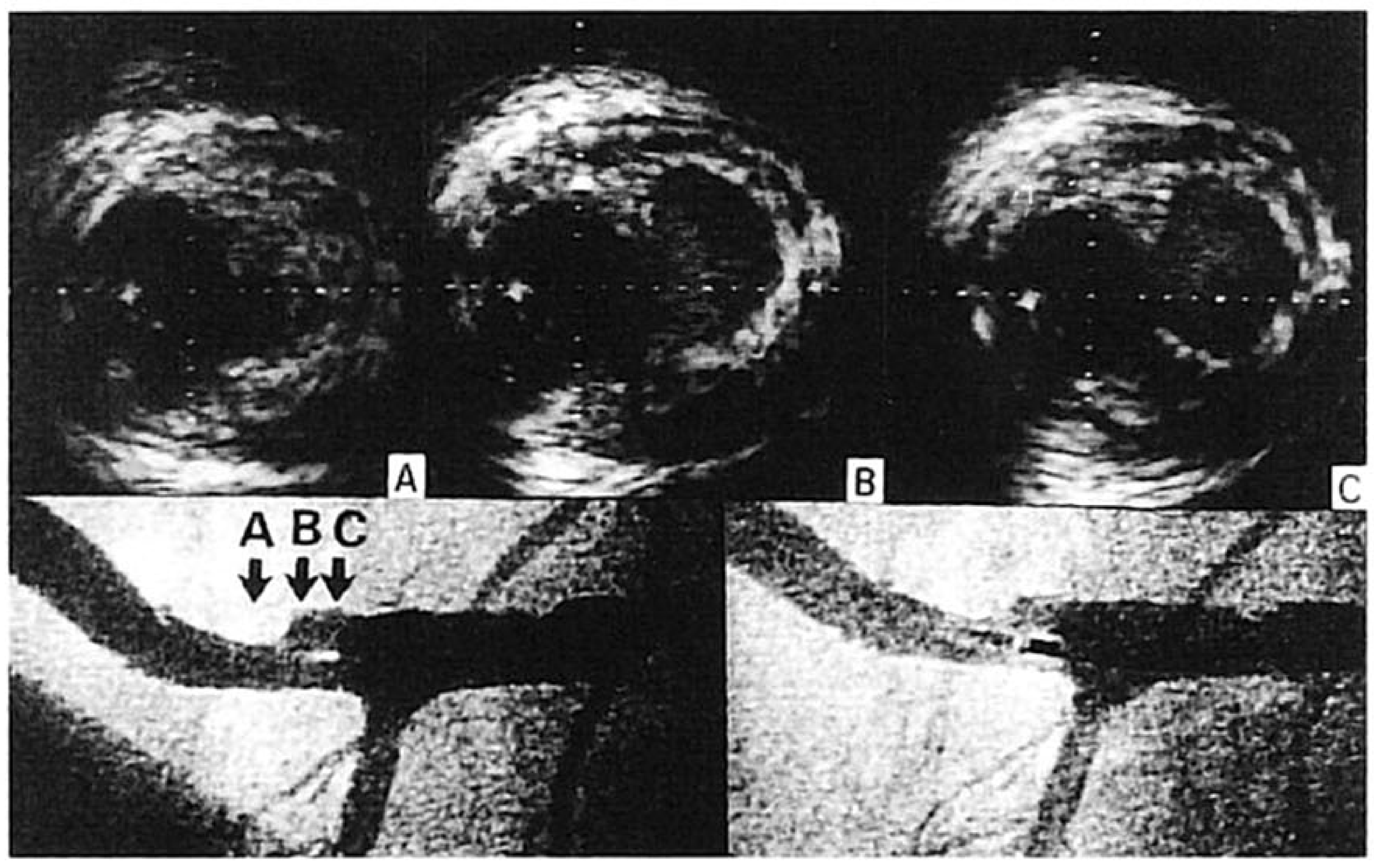

Fig. 4. Upper panels: Intravascular ultrasound identifies proximal to the plaque ulceration detected with angiography a large eccentric "soft" plaque (A). In the panels B and C a second channel communicates with the true lumen. Note the increased echogenicity of the blood elements in this second lumen. This spontaneous contrast effect suggests a lower flow velocity in this second lumen. Calibration 0.5 mm.
Lower panels: Cineangiogram showing a complex atherosclerotic plaque proximal to the anastomosis on the left anterior descending coronary artery of a sequential saphenous vein bypass graft seen years after surgical insertion.

angiography (6). Various interventions such as transluminal angioplasty, atherectomy, laser angioplasty and endovascular stent delivery are accurately monitored (18). In comparison with angiography, intravascular echography demonstrates a higher sensitivity in depicting presence and extent of dissection, length of intimal tears and characteristics of flow in the true and false lumen. Direct insertion of the ultrasound catheter during surgery can be used to replace more complex angiographic procedures in the evaluation of the efficacy of arterial bypass operation or endoarterectomy in peripheral vessels (38).

Smaller and more flexible catheters, amenable to guidewire insertion, have stimulated the clinical intracoronary application, mainly in combination with intracoronary interventions. In the coronary system intravascular ultrasound is able to detect and characterize atherosclerotic changes in angiographically normal segments (Fig. 3) and in the presence of edge irregularities or luminal stenoses (26, 37) (Figs 3, 4). Serial coronary arteriography is used to uncover the development of diffuse coronary narrowing in the transplanted heart (34, 35). With intracoronary ultrasound, however, marked coronary intimal thickening has been detected despite a normal angiographic appearance of the coronary arteries.

Before coronary interventions, intravascular ultrasound has the potential to distinguish "soft" plaques, more likely to be dilated by compression, stretching and superficial intimal tears, from "hard" or clearly calcific plaques, at risk of extensive dissection (23). The presence of diffuse subendothelial calcification is associated with a lower success rate and higher risk of complications after directional coronary atherectomy, suggesting that alternative techniques such as rotational or laser atherectomy should be used (8). A "smooth-walled" appearance is the most common angiographic pattern after balloon dilatation (41 %), followed by intimal flaps (22 %) and intraluminal haziness (17 %) (15). The presence of a dissection flap with angiography is a predictor of abrupt occlusion after angioplasty, resulting in a 6,5-fold increase of

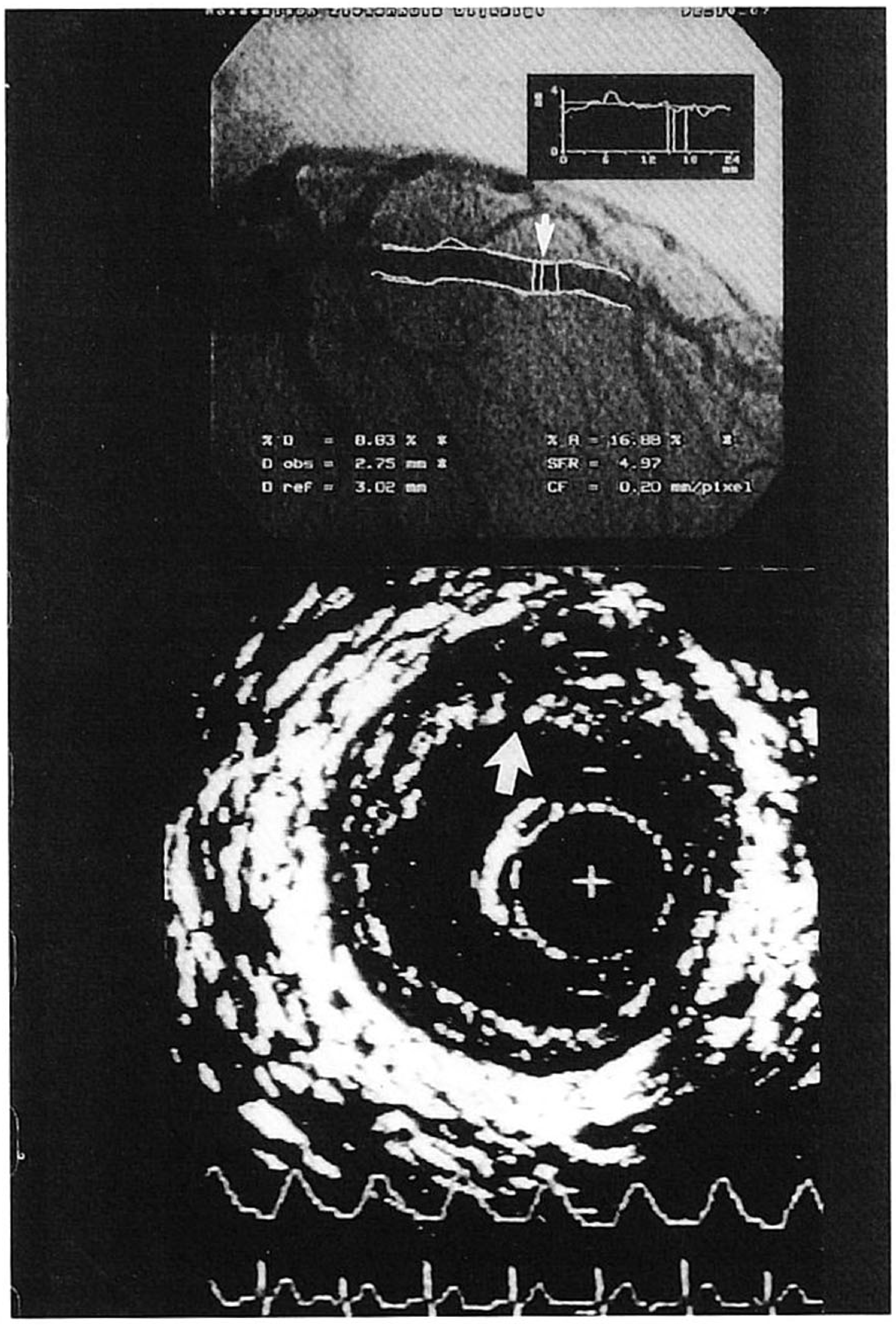

Fig. 5. Upper panel: Smooth regular appearance of the middle segment of the left anterior coronary artery after successful balloon dilatation. Note the quantitative angiographic analysis showing a residual diameter stenosis < 10 %.
Lower panel: The corresponding intravascular ultrasound cross-section at the site of treated lesion shows a clear intimal dissection involving the arterial media for less than 50 % of its circumference.
Calibration: 1 mm.

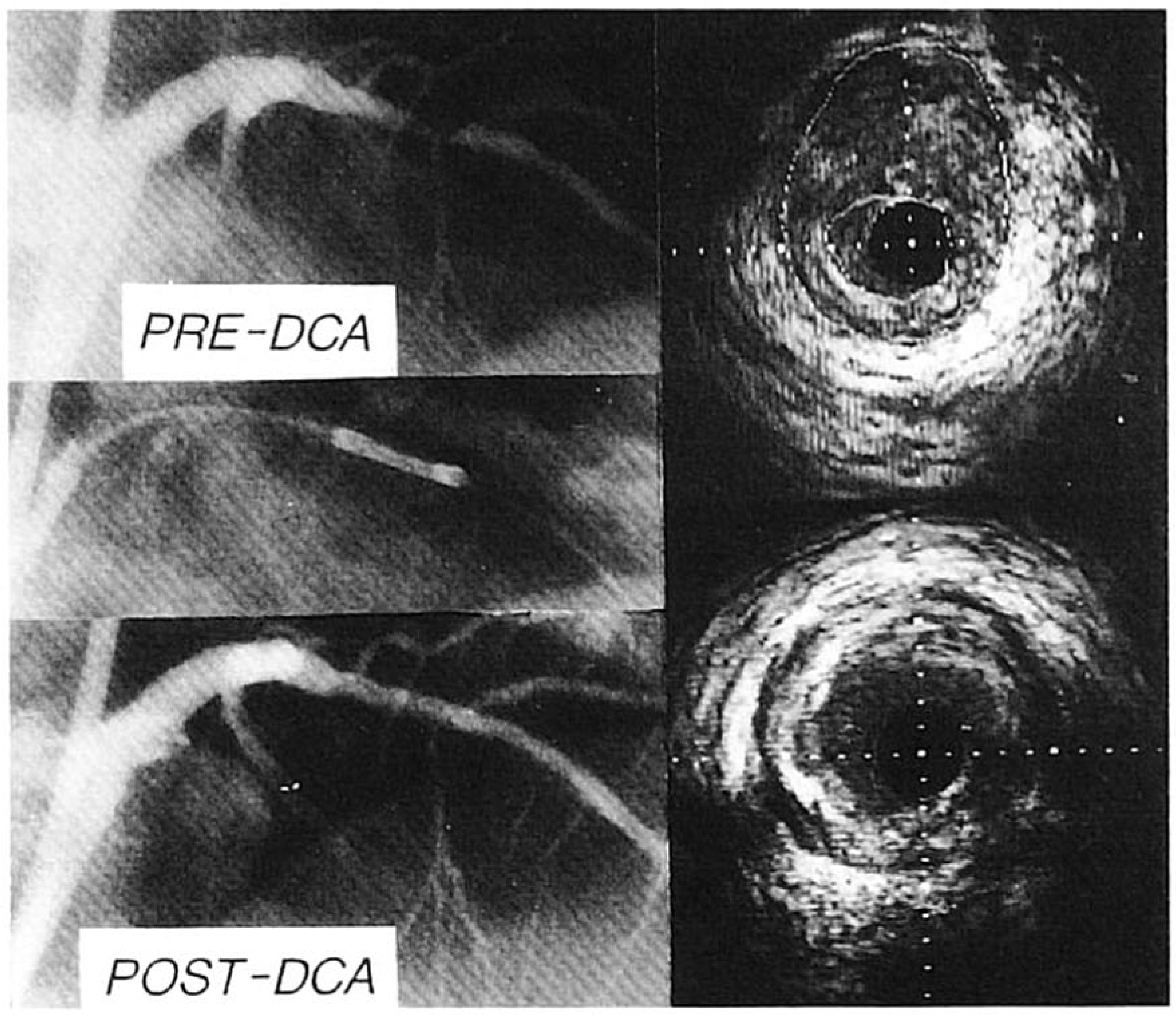

Fig. 6. Left panels: Cineangiogram of a left anterior descending coronary artery before and after successful directional atherectomy (DCA).
Right panels: The corresponding cross-section before coronary atherectomy shows a large eccentric "soft" plaque delineated by manual contour tracing. Post-atherectomy a clear reduction of the plaque area and a polylobulated contour of the lumen indicates successful plaque ablation. Thrombus material with various degree of organization and fibrous tissue were observed in the retrieved specimens with histology.

a major complication in the following 24 hours (3). However, the identification of the patients at high risk, requiring prophylactic treatment such as stent implantation, is not possible based on the angiographic findings. Furthermore, the presence of dissection immediately after balloon angioplasty is not a predictor of late restenosis (13). Intravascular ultrasound is more sensitive than angiography in detecting development and characteristics of dissection following interventional procedures (16, 36, 42, 44) (Figs 5, 6). Immediate complications and long-term results can be predicted based on the morphological findings after the interventional procedure. Pathological studies have shown that intimal splits or cracks with localized medial dissection are an essential mechanism of successful balloon angioplasty. Extensive medial tears (> 50 % of the vessel circumference), however, are at risk of abrupt closure (39, 40). Intravascular ultrasound can identify circumferential and longitudinal extension of a dissection postangioplasty (16, 20). An increased risk of abrupt occlusion requiring stent implantation or emergency coronary bypass graft implantation was observed in the presence of circular dissections. These lesions showed an increased risk of long-term restenosis (> 50 %). At the other extreme, a higher restenosis rate has been reported in the absence of intimal dissection, when only plaque stretching is the mechanism of lumen enlargement (16). The delivery of stents and the evaluation of the development of intimal hyperplasia inside these poorly radio-opaque devices can be more accurately monitored. Intraoperatively, ultrasound catheters can be used in native arteries and bypass grafts in order to exclude severe stenosis distal to the anastomosis and to examine the anastomotic site.

APPLICATIONS IN NON-ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

Intravascular ultrasound can be used in the assessment of various cardiac and vascular structures. Using 20 MHz (29) and, more recently, 12.5 MHz (28) transducers this technique has been used for intracardiac imaging. Cardiac structures including the interatrial septum, *fossa ovalis*, atrial wall, coronary sinus, tricuspid valve, right ventricular myocardium, pulmonary valve and arteries, aorta, aortic valve, mitral valve (transseptal catheterization) and left ventricular myocardium have been visualized with excellent image quality.

Valvular heart disease: In patients with calcific aortic stenosis, a condition in which conventional echographic assessment is difficult, intravascular ultrasound can discriminate bicuspid from tricuspid valves and may allow direct assessment of valve area (17).

Diseases of the aorta: Recent reports of intravascular ultrasound detection of acute aortic dissection have shown that this technique can determine location and extent of this vascular lesion (27).

Congenital heart diseases: Intravascular ultrasound has been applied with success in the evaluation of patients with aortic coarctation before and after balloon angioplasty (12) and in patients with right ventricular outflow tract obstruction. Other potential applications include monitoring of percutaneous closure of atrial septal defect or patent *ductus arteriosus* (30).

Detection of venous thrombosis and pulmonary embolism: Fresh thrombus has a "soft" and characteristic granular appearance and can be differentiated from vascular structures and the surrounding circulating blood (7). In both animal and human experience, intravascular ultrasound has been found superior to both cavography or external sonography for the detection of the presence and extent of intraluminal thrombi after application of inferior vena caval filters (22). In patients with pulmonary hypertension due to chronic pulmonary thromboemboli precise assessment of their location and extent has been obtained with the ultrasound catheter in the pulmonary trunk and branches. These echographic findings have been subsequently confirmed at surgery (31).

PROBLEMS AND LIMITATIONS

At present, intravascular ultrasound must still be considered as a research tool and several technical limitations are to be solved before it will find widespread application in daily clinical practice. The miniaturization of the currently available ultrasound catheter is still insufficient to allow the study of a clinically significant stenosis and of distal coronary arteries. Prototype catheter systems smaller than 3 F are under clinical evaluation.

All the elements of the catheter, including the distal end where the echo-transducer is mounted, must be fully flexible in order to allow safe and successful negotiation of tortuous vessels, especially in intracoronary application.

The present images are not consistently of sufficient quality to allow a complete evaluation of vascular dimensions and morphologic changes with the currently available systems.

Shorter acquisition times are desirable for a more precise analysis if one wishes to study systo-diastolic changes in luminal dimensions and for imaging cardiac chambers and valves.

Limited steerability of the intravascular ultrasound catheters precludes the correction of a non-coaxial or eccentric intravascular position. The perpendicularity of the ultrasound beam to the vascular wall influences the intensity with which the structure is visualized and partial drop-outs occur above a critical angle (20). In addition, the "blooming" effect induced by off-axis position of the catheter results in an overestimation of the vascular lumen and wall (24).

Intravascular ultrasound is an expensive technology. The additional diagnostic and prognostic information in recanalization procedures must be confirmed in large studies before the expected benefit outweighs the cost.

Knowledge of the appearance of normal and diseased vascular walls together with technical skills for its use in complex interventional procedures are mandatory for a successful clinical application of this technique. Consequently, a relatively long learning curve is required in order to optimize the results of individual operators.

POTENTIAL CLINICAL AND RESERACH DIRECTIONS

Efforts are directed in the combination of intravascular imaging with ablation techniques, so that the echographic cross-sectional image can be used for accurate application of the selected atherectomy technique aiming at maximal plaque removal without damage to the underlying vessel wall (1, 5).

Forward imaging would make assessment of vascular disease more comprehensive and guidance for intervention more practical.

The implementation of software systems for quantitation and three-dimensional reconstruction (33, 20), providing spatial orientation and safe application of ablation devices, is a research goal.

Analysis of the backscatter signals would allow a more accurate and quantitative characterization of plaque components (19).

The combination of intravascular imaging with recording of blood velocity with a Doppler transducer mounted on the same catheter or on a separate guidewire would allow measurement of basal and postintervention absolute regional vascular flow. In this way the effects of vascular stenoses can be adequately studied by integrating anatomic (stenosis cross-sectional area) and physiologic data (velocity increase at the site of the stenosis, regional flow reserve).

With the combination of intravascular imaging with simultaneous recording of high-fidelity blood pressure, arterial compliance can be accurately calculated from the slope of the pressure-dimension relationship (43). With this method the changes induced by disease or aging on the arterial wall can be evaluated and the effects of pharmacologic agents can be monitored.

CONCLUSIONS

Intravascular ultrasound offers the potential to obtain unique information for selection and guidance of catheter-based vascular interventions, detects the complications of these treatments, provides prognostic information on atherosclerosis and allows the assessment of the effects of dietary and pharmacologic interventions in high-risk patients. Furthermore, if reliable information on medial thickness can be obtained, the technique can have a tremendous impact on the study of the arterial changes in systemic arterial hypertension and of the effects of drug treatment. At present, however, intravascular ultrasound remains largely a research tool and the acquisition of a larger and systematic clinical experience is needed to determine the diagnostic and prognostic role of this technique.

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