INTRAVASCULAR ULTRASOUND IN PERIPHERAL VESSELS

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INTRAVASCULAR ULTRASOUND IN PERIPHERAL VESSELS

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Een vrolijk hart bevordert de genezing, maar een verslagen geest doet het gebeente verdorren.

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Aan mijn vader en ter nagedachtenis aan mijn moeder.
Voor Karin, Nikkie en Maarten.

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CHAPTER 1

GENERAL INTRODUCTION

Salem H.K. The, Elma J. Gussenhoven, Hero van Urk

CHAPTER 1

GENERAL INTRODUCTION

Atherosclerosis is the principal cause of death in western civilization, with high morbidity and mortality rates [1,2]. This common vascular disease represents a series of cellular changes in the arterial wall resulting in the growth of an atheromatous plaque with encroachment on the media and significant reduction of the lumen.

It is a challenge for medical practitioners and researchers to fully understand the complex etiology of atherosclerosis. To arrest the atherosclerotic process, to stimulate regression of the vascular lesion, or to treat symptoms, a variety of vascular treatments, both medical and surgical, have been and are still being developed. In all cases an eminent need exists to correctly diagnose the extent and severity of disease and the effects of therapy.

Angiography still is the standard method for identifying the location and severity of stenotic lesions. The technique provides a silhouette of the vessel lumen, so that the presence of vascular lesions is derived indirectly from irregularities of the luminal contour and its diameter. The technique, however, does not provide a sufficient insight into the cross-sectional area, the shape of the stenotic lesion or the morphology of the lesion. Pathology studies and, more recently, the application of intravascular ultrasound have shown that in the process of atherosclerosis arteries undergo an enlargement in relation to an increase in plaque area. These findings explain why a mild degree of luminal narrowing assessed angiographically may in fact represent an advanced atherosclerotic lesion [3,4]. The limitations of angiography may be overcome by using intravascular ultrasound, which has the unique capability to study vessel wall morphology and pathology beneath the endothelial surface in a cross-sectional manner [5-12]. The technique has proven reliable in *in vitro* studies to determine the constituents of the vessel wall, qualitatively as well as quantitatively.

The precise role of intravascular ultrasound in the clinical setting is currently being determined in ongoing studies. The major goals in the treatment of vascular obstructive disease are to improve the primary and long-term success rate of interventions and reconstructions, to reduce the restenosis rate and to reduce complications. The use of intravascular ultrasound may contribute to these goals. In the first place, it may help to improve the definitions of *in vivo* vascular pathology. In doing so, it may provide useful information to better select patients for specific and/or additional treatment modalities such as balloon angioplasty, atherectomy, stenting or a bypass operation - and in this way improve overall results of therapy.

It is realistic to say that only if intravascular ultrasound provides important data that affect clinical decisions or prognoses, this new technique may be here to stay.

History of intravascular ultrasound

During the last decades, several attempts have been made to obtain information on cardiac movements or intraluminary observations with various ultrasound catheter tip systems.

Wells reported in 1966 the first mechanical device applied in veins [13]. A 3 mm intravascular catheter containing a 1.5 MHz ultrasound crystal brazed onto a long stainless steel tube of 1.63 mm diameter was inserted in the inferior caval vein in 2 patients. Although the registration was not perfect, several features were clearly seen in the echogram, whilst others, equally important, were not displayed at all. The disappointed result was due to the poor sensitivity and long transmission pulse of the probes in those days.

In 1967 Omoto described a mechanical system whereby scanning of the heart was attained by rotation of a catheter [14]. Two years later (1969) Carleton and coworkers described a non-directional cylindrical catheter tip crystal [15]. At the same time, Eggleton and colleagues used a four-crystal catheter [16]. This system depends on a stable state of the heart, so that each beat is identical. By rotating the catheter and accumulating the data over many beats, a cross-sectional view in a selected 'steady state' is reconstructed. However, none of these systems has ever been developed to a practical level, or was able to provide real-time cross-sectional information on moving cardiac structures or real-time images of arteries or veins.

In 1972, Bom and coworkers stimulated the development of a catheter device which could be used to instantaneously visualize cross-sections of larger arteries and could be positioned inside the heart for observation of the moving cardiac structures [17]. It was suggested that for analysis of the heart function, continuous visualization of the cardiac wall would be of great importance. Developed in Bom's laboratory, the system contained a 32-elements 5.5 MHz catheter tip system (outer diameter 3 mm) based on a phased array principle. It was shown that such a catheter, applied in a pig, provided real-time information on the cardiac function (Figure 1).

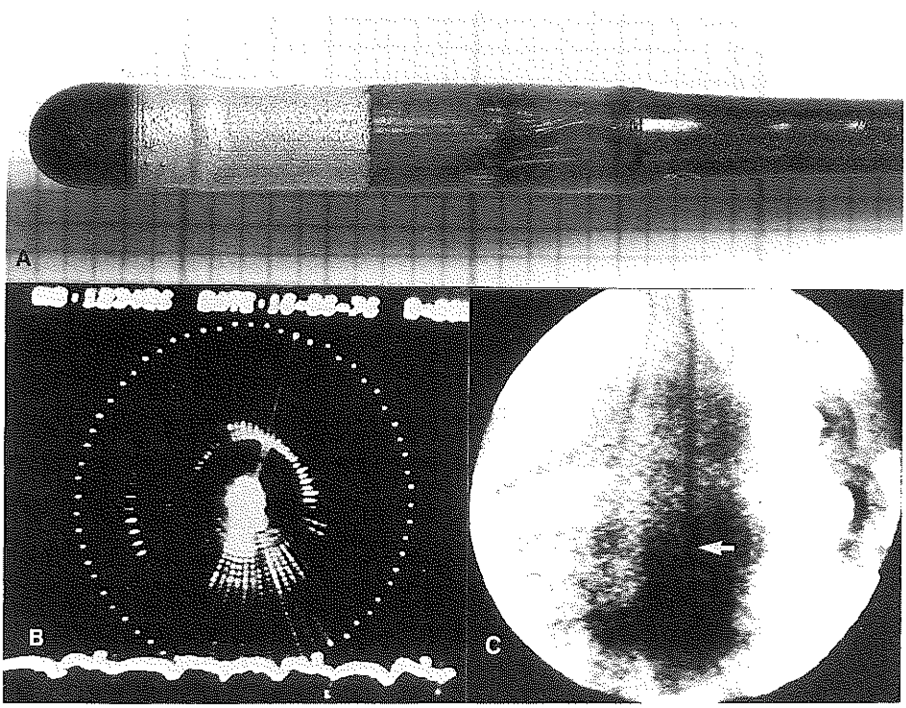

Figure 1. A, The phased array 32-elements 5.5 MHz catheter as described by Bom in the early seventies. **B and C**, Ultrasound cross-sectional cardiac structure of a pig's heart is visualized while the catheter is situated inside the heart (arrow).

Given the limitations in technology, it took another 15 years before intravascular ultrasound catheter tip devices became available that provided more detailed and sophisticated images. An important improvement of the image quality was attributed to the availability of higher frequency transducers. The advantage of high frequency ultrasound transducers is that these elements are smaller and can be mounted into small diameter catheters. With the introduction of endovascular intervention techniques, the initial interest of intracardiac imaging could now be expanded to intravascular imaging.

Current intravascular ultrasound systems are either based on electronically switched elements, synonymous with phased array or on mechanical single-element devices. All available catheters have in common that they are very flexible.

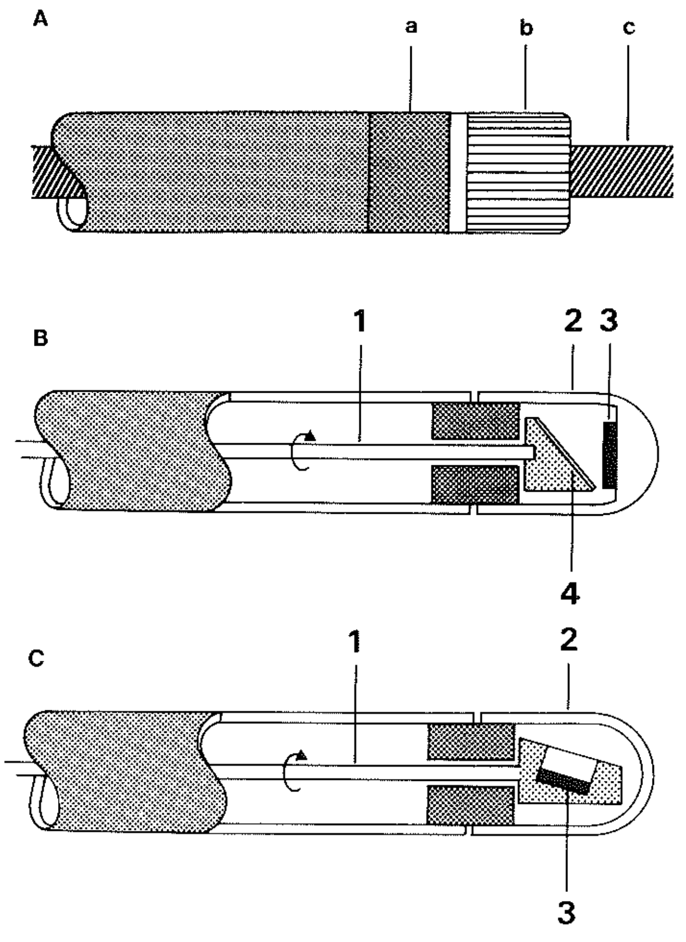

Figure 2. **A**, Electronically switched phased array (multi-element) catheter tip. **B**, Mechanically driven single-element catheter tip with mirror. **C**, Mechanical rotating single-element catheter tip. a= integrated circuitry for reduction of the number of wires; b=transducer elements; c=guide wire; 1=rotating shaft; 2=transparent dome; 3=transducer element; 4=acoustic mirror.

Electronic switched-phased array (multi-element) system

The principle of this system has been described by Bom and coworkers [17]. The catheter contains a number of small acoustic elements which are positioned cylindrically around the catheter tip (Figure 2).The number of elements may be any practical number, such as 32 or 64. Each transducer element transmits and receives independently. The tip may contain an electronic component to reduce the number of wires. The construction allows for a central guide wire for easy introduction into an artery. Another advantage of this system is the absence of image distortion due to inhomogeneous mechanical rotation. Conversely, near-field artifacts and limited resolution form the major disadvantages of the system.

Mechanical rotating mirror (single-element) system

In this system real-time images are obtained by a rotating mirror which deflects the ultrasound emitted by a stationary single-element transducer which is situated in front of the acoustic mirror (Figure 2). The non-moving transducer avoids the necessity of rotating electrical wires. The rotational force of the mirror is provided by means of a long, flexible driving shaft through the catheter. Inconsistent mechanical rotation due to excessive jerking or lagging of the driving rod could cause image distortion, especially when the catheter is bended; the situation which may occur in tortuous vessels. In addition, interference of the mirror holder and the ultrasound beam creates a dropout in the echo image. This problem is no longer present when the rotating element system is used (vide infra). Both the rotating mirror and rotating element systems enable to image structures close to the catheter tip, due to the absence of near-field artifacts.

Mechanical rotating single-element system

The technique of the rotating single-element system is similar to the rotating mirror system. The difference is that the transducer is no longer stationary but instead rotates (Figure 2). This device requires a very flexible shaft containing the electrical wires of the transducer in order to prevent inhomogeneous mechanical rotation. The element is positioned at an angle (15°) such that no transmission pulse effect, as result of the dome, appears on the display. Both the mechanical systems can be advanced into the human body using a guide wire or a guiding catheter device.

The scope of this thesis

Intravascular ultrasound was introduced into the clinic as a new diagnosticum in the late 1980s. The development of this new modality is a continuous process and ongoing evaluation of the technique remains imperative. The aim of this work is to evaluate the potential application of intravascular ultrasound to assess vascular pathology both *in vitro* and *in vivo* in peripheral vessels.

As histology constitutes the basis of our understanding of intravascular ultrasound images, a review of *in vitro* studies with intravascular ultrasound is provided in **Chapter 2**. The use of intravascular ultrasound in detection, characterization and quantitative assessment of atherosclerotic plaques both *in vitro* and *in vivo* are presented in more detail in **Chapters 3 and 4**. The phenomenon of medial thinning, as evidenced by intravascular ultrasound and confirmed by histology, is explored in **Chapter 4**.

In **Chapter 5** the *in vitro* experience with intravascular ultrasound is expanded *in vivo* in patients undergoing vascular intervention. The ability of the ultrasound technique to provide the operator with essential clinically relevant information, not obtained otherwise, is addressed in **Chapters 6 and 7**.

The potential role of intravascular ultrasound in documenting the mechanism of balloon angioplasty in patients with disabling claudication is elucidated in **Chapters 8** and **9**. **Chapter 10** describes the use of intravascular ultrasound in assessing extrinsic compression of the superficial femoral artery.

Chapter 11 presents a qualitative and quantitative comparative study of intravascular ultrasound versus angiography.

Finally, **Chapters 12** and **13** address the potential role of intravascular ultrasound in the assessment of vascular distensibility.

Chapter 14 summarizes the chapters presented in this thesis.

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CHAPTER 2

IN VITRO INTRAVASCULAR ULTRASOUND : A REVIEW

Salem H.K. The, Elma J. Gussenhoven, Hero van Urk

CHAPTER 2

IN VITRO INTRAVASCULAR ULTRASOUND : A REVIEW

In vitro studies form the basis for *in vivo* application of various diagnostic techniques, such as intravascular ultrasound. The accuracy of qualitative and quantitative data derived from intravascular ultrasound can best be tested *in vitro*. The first qualitative *in vitro* study in iliac and femoral arteries was reported in 1988 by Meyer et al using a 20 MHz transducer [1]. An echogenic intima, a hypoechoic media and a hyperechoic adventitia are seen on ultrasound. It was suggested that, compared with connective tissue, the muscular media appeared hypoechoic on ultrasound scans due to the relative lack of collagen. In the same year, Pandian and colleagues examined the aorta, iliac, carotid and coronary arteries derived from animals [2]. The ultrasound images (20 MHz), however, portray a bright homogeneous arterial wall without distinction between intima, media and adventitia. Subsequently, in 1989, using a 40 MHz ultrasound system, Gussenhoven and coworkers reported for the first time that intravascular ultrasound has the unique ability to differentiate elastic from muscular type of arteries [3-5]. The difference between the two types of artery is found histologically in the media. The media of a muscular artery is composed of smooth muscle cells and is practically devoid of elastin fibers. In contrast, the media of an elastic artery consists mainly of densely packed, concentrically arranged elastin fibers amidst smooth muscle cells. On ultrasound examination, a muscular artery is recognized by the hypoechoic media, with clear definition of the intima and adventitia showing bright echoes. An elastic artery is recognized by a media that is as bright as its surrounding tissues. It was suggested that the presence of elastin fibers regularly arranged in the media is responsible for a significant amount of acoustic backscatter, with a power level comparable with that from the intima and adventitia [3-5]. The aorta, carotid, subclavian and internal thoracic arteries presented as elastic arteries; whereas the coronary, brachial, mesenteric, splenic, renal and iliofemoral arteries were of a muscular nature. These observations were subsequently confirmed by others [6-10].

Visualization of the arterial wall by intravascular ultrasound

It became clear that atherosclerotic lesions were more readily envisioned in muscular arteries with a hypoechoic media than in the elastic type of arteries [5,7]. On ultrasound muscular arteries present as a characteristic three-layered arterial wall. It is fortuitous that peripheral arteries are predominantly muscular in nature. The echolucent media acts as an important landmark for the assessment of plaque burden by intravascular ultrasound. However, the medial layer may not always be visible on ultrasound. Thinning of the media is a well-known process of atherosclerosis, which affects the visualization of the media on ultrasound images [11]. In addition, the echolucent layer of the media may be barely discernible by ultrasound when medial collagen content is increased [12,13].

Similarly, in coronary arteries the hypoechoic media may not be always seen. Borst et al [14] reported on the absence of a visible hypoechoic media in relatively normal coronary arteries: they questioned whether the presence or absence of an echolucent zone was related to age. Fitzgerald and associates [15] observed that the presence of intimal thickening of at least 0.18 mm facilitates identification of the hypoechoic media in normal coronary arteries. In addition, they found that the degree of intimal thickening was age related. As the visibility of the hypoechoic media is related to the limits of the (axial) resolution of the ultrasound system used, it is likely that higher ultrasound frequency facilitates improved resolution and, thus, identification of the tunica media.

Characterization of the arterial plaque by intravascular ultrasound

It is now generally accepted that lesion morphology and the composition of atherosclerotic plaque are related to the initiation of arterial disease [16]. The assessment of plaque subtypes may be useful in the staging of arterial disease and for the selective application of interventional procedures such as balloon angioplasty, laser angioplasty, and the placing of stents and atherectomy devices. Tissue characterization by intravascular ultrasound imaging can be used not only to detect the presence and severity of atheromatous plaques but also to differentiate fatty, fibrous, and calcified regions of atheromatous plaque and to assess the presence of thrombus [17]. Results of *in vitro* studies on both peripheral and coronary arteries have demonstrated that fibrocellular lesions and thrombus both presented as soft echoes. Deposits of extracellular lipid seen in the histologic section may appear as a hypoechoic region inside the lesion on ultrasound examination. Dense fibrous tissue or calcified deposits inside the lesion presented as an echogenic (hard) lesion (Figure 1). In the presence of dense fibrous tissue the adventitia can still be visualized beyond the lesion, whereas calcification obscures this structure due to acoustic shadowing. In addition, calcification may often be associated with acoustic reverberation [5,7]. The reported sensitivity and specificity of lesion topography (eccentric or concentric) and lesion morphology (soft or hard) is high. The specificity of lipid was also high, however, its sensitivity was low [18-20].

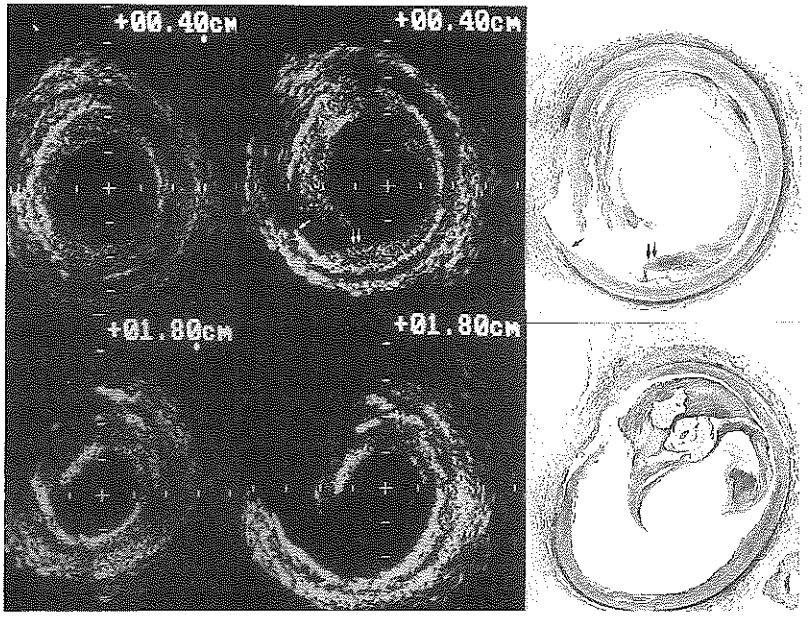

Figure 1. Intravascular ultrasound cross-sections *in vitro* of the superficial femoral artery before and after balloon angioplasty. A displacement sensing device was used to facilitate comparison of the corresponding ultrasound cross-sections with its histologic counterpart. **Top panel:** Before balloon angioplasty a concentric soft lesion is seen at level 0.40 cm which became dissected after intervention. An internal elastic lamina rupture is present at 8 o'clock on both intravascular ultrasound and histology (arrows). **Lower panel:** At level 1.80 cm an eccentric hard lesion is observed casting acoustic shadowing. Both a dissection and an internal elastic lamina rupture are seen after intervention. Calibration = 1 mm.

Quantitative assessment by intravascular ultrasound

In vitro investigations have shown the ability of intravascular ultrasound to provide accurate measurements of luminal area, lumen diameter, plaque area and wall thickness of normal and abnormal arteries of varying size. Measurement of free lumen area, media-bounded area and percentage lumen obstructions with intravascular ultrasound revealed a high correlation with measurements performed on histology (Table 1). Moreover, reported inter-observer and intra-observer variation was low [2,7,9,21-23].

Results of intervention using intravascular ultrasound

Imaging of the vessel after intervention would enable assessment of the response of the atheroma to the treatment, and identification of features associated with satisfactory long-term outcome *in vivo*. Reports on the effect of intervention studied *in vitro* by intravascular ultrasound are limited [4,18,24]. It was observed that balloon angioplasty may result in plaque disruption, dissection and residual flaps resulting in a new echolucent zone. In addition, it was found that media rupture in conjunction with internal elastic lamina rupture can also be visualized on intravascular ultrasound [18] (Figure 1). This observation proved to be very similar to data obtained from *in vivo* studies in patients [25].

Table 1. In vitro studies concerning quantitative correlations between intravascular ultrasound and histology.

Authors	Publication Year	Artery	Correlation coefficients (r)				*p* - value
			LA/LD	VA/VD	PA/PT	WT	
Gussenhoven [5]	1989	CCA/IA	0.85	—	0.84‡	—	< 0.0001
Pandian [2]	1989	CA/IA/FA	0.98	—	—	0.76	< 0.001
Potkin [7]	1990	CA	0.85	0.94	0.84	0.92	< 0.0001
Nishimura [26]	1990	Peripheral	0.98	—	—	—	—
Tabbara [27]	1990	IA/FA	0.96‡	0.83‡	—	0.68	< 0.05
Pandian [28]	1990	Pulm	0.99	—	—	0.85	< 0.001
Bartorelli [9]	1992	CA/FA	0.85/0.96‡	0.94	—	0.92	< 0.0001
Yoshida [29]	1992	CCA/IA	0.92	—	0.88‡	—	—

CA=coronary artery; CCA=common carotid artery; FA=femoral artery; IA=iliac artery; LA/LD=lumen area/lumen diameter; PA/PT=plaque area/plaque thickness; Pulm=pulmonal artery; VA/VD=vessel area/vessel diameter; WT= wall thickness; ‡=diameters; —=not mentioned.

Intravascular ultrasound and veins

Little attention has been given to *in vitro* intravascular ultrasound studies using veins and veins used for bypass grafting. It was found that these vessels do not show a characteristic hypoechoic media [4,30]. The media is relatively thin and consists of circularly, or circularly and longitudinally disposed smooth muscle cells and collagen, and few elastin fibers. In the presence of a lesion intravascular ultrasound has the ability to distinguish between normal veins and veins with intimal hyperplasia, vein wall fibrosis and atheromatous plaque (Figure 2).

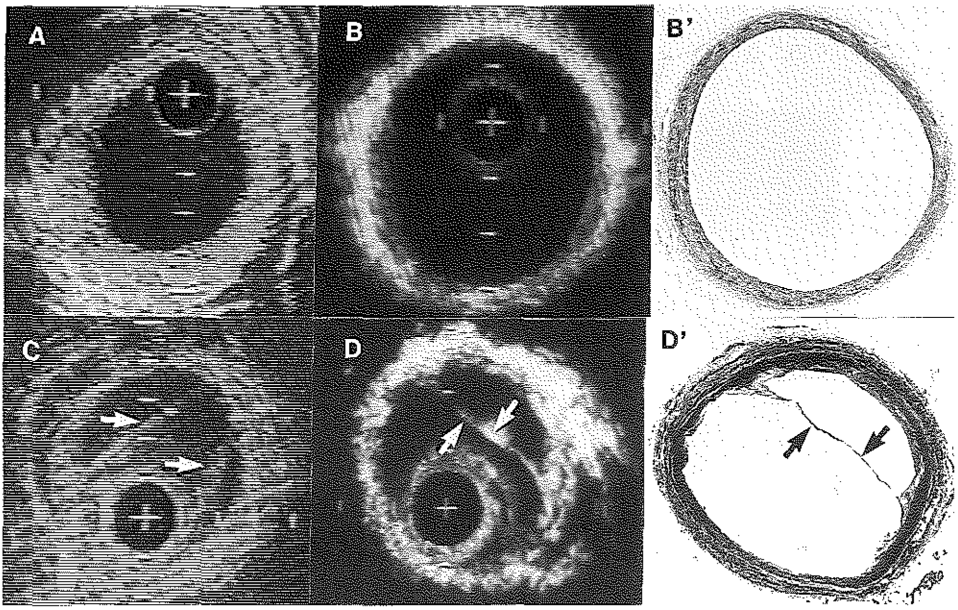

Figure 2. Intravascular ultrasound cross-sections obtained *in vivo* (**A,C**) and *in vitro* (**B,D**) and its histologic counterpart (**B',D'**) showing the homogeneous vessel wall structure of the veins. Saline flushing is used *in vivo* to elucidate the vessel wall and the valve structure. Note the presence of valves (arrows) inside the lumen (**C,D,D'**). Calibration = 1 mm.

From in vitro to in vivo intravascular ultrasound and its future implications

Altogether the relevance of *in vitro* studies is elucidated when applying intravascular ultrasound *in vivo* in humans [18,25,27-34]. It is understood why the vascular wall may be three-layered both in coronary and iliofemoral arteries (Figure 3). With its ability to visualize the three-layered structure of the arterial wall, intravascular ultrasound can determine the presence of eccentric versus concentric lesions. It has been suggested that the presence of a disease-free wall in case of an eccentric lesion may have clinical implications such as vessel spasm, stretching and recoil [35].

Lesions present may be either soft or hard in nature. It is assumed that soft lesions may represent either fibrocellular, fibrous lesions or thrombus, whereas hard lesions casting ultrasonic shadowing represent calcified lesions [25,30-34]. The precise morphology and the constitution of atheroma may be important in determining the initial success rate after intervention for stenosis [36]. Recognition of soft versus hard plaques may alter procedural aspects and ultimately the end result of intervention. Moreover, intravascular ultrasound can be applied to center angioplasty and atherectomy devices, and to assess the adequacy of these interventional devices.

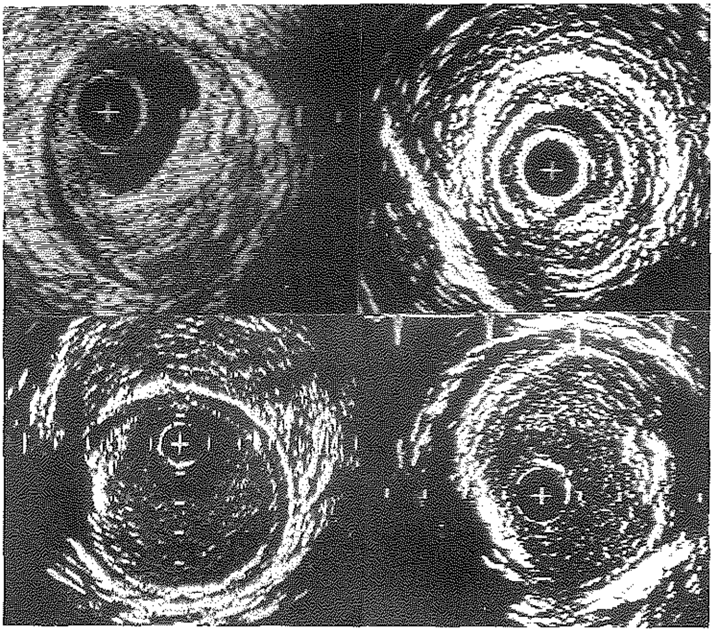

Figure 3. Intravascular ultrasound cross-sections obtained *in vivo* showing the similarities between the femoral (left) and coronary (right) arteries. **Top panel:** cross-sections showing similarities of a soft lesion. **Lower panel:** cross-sections showing similarities in the presence of hard lesion casting ultrasonic shadowing. Note the echogenicity of blood inside the lumen in the lower panel. Calibration = 1 mm.

Besides, the information may be useful to prevent arterial injury or perforation during the use of plaque ablation or atherectomy techniques [35]. It may help to evaluate the true size of the new lumen or to assess the extent of any dissections, and help to determine whether further inflations, or inflations with a larger balloon are advisable [6].

Whether the presence of dissections, plaque rupture and/or internal elastic lamina rupture seen on intravascular ultrasound following balloon angioplasty have clinical implications for patients, remains to be further investigated in ongoing clinical studies. The indications are that intravascular ultrasound will facilitate a better choice of interventional device and, thus, better guidance during the intervention leading to reduction in procedural costs and time. In addition, distinction of the arterial layers with intravascular ultrasound may have clinical relevance in the assessment of the progression or regression of atherosclerosis.

Difference between an in vitro and an in vivo setting

Although *in vitro* studies are necessary in order to understand the images acquired in patients, a number of differences between *in vitro* and *in vivo* use of intravascular ultrasound may be taken into account.

Influence of blood. Intravascular ultrasound studies performed in an *in vitro* setting using saline solution result in higher quantitative values than *in vivo* studies, where blood is the medium, due to the different velocities of sound [37,38]. For this reason, the ultrasound system should be calibrated properly, i.e. for blood medium, to allow correct measurements during clinical use.

The presence of blood in clinical studies may facilitate recognition of vessel wall morphology, and particularly of dissection, by serving as a contrasting acoustic interface [39]. However, quantitative analysis of the ultrasound image may be hampered on a still-frame [38]. For this purpose, saline flushing or averaging of the ultrasound images may eliminate the echogenic blood [25,38]. Using a 50 MHz ultrasound backscatter microscope, Lockwood and associates found that the average attenuation in blood was approximately one-half that measured in the arterial wall at the same frequency range, thus leaving the appearance of the arterial wall similar to that in saline medium [40].

Influence of blood pressure. Albeit intravascular ultrasound studies *in vitro* are not commonly performed under physiologic pressures, it is expected that no noticeable changes in vessel wall and lesion morphology will occur when the latter condition is not attainable. Physiologic pressure may result in thinning of the arterial wall but leaving the three-layered appearance of the arterial wall visualized [39,41].

Influence of tissue fixation and processing. In general, the reported studies indicate that quantitative histologic data were consistently smaller (4-31 %) than the ultrasonic data [7,24,42]. The reason for this is shrinkage during processing of the specimens (e.g. dehydration, clearing, embedding, sectioning and staining). Nevertheless, intravascular ultrasound images of atherosclerotic arteries are accurate and represent the true vessel wall geometry and disease severity.

In conclusion, histopathological studies have demonstrated the ability of intravascular ultrasound to characterize both vessel wall and plaque morphology, and the results have been extrapolated to provide a novel method of examining the arterial disease *in vivo*. Indeed, morphologic appreciation of *in vivo* studies is much facilitated by knowledge obtained *in vitro*. One general limitation of *in vitro* studies is that they are time-consuming. However, verification of the ultrasound data with its histologic counterpart continues to be a fascinating event.

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CHAPTER 3

NORMAL AND ATHEROSCLEROTIC ARTERIAL WALL EXAMINED WITH INTRAVASCULAR ULTRASOUND

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CHAPTER 3

NORMAL AND ATHEROSCLEROTIC ARTERIAL WALL EXAMINED WITH INTRAVASCULAR ULTRASOUND

ABSTRACT

Clinical application of intravascular ultrasound to assess arterial atherosclerotic disease was introduced in humans after extensive *in vitro* studies. High frequency, 30 and 40 MHz, mechanical intravascular ultrasound systems were used. The ultrasound images of 100 arterial specimens were compared with the corresponding histologic cross-sections. The purpose of this chapter is to present our initial experience with intravascular ultrasound obtained *in vitro* and subsequently in patients *in vivo* with peripheral artery disease. It was found that ultrasonic cross-sectional imaging provided information on the size and shape of the lumen and on the dimension and composition of the atherosclerotic lesions. It is considered that based on the histologic information obtained with intravascular ultrasound a better insight into arterial morphology is provided. A practical application of this imaging technique may be to guide planning, monitor and assess the results of interventional or reconstructional procedures.

INTRODUCTION

Intravascular ultrasound is one of the most recent and promising applications of ultrasound

[1-10]. This technique allows the arterial wall to be imaged from inside the artery in a cross-sectional view. Contrast angiography provides a silhouette of the vessel lumen but gives no direct information about the morphology of the atherosclerotic lesion present [11]. A mild degree of luminal narrowing assessed angiographically may in fact represent a large atherosclerotic lesion [12,13].

In particular, interventions designed to selectively ablate atherosclerotic lesions - such as laser and atherectomy - require a technique that allows accurate measurement of the thickness of the lesions involved in order to properly plan and monitor the interventional procedure and judge its effects [14,15]. Furthermore, knowledge concerning morphology of the obstructive lesion can be helpful in the selection of the most appropriate intervention [16].

This chapter aims to demonstrate the potentials of intravascular ultrasound to document morphologic features. We report our *in vitro* experiences with the intravascular ultrasound catheter devised by Bom and associates at the Department of Biomedical Engineering of the Erasmus University in Rotterdam [17-19]. In addition, the usefulness of these *in vitro* data verified with histology to understand human *in vivo* images will be shown.

MATERIAL AND METHODS

In vitro

The imaging catheter used contains a single piezo-electric crystal with a diameter of 1 mm focused at 30 or 40 MHz (Du-MED, Rotterdam, The Netherlands). In order to avoid reflections of the dome the transducer element is mounted 15° to the catheter-axis. This element is connected to a flexible rod and is rotated using an external motor. The catheter has a diameter of 1.6 mm (5F) and a length of 90 cm.

One hundred segments of human arterial autopsy specimens (10 mm in length) were positioned vertically, fixed in agar-agar solution (1.2%) and placed in a beaker filled with purified water. The examined arteries included coronaries, carotid, subclavian, internal thoracic, brachial, mesenteric, renal, splenic, iliofemoral, popliteal and pulmonary arteries. Cross-sectional images at 1 mm intervals were obtained along the course of the artery segment.

The type of vessel and presence and characteristics of intimal changes were evaluated on the basis of the criteria which are currently used in our laboratory (Table 1).

Table 1. Criteria for ultrasonic classification of arterial specimens and intimal lesion.

		Type of Artery
Three-layered appearance	:	presence of a circumferential hypoechoic middle layer.
Homogeneous appearance	:	arterial wall presents as a homogeneous echo bright structure.
Non-classifiable	:	arterial wall not imaged because of concentric atherosclerotic lesion (shadowing or attenuation).
		Intimal Lesion
Normal intima	:	single echoreflective line between vessel lumen and hypoechoic intermediate layer or, in the absence of a hypoechoic media, homogeneous echointensity of the vessel wall.
Fibrous intimal thickening	:	increased intimal thickness (when defined by a hypoechoic media) or different intimal echointensity, without ultrasonic changes suggestive of lipid or calcium deposition.
Lipid deposits	:	markedly hypoechoic areas inside the intimal lesion.
Calcium deposits	:	highly echoreflective areas with shadowing and/or reverberations.

And the end of the ultrasound investigation the proximal site of the vessel was marked with India-ink at the 12 o'clock position of the ultrasonic cross-section at which ultrasound imaging was started. The vessels were fixed in 10% buffered formalin for 12 hours, decalcified and further processed for routine paraffin embedding. Starting at the ink-marked level, cross-sections (5 μm) perpendicular to the vascular long axis were cut at 1 mm intervals. One slice was stained with Verhoeff's elastin van Gieson and the other with hematoxylin azophloxin.

The histologic examination was aimed at the classification of the type of vessel and characterization of the vascular lesions (Table 2).

In vivo

A 30 MHz real-time intravascular ultrasound imaging system was used in 32 patients with disabling claudication (mean age: 67 years [range: 49 - 83]; 25 males and 7 females) undergoing balloon angioplasty or femoro-popliteal bypass. Via an 8F introducer sheath placed into the femoral artery the intravascular ultrasound catheter was advanced anterograde into the femoral artery.

Table 2. Criteria for histologic classification of arterial specimen and intimal lesion.

		Type of Artery
Muscular artery	:	prevalence of smooth muscle cells in the medial layer of the artery.
Transitional artery	:	smooth muscle component sandwiched among multiple parallel laminae of elastin fibers.
Elastic artery	:	densely packed multiple elastic laminae in the medial layer.
		Intimal Lesion
Normal intima	:	absence of subendothelial intimal layer, dividing endothelium and internal elastic lamina.
Fibrous intimal thickening	:	diffuse or focal thickening without lipid or calcium deposition.
Lipid deposits	:	focal plaque within the intima having a core of lipid cells.
Calcium deposits	:	microscopically evident islands of calcium degeneration.

Successive cross-sections were obtained at 1 cm distance using a radiopaque ruler for orientation. The images were stored on VHS.

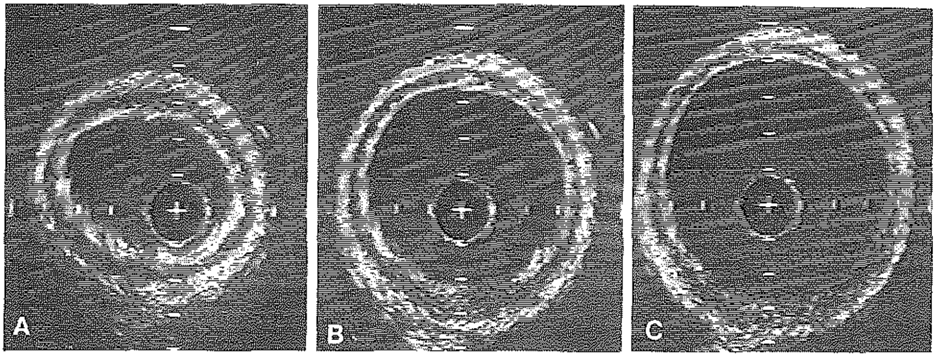

Figure 1. *In vitro* images of a normal iliac artery (30 MHz) with intraluminal pressures of 0, 20 and 100 mmHg respectively (**A-C**). The middle hypoechoic layer corresponding to the muscular media is well appreciated over the entire circumference. Note that intraluminal pressure has influence on the thickness of the hypoechoic media. Calibration = 1 mm.

RESULTS

In vitro

Vessel wall. Muscular type of arteries had a typical three-layered appearance of the arterial wall in 44/58 specimens (76%). The middle hypoechoic layer corresponding to the muscular media was clearly evident, also when an intraluminal pressure in the physiologic range was applied (Figure 1).

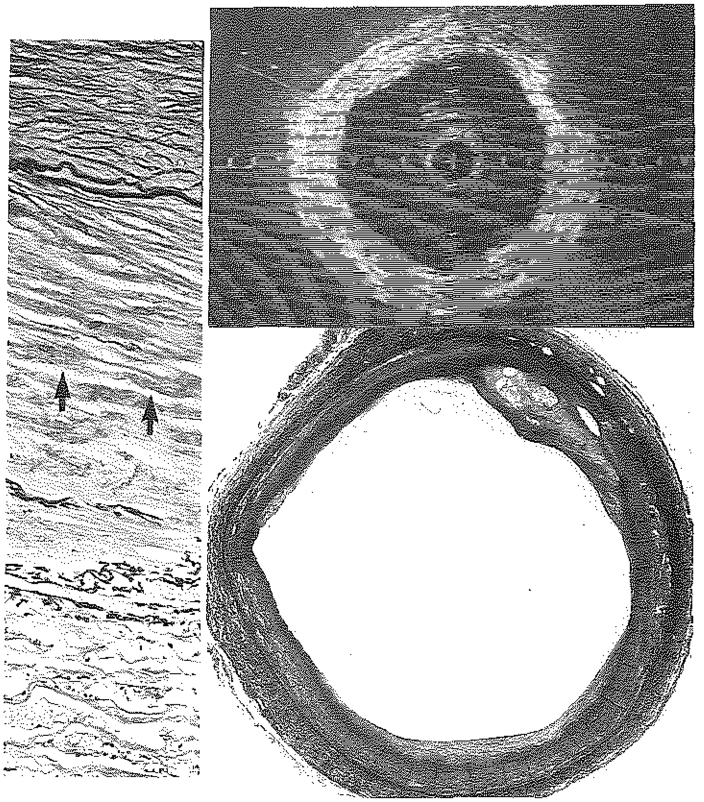

Figure 2. Histologic and echographic (30 MHz) cross-sections of an iliac artery. The homogeneous appearance of the vessel wall at intravascular ultrasound corresponds with an originally muscular media for the major part replaced by dense fibrous tissue (see detail, arrows). Detection with ultrasound of a diffuse area of fibrous intimal thickening at 6 o'clock is hampered by the lack of a hypoechoic landmark seen normally in muscular type of arteries. The lesion at 1 o'clock contains large amounts of calcium typically casting ultrasonic shadowing. Calibration = 1 mm.

In 10 arteries (17%) fibrous degeneration of the muscular media resulted in a homogeneous appearance of the vessel wall (Figure 2), whereas atherosclerotic plaque precluded the visualization of the arterial media in 4 (7%).

At intravascular ultrasound transitional arteries showed either a homogeneous wall in 78% (7/9) or a three-layered arterial wall (22%), according to the content of elastin fibers present in the media. When the histologic cross-sections showed an elastic type of artery a homogeneously echoreflective vessel wall was observed in 91% (30/33) of the intravascular ultrasound cross-sections (Figure 3). In the remaining specimens (9%) the outer wall could not be adequately imaged due to ultrasonic shadowing or attenuation from fibrocalcific intimal lesions.

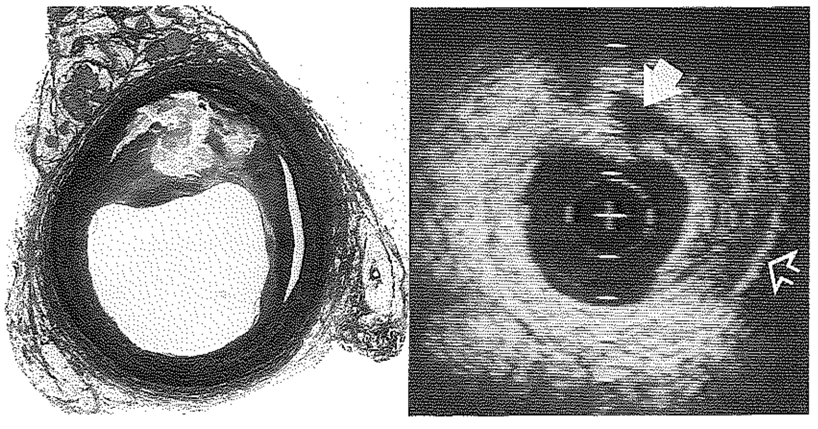

Figure 3. Histologic and echographic (30 MHz) cross-sections of a carotid artery showing a homogeneous echo bright vessel wall between 5 and 11 o'clock, typical for an elastic type of artery. Calcium evidenced histologically in the eccentric atherosclerotic lesion was seen echographically at 3 o'clock together with a shadow and a reverberation (open arrow). A large intimal lipid deposit was noted echographically at 1 o'clock (bold arrow). Calibration=1 mm.

Lesions. Histologically diagnosed fibrous intimal thickening was best seen in vessels with a three-layered appearance in 81% (21/26) (Figure 4). Conversely, large areas of intimal thickening were not recognized in 50% (11/22) of the specimens without a three-layered appearance (Figures 2 and 3).

Depending on the histologic characteristics of the lesion, the echointensity of the thickened fibrous intima was variable: a low echointensity corresponded to cell-rich loose collagen and fibromuscular tissue (Figure 4).

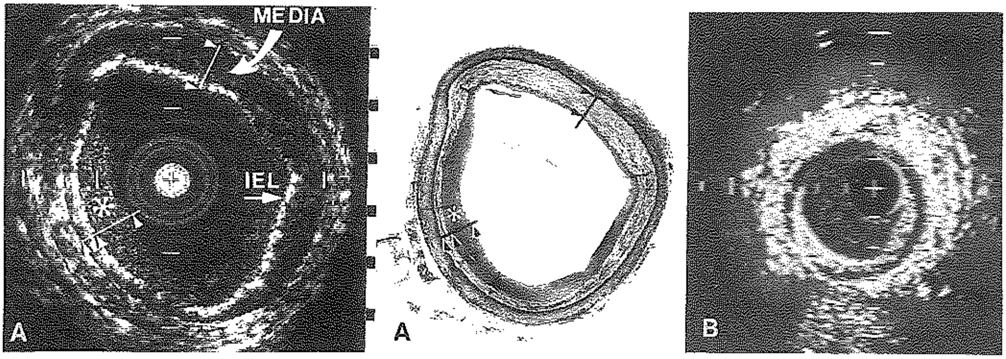

Figure 4. A, Echographic and corresponding histologic cross-section (40 MHz) of a renal artery showing the influence of a lesion (asterisk) on the thickness of the arterial media. **B**, *In vivo* cross-section of the femoral artery showing a similar feature. Beyond the lesion (arrow) the hypoechoic media reduced significantly. IEL=internal elastic lamina. Calibration=1 mm.

On the other hand, densely packed fibrous connective tissue or collagen-rich tissue revealed a high echointensity on ultrasound. Fibrous tissue occasionally induced excessive attenuation of the ultrasound, so that no echo information could be derived from remote areas (Figure 5).

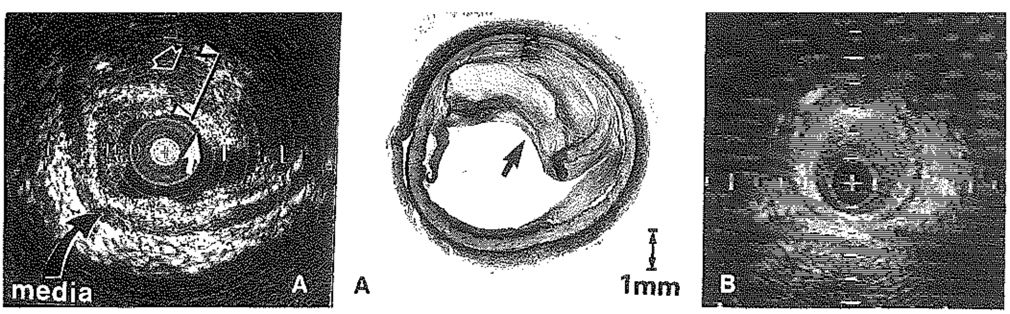

Figure 5. Echographic and histologic (40 MHz) cross-section of a femoral artery showing an obstructive atherosclerotic lesion (**A**). Fatty debris is the major plaque component recognized echographically as a hypoechoic structure (open arrow). The fibrous cap produced a bright echo structure. Probably due to attenuation, the arterial wall beyond the lesion is not seen echographically. A similar observation can be seen *in vivo* (30 MHz) in the superficial femoral artery (**B**, right panel). The lesion present between 9 and 2 o'clock is classified as a "hard" lesion echographically. Calibration=1 mm.

Large intra-intimal lipid deposits could be identified as hypoechoic areas on ultrasound in 32/36 specimens (89%) (Figures 3 and 5).

When deposits of calcium were present bright areas, lines or spots casting a shadow with or without reverberations were almost invariably observed (35/36, 97%) (Figures 2 and 3).

Media thickness. The ultrasonic visibility of the hypoechoic media largely depended on the nature and extent of a lesion. It was observed that media thickness is inversely related to the extent of atherosclerosis. Minor lesions, histologically classified as diffuse intimal thickening, were associated with some degree of medial thinning. Histologically classified atherosclerotic lesions were associated with marked thinning of the media. In some specimens an abrupt transition of a normal media to a very thin media was seen (Figure 4).

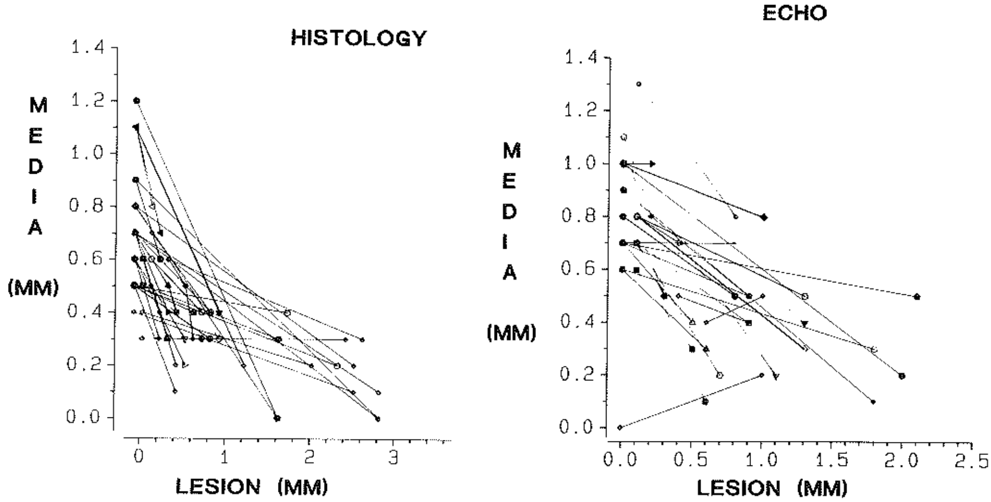

Figure 6. Graphs showing the correlation between ultrasonic and histologic findings for maximal lesion thickness and maximal media thickness (in both cases $r = 0.83$, $p \geq 0.00001$).

For quantitative purposes the *in vitro* cross-sectional ultrasonic images from 39 muscular arteries were used to measure media and lesion thickness at the area of minimal and maximal lesion thickness. Histology measurements were obtained independently from the ultrasonic cross-sections and were used as the standard reference. A lesion was defined as present when visible superimposed on the hypoechoic media (≥ 0.1 mm). Lesion thickness was calculated as the perpendicular distance between lesion surface and the junction internal elastic lamina - media. The corresponding media thickness was judged as the distance between internal elastic lamina and adventitia.

Linear regression analysis, applied to establish the correlation between ultrasonic and histologic findings for maximal lesion thickness and maximal media thickness, demonstrated for each a correlation coefficient of $r = 0.83$ ($p \geq 0.00001$ in both cases) (Figure 6).

The decrease in media thickness (0.8 to 0.3 mm) was inversely proportional to the increase in lesion thickness (0.0 to 1.0 mm) measured at the same location. Measurements from the histologic cross-sections were concordant.

In vivo

In 1 patient the study was cancelled as no reliable image could be obtained due to failure of the ultrasound device, whereas in 3 patients the image quality was considered to be less superior than *in vitro*, probably caused by a transducer of low sensitivity.

Intravascular ultrasound provided high resolution real-time cross-sectional images in 28 patients. The inner surface of the vessel lumen was well defined in these *in vivo* images. Changes in shape and luminal area could clearly be recognized when the catheter was advanced into the artery. The characteristic hypoechoic medial layer resulted in a three-layered appearance of both the superficial femoral and popliteal arterial wall.

As *in vitro*, the hypoechoic media proved to be a useful landmark to measure the extent of an atherosclerotic lesion along the circumference of the artery. In the presence of a hypoechoic media the size of the original lumen area and lesion area could be determined off-line using a computerized analysis program [20].

Differences in lesion echoreflectivity allowed the discrimination between soft and hard lesions (Figures 5 and 7). Soft lesions may correspond to cell-rich fibrous tissue or fibromuscular intimal thickening, a configuration frequently encountered following previous balloon angioplasty. On the other hand, hard lesions recognized as bright echoes possibly casting shadowing of the underlying structure are likely to contain densely packed fibrous tissue or calcific degeneration (Figures 5 and 7). Atherosclerotic lesions containing a large lipid deposit were observed only sporadically during the *in vivo* studies.

Quantitative measurement *in vivo* revealed that the media thickness measured in the disease-free arterial wall was 0.6 mm. In the presence of a lesion the media thickness was smaller, with a median value of 0.1 mm. Similarly, it was noted that the media thickness of the disease-free arterial wall measured before the intervention reduced up to 38% following balloon angioplasty.

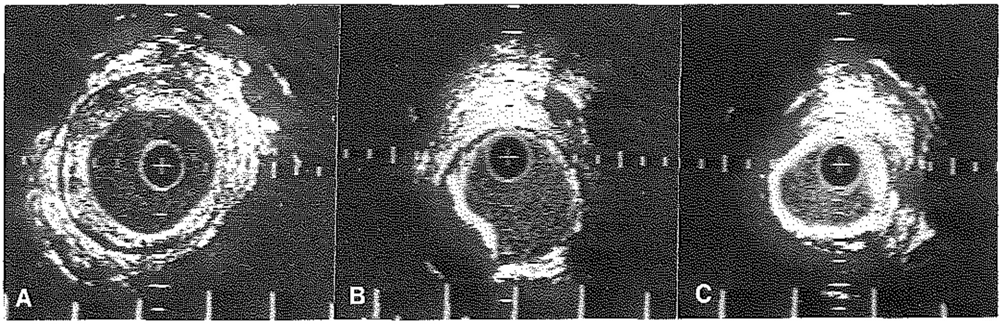

Figure 7. *In vivo* echographic images of the superficial femoral artery (30 MHz) obtained at 3 different levels. **A**, proximally a soft lesion is seen as a diffuse echo bright structure superimposed to the hypoechoic media. **B**, more distally an eccentric hard lesion is seen as a bright structure casting ultrasonic shadowing. The underlying arterial wall can no longer be seen. **C**, the hard lesion is now seen affecting the arterial wall circumferentially, resulting in a stenosis. Calibration = 1 mm.

Difference between *in vitro* and *in vivo* imaging

The most significant difference between the images obtained *in vitro* and *in vivo* is that blood appears echogenic with the high-frequency transducer, whereas the purified water used as medium in the *in vitro* study does not generate echoes.

In cases of significantly reduced blood flow due to a stenosis, echogenicity of blood appears to increase and can then obscure the dividing line between lumen and atherosclerotic lesion [21]. This border could be more easily appreciated by flushing the arterial lumen through the introducer sheath with small amounts of saline (Figure 8).

DISCUSSION

From this *in vitro* and *in vivo* experience we have learned that histologic features of the vessel wall can be imaged with intravascular ultrasound, thus providing information that is not available from angiography. This unique diagnostic information might well be of help in planning type and the modalities of therapeutic approach.

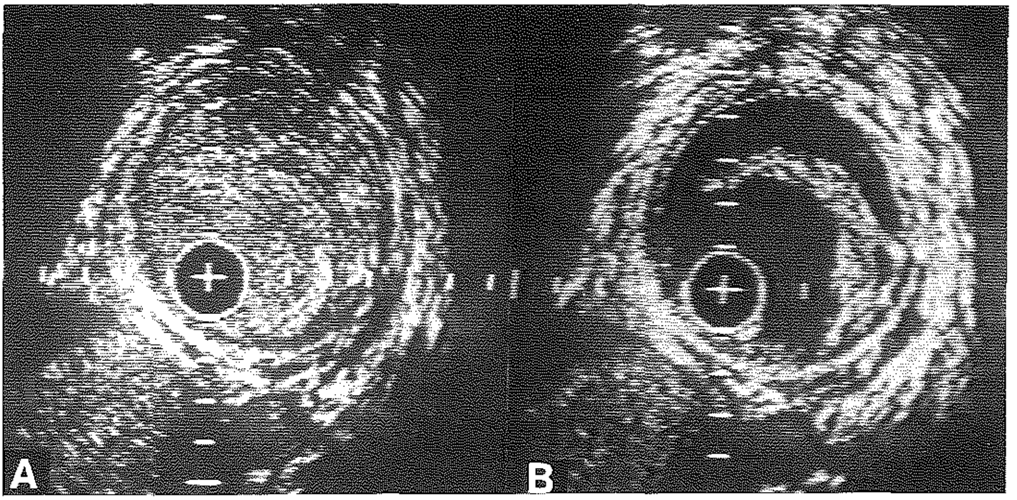

Figure 8. Intravascular ultrasonic cross-sections of the superficial femoral artery (30 MHz) obtained *in vivo* showing the advantage of saline injection for off-line analysis of still-frames. **A**, echogenicity of blood hampers delineation of the lumen contour. **B**, dissection became evident following injection of saline. Calibration = 1 mm.

The information obtained with intravascular ultrasound is primarily morphologic, providing data about the structure and location of the lesion. Using computer-based software analysis, however, quantitative information concerning luminal and lesion area can be obtained before and after intervention.

Experience, longer follow-up and controlled clinical trials will be needed to define the future role of intravascular ultrasound in the diagnosis and management of atherosclerotic vascular disease.

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CHAPTER 4

ASSESSMENT OF MEDIAL THINNING IN ATHEROSCLEROSIS BY INTRAVASCULAR ULTRASOUND

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Assessment of Medial Thinning in Atherosclerosis by Intravascular Ultrasound

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This study investigated the in vitro (40 MHz) and in vivo (30 MHz) feasibility of intravascular ultrasound to document the influence of atherosclerotic lesions on the typical 3-layered appearance of muscular arteries.

The in vitro images of 39 arteries were compared with the corresponding histologic sections. Media and lesion thickness were measured at the areas of minimal and maximal lesion thickness. The median media thickness was 0.8 mm in the absence of a lesion, decreasing to 0.3 mm in the area of maximal atherosclerosis. The ultrasonic data correlated closely with histologic measurements (0.6 and 0.3 mm, respectively).

The in vivo study was performed in 29 patients undergoing coronary or peripheral vascular procedures. A total of 150 still-frames were selected for quantitative analysis. The median media thickness was 0.6 mm in the absence of a lesion, decreasing to 0.1 mm in the area with maximal atherosclerosis. This study revealed that intravascular ultrasound imaging accurately determines that media thickness of muscular arteries is inversely related to lesion thickness. In vitro data, verified with histology, can be translated to humans in vivo.

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A new imaging method, catheter-based intravascular ultrasound, has had the capacity to provide qualitative[1-5] as well as quantitative[6-12] assessment of arterial morphology and dimensions. With intravascular ultrasound, encouraging data have been obtained in vitro to differentiate elastic from muscular arteries, and to distinguish between the various components of atherosclerotic lesions.[7,8,13,14]

Intravascular ultrasonic in vitro studies have indicated that lesion location and thickness can accurately be determined in the presence of a visible landmark determined by a hypoechoic media in a muscular artery.[7,14] An atherosclerotic lesion may obscure this medial reference band due to ultrasound attenuation, especially in advanced stages when fibrosis and calcium are present. Furthermore, histologic studies have shown that atherosclerosis affects the media and, in advanced stages, may obliterate the media entirely.[15-18]

The aim of this study was to evaluate the potential of intravascular ultrasound to provide quantitative data in vitro for assessing the effect of atherosclerosis on the arterial media of muscular arteries, to compare these data with those from corresponding histologic sections, and with in vivo data from normal and diseased human peripheral arteries.

METHODS

Intravascular ultrasound: In a laboratory set-up, a 1 mm diameter, 40 MHz, mechanically rotated, single-element transducer mounted on an 8Fr catheter was used for in vitro studies. For in vivo study, a 5Fr mechanically motor-driven, rotating imaging catheter was used with a 1 mm diameter, 30 MHz transducer. The axial resolution of the 40 and 30 MHz systems was 75 and 80 μm, respectively; the lateral resolution was better than 200 and 225 μm, respectively, at a depth of 1 mm (Du-Med, Rotterdam, the Netherlands). The images were displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 shades of gray. Markers were displayed for calibration purposes. For review and analysis the ultrasound images were recorded on VHS videotape together with calibration markers.

Human specimens: Intravascular ultrasound was evaluated in 39 human vascular specimens of muscular nature obtained 2 to 14 hours after death. They include coronary, iliac, femoral, popliteal, mesenteric and renal artery. The details of processing the specimens, echographic imaging and histologic preparation have been described previously.[5,7] For each vascular specimen studied, 1 histologic cross-section with the most significant lesion thickness was selected and compared with the corresponding ultrasonic cross-section. Photographs were obtained of the ultrasonic images and histologic sections (the latter together with a 1 mm calibrator).

Patient studies: Seven patients undergoing diagnostic cardiac catheterization and 22 patients undergoing balloon angioplasty of the superficial femoral artery were studied after signing an informed consent. An introducer sheath was placed into the femoral artery for diagnostic catheterization and intervention. In 3 patients in whom the superficial femoral artery was totally occluded, laser therapy was performed (Nd-YAG, Medilas – 2, Messerschmidt Bölken Blöhm) to create a lumen accessible for the intravascular ultrasound study. The intravascular ultrasound catheter was advanced through the sheath in a retrograde manner into

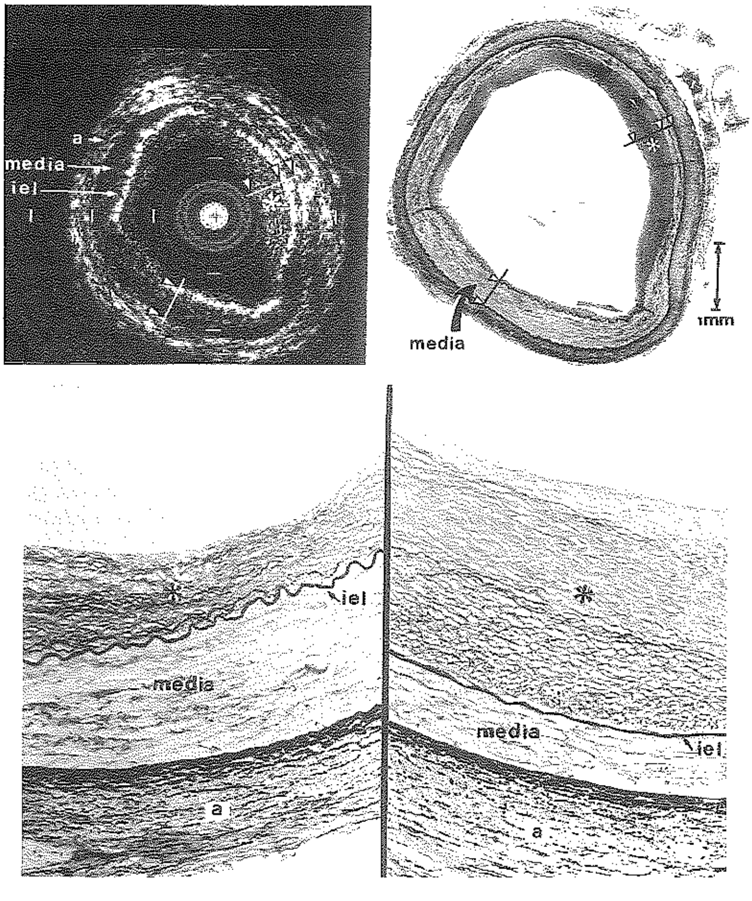

FIGURE 1. Ultrasonic cross-section obtained in vitro (40 MHz) from a renal artery together with photomicrographs of the corresponding histologic cross-section. The media of this muscular artery, mainly composed of smooth muscle cells, appears characteristically hypoechoic on ultrasound. Bright echoes of the internal elastic lamina (iel) and adventitia (a) circumscribe the hypoechoic media. No lesion is noted echographically at 7 o'clock. Diffuse intimal thickening, most prominent at 2 o'clock *(asterisk)*, is lying in a shallow pouch of the media. Media thickness is influenced by the presence of the lesion *(arrow heads)*. *Lower panel* details the changes caused by the lesion to the histologic architecture of the arterial media *(asterisk)*. An insignificant lesion corresponded with a corrugated internal elastic lamina *(left panel)*; a significant lesion was associated with a stretched internal elastic lamina *(right panel)*. Echographically, both structures were equally bright (compare 7 and 2 o'clock). (Verhoeff van Gieson stain [calibration 1 mm], magnification: *top*, ×16; *bottom*, ×90.)

the iliac artery (n = 7) and in an anterograde manner into the femoral artery (n = 22). Continuous recordings were obtained at different sites of the arterial system before diagnostic catheterization and intervention. A total of 150 representative still-frames were selected and photographed for quantitative analysis.

Quantitative analysis: From the in vitro cross-sectional ultrasonic images the media and lesion thicknesses were measured independently by 2 observers at 2 sites: where lesion thickness was minimal and maximal (Figures 1 to 4). Linear regression analysis was applied to establish the correlation between ultrasonic and histologic measurements on both maximal lesion and media thicknesses (Figure 5). Wilcoxon's signed rank test was used to determine interobserver compatibility.

For the in-vitro study, histologic measurements were obtained independently from the echographic cross-sections and were used as the reference standard. A lesion was defined as present when seen superimposed on the hypoechoic media ($\geq$0.1 mm). Lesion thickness was calculated as the perpendicular distance between the lesion surface, i.e., intimal leading edge and the leading edge of the internal elastic lamina. The corresponding media thickness was calculated as the distance between the leading edge of the internal elastic lamina and the leading edge of the adventitia (Figure 1). In the absence of a distinct internal elastic lamina the junction lesion versus hypoechoic media was used (Figure 2). In the presence of calcification, the media could not be envisioned because of ultrasonic shadowing. These regions were excluded for comparison. Instead the area showing a measurable maximal lesion thickness was chosen (Figure 2). In the ultrasound images where lesion could not be acoustically separated from the un-

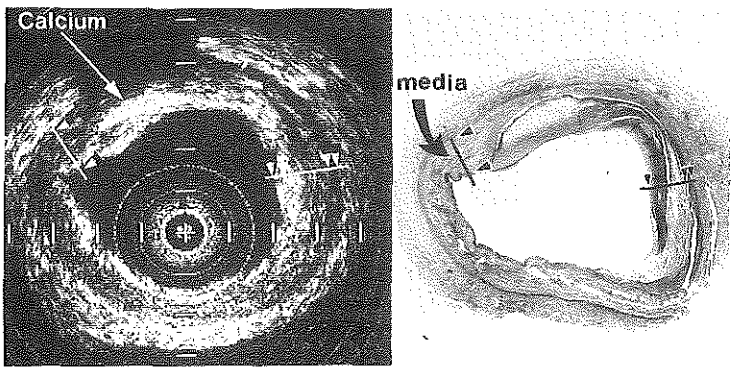

FIGURE 2. Ultrasonic cross-section obtained in vitro (40 MHz) with corresponding histologic cross-section of a femoral artery showing a classic eccentric atherosclerotic lesion. The lesion-free wall showing a distinct media is seen between 5 and 10 o'clock. Media thickness was measured at 10 o'clock. Distinct medial thinning in the presence of an atherosclerotic lesion is seen at 3 o'clock. Note that calcium seen at 11 o'clock is casting ultrasonic shadowing. The hypoechoic region inside the lesion at 2 o'clock *(arrow)* corresponds with lipid. Calibration 1 mm. (Verhoeff van Gieson stain, magnification ×7.)

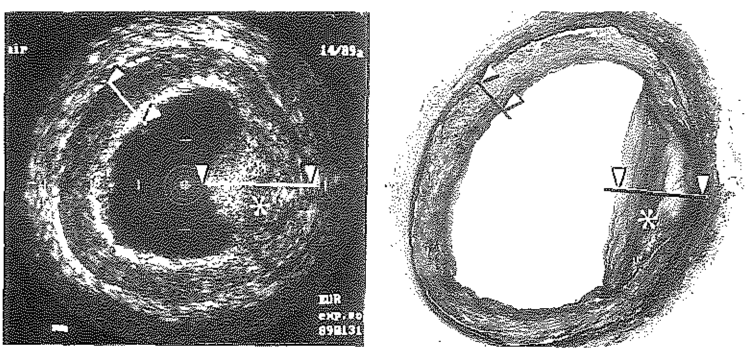

FIGURE 3. Ultrasonic cross-section obtained in vitro (40 MHz) together with the corresponding photomicrograph of the histologic cross-section obtained from a mesenteric superior artery. Bright echoes of internal elastic lamina and adventitia circumscribe the hypoechoic media. A distinct media was observed echographically in the absence of a lesion (at 10 o'clock). In the presence of an extensive lesion *(asterisk)* the media becomes invisible echographically. The corresponding histology reveals absence of the media in this region. (Verhoeff van Gieson stain [calibration 1 mm], magnification ×6.)

derlying media, the media thickness was classified as absent (Figures 3 and 4). In the presence of a fibrous lesion with sufficient collagen casting a shadow, the maximal measurable lesion was calculated with ultrasound, and the corresponding invisible media was classified as absent. Similar to the in vitro quantification study, media and lesion thicknesses in vivo were measured at the sites where lesion thickness was minimal and maximal (Figures 6 to 8).

To establish the correlation between the media and lesion thicknesses, the difference in media thickness measured at the sites of minimal and maximal lesion thickness were evaluated by means of the sign test.[19]

RESULTS

In vitro studies: Ultrasound and histologic examination in vitro revealed no lesion in 3 cross-sections, a concentric lesion in 3 other specimens and an eccentric lesion in 33 specimens. Evidence of calcium noted echographically in 11 cross-sections was confirmed histologically.

Linear regression analysis between intravascular ultrasound and histologic measurements for maximal lesion and media thicknesses showed each a correlation coefficient of r = 0.83 ($p < 0.00001$ in both cases) (Figure 5).

There was good agreement between the 2 observers, with no significant difference in measurements of media and lesion thickness ($p > 0.10$ in all cases). The correlation coefficients between the measurements of the 2 observers varied from r = 0.73 to r = 0.97.

With use of the sign test, correlation was significantly negative ($p < 0.00001$ in all cases) for both observers and for echographic and histologic measurements (Fig-

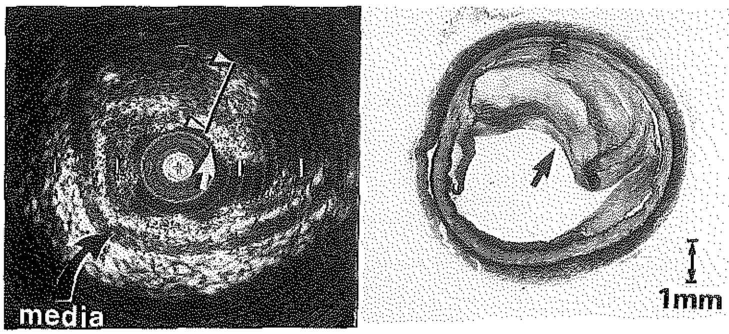

FIGURE 4. Intravascular ultrasound cross-section obtained in vitro (40 MHz) from a femoral artery with the corresponding histologic cross-section. The lesion-free arterial wall showing a distinct media is seen between 4 and 9 o'clock. On the opposite side a large atherosclerotic lesion is present *(arrow)*. Clear imaging of the remote tissues was not possible with ultrasound, probably due to the collagen present in this lesion. The hypoechoic region at 3 o'clock *(asterisk)* is due to a dissection. *Arrowheads* indicate the maximal lesion thickness measured echographically. (Verhoeff van Gieson stain [calibration 1 mm], magnification ×6.)

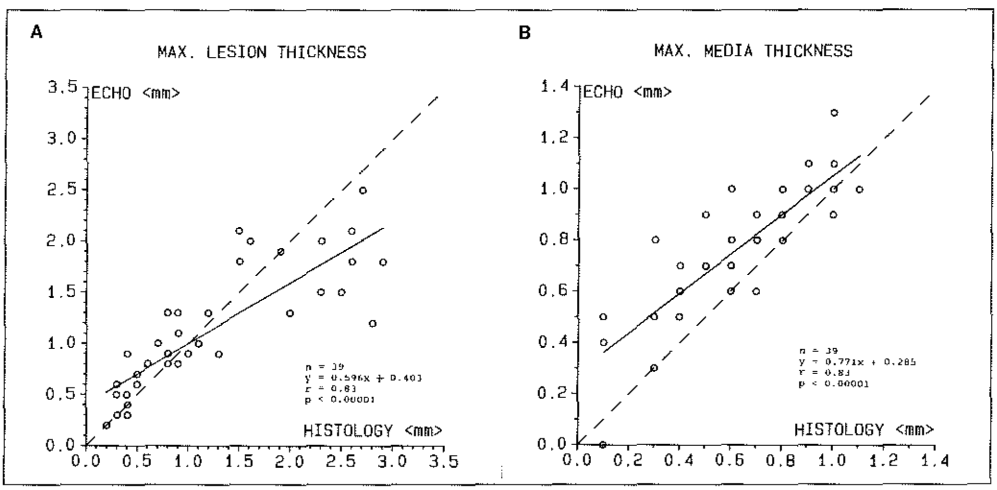

FIGURE 5. Linear regression analysis between intravascular ultrasound and histology for maximal (MAX.) lesion thickness *(A)* and maximal media thickness *(B)* in millimeters.

ure 9). Because distribution of the data was rather skewed, the location of a distribution was characterized by the median and the variability by the interquartile range. Table I lists the parameters, median, range and interquartile range. A decrease in median media thickness (0.8 to 0.3 mm) is inversely proportional to an increase in median lesion thickness (0.0 to 1.0 mm) measured at the same location. Measurements from the histologic cross-sections were concordant (Table I, Figure 9).

In the ultrasound images where lesion could not be acoustically separated from the underlying media (n = 10), corresponding histology revealed a fibrotic lesion and a media thickness of 0.0 mm in 4, 0.1 mm in 3 and 0.2 mm in 3 specimens, respectively.

In vivo studies: In all patients, intravascular ultrasound studies provided high resolution real-time, cross-sectional images. There were no complications caused by the ultrasound study. The presence of a hypoechoic layer, giving a characteristic 3-layered appearance of both iliac and superficial femoral arteries, was defined in all instances. From the in vitro information, we conclude that the hypoechoic vascular layer corresponds with the media of a muscular artery. In the iliac artery, normal vascular morphology without evidence of a superimposed lesion was found. In the superficial femoral artery normal segments as well as cross-sections with nonobstructive and obstructive lesions were envisioned (Figures 6 to 8). In 21 still-frames, ultrasound shadowing was noted beyond the area of a lesion that may have contained calcium.

Quantitative measurements in vivo (derived from 150 still-frames) showed that in the absence of a lesion, median value of media thickness was 0.6 mm. In the presence of an atherosclerotic lesion, the media was reduced in thickness to a median value of 0.1 mm (Table I).

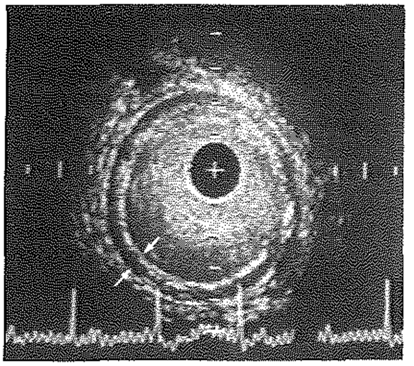

FIGURE 6. Ultrasonic cross-section obtained in vivo (30 MHz) representing a normal femoral artery. The 3-layered appearance of the arterial wall is similar to that seen in the in vitro study (compare Figures 1 and 4). Media thickness is indicated by *arrows*. Echogenicity of blood is seen within the arterial lumen (calibration 1 mm).

DISCUSSION

The results of this study support the hypothesis that intravascular ultrasound is able to evaluate the manner in which the media of a muscular type of artery is affected by atherosclerosis. The hypoechoic media was always typically seen adjacent to the bright adventitia, whereas hypoechoic zones due to lipid deposits or dissection were typically present inside or near a lesion (Figures 2 and 4).

Definite medial thinning was noted in vitro in undistended vessels and in vivo in vessels under pressure. Media thickness measured echographically and histologically decreased 60 and 50%, respectively, in diseased segments compared with disease-free wall segments of the same vessel. Although a few observations in this study showed discordant measurements, the

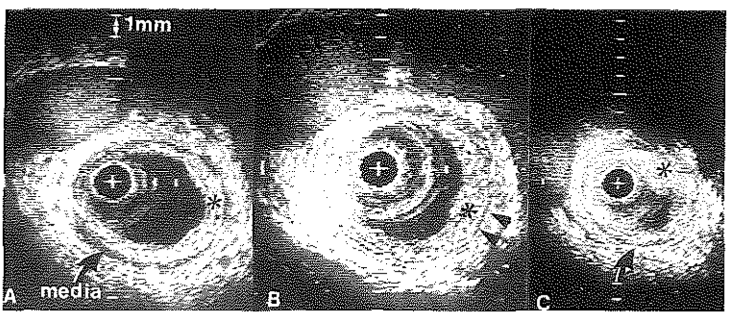

FIGURE 7. Ultrasonic cross-sections obtained in vivo (30 MHz) in a patient undergoing balloon angioplasty of the superficial femoral artery. The cross-sections *(A to C)* are taken from 3 different levels in the femoral artery and are arranged proximal to distal. *A*, proximally the lumen is not obstructed. There is evidence of diffuse intimal thickening *(asterisk)*. The dark layer corresponds with the hypoechoic media *(bold arrow)*. *B*, more distally the lesion *(asterisk)* is seen to expand progressively, resulting in conspicuous medial thinning at 3 o'clock *(arrowheads)*. *C*, finally the ultrasound catheter images the atherosclerotic lesion *(asterisk)* casting a shadow at 1 o'clock. Between 1 and 4 o'clock the lesion prevents visualization of the media. Media is visible between 5 and 1 o'clock *(bold arrow)*. At 11 o'clock a vein is noted (calibration 1 mm).

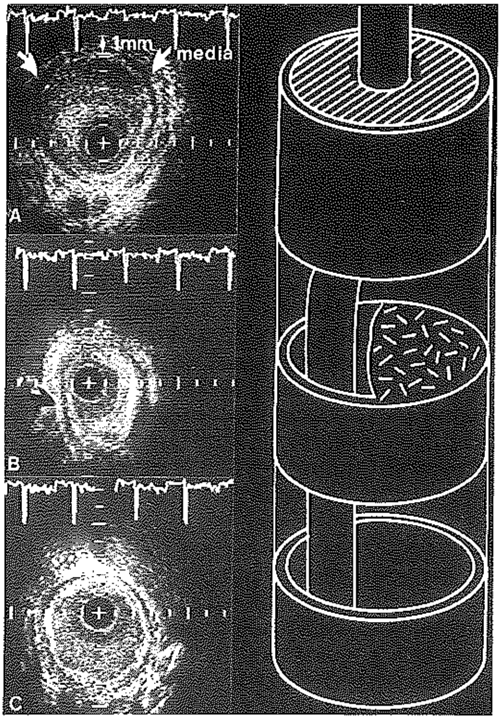

FIGURE 8. Ultrasonic cross-sections and corresponding diagram obtained in vivo (30 MHz) from a patient with obstructive disease of the superficial femoral artery. *A*, proximally the lumen is seen completely filled with a lesion. Real-time images revealed no normal movement of blood in this cross-section. The dark layer *(bold arrow)* corresponds with the media. *B*, at the level of stenosis the medial layer *(bold arrow)* is visible only between 7 and 11 o'clock, indicating an eccentric lesion. *C*, more distally a normal vessel geometry with a hypoechoic media is identified in which blood flow was recognized (calibration 1 mm).

overall evaluation revealed an inverse relation between the lesion and media thickness (Figure 9).

The frequency of the 2 echographic systems used for the in vitro (40 MHz) and in vivo (30 MHz) studies differed by one-third octave; their axial resolution was comparable. Comparison of mean data of media thickness measured with ultrasound in vitro (0.8 mm) and in vivo (0.6 mm) at the site of a minimal lesion showed a difference of 0.2 mm (25%) (Table I). We believe that this difference is due to the influence of blood pressure. The observation is further validated by recent in vitro work at our laboratory indicating that pressure reduced arterial wall thickness to one-third of its unpressurized state (unpublished observations). Furthermore, no significant difference was found in media thickness when calculated from diastolic and systolic still frames, suggesting that blood pressure had no notable influence on media thickness during the cardiac cycle itself.

Our data on decrease in media thickness correlated closely with that of other histologic studies (60 and 55%, respectively) on diseased coronary arteries.[16,18] This supports the contention that medial thinning is an essential part of atherosclerosis.[16] The lesion, seen lying in a shallow pouch of the media, may lead to medial thinning and, consequently, to an increase in internal elastic lamina area. Thus, the artery may enlarge as a result of a developing lesion on the underlying wall.[20] Intravascular ultrasound imaging has the unique potential to document the positive relation between arterial size and the degree of atherosclerosis.[21]

Furthermore, we observed that media thickness is inversely related to the extent of atherosclerosis. In vitro data revealed that minor lesions, histologically classified as diffuse intimal thickening,[22,23] were associated with

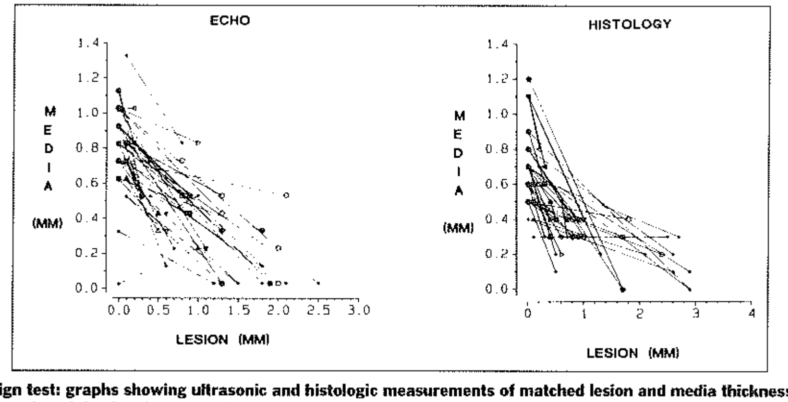

FIGURE 9. Sign test: graphs showing ultrasonic and histologic measurements of matched lesion and media thickness measured in millimeters at the minimal and maximal lesion sites, interconnected. Each segment is represented by a specific symbol to connect the media thickness at the sites of minimal and maximal lesion thickness. Corresponding symbols in echo and histology represent the same segment.

TABLE I Media and Lesion Thickness (median value, interquartile range and range) Determined In Vitro (n = 39) and In Vivo (n = 150) Using Intravascular Ultrasound in the Area with Minimal and Maximal Lesion Thickness

	In Vitro Echo			Histology			In Vivo Echo		
	M	IR	R	M	IR	R	M	IR	R
Minimal lesion	0.0	(0.0–0.1)	(0.0–0.6)	0.0	(0.0–0.1)	(0.0–0.4)	0.0	(0.0–0.0)	(0.0–1.5)
Media	0.8	(0.6–0.9)	(0.0–1.3)	0.6	(0.4–0.8)	(0.1–1.1)	0.6	(0.4–0.7)	(0.1–0.9)
Maximal lesion	1.0	(0.6–1.5)	(0.1–2.5)	0.9	(0.4–1.9)	(0.2–2.9)	1.5	(1.0–2.0)	(1.0–2.0)
Media	0.3	(0.0–0.5)	(0.0–1.0)	0.3	(0.1–0.4)	(0.1–0.8)	0.1	(0.0–0.4)	(0.0–0.9)

All parameters are expressed in millimeters.
IR = interquartile range; M = median value; R = range.

some degree of medial thinning. Histologically classified atherosclerotic lesions were associated with significant medial thinning. Because of calcium in the atherosclerotic lesion, the maximal region of the lesion could not be identified echographically. This occurred echographically in 11 cross-sections and corresponding histology confirmed the presence of calcium. However, the presence of calcium itself is an indication that the lesion represents a more advanced stage of the disease.[22,23] This is of major clinical importance for in vivo interpretation using intravascular ultrasound. A distinct 3-layered appearance was observed in vivo in the iliac and femoral artery. Distinct medial thinning was seen in the presence of atherosclerosis. Similarly, ultrasound shadowing was noted in vivo (in 21 cross-sections) beyond the area of a lesion that may have contained calcium. Conversely, despite a large lesion filling the entire lumen area of a femoral artery in 6 patients, medial thinning had not occurred. The lesion was located proximal to the atherosclerotic lesion in the same vessel (Figure 8). We assumed that the structure presented a young rather than an old atherosclerotic lesion, since visualization of the medial layer was not hampered. This assumption is further validated by the fact that histologic study by atherectomy in 2 of these patients revealed thrombus. Thus, the underlying media thickness may be a helpful guide during in vivo studies to determine the nature of the lesion.

Limitations of intravascular ultrasound: With regard to the frequency used for the in vitro studies (40 MHz), the medial layer may be better visualized in the presence of a large fibrous lesion with a transducer of lower frequency. In this study, the media was echographically deemed absent in 6 cross-sections, whereas histologic examination revealed a media thickness of 0.1 and 0.2 mm, respectively.

The noncoaxial positioning as well as the eccentric location of the catheter may influence the precision of the medial measurement. In the in vitro studies, care was taken to avoid eccentricity and misalignment of the catheter. To overcome this problem in the in vivo setting, a large number of still-frames were evaluated.

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CHAPTER 5

INTRAVASCULAR ULTRASOUND AND VASCULAR INTERVENTION

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Intravascular Ultrasound and Vascular Intervention

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An intravascular ultrasonic imaging device (40 MHz) was used to obtain in vitro ultrasonic images and matching histologic cross-sections, derived from human vascular specimens. The feasibility of assessing vessel wall morphology as well as the ability to accurately document plaque thickness was determined. Based on the echogenicity of the arterial media, intravascular ultrasound could distinguish muscular arteries from elastic arteries, veins, and bypass grafts. The hypoechoic media only present in the muscular type of artery proved to be an essential landmark to document superimposed atherosclerosis. Plaque thickness calculated in these arteries showed close relationship with the corresponding histologic cross-section. Using real-time in vivo intravascular imaging (30 MHz), the morphology of the vessels interrogated was studied. The dynamic change of the arterial wall, as well as the outcome after intervention, is discussed.

Introduction

Significant progress has been made in methods for the nonoperative treatment of arterial disease. Optimal use of methods such as balloon dilatation, atherectomy, laser, and stent implantation require knowledge of the site, geometry, and structural characteristics of arterial obstruction. This has stimulated the development of an imaging method to characterize and accurately locate the arterial wall disease. Ultrasound intravascular imaging has the potential to document the anatomy under the endothelial surface. The technique has developed to the extent that qualitative[1–5] as well as quantitative[6–12] assessment of vessel lumina and plaques is no longer utopia. We report the Rotterdam experience using an ultrasound catheter constructed at the Thoraxcenter. An ultrasound system based on principle of a rotating single element transducer mounted at the tip of the catheter was used.

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Methods and Materials

In Vitro Studies. In vitro studies were performed with a 40-MHz single element transducer mounted on an 8 French catheter. The axial resolution of the system was 75 μm, the lateral resolution was better than 200 μm at a depth of 1 mm. Using a stepper-motor, one complete cross-sectional image was obtained in 20 seconds. The images were displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 shades of gray. Markers were displayed for calibration purposes.

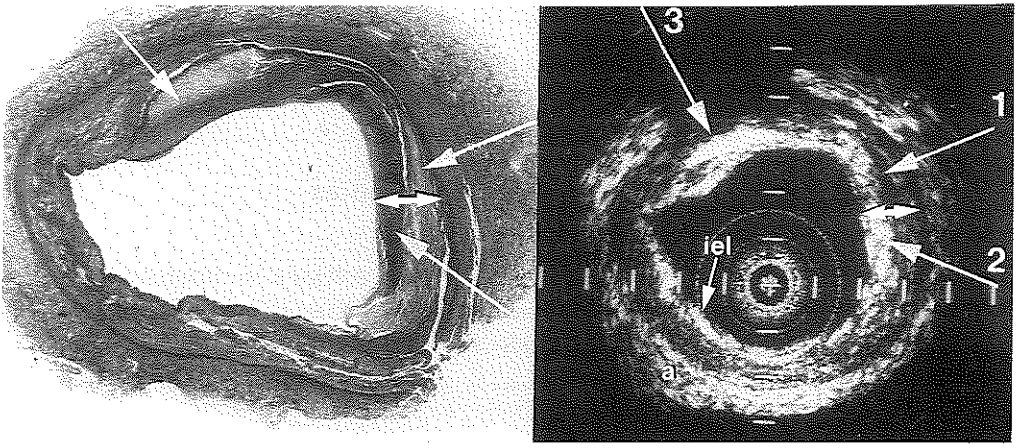

Figure 1. Ultrasonic cross-section obtained from the femoral artery together with photomicrograph of the corresponding histologic cross-section. The media of this muscular artery is mainly composed of smooth muscle cells and appears characteristically hypoechoic on ultrasound. The eccentric lesion most prominent between 9 and 5 o'clock lies in a shallow pouch of the media, and flushes with the adjacent normal intima. Bright echoes of the internal elastic lamina (iel) and adventitia (a) circumscribe the hypoechoic media of the normal plaque-free arterial wall. The atheroma, characterized as a large deposit of lipid, is recognized as a hypoechoic area (arrow 1), the fibroelastic cap as a bright echo (arrow 2), and calcium as a bright echo with shadowing (arrow 3). At 3 o'clock the maximal plaque thickness measured echographically is indicated between arrow heads.

Human Specimens. At autopsy, 77 human vascular specimens were obtained and stored at −20°C, including: 66 arteries, 7 veins, and 4 bypass Goretex grafts (WL Gore & Assoc., Inc., Elkton, MD, USA). The segments were brought to room temperature for in vitro ultrasonic imaging. In order to allow adequate access of the ultrasound catheter, the segments were positioned vertically, as previously described.[5,7,8]

Cross-sectional ultrasonic images and histologic sections were obtained proximal to distal in 1-mm increments. Thus, a given histologic section corresponded within 0.5 mm to the ultrasonic section. The histologic sections were stained with the Verhoeff's elastin van Gieson stain technique, which gives selective black staining of elastin fibers. The van Gieson technique is used to counterstain muscle and connective tissue.[13] In addition, sections were stained with hematoxylin azophloxine for differentiation of connective tissue and calcium.

For each vascular specimen studied, one histologic cross-section with the most significant plaque thickness was selected and compared with the corresponding ultrasonic cross-section. Photographs were made of the ultrasonic images and histologic sections.

Qualitative Analysis: In Vitro. Two independent observers defined whether or not the ultrasonic cross-section showed a typical three-layered appearance indicative of a muscular artery. The in vitro data were compared with the matched histologic cross-sections analyzed by the pathologist. In addition, the plaque characteristics as documented by the echographic cross-sections were compared with the corresponding histologic study.

Quantitative Analysis: In Vitro. From the in vitro cross-sectional ultrasonic images, the maximal plaque thickness was measured independently by two observers (Fig. 1). Histology was used as the reference standard. Plaque thickness was defined as the perpendicular distance between the plaque surface and the internal elastic lamina. In the presence of calcification, the media could not be envisioned due to ultrasonic shadowing. This region was excluded for comparison and the nearest area showing maximal plaque thickness was chosen instead.

In Vivo Studies. For in vivo study, a 5 French imaging catheter with a 30-MHz transducer was used (Dumed, Inc., Rotterdam, the Netherlands). The system is based on a mechanically motor-driven rotating catheter tip element connected to a flexible drive shaft. The element is covered by an acoustically transparent dome. The axial resolution of the system was 80 μm, the lateral resolution was better than 225 μm at a depth of 1 mm. The unit provided continuous real-time cross-sections of the vessel wall interrogated (up to 16 images per second). The ultrasonic images were displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 shades of gray. The ultrasound images were recorded on VHS videotape together with markers for calibration purposes.

Patient Studies. Eight patients who underwent coronary angiography and seven patients undergoing balloon angioplasty of the superficial femoral artery were studied after signing an informed consent. Prior to the intervention, the intravascular ultrasound catheter was introduced using an 8 French sheath into the iliac artery. The catheter was advanced retrograde into the iliac artery or antegrade into the femoral artery. With intravascular ultrasound, continuous recordings were collected at different sites.

Quantitative Analysis: In Vivo. Human in vivo studies represent real-time cross-sections of the arterial wall. The quantitative assessment of the luminal area and its change during the cardiac cycle was assessed in arteries without atherosclerosis. A computer-aided analysis system was used developed on an IBM PC/AT (IBM Corp., Boca Raton, FL, USA). The intravascular images recorded on video are digitized with a frame grabber and compressed with the run length coding method. The measurement is performed by tracing the boundary of the internal elastic lamina manually by a mouse. In the presence of a lesion, the edge of the lesion is traced to obtain the area of the free lumen. The rough, unconnected, manually-drawn contour is processed to produce a close connected and smoothed luminal contour

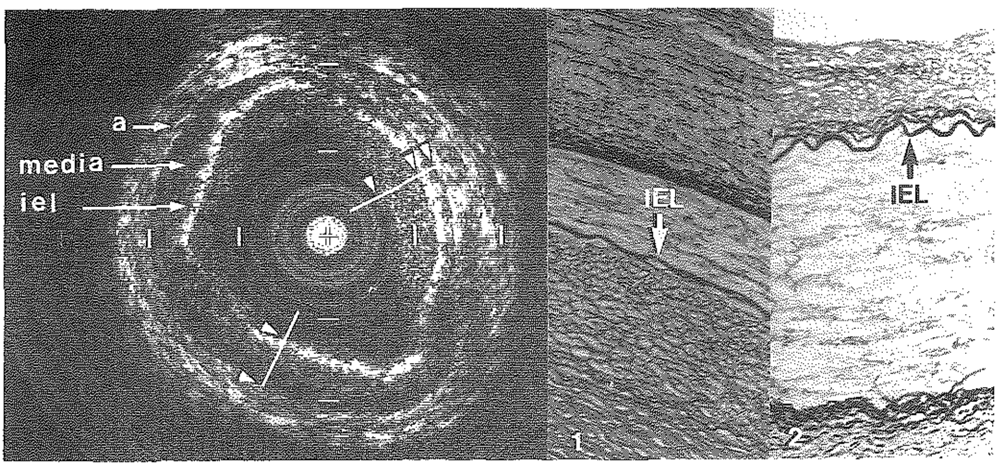

Figure 2. Ultrasonic and corresponding histologic cross-sections of a muscular type of artery. On the ultrasonic cross-section, internal elastic lamina (IEL) and adventitia (A) present with an equal amount of echoes. The superimposed fibromuscular lesion is adequately distinguished from the underlying layers. The internal elastic lamina, bright on ultrasound, showed on the corresponding histologic cross-section as having either a stretched (1), or corrugated (2) appearance.

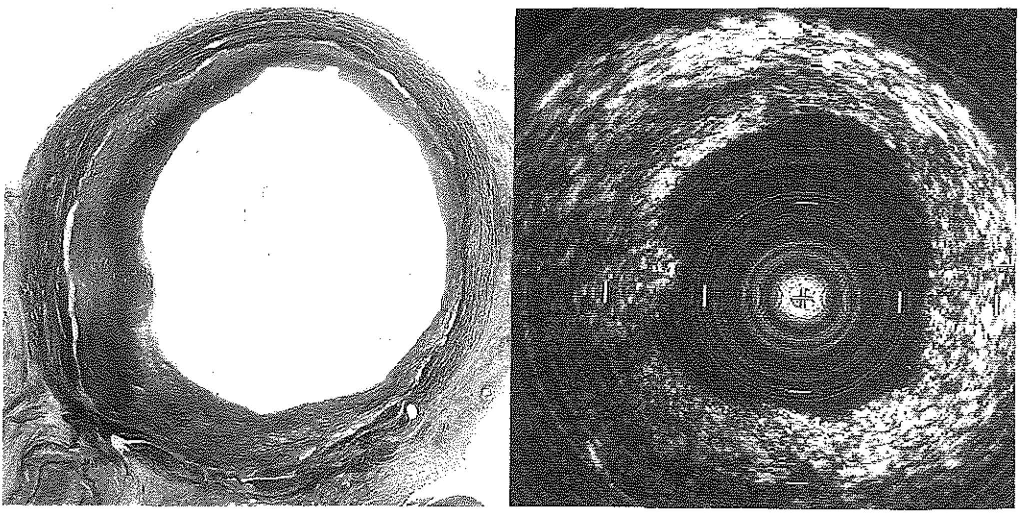

Figure 3. Ultrasonic and corresponding histologic cross-section of a coronary venous bypass graft. On the ultrasonic cross-section, media and adventitia present with an equal amount of echoes. The superimposed atherosclerosis cannot be adequately distinguished from the underlying layers. On the corresponding histologic cross-section, the media shows diffuse fibrosis, and the adventitia is composed of collagen-rich connective tissue. Atherosclerotic lesion is most prominent between 6 and 12 o'clock.

without overlapping pixels. Intravascular ultrasound images of end-diastolic and early systole were selected visually in accordance with the curve of the blood pressure. The intravascular ultrasound data were compared with the measurements of angiography using the C.A.A.S. system (Pie Medical USA, Neptune, NJ, USA). In addition, in order to document the accuracy of the system employed, the cross-sectional area was calculated frame-to-frame during two subsequent cardiac cycles.

Results

Qualitative Analysis: In Vitro. From each of the 77 specimens studied, the characteristics, documented by histology, were compared with the corresponding echo cross-section.

Three recognizable concentric layers were recognized in 39 ultrasonic cross-sections: (1) the internal elastic lamina showing a bright echo, (2) the hypoechoic muscular media, and (3) the adventitia presenting as a second echo (Figs. 1, 2). The internal elastic lamina provided bright echoes irrespective of being corrugated or stretched on the corresponding histologic cross-section (Fig. 2). The external elastic lamina could not be discriminated from the adventitia using ultrasound. In 38 ultrasonic cross-sections, no hypoechoic layer could be identified and the corresponding histology variously revealed an elastic artery, a vein, a venous bypass graft, and a human Goretex bypass prosthesis. From those ultrasonic cross-sections without a recognizable media, atherosclerosis could not be measured due to a lack of landmark (Fig. 3). Conversely, the lesion could adequately be documented in the muscular type of artery. Based on the echogenicity of the lesion, three basic types of atherosclerotic plaque components could be distinguished:

1. Hypoechoic: a reflection of lipid deposits (Fig. 1).
2. Soft-bright echoes: reflective of diffuse intimal thickening (Fig. 2).
3. Bright echoes with shadowing behind the lesion, representing calcium (Fig. 1).

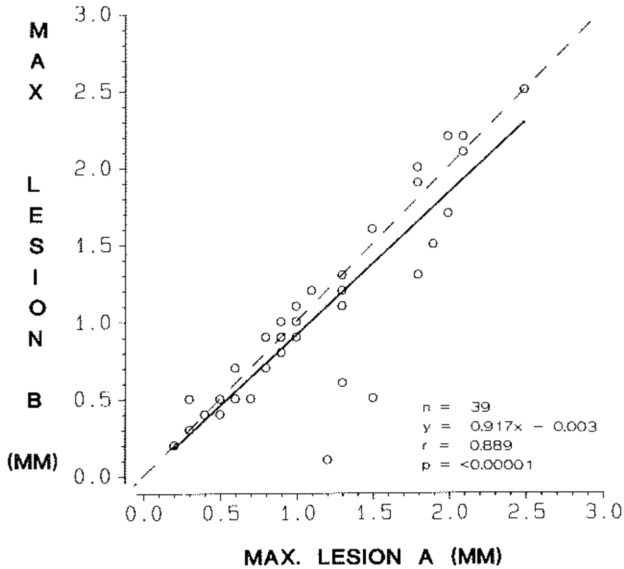

Figure 4. Graphs showing ultrasonic measurements by two observers of the maximum lesion thickness (A and B).

Quantitative Analysis: In Vitro. From the in vitro data, the maximum plaque thickness was calculated echographically and histologically (Fig. 1). There was good agreement between the measurements of the two observers (Fig. 4). In addition, measurements from the histologic cross-sections were concordant.

It was found that lesions characterized as diffuse intimal thickening were generally not so thick as the atherosclerotic lesions.[14,15]

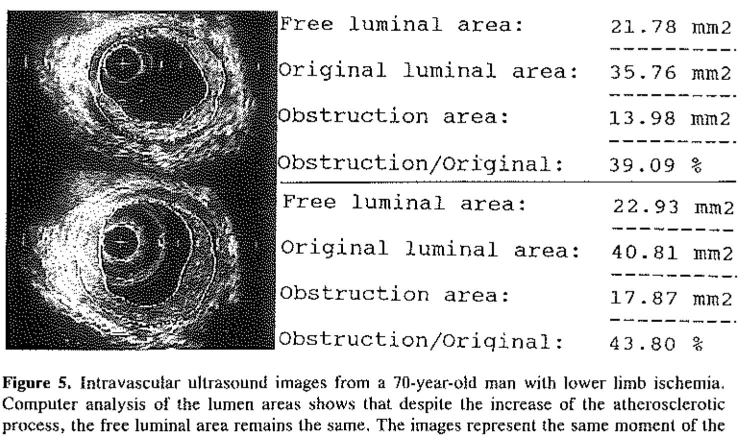

Figure 5. Intravascular ultrasound images from a 70-year-old man with lower limb ischemia. Computer analysis of the lumen areas shows that despite the increase of the atherosclerotic process, the free luminal area remains the same. The images represent the same moment of the cardiac cycle. The lesion is thought to be diffuse intimal thickening.

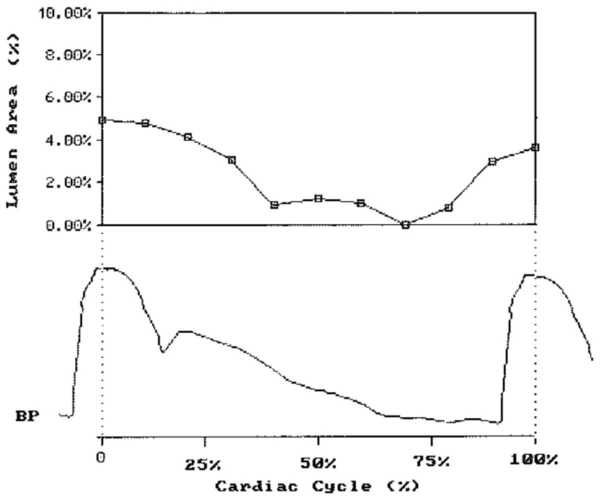

Figure 6. Diagram showing the change in lumen area as a function of blood pressure (BP). The lumen area represents the net result obtained from two cardiac cycles in four patients.

Qualitative Analysis: In Vivo Studies. A characteristic three-layered appearance of the iliac and femoral arteries were noted with the intravascular ultrasound studies. From the in vitro information we conclude that the hypoechoic vascular wall corresponds with the media of a muscular artery. In contrast, the abdominal aorta and very proximal iliac artery were of elastic nature, as they did not show a hypoechoic media. In the normal arterial segments, as well as a variety of pathological cross-sections, diffuse intimal thickening and atherosclerotic lesion with atheroma

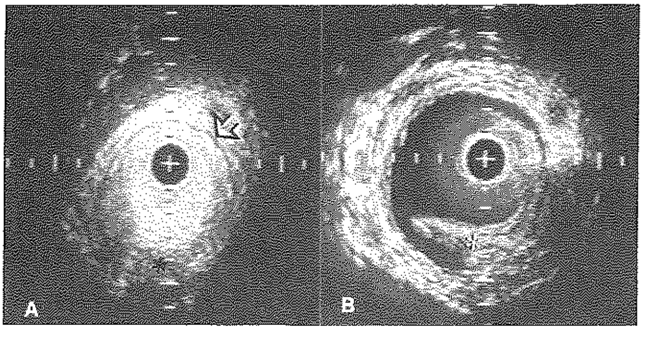

Figure 7. (A) Intravascular ultrasound images obtained from a 66-year-old man with lower limb ischemia. Before intervention, blood was seen to be extremely echogenic indicating a flow rate of < 0.1 L/minute. The black band corresponds to the muscular media (open arrow). A lesion was evident (*). (B) Following dilatation, the lesion was dissected from the arterial wall at its thinnest portion. The lesion area did not change (14 mm^2), whereas the free luminal area changed drastically from 27 to 38 mm^2. Calibration 1 mm.

and calcium were found (Fig. 5). The lesions envisioned were located eccentrically. Thrombus located proximally to the atherosclerotic lesion could be differentiated from the lesion. This differentiation was based on the attenuation of the ultrasound due to collagen-rich connective tissue in the atherosclerotic lesion; this did not occur in the thrombus. We also observed that the artery may enlarge as an effect of the developing plaque on the underlying arterial wall[16] (Fig. 5). Following laser and balloon angioplasty, a variety of anatomic features were readily seen including: normal patency of the vessel, rest stenosis, perforation, dissection, and plaque rupture. It was observed that in the presence of a dissection, the dissection occurred at the thinnest part of the lesion.

Quantitative Analysis: In Vivo. Quantitative assessment of the luminal area of the ultrasound images revealed a 5% difference between end-diastole and early systole image (Fig. 6). The free lumen area may increase due to dilatation of the diseased-free arterial wall, whereas the plaque area remained the same (Fig. 7). Furthermore, the frame-to-frame analysis of the cross-sectional area revealed that the measurements were highly reproducible.

Discussion

This article reviewed the current status of intravascular ultrasound experiences derived with the equipment developed at the Thoraxcenter. Intravascular ultrasound has been shown to delineate normal and pathological arterial morphology as well as discriminating between the muscular type of arteries and others. The technique has the ability in vitro to differentiate between the various components of atherosclerosis. Quantitative studies showed strong correlation between ultrasound and histology for plaque thickness, and there was a good interobserver agreement.

Experience obtained in vitro was extremely valuable for the validation of our in vivo human studies. Ultrasound images could display normal arterial anatomy and assess the very site of atherosclerotic lesion. Following intervention intimal tears, intimal flaps and plaque rupture could be displayed. How useful such information might be in predicting the success of intervention is a matter to be studied prospectively. Equally intriguing is the possible value of intravascular ultrasound for understanding the pathogenesis of atherosclerosis.

Thus, intravascular, real-time, high-resolution ultrasound is an exciting new development. Its unprecedented diagnostic potential opens new horizons for clinical research, and practical applications are rapidly emerging. It can be used to characterize and quantify the degree of arterial disease, to study its natural history and, perhaps in the future, to grade the effects of pharmacological interventions. It will become a major adjunct to second-generation angioplasty procedures as a guidance tool, and for the immediate evaluation of results since it is easier to use and provides unique information faster than other imaging modalities.

Acknowledgment: We deeply appreciated the cooperation and assistance of Peter Frietman, M.D. and Robert Jan v. Suylen, M.D.; and Wim van Alphen and Leo Bekkering for constructing the transducer.

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CHAPTER 6

ASSESSMENT OF ARTERIAL DISEASE AND ARTERIAL RECONSTRUCTIONS BY INTRAVASCULAR ULTRASOUND

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Assessment of arterial disease and arterial reconstructions by intravascular ultrasound

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Key words: intravascular ultrasound, femoral artery, balloon angioplasty, bypass surgery

Abstract

Clinical application of intravascular ultrasound to assess arterial atherosclerotic disease was introduced in humans after extensive *in vitro* and *in vivo* animal studies. Real-time images, obtained with a 30 MHz element mounted on a 5 F catheter, consistently confirmed angiographic images, up till now considered to be the gold standard. In addition to these data, ultrasonic cross-sectional imaging provided information on the composition of atheroselectic lesions and the size and shape of the lumen. Based on the experimentally derived criteria for tissue characterization, a better insight into arterial morphology could be obtained, allowing improved planning of interventional or reconstructional procedures.

Moreover intravascular ultrasound has proved valuable as a post-interventional procedure to monitor and assess the quality of interventional results. The ultrasound images are clearly superior to angiographic studies, albeit the ultrasonic information is an adjunct to angiography and, as yet, not a substitute.

We present our initial experience with intravascular ultrasound obtained in patients with substantial peripheral arterial disease.

Introduction

The tendency to minimize surgical procedures, or abolish the necessity for operation, has led to an enormous increase in the use of interventional catheter-based therapeutic techniques for treatment of peripheral vascular obstructive disease. In the eagerness to introduce these various new techniques, a hypothetical mechanism was frequently assumed for the effects on atherosclerotic lesions.

An example of an erroneous interpretation of the results of such a procedure is provided by the original 'percutaneous transluminal angioplasty' described by Dotter and Judkins in 1964 [1]. Dotter theorized that the atheromatous plaque obstructing the lumen of an artery would be compressed by the coaxial catheter, much as fresh snow is compressed by footsteps. This theory was still held in 1978 when Grüntzig [2] introduced the balloon catheter that subsequently became accepted worldwide. The method certainly worked and a scientific explanation was not deemed necessary until it later became evident that the positive initial results were often followed by restenosis months later [3].

Intravascular ultrasound has the unique capability to characterize arterial wall structure in cross-sectional images [4]. When applied before and after catheter interventional procedures these images provide useful information, not only on the catheter procedure, but also on the pathophysiologic changes occurring in the vessel wall as a result of intervention. These changes can be recorded and measured quantitatively by computer contour analysis, as developed by Wenguang and coworkers [5]. Qualitative information, such as exact localization and extent of plaque rupture and vessel wall dissection, may prove useful to better define criteria for the effectiveness and completeness of these catheter interventions [6].

Similary, ultrasound provides useful information when used as 'completion echography' after arterial vascular reconstructive procedures, such as venous or prosthetic bypasses.

Material and methods

Ultrasound system

A 5 F real-time imaging catheter with a 1 mm diameter 30 MHz single element transducer at its tip was used. The system is based on a mechanically motor-driven rotating catheter tip element connected to a flexible drive-shaft. The element is covered by an acoustically transparent dome. Axial resolution of the system is 80 μm, and lateral resolution is better than 225 μm at a depth of 1 mm. The unit is connected to a prototype instrument (Du-Med, Rotterdam, The Netherlands) providing continuous real-time cross-sections of the vessel wall (up to 16 images per second). The ultrasonic images are displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 gray levels.

Technique

The catheter was introduced through a 7 F introducer sheath, either percutaneously or by direct puncture of the common femoral or superficial femoral artery, which was dissected free through a small groin incision. Percutaneous studies were performed under local anesthesia only; intra-operative studies were done under general anesthesia.

After introducing the catheter as far as possible in cases of total occlusion, or at some distance beyond the lesion in cases of stenotic disease, cross-sectional images were obtained by retracting the catheter from distal to proximal. The position of the catheter tip was recorded under fluoroscopy with the use of a radiopaque ruler.

Twenty-two patients with long or short superficial femoral artery (SFA) occlusions or severe stenosis were selected for a recanalization procedure consisting of Nd-Yag laser-assisted balloon angioplasty. Patients with an occlusion at the level of the orifice of the SFA underwent surgical exploration of the common femoral artery (CFA). Patients with an open proximal SFA and occlusion in the midportion, or at the level of Hunter's canal, were explored percutaneously in the angiography suite.

When recanalization was unsuccessful, or when the SFA occlusion was considered too long for successful recanalization, a surgical bypass procedure was performed using either autologous (saphenous vein) or prosthetic (Gore-tex®) material. Recanalization procedures were considered unsuccessful when the stenosis or occlusion could not be passed by the catheter (with or without the use of laser energy); when the lesion was passed but was immediately followed by early rethrombosis; or when the final result of the procedure, as judged by completion was deemed as not remaining open for up to 30 days.

Control angiography was performed in all patients after completion of the angioplasty or bypass procedure.

Clinical results

A multitude of echo data was produced and some of this information was interpreted and used during operation. All information was stored on videotape and reviewed after completion of the surgical or interventional treatment. The whole period was considered as a learning phase: identical images were often interpreted differently in the beginning compared to later stages.

The following aspects reflect the main features that we came to recognize and interpret during this study.

Characterization of lesions
In all patients atherosclerotic lesions could be rec-

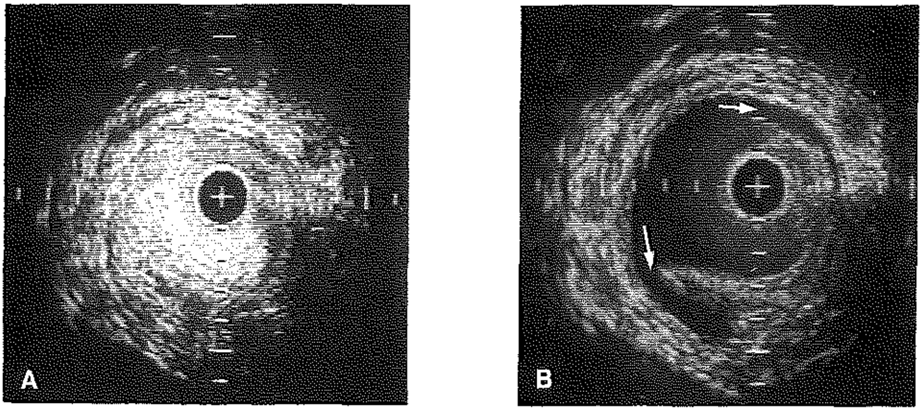

Fig. 1. Intravascular ultrasound cross-sections of the superficial femoral artery showing the advantage of saline injection for off-line analysis of still-frames. A, Echogenicity of blood hampers delineation of the lumen contour. B, Following saline injection plaque dissection (arrow) became evident on the still-frame. Calibration 1 mm.

ognized and localized based on the angiographic findings. In some cases the occlusion appeared to cover a longer distance than apparent on the pre-interventional angiogram; this could be attributed to the delay between the angiographic and interventional procedures. All stages of atherosclerotic disease were encountered in the interrogated vessels, according to the previously described criteria for echographic identification of vessel wall characteristics [7, 8].

Hypoechoic media

The importance of recognizing a hypoechoic media became evident during these investigations. As the superficial femoral artery is a muscular type of artery, an echolucent zone represents the area between the internal elastic lamina and adventitia. The presence of this area allows to compare the size of the 'original' arterial lumen with the size of the 'free' lumen at the site of a stenosis. The 'free' lumen is easily outlined by the constantly moving echoes of blood. The difference between 'original' and 'free' lumen is the area occupied by the atherosclerotic lesion, whether that lesion consists of fibrous thickening only or of stenotic disease. The borders of these areas, and subsequently their surfaces, can be determined off-line by computer analysis [5]. These calculations play a role in describing the definition for – or the degree of – successful intervention. Change in luminal size, especially at the level of most severe stenosis, can now be calculated with greater accuracy when compared to the changes in lumen diameter determined angiographically. This is so even when angiography is performed in two directions, which is generally not the case, and is not routine procedure in our department.

Saline flushing

In cases of significantly reduced blood flow due to a stenosis, echogenicity of blood appears to increase and as a result can obscure the dividing line between lumen and vessel wall, or between lumen and atherosclerotic lesion. This division can be greatly enhanced by flushing the lumen through the introducer sheath with small amounts of saline (Fig. 1). The dense echoes of blood are immediately replaced by an echolucent area. This area is then slowly replaced by moving echoes, whilst the separation between blood and saline can sometimes be observed over a longer period, depending on the flow rate.

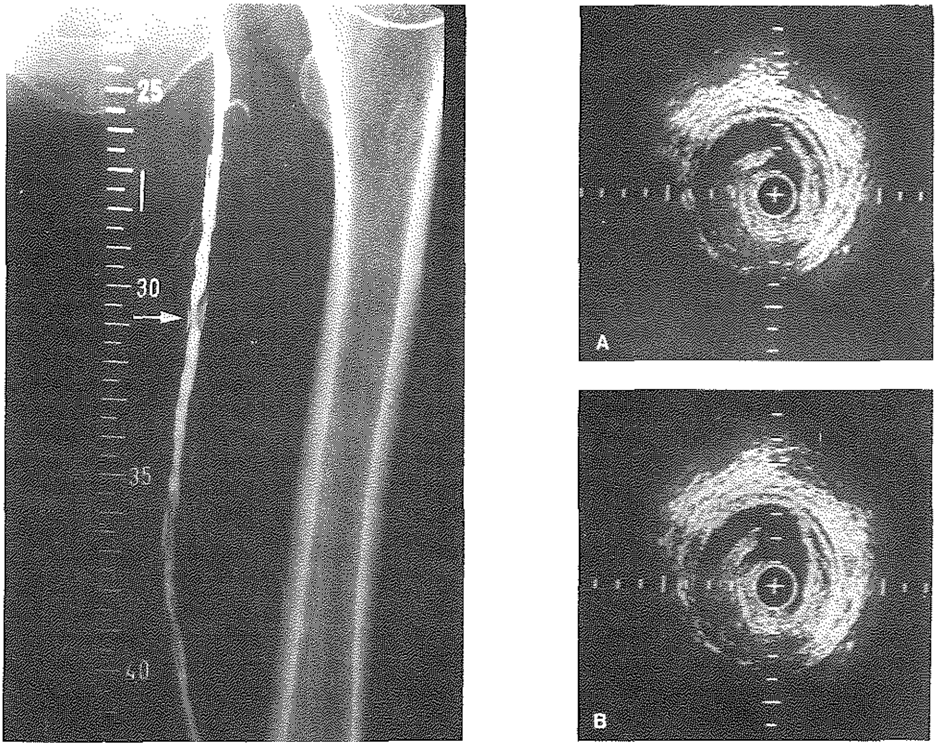

Fig. 2. Angiogram and intravascular ultrasound cross-sections of the superficial femoral artery obtained after balloon angioplasty. The angiogram reveals a distinct dissection at level 31. Ultrasound cross-sections obtained at the corresponding level (31) evidenced plaque dissection. Pulsatile flow resulted in a slight difference between the images (A = diastole; B = systole). Calibration 1 mm.

Plaque rupture

Plaque rupture and vessel wall dissection almost invariably occur after balloon angioplasty [3]. Occurring so frequently and at multiple sites, it could be argued that this phenomenon is mandatory for a positive angioplasty result.

Dissections are sometimes very obvious on angiography (Fig. 2), but can only be suspected in other cases. This may largely depend on the location of the rupture with regard to the direction of the X-rays. Tangential projection reveals a dissection easily, whereas a rupture in the ventral or dorsal part of the vessel can be obscured.

Intravascular ultrasound not only recognizes this type of lesion at any sector of the circumference of the vessel wall, it actually visualizes the movements of a ruptured plaque inside the lumen (Fig. 2). Real-time assessment of vessel wall dynamics offers a great advantage over angiography in these cases.

The false lumen created by dissection can be differentiated from the original lumen, partially by its shape and partially by decreased flow in the false lumen, causing increased echogenicity of blood. Decreased flow in this part of the lumen can sometimes be observed on angiography when the contrast medium is still visible in a dissected area, while in the mainstream the contrast is already replaced by blood. We were surprised to see how devastating the effects of balloon angioplasty can be, evidenced by a highly irregular contour of the

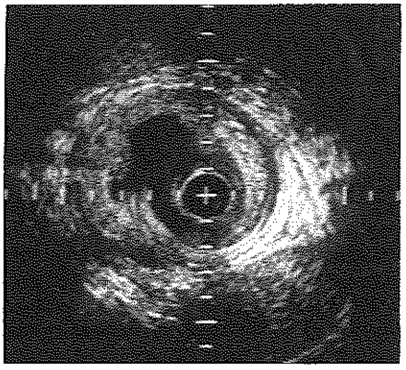

Fig. 3. Intravascular ultrasound cross-section of the superficial femoral artery showing the irregular lumen contour following balloon angioplasty. Calibration 1 mm.

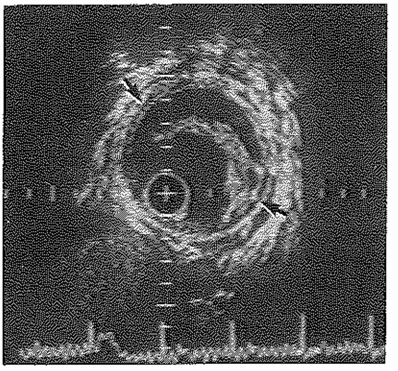

Fig. 4. Intravascular ultrasound cross-section of the superficial femoral artery revealing a dissection following balloon angioplasty. The thinned hypoechoic muscular media is seen between 3 and 11 o'clock. Calibration 1 mm.

lumen (Fig. 3). However, follow-up of these patients has learned that no direct relationship exists between the shape of the lumen at the end of the procedure and patency of that vessel at long-term follow-up.

Computer contour analysis has confirmed that the cross-sectional area occupied by the atherosclerotic lesion does not change markedly after angioplasty. This means that any increase in lumen area has to be gained by (over)stretching the part of the vessel wall that is relatively 'most normal'. In an excentric lesion this part is opposite the lesion; ruptures occur most frequently at the borderline between the plaque and the 'normal' wall (Figs 2 and 4).

Presence of thrombus

In the early stages of chronic atherosclerotic arterial disease the loss of luminal area due to intimal thickening is largely compensated for by thinning of the media, resulting in a 'steady state' of the lumen area. In more progressive stages of the disease, however, medial thinning no longer compensates for intimal thickening, eventually resulting in stenosis.

This process was first described in coronary arteries by Glagov and coworkers [9] in 1987, but it also occurs in peripheral arteries. We used this phenomenon of medial thinning [10] to discriminate fibrous intimal hyperplasia from mural thrombus. Both thrombus and soft atherosclerotic lesions produce relatively soft echoes and therefore cannot be identified on their ultrasound appearance alone. The presence of a normal media behind a thick 'intimal' area consisting of soft echoes may be an indicator that this lesion consists of mural thrombus (Fig. 5).

Distal anastomosis of bypass

After construction of a femoro-popliteal or femoro-crural bypass, using either autologous material or a vascular prosthesis, the whole length of the bypass and more specifically the distal anastomosis can be examined with ultrasound. Intimal flaps, mural thrombus (Fig. 5), retained venous valves (Fig. 6), and torsion of the bypass or external compression (Fig. 7) can all be recognized as distinct features.

Complications

To date, we observed no adverse effects that could be attributed to the use of the ultrasound catheter.

The potential risks include: a) unintended dissection resulting in early occlusion; b) perforation of the vessel wall caused by the relative stiffness of

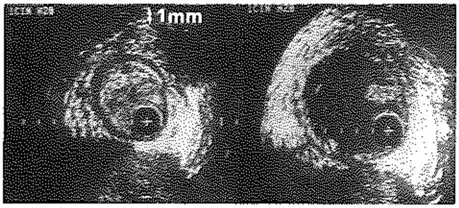

Fig. 5. Intravascular ultrasound cross-sections obtained before (left) and after (right) balloon angioplasty of the superficial femoral artery. The lumen area is completely obstructed by a soft lesion and is circumscribed by the hypoechoic muscular media. Following dilatation the lumen area is increased. The hypoechoic media is thinned and a small remnant of the lesion is still present.

the catheter; c) distal embolization caused by the (extra) passage of the ultrasound catheter; d) wound infection or sepsis.

During this period of limited experience we encountered minor complications (wound hematoma, false aneurysm) that are normal for any catheter procedure; there were no major complications.

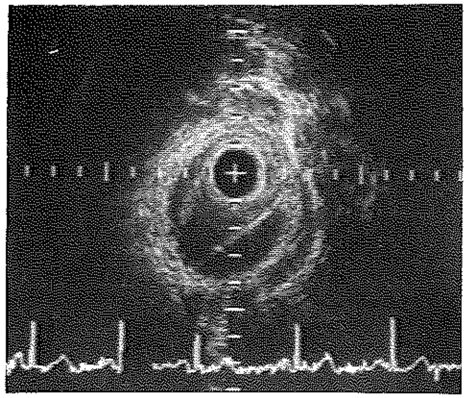

Fig. 6. Intravascular ultrasound cross-section of a normal venous bypass-graft. The valves of the vein are clearly demonstrated. Calibration 1 mm.

Discussion

From this experience with only 22 patients we cannot draw firm conclusions. However, this investigational experience allowed us to learn something about the possible applications of intravascular ultrasound in the diagnosis and treatment of atherosclerotic peripheral vascular disease.

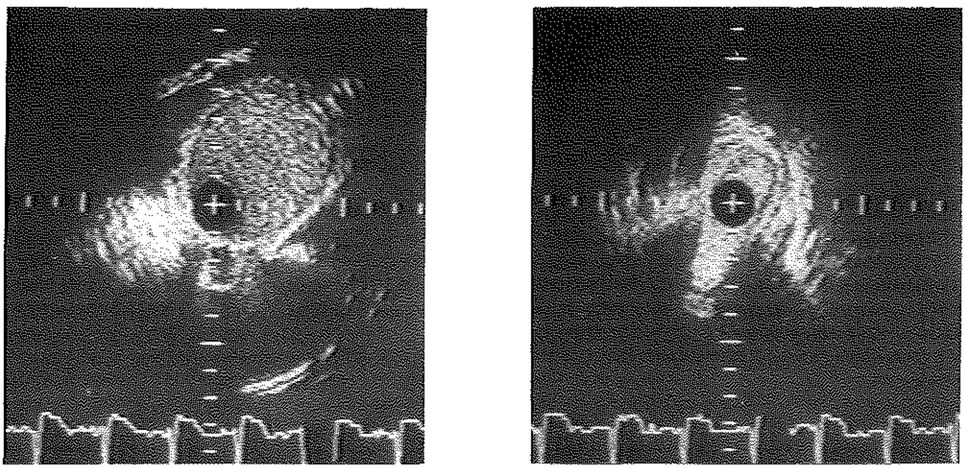

Fig. 7. Intravascular ultrasound cross-sections obtained from a venous bypass graft that was partially obstructed by external compression at 9 o'clock. (left: normal cross-section; right: compressed cross-section). Note that blood is echogenic. Calibration 1 mm.

Especially in the field of endoluminal catheter interventions the use of ultrasound seems a welcome addition in the armamentarium of the vascular surgeon and interventional radiologist. The ultrasonic cross-sections provide information that is not, or insufficiently, provided by angiography. Whether this pre-interventional diagnostic information will be of help in deciding which therapeutic modality (laser; laser-assisted balloon; mechanical atherectomy device or conventional operation) should be used, remains to be seen.

The post-interventional information will almost certainly lead to a better understanding of the pathophysiological processes that play a role in the different bypasses or the interventions, and – perhaps – will provide some keys to prevention of the most difficult complication that seems inherent with all types of intervention: restenosis.

The method is not without some pitfalls, but no serious complications were encountered. As the method depends on the emission of ultrasound and receiving the reflected echo-sound, it is evident that no image can be obtained when the ultrasound is not reflected in the direction of the ultrasound element. This is sometimes the case when the angle of insonification is not perpendicular to the vessel wall or lesion. A hypoechoic sector of the echo-image will then result, which can lead to erroneous interpretation. As flexing of the catheter causes friction of the motor-driven axis against the catheter shaft, this will result in rotational instability, causing striation in digitalized images. Consequently, the current type of the Du-Med® catheter can not be used in vessels with too much bending. As the femoral and popliteal arteries usually do not show such patterns, this has not been a problem in our experience.

Summary

The application of intravascular ultrasound in the treatment of peripheral vascular obstructive disease is feasible and provides distinct information, not available with any other diagnostic procedure. The information is primarily morphologic, providing data about the type, structure and location of atherosclerotic lesions. In addition some hemodynamic information is provided, such as blood flow and flow velocity. Using computer calculations, quantitative information (luminal area, lesion area, etc.) can be obtained before and after intervention.

Although perhaps unlikely to become a routine procedure in peripheral surgical reconstructions, intravascular ultrasound has proven to be of potential value in this field. More experience, longer follow-up and controlled clinical trials will be needed to define the future role of intravascular ultrasound in assessment and treatment of peripheral vascular disease.

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CHAPTER 7

FEMORO-POPLITEAL VEIN BYPASS GRAFT STUDIED BY INTRAVASCULAR ULTRASOUND

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Femoro-popliteal Vein Bypass Grafts Studied by Intravascular Ultrasound

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The usefulness of intra-operative intravascular ultrasound (30 MHz) was evaluated in three patients who underwent a femoro-popliteal vein bypass. Intravascular echography analysis of the surgical procedure revealed a normal uneventful result in one patient. In two other patients obstructions in the vein grafts were identified either caused by internal obstruction or external compression. Angiography in these two patients provided equivocal data.

We conclude that intravascular ultrasound imaging may be a useful adjunct to angiography and may offer important clinical data to facilitate the surgeons in analysing the results of the interventional procedures.

Key Words: Intravascular ultrasound; Femoro-popliteal bypass graft; Vein bypass.

Introduction

There are several reports on the feasibility of intravascular ultrasound to assess pathology in the arterial circulation both *in vitro* and *in vivo*.[1–8] The technique allows a distinction to be made between normal and pathological vessels and has the potential to guide interventional therapeutic procedures.[6–8]

We report the use of intravascular ultrasound in three consecutive patients with normal, internal and external obstructed femoro-popliteal bypass. Important information on the vein bypass grafts was obtained indicating the additional clinical relevance of this technique.

Patients and Methods

Patient 1

A 77-year-old man with extensive atherosclerosis was admitted for a femoro-popliteal vein bypass graft of the right superficial femoral artery. The patient had undergone the same procedure 5 months previously, but the graft had occluded in spite of the use of oral anticoagulant drugs.

Angiography showed a total occlusion of the superficial femoral artery and vein bypass graft with the presence of wall irregularities. A femoro-popliteal reversed vein bypass was performed using the contralateral long saphenous vein.

Patient 2

A 55-year-old diabetic female patient with a non-healing wound at the site of amputation of the first toe of the right foot underwent angiography. Extensive peripheral vascular atherosclerosis was present. An *in situ* femoro-popliteal vein bypass graft was inserted.

Patient 3

Reversed saphenous vein bypass grafting was performed for a 69-year-old man who previously underwent unsuccessful percutaneous transluminal angioplasty of the right superficial femoral artery because

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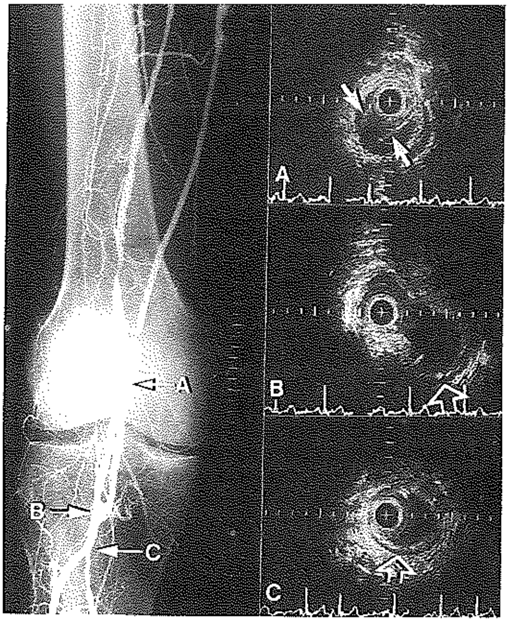


Fig. 1. Angiogram after intervention revealing a patent vein bypass graft anastomosis. Intravascular ultrasound images (A–C) correspond to positions indicated on the angiogram. A, the vein is recognised as a homogeneous vessel wall. Valves of the vein (arrows) are visualised as straight echogenic lines. B, the anastomosis is seen to be patent. Note that at this junction the muscular nature of the popliteal artery is characterised by a hypoechoic media (open arrow). C, more distally a patent popliteal artery displays a three-layered arterial wall (open arrow). Calibration = 1 mm.

of disabling intermittent claudication. Angiography demonstrated a total occlusion of the right superficial femoral and popliteal artery, whereas the distal tibioperoneal trunk was patent.

Ultrasound imaging

The study was performed with a 5F catheter (diameter = 1.6 mm) containing a motor-driven 32 MHz single-element transducer at its tip (Du-Med, Rotterdam, The Netherlands).

After completion of the arterial reconstruction the ultrasound catheter was advanced via an introducer sheath through the bypass graft into the distal popliteal artery and images were recorded pulling the catheter back from distally to proximally. The position of the ultrasound catheter was marked by a ruler and monitored under fluoroscopic control. When necessary, small amounts of 0.9% saline were injected via the sheath in order to eliminate echogenic blood from the lumen and to clearly assess the patency of the vessel.

Results

Patient 1

After intervention, control angiography revealed both a patent vein bypass graft and an angiographically acceptable distal anastomosis. The graft was subsequently analysed by intravascular ultrasound (Fig. 1).

Distally in the popliteal artery, a three-layered structure was observed, typical for a muscular type of artery. The anastomosis between the popliteal artery and bypass graft was unremarkable. Proximally an echographically homogeneous vascular wall was seen without evidence of stenosis. Valves within the

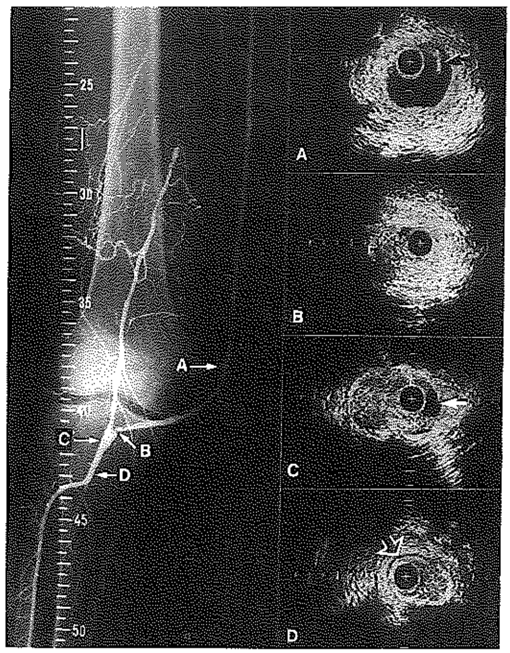


Fig. 2. Angiogram with corresponding intravascular ultrasound cross-sections, revealing a patent anastomosis between the vein bypass graft and popliteal artery; proximal to the anastomosis a lesion is apparent (arrow). Intravascular ultrasound images (A–D) correspond to positions indicated on the angiogram. A, remnants of a vein valve (arrow) are seen echographically in the patent lumen. B, proximal to the anastomosis the diameter of the vein bypass graft is significantly reduced. C, the anastomosis is partly obstructed by a lesion (*). The black area (arrow) indicates saline flow unable to pass the anastomosis. D, distally a normal popliteal artery is seen. Open arrow: hypoechoic media; calibration = 1 mm.

vein were visualised as straight echogenic lines. It was concluded that there were no technical faults and that the surgical procedure was successful. Clinical follow-up, 1 year later, showed no late vascular complications.

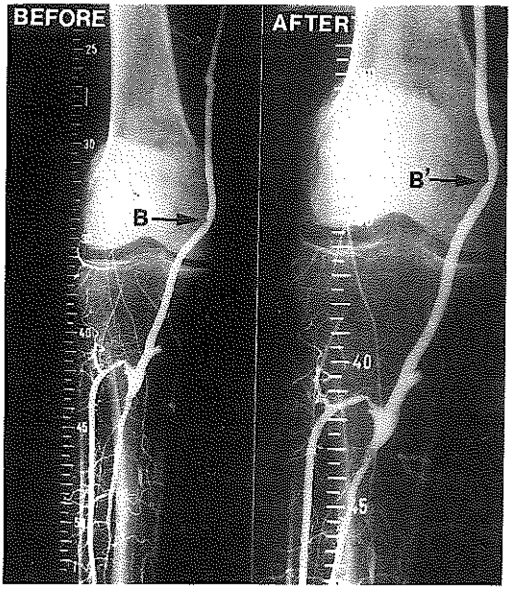
Patient 2

After the surgical procedure, control angiography showed a patent anastomosis between the vein bypass graft and popliteal artery. Just proximal to the anastomosis a stenotic lesion was apparent. Intravascular ultrasound imaging was then applied to examine the bypass (Fig. 2).

As the ultrasound catheter entered the popliteal artery, cross-sections showed a patent muscular artery with a clear hypoechoic media. Just proximal to the level of the anastomosis the luminal size changed drastically. A solid structure, presumably consisting of a thrombus was seen inside the bypass graft, partly obstructing the anastomosis. In addition, the adjacent vein bypass revealed no lumen exceeding the 1.6 mm diameter of the ultrasound catheter. The venous wall had a homogeneous texture of echogenicity, which distinguished it from the popliteal artery. Pulling the catheter further back into the vein bypass graft, a normal patent lumen was noted 1 cm proximal to the anastomosis with a diameter of 4 mm. Vein valves in this *in situ* graft had already been rendered incompetent with a valvulotome and only remnants of vein valves were visualised. Based on the echographic findings it was concluded that the anastomosis was inadequate. Because peripheral pulsations were present, the surgical team decided that re-exploration of the distal anastomosis was not necessary in spite of the angiographic and echographic data. Perfusion of the patient's leg continued to decline progressively during the next few days. Reoperation was performed 1 week later, followed by a below knee amputation 2 weeks later.

Patient 3

After surgical intervention, angiography revealed a very short stenosis at the level of the medial condyle of the knee joint (level 34 cm on the ruler) (Fig. 3).



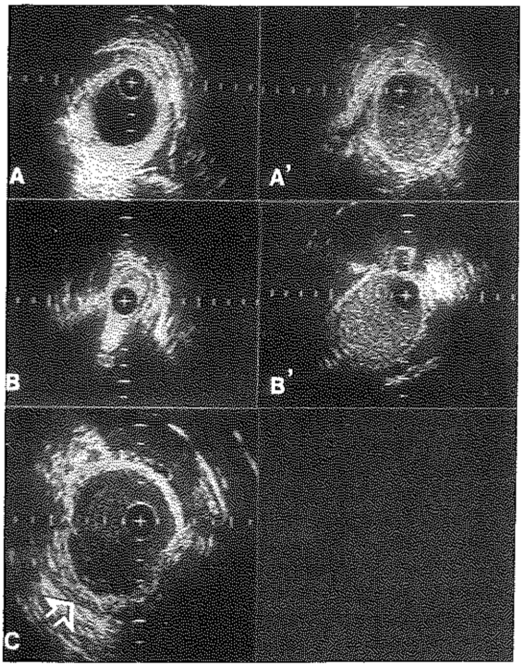


Fig. 3. Angiograms and corresponding intravascular ultrasound cross-sections of a vein bypass graft before and after cleaving. Before cleaving a stenosis is seen at the level of the medial condyle of the knee (arrow B), that is no longer visible angiographically following cleaving (arrow B'). A and C, intravascular ultrasound reveals a patent bypass graft and anastomosis. B, local external compression of the bypass seen at level 34 changes the shape of the lumen to ellipsoid, whereas after cleaving, its normal circular shape is seen (B'). Note the effect of saline to clear the lumen from blood (compare A–A'). Open arrow: hypoechoic media; calibration = 1 mm.

Intravascular ultrasound imaging showed the distal anastomosis to be patent with normal blood flow in the tibioperoneal trunk and vein bypass graft. Eight centimetres proximal to the anastomosis, just above the level of the knee joint, a change in the shape of the vessel from circular to ellipsoid was observed, probably due to external compression of the bypass graft. No internal abnormality or thrombus was seen. About 1 cm above this level the vein bypass reverted to its normal circular contour. Based on these findings it was decided to re-explore the graft and look for compression or torsion. It appeared that the graft was compressed by the tendon of the gastrocnemius muscle. The tunnel for the graft was erroneously made partly through the medial head of the gastrocnemius muscle. After dividing a small part of the tendon, intravascular ultrasound exhibited the vein bypass graft to have resumed its normal circular shape with a normal blood flow along its entire length.

Subsequent intra-operative angiography confirmed that the obstruction had been eliminated.

Discussion

Intravascular ultrasound uniquely provides tomographic cross-sections of vessels and offers relevant clinical information to assist surgeons in decision-making during and after intervention. The patients described in this report underwent intravascular ultrasound imaging to assess the results of a vein bypass graft procedure of the superficial femoral artery.

In vitro histological studies have demonstrated that the popliteal artery is muscular and has a typical three-layered structure. In contrast, a vein echographically displays the thin and homogeneous appearance of the vessel wall.[9]

This study demonstrates that intravascular ultrasound enables the surgeon to differentiate normal from obstructed vein bypass grafts. Obstructions in the vein grafts were either caused by mural thrombus or by external compression. Angiography in these two patients provided equivocal data whereas intravascular ultrasound was accurate and conclusive. Intravascular ultrasound may therefore contribute independent additional information of clinical relevance but it will take time and good documentation to assess the real value of this new instrument.

We conclude that intravascular ultrasound imaging may be a useful adjunct to angiography and allow vascular surgeons to accurately analyse the results of interventional procedures, such as an intra-operative balloon angioplasty, or reconstructive procedures such as a venous or prosthetic bypass grafting.

Acknowledgements

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CHAPTER 8

REAL-TIME INTRAVASCULAR ULTRASONIC IMAGING BEFORE AND AFTER BALLOON ANGIOPLASTY

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Real-Time Intravascular Ultrasonic Imaging Before and After Balloon Angioplasty

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Intravascular ultrasonic imaging is a promising technique for the study of arterial disease. Several investigators have shown that intravascular ultrasonography can differentiate normal from abnormal arteries in both the in vitro and in vivo setting.[1–10] The technique allows characterization of atherosclerotic plaque constituents and can be used for assessment of the effect of intravascular intervention. The ability to study in vitro the effects of balloon dilatation angioplasty on human atherosclerotic artery segments has been documented.[4,5] This paper describes in vivo results obtained in a patient using a real-time imaging system before and immediately after balloon dilatation angioplasty. The study was performed with a 5F catheter (1.6 mm) containing a motor-driven 32-MHz single-element transducer at its tip (Du-Med). The images were stored on a ½-inch videotape.

CASE REPORT

A 70-year-old man underwent percutaneous transluminal angioplasty of the right superficial femoral artery in 1985 for intermittent claudication. He returned 5 years later with recurrent symptoms of right-sided claudication. Angiography revealed a 50% stenosis of the right superficial femoral artery (Figure 1). Because the radiologist was unable to obtain transcutaneous access, the artery was dissected free under general anesthesia. Skin markers were placed for radiographic reference. Via direct puncture a 9F sheath was advanced distally into the artery. Intraoperative angiography was carried out to assess the site of obstruction. The ultrasound catheter was introduced and the artery was imaged from proximal to distal.

Proximally, a three-layered structure was observed, typical for a muscular vessel. The entire circumference of the artery was covered by a 1-mm thick lesion; more distally, the lesion expanded progressively. When the catheter was advanced to the level of stenosis, the lesion proved to be impassable (area 11 mm^2). X-ray screening confirmed that the catheter arrived at the obstructive site.

Intravascular ultrasonography indicated that the lesion was eccentric and presumably consisted of collagen-rich connective tissue, as no reliable echo information was obtained from peripheral tissues in the arterial wall (such as the medial layer). Calcium noted near the obstructive site was visualized as a highly reflective structure causing shadowing in the outer structures. The catheter was then removed.

Angioplasty of the lesion was performed using a 6-mm and 8-mm balloon. The results assessed angiographically were deemed satisfactory.

Immediately following the angiographic study, the imaging catheter was reinstalled to the level of prior stenosis. It was noted that the diameter of the lumen had increased by 80% (area 19 mm^2). Flushing with 0.9% saline (5 mL) through the sheath promptly resulted in a clearer outline of the inner surface of the vessel, particularly at the site of an apparently ruptured atherosclerotic plaque. Blood flow within both the ruptured area and dissection was so slow that the erythrocytes became echogenic.

The location of the ruptured plaque was variable. The dissection noted at various levels was interposed between the lesion and arterial wall (Figure 2). Control angiography performed five days later revealed multiple dissections appar-

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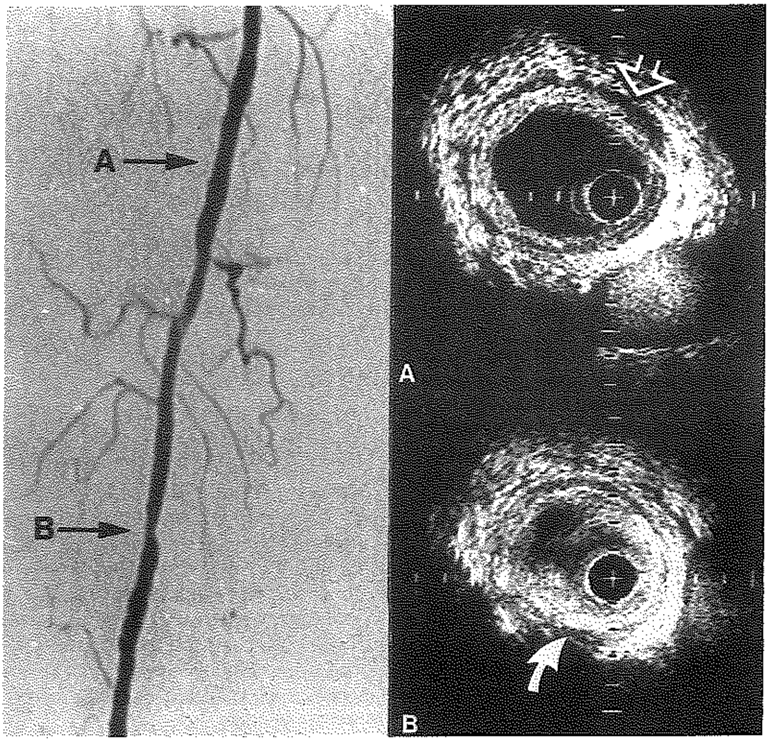

FIGURE 1. Angiogram reveals a 50% stenosis of the right superficial femoral artery. Intravascular ultrasound images (**A,B**) are from the positions indicated in the angiogram. Proximally a large lumen is imaged with diffuse intimal thickening (1 mm). The dark layer corresponds with the media (open arrow). The femoral vein is noted at 5 o'clock. At the level of stenosis (B) the medial layer is visible between 11 and 6 o'clock. Evidence of calcium deposition causing shadowing is seen at 7 o'clock (solid arrow). Calibration markers are 1 mm.

ently corresponding to the ruptured plaques noted with intravascular ultrasonography (Figure 2). The patient has remained asymptomatic since discharge.

DISCUSSION

Intravascular ultrasonic imaging provided unique qualitative and quantitative information about the diseased femoral artery before and after intervention; combined with angiography, a "three-dimensional" insight was obtained of the pathology involved.

It is noteworthy that single-plane angiography suggested a 50% stenosis whereas intravascular ultrasonic imaging revealed a lesion impassable for a 1.6-mm diameter catheter.

This case report highlights the potential of intravascular ultrasonic imaging for a better understanding of angiographic images during and following intravascular interventions.

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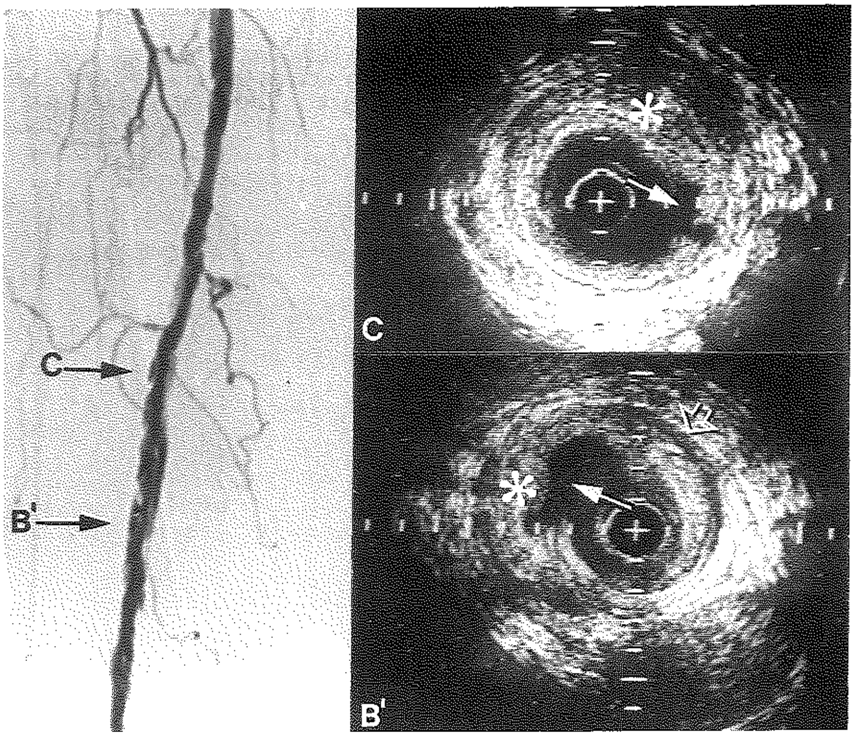

FIGURE 2. Angiogram and intravascular ultrasound images obtained following balloon dilatation. The angiogram reveals a larger lumen and an irregular surface suggesting intimal tears. Corresponding ultrasound images (B' and C) are from the level that was previously occluded and dilated. The lumen is significantly increased (80%). Substantial residual atherosclerotic lesion is still present (asterisk). The ruptured plaque (arrows) and dissection (open arrow) became apparent only after saline injection. The dark layer corresponding with the thinned media is seen between 5 and 8 o'clock in C. Calibration markers are 1 mm.

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CHAPTER 9

EFFECT OF BALLOON ANGIOPLASTY ON FEMORAL ARTERY EVALUATED WITH INTRAVASCULAR ULTRASOUND IMAGING

Salem H.K. The, Elma J. Gussenhoven, Yin Zhong, Wenguang Li, Frans C. van Egmond, Herman Pieterman, Hero van Urk, G. Pieter Gerritsen, Jos R.T.C. Roelandt, Cees Borst, Richard A. Wilson, Nicolaas Bom

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Effect of Balloon Angioplasty on Femoral Artery Evaluated With Intravascular Ultrasound Imaging

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Background. **Intravascular ultrasound was used to assess the immediate effect of balloon angioplasty on the superficial femoral artery.**

Methods and Results. **In 16 consecutive patients, corresponding ultrasonic cross sections (n=72) before and after balloon angioplasty were qualitatively and quantitatively analyzed. The qualitative data were compared with angiographic findings. Before intervention, the angiographically demonstrated obstructive lesions were confirmed by intravascular ultrasound. Ultrasound enabled discrimination between soft (n=43) and hard (n=29) lesions, as well as between eccentric (n=57) and concentric (n=15) lesions. After balloon angioplasty, the presence of a dissection assessed angiographically in 14 patients was confirmed by intravascular ultrasound. Additional morphological information provided by ultrasound included plaque rupture in 14 patients and internal lamina rupture in six patients. Quantitative ultrasound data revealed an increase in free lumen area from 9.7±4.7 to 18.3±7.0 mm² ($p \leq 0.01$), an increase in minimal lumen diameter from 2.8±0.7 to 3.6±1.2 mm ($p \leq 0.01$), and an increase in media-bounded area from 21.7±5.4 to 28.3±5.8 mm² ($p \leq 0.01$). The lesion area for the majority of cases (n=32) remained unchanged (13.0±4.9 mm² versus 12.9±4.6 mm²), or the lesion disappeared partially (from 9.1±0.9 to 4.3±1.4 mm², n=4, $p \leq 0.01$) or totally (from 10.1±4.2 to 0 mm², n=6). Stretching of the arterial wall was further evidenced by medial thinning from 0.55±0.19 to 0.34±0.11 mm ($p \leq 0.01$).**

Conclusions. **Luminal enlargement by balloon dilatation is achieved primarily by overstretching the arterial wall, with the lesion volume remaining practically unchanged. Overstretching is accompanied almost always by dissection and plaque rupture and occasionally by an internal lamina rupture. (*Circulation* 1992;86:483–493)**

Key Words • arteries • ultrasound imaging, intravascular • atherosclerosis • balloon angioplasty

The exact mechanism by which balloon angioplasty leads to successful luminal enlargement has not been established definitively. A review of the literature provides information on the various mechanisms proposed to explain the arterial dilatation obtained by balloon angioplasty (Table 1).

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Initially, it was postulated that enlargement of the vascular lumen is caused by compression and redistribution of the atheromatous plaque to the subadjacent area.[1,2] Overstretching or even rupture of the vessel wall has also been advocated as the primary mechanism of a successful procedure.[3–9] Other studies reported splitting of the intima near the edges of the plaque or rupture of the plaque itself.[3,7–11] Finally, embolization of the lesion as the ultimate result of the intervention has also been described.[6,8,11] The proposed mechanisms have been based on the study of postmortem specimens,[3–5,7–9,11] experimentally controlled models,[10] experiments using animal models of atherosclerosis,[4,6,8,11] and clinical observations.[1,2,11] Consensus on the precise contribution of each mechanism has not yet been reached.

For in vivo diagnostic assessment of the changes after balloon angioplasty, angiography has been the method of choice. The recent introduction of high frequency intravascular ultrasound allows detailed imaging of the arterial wall from within the artery. In vitro studies have demonstrated that intravascular ultrasound is a reliable technique to determine the constituents of the vessel

Table 1. Proposed Mechanisms of Arterial Dilatation by Balloon Angioplasty

Investigator	Year	Compression and redistribution of plaque	Stretching of medial layer	Rupture of wall (tunica muscularis, vessel layer)	Detachment of plaque edges from media (dissection)	Plaque rupture	Embolization of lesion
Dotter et al[1]	1964	X					
Grüntzig et al[2]	1974	X					
Freudenberg et al[9]	1978			X	X	X	
Castaneda et al[4]	1980		X	X			
Block et al[8,11]	1980, 1984		X	X	X	X	X
Isner et al[5]	1983		X	X			
Chin et al[3]	1984	X		X	X		
Lyon et al[7]	1987		X	X	X		
Faxon et al[6]	1987		X	X			X
Ebner et al[10]	1989				X		

wall qualitatively as well as quantitatively.[12–18] Intravascular ultrasound is a promising technique to assess the results of various intervention techniques, which includes balloon angioplasty.[13,14,19–24]

The purpose of this study was to study the effects of balloon angioplasty in the clinical setting using intravascular ultrasound. Sixteen consecutive patients, presenting with disabling claudication, were examined with intravascular ultrasound before and immediately after balloon angioplasty of the superficial femoral artery. First, qualitative data with respect to vessel wall and lesion morphology were obtained and then the morphology seen after intervention was described. Second, quantitative measurements of free lumen area, minimal lumen diameter, media-bounded area, lesion area, and medial thickness obtained before and after intervention were compared.

Methods

Study Group

The investigation was approved by the local Committee on Human Research, and informed consent was obtained from each patient. Sixteen consecutive patients (12 men, four women; age range, 45–83 years; mean age, 67 years) scheduled for routine balloon angioplasty of the superficial femoral artery to treat disabling claudication were studied. In 11 patients, the procedure was conducted under local anesthesia. Five patients were explored surgically because previous attempts to perform the transcutaneous balloon angioplasty procedure were unsuccessful. In these patients, a femoral artery cut down was performed under general anesthesia. Five of the 16 patients had been treated earlier by balloon angioplasty (interval, 3–14 months).

In all 16 patients, balloon angioplasty was performed over the entire length of the femoral artery using a standard 6-mm balloon (Cordis, Roden, The Netherlands).

Intravascular Ultrasound Investigation

A mechanical 30-MHz imaging system was used (Du-MED, Rotterdam, The Netherlands).[23,24] The transducer was mounted on a blunt-tipped 5F catheter that rotated up to 16 images per second. The axial resolution of the system was 80 μm. Lateral resolution was better than 225 μm at a depth of 1 mm. The resulting images were displayed on a monitor via a video-scanned memory and stored on a VHS system. Sterilization of the ultrasound catheter was accomplished with gamma radiation. A radiopaque ruler was used to match angiographic and ultrasound data.

The presence and location of obstructive lesions were first assessed by single-plane angiography using a 7F sheath in the common femoral artery. Then, the ultra-

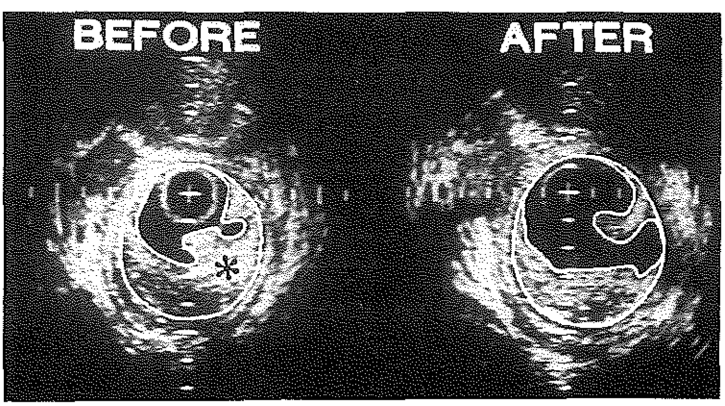

FIGURE 1. *Intravascular ultrasound cross sections of the superficial femoral artery, which is traced for free luminal and media-bounded contours before and after balloon angioplasty. The region enclosed by the two contours represents the eccentric lesion (asterisk). The hypoechoic media is used as landmark for the media-bounded area. Calibration = 1 mm.*

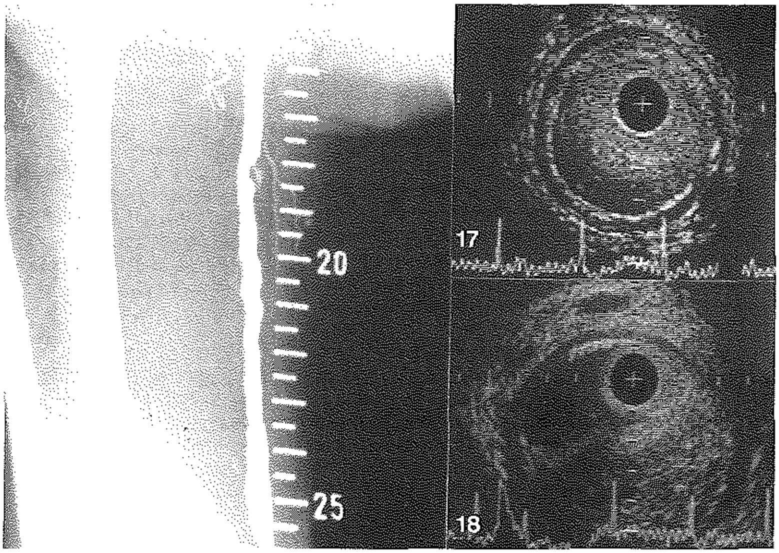

FIGURE 2. *Angiogram with radiopaque ruler and intravascular ultrasound cross sections of the superficial femoral artery obtained before balloon angioplasty. Intravascular ultrasound confirmed the sites of normality (level 17) and abnormality (level 18) as assessed angiographically. The three-layered appearance of the vessel wall indicates its muscular nature. Calibration=1 mm.*

sound catheter was advanced to the level of the obstruction and, if possible, beyond the obstructive lesion. Subsequently, under fluoroscopic control a series of cross sections were recorded during pull back of the catheter. Systematically, the location of the catheter was compared with the ruler; its location was indicated on the video monitor. When a stenosis was present, recordings were made with a 1-cm interval. At each level, the catheter was kept in position for a period of time sufficient for recording. To eliminate the echogenic blood, 5 ml saline was injected via the sideport of the sheath. This procedure facilitated off-line analysis of the still-frames.

After intervention, a repeat angiogram was made and followed by a second examination by intravascular ultrasound. Care was taken to study those segments that had been dilated. The mean time interval between balloon angioplasty and the postangioplasty ultrasound examination was usually 20 minutes (range 15–25 minutes). The total ultrasonic investigation took no longer than 15 minutes.

Definition and Terminology

Muscular artery. This was recognized by three contiguous layers encircling the lumen; the hypoechoic media was seen between the inner echodense layer (intima and internal elastic lamina) and outer echodense layer (external elastic lamina and adventitia).[12,13,15,17]

Soft lesion. A soft lesion was recognized as having a homogeneous echo structure without shadowing.

Hard lesion. This lesion was recognized by the presence of a bright echo structure casting peripheral shadowing.

Concentric lesion. This was defined as a lesion distributed along the entire circumference of the vessel wall in a cross section.[25]

Eccentric lesion. An eccentric lesion was defined as a lesion involving one part of the circumference of the

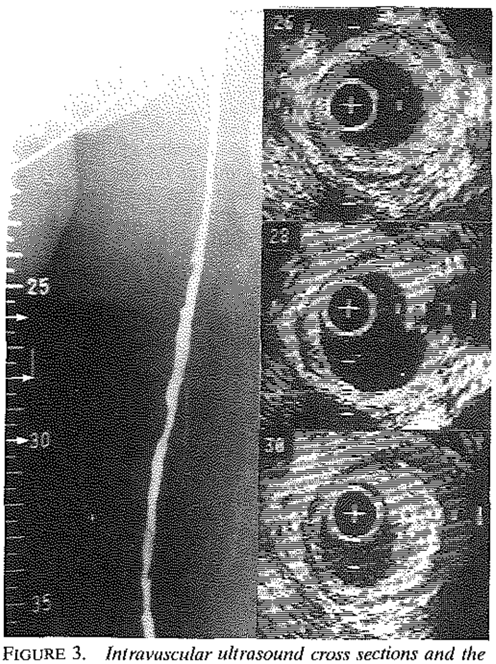

FIGURE 3. *Intravascular ultrasound cross sections and the corresponding angiogram of the superficial femoral artery obtained before intervention. Proximally at level 26, a concentric soft lesion distributes along the entire circumference of the vessel wall. Distally at level 28, an eccentric hard lesion is visualized causing ultrasonic shadowing at 3 o'clock. Level 30 shows an eccentric lesion predominantly involving one segment of the vessel wall. At the outer perimeter of the lesion adjacent to the media at 3 o'clock an intense echoreflection is seen interpreted as calcium. Calibration=1 mm.*

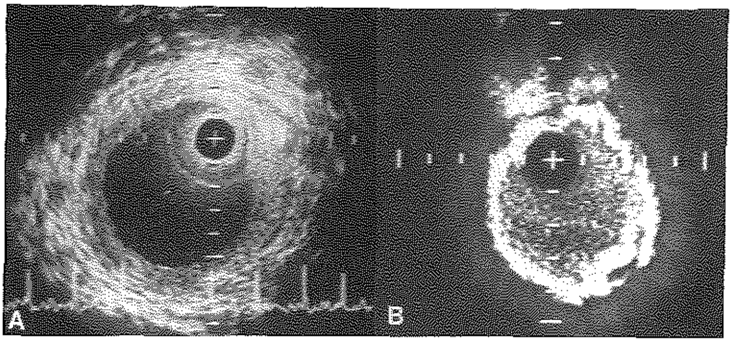

FIGURE 4. *Intravascular ultrasound cross sections obtained from two patients without the normal three-layered appearance of the superficial femoral artery wall.* Panel A: *A homogeneous arterial wall is seen.* Panel B: *A bright homogeneous arterial wall presumably represents a circumferential calcific plaque. Note echogenicity of blood inside the lumen. Calibration=1 mm.*

vessel wall in a cross section, which leaves the remaining part disease-free.[25]

Dissection. Dissection was defined as the presence of a separation of the lesion from the underlying arterial wall. Angiographically, a dissection was defined as a longitudinal intimal tear that resulted in a double lumen of the vessel.

Plaque rupture. A plaque rupture was identified as an interruption in the lesion (intimal) surface.

Internal lamina rupture. An internal lamina rupture was defined as an interruption in the internal elastic lamina.

Quantitative Analysis

Angiography was performed in a single plane (anterior-posterior); therefore, no attempt at quantitative analysis was made. Corresponding ultrasound images that had a lesion, subsequently dilated by balloon angioplasty, were analyzed with a digital video analyzer as described previously.[26,27] Briefly, the analysis system was developed on an IBM PC/AT (IBM Corp., Boca Raton, Fla.) that was equipped with a framegrabber and a PC mouse device. Each image reproduced on the analyzer video screen was contour traced (Figure 1). To facilitate the quantitative analysis, real-time images were replayed on a separate video monitor. From each corresponding cross section, the following parameters were assessed before and after intervention.

Free lumen area (mm^2). The free lumen area was defined as the area encompassed by the inner boundary of the intimal surface (characterized also by the presence of blood flow).

Minimal diameter (mm). The minimal diameter of the free lumen was calculated from the traced contour and its geometrical center.[28]

Media-bounded area (mm^2). This was defined as the native vessel area bounded by the hypoechoic medial layer.

Lesion area (mm^2). The lesion area was calculated as the difference between media-bounded area and free lumen area.

Media thickness (mm). Media thickness was measured at the site where lesion thickness was absent or minimal. The thickness was calculated as the perpendicular dis-

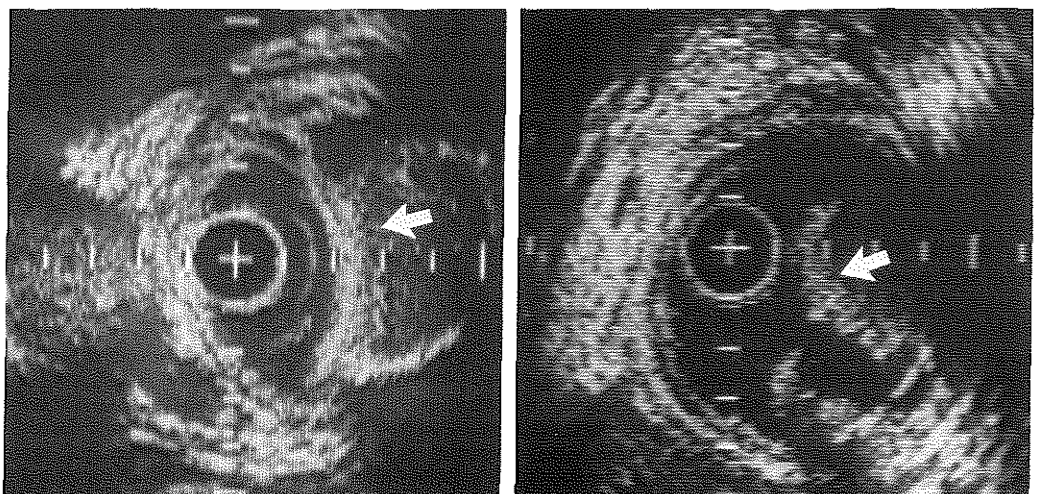

FIGURE 5. *Intravascular ultrasound cross sections obtained from two patients after balloon angioplasty revealing a large intimal flap (arrow) beyond which no reliable echo data can be obtained. Calibration=1 mm.*

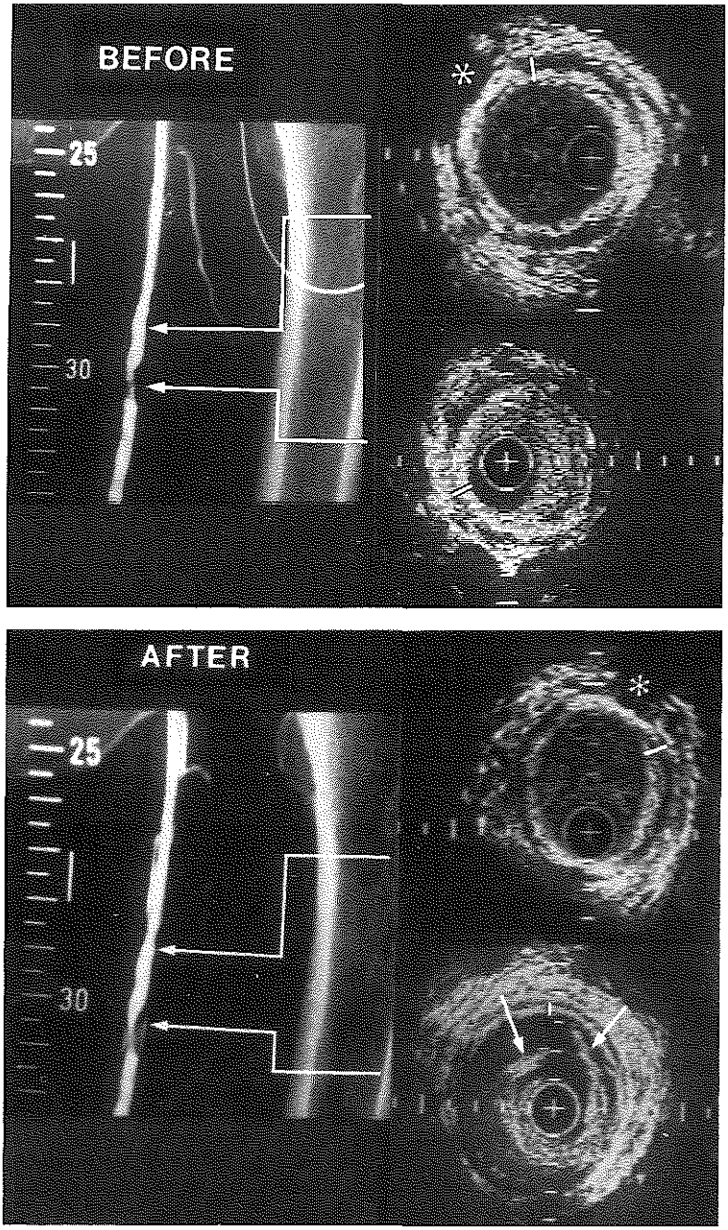

FIGURE 6. *Intravascular ultrasound cross sections obtained at the same levels before* (upper panel) *and after* (lower panel) *balloon angioplasty. A dissection is noted angiographically and echographically after (lower panel) balloon angioplasty (bold arrows). Note the unchanged media thickness at level 29 and the reduction in media thickness at level 30 after intervention (media thickness indicated by white marker). Given the orientation of the shadow (level 29, asterisk) before and after intervention, the image is rotated clockwise 15 minutes. Calibration=1 mm.*

tance between the leading edge from the internal elastic lamina and the leading edge resulting from the adventitia. In the absence of a distinct internal elastic lamina the transition of the lesion to the hypoechoic media was used.[29]

In those instances in which partial drop-out of echoes from the luminal contour (for free lumen area) or medial layer (for media-bounded area) were noted, the contours were estimated by continuity from adjacent sections.

Statistical Analysis

All measured values are presented as mean±SD. The paired Student's t test was used to compare the data before and after intervention; a $p \leq 0.01$ was considered statistically significant.

Intraobserver and interobserver variability of the ultrasound measurements were determined by remeasuring the free lumen area, media-bounded area, and lesion area without knowledge of the values obtained previously. This second set of measurements was ob-

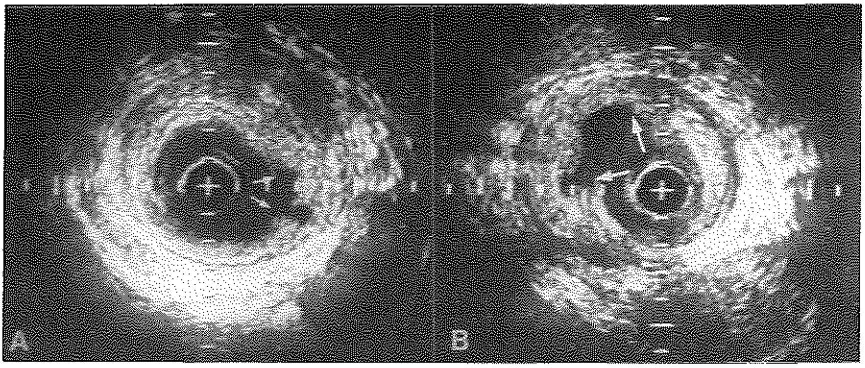

FIGURE 7. *Intravascular ultrasound cross sections showing plaque rupture (arrows) after balloon angioplasty as observed in one patient.* Panel A: *Medial thinning is evident between 5 and 9 o'clock.* Panel B: *An additional dissection was present between 12 and 4 o'clock (black arrow). Calibration=1 mm. (Reprinted with permission of the* Journal of Clinical Ultrasound *1991;19:294–297).*

tained 1 month after the first set. Linear regression analysis was applied to determine intraobserver and interobserver compatibility, presenting the correlation coefficient (*r*) and its standard error of the estimate (SEE).

The media thickness data before and after intervention was measured independently by two observers. Interobserver variability of each measurement was validated by the use of linear regression analysis and expressed as mean±SD of the difference between the measurements.

Results

Qualitative Analysis

In four patients, the superficial femoral artery was not visualized angiographically because of proximal obstruction. In the remaining 12 patients, angiography evidenced a long stenosis in six patients and multiple subcritical stenoses in the other six patients.

Intravascular ultrasound studies were completed in all 16 patients. In three patients, the echocatheter could not be advanced across a distally located obstruction. No complications related to the intravascular ultra-

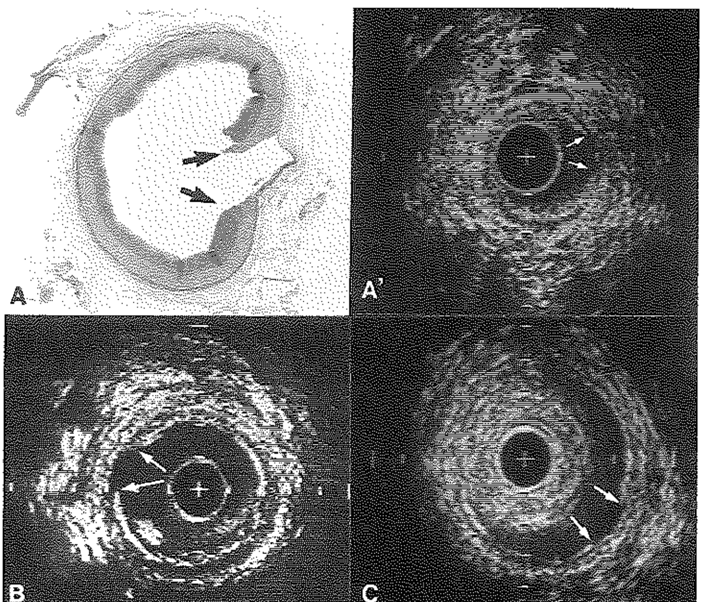

FIGURE 8. Panels A and A': *Histological and corresponding echographic cross sections obtained in vitro of a coronary artery after balloon angioplasty. An internal lamina rupture was observed (arrows).* Panels B and C: *Similar findings following balloon angioplasty were noted in this study in humans. Arrows indicate the interruption in the internal elastic lamina. The echocatheter in panel C is encompassed by the lesion. Calibration=1 mm.*

Table 2. Characteristic Morphological Features After Balloon Angioplasty With the Number of Cross Sections and Their Relation to the Type of Lesion

		Lesions							
		Soft		Hard		Eccentric		Concentric	
	n	%	No.	%	No.	%	No.	%	No.
Single features									
Lumen area enlargement	31	35	15	55	16	44	25	40	6
Dissection	17	30	13	14	4	26	15	13	2
Plaque rupture	4	7	3	3	1	5	3	7	1
Internal lamina rupture	1	2	1	0	0	0	0	7	1
Combination of features									
Dissection and plaque rupture	11	19	8	11	3	16	9	13	2
Dissection and internal lamina rupture	3	0	0	11	3	5	3	0	0
Plaque rupture and internal lamina rupture	3	5	2	3	1	0	0	20	3
Dissection, plaque rupture and internal lamina rupture	2	2	1	3	1	4	2	0	0
Total	72	100%	43	100%	29	100%	57	100%	15

sound studies were observed. The mean length of the investigated arteries was 20 cm. During pull back of the ultrasound catheter from distal to proximal, it was noted that morphological aspects of the vessel wall and the lesion, as well as the shape of the lumen, could change markedly. Angiographically assessed sites of stenosis were confirmed by intravascular ultrasound (Figures 2 and 3). The use of the radiopaque ruler for this purpose was essential. Intravascular ultrasound evidenced a muscular artery in all 16 patients (Figures 1–3). However, in two patients the three-layered appearance of the arterial wall was not seen over a long segment of the vessel (≥7 cm) (Figure 4). Clinical history revealed that one of these patients underwent balloon angioplasty twice. In the second patient, a bright circumferentially echodense arterial wall was seen, which presumably represented a fibrocalcific lesion (Figure 4).

A total of 136 corresponding cross sections with lesions that were subsequently dilated by balloon angioplasty were available for comparison. Of these, 19 cross sections (from seven patients) revealed inadequate image quality because of the low sensitivity of the ultrasound catheter and/or an inappropriate angle of the ultrasound beam. In 45 cross sections (from eight patients), a large dissecting flap occurred after intervention, which caused significant drop-out of the acoustic interface and, therefore, prevented reliable quantitative analysis (Figure 5). These cross sections were excluded from further study.

Of the remaining 72 corresponding sites (from 15 patients) analyzed for comparison purposes, the lesions were of a soft (n=43) or hard nature (n=29, Figure 3) and were concentric (n=15) or eccentric (n=57, Figures 1–3).

After the intervention, dissections and wall irregularities were noted angiographically in 14 patients. Intravascular ultrasound confirmed the presence of a dissection and its proximal site in each of the 14 patients (Figure 6). In addition, plaque rupture was observed in 14 patients (Figure 7) and internal lamina rupture in six patients (Figure 8). Table 2 summarizes the number of cross sections showing the characteristic morphological single and combined features after balloon angioplasty.

Table 2 indicates that soft lesions present before intervention have a higher occurrence of dissection and/or plaque rupture after intervention as compared with hard lesions (56% versus 28%).

Quantitative Analysis

The results of the quantitative analysis assessed by intravascular ultrasound before and after intervention are summarized in Tables 3 and 4 and shown in Figure 9.

The free lumen area measured from 72 corresponding cross sections (15 patients) increased significantly by 89%. It was observed that lumen area seen postangioplasty was not related to the plaque type seen before intervention (soft and hard lesions; respectively, 9.8±5.1 mm^2 and 9.6±4.2 mm^2 before intervention; 18.3±6.8 mm^2 and 18.4±7.4 mm^2 after intervention).

The minimal diameter of the lumen increased by 41%. In 30 of the 72 cross sections (five patients), the major part of the media was not seen because of calcium deposits (n=24), previous balloon angioplasty in one

Table 3. Results of Quantitative Analysis Before and After Balloon Angioplasty

	Cross sections (n)	Before	After	Increase/decrease (%)
Free lumen area (mm^2)	72	9.7±4.7	18.3±7.0	+89±65%
Minimal lumen diameter (mm)	72	2.8±0.7	3.6±1.2	+41±43%
Media-bounded area (mm^2)	42	21.7±5.4	28.3±5.8	+29±20%
Lesion area (mm^2)	32	13.0±4.9	12.9±4.6	0±4%
	4	9.1±0.9	4.3±1.4	−53±6%
	6	10.1±4.2	0	−100±0%

Free lumen area from 15 patients; media-bounded area and lesion area from 11 patients.
$p \leq 0.01$ for all values.

TABLE 4. **Results of Media Thickness Measurements Before and After Balloon Angioplasty**

	Cross sections (n)	Media thickness (mm) Before	After	Thickness decrease (%)	p
Balloon angioplasty as primary intervention (11 patients)	25	0.55±0.19	0.34±0.11	−38	≤0.01
Treated previously with balloon angioplasty (5 patients)	17	0.35±0.17	0.24±0.11	−31	≤0.01

patient (n=4) and because of inadequate image quality in another patient (n=2).

The media-bounded area to be measured from the remaining 42 corresponding cross sections (11 patients) increased markedly by 29%.

As with the media-bounded area, the lesion area could only be assessed in these 42 cross sections. The lesion area revealed no significant change in 32 corresponding cross sections (11 patients). In four cross sections from two patients, the lesion area was reduced significantly (53%), and in six cross sections from another two patients the lesion disappeared completely. This occurred only in so-called soft lesions, which were either eccentric or concentric.

Media thickness of the arterial wall assessed in 11 patients treated with balloon angioplasty as the primary intervention revealed a significant decrease of 38%. In five patients who had been treated previously with balloon angioplasty, a 31% decrease in media thickness was observed (Table 4; compare Figures 2, 3, 6, and 10 before with Figures 5–8, 10, and 11 after).

Reproducibility

Measurements for the free lumen, media-bounded, and lesion areas showed highly significant correlations between the repeat measurements by the same or a different observer. All paired measurements obtained by one observer revealed a correlation coefficient of r=0.99 ($p \leq 0.01$) with SEE values of 0.40, 0.99, and 0.90 for free lumen, media-bounded, and lesion area measurements, respectively. The interobserver variability test for free lumen, media-bounded, and lesion areas showed correlation coefficients of r=0.98 (SEE=1.33), r=0.95 (SEE=1.98), and r=0.94 (SEE=2.06), respectively (all $p \leq 0.01$). All measurements on the media thickness showed a mean difference of −0.01±0.15 mm (p=0.652) between the two independent observers.

Discussion

It is well accepted that any new technique must be compared with existing and acknowledged techniques. In this respect, systematic in vitro research aimed at correlating intravascular ultrasound with histology has been particularly useful to establish that the three-layered appearance of the arterial wall seen in vivo represents a signature image of a muscular artery.[12–20] The hypoechoic muscular media was an important echographic landmark for the recognition of the media-bounded cross-sectional area and, therefore, for the determination of lesion area.

Effect of Balloon Angioplasty

It is suggested that, using intravascular ultrasound, interventional therapy could benefit from more detailed feedback and better understanding of the immediate effects of the intervention.[18–24,30–33] This study demonstrates that intravascular ultrasound indeed has the unique ability to gain qualitative and quantitative data before and after balloon angioplasty in humans. Intravascular ultrasound enables discrimination between hard and soft lesions as well as between eccentric and concentric lesions. After balloon angioplasty dissection,

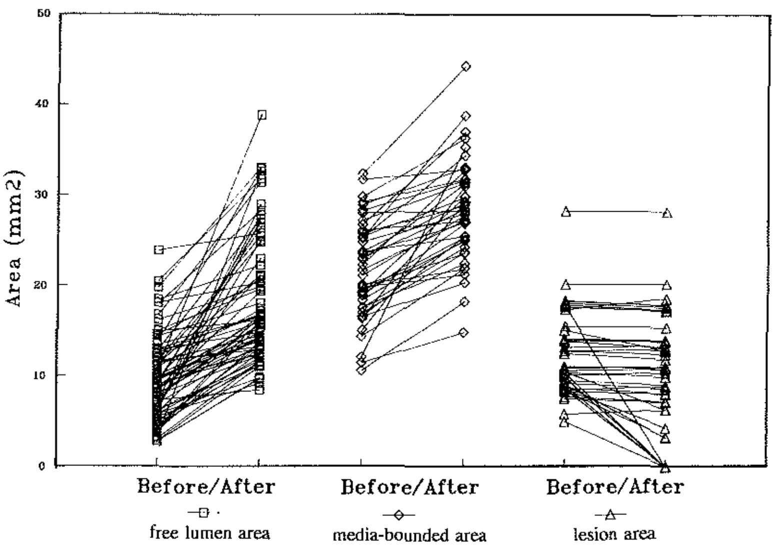

FIGURE 9. *Graphs showing comparison of free lumen, media-bounded areas, and lesion areas before and after balloon angioplasty in a total of 72 ultrasonic cross sections. Each pair of cross sections before and after intervention is interconnected. Note the increase in free lumen and media-bounded areas, whereas the lesion area mostly remains unchanged. In some cases, partial or total disappearance of the lesion occurs (see Table 3).*

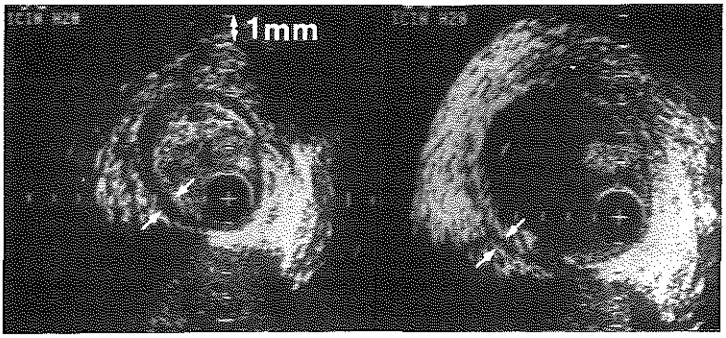

FIGURE 10. *Intravascular ultrasound cross sections obtained at the same level before* (left panel) *and after* (right panel) *balloon angioplasty showing an increase in free lumen and media-bounded areas associated with a decrease in media thickness after intervention (arrows). Embolectomy before the balloon angioplasty in this surgical patient has evidenced thrombus. Calibration=1 mm.*

plaque rupture and internal lamina rupture could be identified; these features were not seen before intervention. It is noteworthy that a combination of these morphological features were encountered frequently in the same patient (Table 2). Soft lesions were more frequently associated with a dissection and/or plaque rupture than were hard lesions (56% versus 28%). The long-term prognostic value of all these morphological features, seen individually or in combination, needs to be determined.

Increased free lumen area is generally associated with an increase in media-bounded area and unchanged lesion area; the increased free lumen area noted was unrelated to the type of lesion (hard or soft). The soft lesions involved are apparently compliant lesions and subject to elastic recoil.[18] The mean lesion area obstruction in this study was reduced from 57% before to 36% after balloon angioplasty. Tobis et al,[20] in contrast, observed a more outspoken area obstruction of 63% after balloon angioplasty of the coronary arteries. Compared with angioplasty of the coronary arteries, the disruption and embolization of thrombi in association with superficial femoral artery angioplasty is not uncommon and is perhaps an explanation for the difference in area obstruction reported in this study and that of Tobis. This assumption is validated by the fact that histology gained via embolectomy in two patients before the intervention evidenced thrombi; in both patients, embolization of the lesion had occurred without causing symptoms (Figure 10). These lesions were never found in the adjacent cross sections.

The increase in media-bounded area was related intimately to the stretching of the arterial wall and, as a result, the lesion became dissected from the underlying arterial wall. Stretching of the arterial wall was shown to be associated with internal lamina rupture and/or thinning of the arterial media. It is noteworthy that the presence of internal lamina rupture was seen only after intervention.

Castaneda-Zuniga et al[4] assumed that arteries behave as truly elastic bodies, which will be overstretched when a certain level of wall stress is applied during balloon angioplasty, which results in permanent deformation. The results of this study support this contention: a decrease in the media thickness is measured immediately after the first balloon angioplasty (0.55–0.34 mm). In five patients who had been treated previously with balloon angioplasty (interval, 3–14 months), the media thickness was 0.35 mm before intervention and reduced to 0.24 mm immediately after intervention.

Conversely, Losordo et al[31] reported that stretching of the arterial wall does not contribute to the effect of increased lumen area; increased lumen area was believed to probably result from plaque fracture and, to a lesser extent, from plaque compression. In our study, the lesion area remained unchanged in the majority of cross sec-

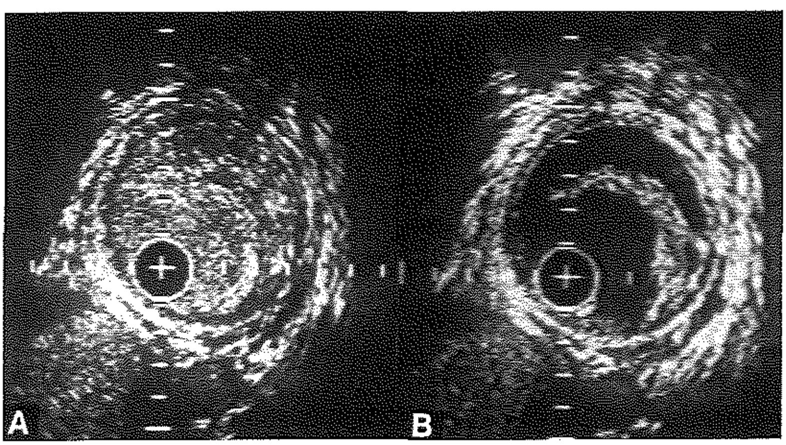

FIGURE 11. *Intravascular cross sections obtained at the same level after angioplasty without* (panel A) *and with* (panel B) *flushing with saline. Saline is used to eliminate the echogenic blood to clearly visualize the dissection and the free lumen area. Calibration=1 mm.*

tions, whereas partial or total disappearance of the lesion was seen infrequently and occurred only in the so-called soft lesions. This latter observation is consistent with the study of Block et al,[8,11] who reported that "plaque disruption and splitting of the atheromatous plaque might cause partial dissolution and extrusion of the atheromatous material, and that this mechanism might account for the changes seen physiologically following successful angioplasty."

Hypoechoic Media

It is known from previous intravascular ultrasound studies that an inverse relation exists between the lesion and the media thickness.[29] This in vivo study showed definite medial thinning in diseased segments compared with disease-free wall segments of the same vessel. However, discordant observations were also observed. In some cross sections, in spite of a large lesion filling the media-bounded area, the media was not thinned (Figure 10). It was observed that the echolucency of the media may vary in the same cross section (Figure 6). This may be related to the eccentric catheter position, the gain setting, and the angle of incidence. Near the catheter, the media may become invisible because of the relatively high gain setting. In other parts of the image distant from the ultrasound catheter, the echolucent media is visible, given an adequate gain setting. Its extent further depends on the angle of incidence; an oblique angle may result in a large echolucency compared with a perpendicular angle of insonification. For this reason, the media thickness in this study was measured from leading edge to leading edge.

Limitations of Intravascular Ultrasound

Because the scattering effect of blood is disturbing, particularly for off-line quantitative analysis, it was found necessary to keep blood away from the images of interest (Figure 11). Injection of saline is a time consuming procedure and is generally considered to be disadvantageous. The influence of blood on the overall image quality led to minor attenuation of the tissues examined. Another disadvantage of intravascular ultrasound is the requirement that the procedure should be recorded via a strict protocol to ensure that images obtained before intervention are to be compared with their corresponding cross sections obtained after intervention. Only such a protocol will provide the investigator with an accurate and reliable comparison. Although on-line analysis provides an impression with respect to the direct result of balloon angioplasty, off-line analysis is required to fully appreciate the quantitative changes involved in the intervention.

Mechanical artifacts from rotational inconsistencies were deemed negligible as the quantitative data on lesion area before and after intervention were very similar (Figure 9). This implies that the transducer and drive-shaft used in the catheter system have adequate torsional rigidity.

It should be acknowledged that the conclusions from this study may be influenced by the exclusion of 64 of 136 cross sections that could not be used for quantitative analysis. In the majority of these cross sections (45 of 64), however, intravascular ultrasound provided qualitative information on a dissection that may have important clinical implications for the interventionist. Finally, the inadequate image caused by low sensitivity of the ultrasound catheter and/or inappropriate angle of the ultrasound beam in the remaining 19 of 64 cross sections reflects the limitation of the system used.

This intravascular ultrasound study showed for the first time that luminal enlargement by balloon angioplasty is produced primarily by overstretching the arterial wall with the lesion volume remaining constant. Overstretching is almost always accompanied by dissection and plaque rupture and sometimes by an internal lamina rupture. In some instances, partial or complete disappearance of the lesion suggests dislodging and embolization of the lesion as an additional effect of balloon angioplasty.

Acknowledgment

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CHAPTER 10

EXTRINSIC COMPRESSION OF THE SUPERFICIAL FEMORAL ARTERY AT THE ADDUCTOR CANAL: EVALUATION WITH INTRAVASCULAR SONOGRAPHY

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Extrinsic Compression of the Superficial Femoral Artery at the Adductor Canal: Evaluation with Intravascular Sonography

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Balloon angioplasty of the superficial femoral artery was performed in 15 consecutive patients with obstructive atherosclerotic disease near the adductor hiatus. After angioplasty, extrinsic compression of the femoral artery at the adductor hiatus was shown on intravascular sonograms in five patients (33%). In retrospect, this inward deformation of the arterial wall was thought to be present in only one case before angioplasty.

After angioplasty, intravascular sonography was used successfully to differentiate between residual stenosis due to residual plaque and that due to extrinsic compression of the wall of the femoral artery near the adductor hiatus. We conclude that intravascular sonography may be a useful adjunct to angiography for determining the cause of residual stenosis.

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The distal femoral artery and vein pass through the adductor canal and exit the canal in the lower third of the thigh to enter the popliteal fossa [1, 2]. The high prevalence of acute [3, 4] and chronic [5-11] atherosclerotic disease in this region is well known. External mechanical factors that intermittently compress the femoral artery have been used to explain the localization of the disease in this particular region of the artery [2-12]. In a recent study, external sonography was used to localize the adductor hiatus [2]. However, to the best of our knowledge, intravascular sonographic evidence for external forces at the adductor hiatus that compress the femoral artery has not been reported. We describe the use of intravascular sonography to show such external compression on the femoral artery in the adductor canal.

Subjects and Methods

Intravascular sonography and angiography were performed in 15 consecutive patients with atherosclerotic disease of the distal femoral artery near the adductor canal, 8-13 cm craniad to the popliteal fossa [2]. Patients with symptoms of disabling claudication were selected for this study on the basis of preangioplasty arteriographic findings of a stenotic or obstructed superficial femoral artery. The study population included 13 men and two women 49-83 years old (mean age, 66 years).

A 7-French introducer sheath was placed by percutaneous or direct puncture of the common femoral or superficial femoral artery. Percutaneous studies ($n = 9$) were performed by using local anesthesia only; intraoperative studies ($n = 6$) were performed with the patient under general anesthesia. An angiographic catheter was advanced distally in the femoral artery under fluoroscopic guidance. All patients received 5000 IU of heparin IV. A radiopaque ruler was placed under the leg throughout the study to allow reproducible registration of both angiograms and sonograms before and after intervention. A 100-mm spot-film angiogram was obtained after administration of approximately 15 ml of Iopamiro 370 (Dagra, Diemen, the Netherlands).

A 5-French echocatheter (Du-MED, Rotterdam, the Netherlands) was advanced under fluoroscopic guidance across the region of the stenosis. Use of the echocatheter has been

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described in detail previously [13–15]. Briefly, the echocatheter contains a 1-mm-diameter, 30-MHz, single-element transducer at its tip. The transducer is mechanically rotated by a flexible drive shaft and is covered by an acoustically transparent dome. Axial resolution of the system is 80 μm, and the lateral resolution is better than 225 μm at a depth of 1 mm. The catheter is connected to a prototype instrument providing continuous real-time cross sections of the vessel (up to 16 images per second). The sonograms are displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 shades of gray.

If sonography showed definite invagination of part of the arterial wall that remained unaltered during injection of saline under pressure, extrinsic compression of a length of 1–2 cm near the adductor hiatus was judged to be present. Angioplasty was done with a 6-mm-diameter, 4-cm-long balloon (Cordis Corp., Miami, FL) with inflation pressures between 4 and 10 atm (4–10 × 10^5 Pa). Angiographic evidence of successful dilatation of the stenotic region was defined as a decrease in narrowing of the lumen diameter to less than 50%.

Results

Intravascular sonograms were of excellent quality, with clear visualization of intimal thickening, calcification, and medial thickness. Sites of stenosis shown angiographically before intervention were accurately verified with intravascular sonography. The use of the radiopaque ruler was essential for this purpose.

Intravascular sonography could be used to differentiate among various types of residual stenosis. Generally, obstruction was caused by residual plaque inside the vessel lumen; evidence of extrinsic compression of the femoral artery in the adductor canal was seen in five (33%) of the 15 studies (Figs. 1–4). In two patients, mild compression (≤25% and ≤50%) resulting in minimal lumen reduction was confirmed by angiography (Fig. 2). In three other patients, the compression resulted in a significant lumen reduction (50–90%) (Figs. 3 and 4). The angiographic data were consistent with residual stenosis: 50% or less in two patients and 50–90% in one patient.

Surgical evidence of extrinsic compression at the adductor canal was obtained in one patient. In this patient, an attempt at laser ablation in the femoral artery resulted in perforation. Surgery confirmed the location of the adductor hiatus, as indicated earlier by intravascular sonography (Fig. 3).

The reproducibility of this typical inward deformation was noted in another patient. Five months after angioplasty, this patient had angioplasty again because of recurrence of claudication symptoms. Just before the second angioplasty, intravascular sonography revealed a significantly reduced arterial

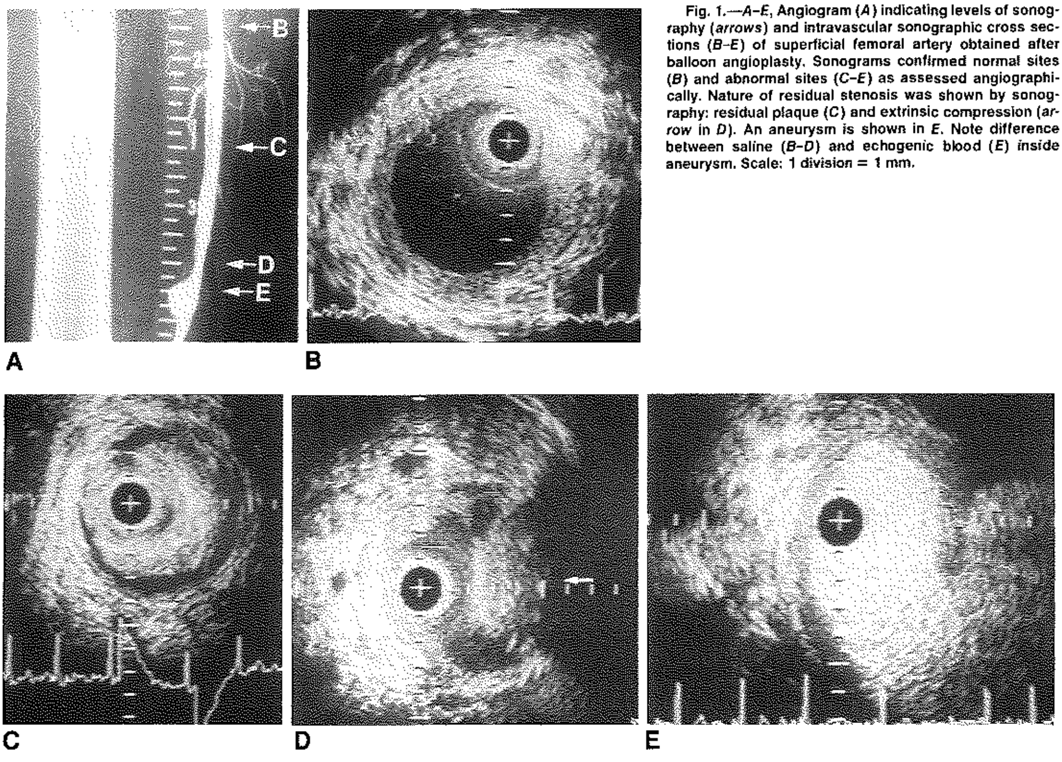

Fig. 1.—*A–E*, Angiogram (*A*) indicating levels of sonography (*arrows*) and intravascular sonographic cross sections (*B–E*) of superficial femoral artery obtained after balloon angioplasty. Sonograms confirmed normal sites (*B*) and abnormal sites (*C–E*) as assessed angiographically. Nature of residual stenosis was shown by sonography: residual plaque (*C*) and extrinsic compression (*arrow* in *D*). An aneurysm is shown in *E*. Note difference between saline (*B–D*) and echogenic blood (*E*) inside aneurysm. Scale: 1 division = 1 mm.

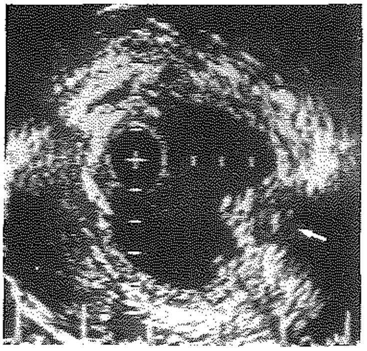

Fig. 2.—Intravascular sonogram after angioplasty shows mild extrinsic compression. Arterial wall is partially compressed into lumen (*arrow*), suggesting that external forces exceed intraluminal pressure.

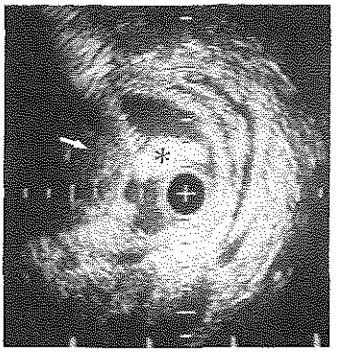

Fig. 3.—Intravascular sonogram after angioplasty shows moderate extrinsic compression, with arterial wall partially compressed into lumen (*arrow*).

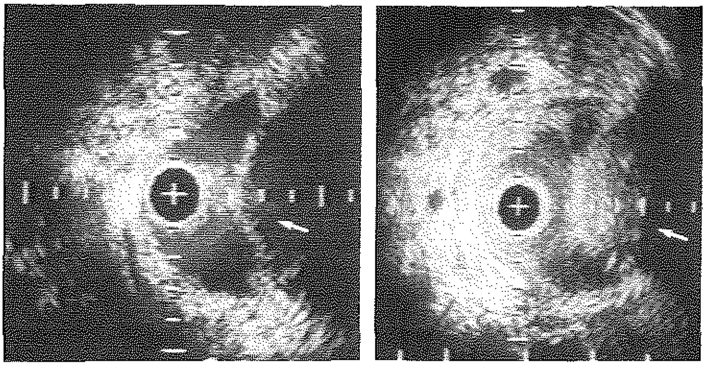

Fig. 4.—*A* and *B*, Intravascular sonograms obtained at initial angioplasty (*A*) and when angioplasty was repeated 5 months later (*B*) show soft-tissue lesion (*arrow*) partially filling lumen. Scale: 1 division = 1 mm.

lumen. After angioplasty, angiograms showed equivocal indications of extrinsic compression but the intravascular sonograms showed definite invagination of the arterial wall consistent with external compression (Fig. 4B).

Discussion

Previous studies have shown that atherosclerotic disease involving the femoral artery occurs most often near the adductor hiatus [9]. It is also believed that restenosis occurs more frequently in this region and could partially explain the higher success rate for balloon angioplasty in the iliac artery compared with the femoral artery [16].

Femoral vessels pass through the adductor canal between thigh muscles. The adductor canal is triangular on transverse section, bounded anteriorly and laterally by the vastus medialis muscle; posteriorly by the adductor longus and adductor magnus; and superiorly by an aponeurosis of these muscles, which extends across the femoral vessels to the vastus medialis muscle [1]. It is postulated that the predilection for obstructive disease in this region may be related to external mechanical factors that result in repetitive microtrauma and, consequently, damage to the vessel wall [2–11] with intimal fissuring [3–5] and intimal proliferation [6].

In this study, the intravascular sonograms obtained before angioplasty showed diffuse intimal thickening proximal to the site of extrinsic compression, but no calcified lesions, intimal tears, or dissection were observed near the adductor canal. With intravascular sonography, the specific location of the adductor canal could not be determined before intervention. However, all lesions were in the distal third of the thigh at the level of the adductor hiatus.

In five cases, intravascular sonography showed localized invagination of the arterial lumen that was not evident with angiography. Compared with intravascular sonography, the angiographic significance of the stenosis was less clearly shown in two patients. The technique was routinely performed in a single-plane (anteroposterior) direction. Additional angiographic views might have defined the degree of narrowing more precisely. Intravascular sonography provides tomographic cross sections of the vessel and can image the constituents of the arterial wall [17, 18]. This is an advantage, especially in those cases with significant vessel wall compression that might otherwise be considered residual plaque [15]

Stretching and damage of the arterial wall after angioplasty appeared to allow external forces to exceed internal distending pressure, with consequent partial deformation of the vessel wall toward the center of the lumen. However, other explanations for the postangioplasty luminal deformity must be considered. Luminal encroachment did not mimic an intimal flap, which might be misinterpreted as external compression. No blood flow was observed around the deformity to suggest an intimal tear or localized dissection in any of the studies, and injection of saline under pressure had no effect on the inward deformation. Spasm of the artery or elastic recoil are unlikely alternative explanations for luminal deformity, as these events generally involve the entire circumference of the artery. Patients were not treated with nitroglycerin or other vasodilators.

Although angiography was considered the reference method in this study, intravascular sonography provided valuable additional information [14, 15]. The results of this study may have clinical implications: if the arterial wall has been weakened by the angioplasty [19] and has partially invaginated into the lumen, then care must be taken to avoid more aggressive recanalization with atherectomy or laser devices. In addition, such partially invaginated vessels may be more effectively treated with intravascular stents or bypass surgery.

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CHAPTER 11

INTRAVASCULAR ULTRASOUND BEFORE AND AFTER INTERVENTION: IN VIVO COMPARISON WITH ANGIOGRAPHY

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Intravascular ultrasonography before and after intervention: In vivo comparison with angiography

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Purpose: To compare the additional capacity of intravascular ultrasonography versus angiography to assess morphologic features and lumen dimension, 37 patients undergoing vascular intervention of the common iliac or superficial femoral artery were studied. A total of 181 ultrasonic cross sections were analyzed (94 before and 87 after intervention).
Methods and Results: Before intervention intravascular ultrasonography distinguished normal cross sections (n = 17) from cross sections with a lesion (n = 77): soft (51%) versus hard (31%) lesions, and eccentric (75%) versus concentric (7%) lesions. After intervention intravascular ultrasonography documented dissection (43%), plaque rupture (10%), and internal elastic lamina rupture (8%). A good correlation between ultrasonography and angiography was found for the recognition of eccentric or concentric lesions and dissections. The degree of stenosis was assessed semiquantitatively by visual estimation of the degree of luminal narrowing from the angiograms and intravascular ultrasonic images and was categorized into four classes: (1) normal, (2) less than 50% stenosis, (3) 50% to 90% stenosis, and (4) greater than 90% stenosis. Intravascular ultrasonographic assessment of stenosis was in agreement with angiography in 78% of cases and showed more severe lesions in 22% before intervention. Similar data were observed after intervention, with 72% of results being in agreement and 28% of cases showing more severe lesions. The degree of stenosis was also quantitatively evaluated by computer-aided analysis of the intravascular ultrasonic images. The semiquantitative analysis by intravascular ultrasonography corresponded well with the quantitative analysis done by the computer-aided system. When both echography and angiography suggested that arteries were normal, quantitative intravascular ultrasonography identified lesions that occupied an average of 18% of the cross-sectional area of the vessel.
Conclusions: This in vivo study shows that intravascular ultrasonography is capable of documenting detailed morphologic features. Semiquantitative ultrasonic data correlate closely with those of angiography, albeit stenoses were assessed as more severe on ultrasonography. (J VASC SURG 1993;18:31-40.)

Balloon angioplasty is a widely used technique for the endovascular treatment of limited vascular obstructive disease. There seems, however, to be a discrepancy between the initial (technical) success rate (88%) and the disappointing late patency rate as a result of the high incidence (48%) of restenosis after 5 years.[1,2] Apparently, there is room for improvement by better diagnostics and, perhaps, intravascular ultrasonography may lead the way.

Contrast angiography is still the standard procedure for evaluation of vascular diseases. The system is able to map the vascular tree, by giving a luminal silhouette of the vessel. However, data on the composition of the atherosclerotic lesion are difficult to obtain. In contrast, intravascular ultrasonography enables analysis of the vessel wall components by

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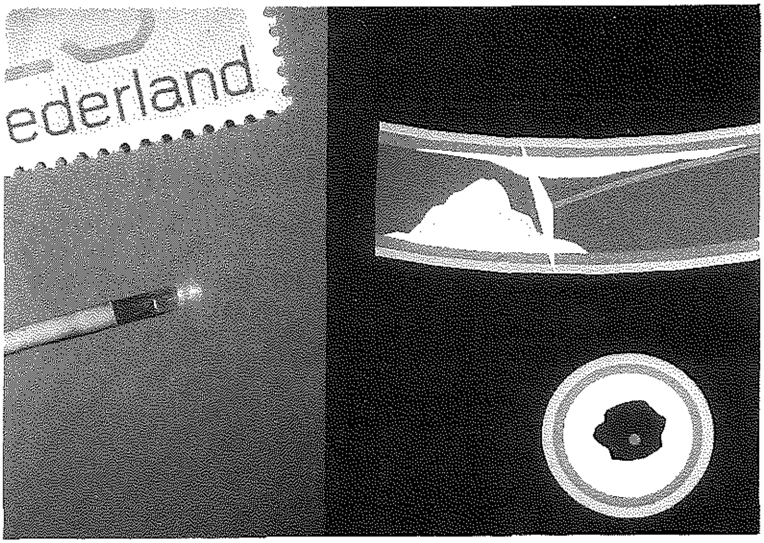

Fig. 1. Intravascular ultrasound catheter together with diagram. Ultrasound crystal inside dome rotates so that cross-sectional image of artery can be obtained. (Reprinted with permission of the *European Journal for Vascular Surgery* from Gussenhoven WJ, Essed CE, Frietman P, et al. Eur J Vasc Surg 1989;3:571-6.)

providing cross-sectional images.[3-8] Changes in size can be measured quantitatively, thereby defining criteria for effectiveness of intervention.[9-16]

This study was done in patients undergoing recanalization procedures to identify the additional value of intravascular ultrasonography compared with single-plane angiography in determining morphologic features and the reliability of intravascular ultrasonography for semiquantitative assessment of luminal dimensions.

PATIENTS AND METHODS

From November 1989 to February 1992, 29 male and eight female patients (mean age 67 years; range 49 to 83 years) underwent vascular recanalization for disabling claudication. The common iliac artery was involved in six patients and the superficial femoral artery in 31 patients. Balloon angioplasty was performed in 28 patients of whom five underwent a laser-assisted balloon angioplasty. Balloon angioplasty was performed with a standard 10 mm balloon for the iliac artery and a 6 mm balloon for the superficial femoral artery (Cordis, Roden, The Netherlands). A Gore-Tex* fabric bypass graft was used in six patients (one common iliac artery, five superficial femoral arteries) and a saphenous vein bypass graft in three other patients (superficial femoral artery).

Intravascular ultrasonography. A 5F (1.6 mm diameter) real-time imaging catheter with a 1 mm diameter, 30 MHz single-element transducer at the tip was used (Du-MED, Rotterdam, The Netherlands) (Fig. 1). The system is based on a mechanically motor-driven rotating catheter tip element connected to a flexible drive shaft. The element is covered by an acoustically transparent dome. Axial resolution is 75 µm and lateral resolution is better than 225 µm at a depth of 1 mm. The unit is connected to a prototype instrument that provides continuous real-time cross sections of the vessel wall (up to 16 images per second). The ultrasonic images are displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 gray levels.

Procedure. The intravascular ultrasonography

*Gore-Tex is a registered trademark of W.L. Gore & Associates, Inc., Flagstaff, Ariz.

study was approved by the local Committee on Human Research and informed consent was obtained from each patient.

First a 7F introducer sheath, either percutaneously or by direct puncture of the common femoral or superficial femoral artery, was positioned. In cases of origin occlusion of the femoral artery the sheath was placed via surgical dissection through a small groin incision. The presence and location of obstructive lesions were first reconfirmed routinely by single-plane angiography. A radiopaque ruler was used to match angiographic with ultrasonographic data. Then the ultrasound catheter was advanced. After the catheter was introduced beyond the stenosis, or as far as possible in cases of total occlusion, cross-sectional images were obtained by slow retraction of the catheter. The position of the catheter tip was recorded under fluoroscopy with the use of a radiopaque ruler (Fig. 2). If necessary, 5 ml of heparinized saline solution was injected through the introducer sheath to replace the echogenic blood to achieve a better outline of the lumen.[15,16] After intervention a repeat angiogram was made followed by a second examination with intravascular ultrasonography (Fig. 2). The total ultrasonic investigation took no longer than 15 minutes.

Definition of echographic features. *Soft lesion* was recognized as having a homogeneous echo structure without shadowing. *Hard lesion* was recognized by the presence of a bright echo structure with complete shadow of the ultrasonic signal beyond the lesion.[16] *Concentric lesion* was defined as a lesion distributed along the entire circumference of the vessel wall in a cross section.[17] *Eccentric lesion* was defined as a lesion that involved one part of the circumference of the vessel wall in a cross section, leaving the remaining part free of disease.[17] *Dissection* was defined as the presence of a separation of the lesion from the underlying arterial wall. *Plaque rupture* was identified as an interruption in the lesion (intimal) surface. *Internal elastic lamina rupture* was defined as an interruption in the internal elastic lamina.[16]

Analysis of data. From each patient corresponding angiographic sites and intravascular cross sections with and without pathologic conditions before and/or after intervention were selected for comparison. Angiographic and ultrasonographic data were analyzed independently by two blinded investigators (M.F. and E.J.G.). Quantitative ultrasound measurements were performed by one investigator (Y.Z.) without knowledge of the semiquantitative data.

Qualitative analysis included determination of lesion composition (hard/soft) and lesion topography (eccentric/concentric) before intervention and

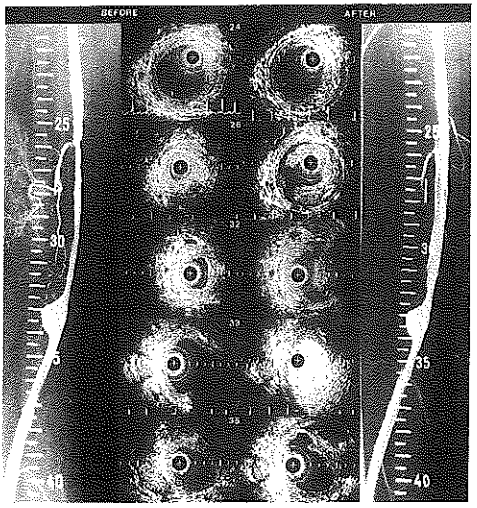

Fig. 2. Angiographic and intravascular ultrasonographic cross sections obtained from superficial femoral artery before and after balloon angioplasty. Under fluoroscopy radiopaque ruler is used to mark position of ultrasound catheter. Before intervention normal arterial segment is seen proximally (at level 24). From level 26 to 32, 6 cm long stenosis is observed. At level 26 stenosis seen angiographically is 50% to 90%; with ultrasonography stenosis is greater than 90%. At level 32 angiography and ultrasonography classify obstruction as 50% to 90% stenosis. Aneurysm is seen at level 33. At level 34 obstruction is classified as less than 50% by both angiography and ultrasonography. Lesions seen at levels 26, 32, and 35 are classified as eccentric soft lesions. After balloon angioplasty, normal cross-sectional site is seen at level 24 angiographically and on ultrasonography. At level 26 dissection is seen with both techniques, but degree of stenosis is discordant: less than 50% on angiography and 50% to 90% on ultrasonography. Obstruction is related to large lesion dissected from arterial wall. At level 32 similar discordant analysis is found: on angiography less than 50% and on ultrasonography 50% to 90%. At level 34 aneurysm is seen. Note echogenicity of blood inside aneurysm in postinterventional photograph compared with other cross sections in which saline is used to replace blood. At level 35 both angiography and ultrasonography reveal residual stenosis of less than 50%. *Plus sign* indicates catheter; calibration, 1 mm.

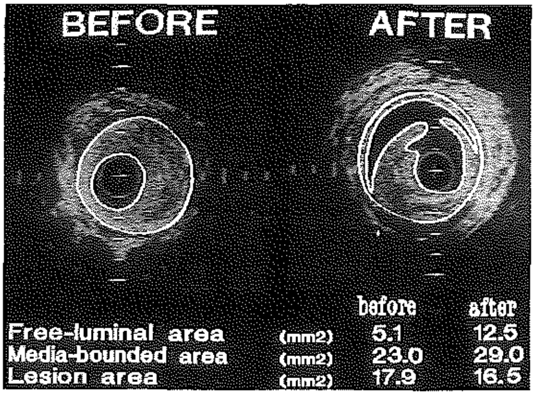

Fig. 3. Intravascular ultrasonographic cross sections of superficial femoral artery before and after balloon angioplasty showing traced contours of free lumen and media-bounded lumen area. Region enclosed by two contours is lesion area. Quantitative results before and after intervention are provided. (Reprinted in part with permission of *Circulation* from The SHK, Gussenhoven EJ, Zhong Y, et al. Circulation 1992;86:483-93.)

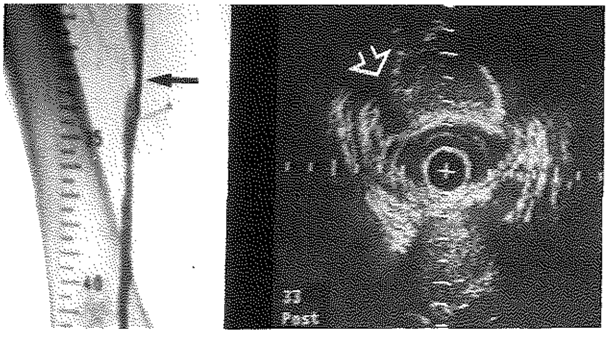

Fig. 4. Angiographic and intravascular ultrasonographic cross section of superficial femoral artery after balloon angioplasty. At level 33 both techniques reveal dissection. Semiquantitative and quantitative analyses with respect to degree of stenosis were not possible echographically given inadequate ultrasound information seen beyond dissection *(arrow)*. *Plus sign* indicates catheter; calibration, 1 mm.

assessment of dissection, plaque rupture, and internal elastic lamina rupture after intervention.

In *quantitative analysis* the degree of stenosis was semiquantitatively characterized by visual estimation from angiograms and intravascular ultrasonic images into four classes: (1) normal, (2) less than 50% stenosis, (3) 50% to 90% stenosis, and (4) greater than 90% stenosis.

Angiographically, with the normal proximal vessel segments used as reference, the percentage *diameter* stenosis was determined. Because only single-plane (anteroposterior) angiograms were available, no absolute quantitative measurements could be obtained.

Echographically the percentage *area* stenosis was determined with the area bounded by the hypoechoic media layer used as reference to the free lumen area. When the hypoechoic media was not well seen circumferentially because of a calcified lesion, an adjacent cross section was used to determine the media-bounded area. Ultrasonic cross sections that showed the remaining free lumen completely filled by

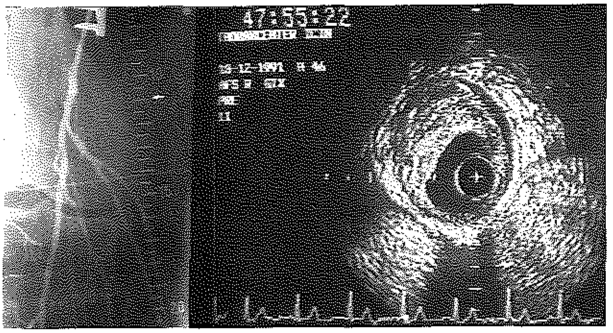

Fig. 5. Angiographic and intravascular ultrasonographic cross sections obtained before intervention showing discrepancy in classification of stenosis. At level 11 angiography judges stenosis less than 50% *(arrow)*. On ultrasonography large eccentric soft lesion is seen classified as 50% to 90% stenosis. *Plus sign* indicates catheter; calibration, 1 mm.

the ultrasound catheter were classified as having greater than 90% stenosis.

The accuracy of the proposed semiquantitative assessment by visual estimation derived from the ultrasonic cross sections was first tested with data derived from a computer-aided method for quantification available from 100 ultrasonic cross sections with atherosclerosis.[18,19] With this computer-aided analysis system the quantitative assessment of lumen area and lesion area was performed by tracing the contours of the free lumen and the lumen bordered by the arterial media (Fig. 3). To facilitate the off-line quantitative analysis ultrasound images were replayed on a separate video monitor. In those instances in which partial dropout of the echoes from the luminal contours (for free lumen area) or medial layer (for media-bounded area) was noted, the contours were estimated by means of continuity from the adjacent cross sections. From these data the percentage area obstruction was calculated.

For the present study all ultrasonic cross sections selected were analyzed with this computer-aided system to compare the absolute measurements with the semiquantitative assessment by visual inspection.

RESULTS

In this study no adverse effects attributable to the use of the ultrasound catheter were observed. In 23 patients intravascular ultrasonographic data were available both before and after intervention. In three of these 23 patients no corresponding angiographic data were available before the intervention because of occlusion of the origin of the superficial femoral artery. In seven patients the ultrasonographic data were obtained before intervention only for the following reasons: no intervention was deemed necessary in two patients; operation was more appropriate than the planned balloon angioplasty in two other patients; the sheath was accidentally removed after balloon angioplasty in another two patients; and in one patient the radiologist refrained to use the ultrasound catheter within the dilated segment given the potential risk for additional vessel dissection.

In seven other patients ultrasonographic data were obtained only after intervention for the following reasons: a total occlusion was known in four patients for which saphenous vein bypass (in three patients) or prosthetic bypass grafting (in one patient) was planned, and in three other patients inexperience with logistics of the procedure resulted in absence of data before intervention.

Initially 193 ultrasonic cross sections were selected for comparison with the corresponding angiographic site (as determined by the radiopaque ruler): of these, 12 sites could not be used for semiquantitative analysis by visual inspection because of inadequate quality of the angiogram at six sites and inadequate quality of the ultrasonic image in six cross sections because of a dissection that resulted in a dropout of the echoes in a large sector of the images (Fig. 4).

Qualitative analysis

Before intervention (n = 94). For eight ultrasonic cross sections no corresponding angiographic sites were available for comparison because of total obstruction. On comparison of the remaining 86

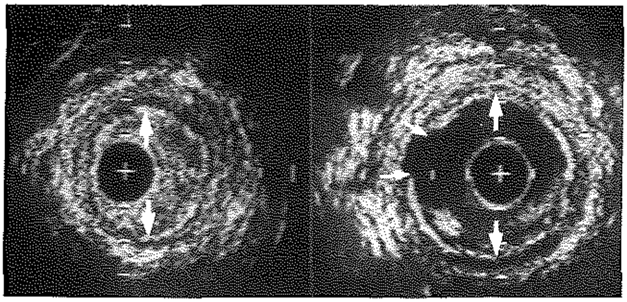

Fig. 6. Intravascular ultrasonographic cross sections obtained from superficial femoral artery at corresponding levels before *(left)* and after *(right)* balloon angioplasty with 6 mm diameter balloon. No angiogram was available before intervention because of origin obstruction of superficial femoral artery. Before laser angioplasty, ultrasound catheter was advanced blinded proximally to distally through lesion. Ultrasound catheter is seen to be completely surrounded by soft concentric lesion. Hypoechoic media is circumferentially seen, indicating diameter of vessel of 3.5 mm (between *arrows*). After intervention, lesion for major part has disappeared; diameter of vessel increased to 4.5 mm. Internal elastic lamina rupture is seen at 9 o'clock position evidenced as interruption of internal elastic lamina echoes *(small arrows)*. *Plus sign* indicates catheter; calibration, 1 mm. (Reprinted in part with permission of Circulation from The SHK, Gussenhoven EJ, Zhong Y, et al. Circulation 1992;86:483-93.)

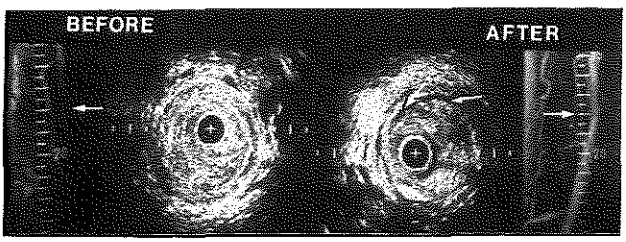

Fig. 7. Angiographic and intravascular ultrasonographic cross sections obtained from superficial femoral artery before and after balloon angioplasty. Before intervention, concordant classification is obtained from angiography and ultrasonography. At level 18 stenosis of greater than 90% was observed. Lesion is classified as concentric soft. After intervention, dissection is seen both angiographically and on ultrasonography. Angiography judges stenosis as less than 50%; ultrasonography, however, reveals 50% to 90% stenosis. Lesion is seen dissected from arterial wall. *Plus sign* indicates catheter; calibration, 1 mm.

intravascular ultrasonographic and angiographic data, a total of 74 concordant observations (86%) were noted with respect to the absence or presence (eccentric/concentric) of the lesion.

In 17 (18%) of 94 ultrasonic cross sections no pathologic conditions were observed. The lesions present were classified as being eccentric in 70 (75%) cross sections (Fig. 5), concentric in 7 (7%) cross sections (Fig. 6), soft in 48 (51%) cross sections (Figs. 5 and 6), and hard in 29 (31%) cross sections. Similarly, in 22 (25%) of 86 corresponding angiographic sites no pathologic conditions were observed (no angiogram was available for comparison at eight sites for reasons previously cited). An eccentric lesion was noted in the majority of the sites ($n = 60$; 70%) and in four (5%) a concentric lesion was involved. The available angiograms did not allow distinction between hard and soft lesions.

After intervention ($n = 87$). The occurrence of a dissection was the most common finding seen both ultrasonographically ($n = 37$, 43%) and angiographically ($n = 34$; 39%; Figs. 2 through 4 and Fig. 7). In only three sites a small dissection seen echographically was missed angiographically. Conversely, plaque rupture was more common on ultrasonography ($n = 9$, 10%), whereas its incidence noted on angiography was lower ($n = 4$, 5%). Internal elastic lamina rupture present in seven cross sections (8%) was evidenced on ultrasonography only (Fig. 6). Dissection occurred after either balloon angioplasty or laser angioplasty; plaque rupture and internal elastic lamina rupture were seen only after balloon angioplasty. A combination of these morphologic features noted in the same patient occurred in nine patients (12 cross sections).

Quantitative analysis

Computer-aided method versus semiquantitative assessment. The degree of percentage area obstruction assessed with the computer-aided method for quantification available from 100 ultrasonic cross sections with atherosclerosis was compared with the semiquantitative method by visual inspection. The methods were in agreement in 97 cross sections. In three cross sections the judgments were discordant: visual inspection suggested 50% to 90% area obstructions, but the computer analysis subsequently revealed 42%, 45%, and 48% area obstructions.

Semiquantitative assessment. Table I summarizes the semiquantitative analysis by visual inspection of the intravascular ultrasonographic and angiographic data derived from 181 corresponding sites. It was found that before intervention (94 sites) the intravascular ultrasonographic data were for the majority of the cases (73 sites, 78%) in agreement with the angiographic data. In the remaining 21 cases (22%), the ultrasonic images indicated a more severe stenosis than judged angiographically (Figs. 2 and 5).

After intervention similar observations were found: of 87 corresponding sites, intravascular ultrasonography and angiography were concordant in 63 (72%). In 24 cross sections (28%) intravascular ultrasonography showed a higher percentage of area stenosis compared with that found by angiography (Figs. 2 and 7). In no instance did angiography score a higher degree of stenosis than ultrasonography.

Computer-aided method. The data of 181 ultrasonic cross sections subjected to the computer-aided analysis method are summarized in Table II. It was found that the mean percentage area obstruction calculated before and after intervention was in accordance with the percentage area obstruction classified by the semiquantitative analysis by visual inspection. Before intervention, in segments that were angiographically and echographically judged as normal, the computer-aided analysis method revealed the presence of a lesion that resulted in 18.8% ± 9.5% obstruction of the media-bounded area. Similar data were found in the "normal" cross sections analyzed after intervention (16.8% ± 11.0%). The degree of stenosis from the ultrasonic cross sections semiquantitatively classified as having more than 90% area obstruction was judged as being less severe when analyzed by the computer-aided method (before intervention 83.6% ± 9.1%; after intervention 85.8% ± 5.0%). This may be related to a potential stenting effect of the ultrasound catheter, which itself has an area of 2.3 mm^2.[20]

Table I. Semiquantitative assessment by visual inspection of the degree of stenosis assessed by angiography (percent diameter stenosis) and intravascular ultrasonography (percent area stenosis) before and after intervention

	Intravascular ultrasonography			
Angiography	*Normal*	*<50%*	*50%-90%*	*>90%*
Before ($n = 94$)				
Normal ($n = 22$)	17	5		
<50% ($n = 31$)		21	10	
50%-90% ($n = 27$)			21	6
>90% ($n = 14$)				14
After ($n = 87$)				
Normal ($n = 16$)	13	3		
<50% ($n = 57$)		37	20	
50%-90% ($n = 11$)			10	1
>90% ($n = 3$)				3

n, Number of sites analyzed.

The mean luminal diameter of the native iliac artery derived from the media-bounded area, measured by intravascular ultrasonography, varied from 5 to 10.5 mm (mean 8.06 ± 1.74 mm). In the femoral artery the diameter measured from 4.5 to 8 mm (mean 5.82 ± 0.89 mm).

DISCUSSION

Parallel with the rapid development of vascular interventions, there is a need for new and improved instrumentation for vascular imaging. The introduction of intravascular ultrasonography has received considerable interest because it not only yields high-resolution images of the vessel lumen but also has the unique potential to enable visualization of the vessel wall and its pathologic condition. This stimulated the application of intravascular ultrasonography as an important research direction in several centers throughout the world.

This article reports our experience with conventional single-plane angiography and intravascular

Table II. Results of the quantitative assessment of the percentage area obstruction with a computer-aided analysis system compared with semiquantitative assessment by visual inspection of the 181 ultrasonic cross sections before and after intervention

	Percentage area obstruction			
	Normal	*<50%*	*50%-90%*	*>90%*
Before (n = 94)	18.8 ± 9.5 (n = 17)	42.9 ± 8.1 (n = 26)	68.2 ± 8.1 (n = 31)	83.6 ± 9.1 (n = 20)
After (n = 87)	16.8 ± 11.0 (n = 13)	43.5 ± 6.8 (n = 40)	63.9 ± 8.9 (n = 30)	85.8 ± 5.0 (n = 4)

Data are presented as mean ± SD.
n, Number of sites analyzed.

ultrasonography to assess morphologic and semiquantitative data in a group of patients before and/or after vascular intervention.

Qualitative analysis. When intravascular ultrasonographic and angiographic data before intervention were compared, a total of 74 concordant observations (86%) were noted by visual inspection with respect to absence or presence (eccentric/concentric) of a lesion. This is in contrast to studies in coronary arteries in which the two methods corresponded in only 73% of the cases.[20] The reason for this discrepancy is speculative. In addition, there was a good correlation between intravascular ultrasonography and angiography for recognition of dissection after intervention. In only three sites was a small dissection seen echographically missed angiographically. Conversely, plaque rupture was more frequently seen on ultrasound imaging. Internal elastic lamina rupture was uniquely evidenced by intravascular ultrasonography. With respect to the internal elastic lamina rupture, which occurred only in the superficial femoral artery, it was found that the original diameter of the vessel was relatively small (4 mm) in relation to the balloon size (6 mm) used (Fig. 6). This suggests that intravascular ultrasound imaging may help in the identification of the truly normal reference segment for selection of the proper size of the balloon.

It should be realized that the morphologic features seen in this study, including dissection, plaque rupture, and internal elastic lamina rupture, can all be observed together in one patient. As yet we do not know the significance of these features with regard to restenosis. For this reason a collaborative study involving four universities in The Netherlands has been established. Patients will be studied with intravascular ultrasonography before and after balloon angioplasty to determine the predictive value of intravascular ultrasonography in assessing restenosis.

Quantitative analysis. This study shows that the standard semiquantitative angiographic analysis that provides percentage diameter stenosis corresponds well with the intravascular ultrasonographic image technique that yields semiquantitative percentage area stenosis. The data were in agreement in 78% of cases before and 72% of cases after intervention. The degree of the stenosis was found to be more evident by echographic analysis in the remaining sites (before intervention in 22% and after intervention in 28%). It is, of course, questionable whether angiography or intravascular ultrasonography is the more accurate method. The reported data from the literature support the conception that intravascular ultrasonography may indeed provide accurate quantitative data.[4-7,18,20-24]

One reason intravascular ultrasonographic analysis in this study overestimated the degree of obstruction is that, from a mathematic point of view, a 50% diameter stenosis is equivalent to a 75% area stenosis. Thus the ultrasonic grade would appear more severe than the angiographic grade. This was confirmed in one quarter of the analyses in this study. However, Tabbara et al.,[21] who compared luminal cross-sectional area measurements obtained from both angiography and intravascular ultrasonography, found that in diseased segments the ultrasonic grade was more severe than the angiographic grade. In the present study, however, no absolute angiographic diameters were available, therefore the percentage diameter reduction and not percentage area stenosis was determined. Conversion of the angiographic diameter stenosis to an area stenosis with the use of a formula is only valid in a perfect circular model;[21] we believe that the percentage area stenosis derived from intravascular ultrasonography is more informative than that derived from angiography (for both percentage diameter and area stenosis).

A second reason why contrast angiography may overestimate the true lumen diameter during projection imaging is that angiography uses the alleged normal vessel segment as reference. In contrast, intravascular ultrasonography uses the arterial media as reference to quantify the degree of area obstruction. The existence of a lesion in the normal segments found by quantitative analysis from the ultrasonic images resulting in an 18% area obstruction (Table II) underlines the fact that angiographic reference segments may indeed not be as "normal" as alleged.[20]

A third explanation is that contrast will fill the dissection plane beyond a lesion that occurred after balloon angioplasty. This latter situation perhaps exemplifies the disappointing late patency rate given the high incidence of restenosis after balloon angioplasty.[2]

A fourth reason angiography may overestimate the lumen area is that in diseased arteries the free lumen may be elliptic. To address the question of whether biplanar angiography would have been more accurate in this study to describe the degree of area stenosis, we reviewed the ultrasonic cross sections that showed a greater percentage stenosis than their angiographic counterparts. It was found that before intervention the free lumen was circular in 16 of 21 and elliptic in 5 of 21 ultrasonic cross sections. Thus biplanar angiography might have been beneficial at five sites. Similarly, after intervention biplanar angiography might have been beneficial at 10 of 24 sites inasmuch as ultrasonography evidenced an elliptic lumen. Conversely, a circular lumen (5 of 24) and the presence of a dissection (9 of 24) would not have provided more accurate estimation by the biplanar angiographic technique.

From the computer-aided method we learned that the semiquantitative analysis of intravascular ultrasonic images used in this study was adequately performed. This suggests that the technique may serve as an on-line decision-making device before and after intervention to provide independent objective information.

Follow-up studies will serve to determine the prognostic value offered by intravascular ultrasonographic information to predict in which patient restenosis may develop that necessitates reintervention.

It is known that the likelihood of restenosis is related to the degree of residual stenosis.[25] In this study, the significance of residual stenosis evidenced echographically after intervention is suggested by the fact that, so far, 7 of the 30 patients (23%) examined by intravascular ultrasonography after intervention needed reintervention for recurrent stenosis.

During this preliminary study it was not a specific aim to use intravascular ultrasonographic data to alter the physician's decision; however, in some patients the information derived from intravascular ultrasonography did in fact have an impact on the course of the intervention when the surgeon or radiologist deemed the information to be beneficial to the patient.[26]

Limitations. The transducer used in this study was blunt-tipped and rather inflexible; this was believed to be disadvantageous. For this reason one patient was not studied after balloon angioplasty for fear of damage to the freshly dilated vessel wall. This problem is solved with the introduction of a new type of flexible, "over the wire" catheter (4.1F) available (Du-MED, Rotterdam, The Netherlands) in our department. In four patients with known femoral artery occlusion the ultrasound catheter was not applied before intervention, whereas in five other patients, despite an occlusion, the ultrasound catheter could be advanced distally through the obstructed vessel before intervention.

Conclusion. Albeit angiography has been considered the gold standard for diagnosis in vascular disease, this study shows that intravascular ultrasonography supplements angiography by providing a real-time topographic and tomographic perspective of the vessel. An important potential benefit of the technique is its use as an on-line decision-making device before and after surgical reconstruction or endovascular intervention. Particularly, the reliability of the semiquantitative analysis by visual inspection might be advantageous in the assessment of significant residual stenosis that requires additional intervention. Furthermore, the potential role for intravascular ultrasonography exists in assessment and increased understanding of the effects of vascular intervention, which can subsequently be applied for the enhanced benefit of patient care.

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CHAPTER 12

INTRAVASCULAR ULTRASONIC ASSESSMENT OF LUMEN GEOMETRY AND DISTENSIBILITY OF THE ANGIOGRAPHICALLY NORMAL ARTERY: A CORRELATION WITH QUANTITATIVE ANGIOGRAPHY

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Intravascular Ultrasonic Assessment of Lumen Geometry and Distensibility of the Angiographically Normal Artery: A Correlation with Quantitative Angiography

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The feasibility of assessing lumen diameter and area using a 30-MHz mechanically driven ultrasound imaging device was evaluated in vitro in phantoms and in vivo in eight human arteries (six iliac, two brachial). Ultrasound data were compared to angiographic data derived from the cardiovascular angiographic analysis system. In addition, the change of lumen area in a given cardiac cycle was determined in each patient. A close relation between ultrasound and angiography was observed in the phantom studies. In the first three patients there was disagreement; ultrasound images showed larger values compared to the angiographically derived values. Disagreement was related to the use of nominal measurements of the sheath supplied by the manufacturer as calibration. Data on the five other patients showed a close relation between the values derived with ultrasound and angiography. The arterial lumen area revealed a 5% ± 2% change during one cardiac cycle. The intra- and interobserver variability test showed good correlation for the ultrasound study. This study demonstrates that intravascular ultrasound is an accurate and reproducible technique to measure vascular diameter, lumen area, and arterial wall distensibility in vivo. (ECHOCARDIOGRAPHY, Volume 9, March 1992)

intravascular ultrasound imaging, arteries, distensibility

Angiography is currently the method of choice to evaluate coronary and peripheral vascular anatomy in humans, but limitations remain in providing assessment of stenosis and pulsations of the arteries.[1–3] A new modality, intravascular ultrasound imaging, permits tomographic display of blood vessels.[4–8] Moreover, it allows real-time cross-sectional imaging of the pulsatile artery, which may provide useful data for studies of arterial compliance and blood flow.[9–12]

In this study, intravascular ultrasound measurements of lumen diameter and area were compared with angiographic data in phantoms and humans. Subsequently, the feasibility of intravascular ultrasound imaging to evaluate distensibility of the vessel wall in angiographically normal arteries during a cardiac cycle was assessed.

Methods

Ultrasound System

A 5-Fr real-time imaging catheter with a 1-mm diameter, 30-MHz single element transducer at its tip was used. The system was based

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on a mechanically motor-driven rotating catheter tip element connected to a flexible drive shaft. The element was covered by an acoustically transparent dome. Axial resolution of the system was 80 μm, and lateral resolution was better than 225 μm at a depth of 1 mm. The unit was connected to a prototype instrument (Du-MED, Rotterdam, The Netherlands) providing continuous real-time cross sections of the vessel wall (up to 16 images per sec). The ultrasonic images were displayed on a monitor by means of a videoscanned memory of 512 × 512 pixels with 256 gray levels.

Phantom Study

Two circular tubular phantom models of 8- and 16-mm diameter were used; eight cross sections were selected from each model for quantitative analysis. The mean values of the diameter and area were calculated.

Human Study

Approval from the local Committee on Human Research was granted and informed consent was obtained from each subject. Eight consecutive male patients (age range 31–73 years; mean 55 years) underwent diagnostic cardiac catheterization. In six patients, a 7-Fr introducer sheath was placed in the femoral artery, whereas in two patients, the brachial artery was cannulated with a 6-Fr sheath. The ultrasound catheter was advanced retrogradely into the iliac and brachial arteries. Real-time cross-sectional images of the arteries were obtained at different sites of the arterial system. The catheter was aligned coaxial to the arterial wall. For review and analysis, the ultrasound images were continuously recorded on a VHS video tape from the moment of introduction of the catheter. Electrocardiogram and/or internal pressure measurements were recorded simultaneously with the ultrasound images (Fig. 1). To compare angiographically assessed lumen geometry with the ultrasound images, a grid was used to mark the position of the ultrasound catheter. The level was indicated on the video (Fig. 1). This position was matched carefully to the level on the grid with fluoroscopy and angiography.

A total of 30 representative ultrasonic images were selected for comparison with angiography. At each site, systolic and diastolic cross sections were selected. Mean values of lumen diameter and area were calculated.

Additionally, for each patient, all ultrasonic cross sections at one given location were used to determine the change in lumen area in one cardiac cycle (Fig. 2). Increase in lumen area during the cardiac cycle was defined as the distensibility of the vessel. For the ultrasound analysis, lumen diameter and area were deter-

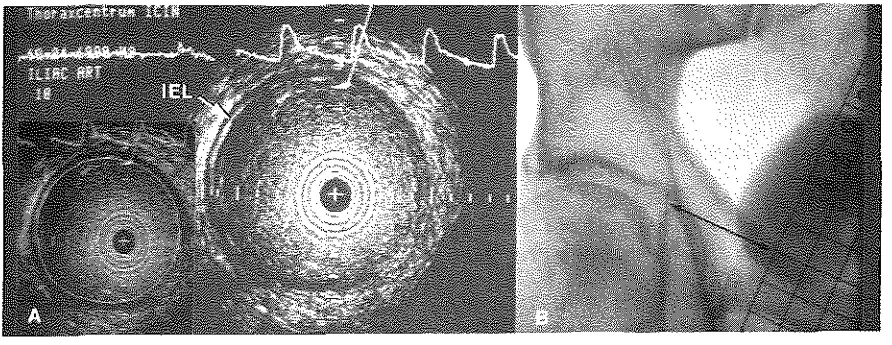

Figure 1. *(A) Ultrasonic cross section of the iliac artery without and with contour tracing of the arterial lumen. (B) Corresponding angiogram of the same patient showing the grid. Ultrasonic and angiographic measurements were taken at level 10. The intima-internal elastic lamina echo (IEL) has been used as a landmark to trace the lumen contour.*

TABLE I

Phantom Measurements on Luminal Diameter (mm) and Area (mm^2) by Intravascular Ultrasound Imaging and Angiography (Mean ± SD)

		Ultrasound	Angiography
Phantom 1	Diameter	8.0 ± 0.04	8.0 ± 0.01
[8.0 mm]	Area	49.9 ± 0.54	50.1 ± 0.10
Phantom 2	Diameter	16.2 ± 0.06	16.3 ± 0.01
[16.0 mm]	Area	207.2 ± 1.44	207.9 ± 0.10

ages of the artery in all eight patients. No complications during and following the intravascular ultrasound study occurred. Proximally, near the junction with the aorta, the artery exhibited no three-layered wall, indicating its elastic nature.[5–7] Distally the iliac arterial wall displayed a three-layered appearance, indicative of its muscular nature. A similar observation was found in the brachial artery. Albeit there was no angiographic evidence of atherosclerosis (Fig. 1), intravascular ultrasound revealed distinct intimal thickening in two patients.

Table II summarizes ultrasonic and angiographic measurements for lumen diameter and area obtained in the patients studied. The 12 selected ultrasound images acquired in the first three patients showed larger diameter and area than angiography. In these patients, the angio-

TABLE II

Intravascular Ultrasound (IVUS) and Angiographic (ANGIO) Measurements in Lumen Diameter and Area in 8 Patients (Mean Values)

	Diameter (mm)		Area (mm^2)	
Patient	IVUS	ANGIO	IVUS	ANGIO
1	6.4	5.1	32.6	20.2
2	9.3	7.5	67.6	44.4
3	8.2	6.4	52.4	32.6
4	7.4	7.0	42.8	38.3
5	9.6	9.3	70.1	67.4
6*	5.9	5.6	27.7	24.7
7	6.3	5.9	31.3	28.8
8*	3.6	3.6	10.3	10.0

* Brachial artery.

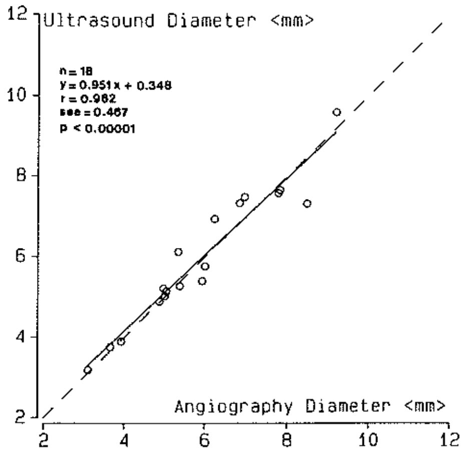

Figure 3. *Linear regression analysis between intravascular ultrasound and angiography for 18 measured arterial segments.*

graphic measurements used the nominal catheter diameter values for calibration. In the other five patients, the two techniques produced analogous results when the catheter diameter was measured directly for calibration of the angiographic dimensions.

Statistical analysis of the measured diameters in the last five patients for the 18 measured segments showed a close relation between ultrasound and angiography with a mean paired difference of −0.060 ± 0.461 (P = 0.588) (Fig. 3). Intra- and interobserver variability tests revealed a mean paired difference of 1.011 ± 1.765 (P = 0.0371) and 0.030 ± 1.687 (P = 0.944) (Fig. 4).

The mean increase in lumen area in relation to the blood pressure measured during one cardiac cycle in each patient was 5% ± 2% (range 2%–10%). The largest area occurred during systole and at end-diastole the arterial area was smaller (Figs. 2 and 5).

Discussion and Conclusion

The aim of this study was to compare intravascular ultrasound measurements of lumen diameter and area with those derived from an-

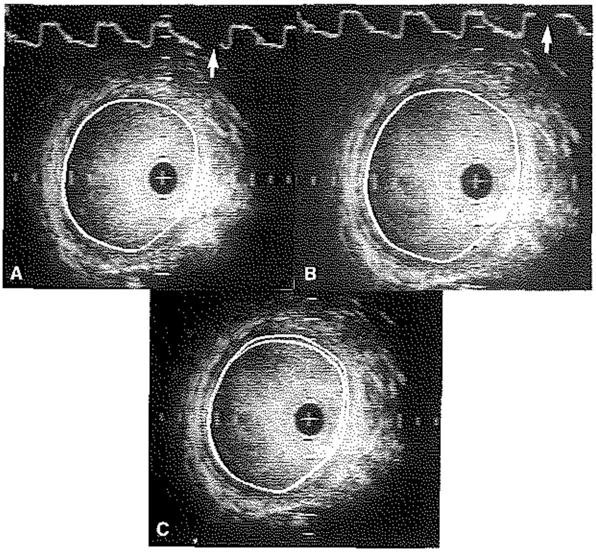

Figure 2. *Intravascular ultrasound cross sections obtained in the common iliac artery at the same level. Contour detection was used to determine the change in lumen area at end-diastole (A) and systole (B), triggered by pressure data (arrow). (C) Both contours were plotted on the same cross section to visualize the difference.*

mined by planimetry using an IBM-compatible PC/AT equipped with a frame grabber.

The angiograms were calculated by a cardiovascular angiography analysis system (CAAS) (Pie Medical USA, Neptune, NJ, USA), which has been described in detail elsewhere.[13] Briefly, this computer-assisted analysis system detected automatically contours of arterial segments and measured arterial dimensions from a selected arterial segment, which was optically magnified and converted into video format by means of a specially constructed cine-video converter and digitized for subsequent analysis by computer. For calibration purposes, the sheath size according to normal values supplied by the manufacturer was used in the first three patients as reference. In the other five patients, calibration was made by measuring the ultrasound catheter using a micrometer.

Statistics

Two independent investigators assessed the intravascular ultrasound measurements. Intra- and interobserver variability tests were determined. The angiographic measurements were obtained by one observer using the automated edge contour detection. Linear regression analysis was used and mean paired differences and their standard deviation were calculated. All data were expressed as mean values (± SD).

Results

In the phantom study, ultrasound images showed excellent agreement with angiography for lumen diameter and area (Table I). In vivo ultrasound yielded high-quality pulsatile im-

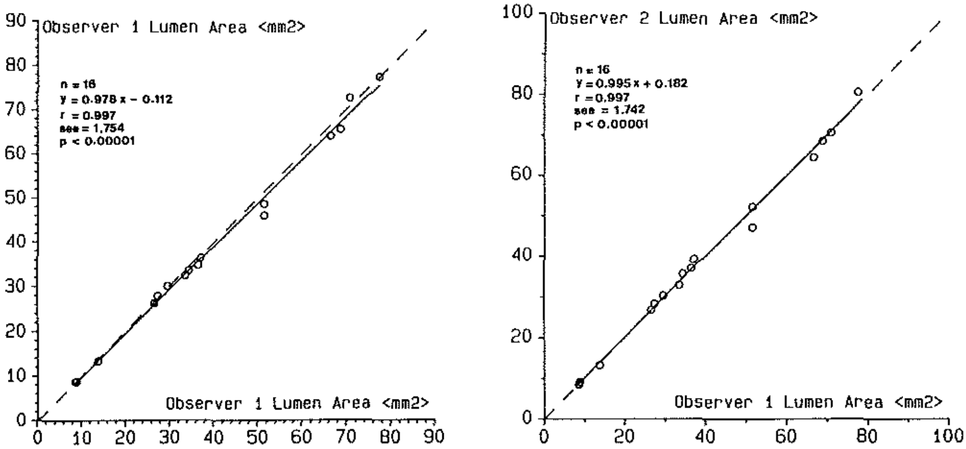

Figure 4. *Intra- and interobserver variability of lumen area measurements in 16 arterial segments by intravascular ultrasound.*

giography in phantoms and humans. Additionally, the feasibility of ultrasound to evaluate distensibility of the artery during a cardiac cycle was investigated.

Phantom studies revealed a close relation between the two techniques in the calculated lumen diameter and area. This is in agreement

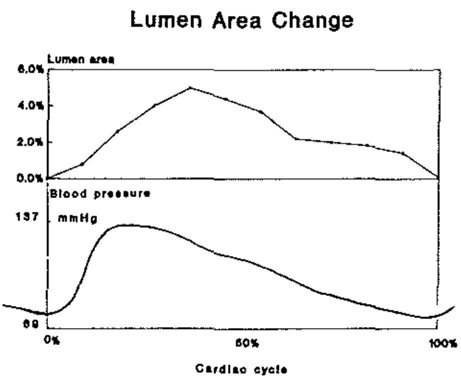

Figure 5. *Mean change of lumen area in relation to blood pressure during one cardiac cycle in all patients. Note a mean difference of 5% in lumen area between systole and diastole.*

with the phantom study of Nishimura and colleagues.[8]

In vivo, similar measurements of the two parameters were determined in five patients. Obviously, good calibration and localization within the vessel were necessary to obtain a reliable comparison between the two techniques; the best calibration for angiography proved to be the measurement of the diameter of the catheter at the level corresponding to the ultrasound study. This underlines the report of Reiber et al.,[14] who found that the size of the catheter specified by the manufacturer often deviates from the true size. Moreover, it should be noted that each technique is based on a different basic principle. In angiography, measurements were taken from projected diameters, whereas intravascular ultrasound provided tomographic cross sections. It is expected that correlation between angiography and intravascular ultrasound in measurement of luminal sizes is likely to decrease in the presence of segmental vessel distortion due to atherosclerosis or dissection following intervention.[10,15,16] Therefore, we believe that intravascular ultrasound has the potential to be more sensitive than angiography to define the nature of the disease and the effects of interventional procedures aimed at dilatation of the obstructive vessel.

Before the introduction of intravascular ultrasound, studies on the elastic properties of the human artery revealed the lack of a proper method to examine the arterial dimensions and wall morphology of the vessel.[17,18] Intravascular ultrasound has the unique potential to overcome this deficiency.

Our experience shows that for assessment of the distensibility of arteries, the technique yields cross-sectional real-time images useful in determining the function and anatomy of the vessel wall. Pulsatile changes in lumen area in response to changing pressure during the cardiac cycle were obtained, revealing a 5% ± 2% increase in lumen area in normal iliac arteries. This area/pressure relationship reflects the compliance of the vessel wall. Bartorelli et al.,[19] working with sheep, observed larger pulsatile changes in normal femoral and carotid artery diameters of 8% ± 2% (i.e., area changes of 17% ± 4%) using intravascular ultrasound. Tutar et al.[20] assessed percentage arterial distensibility of 8% ± 5% by measuring percentage changes of segmental wall expansion in normal human iliofemoral arteries. Apart from pulsatile changes due to the cardiac cycle, it is known that drugs also have influence on the arterial compliance.[11,21]

Linker and co-workers[22] determined aorta wall stiffness in pigs using intravascular ultrasound, whereas Lee and associates[23] found in autopsy material that intravascular ultrasound can distinguish atherosclerotic plaque components with different biomechanical properties. In patients with atherosclerosis, it is known that reduction in distensibility of an artery may occur.[20,24–26] It is noteworthy that from our experience with intravascular ultrasound in humans with atherosclerotic superficial femoral arteries, we learned that the distensibility virtually disappeared in those segments that are grossly diseased. Normal vessel anatomy proximal to the atherosclerosis, however, still has the potential to show pulsatile changes.

This study established baseline values for future studies on wall compliance in patients with atherosclerosis. Whether this will have direct clinical value for patients is a matter for further study. However, it should be kept in mind that a 5% change in a normal vessel area may be marginal.

Thus, intravascular ultrasound imaging is a safe and feasible technique to measure accurate and reproducible vascular diameter and area in humans. In addition, this technique is the first that offers the potential to study the distensibility of the arterial wall.

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CHAPTER 13

ASSESSMENT OF REGIONAL VASCULAR DISTENSIBILITY IN DISEASED ILIOFEMORAL ARTERIES BY INTRAVASCULAR ULTRASOUND

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CHAPTER 13

ASSESSMENT OF REGIONAL VASCULAR DISTENSIBILITY IN DISEASED ILIOFEMORAL ARTERIES BY INTRAVASCULAR ULTRASOUND

ABSTRACT

The influence of atherosclerosis on distensibility of iliac and superficial femoral arteries was assessed retrospectively in 28 patients using intravascular ultrasound. Distensibility was related to lesion morphology, lesion geometry, percentage area stenosis, effect of balloon angioplasty, hypertension and patient's age. In 10 patients, free lumen area remained unchanged during the cardiac cycle. From the remaining 18 patients, a total of 135 cross-sections underwent qualitative and quantitative analysis. Cross-sections without a lesion were compared with those showing soft/hard and eccentric/concentric lesions.

At normal sites, iliac arteries showed greater distensibility than femoral arteries (6.5 ± 2.4% vs 3.5 ± 0.9%; $p \leq 0.05$). Hard lesions in iliac arteries were less distensible than soft lesions; in femoral arteries this difference was less pronounced. Lesion geometry did not influence arterial distensibility. Intravascular ultrasound revealed no difference in distensibility when normal cross-sections were compared with those having a < 50% or a 50-90% area stenosis. In contrast, a significant decrease in femoral artery distensibility was found in the presence of > 90% stenosis (0.4%). Comparison of cross-sections

before and after balloon angioplasty revealed a marked increase in distensibility of iliac arteries following intervention; in the femoral artery, there was practically no change in distensibility. Hypertension and increasing age proved to have no significant influence on arterial distensibility.

This study demonstrates that intravascular ultrasound is potentially a powerful tool to assess arterial distensibility and the influence of atherosclerosis on vascular dynamics.

INTRODUCTION

Intravascular ultrasound allows both visualization and characterization of the arterial wall, as well as measurement of the luminal cross-sectional area (Gussenhoven et al. 1989; Gussenhoven et al. 1991; Isner et al. 1990; Nissen and Gurley 1991; Pandian et al. 1990; Potkin et al. 1990; Tobis et al. 1991; Yock et al. 1991). In addition, this real-time technique permits visualization of arterial distensibility (i.e. lumen area change) during the cardiac cycle, enabling the study of vascular dynamics (Nissen and Gurley 1991; The et al. 1992a).

Arterial distensibility is reported to be reduced in patients with atherosclerosis, hypertension, and with increasing age (van Bortel et al. 1992; Isnard et al. 1989; Kawasaki et al. 1987; Levenson et al. 1985; van Merode et al. 1993; Mourlon-Le Grand et al. 1993; Mozersky et al. 1972; Park et al. 1993; Reneman et al. 1985; Safar et al. 1984; Santamore et al. 1982). However, studies so far have not investigated the influence of lesion morphology, lesion geometry and lesion volume on vascular distensibility. Therefore the aims of this retrospective study were to: 1) assess the influence of lesion morphology and lesion geometry on the distensibility of iliac and superficial femoral arteries; 2) establish to what extent distensibility is influenced by the percentage area stenosis of the vessel; 3) establish the effect of balloon angioplasty on arterial distensibility and 4) assess the effects of hypertension and patients' age on arterial distensibility.

METHODS AND PATIENTS

Intravascular ultrasound. A mechanically 5F real-time imaging catheter operating at 30 MHz was used (Gussenhoven et al. 1991). Axial resolution of the system is 80 μm and lateral resolution is on the order of 225 μm at a depth of 1 mm. The catheter was connected to a prototype instrument (Du-MED, Rotterdam, The Netherlands) providing continuous real-time cross-sections of the vessel wall (up to 16 images per second). The ultrasound images were displayed on a monitor by means of a videoscanned memory of

512 x 512 pixels.

Study group. Twenty-eight patients with disabling claudication (22 men, 6 women; aged 49-83 years; mean age 65 years) were scheduled for balloon angioplasty (the iliac artery in 7 and the superficial femoral artery in 21 patients). The study was approved by the local Committee on Human Research and informed consent was obtained from each patient.

The common femoral artery was cannulated with a 7F introducer sheath and the intravascular ultrasound catheter was advanced into the iliac or superficial femoral artery. Under fluoroscopic guidance the position of the catheter was marked using a radiopaque reference ruler (The et al. 1992b). The electrocardiogram was registered simultaneously with the ultrasound studies. During pull-back of the catheter, real-time images of the arteries were continuously recorded on a VHS videotape. At levels of interest, the catheter tip was not moved during at least 10 seconds.

Off-line analysis. From each cross-section the free lumen area, bounded by the lumen-intima interface, was first manually contour traced using a semiautomatic contour detection technique (Wenguang et al. 1991a); this contour was used as reference. Then, using a template-matching based method, the displacement of the arterial wall during two subsequent cardiac cycles was automatically assessed by analyzing all cross-sections involved (Wenguang et al. 1991b) (Figure 1). The analysis software was implemented on an IBM-compatible PC/AT (IBM Corp. Boca Raton, FL, USA) equipped with a framegrabber.

Arterial distensibility was defined as the area difference between the systolic and diastolic measurements divided by the mean lumen area registered during the two cardiac cycles. From each arterial cross-section selected the data on lesion morphology (hard/soft) and lesion geometry (eccentric/concentric) were gained. A soft lesion was recognized as having a homogeneous echo structure without shadowing, whereas a hard lesion was recognized by the presence of a bright echo structure casting peripheral shadowing (The et al. 1992a). A concentric lesion was defined as a lesion distributed along the entire circumference of the vessel wall, and an eccentric lesion was defined as a lesion involving one part of the circumference of the vessel wall leaving the remaining part disease-free (Vlodaver and Edwards 1971). For each cross-section the percentage area stenosis, semiquantitatively assessed using the media-bounded area as circumferential reference, was classified as: no lesion or having a $< 50\%$, 50-90% or $> 90\%$ stenosis (Gerritsen et al. 1993).

Statistical analysis. Distensibility was expressed as the percentage free lumen area change (mean $\pm$ standard deviation, SD). Using an unpaired t-test the data were analyzed for the confidence value between two different groups. A $p \leq 0.05$ was considered to be statistically significant. Linear regression analysis was used to calculate the correlation between age and distensibility. Data are plotted as mean values for each group, with error bars signifying ± SD of the mean.

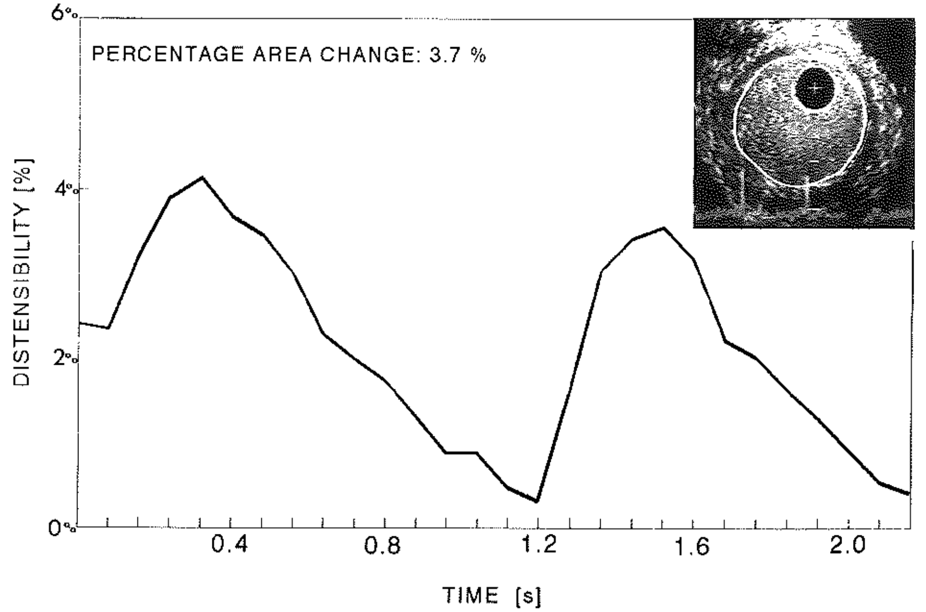

Figure 1. Intravascular ultrasound cross-section obtained from a normal femoral artery. Contour detection was employed to determine the change in lumen area during the cardiac cycle. The percentage lumen area change (i.e. distensibility) was 3.7%. Note the resemblance of the shape of this curve with the pressure curve, indicating the pressure pulse "waving" down inside the artery. Calibration= 1 mm; += catheter.

RESULTS

In 10 of the 28 patients no change in free lumen area was evidenced: 9 of these patients (femoral artery) presented with cross-sections showing >90% stenosis over a long segment and in one patient (iliac artery) diffuse calcified pathology was involved (50-90% stenosis). From these 10 patients, 7 had normotensive blood pressures (mean systolic/diastolic blood pressure (BP) and heart rate (HR): 119/84 mmHg and 75 beats per minute (bpm), respectively) and 3 had borderline hypertension (mean BP and HR: 170/90 mmHg and 87 bpm, respectively). These patients were excluded from further qualitative and quantitative measurements.

From the remaining 18 patients, 15 patients were normotensive (mean BP and HR: 150/82 mmHg and 77 bpm; blood pressure was measured using a sphygmomanometer). In 3 patients known to be borderline hypertensive, (mean BP and HR: 173/93 mmHg and 82 bpm) the study was performed in the superficial femoral artery. Mean pulse pressure of the iliac arteries was in the same range as the femoral arteries (72 mmHg versus 69 mmHg).

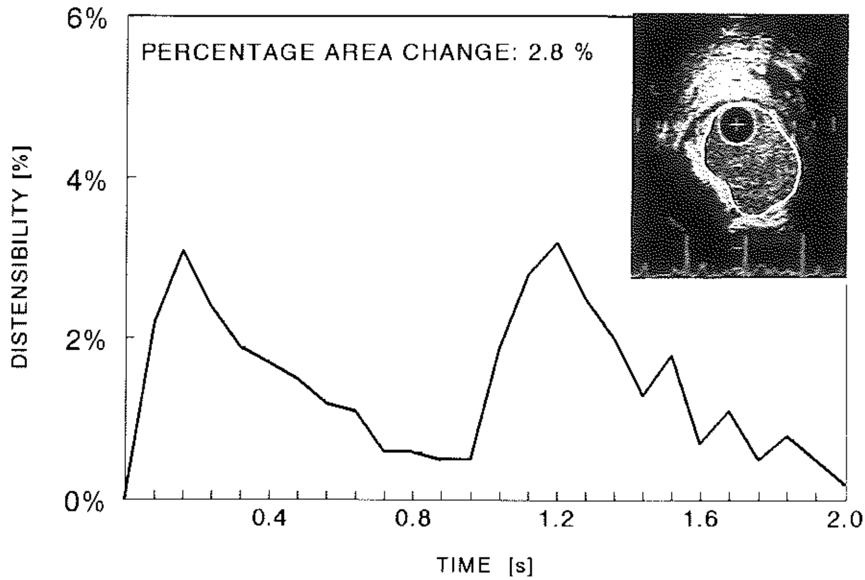

Figure 2. Distensibility (%) measured in a femoral arterial cross-section showing an eccentric-hard lesion (< 50% stenosis) The percentage lumen area change was 2.8%. Calibration= 1 mm; += catheter.

A total of 135 ultrasound cross-sections (mean 7-8 cross-sections per patient) were subjected to qualitative and quantitative analysis: including 44 sites (33%) from 6 iliac arteries, and 91 sites (67%) from 12 femoral arteries. Of the 44 sites examined from the iliac arteries, 11 (25%) demonstrated a normal three-layered vessel wall structure with no lesion. At 33 sites an eccentric lesion was present: 18 (41%) of which were classified as soft and 15 (34%) as hard lesions. Of the 91 sites from the femoral arteries, no pathology was observed at 8 (9%) sites (Figure 1); eccentric lesions were evidenced in 66 (72%) and concentric lesions were present at 17 (19%) sites. Soft and hard lesions were evidenced at 41 and 42 sites, respectively (Figure 2).

It was observed that arterial distensibility could vary from location to location within the same artery (Figure 3).

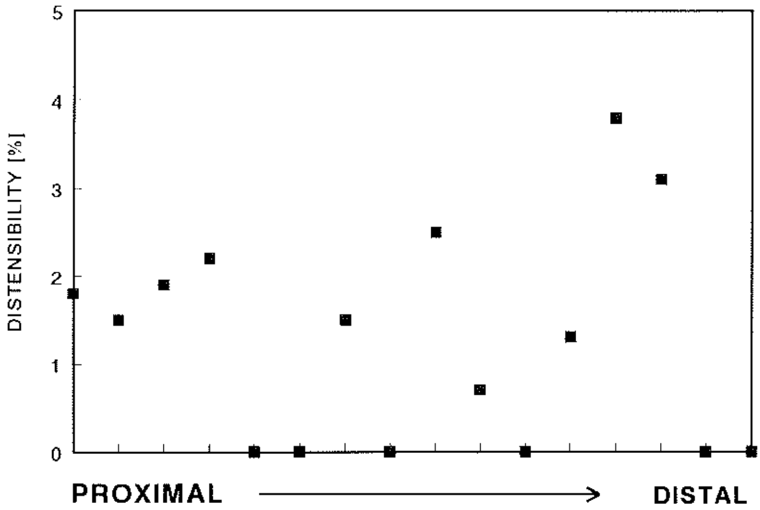

Figure 3. Distensibility (%) measured in one patient from proximal to distal in the superficial femoral artery. Note that the distensibility varies from location to location inside the artery (range: 0% to 3.8%).

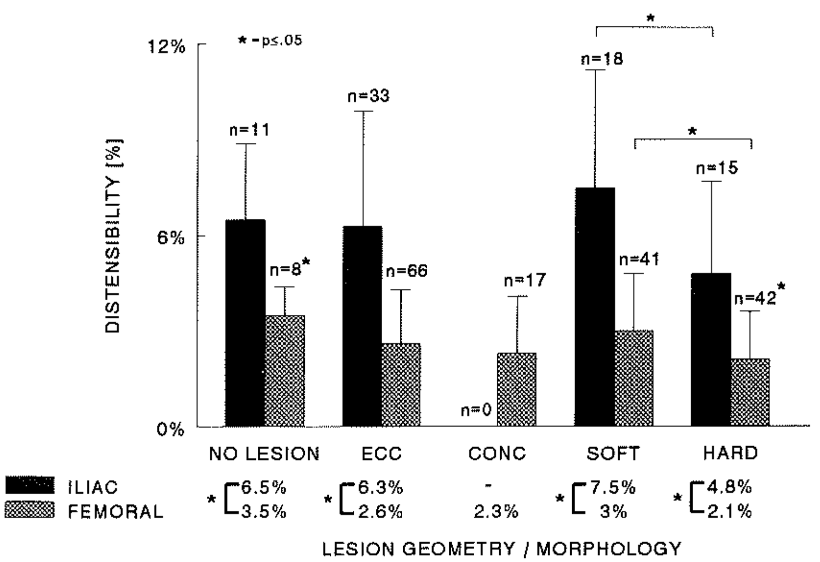

Figure 4. Distensibility (%) of iliac and superficial femoral arteries grouped according to lesion morphology and geometry. The distensibility was lower in the femoral artery than in the iliac artery in all groups ($p \leq 0.05$). A significant decrease was found when soft lesions were compared to hard lesions for both iliac and femoral arteries. The femoral artery distensibility also decreased when no lesion sites were compared with those having hard lesions ($p \leq 0.05$). ECC=eccentric; CONC=concentric; n=number of cross-sections.

The distensibility of the iliac and superficial femoral arteries grouped by lesion morphology and geometry is shown in Figure 4. A significant decrease in distensibility was found when the followings groups were compared: 1) iliac versus femoral artery, irrespective of the presence or absence of a lesion, lesion morphology, lesion geometry; 2) soft versus hard lesions, both in the iliac and the femoral artery; and 3) hard versus normal in the femoral artery ($p \leq 0.05$) (Compare Figures 1 and 2).

The distensibility of the arteries grouped according to the degree of percentage area stenosis is shown in Figure 5.

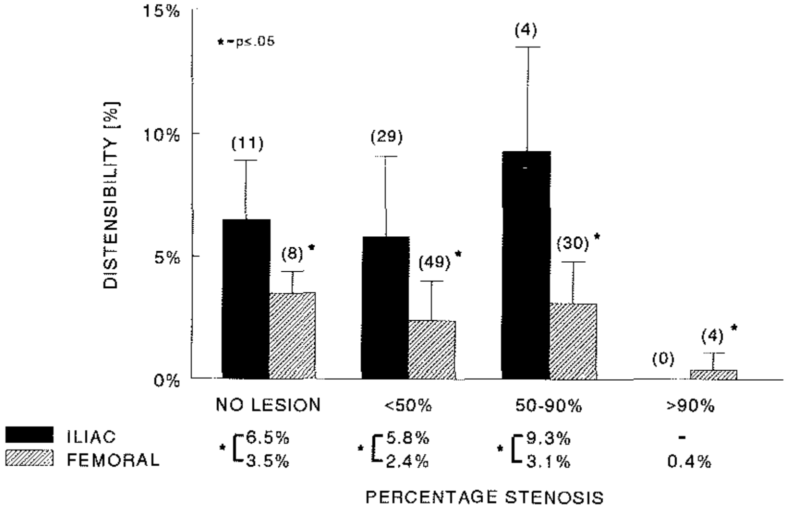

Figure 5. Distensibility (%) in iliac and femoral arteries grouped according to the degree of percentage area stenosis. The distensibility was lower in the femoral artery than in the iliac artery in all groups ($p \leq 0.05$). No difference in distensibility in both iliac and femoral artery was observed when sites with no lesion were compared with those having < 50% or 50-90 % area stenosis. A significant decrease in distensibility was found in femoral arteries when sites with no lesion or sites with <50% area stenosis or sites with 50-90 % area stenosis were compared with sites with >90% area stenosis. The number of cross-sections is given in parenthesis.

It was observed that distensibility values in iliac arteries were significantly higher than those in the femoral arteries. In addition, no significant change in distensibility was evidenced when lesion volume increased up to 90% stenosis both in iliac and femoral arteries. Conversely, a significant decrease in distensibility (0.4%) was observed in 4 femoral artery cross-sections (3 patients) where the percentage area stenosis was > 90% ($p \leq 0.05$). Lesions with > 90% stenosis were not found in the iliac artery. The influence of balloon angioplasty on arterial distensibility was more marked in iliac than in femoral arteries (Figure 6).

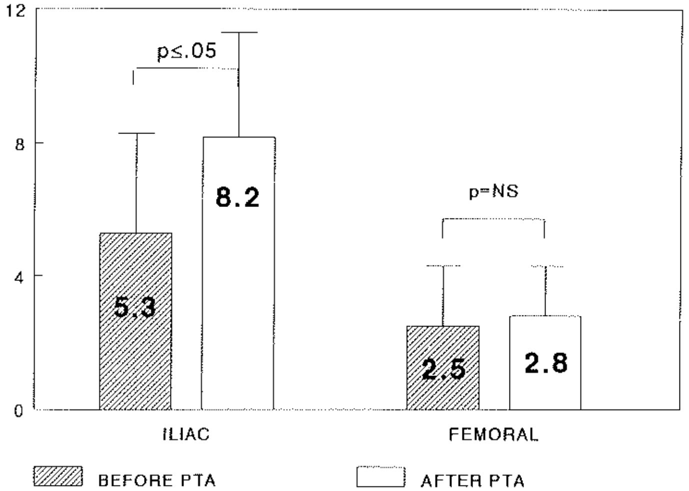

Figure 6. Arterial distensibility (%) measured before and after percutaneous transluminal angioplasty. Following intervention, a significant increase in distensibility was observed in iliac arteries, whereas no significant change was found in the femoral artery.

In iliac arteries distensibility increased significantly from 5.3 ± 3.0% (29 cross-sections from 5 patients) pre-intervention to 8.2 ± 3.1% (15 cross-sections from 2 patients) post-intervention ($p \leq 0.05$); in femoral arteries the distensibility showed practically no change after intervention: 2.5 ± 1.8% (n=47 from 11 patients) before versus 2.8 ± 1.5% (n=44 from 11 patients) after intervention.

Arterial distensibility in the 3 borderline hypertensive patients (3.0 ± 1.7%; 15 cross-sections) did not differ significantly from that of the 15 normotensive patients (2.6 ± 1.6%; 76 cross-sections).

Finally, concerning increasing age and distensibility, no correlations were found for the iliac artery group ($r=0.54$, $p=0.27$), femoral artery group ($r=0.47$, $p=0.12$), or the entire group (combined iliac and femoral artery groups) ($r=0.19$, $p=0.46$) (Table I).

Table I. Distensibility (mean ± SD %) in iliac and superficial femoral arteries related to patient's age, with correlation coefficients (r) and confidence values (p).
Note absence of correlation between increasing age and distensibility in iliac and femoral arteries.

	Age (yr)	Distensibility	Age (yr)	Distensibility
ILIAC (6 patients)	49	3.5 ± 1.0 %		
	50	5.0 ± 0.8 %		
	51	4.3 ± 1.6 %		
	59	5.8 ± 1.9 %		
	73	3.6 ± 0.8 %		
	75	9.3 ± 3.4 %		
FEMORAL (12 patients)	49	2.0 ± 0.5 %	71	2.7 ± 1.6 %
	54	3.3 ± 2.2 %	73	4.2 ± 0.9 %
	60	1.2 ± 1.2 %	73	2.9 ± 1.3 %
	63	3.9 ± 1.7 %	79	2.6 ± 1.1 %
	66	4.1 ± 0.6 %	79	3.0 ± 0.4 %
	68	2.0 ± 0.7 %	83	6.2 ± 1.8 %

		r	*p*
Iliac	:	0.54	0.27
Femoral	:	0.47	0.12
Iliac and Femoral	:	0.19	0.46

DISCUSSION

It is reported that vascular disease (such as atherosclerosis), hypertension and increasing age may affect arterial distensibility (van Bortel et al. 1992; Isnard et al. 1989; Kawasaki et al. 1987; Levenson et al. 1985; van Merode et al. 1993; Mourlon-Le Grand et al. 1993; Mozersky et al. 1972; Park et al. 1993; Reneman et al. 1985; Safar et al. 1984; Santamore et al. 1982). In order to better appreciate the dynamics of the arterial wall, a more detailed description of the mechanical and elastic properties of the arteries is required (Mozersky et al. 1972). The introduction of intravascular ultrasound imaging may meet this need, as it allows visualization of the pulsatile changes of vessel lumen area (defined here as arterial distensibility during the cardiac cycle) in relation to the pathology of the wall and, thus, enabling the study of vascular dynamics. Recently, Wilson and coworkers (1992) demonstrated in animals that intravascular ultrasound enables to measure the effects of adenosine and norepinephrine on arterial compliance, i.e. the distensibility/pressure relationship. In an earlier study on humans, it was demonstrated that the technique yields cross-sectional real-time images useful in determining the function and anatomy of the vessel wall (The et al. 1992b). However, no study so far has investigated arterial distensibility in relation to lesion morphology, lesion geometry, percentage area stenosis, effect of balloon angioplasty, hypertension or patient's age.

Early studies using non-invasive techniques to measure distensibility have been performed in normal arteries (Reneman et al. 1985). Changes in lumen area, however, were derived from calculations of changes in diameter rather than measurements from absolute lumen area. This could lead to erroneous measurements and misinterpretation when used in diseased arteries (e.g. non-circular lumen). In contrast, the major advantage of intravascular ultrasound is to display the total vessel wall and its pathology in 360° polar mode. At the same time, changes in lumen area can be appreciated by high speed rotation of the ultrasound catheter.

The first aim of this study was to assess whether distensibility in diseased iliac and superficial femoral arteries differs from that of normal arteries and whether the morphology of a lesion influences vessel distensibility. In this study, the distensibility in normal segments of the iliac artery was 6.5 $\pm$ 2.4%: these values confirming those of an earlier study, i.e. 5.9 $\pm$ 2.4% (The et al. 1992a). In normal femoral arteries, however, lower values were encountered (3.5 $\pm$ 0.9%). From histologic and intravascular ultrasound studies it is known that both the iliac and femoral artery are of a muscular nature (Gussenhoven et al. 1989). One reason for the difference in distensibility between the two arteries may be the presence of the introducer sheath within the common femoral artery: the iliac artery is proximal to the sheath, whereas the femoral artery is distal to the sheath. Another reason to explain the difference is that the distensibility of an artery may depend on its location in the vascular system: the more distally the artery is situated, the more reduced is the arterial distensibility. It is likely, therefore, that the distensibility in normal coronary arteries assessed with intravascular ultrasound gives a much larger value of 18% (Nissen and Gurley 1991).

The observation in this studies that arterial distensibility could alter along the artery was also seen in previous studies using non-invasive techniques (Van Merode et al. 1993; Reneman et al. 1985). Furthermore, it was observed that in the presence of a lesion, the iliac artery had significantly greater distensibility than the femoral artery, irrespective of the type of lesion (Figure 4). With regard to morphologic features (soft or hard), intravascular ultrasound revealed a significant reduction in the distensibility of hard lesions compared to soft lesions in both types of arteries (7.5% vs 4.8% and 3.0% vs 2.1%, respectively; $p \leq 0.05$). These data are in agreement with *in vitro* results reported by Park and associates (Park et al. 1993).

The second aim of this study was to test the hypothesis that the degree of percentage area stenosis may influence the distensibility of the vessel. Intravascular ultrasound revealed that in the 18 patients examined the arterial distensibility diminished significantly only in the presence of a significant i.e. > 90% stenosis. Taking into account the absence of distensibility observed in 10 other patients in this study in whom 9 patients presented with cross-sections showing an area stenosis of > 90%, we speculate that a significant area reduction may influence arterial distensibility.

As third aim, the effect of balloon angioplasty on arterial distensibility was investigated. Following intervention a significant increase in distensibility was observed in iliac arteries, whereas no significant change was found in femoral arteries (Figure 6). This might be explained by the interposition of the sheath during the study.

In the present study no significant difference in vascular distensibility was found between normotensive and borderline hypertensive patients (3.0% and 2.6%, respectively; p=NS). It should be mentioned, however, that our study group contained only 3 borderline hypertensive patients.

Finally, in this study no correlation was found between increasing age and arterial distensibility. This observation underscored the work of Benetos and coworkers (1993) who found similar observation for the femoral artery. In contrast, the authors observed a significant correlation at the site of the carotid artery between increasing age and arterial distensibility. Similarly, Reneman and co-workers (1985) reported a significantly lower distensibility in the carotid artery of older normotensive patients compared to younger normotensive patients; all patients were without history of cardiovascular diseases. Their definition of vascular distensibility differs slightly from that used in our study. It is noteworthy that Kawasaki et al. (1987) observed that with advancing age a significant increase in the diameter of normal arteries was seen associated with a reduction in percentage change in diameter. However, in the brachial and femoral arteries a considerable variation was found in the individual values for a given age.

One explanation for the discrepancy between these observations and our study, may be that the age range of our study group was small (65 ± 9 years) and the number of patients may be too limited to reach significance level in the sample size. Moreover, this study included patients with angiographically proven vascular disease; when sites without a lesion were compared to those with calcified lesion, the arterial distensibility diminished. Another argument may be that carotid arteries are of an elastic type, whereas both iliac and femoral arteries are of a muscular type. Finally, when a greater distensibility is to be expected in the proximal elastic arteries, the effect of age in these arteries may therefore be seen more easily than in arteries with less distensibility, such as the distal femoral arteries.

Study limitations. Although intravascular ultrasound imaging is a welcome addition for intravascular catheter interventions, its use solely for distensibility studies of the vascular system needs justification. In 10 patients (36%) no pulsations were encountered. The change in luminal area seen in normal femoral arteries (i.e. 3.5 %) was marginal. The influence of the pulse pressure on the distensibility has been ruled out in the present study, as the difference in pulse pressure between the two types of arteries interrogated was minimal. Recently, Benetos and co-workers (1993) reported that blood pressure measured using both conventional sphygmomanometry and tonometry in the relatively normal brachial and femoral artery were of the same magnitude. However, in order to examine the precise relation between vascular distensibility and direct pulse pressure measurements, we recommend that in future studies using intravascular ultrasound, the distensibility coefficient ($\Delta A/A/\Delta P$) would better reflect the property of the vessel wall. For this purpose, direct pressure measurement using a catheter-tipped pressure microtransducer positioned at the same level as the ultrasound catheter is necessary. In the present study this was not feasible. Finally, off-line quantitative analysis in this study was time-consuming: approximately 20 minutes was required for each cross-section. Newly developed software programs will diminish the required time to about 5 minutes.

Conclusions. This preliminary study has established baseline values on vessel wall distensibility in patients with diseased iliac and superficial femoral arteries. Arterial distensibility was determined by the nature of the lesion; hard lesions having reduced distensibility. Lesion volume influenced distensibility only when there was a significant reduction in luminal area. Vascular intervention increased the distensibility in iliac arteries, whereas no change was found in femoral arteries after intervention. Albeit the clinical value of intravascular ultrasound for assessment of vascular distensibility needs to be determined, the data presented here may provide a basis for future studies.

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CHAPTER 14

SUMMARY

SAMENVATTING

CHAPTER 14

SUMMARY

Atherosclerosis is a common vascular disease that involves a series of cellular changes in the arterial wall resulting in the growth of an atheromatous plaque with encroachment on the tunica media and reduction of the lumen. For the vascular surgeons, interventional radiologists and cardiologists it is necessary to visualize and to assess the effects of therapy correctly for the maximal benefit of the intervention. Angiography is still the standard method to assess the location and severity of stenotic lesions, but it does not provide sufficient insight into the shape of the stenotic lesion or the morphology of the lesion. Intravascular ultrasound (IVUS) has the unique capability to study vessel wall morphology and pathology beneath the endothelial surface in a cross-sectional manner. *In vitro* studies have proven that the technique is reliable to determine the constituents of vessel wall, both qualitatively and quantitatively.

The aim of the studies described in this thesis was to evaluate the ability of IVUS to assess vascular pathology *in vitro* and *in vivo* in peripheral vessels before and after vascular intervention.

Chapter 1 describes the need for a better diagnostic tool to assess vascular pathology. The history of the IVUS imaging technique is given and the aim of the thesis is addressed and summarized.

Chapter 2 gives a review of *in vitro* studies with IVUS. As histology forms the basis of our understanding of IVUS images, *in vitro* studies have proven that this modality provides important information of lesion morphology and topography. The important role in visualizing the hypoechoic medial layer of the artery using this imaging technique and, thus, in quantifying the plaque burden, is emphasized. The knowledge gained from *in vitro* studies is employed for the application of this modality *in vivo* in humans. Future implications of the use of the technique in the clinical situation are discussed.

Chapter 3 deals with the use of IVUS in detection, characterization and quantitative assessment of arterial wall and atherosclerotic plaque both *in vitro* and *in vivo*. In the majority (76%) of the muscular artery specimens studied, the arterial wall displayed a three-layered structure due to the hypoechoic appearance of the muscular media. Fibrous degeneration of the muscular media resulted in a homogeneous aspect of the vessel wall, whereas in some instances circumferential calcified lesions totally precluded visibility of the arterial wall. Lesions consisting of loose collagen and fibrocellular tissue demonstrated low echo-intensity of the intima. Lesions consisting of densely packed fibrous connective tissue, or collagen-rich tissue, revealed a high echo-intensity on IVUS. Large deposits of lipid could be visualized as a hypoechoic area inside a lesion. Deposits of calcium gave typical echo-bright structure casting an acoustic shadow, with or without reverberations. The visibility of the media was intimately related to the nature and extent of a lesion.

It was striking to observe that the difference between soft and hard lesions as seen *in vitro* was maintained in the *in vivo* situation. Both soft and hard lesions were present within the same IVUS cross-section, possibly indicating the presence of a fibrocellular lesion with calcific deposits. Quantitative measurement of the media thickness seen *in vivo* proved that in the presence of a lesion the media decreased from median 0.6 mm in disease-free segment to as small as median 0.1 m in diseased segments.

The phenomenon of medial thinning, as evidenced by IVUS and confirmed by histology, is further explored in **Chapter 4**. The results of this study support the hypothesis that IVUS enables to evaluate the extent to which the media of a muscular artery is affected by atherosclerosis. Medial thinning was demonstrated on both histology and IVUS for 50% and 60%, respectively, when diseased segments were compared with disease-free wall segments in the same cross-section. Measurements on maximal lesion thickness and media thickness on IVUS correlated closely with those found with histology (r=0.83, p<0.00001). Similar observations were found in the clinical situation.

In **Chapter 5** the *in vitro* experience with IVUS is expanded to the clinical *in vivo* situation in patients undergoing vascular intervention. First, the feasibility of assessing vessel wall morphology, as well as the ability to accurately document plaque thickness, was determined *in vitro*. Based on the echogenicity of the arterial media, IVUS could distinguish muscular arteries from elastic arteries, veins, and bypass grafts. The hypoechoic media proved to be an essential landmark to assess superimposed atherosclerosis. The calculated plaque thickness in these arteries revealed a close relationship with the histologic counterpart. A low inter-observer variability between measurements by two observers was found. Second, the effects after balloon dilatation *in vivo* recognized using IVUS by on-line analysis included dissection, plaque rupture, arterial wall perforation and residual stenosis. Dissection occurred at the thinnest part of the lesion. Luminal area measurements obtained by off-line analysis showed a 5% difference between the systolic and diastolic images. Highly reproducible measurements were obtained in frame-to-frame analysis of the cross-sectional area.

The initial experience with IVUS obtained in patients with substantial peripheral arterial disease is presented in **Chapter 6**. Based on angiographic findings, the appreciation and localization of atherosclerotic plaques was confirmed by IVUS. All stages of atherosclerotic disease were encountered in the interrogated vessels according to the previously documented criteria for ultrasound identification of vessel wall characteristics. The importance of recognizing the hypoechoic media in assessing quantitative information about the amount of plaque in a cross-section, became evident. The IVUS imaging technique was useful in identifying dissection and plaque rupture following balloon angioplasty, while these features were sometimes obscured on angiography. The presence of thrombus could be recognized in the presence of a normal media beyond the thrombus. The technique appears to be useful in examining venous bypasses for intimal flaps, retained venous valves, torsion of the bypass or external compression, and anastomoses.

Chapter 7 explores the usefulness of IVUS in three patients who underwent a femoropopliteal vein bypass. In one patient a normal result was echographically assessed, whereas in the two other patients obstructions in the vein grafts were identified. In one patient an internal obstruction at the anastomosis site was involved, in the other patient an external compression of the venous bypass itself was evidenced. Angiography in these two patients provided dubious data. The conclusion is that IVUS may be a useful adjunct to angiography to facilitate surgeons to analyse the reconstruction procedure.

Chapter 8 describes the use of IVUS in documenting the mechanism of balloon angioplasty in the very first patient in our hospital. For the first time this new modality was introduced into the clinic in adjunct to angiography. This historical moment was considered important as a new "three-dimensional" insight was obtained of the pathology involved using IVUS, not obtainable by the standard technique of angiography.

The experience with the effects of balloon angioplasty on the femoral arteries seen with IVUS is further expanded in **Chapter 9.** In 16 consecutive patients, corresponding IVUS cross-sections (n=72) before and after balloon angioplasty were qualitatively and quantitatively analyzed. With IVUS, discrimination was possible between soft and hard lesions and eccentric and concentric lesions. Additional morphological information provided by IVUS included plaque rupture and internal elastic lamina rupture, not seen on angiography. Quantitative results implied that luminal enlargement by balloon dilatation was primarily achieved by overstretching the arterial wall, with lesion volume remaining practically unchanged. Overstretching was almost always accompanied by dissection and plaque rupture and, occasionally, by an internal elastic lamina rupture.

Chapter 10 describes the potential of IVUS in differentiating stenosis due to the presence of a residual plaque, and stenoses due to extrinsic compression of the femoral arterial wall near the adductor hiatus.

A qualitative and quantitative comparative study of IVUS versus angiography in patients undergoing vascular intervention is outlined in **Chapter 11**. A good correlation was found between angiography and IVUS for recognition of lesion topography. Using visual estimation for assessing the degree of stenosis on both angiography and IVUS, it was demonstrated that IVUS assessment of stenosis was in agreement before and after intervention in 78% and 72% of the cases, respectively. The severity of the lesions seen was more outspoken on IVUS than on angiography.

Semiquantitative on-line analysis of the percentage area stenosis corresponded well with off-line quantitative analysis performed using a computer-aided system. When both on-line echography and angiography suggested that the arteries were "normal", quantitative off-line IVUS revealed a mean 18% area stenosis.

Chapter 12 reports the feasibility of assessing lumen diameter and lumen area using

IVUS in phantoms and in patients. The change of lumen area in normal iliac arteries in a given cardiac cycle was determined. The mean change in lumen area measured with IVUS was 5% ± 2%. IVUS data were quantitatively compared with angiography using the cardiovascular angiographic analysis system (CAAS). A close correlation was found between IVUS and angiography for both phantom and patient studies (for patient studies: $r=0.962$, $p<0.00001$). Disagreement between both techniques was found in three patients; IVUS revealed larger values than those obtained from angiography due to the use of nominal measurements of the sheath supplied by the manufacturer as calibration of the CAAS system.

Quantitative IVUS study to measure the lumen area showed a low intra- and interobserver variability.

Chapter 13 discusses the influence of atherosclerosis on the distensibility (i.e. change in lumen area) of iliac and superficial femoral arteries in 28 patients determined with IVUS. Distensibility was related to lesion morphology, lesion geometry, percentage area stenosis, effect of balloon angioplasty, hypertension and patient's age. At normal sites, iliac arteries showed greater distensibility than femoral arteries (6.5 ± 2.4% vs 3.5 ± 0.9%; $p \leq 0.05$). Hard lesions in iliac arteries were less distensible than soft lesions; in femoral arteries this difference was less pronounced. Lesion geometry did not influence arterial distensibility. IVUS showed a significant decrease in femoral artery distensibility in the presence of a >90% stenosis. Comparison of cross-sections before and after balloon angioplasty revealed a marked increase in distensibility of iliac arteries following intervention; in femoral arteries, practically no change in distensibility was found. Hypertension and increasing age proved to have no significant influence on arterial distensibility. The conclusion is that IVUS is a reliable tool to assess arterial distensibility and the influence of atherosclerosis on vascular dynamics.

In summary, IVUS is the best method to determine the transmural composition of lesions and to assess the therapeutic effect of interventional devices, immediately following the procedure. The technique can provide valuable information for the vascular surgeons, interventional radiologists and cardiologists, not obtainable by the standard angiography. Our experiences with IVUS at the University Hospital Rotterdam-Dijkzigt undoubtedly showed a learning curve phenomenon. In the near future IVUS may become indispensable for improving the efficacy of current endovascular procedures by enhancing the appropriate choice of methods and improving the precision of recanalization.

CHAPTER 14

SAMENVATTING

Atherosclerose, ook wel bekend als "aderverkalking", is een veel voorkomende vaatziekte waarbij cellulaire veranderingen in de vaatwand leiden tot het ontstaan en groei van de atheromateuze plaque met ingroei in de tunica media. Hierdoor kan een signifikante reduktie van het vaatlumen ontstaan. Voor vasculaire chirurgen, interventie radiologen en cardiologen is het noodzakelijk om het effekt van een therapie korrekt in beeld te brengen en vast te stellen, ten einde een maximaal rendement van de interventie te bereiken. Angiografie is vooralsnog de standaardtechniek om de lokatie en de ernst van een stenose (vaatvernauwing) te bepalen. De techniek geeft echter onvoldoende inzicht in de vorm en de samenstelling van de atheromateuze plaque. Intravasculaire echografie (IVE) heeft de unieke mogelijkheid om in dwarsdoorsneden de vaatwand morfologie en de pathologie onder het endotheel oppervlakte te bestuderen. *In vitro* studies hebben aangetoond dat deze techniek een betrouwbare methode is om de vaatwand komponenten zowel kwalitatief als kwantitatief te beoordelen.

Het doel van de studies in dit proefschrift was de toepassing van IVE te evalueren, om de vaatwandpathologie in de perifere vaten vast te stellen zowel *in vitro* als *in vivo* voor en na vasculaire interventie.

Hoofdstuk 1 beschrijft de noodzaak van een beter diagnostisch instrument ten einde de vaatpathologie in kaart te brengen. Na een korte beschrijving van de geschiedenis van de IVE wordt het doel van dit proefschrift uiteengezet en samengevat.

Hoofdstuk 2 geeft een overzicht van de *in vitro* studies met IVE. Door histologie als gouden standaard te gebruiken, hebben *in vitro* studies bewezen dat IVE betrouwbare informatie kan geven omtrent de morfologie en topografie van de atherosclerotische lesie. Benadrukt wordt de belangrijke rol die deze beeldvormende techniek heeft om de tunica media te visualiseren voor het kwantificeren van de hoeveelheid plaque. De kennis, verkregen bij *in vitro* studies, kan vervolgens gebruikt worden bij de humane toepassing van de ultrageluidstechniek *in vivo*. Toekomstige implikaties van het gebruik van de techniek voor de kliniek worden besproken.

Hoofdstuk 3 behandelt het gebruik voor het karakteriseren en kwantificeren van de arteriewand en de atherosclerotische plaque zowel *in vitro* als *in vivo*. Uit *in vitro* studies bleek dat de arteriewand van het merendeel (76%) van de onderzochte musculeuze arteriën als een drie-lagig struktuur te zien was dankzij de echoarme verschijning van de tunica media. Fibreuze degeneratie van de media leidde tot een homogeen aspekt van de vaatwand, terwijl in sommige gevallen kalk-afzetting in de lesie de visualisatie van de media verhinderde. Atherosclerotische plaques bestaande uit los, collageen-arm weefsel en fibrocellulair weefsel gaven een lage echo-intensiteit van de intima. Dicht bijeengepakt fibreus bindweefsel, of collageen-rijk weefsel liet daarentegen een beeld zin met een hoge echo-intensiteit. Grote afzetting van vetcellen in een lesie werd met IVE als een echo-arme gebied binnen de lesie weergegeven. Kalk-afzettingen in de lesie vertoonden een typisch beeld van een zeer echo-rijke struktuur met daarachter een akoestische schaduw, die met of zonder reverberaties (herhalingsecho) konden voorkomen. Het zichtbaar zijn van de media was afhankelijk van de lesie samenstelling en van de uitgebreidheid van lesie. Het onderscheid dat bij *in vitro* werd gemaakt tussen zgn. "zachte" en "harde" lesie, bleek ook toepasbaar te zijn voor de *in vivo* situatie. Binnen één echografische dwarsdoorsnede kon zowel een zachte als een harde lesie aanwezig zijn door de aanwezigheid van zowel fibrocellulaire lesie als kalk. Kwantitatitieve metingen lieten zien dat de media in dikte afnam, van mediaan 0.6 mm zonder lesie tot mediaan 0.1 mm wanneer een lesie aanwezig was.

Het fenomeen van de 'media verdunning', gezien met IVE en histologisch bevestigd, wordt verder uiteengezet in **Hoofdstuk 4**. De resultaten van deze studie ondersteunden de hypothese dat het mogelijk is om met IVE de aantasting van de media door atherosclerose te evalueren. Bij vergelijking van de zieke vaatsegmenten met de niet-zieke vaatsegmenten binnen één en dezelfde dwarsdoorsnede was media verdunning zowel met histologisch onderzoek als met IVE zichtbaar (respektievelijk 50% en 60%). De metingen van de maximale lesiedikte en de mediadikte met IVE gaven in beide gevallen een goede korrelatie met de histologische bevindingen ($r=0.83$, $p<0.00001$). Media verdunning was ook waar te nemen bij de klinisch verkregen ultrageluidsbeelden.

In **Hoofdstuk 5** wordt beschreven hoe de *in vitro* opgedane kennis met IVE verder werd toegepast *in vivo* bij patiënten die een vasculaire interventie hadden ondergaan. Ten eerste, werd *in vitro* de uitvoerbaarheid bepaald om de vaatwandmorfologie in kaart te brengen en de plaquedikte te documenteren. Uitgaand van de mate van echodensiteit van de arteriële media, kon met IVE een onderscheid gemaakt worden tussen musculeuze arteriën, aan de ene kant, en elastische arteriën, venen, veneuze bypass en prothesen, aan de andere kant. De echo-arme media bleek een essentiële markering te zijn om de mate van atherosclerose nauwkeurig te kunnen bepalen. De plaquedikte gemeten in deze arteriën liet een goede korrelatie zien met de histologische metingen. Tussen twee waarnemers werd een lage inter-observer variabiliteit gevonden. Ten tweede, bleek dat IVE diverse effekten van een Dotter procedure kon documenteren, zoals de aanwezigheid van dissecties, plaque scheuren, vaatwand ruptuur en een rest-stenose. Dissecties vonden plaats op de dunste plekken van een lesie. Lumen oppervlakte metingen, die off-line werd verricht, lieten een verschil van 5% zien tussen systolische en diastolische beelden. Met beeld-voor-beeld analyse konden bovendien zeer reproduceerbare metingen van de oppervlakten worden verricht.

Onze eerste klinische ervaringen met IVE bij patiënten met perifeer vaatlijden wordt in **Hoofdstuk 6** gepresenteerd. Naar aanleiding van angiografische bevindingen kon met IVE de atherosclerotische plaques gemakkelijk worden herkend en gelokaliseerd. Uitgaande van eerder gedocumenteerde criteria voor echografische eigenschappen van de vaatwand, werden in de onderzochte vaten alle stadia van atherosclerose vastgesteld. Daarbij werd onderkend hoe belangrijk het is om de echo-arme media te kunnen zien ten einde de hoeveelheid plaque te kunnen bepalen. Na ballon dilatatie kon IVE dissecties en plaque rupturen detekteren die soms op angiografie nauwelijks te zien zijn. De aanwezigheid van een trombus kon herkend worden wanneer een normale media achter de trombus aanwezig was. Ook kan met IVE veneuze bypasses onderzocht worden op de aanwezigheid van intimale flappen, intakte veneuze kleppen na veneuze klepstripping, torsie van de bypass prothese of externe kompressie en de doorgankelijkheid van de anastomosen.

Hoofdstuk 7 gaat in op het gebruik van IVE bij de evaluatie van de femoropopliteale veneuze bypass bij 3 patiënten. Een normale bypass werd bij één patiënt echografisch vastgesteld, terwijl in de twee andere patiënten een obstruktie in de veneuze bypass werd gekonstateerd; deze obstruktie was bij één patiënt veroorzaakt door een intrinsieke obstructie, bij de ander patiënt door een extrinsieke kompressie. Angiografie liet in beide gevallen dubieuze resultaten zien. De konklusie is dat IVE naast de angiografie nuttig kan zijn om de chirurgen te helpen om het resultaat van een interventie te analyseren.

Hoofdstuk 8 belicht het eerste klinisch gebruik van IVE bij een patiënt om het mechanisme van de ballon dilatatie te documenteren. Voor het eerst werd in onze kliniek een nieuwe techniek naast de angiografie geïntroduceerd. Dit historisch moment was belangrijk voor ons, met IVE werd een nieuw "drie-dimensionaal" inzicht van de betreffende pathologie verkregen, die niet met de standaard techniek als angiografie waarneembaar was.

De ervaring met IVE om het effekt van de Dotter procedure in de femoraal arterie te zien, wordt verder uitgewerkt in **Hoofdstuk 9**. In 16 opeenvolgende patiënten werden korresponderende echografische cross-secties (n=72) voor en na de behandeling met elkaar vergeleken en kwalitatief als kwantitatief geanalyseerd. Het was mogelijk om met IVE onderscheid te maken tussen zachte en harde lesies, even als het onderscheid tussen excentrische en concentrische lesies. Additionele morfologische informatie die IVE kon verschaffen, was de aanwezigheid van plaque rupturen en scheuren in de lamina elastica interna. Kwantitatieve resultaten lieten zien dat het Dotteren voornamelijk een oprekking van de vaatwand veroorzaakte, waarbij het volume van de lesie praktisch onveranderd bleef. De oprekking ging bijna altijd gepaard met het optreden van dissecties en plaque rupturen, en soms met een ruptuur van de lamina elastica interna.

Hoofdstuk 10 beschrijft de mogelijkheid van IVE om te differentiëren tussen een stenose als gevolg van de aanwezigheid van een plaque residu en een stenose als gevolg van een extrinsieke kompressie op de vaatwand bij het adductoren kanaal.

Een studie waarbij IVE, zowel kwalitatief als kwantitatief, met angiografie wordt vergeleken, bij patiënten die vaatbehandeling hebben ondergaan, is uiteengezet in

Hoofdstuk 11. Er werd een goede korrelatie gevonden tussen angiografie en IVE voor het herkennen van de topografie van de lesie. Gebruikmakend van de visuele schatting van het percentage stenose bij zowel angiografie als IVE, bleek dat bij IVE de visuele schatting van de stenosen overeenkomst vertoonde met angiografie zowel voor als na de behandeling in respektievelijk, 78% en 72% van de gevallen. De ernst van de lesies werd met IVE duidelijker zichtbaar dan met angiografie gezien.

Semikwantitatieve on-line analyse van de mate van stenosering korrespondeerde goed met de kwantitatieve analyse die off-line werd verricht, met het gebruik van een computer analyse programma. Wanneer zowel on-line IVE als angiografie "normale" arteriën beoordeelden, werd met kwantitatieve off-line IVE een oppervlakte stenose gemeten van gemiddeld 18%.

Hoofdstuk 12 rapporteert over de uitvoerbaarheid om IVE te gebruiken bij het bepalen van het lumen diameter en lumen oppervlakte in fantomen en bij patiënten. De lumen oppervlakte verandering in normale iliacale arteriën werd gedurende een hartcyclus bepaald. De gemiddelde lumen oppervlakte verandering gemeten met IVE, bedroeg 5% $\pm$ 2%. Kwantitatieve IVE gegevens werden vergeleken met kwantitatieve angiografische gegevens, verkregen met behulp van het cardiovasculaire angiografische analyse systeem (CAAS). Er werd een goede korrelatie gevonden tussen IVE en angiografie zowel bij de metingen in de fantomen als bij de patiënten ($r=0.962$, $p<0.00001$). In 3 patiënten werd er een verschil tussen de beide technieken gevonden; IVE liet grotere waarden zien dan angiografie. Het is mogelijk dat dit het gevolg is van het gebruik van de nominale waarden van de introduktie catheter bij de calibratie van het CAAS systeem.

Kwantitatieve IVE studie betreffende het meten van het lumen oppervlakte in de iliacaal arterie liet een lage intra- en interobserver variabiliteit zien.

Hoofdstuk 13 bespreekt de invloed van atherosclerose op de distensibiliteit (d.i. de lumen oppervlakte verandering) van de iliacaal en femoraal arteriën in 28 patiënten, bepaald met IVE. Distensibiliteit werd gerelateerd aan de lesie morfologie, de lesie geometrie, het percentage oppervlakte stenose, het effekt van ballon dilatatie, hoge bloeddruk en aan de leeftijd van de patiënt. Wanneer normale segmenten met elkaar werden vergeleken, lieten de iliacale arteriën een grotere distensibiliteit zien dan de femorale arteriën (6.5 $\pm$ 2.4% versus 3.5 $\pm$ 0.9%; $p\leq 0.05$). Harde lesies in iliacaal arteriën hadden een lagere distensibiliteit dan zachte lesies; in de femoraal arteriën was dit onderscheid minder opvallend. Lesie geometrie had geen invloed op de arteriële distensibiliteit. IVE liet bij de aanwezigheid van een >90% stenose in de femoraal arterie een signifikant afname van de distensibiliteit zien. Bij vergelijking van de cross-secties voor en na de Dotter procedure, was er een toename in distensibiliteit waar te nemen na de interventie bij de iliacaal arteriën; in de femoraal arteriën werd er praktisch geen verandering waar te nemen. Hoge bloeddruk en toenemende leeftijd bleken geen signifikante invloed te hebben op de arteriële distensibiliteit. De konklusie is dat IVE mogelijk een betrouwbaar instrument is om de arteriële distensibiliteit en de invloed die atherosclerose heeft op de vasculaire dynamiek, te kunnen bepalen.

Samenvattend, IVE is de beste techniek om de samenstelling van de techniek van de lesie vast te stellen en om het therapeutische effekt van de interventies direkt na de procedure te bepalen. De techniek kan waardevolle inforamtie verschaffen aan de vasculaire chirurgen, de interventie radiologen en de cardiologen, die niet met de standaard angiografie kan worden verkregen. Onze ervaring met IVE in het Academisch Ziekenhuis Rotterdam-Dijkzigt laat ongetwijfeld een leercurve fenomeen zien. In de toekomst zal blijken dat IVE onontbeerlijk is om het rendement van de huidige endovasculaire procedures te verbeteren door een betere keuze van de interventie methode te maken en de precisie van de rekanalisatie te vergroten.

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Salem Hong Kie The

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CURRICULUM VITAE

Salem Hong Kie The werd geboren op 28 februari 1960 in Jakarta, Indonesië. Het lager onderwijs werd deels in Indonesië, deels in Italië en deels in Nederland gevolgd. Het eindexamen Atheneum-B werd in 1979 behaald aan het Develstein College te Zwijndrecht.

Na te zijn uitgeloot voor studie Geneeskunde in hetzelfde jaar, is hij begonnen met de studie Farmacie aan de Rijksuniversiteit te Leiden. Na zijn propadeuse Farmacie werd de studie Geneeskunde in 1981 begonnen aan de Erasmus Universiteit te Rotterdam. Hij behaalde het doctoraal examen in 1988 en het artsexamen in 1990. Gedurende zijn studie (1985-1990) heeft hij gewerkt als student-assistent op de afdeling Experimentele Echocardiografie van het Thoraxcentrum (hoofd: Prof.Dr.Ir. N. Bom) onder leiding van Dr. E.J. Gussenhoven aan de projekten echocardiografie bij congenitale hartafwijkingen (ICIN 5) en transoesofagale- en intraoperatieve echocardiografie (ICIN 8).

Vanaf oktober 1990 is hij als wetenschappelijk onderzoeker in dienst van het Interuniversitair Cardiologisch Instituut Nederland. Hij neemt deel aan de projekten intravasculaire echografie (ICIN 12) en EPISODE (Evaluation Peripheral Intravascular Sonography On Dotter Effect) (ICIN 16). Een en ander heeft geleid tot diverse publikaties met betrekking tot de intravasculaire echografie in de perifere vaten. In deze periode werd ook de basis gelegd voor dit proefschrift.

De auteur is getrouwd met Karin Versteeg, lerares basisonderwijs, en zij hebben twee prachtige kinderen.

CURRICULUM VITAE

Salem Hong Kie The was born on February 28, 1960 in Jakarta, Indonesia. Primary schooling was partly followed in Indonesia, Italy and finally in the Netherlands. He graduated high school (Atheneum-B) at the Develstein College in Zwijndrecht in 1979.

In the same year he started Pharmacy studies at the State University of Leiden after unsuccessful application, due to the limited entry system (numerus fixus), to study Medicine. After passing the propaedeutic examination of Pharmacy, his Medicine studies began in 1981 at the Erasmus University Rotterdam. He graduated for the Master's degree in 1988 and passed the final examination of Medicine in 1990. During his studies (1985-1990) he has worked as a student-assistant at the Department of Experimental Echocardiography of the Thoraxcenter (head: Prof. Dr. Ir. N. Bom) under the supervision of Dr. E.J. Gussenhoven on the project Echocardiography in Congenital Heart Diseases (ICIN 5) and the project Transoesophageal and Intraoperative Echocardiography (ICIN 8).

Since October 1990 he is employed by the Interuniversity Cardiology Institute of the Netherlands as a research scientist. He participated in the project Intravascular Ultrasound (ICIN 12) and the project EPISODE (Evaluation Peripheral Intravascular Sonography On Dotter Effect) (ICIN 16). During this period several publications on the topic Intravascular Ultrasound in Peripheral Vessels have followed, which form the basis of this thesis.

The author is married with Karin Versteeg, primary school teacher, and they have two beautiful children.