INTRAVASCULAR ULTRASOUND:
VALIDATION AND CLINICAL APPLICATION

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Cover illustrations: intravascular ultrasound cross-section obtained in vitro after balloon angioplasty and the histologic counterpart. A dissection is seen at the thinnest region of the plaque. + = catheter; calibration = 1 mm.

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INTRAVASCULAR ULTRASOUND: VALIDATION AND CLINICAL APPLICATION

INTRAVASCULAIRE ECHOGRAFIE: TOETSING EN KLINISCHE TOEPASSING

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ICIN

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voor KJN

Auch der Artz - zumindest der von der modernen naturwissenschaftlichen Medicin geprägte - übt eine Tätigkeit polemischen Typs aus; was in der positiven Sehweise als "Heilkunde" praktiziert wird, erscheint in pragmatischer Perspectieve als *Bekämpfung* der Krankheiten. Heilen (Ganzmachen) und Bekämpfen sind zwei Aspekte derselben Sache. Während aber für den Voyeur der nackte Körper das gesuchte Bild ist, geht der Artz heute vom nackten Körper aus, um in dessen Innern die Gefahrenquellen aufzudecken. Die Analogien zwischen der modernen medischinischen Diagnostik und den Machenschaften der Geheimdienste spring (bis in sprachlichen Details) grell ins Auge; der Artz betreibt gewissermaßen somatischen Spionage. Der Körper ist der Geheimnisträger, der so lange beschattet wird, bis über seine innern Umstände so viel bekannt ist, daß "Maßnahmen" getroffen werden können. Wie in der Geheimdiplomatie und der Spionage wird auch in der Medizin viel "sondiert", adgehorcht und beobachtet. In die Körper werden medizinische Hilfsgeräte wie Agenten "eingeschleust", Sonden, Kameras, Verbindungsstücke, Katheter, Lampen, und Leitungen.

Peter Slotendijk, Kritik der zynischen Vernunft, Suhrkamp Verlag Frankfurt am Main 1983: 627-628.

CONTENTS

CHAPTER 1

INTRODUCTION

Atherogenesis is a process with an insidious onset and course. Once clinical signs and symptoms have become manifest, the obstructive lesion is usually at an advanced stage. Arteriography is the standard method for evaluation of atherosclerotic disease and has been useful in identifying the location and approximate severity of the stenotic lesion. Although arteriography provides a silhouette of the vessel lumen, it does not provide accurate knowledge on cross-sectional lumen area, vessel area, shape and morphology of the stenotic lesion. Intravascular ultrasound (IVUS) may overcome these limitations by providing a tomographic image of the vessel.

The aim of this work is to validate IVUS and to evaluate subsequent clinical application of this imaging technique. The subjects dealt with in this dissertation are categorised into 5 main topics.

1) displacement sensing device;
2) validation of IVUS-derived parameters;
3) the spectrum of vascular morphology before and after intervention determined by IVUS;
4) IVUS as a research tool;
5) IVUS as a clinical tool.

Displacement sensing device

IVUS depicts a two-dimensional tomographic image of a vessel. During pull-back of the ultrasound catheter a sequence of cross-sectional images of a vessel segment is obtained. However, this technique does not provide information on the exact location of the obtained images, nor the distance between consecutive images (spatial orientation). Continuous fluoroscopy may solve this problem, but is imprecise and requires additional exposure to radiation. To overcome this limitation a displacement sensing device has been developed, which allows on-line documentation of the location of the cathetertip. The accuracy of this system was tested (chapter 2) and the advantage of this device, used during in-vitro studies, was demonstrated (chapters 3 and 4).

Validation of IVUS-derived parameters

The accuracy of IVUS to document vascular damage after balloon angioplasty was assessed in an in-vitro study on coronary arteries using histologic sections as gold standard (chapter 3). After histologic validation, IVUS was compared with current standard angiography to define its additional value (chapter 6).

Besides accuracy, the observer reproducibility is an important indicator for the reliability of this diagnostic technique. The observer reproducibility of both qualitative and quantitative parameters determined with IVUS was assessed in coronary (chapter 3) and femoropopliteal arteries (chapter 5).

Spectrum of vascular morphology before and after intervention determined by IVUS

The spectrum of arterial responses to balloon angioplasty both in-vitro in coronary arteries (chapter 5) and clinically in femoropopliteal arteries (chapter 7) was documented with IVUS. Pull-back of an IVUS catheter, which provides a sequence of consecutive slices throughout the vessel, demonstrated that these responses differ throughout the treated artery. Therefore the question was addressed whether the effects of balloon angioplasty at the most stenotic site were representative of the outcome (chapters 3 and 7).

In addition, IVUS was used during peripheral venous bypass surgery to investigate whether this technique is able to document qualitative and quantitative parameters of veins and to detect potential causes for bypass failure (chapter 10).

IVUS as research tool: mechanism of balloon angioplasty

With the use of IVUS some old questions could be answered in a new way. The underlying mechanism of balloon angioplasty had been studied using animal models, human cadaver arteries, and human arteries subjected to balloon angioplasty during life and subsequently studied histologically at autopsy. IVUS enables to study these mechanisms *during* life by imaging the treated arterial segment before and after intervention. The following questions were studied.

1) What is the relation between lesion morphology and topography and the location and presence of dissection seen after balloon angioplasty (chapter 4)? Angiographic studies showing that dissections were related to adverse outcome formed the background to this study. Prediction of the occurrence and location of dissection based on lesion characteristics assessed before intervention might be helpful in preventing an adverse outcome.

2) Is vessel stretch or plaque compression the predominant mechanism of balloon angioplasty? This question was addressed both in an in-vitro (chapter 3) and in an in-vivo study (chapter 7).

3) What is the influence of balloon size on the incidence and extent of vascular damage, and on the quantitative mechanism of balloon angioplasty (chapter 7)?

Besides investigating the mechanism of balloon angioplasty in arteries, IVUS can also be used to study this mechanism in venous bypass graft stenosis. The role of this technique to assess the relation between the pre-existent status of the vein and the development of stenoses, as well as the effect of balloon angioplasty, is described (chapter 11).

Clinical value of IVUS

Until recently interventional procedures have been based on angiographic findings alone. The clinical value of IVUS was investigated in a multicenter study which attempted to identify IVUS parameters related to the outcome of balloon angioplasty of the femoropopliteal artery. The interim and the final results of this study are presented (chapters 8 and 9).

CHAPTER 2

DISPLACEMENT SENSING DEVICE ENABLING ACCURATE DOCUMENTATION OF CATHETER TIP POSITION

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ABSTRACT

The need for reproducible positioning of an intravascular ultrasound catheter tip before and after intervention in relation to the angiographic records, resulted in the development of a dedicated displacement sensing device that provides instantaneous information about the catheter tip position on the videoscreen. The relative distance information can be displayed together with the ultrasound image. The accuracy of this device was tested in vitro.

Intravascular ultrasound images were recorded in 16 pressurized arterial specimens (8 iliac and 8 coronaries) affected by atherosclerosis. From each specimen the free lumen area from 3 pull-back series was determined over a mean distance of 1.85 cm with increments of 0.05 cm. A total of 1,895 cross-sections were analyzed. The variations in free lumen area were very small: 1.7% in iliac and 3.0% in coronary arteries. The cross-correlation in 15 arteries showed no position mismatching. In only one pull-back obtained in a coronary artery was a position shift of 0.05 cm seen.

In conclusion, the displacement sensing device provides accurate reproducible images. Further application of this device in vitro and in vivo in humans before and after balloon angioplasty has shown that the device is a unique tool to accurately compare intravascular ultrasound images before and after intervention and to compare these images with its histologic or angiographic counterpart.

INTRODUCTION

Intravascular ultrasound is a promising technique to document vascular morphology in conjunction with vascular intervention. Currently, comparison of the intravascular ultrasound images obtained before and after intervention is done using a radiopaque ruler or marker as reference [1-4]. The same procedure allows comparison of the ultrasound images with their angiographic counterpart [4-6].

In practice, after introduction of the ultrasound catheter via the sheath, a series of ultrasound cross-sections are recorded under fluoroscopic guidance. The location of the catheter is systematically compared with the ruler and is manually typed via a keyboard on to the videoscreen. This procedure should be performed in the same way following intervention; such a protocol will provide the investigator with an accurate and reliable comparison.

As this procedure is time-consuming and requires additional fluoroscopy, we developed a displacement sensing device that provides instantaneous information of the catheter tip position on a videoscreen. For clinical use the device can simply be attached to the regular introducer sheath. The reproducibility of this device to image the same location has been tested in vitro using vascular specimens affected by atherosclerosis.

METHODS

Displacement device

The displacement sensing device (7 cm x 3 cm x 3 cm; patent application number: PCT-NL92-00072) consists of 2 parts: a sensing unit through which the catheter is pushed or pulled and a registration part which converts the linear movement into an electronic signal (Figure 1). In the sensing unit, a disk with 4 permanent magnets placed equidistantly at its circumference, is mounted on the displacement sensing roller shaft. Each time a catheter is advanced or retracted between the displacement sensing roller and an idler roller, the disk with the magnets will rotate.

The registration part comprises a two-channel optical incremental encoder module and a disk with permanent magnets (identical to the disk in the sensor unit) mounted on the same shaft. The 2 disks with permanent magnets form a tight magnetic coupler of the displacement sensing roller and the optical encoder disk. Rotation of the displacement sensing roller causes identical rotation of the optical encoder disk. The registration part is connected to an electronic box which converts the electronic signal, provided by the optical incremental encoder module, into a video signal that can be displayed on a videoscreen (Figure 2). This signal, which indicates the displacement of the catheter in steps of 0.01 cm, is mixed together with the ultrasound information. The measurement values range from -99.99 to +99.99 cm. The electronic box has the possibility to reset and preset the position values.

Human specimens

Eight coronary and 8 iliac arteries removed at autopsy from humans were used. The arterial specimens, approximately 6 cm long, were stored frozen (-20°C). For in vitro studies, the specimens were thawed, side-branches were tied-off with sutures and the proximal and distal ends were connected to a sheath fixed into a water-bath at room temperature. A reference segment was indicated distally using a needle at the 12 o'clock position. Via the side-arm of the sheath the arteries were filled with saline solution. During the study, the pressure was kept at 100 mmHg and controlled via a syringomanometer connected to the infusate.

The ultrasound catheter is advanced through the sensing unit via the sheath distally into the artery. When the catheter reaches the level of the needle, the displacement device is set to zero. The needle present at the 12 o'clock position in the artery is set to the 12 o'clock position on the ultrasound image (Figure 2).

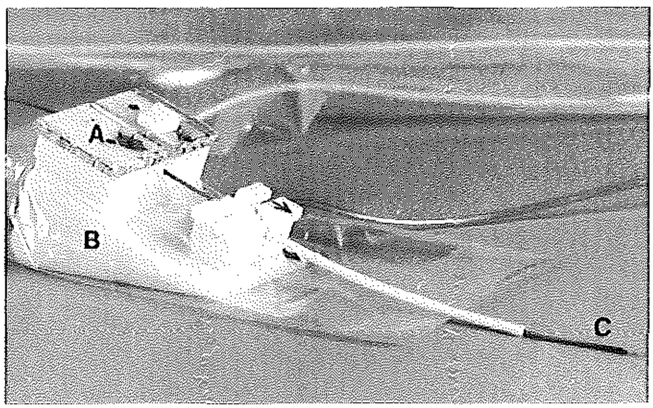

Figure 1. Displacement sensing device showing the sensing unit (A) and the registration part (B). The ultrasound catheter (C) is advanced via the sensing unit and the sheath.

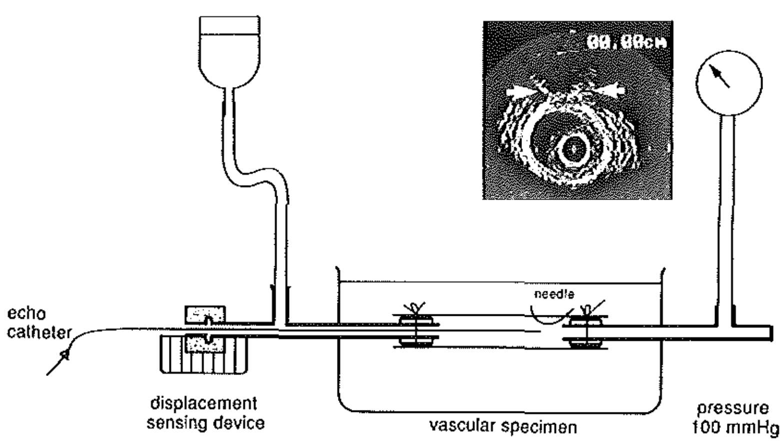

Figure 2. In vitro set-up showing the ultrasound catheter advanced via the sensing unit and the sheath towards the vascular specimen. The needle on the artery is seen at 12 o'clock in the ultrasound cross-section (arrows). The catheter tip position in relation to the needle (00.00 cm) is indicated in the right upper corner of the ultrasound image. Calibration 1 mm.

A series of ultrasound images are then obtained by manual pull-back of the catheter. The speed used varies depending on the time required to optimize the time gain. The sensing device automatically indicates on the videoscreen the position of the catheter tip in relation to the reference needle (Figure 3). When the proximal sheath becomes visible on ultrasound the catheter is taken out the sheath and reintroduced again into the sheath and advanced distally to the reference needle for the second and third pull-back.

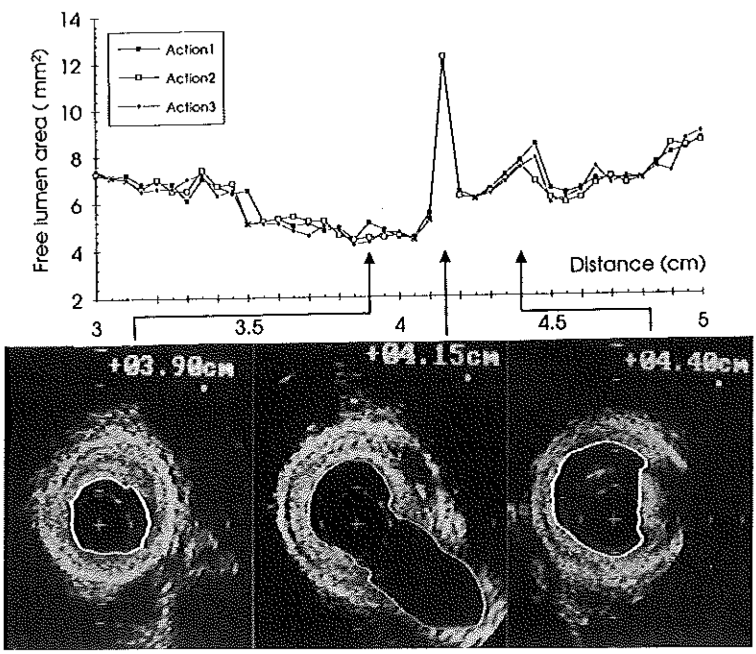

Figure 3. Graph showing the reproducible variation in free lumen area in a coronary artery as assessed by intravascular ultrasound. Calculations (expressed in mm^2) were made at 0.05 cm increments over a distance of 2 cm. The ultrasound cross-sections corresponding to the arrows in the graph exemplify the changes in free lumen area. The catheter tip position in relation to the needle is indicated in the right upper corner of the ultrasound images. Calibration 1 mm.

Intravascular ultrasound

A mechanical 30 MHz imaging system designed for clinical use was employed (Du-MED, Rotterdam, The Netherlands) [3]. The transducer is mounted on a blunt-tipped 5F catheter which rotates up to 16 images per second. The axial resolution of the system is 80 μm. Lateral resolution is better than 225 μm at a depth of 1 mm. The resulting images are displayed on a monitor by means of a video-scanned memory and stored on a VHS system.

Analysis of data

For analysis a digital video analyzer system was used, as described previously [7,8]. Briefly, the analysis system was developed on an IBM PC/AT (IBM Corp. Boca Raton, USA) equipped with a framegrabber and a PC mouse device. Each selected ultrasound cross-section reproduced on the analyzer videoscreen was contour traced for free lumen area. Free lumen area (in mm^2) was defined as the area encompassed by the inner boundary of the intimal surface.

The reproducibility of the displacement sensing device was determined by calculating the free lumen areas from the 3 pull-back series over a distance of maximally 2 cm with increments of 0.05 cm, yielding a total of 41 analyses per pull-back. Care was taken to select a region of the artery showing clear changes in free lumen area either due the presence of atherosclerosis or as a result of a side-branch. When extensive dropout was involved (side-branch) the images were excluded from quantitative analysis. In those instances where partial dropout of echoes of the luminal contour were noted, the contours were identified by means of continuity from adjacent sections [4].

Statistics

The data are presented as mean value $\pm$ standard deviation in mm^2. Measurement repeatability was assessed by analysis of data variance in the 3 pull-backs. The degree of the measurement variability was indicated by the coefficient of the variations defined as: standard deviation/mean value of the measurements. Intra-observer variability was tested by repeating the measurements in the 3 pull-back series in one of the experiments. Observer variations were analyzed using the variance method and are also presented as variation coefficient. Cross-correlation analysis was applied to determine a possible shifting of the catheter position between the pull-backs. A non zero lag of the maximum value in the cross-correlation function was used to indicate the position mismatching of the 2 data series.

RESULTS

From all 16 vascular specimens high quality intravascular images were obtained. The free lumen area imaged by intravascular ultrasound varied in size depending on the degree of atherosclerosis or the presence of side-branches (Figure 3). From each specimen the free lumen area from 3 pull-back series was determined over a mean distance of 1.85 cm

(Figure 3). A total of 1,895 cross-sections were analyzed. Seventy-three ultrasound images (3.7%) were excluded for quantitative analysis due to the extensive dropout of echoes.

The means of the 3 pull-backs in the iliac arteries were 49.1 ± 23.3 mm^2, 49.3 ± 23.1 mm^2 and 49.4 ± 23.0 mm^2, respectively. Measurement variations were 1.7%. The means of the 3 pull-backs in the coronary arteries were 8.35 ± 3.4 mm^2, 8.35 ± 3.4 mm^2 and 8.36 ± 3.4 mm^2, respectively. Measurement variations were 3.0%. The intra-observer variation test showed the variations of the 2 measurements to be 1.2%.

The cross-correlation showed that only one pull-back in the coronary artery had a position shift of 0.05 cm; no other mismatching was found in the remaining data. The mismatch was likely caused by a 0.05 cm movement of the sheath (to which the vessel is connected) during the 2 studies.

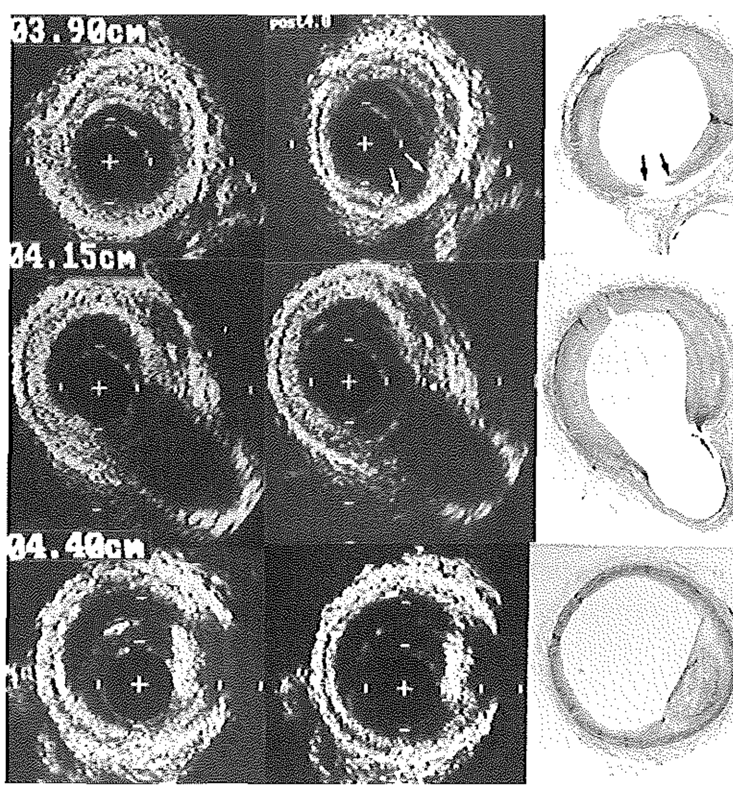

Figure 4. Corresponding intravascular ultrasound cross-sections obtained prior to and following balloon angioplasty (4 mm) and the histologic counterpart. The displacement sensing device indicated the levels (03.90 cm up to 04.40 cm). The presence of a plaque rupture and media rupture is indicated by the arrows. Calibration 1 mm.

DISCUSSION

Currently, intravascular ultrasound imaging systems provide unique tomographic details but restricted axial data. Using the radiopaque ruler ultrasound images can be compared to the corresponding angiograms, both before and after vascular intervention. For accurate comparison, the location of the ultrasound catheter tip must be manually indicated at any site of interest. This procedure is time consuming and requires additional fluoroscopy. Therefore we developed a device capable to provide the information instantaneously.

This in vitro study indicates that the displacement sensing device provides accurate reproducible images. Measurement variations were very small in both iliac and coronary arteries (1.7% and 3.0%, respectively). These variations may be related to the variations in the images and to the intra-observer variation (1.2%).

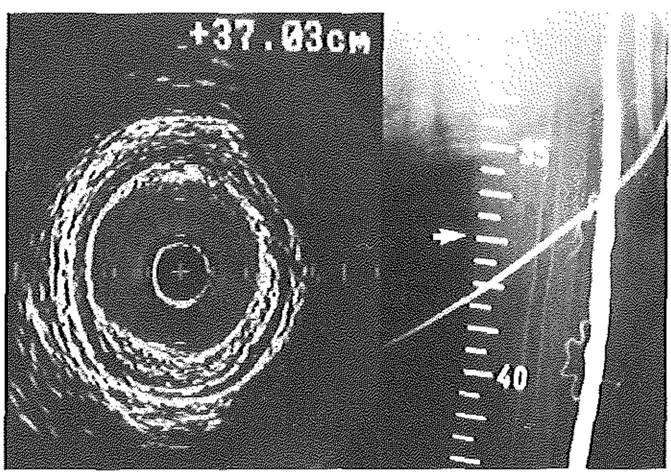

Figure 5. Intravascular ultrasound cross-section and angiogram obtained clinically.The position of the ultrasound catheter at 37.03 cm is indicated on-line by the displacement sensing device. The accuracy of this information was verified by identification of sidebranches seen with angiography and ultrasound. Calibration 1 mm.

The advantage of the displacement sensing device is the possibility to manually move the catheter forward and backward without losing the accurate on-line data of the catheter tip position on the videoscreen. The device provides instantaneous axial information about lesion length and morphology. Ongoing studies using the device in vitro have shown its unique ability to accurately compare ultrasound images prior to and following intervention with its histologic counterpart (Figure 4). Furthermore, by advancing the catheter via this device, externally connected to the sheath, into the coronary or femoral artery, reproducible images could be obtained in the clinical setting. Assessment of the location of the lesion, a dissection or stent implantation thus became feasible. Moreover, instantaneous information on the position of the catheter tip in relation to the angiographic records became available (Figure 5). This implies that the amount of time required for fluoroscopy and documentation of the required intravascular data will be shortened. Another advantage is that, by connecting the device to a computer, a sequence of echo slices can be obtained for on-line three-dimensional reconstruction. Current efforts are aimed at devising a sterilization method for the prototype device, to enable its use on a more regular basis in humans.

We believe that this device, used in the clinical setting in humans, may be a unique tool to accurately compare intravascular ultrasound images before and after intervention (using the radiopaque ruler as reference) and to compare these images with angiographic data.

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CHAPTER 3

COMPARISON OF INTRAVASCULAR ULTRASONIC FINDINGS AFTER CORONARY BALLOON ANGIOPLASTY EVALUATED IN VITRO WITH HISTOLOGY

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Comparison of Intravascular Ultrasonic Findings After Coronary Balloon Angioplasty Evaluated In Vitro With Histology

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This study investigated whether vascular damage and quantitative changes observed with intravascular ultrasound at the most stenotic site are representative of the ultimate outcome after coronary balloon angioplasty. Atherosclerotic coronary arteries (n = 40) were studied in vitro with intravascular ultrasound. From each vascular specimen, 10 corresponding intravascular ultrasound cross sections obtained before and after balloon angioplasty were selected for comparison with their histologic counterpart. Morphologic and quantitative data obtained from all cross sections were compared with data derived from the most stenotic site. The incidence of vascular damage (i.e., dissection, plaque rupture, and media rupture) at the most stenotic site was lower than that seen for each vascular specimen. The sensitivity of intravascular ultrasound in detecting these morphologic features for each vascular specimen was high for dissection and media rupture (79% and 76%, respectively), and low for plaque rupture (37%). After balloon angioplasty, quantitative changes seen at the most stenotic site were greater than those in all cross sections: free lumen area +58% versus +29%, media-bound area +17% versus +12%, and plaque area reduction −9% versus −6%, respectively. The increase in free lumen area was caused predominantly by media-bound area increase (81%) and to a lesser extent by plaque area decrease (19%). This study revealed that a higher incidence of vascular damage is found when the whole segment is analyzed rather than 1 single cross section at the most stenotic site. Quantitative effects of coronary balloon angioplasty seen with intravascular ultrasound were greater at the most stenotic site than at all cross sections.

(Am J Cardiol 1995;76:661–666)

With the introduction of intravascular ultrasound, a unique tool became available that provides morphologic and quantitative data of the diseased arterial wall before and after intervention.[1–15] To date, no systematic validation studies have been undertaken to establish whether intravascular ultrasound is a reliable technique for documenting vascular damage and quantitative effects after coronary balloon angioplasty. The aims of this in vitro study were: (1) to document the incidence and sensitivity of the vascular damage observed with intravascular ultrasound after coronary balloon angioplasty; (2) to assess the quantitative effects of balloon angioplasty; and (3) to investigate whether 1 single ultrasound cross section obtained at the most stenotic site (i.e., smallest free lumen area) is representative of the outcome rather than a sequence of cross sections.

METHODS

Human specimens: Coronary arteries with atherosclerosis (n = 40) were removed from humans at autopsy (n = 21) or from explanted hearts that became available from patients referred for cardiac transplantation (n = 19) (median age 51 years, range 38 to 76). The specimens were stored frozen at −20°C. The investigation was approved by the local committee on human research.

For in vitro studies, the specimens were thawed, sidebranches were tied off with sutures, and the proximal and distal ends were connected to sheaths fixed to a waterbath at room temperature. Distally, a reference segment was indicated using a needle at the 12 o'clock position (Figure 1). During the study, the arteries were pressurized at 100 mm Hg by means of a fluid reservoir containing water connected to the side-arm of the proximal sheath.

For this study, coronary arteries with ≥40% area stenosis at the most stenotic site, as seen by intravascular ultrasound, were subjected to balloon angioplasty. The largest free lumen diameter seen in the segment by intravascular ultrasound was used as a reference for the balloon diameter (Speedy, Schneider AG, Zurich, Switzerland). Balloon angioplasty was performed for 2 minutes with a manometer-controlled pressure of 8 to 10 atm. Intervention was judged successful if the lumen area at the most stenotic site seen on ultrasound increased; otherwise, a larger balloon was used.

Intravascular ultrasound: A mechanical 30 MHz imaging system designed for clinical use was used (DuMED, Rotterdam, The Netherlands). For comparison of intravascular ultrasound images before balloon angioplasty with the same segment after intervention, a displacement sensing device was used.[16] Displacement of

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TABLE I Incidence of Vascular Damage Including Dissection, Plaque Rupture, and Media Rupture Seen With Intravascular Ultrasound After Balloon Angioplasty at the Most Stenotic Site and at Each Vascular Specimen (n = 40), and Sensitivity of Intravascular Ultrasound for These Morphologic Features

	Incidence		Sensitivity of Vascular Specimen (%)
	Most Stenotic Site (%)	Vascular Specimen (%)	
Dissection	40	78	79
Plaque rupture	15	48	37
Media rupture	43	75	76
Vascular damage	63	85	87

the ultrasound catheter tip in steps of 0.01 cm was related to a reference needle and mixed automatically with the ultrasound information on the video screen.

Histology: For histologic comparison, arteries were fixed under pressure (100 mm Hg) in 10% buffered formalin for 2 hours, and subsequently decalcified in a standard RDO solution (Apex Inc., Plainfield, Illinois) for 5 hours. The arteries were then processed for routine paraffin embedding. The site of the reference needle was marked using India ink. Transverse sections (5 μm thick) perpendicular to the long axis of the vessel were cut at 1 mm intervals. Sections were stained with elastic van Gieson and hematoxylin-eosin techniques.

Data analysis: Intravascular ultrasound images obtained before and after balloon angioplasty were photographed at increments of 1 mm. For comparison with the corresponding histologic sections, the site of the reference needle and anatomic markers such as side-branches, calcium, or dissection were used. For each specimen, a total of 10 sets of corresponding intravascular ultrasound images and histologic sections, including the most stenotic site, were selected. These 10 sets were subjected to qualitative and quantitative analysis. To assess whether histologic preparation may introduce laceration to the vessel wall mimicking the effects of balloon angioplasty (dissection, plaque rupture, and media rupture), additional sections (4 per specimen) obtained far from the dilated segment were subjected to a qualitative analysis.

QUALITATIVE ANALYSIS: Histologic sections (n = 400) were evaluated by 1 observer (RJvS), and intravascular ultrasound images (n = 400) were evaluated by 2 observers without knowledge of the histologic results (AvdL and EJG). The presence of vascular damage including dissection, plaque rupture, media rupture, or a combination of all 3, was documented.[7] Dissection was defined as the presence of a radial tear in the internal surface associated with a separation of the lesion from the underlying arterial wall. Plaque rupture was defined as a radial tear in the intimal surface. Media rupture was defined as an interruption in the internal elastic lamina and media that exposes the hyperechoic adventitia to the lumen. The incidence of these morphologic features seen at the most stenotic site and at each vascular specimen was assessed with intravascular ultrasound. In addition, using histologic data as the gold standard, the sensitivity of intravascular ultrasound to detect these morphologic features in each vascular specimen was calculated.

QUANTITATIVE ANALYSIS: Quantitative measurements of intravascular ultrasound cross sections were performed using a digital video analyzer system.[17] Analysis included measurement of free lumen area and media-bound area. The plaque area was calculated by subtracting free lumen area from media-bound area. Percent area stenosis was calculated as plaque area divided by media-bound area (Figure 2). In the absence of a visible media on ultrasound, the outer hyperechoic layer representing the adventitia was used as reference. When extensive dropout due to calcification was encountered, the media-bound area was not calculated. Cross sections showing side-branches were excluded for quantitative analysis. The contribution of media-bound area increase and plaque area decrease to the increase in free lumen area was calculated by the ratio of media-bound area increase and plaque area decrease to the increase in free

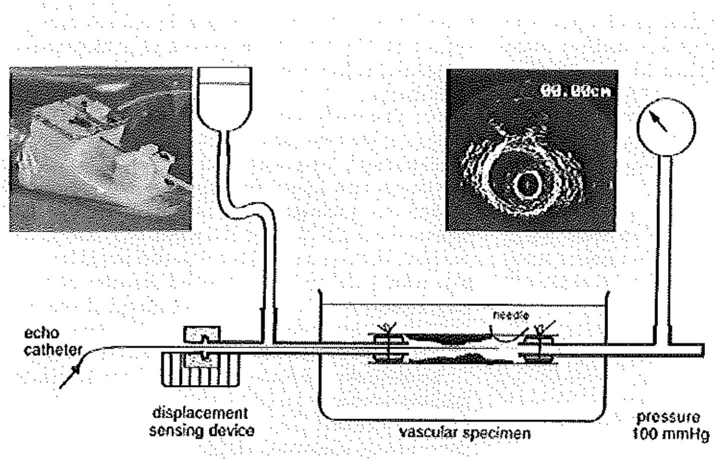

FIGURE 1. In vitro setup showing the intravascular ultrasound catheter advanced through the sensing unit of the displacement sensing device and sheath toward the pressurized vascular specimen. The needle attached distally to the artery used as reference is seen at the 12 o'clock position in the ultrasound cross section *(arrow)*. The catheter-tip position in relation to the needle (00.00 cm) is indicated in the *right upper corner*. Displacement-sensing device is seen in the *insert in left upper panel*. Calibration is 1 mm.

lumen area. To assess intra- and interobserver variability, the free lumen and media-bound areas of 100 corresponding ultrasound cross sections before and after intervention were analyzed by the same observer (MvS) after 2 weeks and by another observer (EvD).

Statistical analysis: Quantitative measurements obtained before and after intervention were compared using Student's paired *t* test. A p value <0.05 was considered statistically significant. Observer differences are expressed as mean ± SD of the paired differences. All values are presented as mean ± SD.

RESULTS

Qualitative results: In 39 of the 40 vascular specimens subjected to dilatation, damage was encountered. The incidence of vascular damage (i.e., dissection, and plaque and media ruptures) seen with intravascular ultrasound and the sensitivity of intravascular ultrasound in detecting these features are summarized in Table I. At the most stenotic site, a lower incidence of vascular damage was seen compared with that for each vascular specimen (Table I). Intravascular ultrasound showed a high sensitivity in detecting dissection and media rupture; the sensitivity for plaque rupture was low. Dissections, often seen at the thinnest part of the lesion, were usually associated with media rupture (Figures 2 to 4). False-positive dissections were not encountered. The reasons for dissections missed on intravascular ultrasound were: (1) the dissected lesion remained adherent to the vessel wall; (2) dissection occurred without connection with the lumen; (3) the ultrasound catheter pushed the dissected lesion against the vessel wall; (4) calcium hindered visualization of a dissection; or (5) plaque rupture was diagnosed instead of dissection (Figures 3 and 4). In sections

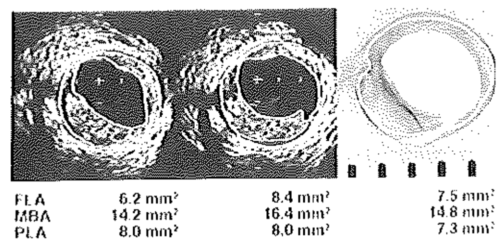

FIGURE 2. Intravascular ultrasound cross sections obtained before and after balloon angioplasty (4 mm) from an atherosclerotic coronary artery and corresponding histologic section. The free lumen area (FLA, *inner contour*) and media-bound area (MBA, *outer contour*) show quantitative results. Note the eccentric soft lesion that became dissected at the thinnest region. At the 9 o'clock position, the origin of a side-branch is seen. Calibration is 1 mm. PLA = plaque area.

obtained far from the dilatation site (n = 160), morphologic features specific for balloon angioplasty were not seen on ultrasound and histologic examination (Figure 3).

False-negative results in detecting media rupture were intimately related to the presence of these ruptures behind an intact plaque or intima, and to the failure of intravascular ultrasound to identify a dissection (Figures 3 and 4).

Quantitative effect of balloon angioplasty: For comparison purposes, cross sections with significant calcification preventing measurement of the media-bound area (n = 35) and those with side-branches (n = 23) were excluded from quantitative analysis.

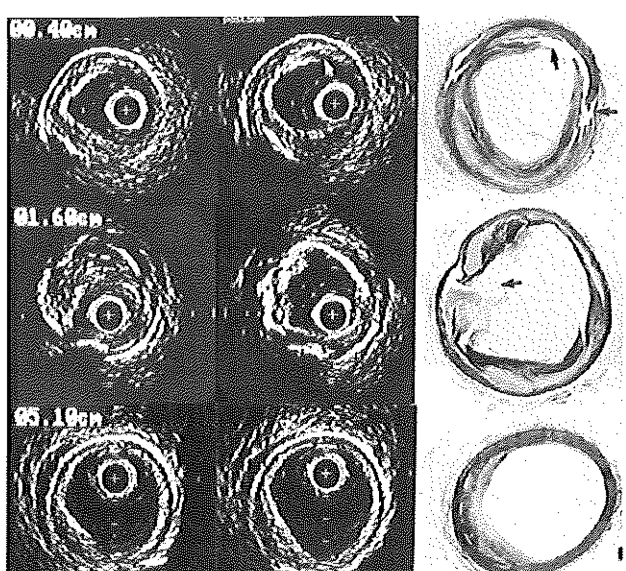

FIGURE 3. Corresponding intravascular ultrasound cross sections obtained before and after balloon angioplasty (5 mm) and histologic counterparts. The displacement sensing device indicated the levels. On ultrasound, the increase in free lumen area after intervention is clearly seen at level 1.6 cm; plaque and media ruptures present histologically at this level (at the 9 o'clock position) were not seen on ultrasound. Level 0.4 cm: On ultrasound a plaque rupture was correctly seen (at 12 o'clock); at 3 o'clock a dissection and media rupture were not seen. Level 5.1 cm: Images obtained far from the dilated site, used as reference, are virtually unchanged. Morphologic features mimicking the effect of balloon angioplasty were not seen on ultrasound or histology. Calibration is 1 mm.

Quantitative data including mean values derived from all cross sections (n = 342) as well as data obtained at the most stenotic site (n = 34) from corresponding intravascular ultrasound cross sections are summarized in Table II.

As a result of balloon angioplasty, the free lumen area increase was associated with an increase in media-bound area, whereas plaque area decreased slightly. Quantitative differences encountered from 342 cross sections were compared with data obtained exclusively at the most stenotic site: greater alterations in areas were seen at the most stenotic site. The contribution of media-bound area increase to the increase in free lumen area was 81%, and the contribution of plaque area decrease was 19%.

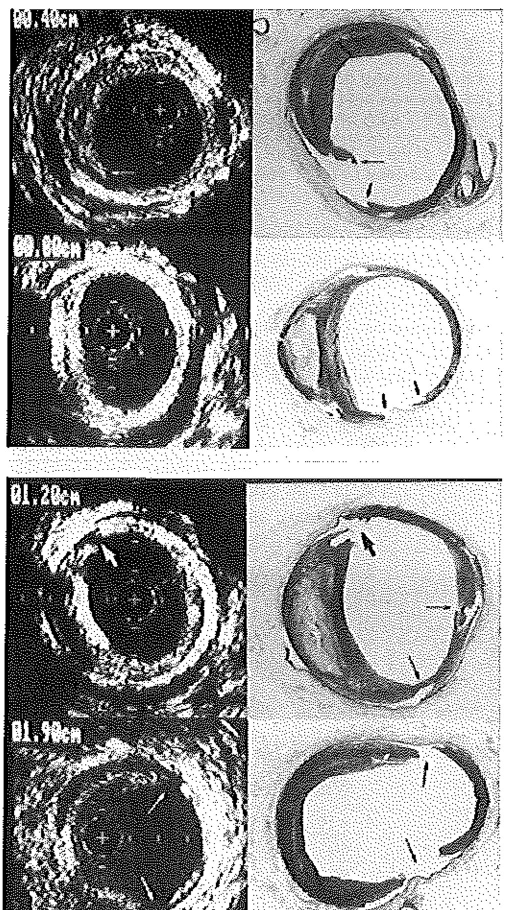

FIGURE 4. Corresponding intravascular ultrasound cross sections obtained after balloon angioplasty (5 mm), and the histologic counterparts showing variability in vascular damage. Level 0.4 cm: Dissection and media rupture were correctly diagnosed at the 7 o'clock position. Laceration (at 1 o'clock) caused by the intervention was also not seen on intravascular ultrasound. Level 0.8 cm: Media rupture (at 6 o'clock) was not seen on ultrasound, nor was a dissection (at 12 o'clock). Level 1.2 cm: At 11 o'clock a media rupture was correctly diagnosed. A dissection and media rupture were not seen on ultrasound at 3 and 6 o'clock. Level 1.9 cm: Both dissection and media rupture were correctly diagnosed on ultrasound (at 2 and 5 o'clock). Calibration is 1 mm.

Intra- and interobserver variability: Intraobserver differences for measurements before and after intervention were 0.1 ± 0.6 and 0.3 ± 0.6 mm^2 for free lumen area, and 0.0 ± 0.7 and 0.0 ± 0.9 mm^2 for media-bound area, respectively. Interobserver differences for measurements before and after intervention were 0.3 ± 0.7 and 0.1 ± 0.7 mm^2 for free lumen area, and 0.1 ± 1.0 and 0.3 ± 1.1 mm^2 for media-bound area, respectively.

DISCUSSION

In the present study, the accuracy of intravascular ultrasound to establish anatomic and quantitative changes after coronary balloon angioplasty was examined. Use of a displacement sensing device offered the unique opportunity to obtain a sequence of tomographic cross sections of the artery with an exact localization within a segment. Consequently, the opportunity was available to answer the question as to whether 1 single cross section at the most stenotic site studied with intravascular ultrasound is representative of qualitative and quantitative outcome rather than a sequence of cross sections.

Qualitative analysis: The results of this study show that at the most stenotic site, the incidence of vascular damage was lower than the incidence for each vascular specimen. Thus, in order to have insight into arterial damage, the entire vascular specimen should be analyzed. Sensitivity for both dissection and media rupture was reasonably good (79% and 76%, respectively), but was low for plaque rupture (37%). Similar sensitivity values for dissection have been reported by other investigators.[3,18,19] We believe that the low sensitivity for plaque rupture in this study can be explained by the fact that axial tears in the plaque were difficult to demonstrate with intravascular ultrasound.

It is noteworthy that the characteristic vascular damage seen after balloon angioplasty with intravascular ultrasound was not encountered before intervention. It is likely that histologic processing itself may have induced arterial disruption, leading to false-negative results on ultrasound.[20] However, in the present study, the histologic sections studied far from the dilatation site did not show vascular damage (Figure 3); the absence of these artifacts may be related to the selection of relatively mildly atherosclerotic segments.

Although media rupture has been diagnosed clinically after balloon angioplasty of the superficial femoral artery,[7] to the best of our knowledge, this anatomic feature has not been documented as a separate feature in coronary artery studies. This may be related to the resolution of the ultrasound transducer used. In most studies, a transducer frequency of 20 to 25 MHz was used[9-15]; in 1 study, 30 MHz ultrasound catheters were used.[8] Potkin et al[12] differentiated between dissection and extensive dissection. We assume that extensive dissection may include the media rupture described in our study.

Quantitative analysis: The increase in free lumen area after balloon angioplasty in this study was caused by an

TABLE II Quantitative Effects of Balloon Angioplasty Assessed With Intravascular Ultrasound*

	Intravascular Ultrasound		
	Before	After	% Change†
Free lumen area (mm^2)			
All cross sections (n = 342)	9.0 ± 4.5	11.6 ± 5.0	+29
Most stenotic site (n = 34)	6.4 ± 3.3	10.1 ± 4.3	+58
Media-bound area (mm^2)			
All cross sections (n = 342)	17.6 ± 6.6	19.7 ± 7.1	+12
Most stenotic site (n = 34)	16.1 ± 6.2	18.8 ± 6.9	+17
Plaque area (mm^2)			
All cross sections (n = 342)	8.6 ± 3.7	8.1 ± 3.6	–6
Most stenotic site (n = 34)	9.6 ± 4.2	8.7 ± 3.8	–9
Percentage area stenosis (%)			
All cross sections (n = 342)	49.2 ± 12.3	41.3 ± 10.8	–16
Most stenotic site (n = 34)	60.4 ± 11.7	46.9 ± 11.0	–22

*Data from all cross sections and data at the most stenotic site where free lumen area and media-bound area could be traced are presented.
†Differences are significant at $p < 0.01$.
Values are expressed as mean ± SD unless otherwise noted.
% change = difference between ultrasound data before and after balloon angioplasty; + = increase, – = decrease.

TABLE III Quantitative Effects of Balloon Angioplasty on Coronary and Iliofemoral Arteries Assessed With Intravascular Ultrasound

	Number of Patients	Year	FLA (%)	MBA (%)	PLA (%)
Coronary arteries					
Potkin[12]	9	1992	+130	+17	–18
Kovach[13]	39	1993	+33	+13	+5
Suneja[14]	25	1993	+126	+1	–21
Braden[15]	30	1994	+108	+14	–4
Present study	34	1995	+58	+17	–9
Iliofemoral arteries					
The[7]	42*	1992	+89	+30	–1
Losordo[22]	40	1992	+120	+6	–33

*Data provided from multiple ultrasound cross sections collected from 16 patients.
FLA = free lumen area; MBA = media-bound area; PLA = plaque area.

increase in media-bound area (81%) and by a decrease in plaque area (19%). The magnitude of increase in free lumen area and media-bound area obtained at the most stenotic site was greater than the mean values derived from all cross sections. The observation that the plaque reduction values obtained at the most stenotic site were in the same order as the overall mean values implies that the decrease in plaque area may be related to a discharge of fluid from the plaque[21] rather than to redistribution of plaque.

The quantitative mechanisms of balloon angioplasty assessed in this study are in agreement with data observed by other investigators[7,12,13,15] (Table III). However, in 2 intravascular ultrasound studies, a different explanation has been proposed for the increase in free lumen area after balloon angioplasty. Losordo et al[22] reported "that plaque compression and plaque fracture in iliac arteries were the principal factors for increased luminal patency; stretching of the arterial wall provided an additional but minor contribution." In the absence of vascular damage, Suneja et al[14] reached similar conclusions for coronary arteries. Reasons why the conclusions with respect to the quantitative effects of balloon angioplasty are controversial remain unclear.

Study limitations: Initially, 124 proximal straight coronary arteries were selected to facilitate comparison with histology. The fact that most were not used because the area of stenosis was <40% at the most stenotic site or because of the inability to cross the stenotic lesion with the ultrasound catheter reflects the difficulty in obtaining appropriate segments for this type of in vitro study. Also, because arteries with severe stenosis were excluded from this study owing to the inability to cross the lesion before intervention, one might not apply the results of this study to severe stenotic lesions encountered clinically. Neither pulsatile flow nor blood was used in this study. Pulsatile blood flow may have facilitated detection of the dissections that were missed because the dissected lesion remained adherent to the vessel wall. Finally, data derived from specimens may represent an anatomic substrate different from that in clinical series of patients undergoing therapeutic balloon angioplasty.

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CHAPTER 4

FAILURE OF INTRAVASCULAR ULTRASOUND TO PREDICT DISSECTIONS AFTER BALLOON ANGIOPLASTY USING PLAQUE CHARACTERISTICS

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ABSTRACT

Intravascular ultrasound (IVUS) may be more sensitive than angiography in the assessment of plaque morphology pre-intervention and vascular damage after balloon angioplasty. This has risen the hope of clinicians to better treat patients by reducing (severe) dissections after PTA by the use of IVUS information. We therefore studied the relation between plaque characteristics and dissections resulting from balloon angioplasty. First, an in vitro study in atherosclerotic arteries (n=42) was performed in which IVUS images were compared with histologic sections to validate this new technique; secondly, the in vitro findings were compared with IVUS findings obtained in vivo (n=73). Dissections were observed in 37 histologic sections and visualized by IVUS in 22 (59%) of the corresponding ultrasonic cross-sections; in vivo dissections were demonstrated by IVUS in 46 (63%) cases. Dissections were generally seen at the thinnest region of the plaque on both histologic sections (92%) and IVUS cross-sections (in vitro 83%; in vivo 93%). No significant relation was found between pre-interventional plaque characteristics such as morphology and eccentricity and the incidence, extent, and location of post-interventional dissections. Thus, IVUS is able to identify dissections after balloon angioplasty, generally occurring at the site of the thinnest plaque diameter. However, the incidence and severity of these dissections were not related to any of the pre-interventional plaque characteristics.

INTRODUCTION

Intravascular ultrasound (IVUS) is a tomographic imaging technique which allows to determine plaque characteristics before and the presence, location and extent of dissection after catheter -based interventions [1-13]. It has been suggested that plaque characteristics, including plaque composition and eccentricity, may be determinants of the incidence and location of vascular damage after vascular interventions [14-18]. Elucidation of this relationship is an important issue as it may result in a more targeted strategy for the treatment of atherosclerotic disease. In this in vitro and in vivo study IVUS was used before and after balloon angioplasty of atherosclerotic arteries to document the presence, extent, and location of post-interventional dissection, and to evaluate a possible relation with plaque characteristics. Histologic sections were used to validate the in vitro IVUS findings.

METHODS

Intravascular ultrasound

A mechanical 30 MHz IVUS imaging system was used (Du-MED, Rotterdam, The Netherlands), mounted on a 4.1 F catheter. The axial resolution of the system is 80 μm; lateral resolution is 225 μm at a depth of 1 mm. Images were displayed on a videomonitor via a videoscanned memory and stored on an S-VHS recorder. Both the in vitro and in vivo study were approved by the Local Committee on Human Research.

In vitro studies: Atherosclerotic human vascular specimens including coronary (n=33) and iliofemoral arteries (n=9) were harvested at autopsy and stored at -20°C. The specimens were thawed, side-branches were tied off with sutures, and proximal and distal ends were connected to sheaths, fixed to a waterbath at room temperature. Distally, a reference segment was indicated using a needle at 12 o'clock (Figure 1). During the study the arteries were pressurized at 100 mmHg by means of a fluid reservoir containing water connected to the side-arm of the proximal sheath. The specimens were studied with IVUS before and after balloon angioplasty. The largest lumen diameter seen in the segment by IVUS was used as reference for the balloon diameter; balloon angioplasty was performed for 2 minutes, with a manometer-controlled pressure of 8 to 10 atm. Intervention was judged successful, if the lumen area at the narrowest lumen site as seen on IVUS increased; otherwise a larger balloon was used. A displacement sensing device was used to assure reliable comparison of IVUS images before balloon angioplasty with the same segment obtained after intervention [19]. Briefly, the ultrasound catheter was advanced through the displacement sensing unit via the sheath distally into the artery. A series of images were obtained during a manual pull-back of the IVUS catheter. The distance between the tip of ultrasound catheter and the reference needle was mixed automatically with the IVUS images on the videoscreen in steps of 0.01 cm (Figure 1).

For histologic comparison the arteries were fixed under pressure (100 mmHg) in 10% buffered formalin for 2 hours and subsequently decalcified in a standard RDO solution (Ampex, Plainfield, Illinois) for 5 hours. The arteries were then processed for routine paraffin embedding. The site of the reference needle was marked using Indian ink. Transverse sections, 5 μm thick perpendicular to the long axis of the vessel, were obtained at 1 mm intervals. The sections were arranged from proximal to distal with notation of the 12 o'clock position indicated by ink. The sections were stained with the elastic van Gieson and the hematoxylin eosin techniques. Qualitative and quantitative analysis of the histologic sections and the corresponding IVUS images was performed. From each vascular specimen studied, the IVUS cross-section at the narrowest lumen area (target site) before intervention and its corresponding ultrasound image after intervention were selected for comparison with the histologic sections. The ultrasound images and the histologic sections were analyzed by different independent and blinded observers.

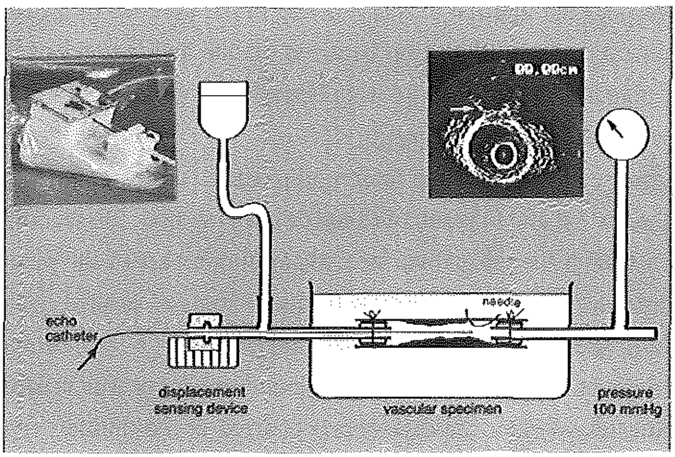

Figure 1. In vitro set up showing the intravascular ultrasound catheter advanced via the sensing unit of the displacement sensing device and sheath towards the pressurized vascular specimen. The needle attached distally to the artery used as reference is seen at 12 o'clock in the ultrasound cross-section (arrow). The cathetertip position in relation to the needle (00.00 cm) is indicated in the right upper corner. Insert left upper panel: displacement sensing device. Calibration = 1 mm.

In vivo studies: After giving informed consent, patients (n=73) undergoing balloon angioplasty of the iliofemoral artery were studied with IVUS before and after intervention. An introducer sheath was placed into the femoral artery; the ultrasound catheter was advanced through the sheath in a retrograde manner into the iliac artery (n=10) and in an anterograde manner into the femoral artery (n=63). A series of IVUS cross-sections of the treated segment were recorded before and after intervention with 1 cm interval during manual pull-back of the IVUS catheter. Corresponding IVUS cross-sections obtained before and after balloon angioplasty were analyzed. From each patient studied, the cross-section with the narrowest lumen area (target site) before balloon angioplasty was selected for comparison with the corresponding image obtained after intervention.

Data analysis and statistics

IVUS cross-sections obtained before intervention were assessed for plaque composition and eccentricity. Plaque composition was divided into soft (echodense without shadowing), mixed (bright echoes with shadowing ≤90°) and hard (bright echoes with shadowing >90°). The extent of calcification was graded as an arc of the circumference with the center of the lumen as reference point (steps of 30°). Minimum and maximum plaque thickness was measured to determine plaque eccentricity (Figures 2 and 3). Plaque thickness was calculated as the perpendicular distance between the plaque surface, i.e. intimal leading edge, and the internal elastic lamina; in the absence of a distinct internal elastic lamina on ultrasound, the transition between plaque and media or adventitia was used. An eccentric plaque was defined as a ratio between maximum and minimum plaque thickness ≥3; a concentric plaque as a ratio <3.

In the IVUS cross-sections following intervention and in the corresponding histologic sections the presence, extent and location of dissection was scored. Dissection was defined as the presence of a tear in the intimal surface, separating a part of the plaque from rest of the underlying arterial wall [5]. The extent of dissection was graded in the same way as the extent of calcification. Dissections were graded as minor (≤90°) or major (>90°). The location of the dissection in relation to the plaque thickness was scored; a nominal yes or no score indicates whether the dissection occurred at the thinnest region or not.

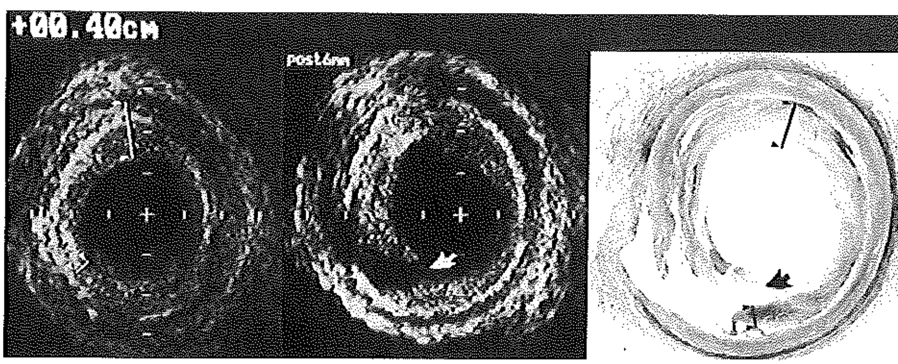

Figure 2. Corresponding intravascular ultrasound cross-sections obtained in vitro at level 0.4 cm before and after balloon angioplasty and the histologic counterpart. Minimum (8 o'clock) and maximum (12 o'clock) lesion thicknesses are indicated by arrowheads. A dissection is seen at the thinnest region of the lesion (arrow). + = catheter; calibration = 1 mm.

In order to test the reproducibility of IVUS plaque thickness measurements in the in vitro and in vivo IVUS images, measurements were repeated by a second blinded observer. The mean and standard deviations of the paired differences between the two observers were calculated. The significance of the interobserver differences were determined by a paired t-test; the degree of observer variability was presented with a coefficient of variation defined as the standard deviation of paired differences divided by the mean of the absolute values. Interobserver variability of IVUS to assess the presence and extent of hard plaques and the presence of dissections in vivo has been assessed previously (hard plaque: kappa value 0.67, agreement 85%; dissection: kappa value 0.69, agreement 85%; paired difference of the extent of hard plaque $6 \pm 33°$) [20]. Chi-squared test was used to assess differences in categorical variables and Mann-Whitney test in continuous variables. A p-value < 0.05 was considered significant.

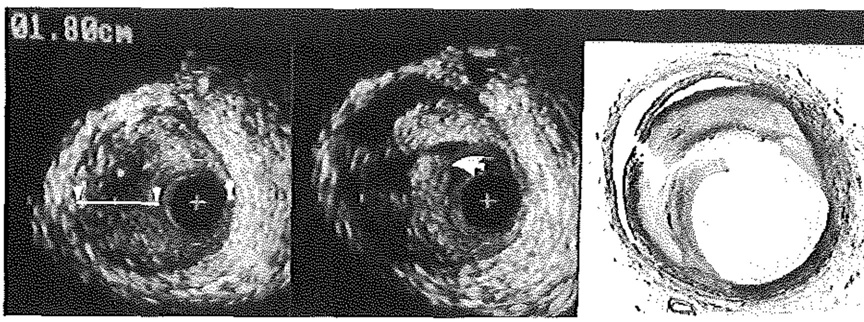

Figure 3. Corresponding intravascular ultrasound cross-sections obtained in vitro at level 1.8 cm before and after balloon angioplasty and the histologic counterpart. Minimum (3 o'clock) and maximum (9 o'clock) lesion thicknesses are indicated by arrowheads. After balloon angioplasty a dissection is seen at the thickest region of the lesion (arrow). + = catheter; calibration = 1 mm.

RESULTS

In vitro studies

Dissections were seen in 37 of the 42 histologic sections occurring at the thinnest site of the plaque circumference in 34 (92%) specimens (Table I). In the corresponding IVUS cross-sections the dissection was correctly detected in 22 (sensitivity = 59%); 18 of those detected dissections were seen at the thinnest plaque site (Figure 2). The occurrence of dissections not seen at the thinnest region on IVUS were histologically confirmed in 3 of the 4 cases (Figure 3). Histologic review of these 3 sections demonstrated fibrous plaques; in 2 of these specimens the dissection was seen at the thinnest region in a nearby cross-section both on IVUS and on the histologic section. Dissections were graded as minor in 19 and as major in 18 histologic sections. IVUS revealed minor and major dissections in 15 and 7 cases, respectively. The extent of dissections measured in the histologic sections was larger (median 90°; range: 0 - 270°) than in the corresponding IVUS images (median 30°, range 0 - 180°)($p<0.001$).

In 15 cases dissections demonstrated by IVUS (7 minor and 8 major) were not identified by IVUS due to one of the following reasons: (1) the dissected portion of the plaque remained adherent to the vessel wall, (2) the ultrasound catheter pushed the dissected plaque against the vessel wall, and (3) calcium hindered the visualisation.

Plaque composition as assessed with IVUS images before intervention was soft, mixed, and hard in 24, 10 and 8 cases, respectively. Thirtyseven of the 42 IVUS cross-sections were available for eccentricity analysis (calcification hampered quantitative assessment of plaque thickness in 5 cases): 21 eccentric plaques and 16 concentric plaques were observed. Data on the relation between plaque characteristics and the incidence and extent of dissection obtained in the in vitro study are summarized in Table II. No relation was found between plaque characteristics and the incidence, extent, and location of dissection. Slightly more major dissections were observed in soft plaques than in the plaques with calcification (mixed and hard plaques)($p = 0.06$). However, analysing the histologic sections, more major dissections were found in plaques with calcification than in soft plaques (11/18 and 7/19, respectively; $p = 0.19$).

Table I. Incidence, location and extent of dissection seen in the histologic sections and with intravascular ultrasound (IVUS).

	Total	Thinnest region	Minor	Major
In vitro (n=42)				
Histology	37 (88%)	34 (92%)	19 (51%)	18 (49%)
IVUS	22 (52%)	18 (82%)	15 (68%)	7 (32%)
In vivo (n=73)				
IVUS	45 (63%)	42 (93%)	33 (72%)	13 (28%)

In vivo studies

In 46 of the 73 cases a dissection was evidenced at the target site (63%) (Table I). Dissections were minor in 33 and major in 13 cases; dissections were seen at the thinnest region in 43 cases (Figure 4). The plaques were classified as soft, mixed, and hard in 38, 27 and 8 cases, respectively. Plaques were eccentric in 47 and concentric in 26 cases.

Data on plaque characteristics and the incidence and extent of dissection in the in vivo study are summarized in Table II. No significant relationship was found between plaque composition and eccentricity, and the incidence and extent of dissection.

Interobserver analysis

There was good agreement between the two observers for the IVUS measurements, without significant differences for the minimum and maximum plaque thickness and ratio. For in vitro IVUS images the mean difference for minimum thickness, maximum thickness, and ratio were low (0.00 ± 0.05 mm, 0.02 ± 0.08 mm, and 0.06 ± 0.88, respectively); in vivo the mean differences were similar (0.01 ± 0.08 mm, 0.01 ± 0.09 mm, and 0.07 ± 0.63, respectively). The coefficient of variation for these measurements did not exceed 17%.

Table II. Relation between plaque characteristics (composition and eccentricity) and the incidence and extent of dissection seen with intravascular ultrasound (IVUS) in vitro and in vivo.

		Dissection			
	n	Absent	Minor	Major	p
In vitro					
Plaque composition					
Soft	24	13 (54%)	5 (21%)	6 (25%)	0.15
Mixed	10	4 (40%)	5 (50%)	1 (10%)	
Hard	8	3 (38%)	5 (62%)	0	
Plaque eccentricity					
Eccentric	21	12 (57%)	6 (29%)	3 (14%)	0.40
Concentric	16	6 (38%)	8 (50%)	2 (13%)	
In vivo					
Plaque composition					
Soft	38	13 (34%)	17 (45%)	8 (21%)	0.16
Mixed	27	10 (37%)	15 (56%)	2 (7%)	
Hard	8	4 (50%)	1 (13%)	3 (37%)	
Plaque eccentricity					
Eccentric	47	19 (40%)	19 (40%)	9 (19%)	0.54
Concentric	24	8 (31%)	14 (54%)	4 (15%)	

DISCUSSION

Intravascular ultrasound enables to study not only the lumen but also the vessel wall before and after intervention. This explains the superiority of IVUS over angiography in assessing plaque characteristics and the presence of vascular damage [4,7,8,10]. Previous histologic studies have shown that the presence and extent of dissection was related to lesion characteristics [14,15,17] which gave rise to the hope to better treat patients by

reducing the incidence of (severe) dissections following vascular interventions, using IVUS-derived parameters of plaque characteristics.
In this study we investigated the potential of IVUS to detect the presence, extent, and location of dissection following balloon angioplasty, and we assessed the relationship of these findings with plaque characteristics.

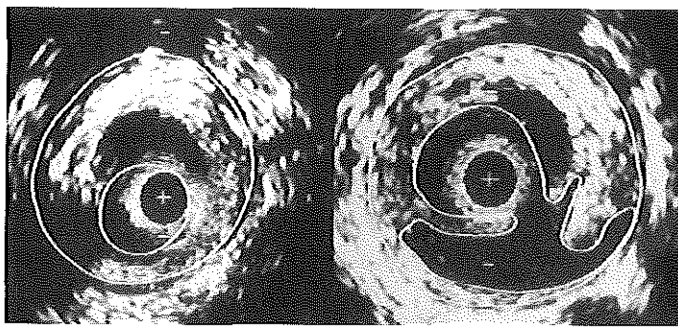

Figure 4. Intravascular ultrasound cross-sections obtained before and after balloon angioplasty in vivo. According to the definition the plaque was defined eccentric. + = catheter; calibration = 1 mm.

In the present study the incidence of dissection at the target site was 88% in the histologic sections, and 52% and 63% in the in vitro and in vivo IVUS images, respectively. Reviewing the IVUS images obtained in the whole vascular specimen the frequency of dissection increased in vitro from 22 (52%) to 30 (71%) and in vivo from 45 (63%) to 72 (99%) dissections, respectively). This raises the question, whether dissections at the target site are in fact absent or rather not visualized by IVUS. It has been suggested that histologic processing may have induced dissections, leading to false negative results by IVUS; this is not likely as we experienced that dissections did not occur in histologic sections far from the dilation site [21].

Moreover, comparison of the histologic sections and corresponding IVUS images revealed that IVUS underestimates the extent of dissections. This is particularly evident in hard plaques where calcification may prevent imaging of the dissection cleft: the median difference in extent of dissection in the histologic section and IVUS image was 15° (range -30° - 150°) for soft plaques and 105° (range 0 - 270°) for hard plaques ($p<0.01$).

In the present study dissections were found generally at the thinnest site of the plaque. Lee and coworkers [22] used a computational structural analysis based on IVUS images to identify regions of high stress in the atherosclerotic vessel wall. They concluded that with the use of this computational method it was possible to predict the location of plaque fracture after angioplasty, but that IVUS may not be useful for predicting the ultimate balloon inflation pressure necessary to cause plaque fracture. Generally, these high stress regions were located near the junction of plaque with more normal vessel wall, which corresponds with the thinnest plaque regions in our study. Our findings are also in agreement with histologic studies following balloon angioplasty showing a separation of the relatively inelastic plaque from the arterial wall near the edges of the plaque, and a stretching of the arterial wall [23-25].

We found no relation between plaque composition and eccentricity, and the incidence, extent, and location of dissection both in vitro and in vivo. This result differs from findings of other IVUS studies; the findings were equivocal as several studies established a relation between hard (calcified) plaque and the incidence of dissection following balloon angioplasty [8-10], while others found a trend towards more post-angioplasty dissections in soft (non-calcified) plaque than in hard (calcified) plaque [5]. The underestimation of the extent of dissection in calcified plaques in the present study may partly explain the absence of a relation between plaque composition and dissection as more major histologically confirmed dissections were found in plaques containing calcium (hard and mixed plaques) than in soft plaques. The latter result confirmed the previously mentioned histologic studies [15,17].

Similarly, contradictory IVUS results regarding plaque eccentricity and dissection were encountered: Tenaglia et al. [6] found 50% dissections in both eccentric and concentric plaques, while Honye et al. [8], found fractures predominantly in eccentric plaques (77% vs 22%). As these contrary results may be explained by different definitions of plaque eccentricity we also searched for a relation between dissection and plaque eccentricity based on the presence of a partly disease-free wall; however no significant relation was found.

Study limitations

The sensitivity of IVUS in detecting dissections at the target site in the in vitro study may have been lower compared to the in vivo study, as mainly coronary arteries were studied in which a stenting effect of the catheter may occur [9]. The incidence of dissection increased when the whole dilated segment rather than the target site was studied. In the present study the relation between plaque characteristics and dissection was studied at the target site as plaque morphology and eccentricity varies significantly throughout the artery. The technical development of 3D-IVUS may result in an axial assessment of plaque morphology in atherosclerotic segments and in a classification of plaque eccentricity based on volumetric measurements [26-28]. Tissue identification by radiofrequency signal processing may perhaps in the future permit the classification of plaques which are prone to severe dissection [29].

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CHAPTER 5

INTEROBSERVER REPRODUCIBILITY OF QUALITATIVE AND QUANTITATIVE ANALYSIS OF INTRAVASCULAR ULTRASOUND IMAGES BEFORE AND AFTER PERIPHERAL BALLOON ANGIOPLASTY

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INTEROBSERVER REPRODUCIBILITY OF QUALITATIVE AND QUANTITATIVE ANALYSIS OF INTRAVASCULAR ULTRASOUND IMAGES BEFORE AND AFTER PERIPHERAL BALLOON ANGIOPLASTY

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Abstract—In this study, interobserver agreement on intravascular ultrasound data obtained before and after balloon angioplasty (PTA) of the superficial femoral artery was assessed. Two observers analyzed intravascular ultrasound cross-sections from 38 patients. Interobserver agreement was good for soft and hard lesions, dissection and vascular damage (kappa values 0.61, 0.67, 0.69 and 0.66, respectively); moderate for eccentric lesions (kappa 0.45); fair for media ruptures (kappa 0.25); and poor for lipid deposits and plaque ruptures (kappa 0.0 and 0.04, respectively). Differences for the arc of normal wall and hard lesion were not significant, but were for dissection. There were no significant interobserver differences between area measurements. The coefficient of variation for free lumen area and media-bounded area before PTA was 17.2% and 10.5% and after PTA 11.2% and 9.2%, respectively. This study identified the intravascular ultrasound parameters that are reproducible.

Key Words: **Intravascular ultrasound, Reproducibility, Peripheral arteries, Balloon angioplasty.**

INTRODUCTION

From intravascular ultrasound studies performed *in vitro* it was shown that the characteristics of both the atherosclerotic lesion and arterial wall seen on ultrasound relate to the histologic composition (Gussenhoven et al. 1989a,b; Mallery et al. 1990; Potkin et al. 1990; Tobis et al. 1989). The location and thickness of the lesion measured from the ultrasound images correlated well with the data derived from the corresponding histologic sections. Intra- and interobserver agreement of *in vitro* and *in vivo* images obtained prior to intervention from normal and diseased peripheral arteries have shown good correlation for quantitative measurements (di Mario et al. 1992; Wenguang et al. 1990, 1991). However, a systematic analysis of the interobserver agreement on the qualitative and quantitative intravascular ultrasound parameters obtained clinically prior to and following balloon angioplasty in peripheral arteries is lacking.

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The purpose of this study was to determine the interobserver agreement on qualitative and quantitative intravascular ultrasound parameters obtained in a clinical setting before and after balloon angioplasty of the superficial femoral artery.

METHODS

Intravascular ultrasound imaging

In 38 patients (29 men, 9 women; ages 64 ± 10 years), intravascular ultrasound was performed before and after balloon angioplasty for treatment of occlusive superficial femoral artery disease. Patients were included in the study after written informed consent. Intravascular ultrasound studies were performed using mechanical systems based on a single ultrasound element (30 MHz). Nine patients were studied with the CVIS "Insight" system (Sunnyvale, CA) using a 4.3F flexible catheter containing a rotating mirror; 29 patients were studied with the Du-MED system (Rotterdam, The Netherlands) using a 4.3F flexible catheter ("Princeps") containing a rotating element. Before and immediately after balloon angioplasty the intravascular ultrasound catheter was advanced distally and cross-sections were recorded during pull-back of the catheter together with their frame number. Images for analysis were recorded with 1-cm intervals. Under fluoroscopic control, the location of the intravascular ultrasound catheter was systematically compared with the radiopaque ruler; its location was indicated manually on the video monitor (Gussenhoven et al. 1991). The resulting images were displayed on the monitor via a video-scanned memory and stored on an S-VHS recorder. The videotapes were reviewed and, according to the protocol, all cross-sections within the treated segment (interval 1 cm) obtained before and after balloon angioplasty underwent qualitative and quantitative analysis.

Two experienced observers from different institutions took part in the data acquisition in their own hospitals. The cross-sections selected by one observer were subsequently analyzed by the other observer using the unique frame number as marker for the cross-sections.

First, the intravascular ultrasound parameters used in this study were defined. To get acquainted with the application of these definitions the selected intravascular ultrasound cross-sections (64 before and 38 after) of the first five patients (not included in this study) were analyzed by the two observers after which disagreement was discussed and solved by consensus. Subsequently, the selected intravascular ultrasound cross-sections of each patient in this study (median five per patient; range 2–12) were independently analyzed by the two observers (n = 192 before and n = 212 after balloon angioplasty).

Qualitative analysis

Cross-sections were assessed for lesion topography and morphology seen before balloon angioplasty and for presence of vascular damage seen after intervention. Criteria for evaluating the qualitative features with intravascular ultrasound have been described previously (Gerritsen et al. 1993; Gussenhoven et al. 1991, The et al. 1992). Lesion topography may be either eccentric or concentric. Lesion morphology may include fibromuscular/fibrous/thrombus (echo-soft), calcification (echo-hard with shadowing) and/or lipid deposit (echo-poor). These morphologic features may be present simultaneously in one cross-section. After balloon angioplasty, the presence of dissection, plaque rupture and media rupture was documented. These features may be present simultaneously in one cross-section. In the presence of one or more of these features "vascular damage" was scored.

The arc of normal wall, hard lesion and dissection that subtends the circumference was graded by visual estimation according to the hours of a clock with the center of the vessel as reference (1 h corresponding to 30° of a sector). In the presence of multiple calcium deposits and or dissections, the total sum was calculated. For instance, a lesion may involve 5 adjacent hours of the circumference leaving the remaining 7 disease-free (normal).

Quantitative analysis

Quantitative measurements were performed using a computer-based analysis system (Wenguang et al. 1990, 1991). Analysis included measurement of free lumen area and media-bounded area (Fig. 1). In the absence of a visible tunica media on intravascular ultrasound, the adventitia was used as reference.

During off-line quantitative analysis of the free lumen area, it was experienced that the presence of strong scattering due to blood may cause difficulties in discrimination of the luminal boundary. To diminish this problem, echo images were replayed several times on real-time on an additional video monitor to distinguish the luminal boundary from the echoes of blood-scatter.

Definitions

Eccentric lesion was involved when part of the vessel wall was disease-free. The vessel wall was judged to be normal when the lesion thickness was 0.5 mm or less. *Soft lesion* was defined as having a homogeneous or bright echostructure superimposed on the arterial wall without shadowing. *Hard lesion* was recognized by the presence of a bright echostructure superimposed on the arterial wall casting peripheral shadowing. *Lipid deposit* was defined as a hypoechoic region inside a lesion.

Dissection was defined as the presence of a tear in the intimal surface separating the lesion from the underlying arterial wall. *Plaque rupture* was defined as a radial tear in the intimal surface perpendicular to the arterial wall. *Media rupture* (*i.e.*, internal elastic lamina rupture) was defined as an interruption in the internal elastic lamina which exposes the hypoechoic media or hyperechoic adventitia to arterial lumen. *Vascular damage* was defined as the presence of dissection, plaque rupture and/or media rupture.

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

Media-bounded area (mm^2) was defined as the native vessel area bounded by the inner medial border.

Statistical analysis

First, the interobserver reproducibility for the presence or absence of each qualitative parameter was expressed as unweighted Cohen's kappa coefficient (Cohen

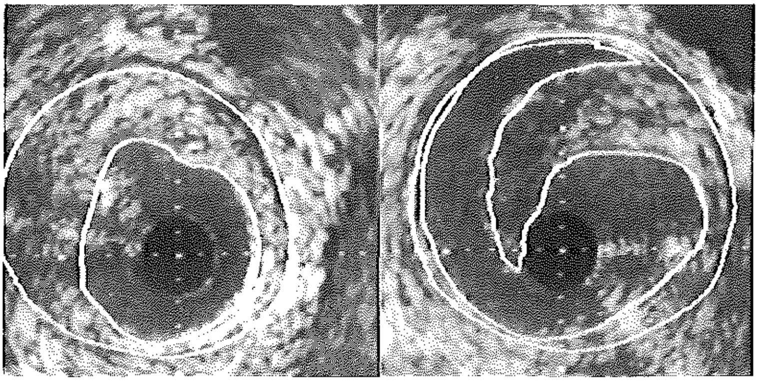

Fig. 1. Corresponding intravascular ultrasound cross-sections obtained from a patient before and after balloon angioplasty (PTA) of the superficial femoral artery using the CVIS system. Before PTA (left), a soft eccentric lesion was involved; after PTA (right) a dissection was diagnosed. The extent of the arterial wall that was disease-free was 1 h (6 o'clock) and of the dissection, 4 h. The intravascular ultrasound cross-sections are contour-traced off-line for free lumen area (inner contour) and media-bounded area (outer contour). Calibration = 0.5 mm.

1960). Kappa values range from −1 to +1. Kappa equals +1 when there is complete agreement between two observers. Kappa equals 0 when observed agreement is equal to that expected by chance alone. When agreement is less than chance agreement then kappa has a negative value. Kappa values below 0.20 represent poor agreement; values ranging from 0.20 to 0.40 represent fair agreement; values from 0.40 to 0.60 represent moderate agreement; those from 0.60 to 0.80 represent good agreement; and values greater than 0.80 represent very good agreement (Landis and Koch 1977).

Second, the total percentage of agreement was calculated as a percentage of all comparisons for each diagnostic category that showed agreement, regarding either the absence or the presence of the diagnostic category.

Third, to describe the agreement between the observers in the extent of the qualitative parameters and the measurements of the free lumen area and media-bounded area, mean and standard deviations of the paired differences between the two observers were given. For data related to the extent of qualitative parameters, images in which both observers agreed on the presence of these features were considered. The Student's t-test for paired observations was used to test whether there were systematic differences between observers. The degree of interobserver variation is presented with a coefficient of variation defined as the standard deviation of the paired difference divided by the mean of the absolute value. A p-value < 0.05 was considered statistically significant.

Fourth, the absolute paired differences in quantitative measurements between the systems used were compared using the Wilcoxon two-sample test.

RESULTS

The interobserver reproducibility of the qualitative intravascular ultrasound parameters obtained before and after balloon angioplasty are summarized in Table 1. There was good agreement for soft lesion, hard lesion, dissection and for vascular damage (Figs. 1–3). Moderate agreement was observed for eccentric lesion. Fair agreement was found for media rupture. Poor agreement was found for lipid deposit and for plaque rupture.

Table 1. Kappa values and total percentage of agreement (TA) for all intravascular ultrasound qualitative parameters seen before (n = 192) and after (n = 212) balloon angioplasty (PTA).

	Kappa	TA
Before PTA		
Eccentric lesion	0.45	73%
Soft lesion	0.61	94%
Hard lesion	0.67	85%
Lipid deposit	0.00	95%
After PTA		
Dissection	0.69	85%
Plaque rupture	0.04	71%
Media rupture	0.25	86%
Vascular damage	0.66	83%

n = Number of cross-sections.

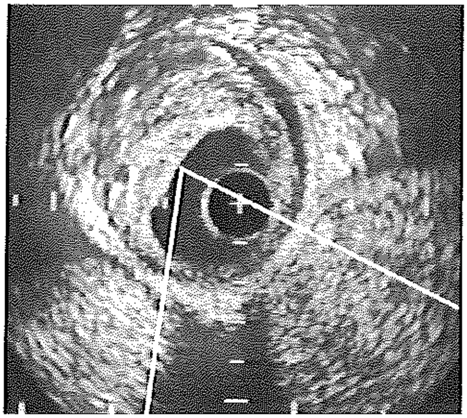

Fig. 2. Intravascular ultrasound cross-section obtained from a patient before balloon angioplasty of the superficial femoral artery using the Du-MED system. The lesion involved was eccentric and soft in nature. The hypoechoic region seen at 10–11 o'clock may suggest the presence of lipid deposit, but could also be an artifact of attenuation. The arc of disease-free arterial wall is 2 h (5 o'clock). + = catheter; calibration = 1 mm.

Differences between the two observers were not significant for the arc of normal wall and hard lesion; differences for the arc of dissection were significant (Table 2).

In 165 of the 192 cross-sections obtained before intervention, and 177 of the 212 cross-sections obtained after intervention, media-bounded area could be assessed. In 62 cross-sections (27 before and 35 after intervention), media-bounded area could not be assessed due to calcification and/or inadequate image quality. There was no significant interobserver bias for free lumen area and media-bounded area calculated before and after balloon angioplasty (Table 3). The coefficient of interobserver variation was 17.2% and 10.5% for free lumen area and media-bounded area, respectively, before intervention and 11.2% and 9.2% for free lumen area and media-bounded area, respectively, after intervention. Results of the Wilcoxon two-sample test showed that the mean absolute difference of the free lumen area and media-bounded area obtained with the two intravascular ultrasound systems used was not significantly different.

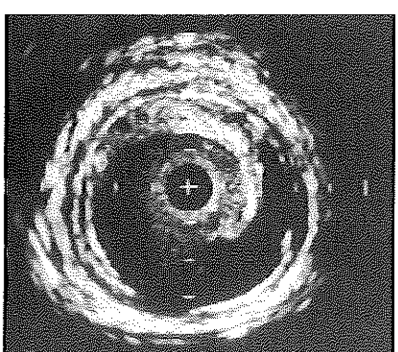

Fig. 3. Intravascular ultrasound cross-section obtained from a patient after balloon angioplasty of the superficial femoral artery. The lesion involved, eccentric and soft in nature, became dissected from the arterial wall. Both the extent of the dissection (between 2 and 4 o'clock) and media rupture were 2 h (at 3 and at 7 o'clock). + = catheter; calibration = 1 mm.

Table 2. Paired difference and coefficient of variation between the two observers of qualitative parameters (normal wall, hard lesion and dissection) expressed as arc in hours.

	n	Paired difference	Coefficient of variation
Normal wall	75	0.2 ± 2.1 (NS)	5%
Hard lesion	50	−0.2 ± 1.1 (NS)	34%
Dissection	70	0.6 ± 1.6 (S)	21%

Data represent mean and standard deviation; n = number of cross-sections; NS = not significant; S = significant.

DISCUSSION

Reliable distinction between different qualitative features and assessment of quantitative parameters with intravascular ultrasound both before and after intervention is important for clinical practice. Tenaglia et al. (1992) were the first to report on the observer agreement on qualitative analysis of intracoronary ultrasound images. The reported kappa values were 0.70

Table 3. Paired differences and coefficient of variation between the two observers of the area measurements obtained before and after balloon angioplasty (PTA).

	Paired difference	Coefficient of variation
Before PTA		
Free lumen area	+0.22 ± 2.07 mm^2 (NS)	17.2%
Media-bounded area	−0.02 ± 3.05 mm^2 (NS)	10.5%
After PTA		
Free lumen area	+0.03 ± 1.94 mm^2 (NS)	11.2%
Media-bounded area	−0.11 ± 3.03 mm^2 (NS)	9.2%

Data represent mean and standard deviation. NS = not significant.

for hard, 0.42 for eccentric and 0.66 for dissection, respectively. Similar kappa values were found by Peters et al. (1994) for calcium (0.9) and for eccentric lesion (0.5). In addition, they reported low kappa values for intimal thickening (0.3), and for lipid (−0.1). Furthermore, Hausmann et al. (1994) established that intravascular ultrasound parameters assessed qualitatively (presence of normal wall, plaque or calcium) showed excellent agreement within and between observers; quantitative parameters also showed low variability. Unfortunately, important issues such as vascular damage and quantitative analyses seen after intervention were not part of their study (Hausmann et al. 1994; Peters et al. 1994).

The present study with intravascular ultrasound performed in peripheral arteries revealed a high reproducibility for the detection of soft lesion, hard lesion, dissection and vascular damage. We postulate that the moderate agreement found for eccentric lesions (kappa value 0.45) may be due to the definition used: "eccentric lesion was involved if the lesion measured 0.5 mm or less at the normal vessel wall." This arbitrary criterion assessed by visual estimation might have influenced the outcome of data.

Unequivocally, the diagnostic accuracy for lipid deposit was poor (see also Fig. 2). Although the total agreement was high, the kappa value was low. Total agreement was high because both observers had not seen lipid deposits inside the lesion in most of the cross-sections. However, as they did not agree in the few cases in which they scored lipid deposit, kappa value was therefore low. The accuracy of intravascular ultrasound to detect lipid deposit in coronary arteries may be hampered because echolucent areas may alternatively represent acoustic drop-out, a dissection, or a thick media (Peters et al. 1994). In addition to lesion composition, gain setting of the system and angle of incidence are known to be important determinants that influence the echogenicity of a lesion (di Mario et al. 1992; Potkin et al. 1990). Recent *in vitro* studies showed that the sensitivity for lipid detection was low (<30%) and the specificity of this finding was high (>80%) (Gussenhoven et al. 1994; Sechtem et al. 1993). For this reason, we are reluctant in diagnosing lipid deposit (*i.e.*, "instable plaque") with the current intravascular ultrasound systems.

After balloon angioplasty, we found a good agreement for dissection and vascular damage; similar kappa values for dissection (0.66) were reported by Tenaglia et al. (1992). However, agreement for media rupture was fair and, for plaque rupture, poor. This may be related to the resolution of the intravascular ultrasound system used. Whereas a dissection may present as a large well-delineated feature, both plaque rupture and media rupture were usually small and may potentially be overlooked.

It is also noteworthy, that differences for the arc of normal wall and hard lesion were not significant, but were for dissection (see Table 2). The reason for this difference may be related to the visual estimation of the arc of the dissection. It is not uncommon that the arc of dissection represents a sum of dissections seen in one cross-section. We assume that, if a protractor was used, a more reproducible measure might have been obtained.

Finally, the reproducibility of the quantitative data in this study was high for free lumen area and media-bounded area calculated before and after balloon angioplasty. Moreover, data obtained with the two ultrasound systems used were not significantly different both before and after intervention. This observation is of crucial importance given the fact that recent intravascular ultrasound studies in both coronary and peripheral arteries have shown that quantitative assessment of free lumen area and diameter seen following balloon angioplasty are predictive factors of failure (Gussenhoven et al. 1995; Jain et al. 1994).

It should be noted that a limitation of this study is the low number of cross-sections available with the CVIS system. In addition, the analyses for this study were executed off-line. It is a challenge to know whether similar results can be obtained on-line, for example, in "battle-field conditions" for decisionmaking during intervention.

In view of the clinical application of intravascular ultrasound, it is important to know which intravascular ultrasound parameters are reproducible for clinical decisionmaking.

SUMMARY

This study indicates that highly reproducible intravascular ultrasound parameters include: (1) soft lesion, hard lesion and dissection; (2) the arc of normal wall and hard lesion; and (3) the quantitative assessment of free lumen area and media-bounded area both before and after balloon angioplasty.

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CHAPTER 6

INTRAVASCULAR ULTRASONOGRAPHY 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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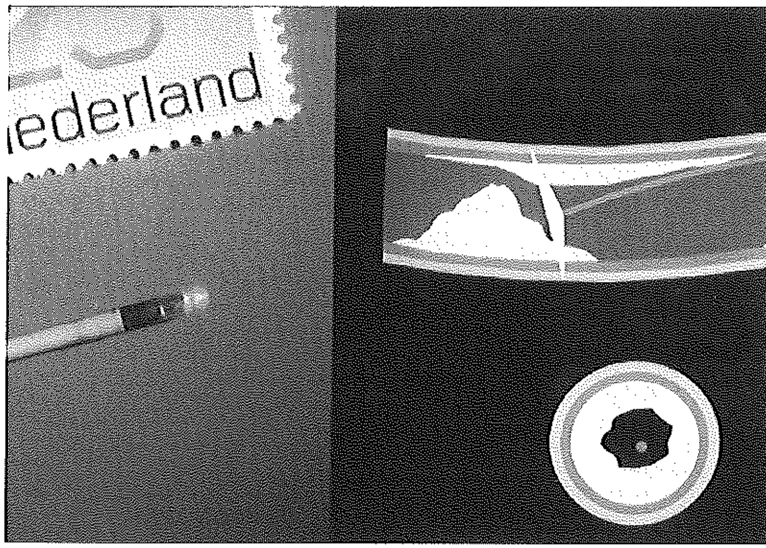

Fig. 1. Intravascular ultrasound catheter together with diagram. Ultrasound crystal inside dome rotates so that cross-sectional image of artery can be obtained. (Reprinted with permission of the *European Journal for Vascular Surgery* from Gussenhoven WJ, Essed CE, Frietman P, et al. Eur J Vasc Surg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

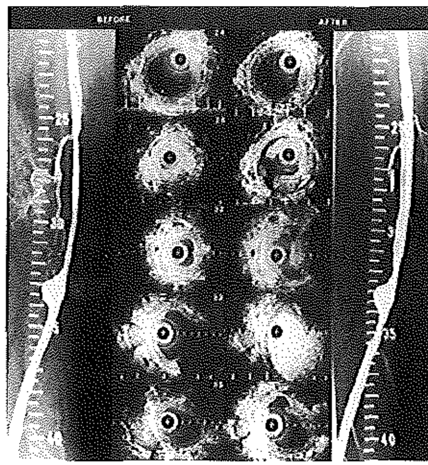

Fig. 2. Angiographic and intravascular ultrasonographic cross sections obtained from superficial femoral artery before and after balloon angioplasty. Under fluoroscopy radiopaque ruler is used to mark position of ultrasound catheter. Before intervention normal arterial segment is seen proximally (at 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.

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

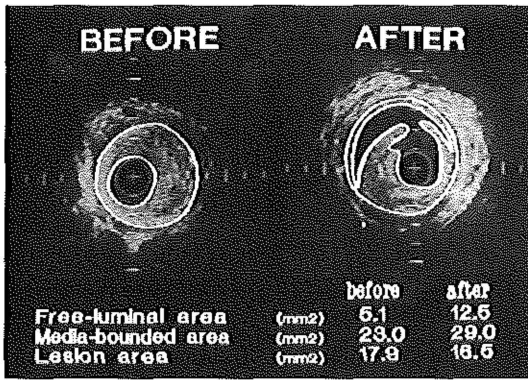

Fig. 3. Intravascular ultrasonographic cross sections of superficial femoral artery before and after balloon angioplasty showing traced contours of free lumen and media-bounded lumen area. Region enclosed by two contours is lesion area. Quantitative results before and after intervention are provided.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

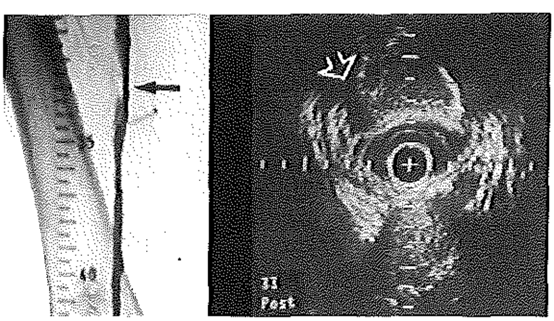

Fig. 4. Angiographic and intravascular ultrasonographic cross section of superficial femoral artery after balloon angioplasty. At level 33 both techniques reveal dissection. Semiquantitative and quantitative analyses with respect to degree of stenosis were not possible echographically given inadequate 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

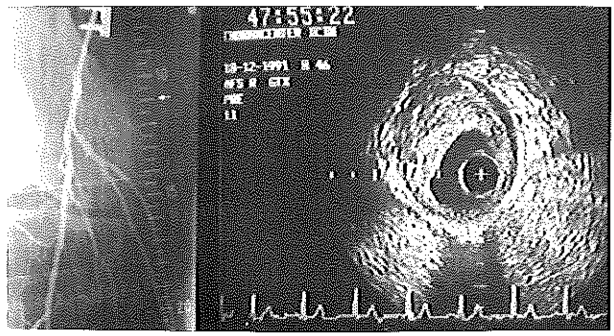

Fig. 5. Angiographic and intravascular ultrasonographic cross sections obtained before intervention showing discrepancy in classification of stenosis. At level 11 angiography judges stenosis less than 50% *(arrow)*. On ultrasonography large eccentric soft lesion is seen classified as 50% to 90% stenosis.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

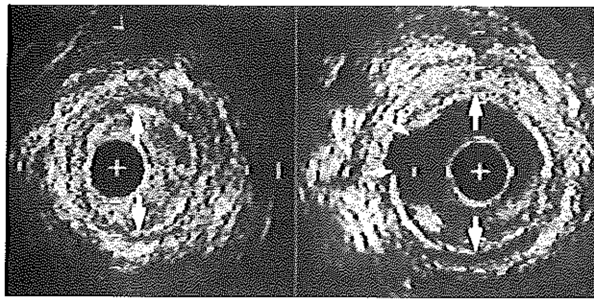

Fig. 6. Intravascular ultrasonographic cross sections obtained from superficial femoral artery at corresponding levels before *(left)* and after *(right)* balloon angioplasty with 6 mm diameter balloon. No angiogram was available before intervention because of origin obstruction of superficial femoral 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.)

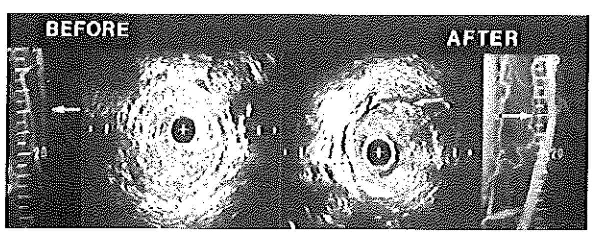

Fig. 7. Angiographic and intravascular ultrasonographic cross sections obtained from superficial femoral artery before and after balloon angioplasty. Before intervention, concordant classification is obtained from angiography and ultrasonography. At level 18 stenosis of greater than 90% was observed. 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 7

EFFECT OF BALLOON ANGIOPLASTY IN FEMOROPOPLITEAL ARTERIES ASSESSED BY INTRAVASCULAR ULTRASOUND

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ABSTRACT

To study the effects of balloon angioplasty (PTA) of the femoropopliteal artery with intravascular ultrasound (IVUS).

Corresponding IVUS cross-sections (n=1033) obtained before and after PTA from 115 procedures were analyzed. Vascular damage including plaque rupture, dissection and media rupture was assessed. Free lumen area (FLA), media-bounded area (MBA) and plaque area (PLA) were measured.

After PTA vascular damage was seen at the target site in 83 (72%) arteries: plaque rupture in 30 (26%), dissection in 66 (57%) and media rupture in 20 (17%) arteries. The FLA increased from 5.4 $\pm$ 3.4 mm^2 to 14.1 $\pm$ 5.0 mm^2 ($p<0.001$), MBA increased from 26.9 $\pm$ 10.0 mm^2 to 32.9 $\pm$ 10.7 mm^2 ($p<0.001$) and PLA decreased from 21.6 $\pm$ 8.5 mm^2 to 18.8 $\pm$ 8.0 mm^2 ($p<0.001$). The increase in MBA accounted for 68% of lumen gain. The frequency of vascular damage and the relative contribution of MBA increase and PLA decrease to luminal gain were not different in procedures with balloon diameter $\leq$5 mm and $\geq$6 mm.

Vascular damage is common following PTA. Lumen gain is mainly due to vessel expansion and, to a lesser extent, to a decrease in plaque area.

INTRODUCTION

Interventional therapy could benefit by greater understanding of the mechanism of balloon angioplasty and subsequent outcome. Since the clinical introduction of intravascular ultrasound (IVUS) in the 1980s, there are indications that this technique may reveal parameters related to success and failure of intervention. Therefore, in September 1992, a multicenter study was started named EPISODE (acronym for Evaluation Peripheral Intravascular Sonography On Dotter Effect) [1]. One of the aims of this study was to address the effects of balloon angioplasty of the femoropopliteal artery.

This study describes the effects of balloon angioplasty as assessed by IVUS imaging. The effects seen at the target site were compared with those seen in the entire dilated segment. The influence of balloon diameter on these effects was investigated.

MATERIAL AND METHODS

Study group

The study group comprised 109 patients of the EPISODE study (69 men, 40 women; age range 36-92 (median 67) years) in which patients with femoropopliteal artery disease eligible for balloon angioplasty were included. Patients were selected from the EPISODE study group based on the availability of IVUS images before and after balloon angioplasty. Thirty-three procedures were not included in the present study. In 19 procedures IVUS images were not available for analysis due to the following reasons: no intervention was performed (n=3), machine failure (n=6), inability of the ultrasound catheter to pass the aortobifurcation in cases of contralateral entry of the artery (n=4) and inability to advance the guidewire and the ultrasound catheter along the diseased segment (n=6). In the remaining 14 procedures IVUS data were not available before intervention because the guidewire or the ultrasound catheter could not be advanced across the lesion (2 stenoses and 12 occlusions). The investigation was approved by the local Committee on Human Research. Patients were included in the study after informed consent. The contribution of patients from each hospital was as follows: University Hospital Rotterdam-Dijkzigt 43 patients; University Hospital Utrecht 20 patients; Academic Medical Center (Amsterdam) 18 patients; Free Hospital (Amsterdam) 12 patients; Catharina Hospital (Eindhoven) 8 patients; Maria Hospital (Tilburg) 5 patients; Groot Ziekenhuis Gasthuis (Den Bosch) 3 patients. The studies performed in the last 4 hospitals were guided by researchers from the first 2 hospitals.

Balloon angioplasty of both femoropopliteal arteries was performed in 6 patients resulting in 115 procedures (88 stenotic and 27 occluded lesions). Patients were referred for intermittent claudication (n=70), rest and/or night pain (n=18), and ischemic ulceration (n=21). The decision to perform an intervention was made in consultation between the vascular surgeon and interventional radiologist. Experienced interventional radiologists performed or directly supervised the intervention.

Balloon angioplasty

Standard balloon angioplasty was performed from the femoral artery approach. The intervention was preceded and followed by routine single plane angiography and IVUS study. The selection of balloon type, diameter, inflation time and inflation pressure were left at the discretion of the interventionalist, and were based on angiography only. Data collected on each procedure included the stenotic or occluded status of the artery, the length of the dilated segment and balloon diameter. The length of the dilated segment was recorded with help of a radiopaque ruler.

Intravascular ultrasound

The IVUS studies were performed using mechanical systems based on a single ultrasound element (30 MHz). The circular image is produced by either a rotating element (Du-MED, Rotterdam, the Netherlands) or by a rotating mirror (CVIS, Sunnyvale, Ca, USA) [2]. Both transducers are mounted on a guidewire tipped 4.3F catheter (Du-MED 0.018" or 0.035"; CVIS 0.014").

The ultrasound catheter was introduced through an introducer sheath in an antegrade manner into the femoral artery. If the lesion was totally occluded, attempts were made to advance the guidewire and subsequently the ultrasound catheter into and across the lesion. According to an established protocol, a series of IVUS images of the diseased segment were obtained with 0.5 or 1 cm interval before and immediately after intervention by manual pull-back of the ultrasound catheter (Figure 1). Under fluoroscopic control the location of the ultrasound catheter was systematically compared with the radiopaque ruler (calibration 0.5 cm); the cathetertip location was indicated manually on the videomonitor [1]. The resulting images were displayed on the monitor via a video-scanned memory and stored on an S-VHS recorder. Care was taken to collect images before and after intervention on the same depth setting. During pull-back the gain setting was optimized and altered if necessary. When blood hampered detection of the luminal boundary, saline (5 cc) was injected via the sideport of the sheath in order to eliminate the echogenic blood (Figure 2). Cross-sections obtained before and after intervention were matched using the location derived from the radiopaque ruler. Anatomic markers such as sidebranches and calcium were helpful to check that the IVUS images corresponded. Corresponding cross-sections obtained within the dilated segment before and after balloon angioplasty (interval 0.5 or 1.0 cm) underwent a qualitative and quantitative off-line analysis.

Qualitative analysis

Cross-sections obtained after balloon angioplasty were evaluated for vascular damage including plaque rupture, dissection and media rupture (Figures 1 and 3). Plaque rupture was defined as a radial tear in the intimal surface; dissection was defined as the presence of a tear in the intimal surface separating the lesion from the underlying arterial wall; and media rupture was defined as an interruption in the internal elastic lamina and media which exposes the hyperechoic adventitia to the arterial lumen [1,3]. These morphologic features could be present simultaneously in one cross-section. Vascular damage was defined as the presence of plaque rupture, dissection and/or media rupture. The extent of dissection, graded as an arc of the circumference (in steps of 30°), was categorized into 4 groups: absent (0°), minor (30°-90°), moderate (120°-180°) and severe (210°-360°).

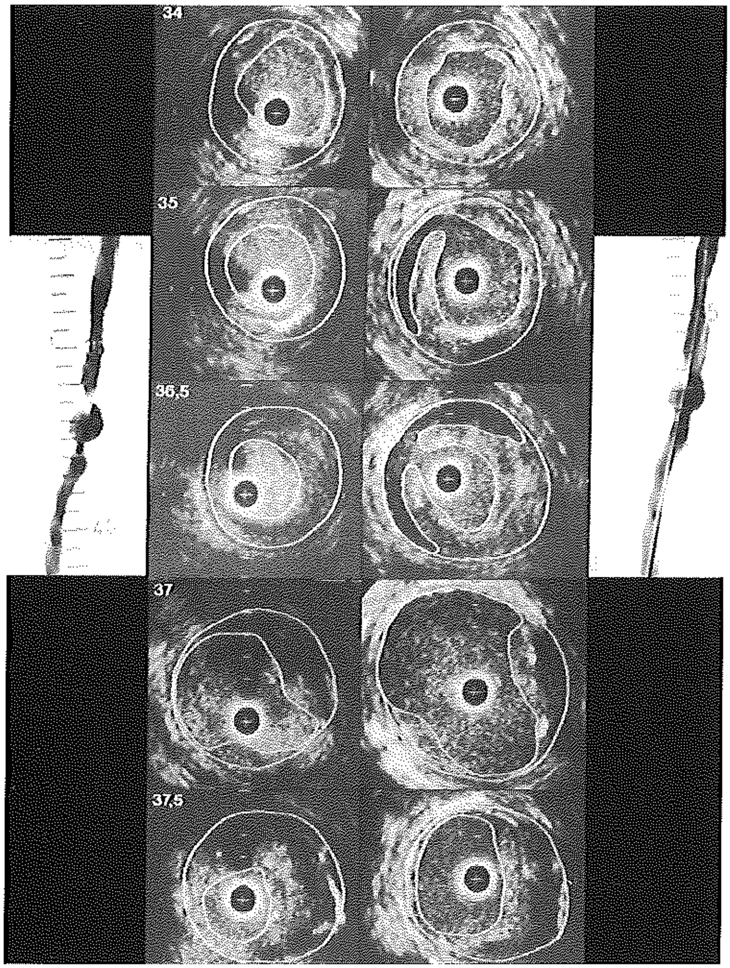

Figure 1. Angiograms and corresponding intravascular ultrasound (IVUS) cross-sections obtained with 0.5 or 1 cm interval from a patient before (left) and after (right) balloon angioplasty (PTA) of the superficial femoral artery. The IVUS cross-sections are contour traced off-line facilitating the recognition of free lumen area (inner contour) and media-bounded area (outer contour). Note the variety in morphologic features seen on IVUS before and after PTA. Dissections were seen at levels 34 to 36.5 cm. Catheter = +; calibration = 1 mm.

Quantitative analysis

Measurements were performed using a digital video analyzer system [4,5]. It was experienced that in still-frames the intensity of bloodscatter may be similar in magnitude to vessel wall scattering causing difficulty in discriminating the luminal boundary. To diminish this problem echo images were replayed in real-time on an additional videomonitor to distinguish the luminal boundary. Analysis included free lumen area defined as the area encompassed by the inner boundary of the intimal surface (characterized also by the presence of blood flow), and media-bounded area defined as the native vessel area bounded by the hypoechoic medial layer (Figs. 1 and 3). The plaque area was calculated by subtracting free lumen area from media-bounded area. The percentage area stenosis was calculated as plaque area divided by media-bounded area. In the absence of a visible media on ultrasound the adventitia was used as reference. When extensive dropout due to calcification was encountered, media-bounded area was not assessed leading to missing data for media-bounded area, plaque area and percentage area stenosis. In arteries with occluded segments the free lumen area before intervention was the same as the area occupied by the ultrasound catheter.

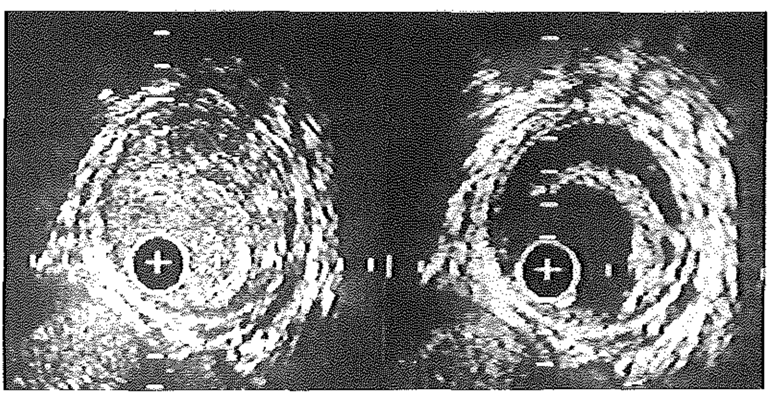

Figure 2. Intravascular ultrasound cross-sections obtained at the same level after balloon angioplasty of the superficial femoral artery without (left) and with (right) flushing with saline. Saline is used to eliminate the echogenic blood to clearly visualize the dissection and the free lumen area. Catheter = +; calibration = 1 mm.

Analysis of data

Qualitative and quantitative analyses of the IVUS images were basically performed by 4 researchers allocated to the participating university hospitals. The analyses were centrally reviewed by a second observer. Differences between the observers were solved by consensus. Intraobserver and interobserver variability has been studied and reported previously [6,7]. Briefly, in cross-sections obtained before (n=192) and after balloon angioplasty (n=212) from 38 patients interobserver agreement was good for dissection and vascular damage (kappa values 0.69 and 0.66, respectively); fair for media rupture (kappa value 0.25); and poor for plaque rupture (kappa value 0.04). Interobserver differences for the extent of dissection was 18 ± 48° ($p=0.001$). Interobserver differences for free lumen area before and after intervention were 0.22 ± 2.07 mm^2 ($p=0.15$) and 0.03 ± 1.94 mm^2 ($p=0.93$), respectively; and for media-bounded area 0.02 ± 3.05 mm^2 ($p=0.85$) and 0.11 ± 3.03 mm^2 ($p=0.62$), respectively [7]. Intraobserver differences were slightly smaller than interobserver differences [6].

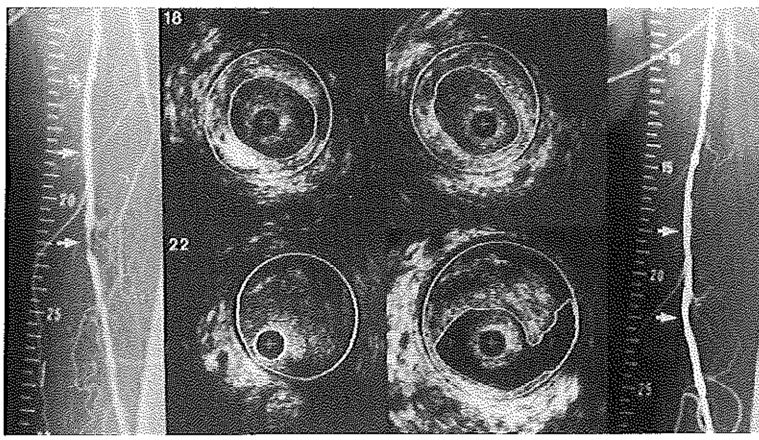

Figure 3. Angiograms and corresponding intravascular ultrasound (IVUS) cross-sections of the superficial femoral artery obtained before (left) and after (right) balloon angioplasty (PTA, 19-23 cm). Before PTA both angiography and IVUS showed a significant stenosis at level 22. Following intervention the IVUS cross-section showed a dissection and media rupture at 4 o'clock. Note that the plaque area remained unaltered. Catheter = +; calibration = 1 mm.

A comparison was made between the frequency of vascular damage seen with IVUS at the target site (defined as the cross-section with the smallest lumen area before balloon angioplasty), in all cross-sections in the dilated segment and per dilated segment. In addition, the extent of dissection at the target site, in all cross-sections and the maximum extent of dissection seen in the dilated segment were compared.

Area measurements obtained at the target site were compared with the measurements in all cross-sections derived from the dilated segment. The relative contribution of media-bounded area increase to luminal gain (increase in free lumen area) was calculated by the ratio of media-bounded area increase to luminal gain. Similarly, the relative contribution of plaque area decrease was calculated by the ratio of plaque area decrease to luminal gain. Differences in effects at the target site in procedures with a balloon diameter ≤5 mm and ≥6 mm were compared.

Data are presented as mean ± SD or as median and range if appropriate for continuous variables and as a percent for categoric variables. Chi-square analyses were used to assess differences in categoric variables. The Student's t test and the Mann-Whitney test were used to assess differences in the area measurements and extent of dissections, respectively. A p-value <0.05 was considered statistically significant.

RESULTS

No complications related to the IVUS study were encountered. The median length of the diseased segment subjected to dilation was 8 cm (range 4-32 cm). During pull-back of the ultrasound catheter it was evident that the lumen size changed markedly, as did the vascular damage after intervention. There were 1033 corresponding IVUS cross-sections before and after intervention available for analysis. The median number of cross-sections collected per dilated segment was 7 (range 3-26). Balloon diameter used was ≤5 mm in 45 and ≥ 6 mm in 70 procedures.

Table I. Frequency of vascular damage seen with intravascular ultrasound after balloon angioplasty of the femoropopliteal artery at the target site (n=115), in all cross-sections (n=1008), and per dilated segment (n=115).

	Target site		All cross-sections		Dilated segment	
	n=115		n=1008		n=115	
Plaque rupture	30	26%	148	15% †	69	60% *
Dissection	66	57%	457	45% ††	101	88% *
Media rupture	20	17%	140	14%	47	41% *
Vascular damage	83	72%	560	56% †	105	91% *

† Differences between target site and all cross-sections, $p<0.01$, †† idem $p<0.05$;
* Differences between target site and dilated segment, $p<0.001$.

Qualitative analysis

In total 1008 (98%) IVUS cross-sections were qualitatively analyzed. Poor image quality was encountered in 25 cross-sections. Data on the frequency of vascular damage including plaque rupture, dissection and media rupture at the target site, in all cross-sections, and per dilated segment are presented in Table 1. The frequency of vascular damage at the target site was 72%, in all cross-sections 56%, and per dilated segment 91%, respectively. Vascular damage not seen at the target site in 22 procedures was evidenced with IVUS elsewhere in the dilated segment. Dissections seen at the target site were graded as minor (62%), moderate (26%) and severe (12%). A similar distribution was encountered in the dissections (n=457) seen in all cross-sections (67%, 24% and 9%, respectively). However, the distribution of the maximum extent of dissection in the dilated segment was different (39%, 42% and 19%, respectively). Neither the frequency of vascular damage nor the extent of dissection seen with IVUS at the target site were different in procedures with a balloon diameter ≤ 5 mm and ≥6 mm (Table 2).

Table II. Frequency of vascular damage and extent of dissection seen with intravascular ultrasound at the target site in procedures with a balloon diameter ≤5 mm (n=45) and ≥6 mm (n=70).

	Balloon diameter ≤ 5 mm		Balloon diameter ≥ 6mm	
Plaque rupture	12	(27%)	18	(26%) *
Dissection	24	(53%)	42	(60%) *
Media rupture	7	(16%)	13	(19%) *
Vascular damage	32	(71%)	51	(73%) *
Dissection				
Absent	21	(47%)	28	(40%) *
Minor	17	(38%)	24	(34%)
Moderate	6	(13%)	11	(16%)
Severe	1	(2%)	7	(10%)

* Differences between procedures with a balloon diameter ≤5 mm and ≥6 mm were not significant.

Quantitative analysis

In 724 of 1033 (70%) corresponding IVUS cross-sections (including 78 of the 115 (68%) cross-sections at the target site) both free lumen area and media-bounded area could be calculated before and after intervention. Poor image quality and/or presence of calcification were the main reasons why quantitative analysis could not be performed in 309 cross-sections (range 0-21, median 2). As result of balloon angioplasty, a significant increase in free lumen area and media-bounded area and a significant reduction in plaque area and percentage area stenosis was noted both at the target site and in all cross-sections (Table 3; Figure 4). Differences in area measurements before and after intervention were larger at the target site when compared with measurements obtained from all cross-sections. The relative contribution of vessel expansion (i.e. media-bounded area increase) and plaque area reduction was 68% and 32% at the target site, and 85% and 15% in all cross-sections, respectively.

At the target site the luminal gain was smaller in the procedures with a balloon diameter ≤5 mm than in the procedures with a balloon diameter ≥6 mm (6.9 ± 3.2 mm^2 and 10.0 ± 4.4 mm^2, respectively, p = 0.001). However, no differences in relative contribution of media-bounded area increase were encountered (70% and 68%, respectively; p=0.82).

Table III. Area measurements before and after balloon angioplasty (PTA) of the femoropopliteal artery assessed with intravascular ultrasound at the target site and in all cross-sections.

	Before PTA	After PTA	% change
Free lumen area (mm^2)			
Target site (n = 78)	5.4 ± 3.4	14.1 ± 5.0	+161%
All cross-sections (n = 724)	11.8 ± 7.1	17.0 ± 6.5	+ 44%
Media-bounded area (mm^2)			
Target site (n = 78)	26.9 ± 10.0	32.9 ± 10.7	+ 22%
All cross-sections (n = 724)	27.4 ± 9.8	31.9 ± 10.0	+ 16%
Plaque area (mm^2)			
Target site (n = 78)	21.6 ± 8.5	18.8 ± 8.0	- 13%
All cross-sections (n = 724)	15.7 ± 7.4	14.9 ± 6.7	- 5%
Percentage area stenosis (%)			
Target site (n = 78)	80.0 ± 9.8	56.2 ± 10.2	- 30%
All cross-sections (n = 724)	57.6 ± 18.3	46.4 ± 12.7	- 19%

Differences between measurement before and after PTA are significant (p < 0.001). n = number of cross-sections; + = increase; - = decrease.

DISCUSSION

Since the introduction of IVUS in clinical practice investigators have acknowledged the ability of this technique to provide more insight in the ultimate effects of balloon angioplasty [8-16] as compared to angiography. Studies dealing with IVUS both in coronary and peripheral arteries generally consider one arterial cross-section for analysis [8-16]. In the present study, multiple adjacent corresponding ultrasound cross-sections obtained before and after balloon angioplasty of the femoropopliteal artery were analyzed.

This study revealed that vascular damage seen with IVUS was a common feature encountered following balloon angioplasty. In 91% of the procedures vascular damage was seen including plaque rupture (60%), dissection (88%) and media rupture (41%). Similarly, Losordo et al. [16] reported vascular damage following balloon angioplasty of the iliac artery in all 40 patients studied with IVUS. The frequency of vascular damage seen with IVUS is higher than reported from angiographic studies [17,18]. This reflects the advantage of this tomographic imaging technique to display more accurately the vascular anatomy compared to angiography.

Moreover, the present study revealed that the frequency of vascular damage at the target site seen with IVUS was lower compared to the frequency per dilated segment (72% vs 91%). The lower frequency of vascular damage seen at the target site may be related to the inability of IVUS to detect vascular damage at the target site in all instances. Similar observations were found in an in vitro IVUS study on coronary arteries (63% vs 95%) [19]. In this in vitro study dissections seen in histologic sections were missed on ultrasound for the following reasons: the dissected lesion remained adherent to the vessel wall; dissection occurred without connection with the lumen, and calcium hindered visualization of a dissection [19]. Thus, in order to have insight in the presence of arterial damage it is recommended to analyze the entire vascular specimen rather than 1 single cross-section.

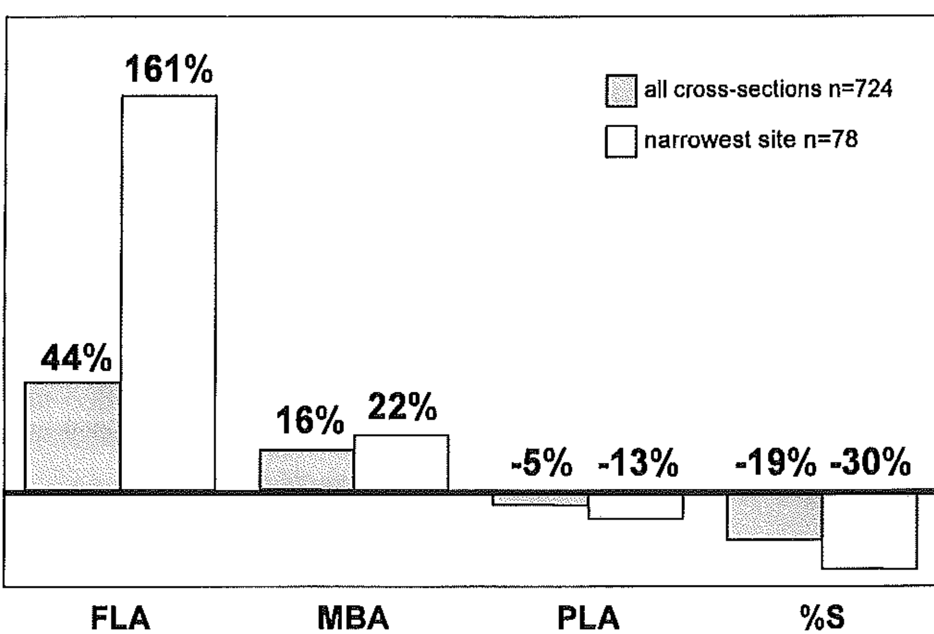

Figure 4. Differences in area before and after balloon angioplasty of the femoropopliteal artery seen in all cross-sections and in those at the target site. FLA = free lumen area; MBA = media-bounded area; PLA = plaque area; %S = percentage area stenosis.

The majority of dissections present was graded as minor (30°-90°) both at the target site (62%) and in all cross-sections (67%). However, evaluating the entire dilated segment it was found that the maximum extent of dissection was >90° in 61% of the procedures. The importance of the presence and extent of vasculatr damage for outcome will be determined in an ongoing follow-up study.

Surprisingly, balloon diameter used did not influence the presence nor the extent of vascular damage at the target site. Comparing quantitative data before intervention in the procedures performed with a ≤5 mm balloon with those treated with ≥6 mm balloon it was found that the free lumen area before intervention was not different (5.3 ± 3.0 mm^2 and 5.4 ± 3.7 mm^2, respectively; $p=0.91$). Conversely, the media-bounded area was larger (23.8 ± 7.8 mm^2 and 29.0 ± 10.8 mm^2, respectively; $p<0.001$). Thus, the fact that larger balloons were used in larger native vessels may explain the same amount and degree of vascular damage in procedures with a balloon diameter ≤5 mm and ≥6 mm.

The basic mechanism of balloon angioplasty has been under investigation since the introduction of this technique by Dotter and Judkins in 1964 [20]. Initially, most of these studies were performed using cadaver arteries [21,22]. The introduction of IVUS has enabled to study the mechanism of balloon angioplasty in vivo more precisely. The present study revealed that the increase in free lumen area following balloon angioplasty was predominantly related to an increase in media-bounded area (i.e. vessel expansion) and, to a lesser extent, to a decrease in plaque area. As expected, the magnitude of increase in free lumen area seen at the target site was larger as compared with the mean increase measured in all cross-sections. This was accompanied by both a larger media-bounded area increase and plaque area decrease. Based on histologic sections and angiographic records Castenada-Zuniga et al. [22] proposed that the increase in lumen size was due to the fact that the media stretches, without significant compression or redistribution of plaque. The present IVUS study confirms the mechanism proposed by Castaneda-Zuniga: when all cross-sections obtained in the dilated segment were taken into account plaque area decreased slightly (5%). However, the relative contribution of plaque reduction was higher at the target sites, suggesting that the plaque at the target site may be crushed more extensively, leading to redistribution of plaque material [23].

Other IVUS studies revealed a similar mechanism of lumen enlargement in coronary arteries [12,15,19]. However, Losordo et al. [16], using IVUS in iliac arteries reported that: "plaque compression and plaque fracture were the principal factors for increased luminal patency; stretching of the arterial wall provided an additional but minor contribution". The reason for this contrary result remains speculative. Probably, the difference in native artery size and vessel structure may result in another mechanism of balloon angioplasty. Although a larger balloon diameter resulted in an increased luminal gain, the relative contribution of media-bounded area increase and plaque area decrease remained the same.

Limitations

In this study IVUS cross-sections were matched using a radiopaque ruler and anatomic markers such as calcification and sidebranches. It is realistic to argue that the accuracy of the matched data may not be 100%. Data on multiple cross-sections mask this potential mismatch. It should be acknowledged that 33 procedures were not included in this study and that due to calcification and inadequate image quality in only 70% of the corresponding IVUS cross-sections both the free lumen area and media-bounded area could be calculated. The latter may have influenced the results as severe calcification may show a different pattern of dilation. Finally, the assessment of IVUS parameters is subjective. However, the kappa value of dissection was good and the variability in measurements was minimal, with the exception of the variability in the extent of dissection.

Conclusions

Vascular damage is a common finding following PTA of the femoropopliteal artery. Lumen gain is mainly due to vessel expansion and to a lesser extent to a plaque decrease. No relation was observed between balloon diameter and the incidence and extent of vascular damage and the relative contribution of media-bounded area increase and plaque area decrease to luminal gain.

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CHAPTER 8

INTRAVASCULAR ULTRASOUND PREDICTORS OF OUTCOME AFTER PERIPHERAL BALLOON ANGIOPLASTY

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Intravascular Ultrasound Predictors of Outcome After Peripheral Balloon Angioplasty*

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Objective: *This study investigates the potential role of intravascular ultrasound (IVUS) in the outcome in patients undergoing percutaneous transluminal angioplasty (PTA) of the superficial femoral artery.*
Materials: *Angiographic and the qualitative and quantitative IVUS data obtained at the narrowest site derived from 39 patients before and after PTA were analysed.*
Results: *Angiographically the diameter of the remaining stenosis seen after PTA was classified as <50% in 31 patients (success); in eight patients a failure was encountered. Evaluating at 6 months the functional and anatomic results of the PTA in 31 patients, the intervention was a success in 14 patients (Group I) and a failure in 17 patients (Group II). The remaining eight patients defined as angiographic failure following PTA comprised Group III. Neither qualitative nor quantitative IVUS data obtained before PTA could predict outcome. Conversely, after PTA, the extent of dissection was significantly more severe in Groups II and III than in Group I. Similarly, significant differences were found between Groups I and II for mean free lumen area (13.2 vs. 9.7 mm^2, respectively) and mean free lumen diameter (4.1 vs. 3.5 mm, respectively). Quantitative data obtained in Group II were similar to those in Group III.*
Conclusion: *This preliminary study demonstrates that following PTA the extent of dissection, free lumen area and diameter seen with IVUS are predictive factors of patency. Future studies with more patients are mandatory to further highlight the sensitivity of these observations.*

Key Words: Intravascular ultrasound; Balloon angioplasty; Angiography; Superficial femoral artery; Restenosis.

Introduction

Since the introduction of intravascular ultrasound (IVUS) numerous investigators have acknowledged the opportunity of this technique to obtain unique additional information about the vessel wall in comparison to angiography.[1–16] One of the benefits of IVUS is the ability to provide more insight in the ultimate effect of balloon angioplasty (PTA) and to measure accurately cross-sectional free lumen area and percentage (%) area stenosis in both coronary and iliofemoral arteries. Studies in which IVUS parameters are related to the occurrence of restenosis are limited to coronary arteries.[11,12] It appeared that qualitative and quantitative variables, other than dissection, derived from IVUS were not of predictive value for restenosis.[11,12]

The purpose of this study was to determine whether IVUS data on morphologic and quantitative parameters, obtained at the site of the smallest free lumen area seen before and after PTA of the superficial femoral artery are predictors of the outcome. This may answer the question whether one single cross-section with the most significant free lumen area obstruction, obtained with IVUS, can be used exclusively for future decision-making. Analysis of the IVUS data combined with angiographic data, clinical and hemodynamic follow-up data up to 6 months, form the basis of this study.

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Patients and Methods

Study group

In this multicentre study, EPISODE (Evaluation of Peripheral Intravascular Sonography On Dotter Effect), in which four university hospitals cooperate, angiographic and IVUS data were collected from 39 patients who underwent a PTA for treatment of *de novo* symptomatic superficial femoral artery occlusive disease. Patients were referred for disabling claudication (n = 29), rest pain (n = 4), and/or ischaemic ulceration (n = 6). The decision to perform a PTA was made in consultation between the vascular surgeon and intervention radiologist. There were 23 men and 16 women: age range 36–85 (mean 64) years. The investigation was approved by the local Committee on Human Research. Patients were included in the study after written informed consent and if they were assumed to be able to return for the follow-up at 1 and 6 months. All PTA procedures were preceded and followed by standard angiography and IVUS study. Experienced vascular radiologists performed or directly supervised the PTA procedure and scored the angiographic results. Each hospital was responsible for collection and analysis of the data including angiographic, IVUS, clinical and hemodynamic follow-up data. Data were stored using a database program written specifically for this study.

Angiography

Before PTA the length of the diseased segment subjected to dilation and the type of lesion (stenosis or occlusion) involved were scored angiographically. After PTA the outcome (success or failure) was defined. Success was classified semiquantitatively as remaining diameter stenosis <50% using the alleged normal vascular segment as reference.

Intravascular ultrasound

The IVUS study was performed using mechanical 30 MHz imaging systems. In two hospitals a CVIS system was used (Sunnyvale, Ca, U.S.A.), in two other hospitals a Du-MED system (Rotterdam, The Netherlands) was used. Care was taken that systems were calibrated properly. Catheters used contained a guide wire lumen (CVIS 0.014"; Du-MED 0.018" or 0.035"). A radiopaque ruler was used to match the IVUS data obtained before and after PTA with the angiographic data. Before, and immediately after, intervention the IVUS catheter was advanced distally beyond the lesion and cross-sections were recorded during pull-back of the catheter. If lesions consisted of a total occlusion, attempts were made to advance the guide wire and subsequently the IVUS catheter into and across the lesion. These attempts were terminated if major resistance was encountered. Images were recorded with 1 cm interval. Under fluoroscopic control the location of the IVUS catheter was systematically compared with the radiopaque ruler; its location was indicated manually on the video monitor.[5,6] The resulting images were displayed on the monitor via a video-scanned memory and stored on an S-VHS system.

The videotapes were reviewed for analysis and all cross-sections within the dilated segment obtained before and after PTA underwent qualitative and quantitative analyses (interval 1 cm). For the present study, qualitative and quantitative data viewed at the cross-section with the smallest free lumen area seen in each patient before and after PTA were selected.

Qualitative analysis. Cross-sections were assessed for lesion topography and morphology before PTA and for vascular damage after PTA (Table 1). Criteria for evaluating the morphologic features with IVUS have been described previously.[3–6] A lesion was judged to be present when the lesion thickness was 0.5 mm or more. The topography of the lesion may be either eccentric or concentric (Figs. 1–3). An eccentric lesion was defined as a lesion involving one part of the circumference of the vessel wall in a cross-section which leaves the remaining part disease-free. Plaque composition may include fibromuscular/fibrous (echo-soft), calcification (echo-hard with shadowing) and lipid deposit (echo-poor). After PTA the presence of dissection, plaque rupture and internal elastic lamina rupture was documented. In the absence of these features 'no effect' was scored. First, the incidence of these features seen before and after PTA was scored. Second, the extent of the normal vessel wall,

Table 1. Qualitative and quantitative intravascular ultrasound data evaluated in the cross-sections showing the smallest free lumen area before and after balloon angioplasty of the superficial femoral artery

Qualitative	Quantitative
Eccentric, concentric	Free lumen area
Soft, hard, lipid	Free lumen diameter
Dissection	Media-bounded area
Plaque rupture	Plaque area
Internal elastic lamina rupture	% area stenosis

the composition of the lesion and the severity of vascular damage involved were graded semiquantitatively as a sector of the circumference (in steps of 30°; range 0–360°). For instance, an eccentric lesion may involve 180° of the circumference leaving the remaining 180° disease-free (normal). If part of the circumference could not be analysed due to a strut or guide wire interposition, then that segment was classified as not analysable.

Quantitative analysis. Quantitative measurements were performed using a digital video analyser system.[17,18] Images that contain strong backscatter echoes from flowing blood may present difficulties in the determination of the lumen boundary on a still-frame. For quantitative analysis echo images have to be replayed on a separate video monitor to facilitate distinction between the luminal boundary from the echoes of blood backscatter. Analysis included measurement of free lumen area, free lumen diameter and media-bounded area (Table 1, Figs. 1–3). The plaque area was calculated by subtracting free lumen area from media-bounded area. The % area stenosis (obstruction) was calculated as plaque area divided by media-bounded area. In the absence of a visible tunica media on IVUS the adventitia was used as reference. When extensive dropout due to calcification was encountered, media-bounded area was not calculated.

Interobserver. Because data were collected from different hospitals, for the present study the qualitative and quantitative analyses collected from the first 29 patients studied with IVUS were controlled and discussed centrally (University Hospital Rotterdam). Differences between observers were solved by consensus. Ultrasound analyses of the remaining 10 patients were repeated by an independent observer (n = 74 cross-sections before and 64 cross-sections

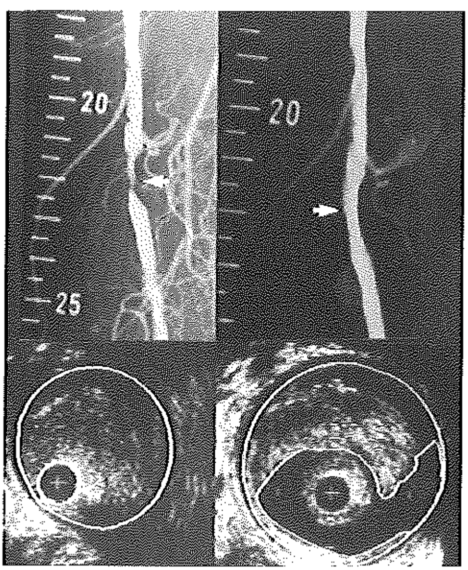

Fig. 1. Corresponding intravascular ultrasound cross-sections and angiograms obtained from a patient before and after balloon angioplasty (PTA) of the superficial femoral artery (Group I: angiographic diameter stenosis < 50%). Before PTA a soft eccentric lesion (330°) was involved at the smallest free lumen area (level 22 cm). After PTA the corresponding cross-section revealed a dissection (60°) and an internal elastic lamina rupture at 4 o'clock. The intravascular ultrasound cross-sections are contour traced off-line facilitating the recognition of free lumen area (FLA; inner contour) and media-bounded area (MBA; outer contour). The FLA increased from 1.9 mm^2 to 18.7 mm^2; the MBA increased from 26.8 mm^2 to 43.0 mm^2; the plaque area decreased from 24.9 mm^2 to 24.4 mm^2; and the free lumen diameter increased from 1.5 mm to 4.9 mm. + = catheter; calibration = 1 mm.

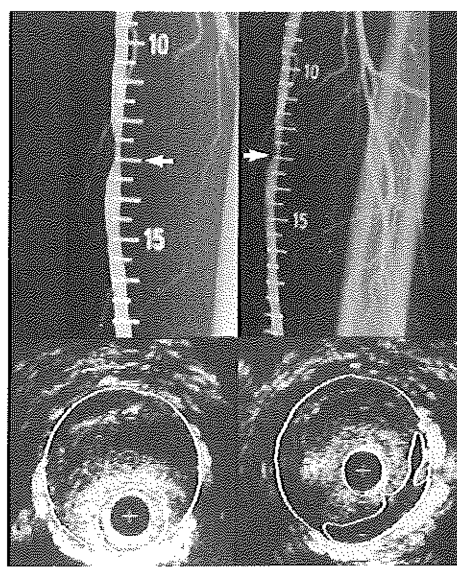

Fig 2. Corresponding intravascular ultrasound cross-sections and angiograms obtained from a patient before and after balloon angioplasty (PTA) (Group II: angiographic diameter stenosis < 50%). Before PTA the smallest free lumen area is seen at level 13 cm. The lesion involved was eccentric and soft in nature. After PTA the lesion became dissected from the arterial wall (dissection = 150°). The free lumen area (FLA; inner contour) and media-bounded area (MBA; outer counter) display the quantitative results. The FLA increased from 3.8 mm^2 to 4.6 mm^2; the MBA increased from 20.3 mm^2 to 21.0 mm^2; the plaque area decreased from 16.5^2 to 16.4 mm^2; and the free lumen diameter increased from 2.2 mm to 2.4 mm. As restenosis developed within 1 month, the patient was referred for repeat balloon angioplasty. + = catheter; calibration = 1 mm.

after PTA). Interobserver differences of the qualitative data were expressed as Kappa's coefficient and total percentage of agreement. Interobserver differences in the measurements of the free lumen area and media-bounded area were expressed as mean values and standard deviation of the paired differences.

Follow-up

After discharge (usually the day after the procedure) patients returned for follow-up at 1 month and at 6 months, or until an adverse event occurred. Criteria for evaluating the continuous success of PTA have been described previously.[19] Success and failure were defined using a combination of clinical and objective vascular laboratory findings. Unequivocal success of PTA was defined as improvement in the clinical condition by at least one Fontaine level (i.e. from ulceration to ischaemic night pain, or rest pain to disabling claudication, or claudication to asymptomatic); and on haemodynamic improvement.[19] Haemodynamic improvement is defined as an improvement in the ankle/brachial index (ABI) of at least 15%. In the presence of noncompressible vessels the ABI was not used. In addition, the information provided during the intervention of both the radiopaque ruler and patella were used as reference when the balloon dilated segment was studied with duplex. The ratio between the peak systolic velocities evidenced within the treated segment and proximal to the stenosis was used to determine the diameter stenosis.[20] A diameter stenosis <50% (PSV ratio <2.5) was defined as a successful PTA. Both vascular laboratory findings (ABI and Duplex) were decisive in assessing the outcome.

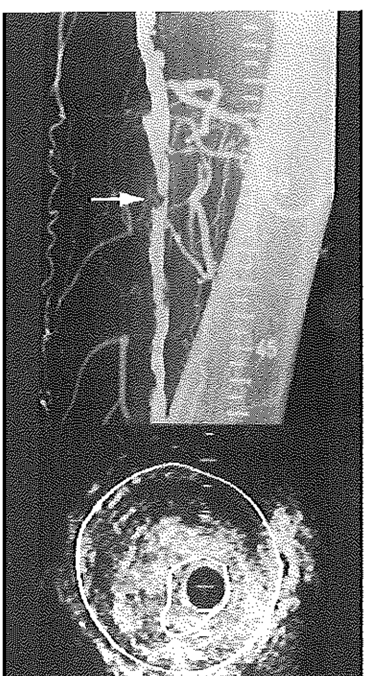

Fig. 3. Intravascular ultrasound cross-section and angiogram obtained from a patient after angiographically defined non-successful balloon angioplasty (Group III). Vascular damage was not encountered (no effect = 360°). The free lumen area (FLA; inner contour) and media-bounded area (MBA; outer counter) display the quantitative results: FLA = 6.6 mm^2, MBA = 56.6 mm^2, plaque area = 50 mm^2 and free lumen diameter 2.9 mm. Two days later the patient was referred for bypass surgery. + = catheter; calibration = 1 mm.

Statistical analysis

The IVUS data are presented as mean ± standard deviation. The IVUS data were divided into two groups according to the data evidenced angiographically (<50% diameter stenosis and failure) and further subdivided at follow-up. The Student's *t-test* was used to compare the IVUS data before and after PTA between the groups; a p value <0.05 was considered statistically significant.

Results

Intravascular ultrasound studies were completed successfully with good quality in all patients. No complications related to angiography or IVUS were encountered. Because the IVUS catheter could not be advanced across the lesion, IVUS data were not available before PTA in five patients (Fig. 3).

The level showing the smallest free lumen area on IVUS before PTA did not necessarily correspond to the level showing the smallest free lumen area after PTA: in 29 patients the levels corresponded within <5 cm; in three patients the distance was between 5 and 10 cm; in two patients the distance was 11 and 14 cm, respectively; in five patients IVUS data were not obtainable at the smallest free lumen area (vide supra).

Angiographically, the PTA procedure was classified as <50% diameter stenosis (success) in 31 patients and

Table 2. Incidence (%) of lesion topography and morphology seen before and pathologic features seen after ballon angioplasty (PTA) of the superficial femoral artery with intravascular ultrasound at the site showing the smallest lumen area

	Angiographic success (n=31)		Angiographic failure
	Group I (n=14) success	Group II (n=17) failure	Group III (n=8)
Before PTA*			
Concentric	71%	88%	63%
Hard	29%	41%	0%
Lipid	7%	6%	0%
After PTA*			
Dissection	43%	71%	50%
Plaque rupture	36%	12%	0%
IEL rupture	14%	18%	12%

n= number of patients.
IEL= internal elastic lamina.
* Differences were not significantly different.

as a failure in eight patients (Table 2). The 31 patients were followed using a combination of clinical and objective vascular laboratory findings to show the degree of success and the time of failure up to the census date of 6 months. Success was scored in 14 of the 31 patients (Group I); failure was scored in 17 of the 31 patients (Group II). Nine of the 17 failures occurred within 1 month after PTA. Of the patients failed: seven had no further treatment within 6 months; three had repeat PTA; five had vascular surgery; and two underwent amputation. The eight patients, classified angiographically as failure following PTA, comprised Group III; all these patients subsequently underwent vascular reconstructive surgery.

The mean length of the diseased segment subjected to dilation was 13.4 cm (range 4–32 cm). No significant differences in the length of the diseased segment was encountered in Group I (12 ± 7 cm) and Group II (11 ± 5 cm). The length of the diseased segment in Group III (21 ± 11 cm) was significant different from that seen in Groups I and II. Angiographically, a stenosis was present in 23 patients and an occlusion in 16 patients. The ratio stenoses *vs.* occlusions in the three groups was: seven stenoses *vs.* seven occlusions in Group I; 14 stenoses *vs.* three occlusions in Group II; and two stenoses *vs.* six occlusions in Group III.

Qualitative analysis

Data on lesion topography and morphology seen before and pathologic features seen with IVUS after PTA are summarised in Tables 2 and 3. Due to strut or guide wire interposition a mean of 10° of the cross-sectional image per cross-section could not be analysed for all groups. When considering the incidence of topography (eccentric/concentric), morphology (soft/hard/lipid) and pathologic features (dissection, plaque rupture and internal elastic lamina rupture), no significant difference between the three groups of patients was encountered (Table 2). In addition, no significant difference in extent of lesion topography and morphology was encountered between the three groups of patients (Figs. 1–3). Conversely, the extent of dissection seen after PTA in Groups II and III was significantly higher compared with the data from Group I (Table 3).

Quantitative analysis

Quantitative data obtained before and after PTA are summarised in Table 4. Before intervention, no significant differences in the quantitative data were observed between the three groups of patients. As result of PTA, a significant increase in free lumen area and free lumen diameter and a significant decrease in % area stenosis was noted in all groups. In addition, after PTA significant larger values were encountered in free lumen area and free lumen diameter in Group I *vs.* Group II. No significant differences were seen in media-bounded area, plaque area and % area stenosis between Groups I and II. Free lumen area, free lumen diameter and % area stenosis seen in Groups I and III were significantly different (see Table 4).

Table 3. Extent of the normal vessel wall and lesion morphology seen before and severity of pathologic features seen after ballon angioplasty (PTA) of the superficial femoral artery with intravascular ultrasound at the site showing the smallest free lumen area

	Angiographic success (n=31)		Angiographic failure
	Group I (n=14) success	Group II (n=17) failure	Group III (n=8)
Before PTA			
Normal	24°±48°	6°±21°	24°±33°
Hard	12°±21°	57°±93°	0°
Soft	306°±96°	267°±135°	279°±108°
Lipid	3°±9°	3 ±6°	0°
After PTA			
Dissection	18°±21°	78°±69° *	75°±102°
Plaque rupture	15°±21°	6°±15°	0°
IEL rupture	6°±18°	12°±24°	12°±30°
No effect	330°±30°	249°±81° *	279°±99°

Data represent the mean and S.D. of the degrees (°) involved along the boundary of the cross-section image.
n= number of patients.
IEL= internal elastic lamina.
* Differences between Groups I and II are significant (p<0.05).

Table 4. Quantitative intravascular ultrasound data obtained at the site showing the smallest free lumen area before and after balloon angioplasty (PTA) of the superficial femoral artery

	Angiographic success (n=31)		Angiographic failure
	Group I (n=14) success	Group II (n=17) failure	Group III (n=8)
Before PTA			
Free lumen area (mm^2)	6.0±3.6	3.6±2.0	3.4±1.6
Free lumen diameter (mm)	2.7±0.8	2.1±0.5	2.0±0.5
Media-bounded area (mm^2)	26.4±8.4	25.3±5.3	25.3±7.1
Plaque area (mm^2)	20.4±6.4	22.2±6.0	22.0±7.7
% area stenosis	77.7±9.2	86.5±7.3	84.4±10.8
After PTA			
Free lumen area (mm^2)‡	13.2±3.6	9.7±3.2*	7.2±2.8†
Free lumen diameter (mm)‡	4.1±0.5	3.5±0.6*	3.0±0.6†
Media-bounded area (mm^2)	29.3±8.5	29.1±11.6	32.4±12.6
Plaque area (mm^2)	16.1±8.2	21.5±8.2	25.2±12.1
% area stenosis‡	51.8±16.9	61.7±20.3	75.4±9.9†

Data represent the mean and S.D.
n= number of patients.
* Differences between Groups I and II are significant (p<0.05).
† Differences between Groups I and III are significant (p<0.05).
‡ Differences in quantitative data between before and after PTA are significant (p<0.05) for all groups.

Interobserver variability

There was moderate agreement for topography (eccentric/concentric) and morphology (soft/hard) and dissection (Kappa values 0.54, 0.59 and 0.46; total agreement of 77%, 91% and 73%). A poor agreement was observed for lipid, plaque rupture and internal elastic lamina rupture (Kappa values 0.0, 0.02 and 0.08; total agreement of 96%, 72% and 70%). The interobserver differences of the area measurements before and after intervention were +0.6 ± 2.3 mm^2 and +0.6 ± 2.1 mm^2, respectively, for free lumen area and –0.3 ± 3.5 mm^2 and –1.7 ± 3.4 mm^2, respectively, for media-bounded area.

Discussion

Given the fact that there is a lack of correlation between angiography and the outcome after PTA, there clearly is a need for a better understanding of the mechanism of restenosis and failure in angioplasty.[1] Since the introduction of IVUS, it has been suggested that this technique is capable to uncover the parameters related to success and failure of PTA. For this purpose we started in September 1992 a multicenter study named EPISODE in which four university hospitals participated. One of the aims of this study was to address the question of whether qualitative and quantitative lesion characteristics — as assessed by IVUS before and after PTA of the superficial femoral artery — are predictors of the long-term outcome. The present study is the first in which IVUS data, obtained at different centres before and after PTA, are analysed in a uniform manner. Besides IVUS studies, the investigation includes a systematic follow-up including clinical assessment, Doppler and Duplex studies.

The following issues of the present study deserve specific comments:

(1) Given the advanced technology and experience with balloon angioplasty in peripheral arteries, results obtained nowadays with PTA should be considerably better than series available a decade ago. However, the overall 6 months success rate, including early failure observed in this study, is markedly low (36%). Failure in this study, noted after angiographically classified < 50% diameter stenosis, was an early phenomenon: 9/17 failures were evidenced within 1 month. Our data are even worse compared to those previously reported by Jeans *et al.*(49%).[21] We realise that variations in results reported from different centers reflect the variation in selection of patients and lesions for intervention. The lesion length is an acknowledged parameter that determines suitability of PTA.[21,22] Becker *et al.* reported a 6 month patency rate of 23% in patients with long (> 7 cm) superficial femoral artery stenosis.[28] In our study, the overall length of the diseased segment subjected to PTA was large (mean 13.4 cm). Nonetheless, no significant difference in length was encountered between the success group (Group I) and the failure group (Group II). Furthermore, it has been suggested that the outcome for stenosis is significantly better than for occlusion.[21–23] Although the number of occlusions in the present study was high 16 (41%) the type of lesion involved (stenosis *vs.* occlusion) did not unequivocally influence the outcome. In Group I the ratio stenosis *vs.* occlusion was seven *vs.* seven, while in Group II this was 14 *vs.* three. These results are in keeping with those of others.[24,25] Altogether, we believe that the high incidence of failure in the present study may be influenced by both the length of the diseased segment as well as the type of lesion involved.

(2) Studies dealing with IVUS both in peripheral and coronary arteries generally consider one arterial cross-section for analysis.[7–16] In the present study, we were able to document different morphologic and quantitative data during pull-back of the IVUS catheter both before and after PTA. Recently, we have executed an *in vitro* study with IVUS to elucidate the effect of PTA on diseased coronary arteries. We learned that the quantitative effects were greater at the site of the smallest free lumen area compared with data obtained from multiple adjacent cross-sections within the dilated segment.[29] Consequently, for the present study we have chosen to select the site showing the smallest free lumen area seen with IVUS for analysis, rather than the available sequence of corresponding cross-sectional levels analysed within the dilated segment.

It proved that the most severely stenotic site seen before PTA may not necessarily correspond with the most stenotic site seen after intervention: in 29/39 cross-sections the levels corresponded closely with a distance < 5 cm. The reason for this may be that the effect of PTA may differ according to the lesion characteristics involved. It is noteworthy, that the observed quantitative changes in the free lumen area and diameter were caused by overstretching of the arterial wall by radial pressure of the balloon, leaving the plaque area virtually unchanged (see also Figs. 1, 2).

(3) Albeit plaque morphology is alleged to be an important determinant in pathologic outcome after PTA, published data do not show consensus.[23–25,30] The presence of calcium may either be prognostic for failure[23] or it does not influence outcome.[25] Similarly, eccentric lesions were more likely to be successfully dilated than were concentric lesions.[24,30] The opposite was claimed by Spies *et al.*[23]: i.e. concentric lesions were easier to treat than eccentric lesions. Similarly, reports on the significance of angiographically evidenced dissection for subsequent restenosis are conflicting. Patients with evidence of dissection may have a decreased long-term patency[31,32]; others demonstrated that the possibility of restenosis is not more likely in patients with dissection.[30,33–35]

According to the current library the ultimate benefit of IVUS is to provide additional information about the vessel wall in comparison to angiography, and its ability to measure accurately the cross-sectional free lumen area and % area stenosis during treatment of vascular disease.[1–16] The results of the present study show that, irrespective of stenosis or occlusion, both qualitative (soft, hard, lipid, eccentric, concentric) and quantitative IVUS data obtained prior to PTA, were comparable in the three patient groups. This suggests that the qualitative IVUS data obtained before PTA delivered no predictors for the ultimate outcome. These conclusions are consistent with those reported by Tenaglia *et al.*[12]

(4) The incidence of qualitative IVUS data after PTA including dissection, plaque rupture and internal elastic lamina rupture were not associated with the outcome. In contrast, the extent of dissection seen on IVUS related significantly with the outcome. Such a relation was also established by Tenaglia *et al.* in coronary arteries.[12] Others, however, suggested that restenosis was more likely to occur when a concentric plaque was involved without a fracture or dissection.[11] Although in our study the severity of dissection rather than the incidence of dissection was related to the outcome, we believe that care should be taken to designate this feature being of prognostic value given the small number of patients studied.

(5) Quantitative IVUS data obtained following PTA reveal that the effect of PTA on free lumen area, free lumen diameter and % area stenosis was significant for all three groups of patients. Because of the delay between balloon deflation after PTA and subsequent IVUS examination we assume the quantitative IVUS data obtained following PTA are not subjected to recoil.[7]

The most important observations in the present study are that after PTA significant differences were encountered for free lumen area and free lumen diameter between Group I *vs.* Groups II and III, respectively. The difference in % area stenosis was significant only between Groups I and III (52% *vs.* 75%). Conversely, no significant difference in % area stenosis was noted between Group I (52%) and Group II (62%). Honey *et al.*[11] reported that restenosis was not related to the % area stenosis involved (62% area stenosis: no restenosis *vs.* 59% area stenosis: restenosis). In this respect, it is important to realise that the calculated degree of % area stenosis does not reflect the actual free lumen area size, given the variability in remodeling of the vessel wall.[36,37] In addition, Tenaglia *et al.*[12] reported that neither free lumen area, diameter nor % area stenosis were predictive for the outcome. The reason why quantitative IVUS parameters in our study were of predictive value for failure, while those obtained following coronary balloon angioplasty were not, is merely speculative.

Limitations

This study was aimed to assess the usefulness of the IVUS parameters obtained at the smallest free lumen area site to predict success or failure of PTA in the superficial femoral artery. Other parameters such as patients' demographic data, the type and calibre of balloon used, qualitative angiographic data, run-off and IVUS data of adjacent segments were not taken into account. The IVUS cross-sections used (the smallest free lumen area) were obtained after off-line analysis. However, in order to use IVUS as a decision-making device during intervention one should be able to pinpoint the haemodynamically significant obstructive stenoses. This implies that the investigator needs to have the skill to recognize on-line the significance of the bottle-neck evidenced by IVUS. Images should be immediately reviewed and quantitatively analysed. Although semi-quantitative analysis of % area stenosis can readily be performed,[4] free lumen area and diameter are more difficult to assess—particularly because PTA causes extensive irregularity of the free lumen area contour. Thus, for on-line quantitative analysis, appropriate analytic equipment is required.

Conclusion

This study indicates that IVUS data obtained following PTA may predict whether a patient is likely—or not—to have a long-term, event-free outcome. Failure is more likely to occur in the presence of a large dissection and a small residual free lumen area and diameter evidenced following PTA. Other qualitative and quantitative IVUS parameters seen before and after PTA were considered to be of no prognostic value. The finding on IVUS of significant luminal narrowing at sites with minor diameter stenosis on angiography (< 50%) underscores the difficulty to accurately assess luminal narrowing using angiography alone.

A large number of failures after angiographic successful (< 50% diameter stenosis) PTA have been shown to occur within the first month (53%). This observation suggests that residual stenosis rather than restenosis due to fibrocellular tissue response may be the underlying mechanism responsible for the failures evidenced. A second significant determinant of failure noted in this study may be the length of the diseased segment. Nonetheless, the large number of successfully treated lesions seen in Group I justifies an aggressive approach when attempting angioplasty of lengthy obstructive superficial femoral artery disease.

Our results have important prognostic implications. Knowing the IVUS parameters associated with an adverse outcome this information may be helpful to more rationally decide when reintervention is indicated. The information could, in addition, be used to indicate which of the available therapeutic options (additional PTA, atherectomy, stent implantation or bypass surgery) is warranted for the individual patient.

Confirmation of the hypothesis that free lumen area and diameter seen on IVUS after PTA may serve to influence the course of interventional management might be gained in the near future when more patients in this multicenter study have a complete follow-up.

Note

Recently, 4 additional hospitals were willing to participate in this study, namely: Maria Hospital Tilburg, Catharina Hospital Eindhoven, Groot ZiekenGasthuis Den Bosch, and Slingeland Hospital Doetinchem. Follow-up of these patients is not completed.

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CHAPTER 9

INTRAVASCULAR ULTRASOUND PREDICTORS OF RESTENOSIS AFTER BALLOON ANGIOPLASTY OF THE FEMOROPOPLITEAL ARTERY

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ABSTRACT

Intravascular ultrasound (IVUS) provides unique information on the vessel wall before and after intravascular procedures which can not be obtained by other imaging techniques. This study attempts to identify IVUS parameters related to the outcome of percutaneous transluminal balloon angioplasty (PTA) of the femoropopliteal artery.

Patients (n=109) were studied with IVUS before and after angiographic successful PTA (n=114). IVUS cross-sections obtained with 1 cm interval in the dilated segment were analyzed. Outcome was assessed within 1 month and at 6 months after PTA. A distinction was made between anatomic (duplex scanning) and clinical (Rutherford criteria) restenosis. The prognostic value of clinical, angiographic and IVUS parameters obtained before and after PTA to predict restenosis was evaluated. IVUS parameters evaluated were obtained from the dilated segment with special attention to the site with the smallest lumen area (LA) before PTA and its matched site after PTA, and the site with the smallest LA after PTA.

Anatomic and clinical restenosis were evidenced in 36 and 49 procedures, respectively. Multivariate analysis revealed that a larger area stenosis after PTA at the matched site of the smallest LA before intervention was an independent predictor of both 1 month (odds ratio = 1.16 (95% CI: 1.07-1.26); p=0.0001) and 6 months anatomic outcome (odds ratio = 1.08 (95% CI: 1.02-1.15); p=0.017). Independent predictor of clinical outcome was the mean arç of hard (calcified) lesion (odds ratio = 1.69 (95% CI: 1.21-2.36) per increase of 30°; p=0.007). No predictors for 6 months clinical outcome were found.

This study revealed that IVUS is able to elucidate parameters predictive of outcome. IVUS can identify a subset of patients in whom restenosis is likely to develop and may, therefore, be used to influence interventional management in order to improve the results.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) is an accepted technique in the management of patients with obstructive disease of the femoropopliteal artery. Success rates vary considerably among series of reported cases (1 year patency: 47% to 73%) [1-6]. Given the lack of correlation between successful angioplasty assessed angiographically and the outcome, there is a need for better prediction of restenosis evidenced following intervention. It has been suggested that intravascular ultrasound (IVUS) is capable to reveal the parameters related to outcome of balloon angioplasty [7-9].

We conducted a multicenter study named EPISODE (Evaluation Peripheral Intravascular Sonography On Dotter Effect). The main objective of this study was to determine the additional value of IVUS compared with angiography in predicting the outcome following PTA of the femoropopliteal artery. Clinical, angiographic and IVUS data obtained before and after PTA were evaluated to identify parameters associated with the outcome of PTA.

METHODS

Study group

Between September 1992 and September 1994 a total of 137 patients referred for treatment of symptomatic obstructive disease of the femoropopliteal artery (n=148) were enrolled in the study. The centers and investigators participating in this study are listed in appendix I. The investigation was approved by the local Committee on Human Research. Patients were included in the study after informed consent.

Data collected on each patient included age, gender, hypertension (medication dependent), hypercholesterolemia (medication dependent or serum cholesterol > 6.5 mmol/l), diabetes, history of smoking and indication for intervention (intermittent claudication, rest pain, ischemic ulceration). Preoperative assessment included measurement of ankle-brachial blood pressure index (ABI) at rest and after treadmill exercise, and angiography using intra-arterial subtraction angiography.

Balloon angioplasty

The intervention was preceded and followed by routine single plane angiography and IVUS study. The selection of balloon type, diameter, inflation pressure and additional inflations were determined by the radiologist in charge and were based on angiography only. Data collected on each patient included the status of the artery before intervention (stenosis; occlusion) and the number of open runoff vessels, the length of the dilated segment and the angiographic diameter stenosis after intervention. Crural runoff vessels were categorized in 2 groups (good: 2 or 3; bad: none or 1). The length of the dilated segment, recorded using a radiopaque ruler, was categorized in 4 groups (≤5 cm, 6-10 cm, 11-15 cm, >15 cm). The degree of angiographic diameter stenosis was visually assessed on the basis of a reduction of the diameter at the most stenotic part of the artery, compared with a nearby "normal" arterial segment. Angiographic diameter stenosis after PTA was categorized into <50% and ≥ 50%. Angiographic success assessed by the radiologist in charge was defined as a decrease in angiographic diameter stenosis.

Intravascular ultrasound

The IVUS study was performed using mechanical 30 MHz imaging systems. In 3 hospitals a CVIS "Insight" system was used (Sunnyvale, Ca, USA), in 5 other hospitals a Du-MED "Intrasound" system (Rotterdam, The Netherlands) was used. Care was taken that systems were calibrated properly. Before intervention the ultrasound catheter was advanced via the sheath over the wire distally beyond the lesion and IVUS cross-sections were recorded along the dilation tract during manual pull-back of the catheter. After completion of the intervention, when the procedure was deemed angiographically successful or no additional interventions would be performed to further improve the angiographic result, the IVUS study was repeated in the same way. Care was taken to image the site with the smallest lumen area (i.e. bottle-neck) both before and after PTA. In order to match the IVUS cross-sections obtained before and after PTA a radiopaque ruler was used. Under fluoroscopic control the location of the ultrasound catheter was systematically compared with the radiopaque ruler; its location was indicated manually on the videomonitor [10], or the fluoroscopic images were mixed automatically together with the IVUS information. The resulting images were stored on an S-VHS recorder. The videotapes were reviewed off-line for analysis. The radiopaque ruler and anatomic markers such as side-branches and calcium deposits were used to match the IVUS cross-sections obtained before and after PTA. The matched cross-sections within the dilated segment (including the bottle-neck) were selected with 0.5 or 1 cm interval for analysis. Qualitative and quantitative analyses of the IVUS images were performed by one of the 4 researchers of the participating academic hospitals. The analyses were centrally reviewed by a second observer. Differences between the observers were solved by consensus.

Qualitative analysis

IVUS cross-sections were assessed for lesion topography and morphology before PTA and for vascular damage after PTA. Criteria for evaluating these features with IVUS have been described previously [10-12]. The topography of the lesion may be either eccentric or concentric. An eccentric lesion was defined as a lesion which leaves part of the vessel wall disease-free. A lesion was judged to be present when the lesion thickness was 0.5 mm or more. Lesion topography in cross-sections obtained from occluded segments was based on the position of the ultrasound catheter. Lesion morphology included the presence or absence of a hard lesion (bright echo with shadowing) representing calcification (Figures 1 and 2).

After PTA, the presence or absence of vascular damage (dissection and media

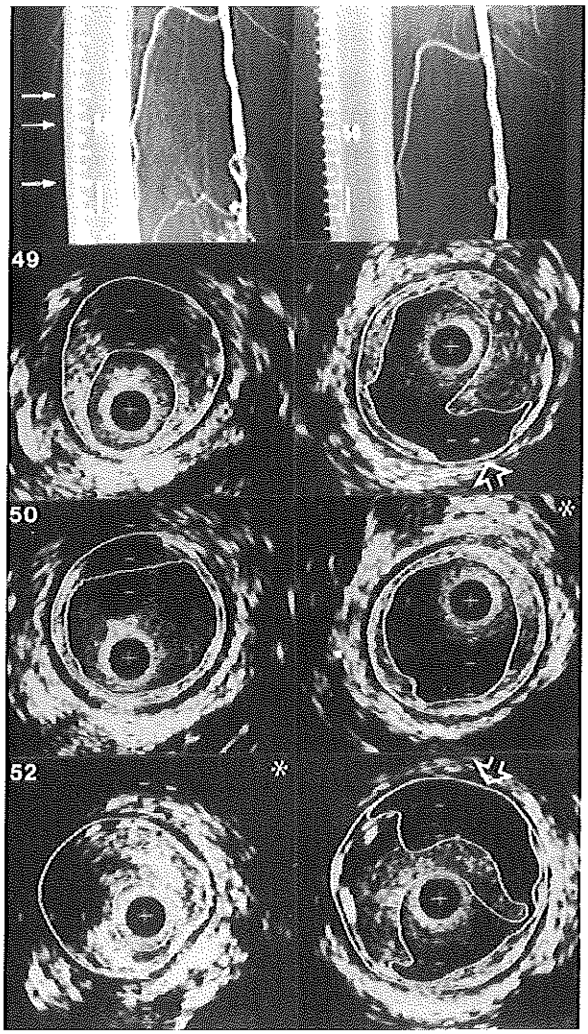

Figure 1. Angiograms and corresponding intravascular ultrasound (IVUS) cross-sections obtained before (left) and after (right) balloon angioplasty (PTA) of the femoropopliteal artery display the variety of anatomic features involved. The IVUS cross-sections are contour traced off-line facilitating the recognition of lumen area (LA; inner contour) and media-bounded area (outer contour). Before PTA soft eccentric lesions were seen. After PTA no effect (level 50), dissection and media rupture (open arrow) were seen (levels 49 and 52). At 6 months follow-up no restenosis was evidenced clinically and anatomically. * = cross-section with the smallest LA. + = catheter; calibration = 1 mm.

rupture) was documented. Dissection was defined as the presence of a tear in the internal surface associated with a separation of the lesion from the underlying arterial wall; media rupture was defined as an interruption in the internal elastic lamina which exposes the hyperechoic adventitia to the lumen [10,11]. These morphologic features could be present simultaneously in one cross-section (Figures 1 and 2).

Quantitative analysis

The extent of hard lesion and dissection was graded as an arc of the circumference with the center of the lumen as reference point (arc in steps of 30°; range 0-360°). Measurements of lumen and media-bounded areas before and after PTA were performed using a digital video analyzer system [13]. Plaque area was calculated by subtracting lumen area from media-bounded area. The percentage area stenosis was calculated as plaque area divided by media-bounded area x 100. In the absence of a visible media on ultrasound the outer hyperechoic layer representing the adventitia was used as reference. When extensive dropout due to calcification was encountered ($\pm > 120°$), media-bounded area was not calculated (Figures 1 and 2). The difference between the measurements obtained at the smallest lumen area before PTA and its matched site after PTA was calculated. In the occluded segments seen angiographically the most proximal IVUS cross-section obtained was considered as the location with the smallest lumen area. In order to rule out a Dotter effect of the wire and/or ultrasound catheter at this site, lumen area of the occluded lumen on IVUS was considered as 0.0 mm^2 and the area stenosis as 100%.

IVUS parameters selected for the analysis are listed in Table 1. They included: 1) qualitative and quantitative data obtained at the smallest lumen area before PTA and its matched site after PTA and those obtained at the smallest lumen area after PTA; 2) the mean arc of hard lesion and the mean and maximum arc of dissection encountered in the dilated segment; and 3) the presence of dissection and media rupture encountered in the dilated segment.

Interobserver analysis

Reproducibility of IVUS parameters assessed by researchers from the participating academic hospitals in cross-sections obtained before (n=192) and after PTA (n=212) from 38 patients has been previously reported [12]. Interobserver agreement was good for hard lesion, dissection and vascular damage (kappa values 0.67, 0.69 and 0.66, respectively); moderate for lesion topography (kappa value 0.45); fair for media rupture (kappa value 0.25); and poor for lipid and plaque rupture (kappa value 0.0 and 0.04, respectively). Interobserver differences for the extent of hard lesion and dissection was $6 \pm 33°$ (p=0.22) and $18 \pm 48°$ (p=0.001), respectively. Interobserver differences of lumen area before and after intervention were 0.22 ± 2.07 mm^2 (p=0.15) and $0.03 \pm$

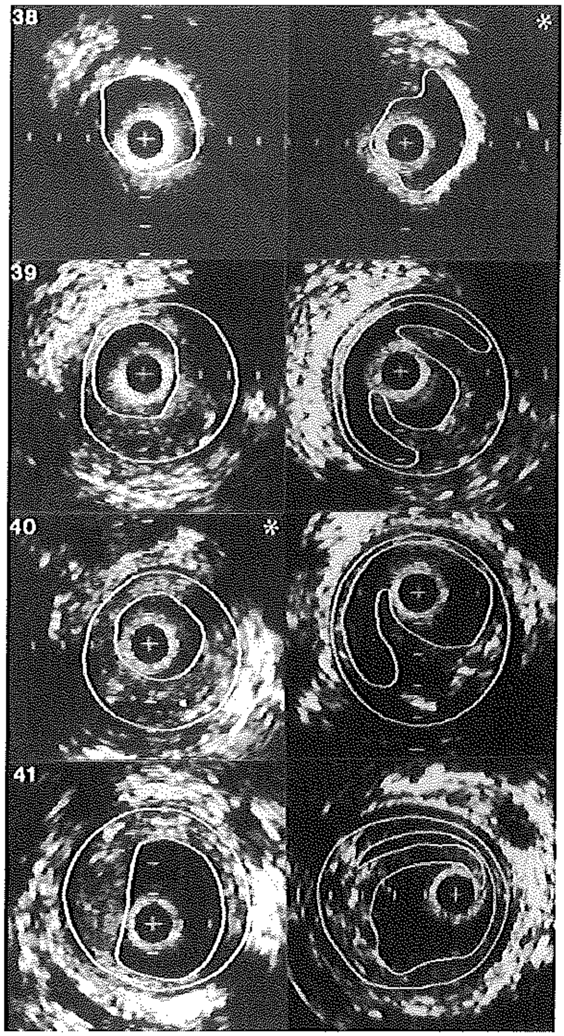

Figure 2. Corresponding intravascular ultrasound (IVUS) cross-sections obtained before (left) and after (right) balloon angioplasty (PTA) of the femoropopliteal artery. The IVUS cross-sections are contour traced off-line facilitating the recognition of lumen area (LA; inner contour) and media-bounded area (MBA; outer contour). At level 38 the presence of a hard lesion prevented measurement of the MBA. Distally the lesion was classified as soft. After PTA, dissections were seen at level 39 to 41. * = cross-section with the smallest LA; + = catheter; calibration = 1 mm.

1.94 mm^2 ($p=0.93$), respectively; and for media-bounded area 0.02 ± 3.05 mm^2 ($p=0.85$) and 0.11 ± 3.03 mm^2 ($p=0.62$), respectively.

Table 1. Intravascular ultrasound parameters selected for analysis at different locations.

	Location		
	Smallest LA before and matched site after PTA	Smallest LA after PTA	All cross-sections
Hard lesion	+/-, extent		extent (mean)
Eccentric lesion	+/-		
Dissection	+/-, extent	+/-, extent	+/-, extent (mean; maximum)
Media rupture	+/-	+/-	+/-
LA, MBA, PLA, %S	before, after, difference	after	

PTA = percutaneous transluminal angioplasty; +/- = present/absent; LA = lumen area; MBA = media-bounded area; PLA = plaque area; %S = area stenosis.

Follow-up

The follow-up protocol included clinical assessment, ABI pressure measurements at rest and after treadmill exercise, and color-flow duplex examination within 1 and at 6 months after intervention.

Anatomic outcome was determined by color-flow duplex scanning of the femoropopliteal artery with special emphasis on the dilated segment. A radiopaque ruler was used to determine the site of a stenosis. Stenotic segments were identified by a locally increased velocity and poststenotic turbulence characterized by color changes. The peak systolic velocity at the site of a stenosis (PSV stenosis) was compared with the peak systolic velocity of a nearby normal proximal arterial segment (PSV artery). The peak systolic velocity ratio was calculated as PSV stenosis/PSV artery. A ratio ≥2.5 was considered a stenosis of ≥50% [14-16]. An occlusion was characterized by the absence of detectable arterial flow. Early (within 1 month) and late (at 6 months) anatomic restenosis were defined as a stenosis ≥ 50%.

Clinical outcome was classified according to the Society for Vascular Surgeons/International Society for Cardiovascular Surgery criteria on a scale from -1 to -3 for deterioration of symptoms and ABI; 0 for unchanged symptoms; +1 for either a categorical improvement of clinical classification or increase of ABI >0.10; +2 for at least a single category improvement combined with ABI increase of >0.10; and +3 for markedly improved or absence of clinical symptoms combined with an ABI >0.90

[17,18]. Early restenosis (within 1 month) was defined as unchanged or deterioration of symptoms (score $< +1$); late restenosis was defined as each deterioration evidenced at 6 months.

Study endpoints and statistical analysis

The relationship between clinical, angiographic and IVUS variables and the outcome of intervention was studied. Predictors of both 1 month outcome (early success versus early restenosis) and 6 months outcome (late success versus early and late restenosis) were assessed. The early success group comprised all procedures with 1 month success and included all procedures with subsequent late success, late restenosis and those without further follow-up. In addition, procedures with late success and late restenosis were compared to determine whether different predictors were found for early and late restenosis.

Results were expressed as mean value $\pm$ SD. For univariate analysis the chi-squared test or Fisher's exact test was used to assess differences in dichotomous variables. The Mantel-Haenszel chi-squared trend test was used to assess differences in ordinal categorical variables. Differences in continuous variables were compared using Student's two sample t-test. Clinical, angiographic and IVUS variables with $p < 0.1$ univariately were entered into a stepwise forward logistic regression analysis (SPSS, SPSS Inc, Chicago) to detect variables that were independently significantly related to the anatomic and clinical outcome of the intervention, respectively. In the presence of missing data, missing value indicators were used in order to enable multivariate analysis on the whole data set, although this may result in the entrance of variables in the multivariate model other than expected on the basis of the univariate analyses. A p-value from a multivariate analysis refers to the simultaneous significance of a variable and its missing value indicator. The statistical significance level was set at $p \leq 0.05$.

RESULTS

Angiographic and IVUS study was completed in 129 of the 148 interventions. Complications were not encountered. In 19 procedures, IVUS images were not available for the following reasons: ultrasound equipment failure (n=6), inability to advance the wire and the ultrasound catheter along the PTA tract (n=6), inability of the ultrasound catheter to pass the aortobifurcation in cases of contralateral entry of the artery (n=4), and intervention was not performed (n=3). Angiographically, the interventions (n=129) were classified as success in 114 and as initial failure in 15 procedures. For the present study, data of the 114 procedures obtained from 109 patients were included in the analysis. Clinical and angiographic data of the angiographic successful interventions (n=114) are presented in Table 2.

Table 2. Clinical and angiographic data obtained in 109 patients with 114 treated femoropopliteal arteries.

Clinical data			Angiography		
Age (median, range),(years)		67 (39-93)	Stenosis		86 (75.4%)
Male		68 (62.4%)	Occlusion		28 (24.6%)
Hypertension		36 (33.0%)	Runoff	good	76 (66.7%)
Hypercholesterolemia		22 (20.2%)		bad	33 (28.9%)
Diabetes		34 (31.2%)		unknown	5 (4.4%)
History of smoking		75 (68.8%)	Length of PTA	≤5 cm	39 (34.2%)
Indication:	Intermittent claudication	78 (68.4%)		6-10 cm	27 (23.6%)
	Rest pain/ulceration	36 (31.6%)		11-15 cm	20 (17.5%)
				>15 cm	28 (24.6%)
			Angiographic diameter stenosis		
			after PTA:	<50%	92 (80.7%)
				≥50%	22 (19.3%)

PTA = percutaneous transluminal angioplasty.

IVUS data were available before and after intervention in 102 of the 114 procedures. In 12 procedures, IVUS data were not available prior to intervention because the wire or the ultrasound catheter could not be advanced across the lesion (11 occlusions and 1 stenosis). In total, 920 cross-sections before and 1171 cross-sections after PTA were subjected to analysis. Lumen area and media-bounded area could be assessed in 97% and 81% of the cross-sections available, respectively; no differences in analyzable cross-sections were encountered before and after intervention. Poor image quality and presence of a hard lesion were the main reasons preventing adequate identification of the media-bounded area.

It was found that the smallest lumen area site seen on IVUS before PTA did not necessarily correspond to the smallest lumen area site seen after PTA: in 73 procedures the distance between the smallest lumen area before and after PTA was ≤2 cm, in 19 procedures between 2 and 5 cm and in 10 procedures >5 cm (Figures 1 and 2).

Anatomic and clinical outcome

Anatomic and clinical outcome of angiographic successful PTA (n=114) evidenced at 1 and 6 months are summarized in Table 3. Early anatomic restenosis was assessed in 18 procedures and late restenosis was evidenced in another 18 procedures. Early clinical restenosis was assessed in 17 and late restenosis in 32 procedures. Within the first month 3 patients died and in 15 procedures duplex scanning was not performed. At 6 months anatomic and clinical follow-up data were not available in 10 and 6 procedures, respectively.

Table 3. Anatomic and clinical outcome of angiographic successful balloon angioplasty (n=114) evidenced at 1 and 6 months.

	Interval (month)	No. at risk	No. of failure	Died	No. of lost to follow-up
Anatomic outcome	0 - 1	114	18	3	15
	1 - 6	78	18	2	8
Clinical outcome	0 - 1	114	17	3	0
	1 - 6	94	32	2	4

n = number of procedures; No. = number.

Predictor variables of anatomic outcome

The angiographic and IVUS parameters in the procedures with early restenosis, late restenosis and late success are listed in Table 4.

Predictors of 1 month outcome (early restenosis versus early success). Neither clinical nor angiographic variables were related to anatomic outcome. IVUS predictors of early restenosis were a smaller lumen area after PTA (11.8 ± 4.8 mm^2 vs 15.0 ± 4.8 mm^2; p=0.019), a larger area stenosis after PTA (66 ± 11 % vs 53 ± 8 %; p=0.001), a smaller lumen area increase (7.3 ± 4.6 mm^2 vs 10.3 ± 4.7 mm^2; p=0.021), a smaller plaque area decrease (1.8 ± 2.3 mm^2 vs 4.0 ± 5.5 mm^2; p=0.035), and a smaller area stenosis decrease (18 ± 12% vs 30 ± 14%; p=0.006) at the smallest lumen area before and its matched site after PTA. Moreover, a larger area stenosis (67 ± 10% vs 58 ± 10%; p=0.002) at the smallest lumen area after PTA was found predictive for early restenosis (Figure 3). The presence and extent of vascular damage were not predictive of early restenosis. Media rupture in the dilated segment was less frequently seen in procedures with early restenosis than early success, but this difference did not reached a significant level (22% versus 46%; p=0.063).

By multiple logistic regression analysis the only independent predictor of early

Table 4. Angiographic and intravascular ultrasound parameters in procedures with early anatomic restenosis, late anatomic restenosis and late anatomic success.

	Early restenosis (n=18)	Late restenosis (n=18)	Late success (n=50)	† p	†† p	††† p
Angiography						
Diameter stenosis < 50%	14 (78%)	16 (89%)	40 (80%)	0.74	0.70	0.49
Occlusion	5 (28%)	5 (28%)	12 (24%)	0.76	0.69	0.76
Bad runoff	5 (28%)	5 (28%)	13 (26%)	1.00	0.84	1.00
PTA length (cm)						
≤5	7 (39%)	4 (22%)	23 (46%)	0.24	**0.043**	0.077
6-10	2 (11%)	6 (34%)	14 (28%)			
11-15	4 (22%)	4 (22%)	7 (14%)			
>15	5 (28%)	4 (22%)	6 (12%)			
Intravascular Ultrasound						
All cross-sections in the dilated segment						
Mean arc of hard lesion (°)	36 ± 54	18 ± 18	25 ± 34	0.49	0.84	0.42
Dissection	14 (78%)	15 (83%)	46 (92%)	0.26	0.19	0.37
Mean arc of dissection (°)	32 ± 30	53 ± 46	37 ± 28	0.33	0.49	0.18
Maximum arc of dissection (°)	122 ± 91	143 ± 90	107 ± 67	0.83	0.13	0.076
Media rupture	4 (22%)	9 (50%)	23 (46%)	0.063	0.36	0.77
Smallest LA before and its matched site after PTA						
Eccentric lesion	4 (25%)	7 (44%)	15 (35%)	0.27	0.96	0.53
Hard lesion	9 (56%)	3 (19%)	15 (35%)	0.10	0.82	0.34
Arc of hard lesion (°)	64 ± 90	19 ± 41	25 ± 38	0.12	0.26	0.58
Dissection	9 (56%)	9 (56%)	27 (60%)	0.97	0.74	0.79
Arc of dissection(°)	64 ± 83	56 ± 67	53 ± 62	0.52	0.64	0.85
Media rupture	3 (19%)	2 (13%)	6 (13%)	0.69	1.00	1.00
LA before PTA (mm^2)	4.6 ± 4.3	3.8 ± 3.2	4.7 ± 3.8	0.89	0.55	0.38
MBA before PTA (mm^2)	30.6 ± 11.9	22.9 ± 8.5	26.8 ± 10.1	0.10	0.90	0.19
PLA before PTA (mm^2)	25.2 ± 10.1	19.3 ± 9.7	21.9 ± 8.4	0.12	0.96	0.35
Area stenosis before PTA (%)	85 ± 15	82 ± 15	83 ± 12	0.45	0.94	0.79
LA after PTA (mm^2)	11.8 ± 4.8	14.5 ± 4.5	15.0 ± 4.7	**0.019**	0.11	0.74
MBA after PTA (mm^2)	33.5 ± 13.4	33.0 ± 11.1	32.4 ± 9.8	0.84	0.74	0.84
PLA after PTA (mm^2)	22.6 ± 11.1	18.1 ± 7.9	17.3 ± 6.3	0.13	0.15	0.68
Area stenosis after PTA (%)	66 ± 11	54 ± 9	53 ± 8	**0.001**	**0.009**	0.76
LA increase (mm^2)	7.3 ± 4.6	10.8 ± 6.1	10.3 ± 4.5	**0.021**	0.28	0.73
MBA increase (mm^2)	3.9 ± 3.0	7.5 ± 8.5	6.3 ± 4.8	0.13	0.71	0.54
PLA decrease (mm^2)	1.8 ± 2.3	3.9 ± 5.2	4.0 ± 6.1	**0.035**	0.39	0.94
Area stenosis decrease (%)	18 ± 12	32 ± 13	29 ± 15	**0.006**	0.25	0.56
Smallest LA after PTA						
Dissection	8 (44%)	8 (44%)	25 (50%)	0.82	0.61	0.69
Arc of dissection (°)	57 ± 82	47 ± 67	44 ± 59	0.52	0.60	0.87
Media rupture	2 (11%)	1 (6%)	2 (4%)	0.31	0.65	1.00
LA after PTA (mm^2)	10.0 ± 4.2	11.2 ± 3.0	12.3 ± 4.2	0.054	0.051	0.32
MBA after PTA (mm^2)	32.1 ± 14.0	27.7 ± 8.4	30.0 ± 9.3	0.47	0.96	0.40
PLA after PTA (mm^2)	22.0 ± 11.1	16.3 ± 7.1	17.5 ± 6.5	0.13	0.40	0.54
Area stenosis after PTA (%)	67 ± 10	57 ± 11	57 ± 9	**0.002**	0.063	0.95

† = Comparison of early restenosis versus early success; †† = Comparison of (early and late) restenosis versus late restenosis; ††† = Comparison of late restenosis versus late success; PTA = percutaneous transluminal angioplasty; LA = lumen area; MBA = media-bounded area; PLA = plaque area; significant values are shown in bold.

Table 5. Angiographic and intravascular ultrasound parameters in procedures with early clinical restenosis, late clinical restenosis and late clinical success.

	Early restenosis (n=17)	Late restenosis (n=32)	Late success (n=56)	† p	†† p	††† p
Angiography						
Diameter stenosis < 50%	14 (82%)	28 (88%)	43 (77%)	1.00	0.25	0.22
Occlusion	2 (12%)	9 (28%)	16 (29%)	0.23	0.47	0.96
Bad runoff	7 (41%)	9 (28%)	13 (25%)	0.25	0.43	0.79
PTA length (cm)						
≤5	6 (35%)	10 (31%)	18 (32%)	0.68	0.89	0.77
6-10	3 (9%)	10 (31%)	13 (23%)			
11-15	3 (9%)	5 (16%)	12 (21%)			
>15	5 (29%)	7 (22%)	13 (23%)			
Intravascular Ultrasound						
All cross-sections in the dilated segment						
Mean arc of hard lesion (°)	68 ± 68	22 ± 33	26 ± 35	**0.028**	0.20	0.63
Dissection	14 (82%)	29 (91%)	51 (91%)	0.45	0.58	1.00
Mean arc of dissection (°)	31 ± 27	53 ± 46	42 ± 34	0.20	0.66	0.21
Maximum arc of dissection (°)	120 ± 85	135 ± 78	123 ± 82	0.94	0.65	0.49
Media rupture	8 (47%)	15 (47%)	22 (39%)	0.61	0.43	0.49
Smallest LA before and its matched site after PTA						
Eccentric lesion	5 (36%)	8 (28%)	17 (36%)	1.00	0.55	0.44
Hard lesion	10 (71%)	7 (24%)	19 (40%)	**0.008**	0.93	0.15
Arc of hard lesion (°)	79 ± 96	20 ± 38	35 ± 59	0.078	0.77	0.21
Dissection	8 (53%)	16 (55%)	30 (61%)	0.85	0.51	0.60
Arc of dissection (°)	46 ± 51	62 ± 68	51 ± 66	0.75	0.67	0.48
Media rupture	2 (13%)	5 (17%)	7 (14%)	1.00	0.83	0.75
LA before PTA (mm^2)	5.0 ± 4.8	4.2 ± 3.6	4.4 ± 3.6	0.66	0.89	0.86
MBA before PTA (mm^2)	30.2 ± 12.6	27.9 ± 10.3	25.6 ± 9.2	0.25	0.23	0.37
PLA before PTA (mm^2)	23.5 ± 9.5	23.8 ± 9.4	20.9 ± 8.5	0.55	0.18	0.21
Area stenosis before PTA(%)	81 ± 13	86 ± 13	83 ± 13	0.60	0.62	0.39
LA after PTA (mm^2)	13.9 ± 7.3	15.0 ± 4.0	14.4 ± 4.0	0.56	0.87	0.58
MBA after PTA (mm^2)	34.7 ± 14.2	35.0 ± 11.2	32.1 ± 8.9	0.60	0.23	0.23
PLA after PTA (mm^2)	20.4 ± 7.2	20.0 ± 8.8	17.6 ± 7.4	0.41	0.16	0.23
Area stenosis after PTA (%)	60 ± 9.7	55 ± 10	54 ± 10	0.073	0.19	0.52
LA increase (mm^2)	8.9 ± 5.9	10.8 ± 4.7	10.1 ± 4.5	0.34	0.96	0.53
MBA increase (mm^2)	3.7 ± 3.6	7.2 ± 7.0	6.3 ± 5.4	0.17	0.99	0.56
PLA decrease (mm^2)	4.3 ± 4.9	3.8 ±4.8	3.3 ± 6.2	0.69	0.67	0.77
Area stenosis decrease (%)	20 ± 14	30 ± 13	28 ± 16	0.089	0.91	0.56
Smallest LA after PTA						
Dissection	8 (47%)	21 (66%)	26 (46%)	0.82	0.19	0.082
Arc of dissection (°)	46 ± 69	71 ± 71	39 ± 60	0.94	0.068	**0.033**
Media rupture	2 (12%)	3 (10%)	3 (5%)	0.35	0.35	0.66
LA after PTA (mm^2)	11.2 ± 6.0	12.3 ± 3.4	11.3 ± 3.2	0.68	0.45	0.19
MBA after PTA (mm^2)	31.1 ± 11.0	33.0 ± 11.0	29.1 ± 8.6	0.75	0.13	0.097
PLA after PTA (mm^2)	19.5 ± 5.9	20.7 ± 9.4	17.5 ± 7.5	0.67	0.10	0.11
Area stenosis after PTA (%)	64 ± 9	61 ± 11	58 ± 11	0.15	0.13	0.34

† = Comparison of early restenosis versus early success; †† = Comparison of (early and late) restenosis versus late success; ††† = Comparison of late restenosis versus late success; PTA = percutaneous transluminal angioplasty; LA = lumen area; MBA = media-bounded area; PLA = plaque area; significant values are shown in bold.

restenosis was a larger area stenosis at the location corresponding to the smallest lumen area before PTA (odds ratio = 1.16 (95% CI: 1.07-1.26); p=0.0001).

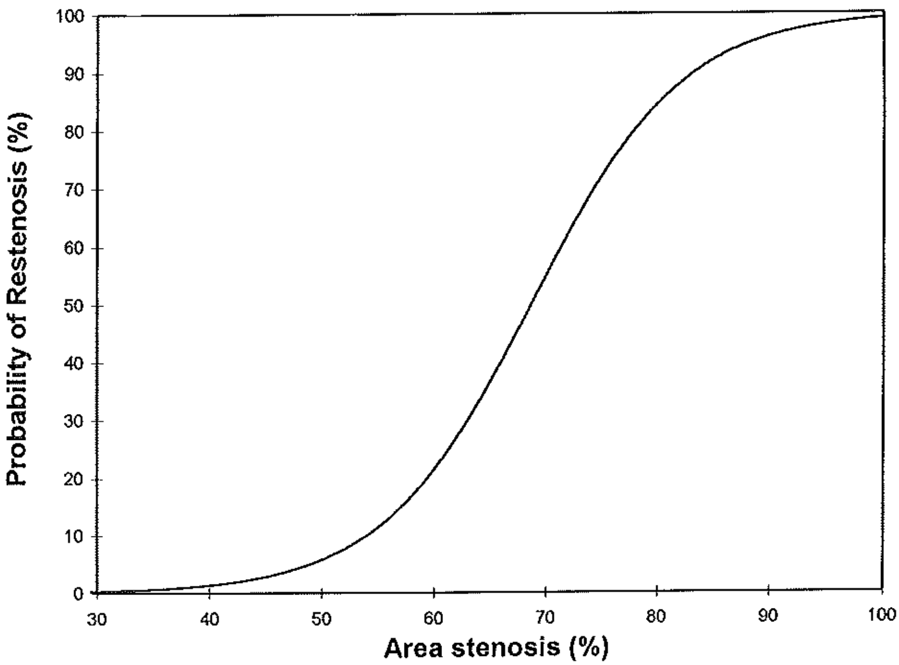

Figure 3. Predictive model of the probability of early anatomic restenosis based on the area stenosis measured with intravascular ultrasound after balloon angioplasty at the matched site of the smallest lumen area before intervention.

Predictors of 6 months outcome (early and late restenosis versus late success). Diabetes and a larger length of dilated segment were more frequently seen in procedures with (early and late) restenosis than late success (diabetes: 36% versus 16%; p=0.032; length of dilated segment p=0.043). The only IVUS parameter found predictive of 6 months outcome was area stenosis at the location with the smallest lumen area before PTA; 53 ± 8% in the late success group and 60 ± 12% in the (early and late) restenosis group (p=0.009). The presence and extent of vascular damage were not predictive of 6 months outcome.

By multiple logistic regression analysis the independent predictor of (early and late) restenosis was a larger area stenosis at the location with the smallest lumen area before PTA (odds ratio = 1.08 (95% CI: 1.02-1.15); p=0.017).

Predictors of late restenosis (late restenosis versus late success). There were no significant differences in the qualitative and quantitative IVUS parameters in procedures with late restenosis compared with those with late success; the maximum arc of the dissection seen in the dilated segment was the most significant variable (143 ± 90° and 107 ± 67°, respectively; p=0.076).

Predictor variables of clinical outcome

The angiographic and IVUS parameters in the procedures with early restenosis, late restenosis and late success are listed in Table 5.

Predictors of 1 month outcome (early restenosis versus early success). Diabetes and rest pain or ulceration were more frequently seen in procedures with early restenosis than early success (53% versus 25%; p = 0.023 and 53% versus 25%; p = 0.023, respectively). IVUS predictors of early restenosis were a larger mean arc of hard lesion (68 ± 68° vs 24 ± 34°; p=0.028) and the presence of hard lesion (71% vs 34%; p=0.008) at the smallest lumen area before PTA. The presence and extent of vascular damage were not predictive of early restenosis.

By multiple logistic regression analysis the only independent predictor of early restenosis was a larger mean arc of hard lesion (odds ratio = 1.69 (95% CI: 1.21-2.36) per increase of 30°; p=0.007).

Predictors of 6 months outcome (early and late restenosis versus late success). No variables were significantly related to 6 months outcome. The arc of dissection at the smallest lumen area after PTA was the most significant variable related to 6 months outcome: (early and late) restenosis and late success 62 ± 71° and 39 ± 60°, respectively (p=0.068).

Predictors of late restenosis (late restenosis versus late success). Comparison of the procedures with late restenosis versus late success revealed that the arc of the dissection at the smallest lumen area after PTA was significantly different (71 ± 71° and 39 ± 60°, respectively; p=0.033).

DISCUSSION

One of the promising features of IVUS was the potential to provide more insight in the mechanism of peripheral PTA and predict which patients may experience restenosis after an angiographic successful intervention. With this in mind the EPISODE study was conducted, which is the first study to determine whether IVUS parameters can predict restenosis after peripheral PTA.

The present study shows that angiographic parameters obtained before and after intervention were not predictive for outcome. Independent IVUS predictors of outcome were the extent of hard lesion and area stenosis after PTA. Other parameters such as lesion topography (eccentric versus concentric) before, and presence and extent of vascular damage (dissection and media rupture) after intervention, were not predictive for outcome. In addition, when the procedures with late success were compared with late restenosis it was found that the maximum arc of dissection was the most significant predictor for late anatomic restenosis and the arc of dissection at the smallest lumen area after PTA for late clinical restenosis.

To compare the present study to intracoronary ultrasound studies the following issues should be addressed.

First, it is common that the outcome of coronary balloon angioplasty is assessed angiographically at 6 months [19-23]. Conversely, the outcome of peripheral PTA is commonly assessed with the use of clinical data and objective vascular laboratory findings, including ABI pressure measurements and duplex scanning. Based on these findings a distinction was made in the present study between anatomic and clinical outcome. As patients with anatomic success may not present with a clinical success, IVUS predictors found were different for anatomic and clinical outcome. It is interesting that clinical restenosis occurred more frequently than anatomic restenosis. The reverse is often the case in coronary arteries. The presence and progression of atherosclerotic disease in the iliac and crural arteries may explain this phenomenon.

Secondly, in the present study a distinction was made between early and late restenosis. This distinction, based on the large number of failures occurring in the first month of intervention, enabled to assess different parameters related to 1 and 6 months outcome. Most of the significant IVUS predictors were related to 1 month outcome while the predictive power of IVUS parameters for outcome at 6 months was limited.

Thirdly, intracoronary ultrasound studies usually present data on one single cross-section obtained at the target lesion following intervention. In the present study, IVUS images were obtained both before and after PTA, and a sequence of cross-sections was collected in the dilated segment. As a consequence the number of IVUS parameters studied was larger than in coronary studies (Table 1).

Comparison with other IVUS studies

Lesion morphology. Mintz et al. [19] demonstrated a relation between hard lesion and restenosis following coronary interventions: the arc of calcified lesion in the success group was smaller than in the restenosis group (94 ± 106° and 135 ± 129°, respectively; $p=0.03$). However, the authors did not confirm this finding in subsequent larger studies using multivariate analysis [20]. In other IVUS studies, no such relation was found [8,9,21-22]. In the present study the presence and extent of hard lesion were found to be predictors of early clinical restenosis but not for late restenosis. This observation suggests that the distinction between early and late restenosis may enable to demonstrate more precisely the role of lesion morphology for outcome. Thus, hard lesion (i.e. calcified lesion) - a sign of more advanced atherosclerotic disease [24] - may preclude early success of intervention. This is in agreement with the report of Potkin and Roberts, who found that initial angiographic success was most often seen in non-calcified fibrous arteries [25].

Vascular damage. Tenaglia et al. [8] found both a higher incidence and greater severity of dissection on IVUS in patients with adverse events after coronary interventions. Similarly, Jain et al. [9] observed that an extensive dissection was more frequently found in a lesion that subsequently developed restenosis. Such a relation was not established in other intracoronary ultrasound studies [20-22]. In the present study no distinct relation was found between vascular damage and outcome. The results seemed in part contradictory. Media ruptures were less frequently seen in procedures with early anatomic restenosis than with early anatomic success ($p=0.063$). Conversely, comparing the procedures with late restenosis and late success revealed that the maximum arc of dissection was larger in procedures with late anatomic restenosis ($p=0.076$). Similarly, the presence and extent of dissection at the smallest lumen area after PTA was larger in procedures with late clinical restenosis ($p=0.082$ and $p=0.033$, respectively). In other words, the presence of vascular damage was related to success at 1 month and to late restenosis at 6 months. An explanation for this may be the difference in mechanism of early and late restenosis. Vascular damage following balloon angioplasty, a prerequisite necessary to allow the adventitia and media to stretch [26,27], resulted in better initial clinical results [25]; however, extensive dissection, which has first led to a successful lumen enlargement, may be a stimulus for a sequence of events leading to smooth muscle cell proliferation and migration resulting in restenosis during follow-up [28,29].

Area measurements. Thus far, intracoronary ultrasound studies presented conflicting results on the predictive value of quantitative IVUS parameters on outcome. In some studies, no quantitative parameters were found to be predictive of outcome [7,8,21,22], whereas others established a relation between area stenosis after intervention and outcome of intervention [9,20,23]. Jain et al. [9] found differences in area stenosis between the success group (34%) and the restenosis (50%) group. Mintz et al. [20] found that the final area stenosis was the most strongest predictor of angiographic restenosis. Finally, the report of the GUIDE trial [23] revealed that area stenosis was a predictor of both angiographic and clinical restenosis. These 3 studies had in common that area stenosis and not lumen area was the (independent) predictor of outcome [9,20,23].

In the present study a number of quantitative IVUS parameters were found to be related to anatomic outcome. It is noteworthy that a number of IVUS parameters found to be predictive for outcome were detected by comparison of the measurements before and after PTA. However, in the multivariate analysis only area stenosis seen after PTA at the site corresponding to the smallest lumen area before PTA was an independent predictor of anatomic outcome. The interrelationship between the quantitative parameters may explain that just one quantitative IVUS parameter is an independent predictor [30,31].

Although in the present study area stenosis after PTA is calculated by the (residual) plaque area divided by the stretched media-bounded area, it is the independent quantitative predictor of outcome rather than lumen area after PTA as is also the case in the 3 above-mentioned studies [9,20,23]. The relative lumen area is probably more important than the absolute lumen area. This is in agreement with the histopathologic study conducted by Farb et al. [32], who concluded that the creation of a larger lumen and a larger lumen as a percentage of vessel size were associated with an improved long-term histologic patency.

Clinical implications

Lesion morphology. The presence and extent of hard lesion were predictors of clinical outcome. If severe calcification is present in the diseased segment other treatment modalities may be considered. The influence of lesion morphology assessed with IVUS on decision making has been reported [33,34]. However, there is still no evidence that the outcome of intervention is improved due to decisions based on IVUS assessed lesion morphology.

Vascular damage. As the presence of a media rupture is beneficial for 1 month outcome the absence of vascular damage, especially in the presence of a small lumen area or small luminal gain after PTA, is an indication of an inadequate dilation and may require a repeat PTA. However, the creation of extensive vascular damage, such as a large dissection, creates a dilemma as a dissection may be a prerequisite for an adequate dilation, while this may result in an increased probability for late restenosis. Large dissections may, therefore, necessitate the placement of stents to prevent the late restenotic process.

Area measurements. Maximizing lumen area, and thus minimizing area stenosis, may reduce restenosis. In the presence of a large area stenosis after PTA several measures are available to optimize the result: repeat PTA, atherectomy or stent placement.

Limitations

The present study is limited by the absence of angiographic follow-up at 6 months. Instead, duplex measurements were used to assess anatomic outcome. Another problem is the difference between clinical and anatomic outcome which resulted in different parameters predictive of outcome. IVUS also had some limitations. Inadequate image quality and the presence of calcification preventing measurement of media-bounded area in 19% of the cross-sections should be acknowledged. The assessment of IVUS parameters may be subjective. However, the kappa values of hard lesion and dissection were good and the variability in measurements was minimal except the variability in the extent of dissection. Finally, as the number of patients studied is limited one should be careful regarding conclusions drawn on the non-significant parameters.

Conclusion

This study revealed IVUS parameters predictive of clinical and anatomic outcome. The parameters for 1 month and 6 months outcome were different. The discriminative power of these parameters were restrictive. Nevertheless, IVUS parameters predicted the probability of restenosis more accurately than angiographic assessed diameter stenosis. Whether interventions based on the IVUS parameters found will result in better outcome should be investigated in further studies. These studies will define the true clinical utility of IVUS.

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CHAPTER 10

FEMORODISTAL VENOUS BYPASS EVALUATED WITH INTRAVASCULAR ULTRASOUND

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Femorodistal Venous Bypass Evaluated With Intravascular Ultrasound*

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Objective: *To evaluate the feasibility of intravascular ultrasound imaging during femorodistal venous bypass procedures to assess qualitatitve and quantitative parameters of the greater saphenous vein and to detect potential causes for (re)stenosis and/or occlusion.*
Methods: *Intravascular ultrasound data obtained from 15 patients were reviewed and compared with angiographic data.*
Results: *Intravascular ultrasound enabled differentiation between normal and thickened vein wall. Venous side-branches could be located. Intact valves could be differentiated from valves disrupted by valve cutting. Patent anastomoses could be distinguished from anastomoses with some degree of obstruction. Intravascular ultrasound imaging of the inflow and outflow tracts revealed obstructive lesions, not evidenced angiographically. Quantitative analysis revealed that the median normal vein wall thickness (tunica intima and tunica media) was 0.25 mm (range 0.17–0.40 mm). The distinct vein wall thickening encountered in three patients measured 0.82, 0.95 and 1.06 mm, respectively, and was associated with narrowing in two patients. In five of 15 patients intravascular ultrasound findings altered surgical management.*
Conclusion: *Intravascular ultrasound is able to assess qualitative and quantitative parameters of the venous bypass and has the potential to influence surgical management based on morphologic and quantitative data.*

Key Words: Intravascular ultrasound; Venous bypass.

Introduction

Autogenous veins are the preferred graft material for femorodistal reconstruction. Although the results are reasonably good (1-year patency, 85%; 5-year patency, 70%),[1–3] much concern has focused on the prevention of graft failure because of the potential disastrous consequences for patients. Graft failure may be caused by several factors.[4] Within 1 month technical errors and poor choice of inflow and outflow sites are the predominant causes of graft failure. Failures during the subsequent 1-18 months have been attributed almost entirely to intrinsic vein graft stenosis at the proximal and distal anastomotic regions, but also in the vein conduit itself. Finally, failures after 18 months have generally been associated with progression of the underlying atherosclerotic process resulting in compromised inflow and/or outflow arteries. Intraoperative and postoperative monitoring using completion angiography, angioscopy and Duplex scanning do not predict all cases of graft failure.[5,6]

Recently, attention has focused on the quality of the venous bypass, as it became clear that morphologic changes such as fibrous thickening of the intima, calcification, media hypertrophy, mediasclerosis and luminal recanalisation may already be present before grafting.[7–14] The influence of these morphologic changes on bypass patency, however, remains unclear. At present, such morphologic changes are difficult to demonstrate prior to or during bypass surgery.[11]

With the introduction of intravascular ultrasound in 1989[15] a new diagnostic tool became available with the capability of identifying various components of vascular pathology and quantitating the mechanism of angioplasty devices. Since our first report on experience with intravascular ultrasound in femoropopliteal bypass surgery in 1991,[16] we have studied an additional group of patients undergoing venous

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bypass grafting. The objective of the present study was to elucidate our expanded experience with intravascular ultrasound in assessing qualitative and quantitative parameters of venous bypass grafts.

Material and Methods

Study Group

In 15 patients (12 males, three females) with a median age of 70 (range 55–83) years scheduled for routine below-knee femorodistal bypass procedure, intravascular ultrasound was used intraoperatively. The indication for operation was intermittent claudication ($n = 5$), rest pain ($n = 3$) and tissue loss ($n = 7$). This report contains data on three patients reported previously.[16]

An *in situ* bypass was performed in 11 patients (in two patients an extension with reversed vein was necessary), an *ex situ* non-reversed bypass in two patients, and a reversed bypass in two patients (a composite graft in one patient). The 11 *in-situ* bypasses were performed via an open technique ($n = 6$), or via a semi-closed technique ($n = 5$) in which the side-branches were closed by means of endovascular placed coils. In the *in situ* and *ex situ* non-reversed bypasses the valves were disrupted with a valve cutter (VaVaCut, William Cook Europe AS, Bjaeverskov, Denmark).

For the proximal anastomosis the common femoral artery ($n = 11$) or the superficial femoral artery ($n = 4$) were used. For the distal anastomosis the below-knee popliteal artery ($n = 11$) and tibial arteries ($n = 4$) were used.

Preoperatively, diagnostic angiography was available in all patients. Intraarterial pressure measurements over the aortofemoral tract were available in seven of 15 patients. Following completion of the bypass, intraoperative angiography was performed in 14 patients. In one patient with renal insufficiency angiography was contraindicated.

Intravascular ultrasound investigation

A mechanical 30 MHz imaging system was used (DuMED, Rotterdam, The Netherlands). The first four patients were studied with a stiff 5F catheter; in the other 11 patients a 4.1F flexible catheter was used. The ultrasound catheters rotate up to 16 images per second. The axial resolution of the system is 80 μm. Lateral resolution is 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 recorder.

The non-reversed bypasses ($n = 13$) were imaged after completion of the proximal anastomosis and valve cutting. The ultrasound catheter was introduced distally into the vein graft and advanced beyond the proximal anastomosis to obtain images of the inflow tract from the anastomosis up to the aorta. After completion of the distal anastomosis, the vein graft and the distal anastomosis were imaged using a proximal side-branch for introduction. The reversed bypasses ($n = 2$) were studied after completion of the distal anastomosis and filled with heparinised saline to facilitate ultrasound imaging. The ultrasound catheter was introduced proximally and advanced to and beyond the distal anastomosis.

Intravascular ultrasound images were recorded during pull-back of the ultrasound catheter. The videotapes were reviewed immediately after imaging; an additional intervention was performed when intravascular ultrasound revealed unequivocal abnormalities in the vein graft, anastomoses or the inflow and outflow tract. The extended analyses were performed off-line.

Analysis

Intravascular ultrasound analysis included the venous bypass, the anastomoses and the inflow and outflow tract. The venous bypass was evaluated for the presence of wall thickening, side-branches, and intact or disrupted valves. Wall thickness in each vein graft was measured in three ultrasound cross-sections showing an apparently normal vessel wall and in those cross-sections showing a distinct wall thickening (Fig. 1). The thickness was calculated as the perpendicular distance between the leading edge from the lumen–intima interface to the leading edge of the outer echogenic layer. The ultrasound cross-section showing the smallest free lumen area of the vein graft was selected to measure the free lumen area and mean free lumen diameter. Free lumen area was defined as the area encompassed by the inner boundary of the intimal surface. Anastomoses were judged semi-quantitatively "sufficient" or "insufficient". The anastomosis was "insufficient" if the free lumen area of the anastomotic region was smaller than the free lumen area of the adjacent vein graft segment. Inflow and outflow tracts were analysed and the images showing the smallest free lumen area were selected to measure free lumen area, media-bounded area and percentage area stenosis.[17]

The measurements were performed with a digital video analyser as described previously.[18,19] Briefly, the analysis system was developed on an IBM PC/AT (IBM Corp. Boca Raton, U.S.A.) equipped with a framegrabber and a PC mouse device. Observer variability in quantitative measurements has been reported to be satisfactorily low.[18–20] All measured values are presented as median values and range.

Results

The intravascular ultrasound study was completed in 14 patients. In one patient, only a small part of the bypass was visualised as the ultrasound catheter could not be further advanced through the vein. In another patient the bypass was perforated by the ultrasound catheter; this was treated with simple closure. No other complications related to the intravascular ultrasound studies were observed. The median duration of the intravascular ultrasound investigation was 14 min (range 3–40 min).

Vein wall

It was noted that the vein wall presented as a two- or three-layered structure. The two-layered structure consisted of a hypoechoic inner layer, representing the tunica intima and tunica media, and a hyperechoic outer layer, representing the tunica adventitia (Fig. 1). When the vein wall presented as a three-layered structure a hyperechoic region was seen at the lumen-intima interface. Intravascular ultrasound images obtained during the open and semi-closed *in situ* technique differed in appearance. Exposure of the vein to air in the open technique caused a more hyperechoic outer layer than in the semi-closed technique (Fig. 2).

Although the free lumen diameter seen with intravascular ultrasound varied along the length of the bypass, the wall thickness (tunica intima and tunica media) remained practically unchanged. Thickening of the vein wall was usually seen in the proximity of the valves. The median thickness of the apparently normal vein wall was 0.25 mm ($n = 45$; range 0.17–0.40 mm) (Figs 1,3). Statistically significant differences were found between the thickness of a vein wall with a two-layered appearance ($n = 20$; median 0.21 mm, range 0.17–0.29 mm) and that with a three-layered appearance ($n = 25$; median 0.28 mm, range 0.17–0.40 mm) ($p < 0.001$, Mann-Whitney test).

A focal, eccentric thickened vein wall, different from the thickening seen in the proximity of the valves, was observed in three patients. This thickening appeared as a homogeneous soft structure superimposed to the outer hyperechoic layer and measured 0.82, 0.95 and 1.06 mm, respectively (Fig. 1). In two of these patients, intimal thickening was associated with free lumen area narrowing (mean diameter 2.4 and 3.1 mm, respectively) (Fig. 1). These abnormalities were not seen with intraoperative angiography.

Free lumen area and diameter

During pull-back of the ultrasound catheter it was noted that the size of the free lumen area of the venous

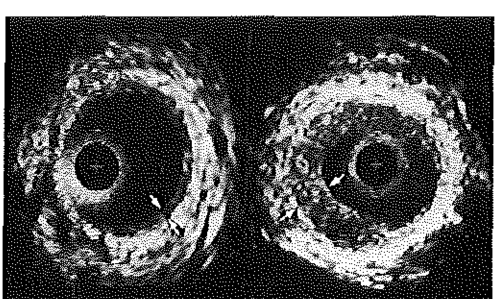

Fig. 1. Intravascular ultrasound cross-sections showing a normal venous bypass (left panel) and a venous bypass with thickening of the vein wall (right panel). + = Catheter; calibration = 1 mm.

Fig. 2. Intravascular ultrasound cross-sections showing the differences between images obtained during the semiclosed and the open technique. Left panel: Using the semiclosed technique the tissue surrounding the vein wall can be identified completely. Right panel: Using the open technique the effect of exposure of the vein to air is seen on ultrasound between 9 and 3 o'clock (arrows) as a more hyperechoic outer layer than seen between 3 and 9 o'clock. + = Catheter; calibration = 1 mm.

bypass changed markedly. Proximal to the valve leaflets the lumen size sometimes increased. Similarly, the free lumen area decreased when imaged distal to large side-branches. The median smallest free lumen area measured was 6.5 mm^2 (range 2.5–19.0 mm^2). The median smallest free lumen diameter was 2.9 mm (range 1.8–4.9 mm) (Fig. 3). In one patient, intraoperative angiography revealed a short local stenosis in the venous bypass, not sufficiently alarming to warrant re-exploration. Intravascular ultrasound revealed a narrowed elliptic lumen as a result of external compression of the vein graft. At surgical inspection it was found that the tendon of the gastrocnemius muscle compressed the venous bypass, caused by a false route during tunnelling of the bypass. After tendon division the intravascular ultrasound image showed a normal circular lumen (Fig. 4).

Side-branches and valves

Side-branches in venous bypasses were seen with intravascular ultrasound as an interruption of the vessel wall (Fig. 5). The median number of side-branches seen per bypass was 10 (range 1–14). In the *in situ* bypass detection was facilitated by blood flow in the side-branches, as imaging was performed before ligation. Both large and small tributaries were detected.

The intact valves in the reversed bypasses were detected as straight echogenic lines. After valve cutting in the *in situ* bypasses, intravascular ultrasound enabled demonstration of the remnants of the valves and differentiation between (partially) intact and totally disrupted valves (Figs 6,7). The presence of blood flow seen with real-time imaging facilitated identification of the valve patency. An intact valve was seen as a straight structure behind which stagnant blood created a higher echogenicity than normal blood flow (Fig. 7). Another way to demonstrate complete or incomplete disruption of the valves was by flushing saline through the bypass, which eliminated the blood and clearly visualised the valve leaflets.

The median number of locations with valves (intact or disrupted) seen per bypass was 5 (range 1–8). A persisting intact valve was detected in two patients after valve cutting which resulted in an additional valve-cutting procedure. An additional 12 (partially) intact valves were detected by off-line analysis in seven patients. Five valves were not imaged on angiography as only the distal anastomosis and the outflow were imaged. The other seven partially intact valves were seen on angiography as an irregular luminal contour in three cases, and were not visualised in the remaining four cases.

Finally, intravascular ultrasound enabled detection of a dissection in the vein wall in three patients, probably caused by the valve cutter (Fig. 8). These were not visible angiographically.

Proximal and distal anastomoses

The proximal anastomosis was studied with intravascular ultrasound in 12 patients and the distal anastomosis in ten patients. In four patients, the ultrasound catheter could not be advanced beyond the distal anastomosis. The vein wall and arterial wall could be distinguished based on anatomic characteristics evidenced on intravascular ultrasound (Fig. 9).

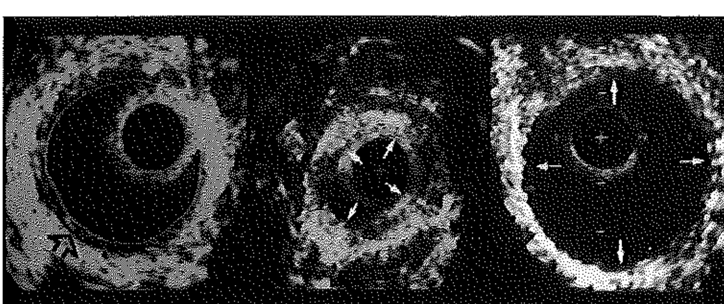

Fig. 3. Intravascular ultrasound cross-sections of venous bypasses showing differences in lumen areas. Left panel shows the contour of the free lumen area (FLA) and the vein wall thickness (open arrow). Middle panel: example of a small lumen (FLA = 5.6 mm^2). Right panel: example of a large patent lumen (FLA = 12.1 mm^2). + = Catheter; calibration = 1 mm.

All anastomoses, except one, were semi-quantitatively judged "sufficient". One distal anastomosis was judged "insufficient" as intravascular ultrasound revealed an intraluminal structure proximal to and within the anastomotic region, suggestive of thrombus. Angiography revealed a stenotic lesion just proximal to the anastomosis. Reexploration was deemed unnecessary because pedal pulsations were present. Perfusion of the patient's leg continued to decline progressively during the following days and reoperation was necessary 1 week later. The graft was thrombosed and a small distal part of the venous bypass was considered insufficient and resected after thrombectomy of the bypass.

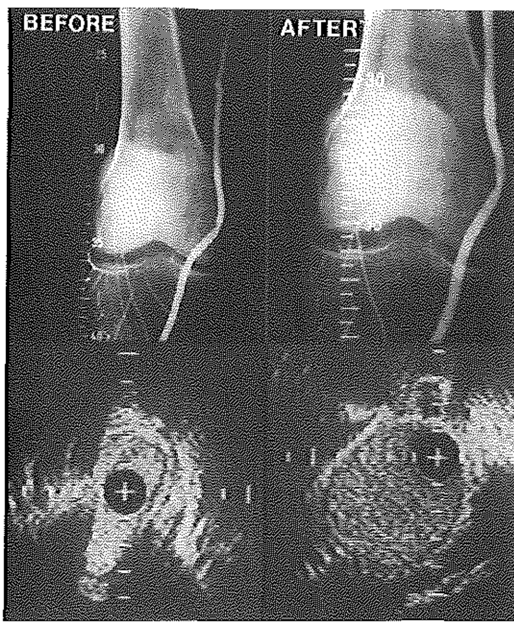

Fig. 4. Corresponding intravascular ultrasound cross-sections and angiograms of a venous bypass before and after cleavage of the tendon of the gastrocnemius muscle. Before intervention (right panel) an ambiguous stenosis is seen angiographically at level 34 that is no longer visible following cleaving (left panel). On ultrasound a local external compression of the bypass seen at level 34 changed the shape of the lumen elliptically (left panel). After cleaving (right panel) a normal circular shape is seen. + = Catheter; calibration = 1 mm. (Reprinted with permission of the *European Journal of Vascular Surgery* 1991; 5: 523–526.)

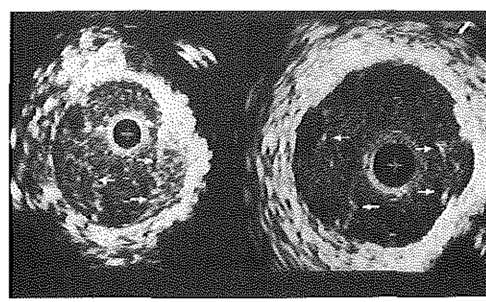

Fig. 6. Intravascular ultrasound cross-sections of a venous bypass showing differences between remnants of valve leaflets and an intact valve. Left panel: four remnants of valve leaflets are seen after valve cutting (arrows). Blood appears as a homogeneous echogenic medium in the lumen. Right panel: after valve cutting an intact valve leaflet (left: 3 arrows) and a disrupted valve leaflet (right: 2 arrows) are seen on ultrasound. The stagnant blood behind the intact leaflet causes a more homogeneous echogenic structure than blood flow in the lumen. + = Catheter; calibration = 1 mm.

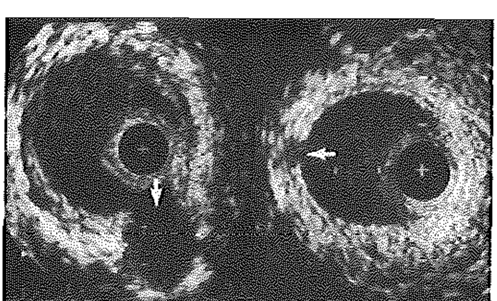

Fig. 5. Intravascular ultrasound cross-sections of a venous bypass showing a large (left panel) and a small (right panel) side-branch (arrow). + = Catheter; calibration = 1 mm.

Fig. 7. Intravascular ultrasound cross-sections of a venous bypass showing an intact valve leaflet (left panel) and the remnants (arrows) of the same valve leaflet after an additional valve cutting procedure (right panel). Beyond the intact valve leaflet blood appears more echogenic than blood flow in the lumen. + = Catheter; calibration = 1 mm.

Inflow and outflow tracts

Intravascular ultrasound images of the iliofemoral inflow tract obtained in 12 patients revealed > 50% area stenosis in eight patients (56%, 61% and 70% in the iliac artery, and 50%, 52%, 60%, 72% and 77% in the common femoral artery). Preoperative angiography was normal in six patients and in two patients wall irregularities were seen. Intraarterial pressure measurements during angiography, performed in three patients, revealed no pressure drop, even with use of papaverine. Based on intravascular ultrasound, additional balloon angioplasty was performed in two patients (area stenosis of 70% in the iliac and 77% in the femoral artery)(Fig. 10). The intervention was deemed successful based on intravascular ultrasound data.

In two patients an atherosclerotic lesion with a dissection was seen in the common femoral artery, probably caused by clamping of the artery.

The outflow tract (popliteal artery and tibioperoneal trunk) was imaged in ten patients. An area stenosis >50% was evidenced in four patients (54% and 62% in the popliteal artery, 60% and 70% in the tibioperoneal trunk). Only the stenoses in the tibioperoneal trunk were visible on angiography as a diameter stenosis <50%. No additional angioplasty was considered because the anterior tibial artery was unaffected.

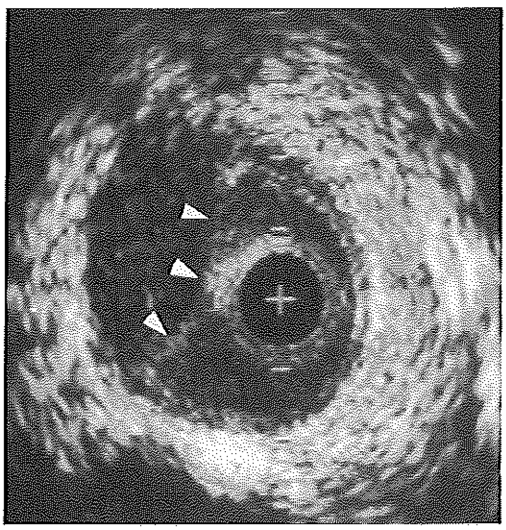

Fig. 8. Intravascular ultrasound cross-section of a venous bypass showing a dissection of the vein wall (arrows). + = Catheter; calibration = 1 mm.

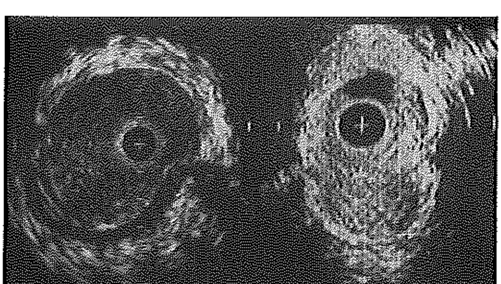

Fig. 9. Intravascular ultrasound cross-sections showing a patent end-to-end anastomosis (left panel) and an "insufficient" end-to-side anastomosis (right panel). In both panels the vein wall is at the top; the arterial wall is seen at the bottom as a three-layered wall with a hypoechoic middle layer representing the tunica media. The lumen in the right panel is severely obstructed by a soft lesion. + = Catheter; calibration = 1 mm.

Discussion

Since the introduction of intravascular ultrasound most emphasis has been on the investigation of atherosclerotic disease and the effect of balloon angioplasty. The number of studies performed on the venous part of the circulation is limited.

The study of The *et al.*[16] was the first to report on the use of intravascular ultrasound in the saphenous vein when used as a conduit in the arterial system.

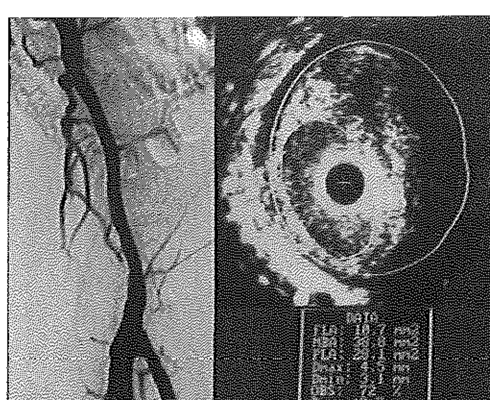

Fig. 10. Angiogram and intravascular ultrasound cross-section of the inflow tract. A 72% stenosis of the common femoral artery evidenced by intravascular ultrasound was not seen on angiography. + = Catheter; calibration = 1 mm.

Using the first generation intravascular ultrasound catheters they reported a homogeneous vein wall. As seen in *in vitro* studies, there was no differentiation between the tunica intima, media and adventitia.[15,20,21] The introduction of newly developed ultrasound catheters enables differentiation between a vein wall with a two- or three-layered appearance. *In-vitro* studies have shown that the inner layers represent the intima–media complex and the outer layer the tunica adventitia (unpublished observation). The difference in median thickness encountered in the present study between a two-layered (0.21 mm) and a three-layered (0.28 mm) vein wall indicates that the axial resolution is an important factor in imaging the vessel layers as distinct features. The intima–media thickness of the veins in this study (median 0.25, range 0.17–0.40 mm) are in the same order as those obtained by external ultrasound imaging with a 7.5 MHz probe of normal femoral (0.39 ± 0.031 mm) and popliteal veins (0.31 ± 0.33 mm).[22]

Visualisation of several layers provides the opportunity to differentiate between normal and thickened vessel walls. In the present study, distinct focal thickening of the intima–media complex evidenced by intravascular ultrasound in three patients was associated with free lumen area narrowing in two patients. In one of these patients, wall thickness was associated with subsequent significant luminal narrowing as Duplex scanning revealed a severe (> 50%) stenosis at 4 months follow-up. Although this finding is suggestive of a causal relation between intimal thickening and stenosis at follow-up, the clinical consequences of vein wall thickening remain to be determined.

At present several methods are available to detect pre-existing venous disease including macroscopic external inspection, histology and angioscopy. Generally, on macroscopic external inspection most veins appear normal, masking underlying abnormalities.[12] Moreover, if endovascular occlusion of side-branches becomes more extensively used, external inspection of the venous bypass will no longer be possible.[23,24] As thickening of the vein wall may be both generalised and focal, histology of remnants of the saphenous vein used for bypass is not sufficient to assess the overall quality. Obviously, histologic processing cannot be performed "on-line" and, therefore, cannot be used as a clinical decision-making device. Angioscopy may demonstrate abnormalities in the venous bypass but wall thickness cannot be established by this technique.[14] In contrast, intravascular ultrasound has the potential to assess wall thickness along the entire length of the bypass.

The influence of diameter on graft patency has been reported.[25] During intravascular ultrasound imaging, on-line information on free lumen area and diameter can be obtained semi-quantitatively. It is noteworthy that in the present study semi-quantitative intravascular ultrasound data on free lumen area influenced surgical management in two patients. Although the quantitative measurements in this study were performed off-line, automatic contour detection may enable these measurements to be performed on-line in the near future. Another issue to consider is the time at which the ultrasound data are collected during the study. In this study most of the veins were examined both in a pressurised condition (after completion of one anastomosis) as well as after restoration of blood flow (after completion of both anastomoses). In the latter instance an increase in free lumen area was experienced. Ligation of side-branches causes an additional increase in free lumen area in the distal part of the graft. Most of the measurements were performed on cross-sections obtained after restoration of blood flow but before ligation of side-branches.

It was possible to detect both the location and size of side-branches. This observation could become important with the introduction of endovascular techniques for occlusion of venous side-branches in which case external inspection of the saphenous vein, including localisation of side-branches, is no longer possible.[23,24] Cikrit *et al.*[23] reported that only side-branches with a diameter larger than 1.5 mm could be cannulated; therefore intravascular ultrasound may be useful to determine the location and size of side-branches.

With the introduction of *in situ* bypass in surgical practice, valve cutting became an important procedure. Angiography and angioscopy have both been used to assess the result of this procedure. The result of valve cutting can also be demonstrated by intravascular ultrasound. A patent valve leaflet detected in two patients resulted in an additional passage of the valve cutter. However, reviewing the videotapes off-line, additional partially intact valves were detected; most of these retained valves were not detected by intraoperative angiography. Although the influence of these retained valves on patency remains unclear, it is generally considered as a possible cause of graft failure.

Normally, venous bypass procedures are performed after diagnostic angiography which enables the proper inflow and outflow tract to be chosen. Apart from angiography, the quality of the inflow tract can be evaluated by pressure measurements in order to detect haemodynamic significant stenoses, which should be treated before performing a bypass. Despite this diagnostic work-up in the present study, intravascular ultrasound revealed obstructive lesions both in the inflow and outflow tracts, which were considered to warrant additional balloon angioplasty in two patients.

Our ability to image the bypass and to interpret the ultrasound images improved considerably during the study. Due to a learning curve, the intravascular ultrasound procedure used in the present study was not performed according to a standard protocol; for future applications it will be important to standardise the procedure as much as possible. Using off-line analysis, abnormalities were detected that were not apparent during the study. Bearing this in mind, the results of the present study should be interpreted with caution. This new technique has a high sensitivity for abnormalities (wall thickening, intact valves and inflow and outflow tract stenosis), but the clinical significance of these abnormalities remains unknown.

In conclusion, intravascular ultrasound provides qualitative and quantitative data on parameters which describe the condition of the venous bypass graft during surgery. To what extent these parameters are predictors of short and long-term patency of these grafts needs to be determined in a prospective study. The results of the present study indicate that intravascular ultrasound has the potential to compete with angiography in evaluating the quality of the bypass procedure intraoperatively.

Acknowledgements

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CHAPTER 11

FEMOROPOPLITEAL VENOUS BYPASS STUDIED WITH INTRAVASCULAR ULTRASOUND: A CASE REPORT

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Femoropopliteal Venous Bypass Studied with Intravascular Ultrasound: A Case Report

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Purpose: To describe the ability of intravascular ultrasound (IVUS) to document the status of the greater saphenous vein during bypass surgery, the long-term changes in the bypass, and the effects of balloon angioplasty on vein graft stenoses.
Methods: An 80-year-old female underwent in situ femoropopliteal venous bypass grafting. Vein graft stenosis developed 6 months later, necessitating balloon angioplasty. The angioplasty failed, and a polytetrafluoroethylene (e-PTFE) interposition graft was placed. Ten months after bypass surgery, balloon angioplasty was performed for new stenoses. This procedure also failed, and the venous bypass and interposition graft were removed and replaced by an e-PTFE graft. IVUS images obtained during the first surgery were compared with those obtained 10 months later. Histologic sections were used to confirm the IVUS findings.
Results: IVUS detected a distinct narrowed venous segment, pre-existent intimal thickening, and disrupted valves. Over the follow-up period, both the pre-existent intimal thickening and the narrowed segment evolved into stenoses, necessitating treatment. Luminal gain after balloon angioplasty of graft stenosis was associated with vascular damage.
Conclusions: This report shows that IVUS has the ability to document long-term venous bypass alterations and to demonstrate the effect of balloon angioplasty on venous bypass stenoses.

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Key words: In situ vein bypass graft, histology, balloon angioplasty, vein graft stenosis

As a complement to angiography, intravascular ultrasound (IVUS) is becoming a common monitoring tool during interventional procedures, including balloon angioplasty (PTA) and bypass surgery. Besides guiding these interventions, IVUS has the potential to study long-term alterations in both the arterial and venous walls during follow-up. Until now, histologic sections have been used to demonstrate pre-existent and postarterialization vein wall thickening.[1–9] This study reports the use of IVUS to document alterations in a venous bypass at follow-up and the effects of balloon dilation on venous bypass graft stenosis, using histologic sections for validation of the IVUS results.

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CASE REPORT

An 80-year-old female was referred for intermittent claudication (walking distance < 100 m). At physical examination, the left lower leg was colder than the right leg, the peripheral arterial pulsations were absent, and reduced capillary refill was present. Ankle-brachial pressure measurements revealed noncompressible arteries.

Angiography demonstrated an occluded superficial femoral and supragenicular popliteal artery. Three months later, as the symptoms progressed to rest pain and a small ulcer on the left foot developed, the patient underwent an in situ (infragenicular) femoropopliteal venous bypass operation. The bypass was studied perioperatively with IVUS using a mechanical 30-MHz imaging system (Du-MED, Rotterdam, The Netherlands) according to previously described methods.[10]

IVUS examination revealed a relatively narrow segment in the proximal part of the bypass caused by duplication of the greater saphenous vein (diameter 3.1 mm). Proximal and distal to this narrow segment, the vein was of normal diameter (4 to 5 mm). The thickness of the venous wall appeared normal (0.28 mm) for the most part, but there was distinct focal intimal thickening (0.65 mm) proximally. Additionally, several disrupted valves could be seen (Fig. 1). Completion angiography was not performed because of renal insufficiency (creatinine = 180 mmol/L).

Follow-up

The diagnostic tests performed and subsequent therapeutic interventions are listed in Table 1. Briefly, the patient experienced relief of symptoms and healing of the foot ulcer postoperatively. Duplex examination at 3 months showed a narrow segment 7 cm long in the upper leg with a high peak systolic velocity (PSV). At 6 months, an increasing PSV indicated a hemodynamically significant stenosis.[11] Subsequent angiography revealed a distinct narrow segment with two subtotal stenoses (Fig. 2) that appeared amenable to PTA. Following dilation with a 6-mm balloon, persistent stenosis and graft rupture with contrast extravasation occurred (Fig. 2), necessitating reconstruction of the bypass with a 6-mm-di-

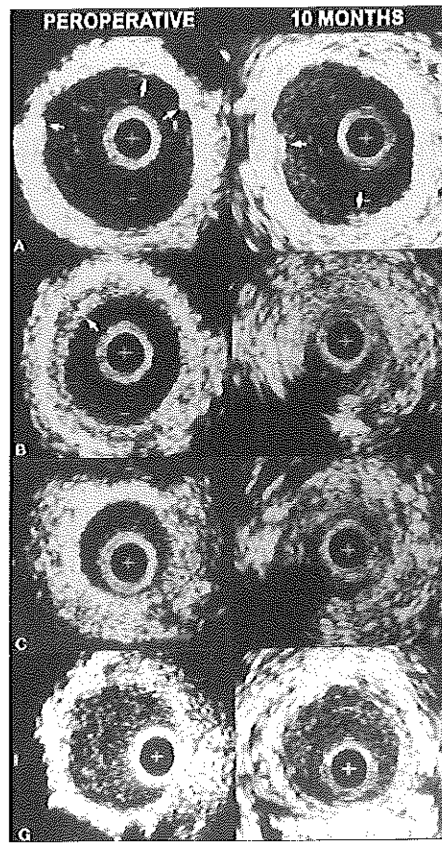

Figure 1 ◆ Corresponding IVUS cross sections of the femoropopliteal venous bypass from proximal (**A**) to distal (**G**) obtained during initial surgery (left) and after 10 months (right). Initially, the luminal diameter ranged from 3.1 to 5.0 mm; at 10 months, the diameter measured from 2.4 to 4.5 mm. Panel **A** shows remnant vein valves (arrows) still visible after 10 months; panel **B** shows venous wall thickening (between arrows: 0.65 mm) evolving into a stenosis with shrinkage of the original vessel wall from 5.0 to 4.0 mm. Panel **C** shows a smaller diameter vein (diameter 3.1 mm) that developed significant intimal thickening evolving into a stenosis. Panel **G** shows a normal caliber vessel with no significant change in diameter 10 months later. Drop-out in the right images of panels **B** and **C** is due to guidewire interposition. Calibration = 1 mm; + = catheter.

TABLE 1
Chronology of Diagnostic Tests and Therapeutic Interventions

Time Span	Diagnostic and Therapeutic Procedures
—	In situ venous bypass—IVUS (Fig. 1)
3 months	Duplex: PSV 164 cm/s (proximal 93 cm/s, distal 37 cm/s)
6 months	Duplex: PSV 250 cm/s (proximal 90 cm/s, distal 65 cm/s)
	Angiography: 2 stenoses (Fig. 2)
	PTA (vessel wall rupture) → e-PTFE interposition graft
10 months	Duplex: PSV 210 cm/s and 150 cm/s (proximal 70 cm/s)
	Angiography: 2 stenoses; aneurysmal dilatation (Fig. 2)
	PTA—IVUS (Figs. 1, 3, and 4)
11 months	Replacement of proximal venous bypass and interposition graft
	Histology (Figs. 3 and 4)
13 months	Amputation

IVUS = intravascular ultrasound; PTA = balloon angioplasty; PSV = peak systolic velocity.

ameter polytetrafluoroethylene (e-PTFE) interposition graft.

At 10 months, duplex scanning detected two new stenoses proximal to the interposition graft. Angiography confirmed these > 50% stenoses and revealed an aneurysmal dilatation of the bypass just distal to the interposition graft (Figs. 2 and 3). IVUS images of the bypass before treatment of the new stenoses were compared with those obtained perioperatively at the initial intervention (Fig. 1). This comparison showed that the normal diameter vessel with pre-existent intimal thickening had altered into a stenotic lesion (lumen diameter decreased from 4.0 to 2.4 mm), with shrinkage of the original vessel wall (diameter decrease from ± 5.0 to ± 4.0 mm). The remaining part of the narrow segment had become stenotic due to intimal thickening (lumen diameter decrease from 3.1 to 2.6 mm). The diameter and wall thickness of the distal part of the bypass were unchanged. The valve remnants were seen. In addition, the interposition graft was patent, with intimal hyperplasia at the anastomoses. Distal to the e-PTFE graft, the bypass appeared to have widened (Fig. 4).

The stenoses were dilated with a 5-mm balloon. At the distal stenosis, a waist remained visible. The angiogram revealed satisfactory dilatation of the proximal stenosis but not of the distal narrowing (Fig. 3). At the proximal lesion, IVUS showed a luminal area increase (4.5 to 11.7 mm^2) associated with a small dissection; however, at the distal site, the lumen area had not changed, and no vascular damage was seen.

One month later (11 months after the initial surgery), the proximal part of the venous bypass and the interposition graft were removed and replaced with a ringed 6-mm e-PTFE prosthesis. This conduit occluded 2 weeks later. Despite successful thrombectomy, the bypass reoccluded, and a transgenual amputation was performed.

Histologic Comparison

The extirpated vein bypass was fixed under pressure (100 mmHg) in 10% buffered formalin for 2 hours and processed for routine paraffin embedding. Transverse sections cut at 1-mm intervals were stained with elastic van Gieson stain and hematoxylin and eosin for comparison with the IVUS images obtained 10 months after initial surgery.

At the level of the proximal stenosis, angioplasty-induced medial rupture and adventitial stretching were evident, with recently formed intimal hyperplasia (Fig. 3). No vascular damage was seen at the distal stenosis, which had a smaller lumen than the proximal site. The medial circumference at the proximal stenosis was smaller compared to that at the distal stenosis, suggesting shrinkage of the vessel at the proximal stenosis. Intimal hyperplasia (pannus formation) in the e-PTFE graft was seen at both anastomotic sites (Fig. 4). The valve remnants were now embedded in inti-

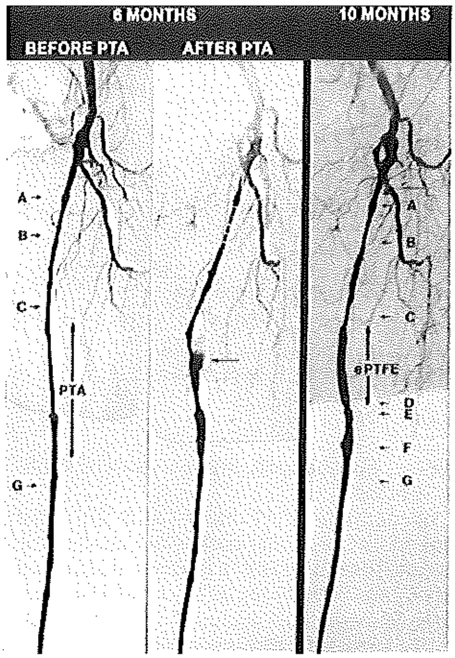

Figure 2 ◆ Angiograms of the femoropopliteal venous bypass obtained 6 months (left and middle panel) and 10 months (right panel) after bypass surgery. The locations A through G correspond to IVUS images in Figures 1, 3, and 4. The left panel shows a distinct narrow segment with two subtotal stenoses that were dilated (between arrowheads). Middle panel shows vessel rupture (arrow) and persistent stenoses following balloon angioplasty (PTA). The right panel shows two stenoses (B and C); the e-PTFE interposition graft; and the aneurysmal dilatation (F).

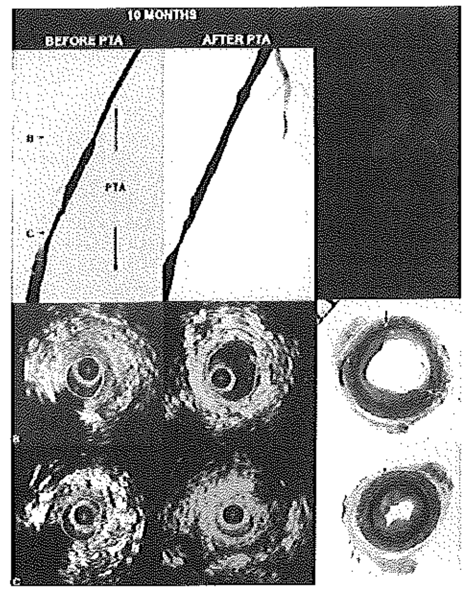

Figure 3 ◆ Angiograms and corresponding IVUS images obtained at 10 months before and after balloon angioplasty are compared with histologic sections obtained 1 month later. Both angiography and IVUS documented successful balloon angioplasty of the proximal stenosis (B). IVUS also detected a small dissection. The histologic section (right) shows medial rupture (arrows) and adventitial stretching. Balloon angioplasty of the distal stenosis (C) was deemed unsuccessful, with no change in luminal area on IVUS. No vascular damage can be seen histologically. Calibration = 1 mm; + = catheter.

mal hyperplasia. Aneurysmal dilatation was noted, with an interruption of the media, presumably a result of the PTA at 6 months. In retrospect, this medial rupture was recognized on IVUS as an interruption in the internal elastic lamina.

DISCUSSION

In the past, histologic sections were commonly used to investigate pre-existing and postarterialization vein wall alterations. IVUS is able to provide "histology-like" cross-sections during venous bypass surgery. A feasibility study using IVUS during venous bypass surgery showed that this imaging technique can determine lumen diameter, distinguish normal from thickened vein wall, identify competent and disrupted vein valves, establish the patency of anastomoses, and detect the presence of stenoses in the inflow and outflow tracts.[10] However, the clinical significance of these features had not been elucidated.

The present study showed that both a portion of a "normal diameter" vein with pre-existent focal intimal thickening and a relatively

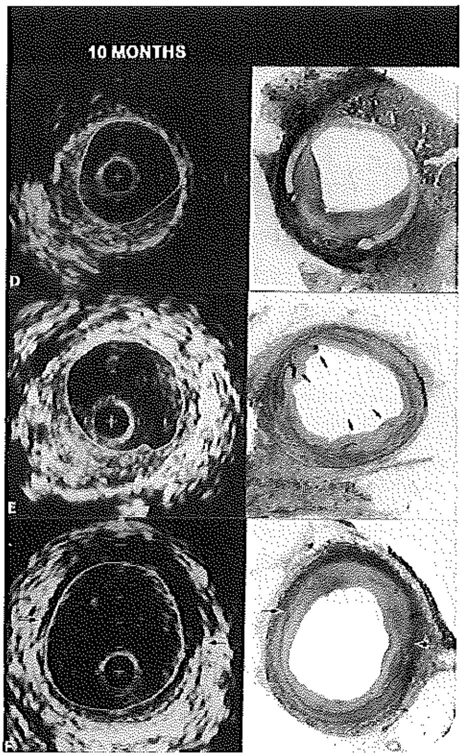

Figure 4 ♦ IVUS cross sections obtained 10 months after bypass surgery are correlated with histologic sections obtained 1 month later. Panel **D** shows the distal end-to-end anastomosis of the e-PTFE interposition graft with intimal hyperplasia. Note the inability to image the perigraft structures with IVUS. Panel **E** shows that valvular remnants have become embedded in intimal hyperplasia but can still be identified histologically (arrows). Panel **F** shows aneurysmal dilatation (6.0 mm). The histologic section revealed medial rupture, probably caused by balloon angioplasty at 6 months. Calibration = 1 mm; + = catheter.

narrow venous segment with normal wall thickness developed into stenoses at 10 months due to intimal hyperplasia. In addition, it appeared that vessel shrinkage contributed to the decrease in the luminal area of the proximal stenosis.

The importance of pre-existing disease as a cause of stenosis has been reported previously.[5,6] However, the contribution of vessel shrinkage (geometric remodeling) to luminal narrowing has been reported in arteries[12] but not in veins. Our study demonstrates that IVUS can provide insight into the underlying mechanisms of vein graft stenosis by serial investigation of the vein graft. Information regarding pre-existing disease and the diameter of the vein may be used to decide which part of the vein should be used as an arterial conduit and which segment(s) should be discarded.

The diagnostic role of IVUS during balloon angioplasty in coronary and peripheral arteries has been acknowledged.[13–15] Thus, we assumed that IVUS could be useful during PTA of vein graft stenosis as well. This case demonstrated that successful PTA was related to vascular damage that enabled the vessel to stretch and increase the lumen area. Moreover, balloon dilation of a vein graft stenosis that had developed in a normal diameter vein with pre-existing focal wall thickening was successful. Conversely, dilatation of stenoses in a relatively narrowed venous segment was either ineffectual or resulted in vessel wall rupture.

Our observations seem to underscore the suggestion by Marin et al.[16] to use "information about intimal thickness and composition prior to balloon angioplasty to improve selection of patients for balloon angioplasty or surgical reconstruction of vein graft stenosis." To this end, IVUS appears to be a useful tool for assessment of vascular pathology and guidance of surgical or catheter-based interventions.

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CHAPTER 12

SUMMARY

SAMENVATTING

Arteriography is the standard method for evaluation of obstructive atherosclerotic disease in coronary and peripheral arteries. This technique provides a silhouette of the vessel lumen, but does not provide accurate knowledge of cross-sectional lumen area, vessel area, shape and morphology of the stenotic lesion. Intravascular ultrasound (IVUS) may overcome these limitations. Basically, the aims of this dissertation were to establish the accuracy and limitations of IVUS and to evaluate the clinical application of this new imaging technique.

For this purpose, practical problems related to the documentation of the actual position of the cathetertip were solved; validation studies were performed to document the reliability, limitations and benefits of the technique; the spectrum of arterial and venous disease and effects of intervention were documented with IVUS; and the value of IVUS as research and clinical tool was explored. The studies presented in this dissertation deal with these main issues.

Chapter 1 gives an introduction to the scope of the dissertation.

Chapter 2 describes a displacement sensing device that provides instantaneous information about the cathetertip position which can be displayed simultaneously with the IVUS image. The accuracy of this device was tested in-vitro using iliac and coronary arterial specimens affected by atherosclerosis. For each specimen the lumen area from 3 pull-back series was determined in multiple cross-sections with an interval of 0.05 cm. A total of 1895 cross-sections were analyzed. The variation in lumen area measurements was small: 1.7% in iliac and 3.0% in coronary arteries. No position mismatching was seen between the pull-back series, with the exception of a position shift of 0.05 cm in one coronary artery. It was concluded that the displacement sensing device provides accurately reproducible images of the same location.

Chapter 3 describes an in-vitro study using 40 human coronary specimens, in which IVUS images obtained before and after balloon angioplasty were compared with histologic sections. The displacement sensing device was essential to accurately compare corresponding IVUS images before and after intervention and to correlate each image with its histologic counterpart. This in-vitro study revealed that vascular damage seen with IVUS after intervention included dissection, plaque rupture and media rupture. The sensitivity of IVUS in detecting vascular damage was high for dissection and media rupture (79% and 76%, respectively), but was low for plaque rupture (37%). Furthermore, the study demonstrated that a higher incidence of vascular damage was found when the whole segment is analyzed (85%) rather than one single cross-section at the most stenotic site (63%). Thus, in order to have insight in the arterial damage the entire vascular specimen should be analyzed.

Intra- and interobserver differences in the measurements of lumen area and media-bounded area before and after balloon angioplasty were low.

Comparison of the quantitative data obtained before and after balloon angioplasty disclosed the mechanism of this type of intervention: the increase in lumen area was caused predominantly by media-bounded area increase (81%) and to a lesser extent by plaque area decrease (19%). The quantitative effects of coronary balloon angioplasty seen with IVUS were greater at the most stenotic site as compared to the adjacent cross-sections from the dilated specimen.

It was concluded that IVUS can accurately assess vascular damage after balloon angioplasty and that quantitative data obtained both before and after intervention are well reproducible. The mechanism of balloon angioplasty, which can now be studied with IVUS in a new manner, is vessel stretch rather than plaque compression.

Chapter 4 describes the use of IVUS both in-vitro and in-vivo to investigate the relation between lesion characteristics (morphology and topography) and dissection produced by balloon angioplasty at the most stenotic site. Dissections were observed in 88% of the histologic sections and visualized by IVUS in 59% of the corresponding ultrasonic cross-sections; dissections were demonstrated in-vivo by IVUS in 63% cases.

The origin of dissections was commonly found at the thinnest part of the lesion (in-vitro 83%; in-vivo 93%). No significant relation was found between pre-interventional plaque characteristics, and the incidence, extent and location of dissections.

Chapter 5 reports the interobserver agreement on IVUS data obtained before and after balloon angioplasty of the femoropopliteal artery in-vivo. Two observers analyzed IVUS images obtained from 38 patients. Interobserver agreement was good for lesion morphology, dissection and vascular damage; moderate for lesion topography; fair for media rupture; and poor for lipid deposit and plaque rupture. There were no significant interobserver differences between area measurements. The coefficient of variation for lumen area and media-bounded area before intervention was 17.2% and 10.5% and after intervention 11.2% and 9.2%, respectively.

Chapter 6 outlines a qualitative and quantitative comparative study of IVUS versus angiography in patients undergoing (laser-assisted) balloon angioplasty. 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. Stenosis was assessed as more severe on IVUS than on angiography. Semiquantitative on-line analysis of the percentage area stenosis seen on IVUS corresponded well with off-line quantitative analysis performed using a computer-aided system. When both on-line IVUS and angiography suggested that the arteries were "normal", quantitative off-line IVUS revealed a mean of 18% area stenosis.

Chapter 7 describes the use of IVUS to study the spectrum of arterial damage and quantitative effects of balloon angioplasty of the femoropopliteal artery. Corresponding IVUS images obtained before and after balloon angioplasty from 115 procedures were analyzed. The incidence of vascular damage assessed per dilated arterial segment was higher (91%) than when assessed at the narrowest site only (72%). Area measurements revealed that luminal enlargement was predominantly achieved by stretching of the arterial wall (85%), while plaque compression contributed to a lesser extent (15%) to luminal enlargement. Comparison of procedures with balloon diameter ≤ 5 mm and ≥ 6 mm revealed that the frequency of vascular damage and the relative contribution of vessel stretch and plaque compression to luminal gain were not different. It was concluded that vascular damage is common following balloon angioplasty, gain in luminal area is mainly due to vessel expansion and, to a lesser extent, to a plaque compression.

Chapter 8 presents the interim results of the EPISODE (Evaluation Peripheral Intravascular Sonography on Dotter Effect) study, which investigated the potential role of IVUS to assess the outcome of patients undergoing balloon angioplasty of the femoropopliteal artery. Immediate angiographic failure was experienced in 8 of the 39 patients studied. Balloon angioplasty was angiographically classified as successful in 31 patients. The functional and anatomic outcome assessed at 6 months was success in 14 patients (45%) and restenosis in 17 patients (55%).

It was found that neither qualitative nor quantitative IVUS data obtained before balloon angioplasty could predict outcome. Conversely, after balloon angioplasty, a larger dissection and a smaller lumen area were found in the restenosis group than in the success group. It was concluded that the extent of dissection and lumen area as seen with IVUS after intervention were predictive factors of patency. Future studies with more patients are mandatory to further highlight the sensitivity and importance of these observations.

Chapter 9 presents the final results of the EPISODE study. In this study, in which 114 procedures with a successful angiographic result were analyzed, a distinction was made between anatomic and clinical outcome. Anatomic outcome was based on duplex examination of the treated artery, while the Rutherford criteria were used to assess clinical outcome. Restenosis was assessed within 1 month (early restenosis) and at 6 months (late restenosis) after balloon angioplasty.

At 6 months anatomic and clinical restenosis was evidenced in 36 and 49 of the 114 procedures, respectively. Independent IVUS predictor of 1 and 6 month anatomic restenosis was a larger area stenosis after balloon angioplasty at the smallest lumen area *before* intervention. The only independent predictor of 1 month clinical restenosis was a larger extent of calcification; no predictors for 6 months clinical outcome were found. It was concluded that IVUS elucidates parameters predictive of outcome. Thus, IVUS can identify a subset of patients in whom restenosis is likely to occur and may, therefore, influence interventional management to improve results.

Chapter 10 describes the use of IVUS during femorodistal venous bypass procedures to assess qualitative and quantitative parameters of the greater saphenous vein and to detect potential causes for (re)stenosis and/or occlusion. In this study IVUS data obtained from 15 patients were reviewed and compared with angiographic data.

It was found that IVUS enabled intraoperative differentiation between normal and thickened vein wall; venous side-branches could be located; persistent intact valves could be differentiated from valves disrupted by valve cutting; and patent anastomoses could be distinguished from anastomoses with obstruction. Imaging of the inflow and outflow tracts with IVUS revealed obstructive lesions, not evidenced angiographically. Distinct pre-existent vein wall thickening was encountered in 3 patients. In 5 patients IVUS findings led to alterations in surgical management. It was concluded that IVUS is able to assess qualitative and quantitative parameters of the venous bypass and has the potential to influence surgical management based on these data.

Chapter 11 describes the use of IVUS to document the status of the greater saphenous vein during bypass surgery, at follow-up and following balloon angioplasty of subsequent stenoses. Peroperatively, IVUS evidenced a distinct narrow segment (without intimal thickening) and pre-existent intimal thickening. At follow-up, both the narrow segment and pre-existent intimal thickening resulted in subsequent graft stenosis, necessitating further intervention. Luminal gain seen with IVUS after balloon angioplasty of graft stenosis was associated with vascular damage. This study elucidated that IVUS is able to document venous bypass morphologic and quantitative alterations during follow-up and to demonstrate the effect of balloon angioplasty of venous bypass stenoses.

In conclusion, IVUS is a technique which provides, in comparison to angiography, more insight in the anatomy and severity of stenotic vessels both before and after vascular intervention. Both in-vitro and in-vivo validation studies clarified which qualitative and quantitative IVUS parameters are accurate and reproducible. The technique can be used on-line during intervention and overcomes the limitations of angiography. It provides insight in the mechanism of balloon angioplasty and establishes parameters predictive of outcome following angiographic successful balloon angioplasty. It is for these reasons that IVUS can currently be used routinely to support and guide vascular interventions to improve overall results.

Angiografie is de standaardtechniek om atherosclerotische vernauwingen in coronaire en perifere arteriën te evalueren. Deze techniek die wel een silhouet van het vaatlumen laat zien, geeft geen nauwkeurige informatie over het lumenoppervlak, het vaatoppervlak, de vorm en de morfologie van een vernauwing. Intravasculaire echografie (IVE) kent deze tekortkomingen niet. Dit proefschrift zal ingaan op de betrouwbaarheid van IVE en zal de waarde van klinische toepassing van deze nieuwe afbeeldingstechniek onderzoeken.

Speciaal voor IVE werd een catheterverplaatsingsmeter ontwikkeld om de positie van de echocathetertip te documenteren. Validatie studies werden uitgevoerd om de betrouwbaarheid, tekortkomingen en voordelen van deze techniek vast te stellen. Het spectrum van afwijkingen in arteriën en venen en effecten van een interventie werden gedocumenteerd en de waarde van IVE als onderzoeks- en klinisch instrument werd geëvalueerd. Dit proefschrift beschrijft bovenstaande thema's.

Hoofdstuk 1 geeft een introductie van de inhoud van dit proefschrift.

Hoofdstuk 2 beschrijft de catheterverplaatsingsmeter die ontwikkeld is om direct informatie te geven over de locatie van de echocathetertip. De informatie wordt tezamen met het IVE-beeld weergegeven. De nauwkeurigheid van dit apparaat werd in-vitro getest in atherosclerotische segmenten van iliacale en coronaire arteriën. Van elk vaatsegment werden 3 opnames verkregen tijdens terugtrekken van de catheter. Met een onderling interval van 0.05 cm werd het lumen van opeenvolgende cross-secties bepaald. In totaal werden er 1895 cross-secties geanalyseerd. De variatie in de metingen van het lumenoppervlak was klein: 1.7% in iliacale arteriën en 3.0% in coronaire arteriën Tussen de 3 opnamen werd geen positieverschuiving gezien, met uitzondering van een verschuiving van 0.05 mm in één arterie. Geconcludeerd werd dat met de catheterverplaatsingsmeter reproduceerbare beelden verkregen kunnen worden van dezelfde locatie.

Hoofdstuk 3 beschrijft een in-vitro studie in 40 segmenten van coronaire arteriën, waarin IVE-beelden verkregen voor en na ballondilatatie werden vergeleken met histologische coupes. De verplaatsingsmeter bleek onmisbaar te zijn om nauwkeurig corresponderende IVE-beelden voor en na de interventie te vergelijken en deze te correleren met de bijbehorende histologische coupes. Deze in-vitro studie liet zien dat vaatschade gezien met IVE na de interventie kan bestaan uit een plaque ruptuur, een dissectie en/of een media ruptuur. De sensitiviteit van IVE voor het vaststellen van vaatschade was hoog voor dissectie en media ruptuur (79% en 76%, respectievelijk), maar laag voor plaque ruptuur (37%). De studie liet verder zien dat een hogere incidentie van vaatschade werd gevonden wanneer het hele vaatsegment werd geanalyseerd (85%) in plaats van één cross-sectie ter hoogte van het meest vernauwde segment (63%). Dit betekent dat, wil men een goed inzicht hebben omtrent de beschadiging van de arterie na de interventie, het gehele vaatsegment beoordeeld moet worden.

Het bleek dat de verschillen in de meting van het lumen- en vaatoppervlak, die tweemaal werden verricht door dezelfde onderzoeker en door verschillende onderzoekers, klein waren.

Door het vergelijken van de kwantitatieve data die verkregen waren voor en na ballondilatatie werd het mechanisme van dit soort interventie blootgelegd: de toename in lumenoppervlak werd voornamelijk veroorzaakt door toename in het oppervlak van de vaatwand (81%) en in mindere mate veroorzaakt door afname in lesieoppervlak (19%). De kwantitatieve effecten van ballondilatatie in coronaire arteriën gezien met IVE waren groter ter hoogte van het nauwste segment dan in de omliggende cross-secties binnen het gedilateerde segment.

Geconcludeerd werd dat men met IVE nauwkeurig de vaatschade na ballondilatatie kan vaststellen en dat de kwantitatieve data verkregen voor en na de interventie reproduceerbaar zijn. Het mechanisme van ballondilatatie, welke met IVE op een nieuwe manier bestudeerd kan worden, is veeleer vaatoprekking dan compressie van de plaque.

Hoofdstuk 4 beschrijft het gebruik van IVE zowel in-vitro als in-vivo om de relatie tussen lesie-morfologie en -topografie en dissecties veroorzaakt door ballondilatatie ter hoogte van het nauwste segment te onderzoeken.

Bij histologisch onderzoek werden dissecties in 88% van de vaatsegmenten gezien. In 59% werden deze dissecties met IVE in beeld gebracht. In-vivo werden door IVE dissecties gezien in 63% van de procedures.

De origo van een dissectie werd voornamelijk gezien op het dunste deel van de lesie (in-vitro 83%; in-vivo 93%). Er werd geen significante relatie gevonden tussen lesie eigenschappen en het optreden, de uitgebreidheid en de origo van een dissectie.

In **Hoofdstuk 5** wordt de overeenkomst gerapporteerd tussen twee onderzoekers ten aanzien van IVE data die verkregen zijn in-vivo voor en na ballondilatatie van de femoropopliteale arterie. De onderzoekers analyseerden IVE-beelden van 38 patiënten. Er was een goede overeenkomst ten aanzien van voor lesiemorfologie, dissectie en vaatschade, redelijke overeenkomst ten aanzien van lesietopografie, matige overeenkomst wat betreft media ruptuur, en een slechte overeenkomst ten aanzien van vetophoping en plaque ruptuur. Er waren geen significante verschillen in de oppervlakte metingen tussen de onderzoekers. De variatie coëfficiënt voor lumenoppervlak en vaatoppervlak was respectievelijk 17.2% en 10.5% voor de interventie en 11.2% en 9.2% na de interventie.

In **Hoofdstuk 6** wordt een studie beschreven waarbij IVE, zowel kwalitatief als kwantitatief, met angiografie werd vergeleken bij patiënten die een (laser) Dotter behandeling hebben ondergaan. Er werd een goede correlatie 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 schatting van de stenose overeenkomst vertoonde met angiografie zowel voor als na de behandeling in respectievelijk, 78% en 72% van de gevallen. De ernst van de lesie werd met IVE duidelijker zichtbaar dan met angiografie.

Semikwantitatieve on-line analyse van de mate van stenosering correspondeerde goed met de kwantitatieve analyse, die off-line werd verricht met behulp van een computer analyse programma. Wanneer men zowel met on-line IVE als met angiografie een arterie als "normaal" beoordeelde, werd met kwantitatieve off-line IVE een oppervlakte stenose gemeten van gemiddeld 18%.

In **Hoofdstuk 7** wordt beschreven hoe IVE wordt gebruikt om het spectrum van vaatschade en de kwantitatieve effecten van ballondilatatie in de femoropopliteale arterie te bestuderen. Corresponderende IVE beelden verkregen voor en na ballondilatatie in 115 interventies werden geanalyseerd. De incidentie van vaatschade vastgesteld per gedilateerd segment was hoger (91%) dan de incidentie vastgesteld ter hoogte van het nauwste segment alleen (72%). Oppervlakte metingen lieten zien dat lumenvergroting voornamelijk werd bereikt door oprekking van de vaatwand (85%), terwijl compressie van de plaque een kleinere bijdrage (15%) levert aan de lumenvergroting. Vergelijking van de interventies met een ballondiameter $\leq$5 mm en $\geq$6 mm liet zien dat de frequentie van vaatschade en de relatieve bijdrage van vaatoprekking en compressie van plaque aan de toename in lumen niet verschillend waren. Geconcludeerd werd dat vaatschade gebruikelijk is na ballondilatatie en dat toename in lumen vooral wordt veroorzaakt door uitzetting van het bloedvat en in mindere mate door compressie van de plaque.

In **Hoofdstuk 8** worden de interim resultaten van de EPISODE (Evaluation Peripheral Intravascular Sonography on Dotter Effect) studie gepresenteerd. In deze studie werd de rol van IVE onderzocht om het resultaat van een ballondilatatie van de femoropopliteale arterie vast te stellen. Direct angiografisch falen werd gezien in 8 van 39 bestudeerde patiënten. In de overige 31 patiënten werd de ballondilatatie als angiografisch succesvol geclassificeerd. De functionele en anatomische uitkomst vastgesteld na 6 maanden was een succes in 14 patiënten (45%) en restenose in 17 patiënten (55%).

Kwalitatieve noch kwantitatieve IVE data verkregen voor ballondilatatie bleken voorspellend te zijn voor de uitkomst. Na de interventie bleek dat in de restenose groep een grotere dissectie en een kleiner lumenoppervlak werd gevonden dan in de succes groep. Geconcludeerd werd dat de uitgebreidheid van dissecties en de grootte van het lumenoppervlak vastgesteld met IVE na de interventie voorspellende factoren zijn voor het succes van de ballondilatatie. Vervolg studies met meer patiënten zijn nodig om de gevoeligheid en het belang van deze resultaten vast te stellen.

Hoofdstuk 9 presenteert de eind resultaten van de EPISODE studie. In deze studie werden 114 ballondilataties van de femoropopliteale arterie die als angiografisch succesvol waren beoordeeld met IVE onderzocht. Bij de follow-up werd een onderscheid gemaakt tussen anatomische en klinische uitkomst. Anatomische uitkomst was gebaseerd op duplex onderzoek van de behandelde arterie, terwijl de Rutherford criteria werden gebruikt om de klinische uitkomst vast te stellen. Restenose werd vastgesteld binnen 1 maand (vroege restenose) en na 6 maanden (late restenose) na ballondilatatie.

Na 6 maanden follow-up werd anatomisch en klinische restenose vastgesteld in respectievelijk 36 en 49 van de 114 interventies. De onafhankelijke IVE parameter voorspellend voor anatomisch restenose na 1 en 6 maanden was een groter oppervlakte stenose na ballondilatatie ter hoogte van het nauwste segment voor de interventie. De enige onafhankelijke parameter voorspellend voor klinisch restenose na 1 maand was een grotere uitgebreidheid van verkalkte lesie. Er werden geen voorspellende IVE parameters van klinische restenose na 6 maanden gevonden. Geconcludeerd werd dat er IVE parameters zijn die voorspellend zijn voor restenose. Dit betekent dat men met IVE patiënten kan identificeren die een grote kans hebben op het ontstaan van restenose. Daarom kan IVE gebruikt worden om het beleid tijdens de interventie te beïnvloeden teneinde het resultaat te verbeteren.

Hoofdstuk 10 beschrijft het gebruik van IVE tijdens het aanleggen van een femorodistale veneuze bypass om kwalitatieve en kwantitatieve parameters van de vena saphena magna vast te stellen en mogelijke oorzaken van (re)stenose en/of occlusie te ontdekken. In deze studie werden gegevens, verkregen bij 15 patiënten, bekeken en vergeleken met de angiografische gegevens.

Met IVE bleek men in staat te zijn om tijdens de operatie een onderscheid te maken tussen een normale en een verdikte vaatwand; veneuze zijtakken konden gelokaliseerd worden; intacte kleppen konden gedifferentieerd worden van kleppen die beschadigd waren door de kleppenstripper; en open anastomosen konden onderscheiden worden van anastomosen met een vernauwing. Afbeelding van het instroom en uitstroom traject met IVE liet stenotische lesies zien, die niet met angiografie waren ontdekt. Een duidelijke reeds aanwezige wandverdikking werd aangetroffen bij 3 patiënten. Bij 5 patiënten leidde IVE tot verandering in het chirurgisch beleid. Geconcludeerd werd dat men met IVE in staat is kwalitatieve en kwantitatieve parameters van de veneuze bypass vast te stellen en dat men de mogelijkheid heeft het chirurgisch beleid te beïnvloeden op grond van deze gegevens.

Hoofdstuk 11 beschrijft het gebruik van IVE om de kwaliteit van de vena saphena magna te documenteren tijdens bypass chirurgie, en om veranderingen tijdens follow-up en na ballondilatatie van daaropvolgende stenosen vast te leggen. Tijdens het aanleggen van de bypass werd met IVE naast een duidelijk vernauwd vaatsegment (zonder intima verdikking) een vaatsegment gezien met reeds bestaande intima verdikking. Bij follow-up bleken beiden veranderd te zijn in stenosen die verder ingrijpen noodzakelijk maakten. De toename in lumen welke met IVE na ballondilatatie van de stenosen in de bypass werd gezien ging samen met vaatschade. Deze studie laat zien dat IVE in staat is morfologisch en kwantitatieve veranderingen in de veneuze bypass tijdens de follow-up vast te leggen en het effect van ballondilatatie van bypass stenosen aan te tonen.

Samenvattend, IVE is een techniek die vergeleken met angiografie beter inzicht geeft in de anatomie en ernst van vernauwde bloedvaten zowel voor als na een vasculaire interventie. In-vitro en in-vivo validatie studies hebben laten zien welke kwalitatieve and kwantitatieve parameters betrouwbaar en reproduceerbaar zijn. De techniek kan on-line gebruikt worden tijdens een interventie, geeft beter inzicht in het mechanisme van ballondilatatie en verschaft parameters die voorspellend zijn voor de uitkomst na een angiografisch succesvolle ballondilatatie. Om deze reden kan IVE thans als routine gebruikt worden om vasculaire interventies te ondersteunen en te begeleiden met als doel het resultaat te verbeteren.

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CURRICULUM VITAE

Adrianus van der Lugt was born on February 3, 1963 in *Berkel en Rodenrijs*. In 1981, after graduating high school (*Gymnasium-ß*) at the *Gereformeerde Scholengemeenschap Rotterdam*, he began medical studies at the Erasmus University Rotterdam. He graduated in 1986 with a Master's degree and passed the final medical examination in 1988. In 1989 and 1990 he was in military service in Middelburg, serving the Army as a medical officer. From May 1990 to May 1992 he was a resident at the Department of Surgery, Maria Hospital, Tilburg; and from July 1992 to January 1993 at the Department of Intensive Care, Catharina Hospital, Eindhoven. During this period intravascular ultrasound research was performed under supervision of Dr. E.J. Gussenhoven at the Department of Experimental Echocardiography (head: Prof.Dr.Ir. N. Bom), Erasmus University Rotterdam. From March 1993 he completed a one-year contract at the Department of Surgery of the Erasmus University Rotterdam to undertake studies on duplex scanning and intravascular ultrasound. Since March 1994 he is employed as a research fellow by the Interuniversity Cardiology Institute of the Netherlands (posted at the department of Experimental Echocardiography, Erasmus University Rotterdam). He participated in the projects "Intravascular Ultrasound" (ICIN 12), "EPISODE" (Evaluation Peripheral Intravascular Sonography On Dotter Effect)(ICIN 16) and "Intervention Cardiology: the arterial vessel wall" (ICIN 18). The studies which form the basis of this thesis were performed mainly during this period. In October 1996, he started training at the Department of Radiology at the University Hospital-Dijkzigt, Rotterdam (supervisor: Prof.Dr. J.S. Laméris).

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Adrianus van der Lugt werd geboren op 3 februari 1963 in Berkel en Rodenrijs. In 1981, na het behalen van het examen Gymnasium-ß aan de Gereformeerde Scholengemeenschap te Rotterdam, werd begonnen met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Hij behaalde het doctoraal examen in 1986 en het artsexamen in 1988. In 1989 en begin 1990 werd de militaire dienstplicht vervuld te Middelburg als controlerend geneesheer. Hij was werkzaam als arts-assistent van mei 1990 tot mei 1992 op de afdeling Heelkunde van het Maria Ziekenhuis te Tilburg en van juli 1992 tot januari 1993 op de afdeling Intensieve Zorg van het Catharina Ziekenhuis te Eindhoven. Tijdens deze periode werd onderzoek verricht met intravasculaire echografie onder leiding van Dr. E.J. Gussenhoven op de afdeling Experimentele Echocardiografie (hoofd: Prof.Dr.Ir. N. Bom), Erasmus Universiteit Rotterdam. In maart 1993 werd hij aangesteld op de afdeling Heelkunde van de Erasmus Universiteit Rotterdam ten behoeve van de diagnostiek met duplex-scanning en intravasculaire echografie. In april 1994 kwam hij in dienst van het Interuniversitair Cardiologisch Instituut Nederland (gedetacheerd bij de afdeling Experimentele Echocardiografie, Erasmus Universiteit Rotterdam) als wetenschappelijk onderzoeker. Hij werkte mee aan de projecten "Intravasculaire Echografie" (ICIN 12), "EPISODE" (Evaluation Peripheral Intravascular Sonography On Dotter Effect)(ICIN 16) en "Interventie Cardiologie: de arteriële vaatwand" (ICIN 18). In deze periode werd de basis gelegd voor dit proefschrift. In oktober 1996 is hij gestart met de opleiding tot radiodiagnost in het Academisch Ziekenhuis-Dijkzigt Rotterdam (opleider Prof. Dr. J.S. Laméris).

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