VASCULAR INTERVENTIONS EVALUATED BY INTRAVASCULAR ULTRASOUND

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ISBN 90-9013514-6

Cover designed by A.W. Zwamborn
Type-setting: A.W. Zwamborn
Illustrations: A.W. Zwamborn
Photographs: T. Rijsdijk

Printed by  Ridderprint B.V. Ridderkerk

VASCULAR INTERVENTIONS EVALUATED BY INTRAVASCULAR ULTRASOUND

VASCULAIRE INTERVENTIES GEEVALUEERD MET INTRAVASCULAIRE ECHOGRAFIE

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. dr. P.W.C. Akkermans M.A.
en volgens het besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 23 februari 2000 om 15.45 uur
door

Winnifred van Lankeren
geboren te 's-Gravenhage

Promotiecommissie

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Studies presented in this dissertation were supported by the Netherlands Heart Foundation and the Interuniversity Cardiology Institute of the Netherlands.
Financial support by the Interuniversity Cardiology Institute of the Netherlands.

Voor mijn ouders

Voor Waldrick

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CONTENTS

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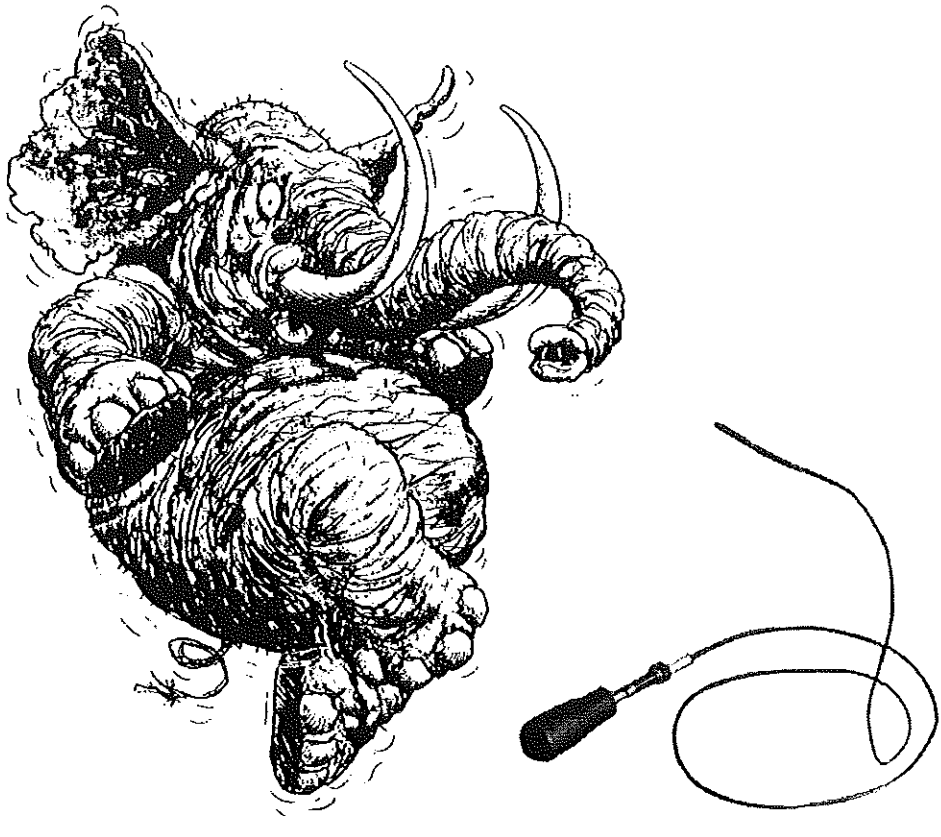
INTRODUCTION



INTRODUCTION

Intermittent claudication is one of the clinical manifestations of obstructive disease of peripheral arteries of the lower extremities. The symptoms may include pain, cramp, and fatigue in the muscles of the affected leg provoked by exercise, which are relieved after several minutes of rest. These symptoms are caused by encroachment of the lumen by atherosclerosis, preventing an adequate supply of oxygen saturated blood. More severe manifestations are night- or restpain, and ulceration or gangrene of the toes or foot.

The evaluation of obstructive atherosclerotic disease of peripheral arteries is based on patient symptoms and hemodynamic findings (measured by ankle/arm index). To evaluate the location and severity of the disease different imaging techniques are available; of these, digital subtraction angiography is the gold standard. Less invasive techniques are also available including color-flow duplex ultrasound, computed tomography angiography, and magnetic resonance angiography. Whereas angiography displays the vascular anatomy in a longitudinal silhouette with no additional information on the vessel wall, intravascular ultrasound is an imaging technique that provides tomographic images of the vessel wall, enabling assessment of plaque constitution and lumen, as well as vessel and plaque dimensions. Intravascular ultrasound is usually applied in addition to angiography.

To treat symptomatic peripheral obstructive disease different approaches are available including exercise programs, percutaneous transluminal angioplasty, stent, endovascular graft placement, endarterectomy or bypass surgery.

In 1964, Dotter and Judkins[1] reported the preliminary results of percutaneous treatment of obstructed femoropopliteal arteries using coaxial catheters to enlarge the encroached lumen. This technique was modified in 1974 by Grüntzig and Hopff[2], who used the coaxial catheters together with dilatation balloon catheters. This latter technique has been further improved and nowadays percutaneous transluminal angioplasty is considered an important technique to treat patients with obstructive atherosclerotic disease.

The success of balloon angioplasty of the femoropopliteal artery is limited by restenosis which is reported to occur in 47 to 81% of the treated patients per year[3-8]. Initially, autopsy studies learned that restenosis following balloon angioplasty was caused by intimal hyperplasia (i.e. smooth muscle cell proliferation)[9-12]. Later, histologic and intravascular ultrasound studies in animals and in human coronary arteries demonstrated that, besides intimal hyperplasia, arterial remodeling (i.e. vascular shrinkage) may contribute to lumen reduction following intervention[13-19]. To eliminate vascular shrinkage as a result of balloon angioplasty, stents were developed to counteract the lumen area decrease following intervention, and to improve immediate and long-term results of the intervention[20]. Serial intravascular ultrasound investigation in stented coronary arteries showed minimal late stent recoil; intimal hyperplasia was the

dominant factor contributing to coronary stent restenosis[21].

Aims and outline of the thesis

The aim of this work was to study the effect of peripheral balloon angioplasty and the mechanism of restenosis following vascular interventions using intravascular ultrasound.

Regression analysis and the use of a reference segment to evaluate vascular remodeling in vitro is discussed in **chapter 2**. **Chapter 3** addresses the morphologic and quantitative effects of balloon angioplasty of the iliac artery assessed with intravascular ultrasound in vascular specimens derived at autopsy. **Chapter 4** presents a study in which the morphologic and quantitative parameters assessed with intravascular ultrasound before and after balloon angioplasty of the femoropopliteal artery were compared using angiography as the gold standard. The differences between both imaging techniques were elucidated. **Chapter 5** deals with an in vivo study investigating the effects of balloon angioplasty of the iliac artery with intravascular ultrasound and evaluating the predictive value of intravascular ultrasound parameters for patient outcome. In **chapters 6 and 7** the use of intravascular ultrasound to assess lumen area change and predictors of restenosis following balloon angioplasty of the femoropopliteal artery is addressed. **Chapter 8** explores the relationship between stent deployment and the balloon size used. **Chapters 9 and 10** discuss the different type of stent remodeling seen in Palmaz and Memotherm stents. In **Chapter 11** the summary of this thesis is presented.

REFERENCES

1. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technique and a preliminary report of its application. Circulation. 1964;30:654-670.
2. Grüntzig A, Hopff H. Perkutane rekanalisation chronischer arterieller verschlüsse mit einem neuen dilatationskatheter. Modifikation der Dotter-technik. Dtsch Med Wschr. 1974;99:2502-2505.
3. Krepel VM, van Andel GJ, van Erp WFM, Breslau PJ. Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results. Radiology. 1985;156:325-328.
4. Jeans WD, Armstrong S, Cole SEA, Horrocks M, Baird RN. Fate of patients undergoing transluminal angioplasty for lower-limb ischemia. Radiology. 1990;177:559-564.
5. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty: factors influencing long-term success. Circulation. 1991;83 (Suppl I):I-70-I-80.
6. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology. 1992;183:767-771.
7. Matsi PJ, Manninen HI, Vanninnen RL, Suhonen MT, Oksala I, Laakso M, Hakkarainnen T, Soimakalloi S. Femoropopliteal angioplasty in patients with claudication: primary and secondary patency in 140 limbs with 1-3-year follow-up. Radiology. 1994;191:727-733.
8. Stanley B, Teague B, Raptis S, Taylor DJ, Berce M. Efficacy of balloon angioplasty of the superficial femoral artery and popliteal artery in the relief of leg ischemia. J Vasc Surg. 1996;23:679-685.
9. Kohchi K, Takebayashi S, Block PC, Hiroki T, Nobuyoshi M. Arterial changes after percutaneous transluminal coronary angioplasty: results at autopsy. J Am Coll Cardiol.1987;10:592-599.
10. Nobuyoshi M, Kimura T, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N, Yokoi H, Kim K. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol. 1991;17:433-439.
11. Ellis SG, Muller DWM. Arterial injury and the enigma of coronary restenosis. J Am Coll Cardiol. 1992;19:275-277.
12. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE , Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol. 1992;19:267-274.
13. Kakuta T, Currier JW, Haudenschild CC, Ryan TJ, Faxon DP. Differences in compensatory enlargement, not intimal formation, account for restenosis after angioplasty in the hypercholesterolemic rabbit model. Circulation. 1994;89:2809-2815.
14. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. Circulation. 1994;89:2816-2821.
15. Blasini R, Mudra H, Klauss V, Regar E, Schömig A. Remodelling of coronary arteries after balloon angioplasty: In vivo documentation in patients using consecutive intravascular ultrasound. J Am Coll Cardiol. 1995 (Supplement); 139 A.
16. Di Mario C, Gil R, Camenzind E, Ozaki Y, von Birgelen C, Umans V, de Jaegere P, de Feyter PJ, Roelandt JR, Serruys PW. Quantitative assessment with intracoronary ultrasound of the mechanisms of restenosis after percutaneous transluminal coronary angioplasty and directional coronary atherectomy. Am J Cardiol. 1995;75:772-777.
17. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong SC, Hong MK, Kovach JA, Leon MB. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation. 1996;94:35-43.
18. Luo H, Nishioka T, Eigler NL, Forrester JS, Fishbein MC, Berglund H, Siegel RJ. Coronary artery restenosis after balloon angioplasty in humans is associated with circumferential coronary constriction. Arterioscler Thromb Vasc Biol. 1996;16:1393-1398.
19. Kimura T, Kaburagi S, Tamura T, Yokoi H, Nakagawa Y, Yokoi H, Hamasaki N, Nosaka H, Nobuyosi M, Mintz GS, Popma JJ, Leon MB. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. Circulation. 1997;96:475-483.

20. Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, Wong SC, Deforty D, Leon MB. Endovascular stents reduce restenosis by eliminating geometric arterial remodeling: A serial intravascular ultrasound study. J Am Coll Cardiol.1995;25:36A.
21. Painter JA, Mintz GS, Wong CS, Popma JJ, Pichard AD, Kent KM, Satler LF, Leon MB. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. Am J Cardiol. 1995;75:398-400.

2 REMODELING OF ATHEROSCLEROTIC CORONARY ARTERIES ASSESSED WITH INTRAVASCULAR ULTRASOUND IN VITRO

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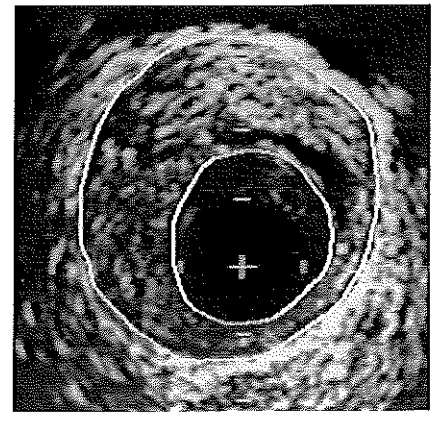

This study was supported by grants from the Netherlands Heart Foundation (91.016;006) and the Interuniversity Cardiology Institute of the Netherlands

Am J of Cardiol 1997;79:699-702

The present intravascular ultrasound study compares the analysis performed by Glagov et al[1] and subsequently adopted by others[2-6], which determined the relation between plaque area and vessel area obtained from a single histologic section per artery, with the analysis presented in later studies which compared the vessel area of the target lesion to an adjacent reference segment[6-8].

• • •

Atherosclerotic coronary arteries (n=47) were removed from humans at autopsy (n=22) or from explanted hearts that became available from patients referred for cardiac transplantation (n=25) (median age 51, range 26-65 years). The specimens (length >4 cm) 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 ends were connected to sheaths fixed to a waterbath at room temperature. A reference point was indicated using a needle. 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. For this study, coronary arteries were used with ≥30% area stenosis at the most stenotic site as seen with intravascular ultrasound. A mechanical 30 MHz imaging system was used (DuMED, Rotterdam, The Netherlands). A displacement sensing device was used to document the displacement of the ultrasound cathetertip in steps of 0.1 mm in relation to the reference needle [9,10]. From each imaged artery the target and a reference site were selected for analysis.

The target site was the cross-section with the smallest lumen area. The reference site was the most normal-looking cross-section (the largest lumen area) within 10 mm of the target site (proximally or distally) without interpositioned side branches. Analysis included measurement of lumen area and vessel area (bounded by the external elastic lamina) (Figure 1). Plaque area was calculated by

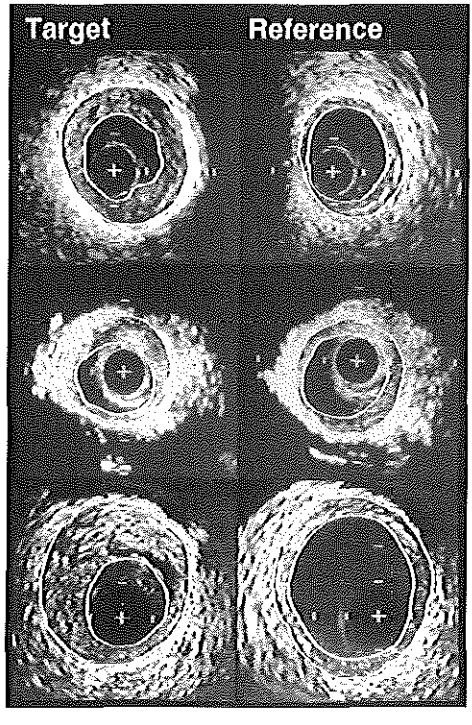

Fig. 1. Intravascular ultrasound cross-sections obtained from atherosclerotic coronary arteries showing the target site (*left panel*) and the reference site (*right panel*). The inner contour presents the lumen area and the outer contour the vessel area. The vessel area at the target site was larger (*upper panel*), in the same order (*middle panel*), and smaller (*lower panel*) than at the reference site.
Calibration = 1 mm; + = catheter.

subtracting lumen area from vessel area. Percentage area stenosis was calculated as plaque area divided by vessel area[11].
First, the relation between plaque and vessel areas was assessed both at the target site and at the reference site; the relation between area stenosis and lumen area (of the target and reference sites combined) was assessed for area stenosis ≤40% and >40%, respectively. Second, the mean values of the measurements obtained at the target and reference site were compared. Third, the measure-ments obtained at the target and reference site in each artery were compared. The vessel area measured at the target site was expressed as a percentage of the vessel area at the reference site:

$$\frac{\text{Vessel area (target site)}}{\text{Vessel area (referencesite)}} \times 100\% \quad (1)$$

At the target site a relative vessel area of >110% indicates enlargement, a relative vessel area of 90 to 110% indicates no alteration in vessel area, and a vessel area of <90% indicates shrinkage with respect to the reference site. A cutoff point of ± 10% was used to correct for tapering and to avoid false demonstration of enlargement or shrinkage (depending on the distal or proximal position of the reference site)[12]. Results are expressed as mean values ± SD. Relations between variables were examined using linear regression analysis. The two sample t-test was used to compare the measurements of the target and reference site. The statistical significance level was set at $p<0.05$.
Intravascular ultrasound images of 40 of the 47 vascular specimens were suitable for analysis. In the remaining 7 specimens vessel area could not be assessed at the target site due to severe calcification and these specimens were excluded from the analysis.

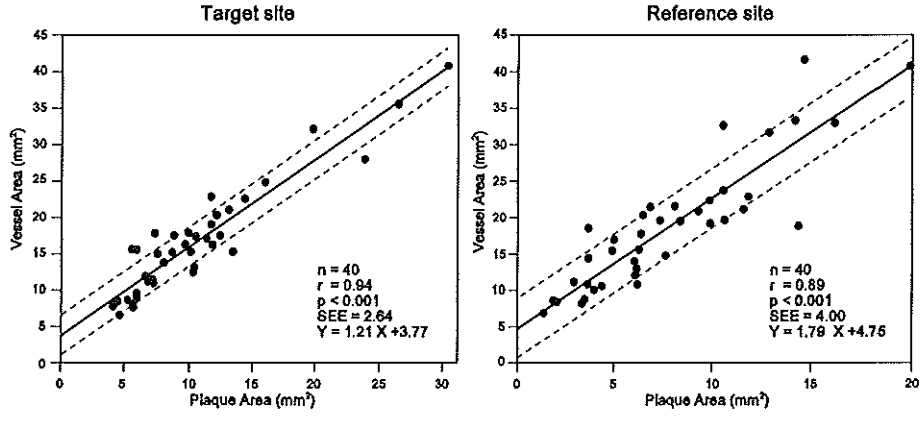

Fig. 2. Graphs showing a positive correlation between plaque area and vessel area at the target *(left panel)* and reference site *(right panel)*. Both correlations are significant. The standard error of the estimate (SEE) is denoted by the *dashed lines* above and below the *solid regression line*.

Table 1. Quantitative differences in measurements obtained at the target and reference site assessed in vitro with intravascular ultrasound in 40 coronary arteries.

	Intravascular ultrasound	
	Target site	Reference site
Lumen area (mm^2)	6.0 ± 2.9	10.8 ± 5.2*
Vessel area (mm^2)	16.3 ± 7.6	18.4 ± 8.7*
Plaque area (mm^2)	10.3 ± 5.9	7.6 ± 4.4*
Area stenosis (%)	62.5 ± 11.7	40.3 ± 11.4*

* differences are significant with $p < 0.001$. Values are expressed as mean ± SD.

A positive correlation was found between plaque area and vessel area both at the target site ($r=0.94$, $p<0.001$) and reference site ($r=0.89$, $p<0.001$) (Figure 2). The regression equation indicated that for every 1-mm^2 increase in plaque area, vessel area increased 1.21 mm^2 at the target site and 1.79 mm^2 at the reference site. No relation was found between lumen area and area stenosis for the combined data of the target and reference site for cross-sections with ≤40% stenosis ($r=0.17$, $p=0.47$). In cross-sections with >40% area stenosis, lumen area decreased as area stenosis increased ($r= -0.56$, $p<0.001$).

The mean quantitative data of area measurements at the target and reference site are listed in Table 1. By definition, the lumen area at the target site was smaller than at the reference site. The vessel area at the target site was smaller than that at the reference site ($p<0.001$). Furthermore, the plaque area and area stenosis were larger at the target site compared with that at the reference site (both $p<0.001$). Comparing the measurements of vessel area at both sites in each artery individually, it was found that the vessel area at the target site was enlarged in 5, not altered in 14, and smaller in 21 arteries with respect to the reference site. Comparing the measurements of plaque area at both sites it was found that the plaque area at the target site was larger in 31 and smaller in 9 of the 40 arteries with respect to the reference site. The 9 target sites with a smaller plaque area also had a smaller vessel area compared with the reference site.

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Using multiple histologic sections, Glagov et al.[1] correlated plaque area and vessel area and concluded that arteries enlarge in relation to plaque area and that functionally important lumen stenosis may be delayed until the lesion occupies 40% of the vessel area. In addition, analysis of mildly diseased sections revealed that vessel enlargement may in fact

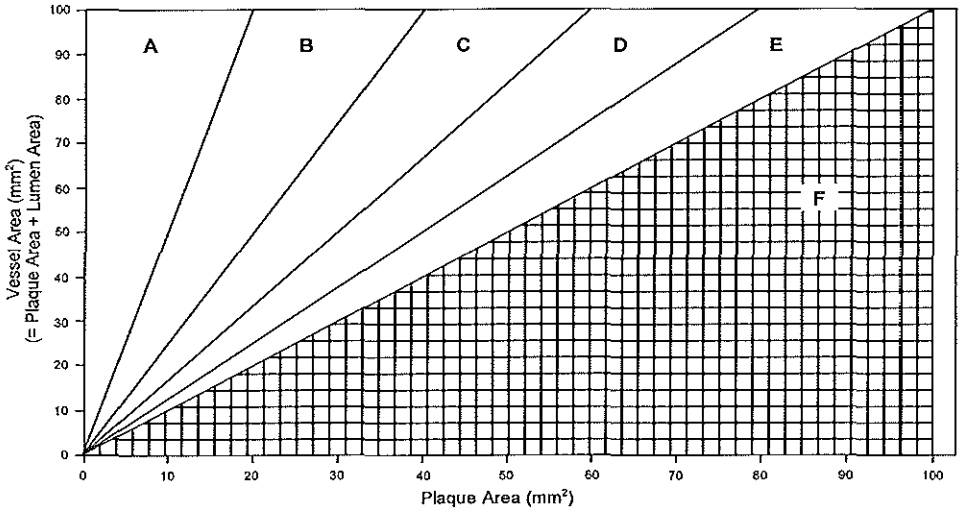

Fig. 3. Graphs showing the theoretical distribution of data in a regression analysis between plaque area and vessel area. Regions A to E represent the cross-sections with an area stenosis of 0 to 20%, 20 to 40%, 40 to 60%, 60 to 80% and 80 to 100%, respectively; the regression equation will show a steeper slope for mildly diseased segments than for severely diseased segments, which falsely suggests overcompensation of vessel area in relation to plaque accumulation. Region F contains no data because plaque area can not be larger than vessel area.

overcompensate for the increase in plaque accumulation. These analyses were subsequently adopted in intravascular ultrasound studies[3-6] which confirmed Glagov's conclusions.

In the present intracoronary ultrasound study, similar results were obtained using this type of analysis: plaque area and vessel area were positively related and the regression equation indicated that for every 1 mm^2 increase in plaque area, vessel area increase was larger at the reference site than at the target site, suggesting overcompensation. However, comparing the vessel area at the target site with the vessel area at the reference site, it was found that both enlargement and reduction of vessel area could occur.

These conflicting results show the limitation of regression analysis to study adequately remodeling of arteries. Firstly, correlating plaque area with vessel area (plaque area + lumen area), which is a correlation between a and a+b, has a high probability of a significant positive relation (Figure 3). In addition, the regression equation will show a steeper slope for mildly diseased segments which falsely suggests overcompensation of vessel area (Figure 3). Secondly, regression analysis will not reveal vessel area reduction during progression of atherosclerosis. Thirdly, conclusions on a time-related phenomenon were based on a cross-sectional study using histologic sections of arteries at different stages of

atherosclerosis which were considered to have the same size at the start of the disease process.

To overcome (in part) the latter limitation, both plaque area and vessel area in an atherosclerotic segment may be compared with a reference segment located in the same vessel [4,6-8]. Losordo et al.[6], used this method in mildly diseased lesions in the femoral artery and found vessel enlargement in the majority of the lesions. However, Pasterkamp et al.[7,8], studying symptomatic lesions in the same type of artery, demonstrated that besides enlargement of the vessel area, also shrinkage may occur.

The present study in coronary arteries revealed that besides plaque accumulation, vessel wall shrinkage contributed to the formation of stenotic lesions. Given the minimal distance between the target and reference site (≤10 mm) and the cutoff point of ± 10% tapering was not considered to influence the analysis in the present study.

However, comparison of a target site with a reference site raises a problem concerning the definition of both sites. Most studies have used the plaque area to define the target (maximum plaque) and reference site (minimum plaque)[4,6-8]. This choice presupposed that the amount of plaque is the main parameter to define the degree of atherosclerosis and that the alteration in vessel area is influenced by plaque accumulation. Furthermore, the target site (defined as the site with the largest plaque area) does not necessarily correspond with the site of the symptomatic stenotic lesion. For these reasons, definition of both the target and reference site in the present study was based on lumen area magnitude: i.e. the target site was based on the smallest lumen area; the reference site was based on the same parameter (largest lumen area), irrespective of the amount of plaque. This method of analysis demonstrated that 21 segments had a smaller vessel area at the target site than at the reference site; in 9 of these segments the plaque area at the target site was smaller compared to the reference site. Thus, the hemodynamic significant stenosis may contain less plaque than the surrounding regions. This may be explained by shrinkage of the vessel at the target site (independent of plaque accumulation) or failure of the vessel to enlarge.

The objection that a large vessel area (reference site) represents overcompensation and is, therefore, responsible for the high incidence of vessel shrinkage found at the target site can be counteracted by the above-described limitations of the regression analysis on which the theory of overcompensation is based (Figure 3).

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Regression analysis of vessel area on plaque area measured in different arteries is unable to discern different patterns of remodeling in vessels. Analyses which compare a target site with a reference site have limitations related to the choice of these sites. An adequate method to analyze the impact of progression of atherosclerosis on vessel area should entail a longitudinal study of a vessel segment over time [13].

REFERENCES

1. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-1375.
2. McPherson DD, Sirna SJ, Hiratzka LF, Thorpe L, Armstrong ML, Marcus ML, Kerber RE. Coronary arterial remodeling studied by high-frequency epicardial echocardiography; an early compensatory mechanism in patients with obstructive atherosclerosis. J Am Coll Cardiol 1991;17:79-86.
3. Hermiller JB, Tenaglia AN, Kisslo KB, Phillips HR, Bashore TM, Stack RS, Davidson CJ. In vivo validation of compensatory enlargement of atherosclerotic coronary arteries. Am J Cardiol 1993;71:665-668.
4. Ge J, Erbel R, Zamorano J, Koch L, Kearney P, Görge G, Gerber T, Meyer J. Coronary artery remodeling in atherosclerotic disease: an intravascular ultrasonic study in vivo. Coron Artery Dis 1993;4:981-986.
5. Gerber TC, Erbel R, Görge G, Ge J, Rupprecht H-J, Meyer J. Extent of atherosclerosis and remodeling of the left main coronary artery determined by intravascular ultrasound. Am J Cardiol 1994;73:666-671.
6. Losordo DW, Rosenfield K, Kaufman J, Pieczek A, Isner JM. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis. In vivo documentation using intravascular ultrasound. Circulation 1994;89:2570-2577.
7. Pasterkamp G, Wensing PJW, Post MJ, Hillen B, Mali WPTM, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. Circulation 1995;91:1444-1449.
8. Pasterkamp G, Borst C, Post MJ, Mali WPTM, Wensing PJW, Gussenhoven EJ, Hillen B. Atherosclerotic arterial remodeling is individually determined: compensatory enlargement revisited. Circulation 1996;93:2818-1825.
9. Gussenhoven EJ, van der Lugt A, van Strijen M, Li W, The SHK, van Egmond FC, Honkoop J, Peters RJG, de Feyter P, van Urk H, Pieterman H. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N (eds.). Intravascular Ultrasound. Dordrecht: Kluwer Academic Press 1993:157-166.
10. van der Lugt A, Gussenhoven EJ, Stijnen T, van Strijen M, van Driel E, van Egmond FC, Suylen RJ, van Urk H. Comparison of intravascular ultrasound findings after coronary balloon angioplasty with histology. Am J Cardiol 1995;76:661-666.
11. Wenguang L, Gussenhoven WJ, Zhong Y, The SHK, Di Mario C, Madretsma S, van Egmond FC, de Feyter P, Pieterman H, van Urk H, Rijsterborgh H, Bom N. Validation of quantitative analysis of intravascular ultrasound images. Int J Card Imaging 1991;6:247-253.
12. Javier SP, Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Leon MB. Intravascular ultrasound assessment of the magnitude and mechanism of coronary artery and lumen tapering. Am J Cardiol 1995;75:177-180.
13. Weissmann NJ, Mendelsohn FO, Palacios IF, Weyman AE. Development of coronary compensatory enlargement in vivo: sequential assessments with intravascular ultrasound. Am Heart J 1995;130:1283-1285.

3 INTRAVASCULAR ULTRASOUND AND HISTOLOGY IN IN VITRO ASSESSMENT OF ILIAC ARTERY ANGIOPLASTY

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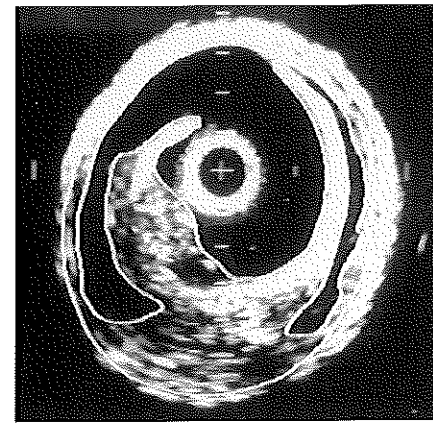

This study was supported by grants from the Netherlands Heart Foundation (94.006; 91.016) and the Interuniversity Cardiology Institute of the Netherlands.

Accepted for publication in: Cardiovasc Intervent Radiol; 1999;22:50-55

ABSTRACT

Purpose: Intravascular ultrasound (IVUS) was used to assess in vitro morphologic and quantitative effects of balloon angioplasty (PTA) of the iliac artery.

Methods: Forty human iliac arteries (≥30% area stenosis) were studied in vitro before and after PTA with IVUS and the findings were validated with histology.

Results: The sensitivity of IVUS for dissection was 74% and for media rupture 59%. Incidence of vascular damage was higher, when the whole segment was analyzed rather than the target site alone. Dissections occurred at the thinnest region of the plaque, unrelated to plaque calcification. Following PTA, quantitative changes at the target site were greater compared with the overall data derived from all cross-sections. Lumen area increase was solely caused by vessel area increase.

Conclusions: IVUS is sensitive in detecting dissections, which occurred irrespective of calcification at the thinnest region of the plaque. Lumen area increase after PTA was caused by vessel stretch.

key words: Iliac artery; Balloon angioplasty; Histology; Intravascular ultrasound

INTRODUCTION

Intravascular ultrasound (IVUS) is a new imaging technique to assist vascular intervention in both coronary and peripheral arteries[1-7].

In vitro studies performed with IVUS in atherosclerotic arterial segments have proven that the technique is reliable to document lesion morphology and to quantify the size of the vessel lumen and the extent of plaque[8-10]. Furthermore, IVUS is able to assess the morphological and quantitative effects of balloon angioplasty (PTA)[11-14]. To date, no systematic IVUS study investigated in vitro the ability of IVUS to assess effects of PTA in the iliac artery. The aims of this in vitro study were: 1) to examine the sensitivity of IVUS to document vascular damage after PTA; 2) to evaluate the relation between plaque calcification and vascular damage; 3) to assess the quantitative effects of PTA; and 4) to establish whether one single ultrasound cross-section obtained at the target site (i.e. smallest lumen area before PTA) is representative for the outcome rather than a sequence of cross-sections.

MATERIALS AND METHODS

Intravascular ultrasound

IVUS was performed using a mechanical 30 MHz imaging system (Endosonics, Rijswijk, the Netherlands). Ultrasound catheters 'Princeps' incorporate a sonographic transducer that is rotated externally by a motor; details of this system have been described previously[6]. The resulting images are displayed on a videomonitor and stored on S-VHS videotape.

In vitro study

Atherosclerotic common iliac arteries (n=40) were removed from humans at autopsy (median age 70 years, range 30-85 years); within 24 hours after death the vascular specimens were stored frozen at -20°C. The investigation was approved by the Local Committee on Human Research.

The specimens were thawed, side-branches were ligatured with sutures and the proximal and distal ends were connected to sheaths fixed to a water bath at room temperature. Distally, a needle at the 12 o'clock position was used as a reference point (Fig. 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.

For this study, iliac arteries with more than 30% area stenosis at the target site seen on IVUS were subjected to PTA and studied before and after intervention. Balloons (OPTA, Cordis Europe, Roden, the Netherlands) with an 8 or 10 mm diameter and 4 cm length were used. The largest lumen diameter seen in the vascular segment on IVUS was used as reference site for the balloon diameter. PTA was performed during 2 minutes with a manometer controlled pressure of 8-10 atmosphere. Intervention was considered successful if the lumen area at the target site seen on ultrasound increased; otherwise, a larger balloon was used. To ensure reliable comparison of IVUS images obtained before and after PTA, a displacement sensing device was used[15]. Displacement of the ultrasound cathetertip in steps of 1 mm was related to the reference needle and mixed automatically with the ultrasound information on the videomonitor.

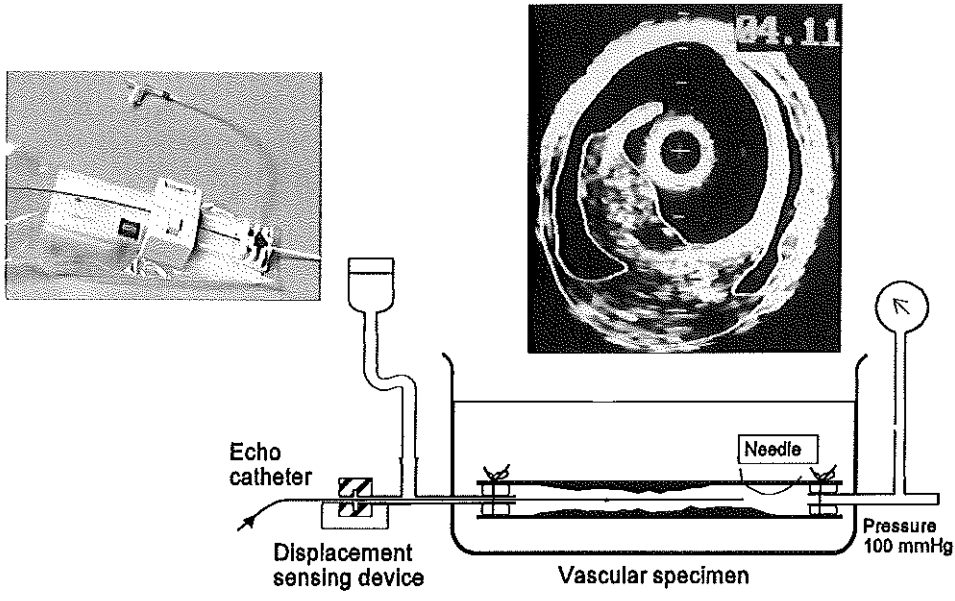

Fig. 1. In vitro set-up showing the intravascular ultrasound catheter advanced via the sensing unit of the displacement sensing device and sheath towards the pressurized vascular specimen. The needle distally attached to the artery is used as reference. The cathetertip position in relation to the needle (+04.11 cm) is indicated in the right upper panel. Insert left upper panel: displacement sensing device.
Calibration = 1 mm.

Histology

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 (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 Indian ink. Transverse sections, 5 μm thick perpendicular to the long axis of the vessel, were cut at 1 mm intervals. The sections were stained with the elastic van Gieson and the hematoxylin eosin techniques.

Analysis of data

IVUS images obtained before and after PTA of each vascular segment were photographed with increments of 1 mm. For comparison with the corresponding histologic sections the site of the reference needle and anatomic markers such as side-branches, calcifications or dissections were used. Cross-sections showing side-branches were excluded from analysis. Of each specimen 4 to 6 matched IVUS images and histologic sections including the target site were selected and subjected to qualitative and quantitative analysis.

Qualitative analysis
The IVUS images were evaluated by 2 observers without knowledge of the histologic results (AQ, WvL). Any differences between observers were solved by consensus. The histologic sections were evaluated by another observer (EJG).
First, the presence of vascular damage after intervention was documented[6]. *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. *Media rupture* was defined as an interruption in the internal elastic lamina and media which exposes the hyperechoic adventitia to the lumen. *Vascular damage* was defined as the presence of a dissection and/or media rupture. The incidence of these morphologic features seen at the target site was compared with data from the sequence of IVUS cross-sections available. In addition, using the histologic data as gold standard the sensitivity of IVUS to detect these morphologic features in each vascular specimen was determined.
Second, the location and occurrence of a dissection at the target site was related to the plaque thickness and the plaque composition. A nominal yes or no score indicates whether or not the dissection occurred at the thinnest region of the plaque. Plaque composition was designated as *calcified* (bright echoes with shadowing) or *non-calcified* (echodense without shadowing).

Quantitative analysis
Quantitative measurement of IVUS cross-sections was performed using a digital video analyzer system[16]. Analysis included measurement of lumen area and vessel area. Lumen area was defined as the area encompassed by the intimal surface. Vessel area was defined as the area bounded by the media-adventitia interface. Plaque area was calculated by subtracting lumen area from vessel area. The percentage area stenosis (obstruction) was calculated as plaque area divided by vessel area. When extensive dropout due to calcification (>120° of the circumference) was encountered, vessel area was not calculated. Data obtained at the target site were compared with those obtained in all selected cross-sections.
To assess interobserver variability on quantitative IVUS parameters, a randomly selected subgroup of 40 pairs of matched cross-sections obtained before and after intervention (one pair per vascular specimen) was subsequently analyzed by a second observer (AvdL).

Statistical analysis
Quantitative measurements obtained before and after intervention and interobserver measurements were compared using Student's paired t-test. 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. The Chi-squared test with continuity correction was performed to determine a relation between categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 224 sets of matched IVUS images, obtained before and after PTA, and histologic sections were selected for comparison.

Qualitative analysis

Following PTA, vascular damage was encountered at the target site in 30 of the 40 (75%) specimens on histology and in 19 (48%) on IVUS (Fig. 2). The incidence of vascular damage (including dissection and media rupture) seen with IVUS and the sensitivity of IVUS in detecting these features are summarized in Table 1. At the target site a lower incidence of vascular damage was seen compared with the incidence of vascular damage seen per specimen (Table 1). IVUS showed a good sensitivity in detecting dissection and a low sensitivity for media rupture. False positive dissections or media ruptures were not encountered on IVUS. The reason for dissections missed on IVUS were: 1) dissection occurred without connection with the lumen; 2) lesion calcification hindered visualization of the dissection; 3) the image quality was not sufficient for diagnosing dissection, and 4) predominantly small dissections remained adherent to the vessel wall. Similarly, for the first 3 reasons media ruptures were missed on IVUS (Fig. 2).

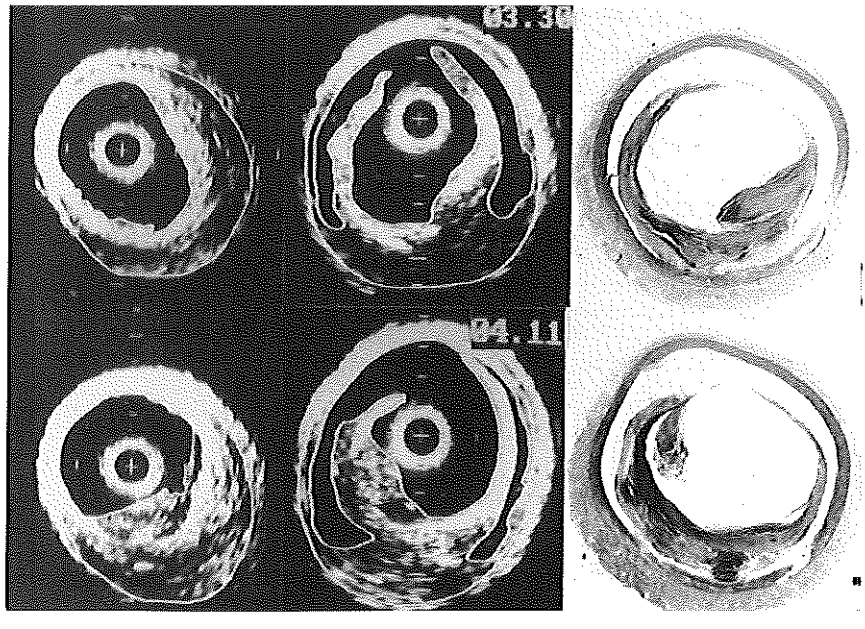

Fig. 2. Matched intravascular ultrasound (IVUS) cross-sections obtained before (left) and after (middle) balloon angioplasty of the common iliac artery and their histologic counterparts (right). Levels are indicated by the displacement sensing device. On both levels vessel area increase contributed to lumen area increase. Level 03.30 cm; on IVUS a dissection (8 to 4 o'clock) and media rupture (4 o'clock) were correctly diagnosed. Level 04.11; at the target site the media rupture at 4 o'clock was not seen with IVUS. Note that the dissections occurred at the thinnest region of the plaque. Calibration = 1 mm; + = catheter.

Table 1. Incidence of vascular damage, including dissection and media rupture seen on histology and with intravascular ultrasound (IVUS) at the target site and per vascular specimen (n = 40), and the sensitivity of IVUS in detecting these features.

	Target site				Vascular specimen					
	Incidence (95% CI)				Incidence (95% CI)					
	% Histology		% IVUS		% Histology		% IVUS		% Sensitivity (95% CI)	
Vascular damage	75	(59-87)	48	(32-64)	98	(87-100)	75	(59-87)	77	(63-91)
Dissection	75	(59-87)	48	(32-64)	95	(83-99)	70	(54-83)	74	(57-87)
Media rupture	48	(32-64)	28	(15-44)	68	(51-81)	40	(25-57)	59	(39-78)

n=number of vascular specimens; CI=confidence interval.

Table 2. Incidence of dissection and media rupture in non-calcified and calcified plaque seen on histology and with intravascular ultrasound (IVUS) at the target site (n=40).

	Non-calcified lesion	Calcified lesion	
	Incidence (95% CI)	Incidence (95% CI)	p-values
Histology	(n=9)	(n=31)	
Dissection	56 (21-86)	81 (63-93)	0.27
Media rupture	56 (21-86)	45 (27-64)	0.87
IVUS	(n=10)	(n=30)	
Dissection	50 (19-81)	47 (28-66)	1.00
Media rupture	40 (12-74)	23 (10-42)	0.54

n=number of IVUS cross-sections, CI=confidence interval.

At the target site dissections occurred at the thinnest region of the plaque in all cases on histology, and in 17 of the 19 cases on IVUS (89%) ($p<0.01$)(Fig. 2). In the 2 remaining dissections, IVUS was not capable to determine the thinnest region of the plaque, due to inability to visualize the adventitia. At the target site

dissections occurred at the thinnest region of the plaque in all cases on histology, and in 17 of the 19 cases on IVUS (89%) ($p<0.01$)(Fig. 2). In the 2 remaining dissections, IVUS was not capable to determine the thinnest region of the plaque, due to inability to visualize the adventitia.
The incidence of dissection and media rupture in non-calcified and calcified lesions seen on histology and with IVUS at the target site are summarized in Table 2. On histology, at the target site 5 dissections occurred in non-calcified plaques (56%) and 25 dissections occurred in calcified plaques (81%) ($p=0.27$). At the target site 5 media ruptures occurred in non-calcified plaque (56%) and 14 media ruptures were evidenced in calcified plaque on histology (45%) ($p=0.87$). Similarly, on IVUS no relation was found between plaque calcification and dissection or media rupture ($p=1.00$ and $p=0.54$, respectively).

Table 3. Quantitative effects of balloon angioplasty (PTA) assessed with intravascular ultrasound.

	Before PTA	After PTA	% Change
Lumen area (mm^2)			
all cross-sections (n = 152)	51.6 ± 17.9	56.3 ± 17.3	+9 ★
target site (n = 24)	46.6 ± 17.1	53.2 ± 17.3	+14 ★
Vessel area (mm^2)			
all cross-sections (n = 152)	90.1 ± 24.9	95.4 ± 23.1	+6 ★
target site (n = 24)	83.9 ± 19.1	91.9 ± 19.0	+10 ★
Plaque area (mm^2)			
all cross-sections (n = 152)	38.5 ± 14.5	39.1 ± 14.3	+2
target site (n = 24)	37.3 ± 10.9	38.7 ± 10.9	+4
Percentage area stenosis (%)			
all cross-sections (n = 152)	43.3 ± 11.4	41.3 ± 11.3	-5 ★
target site (n = 24)	45.5 ± 13.3	43.1 ± 13.3	-5 ★

n=number of cross-sections; % change=difference between ultrasound data before and after PTA; +=increase; - =decrease; ★ significant difference is defined as $p < 0.05$. Values are mean ± SD.

Quantitative analysis

In 152 of the 224 (68%) IVUS cross-sections both the lumen area and vessel area could be assessed: these cross-sections were used to determine the quantitative mechanisms related to PTA. Of the remaining 72 (32%) IVUS cross-sections, the vessel area could not be assessed because of significant calcification in 36 cross-sections: 16 of these cross-sections were at the target site. Quantitative data derived from all corresponding IVUS cross-sections (n=152) as well as from data obtained exclusively at the target site (n=24) before and after PTA are summarized in Table 3.

As a result of PTA, the lumen area increase in all IVUS cross-sections was associated with small increase in vessel area ($p<0.05$), whereas plaque area did not change significantly. A larger increase in lumen area and vessel area (both $p<0.05$) was obtained at the target site.

Interobserver analysis

The paired differences between measurements of the 2 observers for lumen area before and after PTA were -0.69 ± 0.70 mm^2 ($p<0.01$), and -0.46 ± 2.2 mm^2 ($p=0.21$), and for vessel area 0.77 ± 3.0 mm^2 ($p=0.20$) and -0.73 ± 2.7 mm^2 ($p=0.17$), respectively. The coefficients of variation for lumen area before and after PTA were 1.4% versus 4.0%, respectively, and for vessel area 3.3% versus 2.8%, respectively.

DISCUSSION

This study demonstrates that IVUS is an accurate technique to establish morphologic and quantitative changes after PTA of the iliac artery. The sensitivity of IVUS to document dissection was good (74%), but was low for media rupture (59%). Similar sensitivities for dissection have been reported by others[11,17,18]. However, in the present study both incidence (28%) and sensitivity of media rupture (59%) seen with IVUS were lower than reported in coronary arteries studied in vitro (43% and 76%, respectively)[11]. We assume that the low incidence may be due to the relative small increase in lumen and vessel area (14% and 10%, respectively) in the iliac arteries compared with the increase in the more severe diseased coronary arteries (+58% and +17%, respectively)[11] (Table 3). The small increase in vessel dimensions may account for the lower incidence of media rupture.

It is noteworthy that in the present study dissections were found exclusively at the thinnest site of the plaque. Lee et al.[19] found that high stress regions generally were located near the junction of plaque with a more normal vessel wall, which corresponds with the thinnest region in our study. Fitzgerald et al.[20] suggested a relation between increasing shear stress within the plaque during balloon inflation and localized calcium deposits. Similarly, Voigtländer et al.[21] reported that, following coronary PTA, calcified lesions were more likely to lead to dissections involving the media. In contrast, in the present study no relation was found between lesion calcification and the occurrence of a dissection or a media rupture seen on IVUS; this finding is in agreement with the study of Baptista et al.[12]. The absence of a relationship between plaque characteristics and dissection on histology concurs with the

findings of van der Lugt et al.[22] However, the p-value of 0.27 seen on histology in the present study suggests that a larger sample size may have demonstrated a significant relationship between calcified lesion and the occurrence of dissection (Table 2).

Furthermore, our study showed that at the target site the incidence of vascular damage was lower than the incidence per vascular specimen. Thus, in order to have better insight in the arterial damage the entire vascular specimen should be analyzed.

Table 4. Quantitative effects of balloon angioplasty on coronary and iliofemoral arteries assessed with intravascular ultrasound.

		Year	LA	VA	PLA
Coronary arteries					
Potkin[2]	(n = 9)	1992	+130	+17	-18
Kovach[3]	(n = 39)	1993	+33	+13	+5
Suneja[4]	(n = 25)	1993	+126	+1	-21
Braden[5]	(n = 30)	1994	+108	+14	-4
van der Lugt[11]	(n = 34)	1995	+58	+17	-9
Baptista[12]	(n = 60)	1996	+164	+8	-12
Iliofemoral arteries					
The[6]	(n = 42)[A]	1992	+89	+30	-1
Losordo [7]	(n = 40)	1992	+120	+6	-33
van Lankeren[13]	(n = 14)[B]	1996	+56	+8	-16
	(n = 14)[C]		+111	+35	-15
van der Lugt[14]	(n = 109)	1997	+161	+22	-13
Present study	(n = 40)	1997	+14	+10	+4

n = number of patients; Year = year of publication; LA = lumen area; VA = vessel area; PLA = plaque area; + = increase; - = decrease;
[A] data from multiple ultrasound cross-sections collected from16 patients, [B] data from common iliac arteries, [C] data from external iliac arteries.

This IVUS study learned that the increase in lumen area following PTA of the common iliac artery was solely due to an increase in vessel area (i.e. vessel stretch) (Table 3). Both the lumen area and vessel area obtained at the target site increased significantly more than the mean values obtained from all cross-sections. In contrast, a slight increase in plaque area was seen probably caused by a better detection of plaque after PTA; these findings correspond with studies in both coronary and peripheral arteries[3,5,6,11,13,14] (Table 4). However, in 2 other studies a different explanation has been proposed for the increase in lumen area after PTA. Suneja et al.[4] and Losordo et al.[7] reported that the main factor for increased lumen area was plaque compression and that the increase in vessel area contributed only to a small extent. In addition, Potkin et al.[2] and Baptista et al.[12] observed that both plaque compression and vessel wall stretch contributed in similar proportions to the lumen area increase. The absence of plaque compression in our study may be due to the fact that the iliac segments had a relatively small area stenosis (45%) compared to the area stenosis (75%) in the study of Losordo et al.[7]; the smaller area stenosis in our study may account for the restriction of plaque compression.

Limitation of the study

Initially, 43 proximal straight common iliac arteries were selected to facilitate comparison with histology; 3 were not used, because they had < 30% area stenosis at the target site. The remaining 40 arteries were moderate diseased and reflects the difficulty to obtain appropriate segments for this type of in vitro study. A small lumen area increase of 9% at the target site is unlikely to have a significant hemodynamic effect in vivo. Consequently, caution is required when the results of this study are applied to severe stenotic lesions encountered clinically. The inability to determine the vessel area in 32% of the IVUS cross-sections available for analysis should be acknowledged: in 50% of these cross-sections a calcified plaque (arc >120°) was involved. In the remaining cross-sections the image quality did not allow assessment of the media-adventitia interface; the use of a lower ultrasound frequency (20 MHz) might be a solution. Neither pulsatile flow nor blood were used in the present study. Finally, data derived from autopsy specimens may represent an anatomic substrate different from that in a clinical series of patients undergoing therapeutic PTA.

Conclusions

This study showed that IVUS is a sensitive technique for detecting dissection, but is less sensitive for media rupture. Dissections occurred at the thinnest region of the plaque and no relation with plaque calcification was found. The segments studied had a relatively small area stenosis and increase in lumen area after PTA was solely caused by vessel stretch. To evaluate vascular damage the entire vessel must be analyzed rather than one single cross-section at the target site.

REFERENCES

1. Isner JM, Rosenfield K, Losordo DW, Kelly S, Palefski P, Langevin RE, Razvi S, Pastore JO, Kosowsky BD. Percutaneous intravascular US as adjunct to catheter-based interventions: preliminary experience in patients with peripheral vascular disease. Radiology 1990;175:61-70.
2. Potkin BN, Keren G, Mintz GS, Douek PC, Pichard AD, Satler LF, Kent KM, Leon MB. Arterial responses to balloon coronary angioplasty: an intravascular ultrasound study. J Am Coll Cardiol 1992;20:942-951.
3. Kovach JA, Mintz GS, Pichard AD, Kent KM, Popma JJ, Satler LF, Leon MB. Sequential intravascular ultrasound characterization of the mechanisms of rotational atherectomy and adjunct balloon angioplasty. J Am Coll Cardiol 1993;22:1024-1032.
4. Suneja R, Nair RN, Reddy KG, Rasheed Q, Sheehan HM, Hodgson J. Mechanisms of angiographically successful directional coronary atherectomy: Evaluation by intracoronary ultrasound and comparison with transluminal coronary angioplasty. Am Heart J 1993;126:507-514.
5. Braden GA, Herrington DM, Downes TR, Kutcher MA, Little WC. Qualitative and quantitative contrasts in the mechanisms of lumen enlargement by coronary balloon angioplasty and directional coronary atherectomy. J Am Coll Cardiol 1994;23:40-48.
6. The SHK, Gussenhoven EJ, Zhong Y, Li W, van Egmond FC, Pieterman H, van Urk H, Gerritsen GP, Borst C, Wilson RA, Bom N. The effect of balloon angioplasty on the femoral artery evaluated with intravascular ultrasound imaging. Circulation 1992;86:483-493.
7. Losordo DW, Rosenfield K, Pieczek A, Baker K, Harding M, Isner JM. How does angioplasty work? Serial analysis of human iliac arteries using intravascular ultrasound. Circulation 1992;86:1845-1858.
8. Gussenhoven EJ, Essed CE, Lancée CT, Mastik F, Frietman P, van Egmond FC, Reiber J, Bosch H, van Urk H, Roelandt J, Bom N. Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study. J Am Coll Cardiol 1989;14:947-952.
9. Kerber S, Fechtrup C, Thomas B, Fahrenkamp, Werner Bröcker, Breithardt G. Validation of intravascular ultrasound in arteriosclerotic peripheral vessels. Int J Cardiol 1994;43:191-198.
10. Nishimura RA, Edwards WD, Warnes CA, Reeder GS, Holmes DR, Tajik AJ, Yock PG. Intravascular ultrasound imaging: in vitro validation and pathologic correlation. J Am Coll Cardiol 1990;16:145-154.
11. van der Lugt A, Gussenhoven EJ, Stijnen T, van Strijen M, van Driel E, van Egmond FC, Suylen RJ, van Urk H. Comparison of intravascular ultrasound findings after coronary balloon angioplasty with histology. Am J Cardiol 1995;76:661-666.
12. Baptista J, Di Mario C, Ozaki Y, Escaned J, Gil R, de Feyter P, Roelandt JRTC, Serruys PW. Impact of plaque morphology and composition on the mechanisms of lumen enlargement using intracoronary ultrasound and quantitative angiography after balloon angioplasty. Am J Cardiol 1996;77:115-121.
13. van Lankeren W, Gussenhoven EJ, van der Lugt A, Vischjager M, Khajehi P, Pieterman H, Gerritsen PG. Intravascular sonographic evaluation of iliac artery angioplasty: What is the mechanism of angioplasty and can intravascular sonography predict clinical outcome? AJR 1996;166:1355-1360.
14. van der Lugt A, Gussenhoven EJ, Mali WPTM, Reekers JA, Seelen JL, Tielbeek AV, Pieterman H. Effect of balloon angioplasty in femoropopliteal arteries assessed by intravascular ultrasound. Eur J Vasc Endovasc Surg 1997;13:549-556.
15. Gussenhoven EJ, van der Lugt A, van Strijen M, Li W, The SHK, van Egmond FC, Honkoop J, Peters RJG, de Feyter P, van Urk H, Pieterman H. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N (eds.). *Intravascular Ultrasound*. Dordrecht: Kluwer Academic Press, 1993:157-166.
16. Wenguang L, Gussenhoven WJ, Zhong Y, The SHK, Di Mario C, Madretsma S, van Egmond F, de Feyter P, Pieterman H, van Urk H, Rijsterborgh H, Bom N. Validation of quantitative analysis of intravascular ultrasound images. Int J Card Imaging 1991;6: 247-253.
17. Siegel RJ, Ariani M, Fishbein MC, Chae JS, Park JC, Maurer GM, Forrester JS. Histopathologic validation of angioscopy and intravascular ultrasound. Circulation 1991;84:109-117.

18. Coy KM, Park JC, Fishbein MC, Laas T, Diamond GA, Adler L, Maurer G, Siegel RJ. In vitro validation of three-dimensional intravascular ultrasound for the evaluation of arterial injury after balloon angioplasty. J Am Coll Cardiol 1992;20:692-700.
19. Lee RT, Loree HM, Cheng GC, Lieberman EH, Jaramillo N, Schoen FJ. Computational structural analysis based on intravascular ultrasound imaging before in vitro angioplasty: prediction of plaque fracture locations. J Am Coll Cardiol 1993;21:777-782.
20. Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty: An observational study using intravascular ultrasound. Circulation 1992;86:64-70.
21. Voigtländer T, Rupprecht J, Scharhag J, Kearney P, Nowak B, Stähr P, Brennecke R, Meyer J. Intravascular ultrasound detected calcification of coronary lesions as a predictor of dissections after balloon angioplasty. Int J Card Imaging 1996;12:179-183.
22. van der Lugt A, Gussenhoven EJ, von Birgelen C, Tai J-A, Pieterman H. Failure of intravascular ultrasound to predict dissection after balloon angioplasty by using plaque characteristics. Am Heart J 1997;134:1075-1081.

4 COMPARISON OF ANGIOGRAPHY AND INTRAVASCULAR ULTRASOUND BEFORE AND AFTER BALLOON ANGIOPLASTY OF THE FEMOROPOPLITEAL ARTERY

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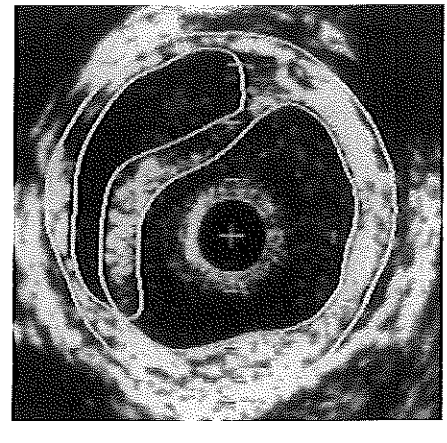

This study was supported by grants from the Netherlands Heart Foundation (900.574.002), the Interuniversity Cardiology Institute of the Netherlands and the Sorbo Heart Foundation.

Cardiovasc Intervent Radiol 1998;21:367-374

ABSTRACT

Purpose: To compare angiographic and intravascular ultrasound (IVUS) data before and after balloon angioplasty (PTA) of the femoropopliteal artery.

Methods: Qualitative and quantitative analyses were performed on corresponding angiographic and IVUS levels obtained from 135 patients.

Results: IVUS detected more lesions, calcified lesion and vascular damage than angiography. Sensitivity of angiography was good for the presence of lesion (84%), moderate for eccentric lesion (53%) and for vascular damage (52%), and poor for calcified lesion (30%). The increase in angiographic diameter stenosis was associated with a decrease in lumen area and increase in percentage area stenosis on IVUS.

Conclusions: Angiography is less sensitive than IVUS to detect lesion eccentricity, calcified lesion and vascular damage. Presence of lesion and amount of plaque were underestimated angiographically. Only before PTA a good agreement was found between angiographic diameter stenosis and lumen size on IVUS.

key words: Angiography; Intravascular ultrasound; Femoropoliteal artery; Balloon angioplasty

INTRODUCTION

Contrast angiography, the 'gold standard' for diagnosis and subsequent treatment of atherosclerotic disorders, displays the vascular anatomy in a longitudinal silhouette. Intravascular ultrasound (IVUS) provides tomographic images which enable determination of plaque morphology and precise measurements on lumen, native vessel and plaque size. Validation studies with histologic sections have shown that IVUS is an accurate technique to document morphologic and quantitative data, both before and after vascular interventions[1-5]. Studies aimed at comparison of data acquired angiographically and on IVUS are numerous in coronary arteries and generally consider one IVUS cross-section obtained at the target lesion for analysis[6-15]. These studies demonstrated that IVUS consistently detects more plaque deposition, more target lesion calcification and significant discrepancies in lesion eccentricity compared to angiography. In the limited number of studies comparing angiography and IVUS in peripheral arteries small numbers of vascular segments were studied before intervention[16-17] and only one study presented pre- and postinterventional data[18].

The purpose of the present study was to assess the agreement between multiple angiographic levels and IVUS cross-sections for morphologic and quantitative parameters obtained before and after balloon angioplasty (PTA) of the femoropopliteal artery.

MATERIAL AND METHODS

Study group

Patients were selected from the EPISODE (Evaluation Peripheral Intravascular Sonography On Dotter Effects) study which investigated the additional value of IVUS compared to angiography for the immediate clinical outcome, and at one and six months after PTA[19]. Selection of patients was based on the availability of angiographic data and IVUS images before and/or after PTA.

The study group comprised 135 patients (87 men and 48 women; mean age 66 years, range 36-93 years) who underwent PTA of the femoropopliteal artery for disabling intermittent claudication (n=92), rest and/or night pain (n=18), or ischemic ulceration (n=25). The investigation was approved by the local committee on Human Research. Patients were included in the study after informed consent.

Angiography and balloon angioplasty

Standard PTA was performed by means of an antegrade percutaneous femoral approach with a 7F sheath. Balloon type, balloon diameter, inflation pressure and inflation time were individually determined by the radiologist in charge and based on angiographic information alone. The intervention was preceded and followed by single-plane angiography and IVUS. Digital subtraction angiography (Philips V3000) was obtained by injection of nonionic contrast (Iopamidol 300). Images were obtained at a rate of 2/sec. A radiopaque ruler located under the leg was used to match angiographic and IVUS data.

Intravascular ultrasound
IVUS studies were performed with mechanical 30 MHz imaging systems with 4.3F catheter. The catheter of the CVIS 'Insight' system (Sunnyvale, CA) houses an ultrasound transducer and a rotating mirror, while the 'Princeps' catheter of the Du-MED system (Rijswijk, The Netherlands) contains a rotating ultrasound transducer. Details of these systems have been described previously [20]. Before and after intervention, the ultrasound catheter was advanced distally over a guidewire beyond the lesion. Care was taken to adjust the settings for time-gain compensation to yield optimal image quality. Images of the diseased segment were obtained at 1 cm interval during pull-back of the catheter; for each image the catheter was kept in position for sufficient time to allow recording. Using fluoroscopic control, the location of the ultrasound cathetertip was systematically compared with the radiopaque ruler and the resulting images were displayed on the video monitor and stored on an S-VHS videotape. The IVUS images were analyzed and subsequently matched with the corresponding angiographic levels. Excluded from analysis are 1) cross-sections obtained in the occluded segment, if the IVUS catheter could be wedged through the occlusion; 2) cross-sections of insufficient image quality to determine lumen or vessel area. Cross-sections showing a calcified lesion of >120° were excluded for quantitative analysis.

Qualitative analysis
Before PTA, the angiographic levels and the corresponding IVUS cross-sections were analyzed for the presence of a lesion and, subsequently, whether the lesion was eccentric or concentric, and/or calcified. After PTA, the presence of vascular damage was assessed.

Angiographic definitions
A *lesion* was present when irregularities of the vessel wall were seen (defined as 1-20% diameter stenosis), or the lumen diameter was smaller than the lumen diameter of an adjacent angiographic normal reference segment (defined as diameter stenosis >20%) (Fig. 1). In the presence of a lesion with >20% diameter stenosis, an *eccentric lesion* was identified as a lesion in which one edge protrudes in the apparently normal lumen;

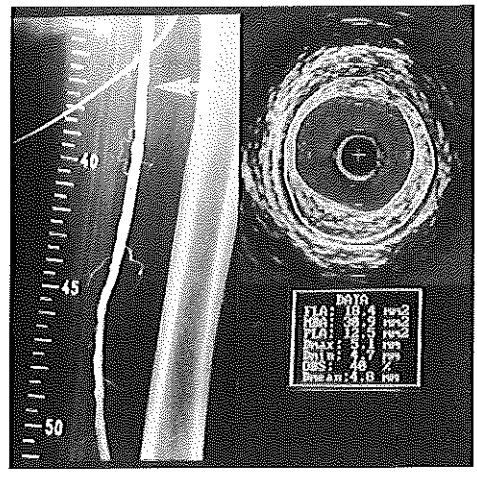

Fig.1. Angiogram and corresponding intravascular ultrasound (IVUS) cross-section of the femoropopliteal artery obtained before balloon angioplasty. At level 37 (*arrow*) the angiogram is classified as normal; the matched IVUS cross-section shows an eccentric lesion. Contour analysis of the lumen area (*inner contour*) and vessel area (*outer contour*) displays the plaque area of 12.5 mm² and percentage area stenosis of 40%. += catheter; calibration = 1 mm.

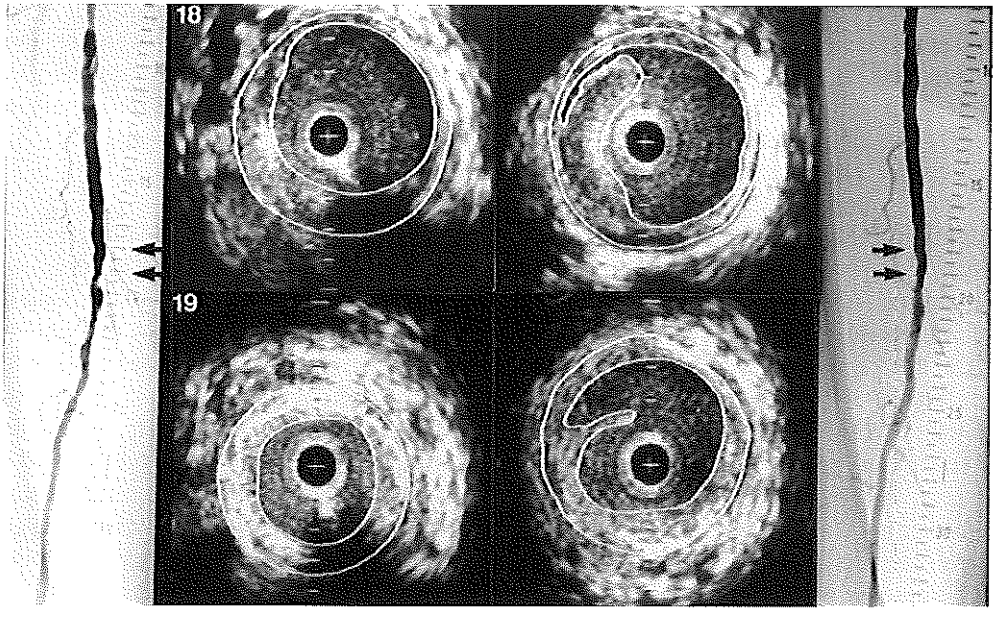

Fig. 2. Angiogram and corresponding intra-vascular ultrasound (IVUS) cross-sections of the femoropopliteal artery before and after balloon angioplasty (PTA). Before PTA (*left panels*): At level 18 the lesion is classified as a wall irregularity; the corresponding IVUS cross-section shows an eccentric lesion. At level 19, both angiography and IVUS classifies the lesion as concentric. After PTA (*right panels*): At level 18 no effect of the PTA is evident whereas at level 19 an intimal crack is seen angiographically; on both levels IVUS shows a dissection of 60°.+= catheter; calibration = 1 mm.

a *concentric lesion* protrudes on both sides of the lumen (Fig. 2). A *calcified lesion* was identified as having readily apparent radiopacity within the vascular wall before contrast injection.
Vascular damage was defined as the presence of a dissection (i.e. an intraluminal filling defect) or intimal crack (i.e. an extraluminal extravasation of contrast material) (Fig. 2,3).

Intravascular ultrasound definitions[21]
A *lesion* was defined as thickening of the intimal layer (≥ 0.5 mm) superimposed on the hypoechoic media (Fig. 1). An *eccentric lesion* was defined as a lesion which leaves part of the vessel disease-free; a *concentric lesion* was defined as a lesion distributed along the entire circumference of the vessel wall (Figs. 1,2). A *calcified lesion* was recognized by the presence of a bright echo structure casting peripheral shadowing (Fig. 3).
Vascular damage was defined as the presence of a dissection (i.e. a tear in the intimal surface separating the lesion from the underlying arterial wall) or media rupture (i.e. an interruption in the internal elastic lamina and media that exposed the hyperechoic adventitia to the lumen) (Figs. 3,4).

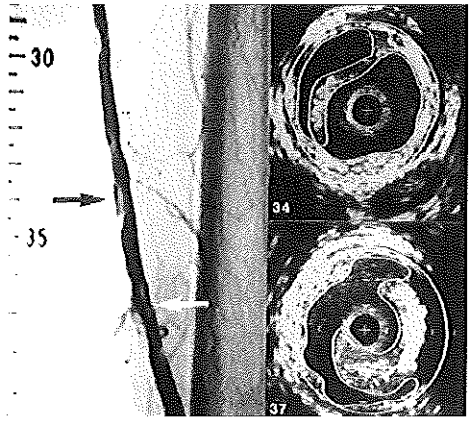

Fig. 3. Angiogram and corresponding intravascular ultrasound (IVUS) cross-sections of the femoropopliteal artery after balloon angioplasty. At level 34 (*black arrow*), the angiogram shows an intimal crack; the matched IVUS cross-section shows a dissection of 150°. At level 37 (*white arrow*), the angiogram evidences a dissection; the matched IVUS cross-section shows a dissection of 210° combined with a media rupture (7 o'clock). Note the calcified lesion at level 37 casting peripheral shadowing from 1 to 4 o'clock. += catheter; calibration = 1 mm.

Quantitative analysis

Angiographically, the degree of diameter stenosis was assessed by visual estimation using an alleged normal proximal segment as reference. Subsequently, diameter stenosis was grouped into 5 classes: (1) normal; (2) 1-20% stenosis; (3) 21-50% stenosis; (4) 51-90% stenosis; and (5) >90% stenosis.

On IVUS, the extent of normal wall, calcified lesion and vascular damage (dissection) was graded as an arc of the circumference with the centre of the vessel as reference point (in steps of 30°; range 0-360°)[22].

Measurement of lumen and vessel area (mm^2) was performed using a digital video analyzer system (IBM Corp. Boca Raton, USA)[23]. The lumen area was defined as the area encompassed by the inner boundary of the intimal surface (characterized also by the presence of blood). The vessel area was defined as the area bounded by the hypoechoic medial layer. The plaque area was calculated by subtracting the lumen area from the vessel area. The percentage area stenosis was calculated as the plaque area divided by the vessel area[21]. When the tunica media was not visible on IVUS, the adventitia was used as a point of reference.

Analysis of data

Angiographic analysis was performed by the radiologist in charge blinded to the IVUS results. Analysis of the IVUS images was performed by 2 observers. The reproducibility of IVUS parameters used in this study has been reported previously[22]. Differences between the observers were solved by consensus.

The incidence of morphologic features seen angiographically and on IVUS was assessed in all matched levels. Using IVUS data as the standard, the sensitivity, specificity, and positive and negative predictive value of angiography were calculated (1) for the presence of a lesion; (2) for lesion eccentricity and calcification in those corresponding levels showing both an angiographic diameter stenosis >20% and a lesion on IVUS and (3) for vascular damage.

The relation between the extent of normal wall, calcification and vascular damage seen on IVUS and the angiographic visualization of these features was assessed. The degree of diameter stenosis seen angiographically was compared with lumen area, plaque area, vessel area and percentage area stenosis seen on IVUS.

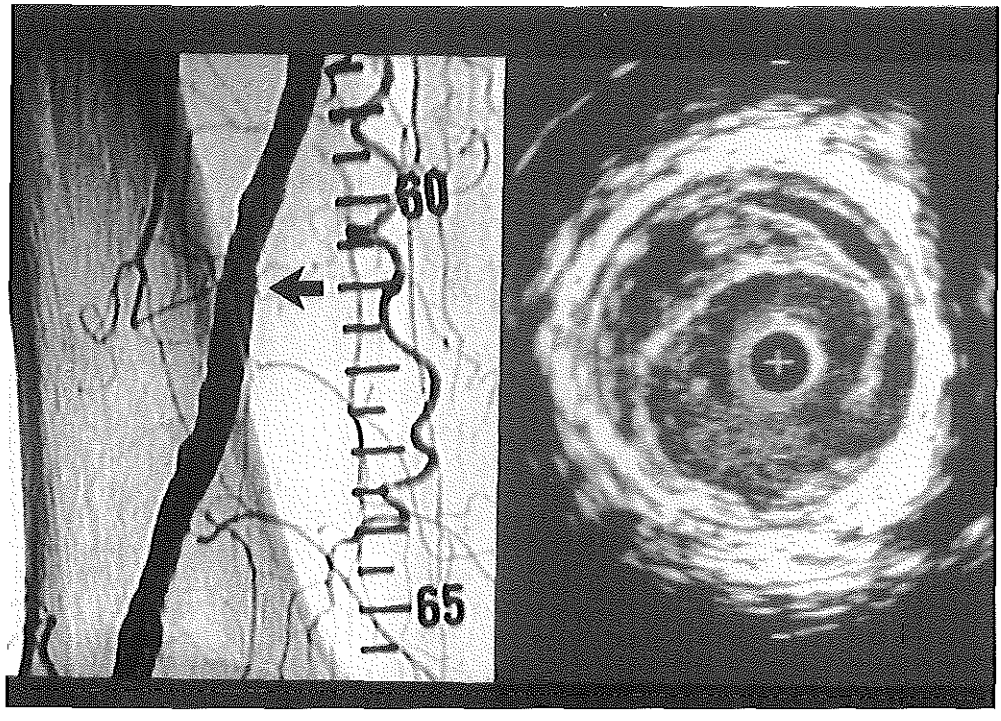

Fig. 4. Angiogram and corresponding intravascular ultrasound (IVUS) cross-section of the femoropopliteal artery after balloon angioplasty. Whereas no vascular damage is evidenced angiographically, IVUS detects a dissection of 120° at level 61. The white lines seen between level 60.5 and level 62.0 are caused by a smaller artery projected over the femoropopliteal artery. + = catheter; calibration = 1 mm.

Statistical analysis

For comparison of continuous variables between 2 groups, the nonparametric Mann-Whitney test was used. Linear trend between the 5 angiographic classes for diameter stenosis and the quantitative IVUS data were tested using one-way analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

RESULTS

Complications as result of the IVUS procedure were not encountered. In 14 patients the IVUS catheter could not be advanced before intervention due to an occluded lesion of the femoropopliteal artery. Therefore, IVUS images obtained in 121 patients before PTA and in 135 patients after PTA were matched with the angiographic levels. Angiographically the intervention was classified as initial failure (>50% diameter stenosis) in 15 patients; thrombosis of the dilated segment was seen in 5 of these patients.

The median length of the dilated segment was 8 cm (range 4-32 cm). The median number of matched levels per patient studied before PTA was 7 (range 4-26), and after PTA 9 (range 4-28). Qualitative comparison between angiography and corresponding IVUS cross-section was

Table 1. Intravascular ultrasound (IVUS) cross-sections available for analysis before and after balloon angioplasty (PTA).

IVUS cross-sections	Before PTA (n)	After PTA (n)
Available for analysis	1095	1370
Excluded due to occluded cross-sections	133	---
Excluded due to low image quality	69	117
Selected for *qualitative* analysis	893	1253
Excluded due to no assessment of vessel area	123	188
Selected for *quantitative* analysis	770	1065

n = number of cross-sections.

possible in 893 images before and in 1253 images after PTA. For quantitative comparison 770 matched images before and 1065 images after PTA were available (Table 1).

Qualitative analysis

Data on the relation between the angiographic and IVUS qualitative features are given in Table 2.

Before PTA

Absence or presence of a lesion was scored in 893 corresponding levels before intervention. Compared to angiography IVUS detected more lesions (83% versus 97%). In most levels angiography agreed with IVUS on the detection of a lesion (sensitivity of angiography 727/869-84%). In 155 angiographic levels lesion was absent and IVUS confirmed this finding in only 13 cases: this finding is reflected in the low negative predictive value of angiography (8%).

In total 493 corresponding levels presented both an angiographic diameter stenosis >20% and a lesion on IVUS; in these cross-sections both lesion eccentricity and calcified lesion evidenced with the two imaging techniques were compared. Angiography evidenced an eccentric lesion in 266 levels and IVUS in 245 levels which resulted in a similar incidence of eccentric lesion for angiography and IVUS (54% and 50%, respectively). Of the 245 IVUS cross-sections showing an eccentric lesion, 130 were confirmed angiographically, indicating a moderate sensitivity of angiography (53%).

Table 2. Relation between angiographic and intravascular ultrasound (IVUS) qualitative data before and after balloon angioplasty (PTA).

	Before PTA						After PTA	
	Presence of lesion (n=893)		Eccentric lesion (n=493)		Calcified lesion (n=493)		Vascular damage (n=1253)	
		CI (%)		CI (%)		CI (%)		CI (%)
Incidence								
Angiography	83%	(80-85)	54%	(42-50)	12%	(0-15)	35%	(32-38)
IVUS	97%	(96-98)	50%	(45-50)	34%	(30-38)	53%	(50-56)
Sensitivity	84%	(81-86)	53%	(47-59)	30%	(23-37)	52%	(49-56)
Specificity	54%	(33-76)	47%	(41-43)	98%	(96-99)	84%	(81-87)
Positive predictive value	99%	(98-99)	49%	(43-55)	86%	(77-95)	79%	(75-83)
Negative predictive value	8%	(4-13)	49%	(43-55)	73%	(68-77)	61%	(58-65)

n = number of cross-sections; CI = Confidence interval. Sensitivity, specificity, positive and negative predictive value of angiography is calculated using IVUS as 'gold standard'.

Similarly, of the 266 levels showing an eccentric lesion on the angiogram, IVUS evidenced a concentric lesion in 136 of these cross-sections. No relationship was found between angiography and IVUS for the assessment of eccentric or concentric lesion. No difference was found in the arc of normal wall seen on IVUS for the angiographic defined eccentric and concentric lesions (91 ± 56° and 99 ± 60°, respectively).

Compared to angiography, IVUS detected more calcified lesions: 12% versus 34%. As a consequence, the sensitivity of angiography was low (30%): in only 50 levels angiography confirmed the presence of the calcified lesion evidenced in 169 IVUS cross-sections. A significant relation was found between the detection of calcified lesion by angiography and the extent of calcified lesion seen on IVUS. In the absence of calcified lesion on angiography, IVUS revealed a mean arc of calcification of 92 ± 69°; in the presence of angiographic calcification the mean arc of calcification seen on IVUS was 148 ± 92° ($p<0.001$).

After PTA

Vascular damage was scored in 1253 corresponding levels after intervention. The incidence of vascular damage evidenced on IVUS (53%) was higher than

Table 3. Relation between angiographic diameter stenosis and quantitative data obtained with intravascular ultrasound (IVUS) before and after balloon angioplasty (PTA).

IVUS	Angiography				
	Normal	1- 20% stenosis	21- 50% stenosis	51-90% stenosis	>90% stenosis
Before PTA (n=770)					
LA (mm^2)	17.3 ± 6.7	14.0 ± 8.0	12.0 ± 5.9	9.5 ± 5.1	6.2 ± 4.1
PLA (mm^2)	13.4 ± 6.1	13.9 ± 5.8	14.7 ± 6.0	17.1 ± 7.0	18.4 ± 8.6
VA (mm^2)	30.7 ± 9.5	27.9 ± 12.0	26.6 ± 8.6	26.6 ± 8.8	24.6 ± 9.0
%S	43.4 ± 14.7	51.3 ± 14.0	55.5 ± 15.0	64.3 ± 14.0	73.1 ± 17.0
	(n=147)	(n=198)	(n=217)	(n=154)	(n=54)
After PTA (n=1065)					
LA (mm^2)	19.2 ± 6.3	16.4 ± 6.1	16.1 ± 6.4	15.7 ± 7.1	
PLA (mm^2)	13.5 ± 5.6	14.5 ± 5.6	16.0 ± 7.7	19.9 ± 10.0	
VA (mm^2)	32.7 ± 8.8	30.8 ± 8.2	32.1 ± 11.0	35.6 ± 14.0	
%S	41.1 ± 12.4	46.8 ± 13.0	48.9 ± 13.0	54.7 ± 13.0	
	(n=319)	(n=182)	(n=500)	(n=64)	

n = number of cross-sections; values are mean ± SD; LA=lumen area; PLA=plaque area; VA=vessel area; % S=percentage area senosis.

angiographically (35%) (Fig 4). Angiography confirmed vascular damage in 346 of the 661 IVUS cross-sections showing vascular damage (sensitivity of angiography 52%). A significant relation was found between the detection of vascular damage by angiography and the extent of the dissection seen on IVUS. In the absence of vascular damage on the angiogram the mean arc of dissection seen on IVUS was 58° ± 56°; if the angiogram showed vascular damage, the mean arc of dissection seen on IVUS measured 91° ± 72° ($p<0.001$).

Quantitative analysis

Data on angiographic diameter stenosis and lumen area, plaque area, vessel area and percentage area stenosis determined on IVUS before and after PTA are summarized in Table 3.

Compared to angiography, IVUS revealed more plaque (Fig.1). In the angiographic segments classified as

normal and as 1-20% diameter stenosis IVUS revealed a percentage area stenosis of 43.4±14.7% and 51.3±14.2%, respectively.
Comparing the angio-graphic groups before PTA, both an increase in plaque area and a decrease in vessel area resulted in a smaller lumen area seen on IVUS (linear variation both $p<0.001$) (Table 3).
With increasing angiographic diameter stenosis the lumen area seen on IVUS decreased significantly at a constant rate after PTA (linear variation $p<0.001$) (Fig. 5). The non-linear variation between the different classes of angiographic diameter stenosis was significant for lumen area after PTA ($p= 0.02$). This indicates that the linear trend was influenced by the variation within the angiographic classes. Similarly, with increasing angiographic diameter stenosis the percentage area stenosis on IVUS increased significantly at a constant rate before and after PTA (linear variation both $p<0.001$)(Fig. 5). The agreement between increasing angiographic diameter stenosis and the decrease in lumen area and the increase in percentage area stenosis on IVUS was good before PTA and poor after PTA (Fig. 5, Table 3).

DISCUSSION

Angiography displays a silhouette of the vessel lumen whereas IVUS presents tomographic imaging of the vessel wall. As a consequence, difference in interpretation of morphologic and quantitative features obtained with these techniques can be expected. Validation studies with histologic sections have shown the accuracy of IVUS on morphologic and quantitative data[1-5]. We therefore decided to use IVUS as 'gold standard' in the present study.
It was found that IVUS detected more lesions than angiography. It is noteworthy that IVUS demonstrated plaque that may not be detected on angiography (Fig. 1). In angiographic levels classified as normal, IVUS demonstrated an area stenosis of 43% before and 41% after intervention. This indicates that reference segments may not be as 'normal' as alleged and concurs with data from coronary arteries[24, 25]. It is reported that vessel area enlargement seen on IVUS may compensate for the effect of plaque accumulation and this may be one of the reasons why the lumen may appear 'normal' on the angiogram[8,9]. It is acknowledged that, single-plane angiography may overestimate the lumen area in arteries with an elliptical lumen and in arteries with a dissection, when contrast is filling the dissection plane beyond the lesion. Finally, it should be taken into account that the degree of stenosis on IVUS appear more severe than the degree on angiography, because mathematically a 50% diameter stenosis is equivalent to a 75% area stenosis. Conversion of angiographic diameter stenosis to an area stenosis, however, is only valid in a perfect circular model[17].
Given the differences in study design between this study and the study described

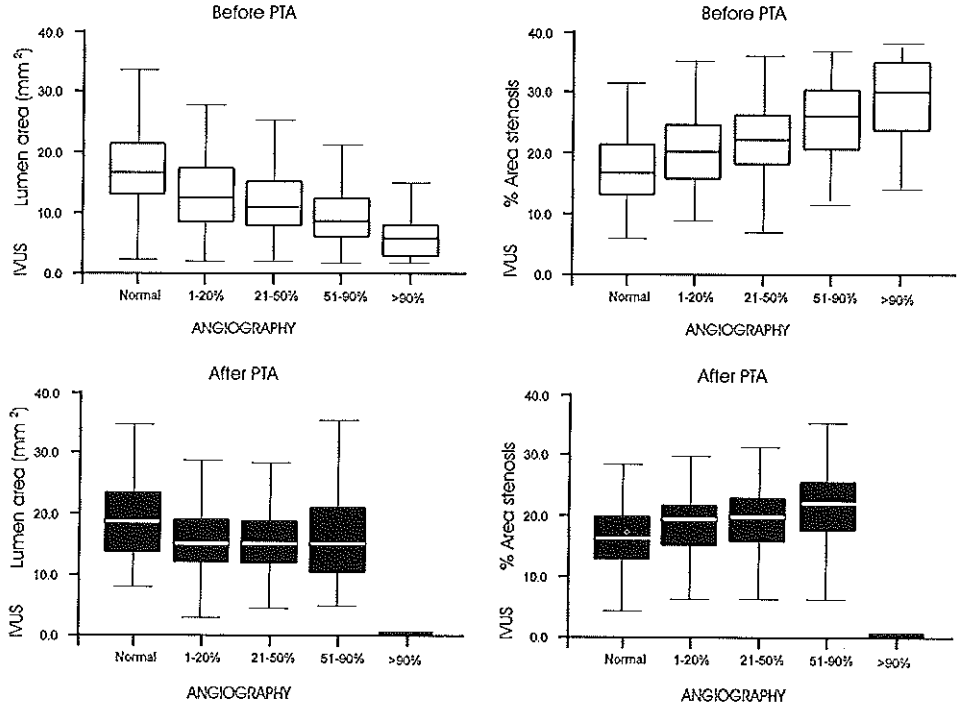

Fig. 5. Comparison of lumen area and percentage area stenosis on intravascular ultrasound (IVUS) and angiographic diameter stenosis before and after balloon angioplasty (PTA) of the femoropopliteal artery. This figure depicts data in box plot. *Upper and lower edges* of box represent the 75th and 25th percentiles, respectively; the *middle line* represents the median. *Upper and lower whiskers* represent the highest and lowest values, respectively.

by Gerritsen et al.[18], it is difficult to compare both the qualitative and quantitative results. Gerritsen et al.[18] presented the concordant observations derived from angiography and IVUS for the absence and the presence of the lesion. Comparison with the present study is not preferable because these concordant observations give a skewed impression of the correlation between the two imaging techniques, as it does not discriminate between the absence or presence of the qualitative parameters involved. Furthermore, Gerritsen et al. [18] reported similar incidences of eccentric lesion with both imaging techniques suggesting a good agreement between angiography and IVUS. This is speculative because similar incidences of eccentric lesion do not necessarily imply that the eccentric lesion seen on the angiogram correspond to the same eccentric lesion evidenced by IVUS.

The finding in the present study that only about 50% of the eccentric lesions defined on IVUS was confirmed angiographically may be explained by the difference in angiographic and IVUS definitions of an eccentric lesion. The anatomic definition was used to define

an eccentric lesion on IVUS (i.e., a lesion which leaves part of the vessel disease-free[21]). Using an eccentricity index (the ratio of maximum to minimum plaque thickness) Mintz et al.[13] found a small concordance rate of 45% for eccentricity between angiography and IVUS.

In the present study, the incidence of calcified lesion on angiography and on IVUS (12% and 34%, respectively) was lower than reported by others. In coronary lesions Mintz et al.[12] and Tuzcu et al.[15] reported higher incidences both on angiography and on IVUS (38% versus 34%, and 73% versus 75%, respectively). The analysis of multiple levels in the present study, instead of one level exclusively at the target site, may account for this discrepancy. Target lesions are more diseased and consequently more calcified than other levels[12].

In the present study angiography had a poor sensitivity for the detection of calcified lesions. This observation and the finding that detection of a calcified lesion by angiography depends on the extent of the calcification seen on IVUS is in agreement with others[12,15].

The same phenomenon was experienced with the detection of vascular damage; in the presence of vascular damage on the angiogram, IVUS showed a significant larger arc of dissection. We postulate that the use of multi-plane angiograms may reveal a higher incidence of vascular damage than seen on the single-plane angiograms used in this study.

Finally, the observation that Gerritsen et al.[18] reported a higher sensitivity (81%) for dissections than encountered in the present study (52%) can be explained by the fact they selected IVUS cross-sections based on the absence or presence of a distinct dissection.

In view of these findings, we believe that the usefulness of assessment of lesion eccentricity, calcified lesion and vascular damage with angiography is limited.

It is noteworthy that quantitative IVUS analysis revealed that the decrease in lumen area was the result of decrease in vessel area, and in a lesser extent to increase in plaque area. This observation subscribes to IVUS studies reporting that vessel wall shrinkage or failure to vessel area enlargement in combination with plaque area increase contribute to lumen narrowing in femoral arteries[26]. Although the mode of arterial remodeling affects the mode of dilatation the therapeutical consequences of this finding is merely speculative.

In the present study before PTA there was good agreement between the increase in angiographic diameter stenosis and the decrease in lumen area and increase in percentage area stenosis seen on IVUS; such a distinct agreement was not seen after PTA. This finding may be related to the vascular damage after PTA which allows contrast filling of dissection clefts, distorting the luminal silhouette of the angiogram. Similarly, others reported poor correlation between angiographic and IVUS quantitative data after PTA, due to significantly altered plaque morphology[1,14].

Clinical implications

According to the current literature , the ultimate benefit of IVUS in comparison to angiography is its ability to measure accurately the lumen area and percentage area stenosis during treatment of vascular disease. In a

previous study we established that despite an angiographic successful PTA of femoropopliteal arteries lumen area size and percentage area stenosis seen on IVUS were found to be related to restenosis[27]. Nowadays, we use the IVUS data, obtained before intervention to guide the length of vessel segment to be subjected to PTA and the data obtained after PTA (lumen size and percentage area stenosis) to decide whether a repeat PTA, a larger balloon or a stent should be used. It is worth mentioning, that despite the use of IVUS, the final result on IVUS after additional intervention may still not be satisfactory.

Limitations

Angiographic levels and IVUS cross-sections were matched based on data available during the procedure, using a radiopaque ruler and anatomic markers such as calcification and side-branches. It should be noted that the data may not be matched with 100% accuracy; data on multiple IVUS cross-sections tend to mask this potential mismatch. Mpreover, lumen area and vessel area could only be calculated in 71% of the corresponding IVUS cross-sections before PTA and in 78% after intervention.

Conclusions

Presence of a lesion, calcified lesion and vascular damage were more frequently detected on IVUS than on angiography. Compared to IVUS, angiography is a less sensitive technique to detect lesion eccentricity, calcified lesions and vascular damage. Both the presence of a lesion and the amount of plaque were underestimated angiographically. There was only before PTA a good agreement between angiographic diameter stenosis and lumen size on IVUS.

Acknowledgments

Participants in this multicenter study: University Hospital Rotterdam-Dijkzigt; University Hospital Utrecht; Academic Medical Center (Amsterdam); Free University Hospital (Amsterdam); Catharina Hospital (Eindhoven); Twee Steden Ziekenhuis (Tilburg); Groot Ziekenhuis Gasthuis (Den Bosch): Slingeland Hospital (Doetichem), the Netherlands.

REFERENCES

1. Gussenhoven WJ, Essed CE, Frietman P, Mastik F, Lancée C, Slager C, Serruys P, Gerritsen P, Pieterman H, Bom N. Intravascular echographic assessment of vessel wall characteristics: a correlation with histology. Int J Card Imaging 1989;4:105-116.
2. Gussenhoven EJ, Essed CE, Lancée CT, Mastik F, Frietman P, van Egmond FC, Reiber J, Bosch H, van Urk H, Roelandt J, Bom N. Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study. J Am Coll Cardiol 1989;14:947-952.
3. Potkin BN, Bartorelli AL, Gessert JM, Neville RF, Almagor Y, Roberts WC, Leon MB. Coronary artery imaging with intravascular high-frequency ultrasound. Circulation 1990;81:1575-1585.
4. Tobis JM, Mallery JA, Gessert J, Griffith J, Mahon D, Bessen M, Moriuchi M, McLeay L, McRae M, Henry WL. Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. Circulation 1989;80:873-882.
5. van der Lugt A, Gussenhoven EJ, Stijnen T, van Strijen M, van Driel E, van Egmond FC, Suylen RJ, van Urk H. Comparison of intravascular ultrasound findings after coronary balloon angioplasty evaluated in vitro with histology. Am J Cardiol 1995;76:661-666.
6. Davidson CJ, Sheikh KH, Kisslo KB, Phillips HR, Peter RH, Behar VS, Kong Y, Krucoff M, Ohman EM, Tcheng JE, Stack RS. Intracoronary ultrasound evaluation of interventional technologies. Am J Cardiol 1991;68:1305-1309.
7. Potkin BN, Keren G, Mintz GS, Douek PC, Pichard AD, Satler LF, Kent KM, Leon MB. Arterial responses to balloon coronary angioplasty: an intravascular ultrasound study. J Am Coll Cardiol 1992;20:942-951.
8. Honye J, Mahon DJ, Jain A, White CJ, Ramee SR, Wallis JB, Al-Zarka A, Tobis JM. Morphological effects of coronary balloon angioplasty in vivo assessed by intravascular ultrasound imaging. Circulation 1992;85:1012-1025.
9. Hermiller JB, Buller CE, Tenaglia AN, Kisslo KB, Phillips HR, Bashore TM, Stack RS, Davidson CJ. Unrecognized left main coronary artery disease in patients undergoing interventional procedures. Am J Cardiol 1993;71:173-176.
10. De Scheerder I, De Man F, Herregods MC, Wilczek K, Barrios L, Raymenants E, Desmet W, De Geest H, Piessens J. Intravascular ultrasound versus angiography for measurements of luminal diameters in normal and diseased coronary arteries. Am Heart J 1994;127(2):243-251.
11. Nakamura S, Mahon DJ, Maheswaran B, Gutfinger DE, Colombo A, Tobis JM. An explanation for discrepancy between angiographic and intravascular ultrasound measurements after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1995;25(3):633-639.
12. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, Ditrano CJ, Leon MB. Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation 1995;91:1959-1965.
13. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, DeFalco RA, Leon MB. Limitations of angiography in the assessment of plaque distribution in coronary artery disease. A systematic study of target lesion eccentricity in 1446 lesions. Circulation 1996;93:924-931.
14. Baptista J, Di Mario C, Ozaki Y, Escaned J, Gil R, De Feyter P, Roelandt JRTC, Serruys PW. Impact of plaque morphology and composition on the mechanisms of lumen enlargement using intracoronary ultrasound and quantitative angiography after balloon angioplasty. Am J Cardiol 1996;77:115-121.
15. Tuzcu EM, Berkalp B, De Franco AC, Ellis SG, Goormastic M, Whitlow PL, Franco I, Raymond RE, Nissen SE. The dilemma of diagnosing coronary calcification: Angiography versus intravascular ultrasound. J Am Coll Cardiol 1996;27:832-838.
16. Sheikh KH, Davidson CJ, Kisslo KB, Harrison JK, Himmelstein SI, Kisslo J, Bashore TM. Comparison of intravascular ultrasound, external ultrasound and digital angiography for evaluation of peripheral artery dimensions and morphology. Am J Cardiol 1991;67:817-822.
17. Tabbara M, White R, Cavaye D, Kopchok G. In vivo human comparison of intravascular ultrasonography and angiography. J Vasc Surg 1991;14:496-504.

18. Gerritsen GP, Gussenhoven EJ, The SHK, Pieterman H, van der Lugt A, Li W, Bom N, van Dijk LC, Du Bois NAJJ, van Urk H. Intravascular ultrasonography before and after intervention: in vivo comparison with angiography. J Vasc Surg 1993;80:31-40.
19. Gussenhoven EJ, van der Lugt A, Pasterkamp G, van der Berg F, Sie LWH, Vischjager M, Li W, The SHK, Pieterman H, van Urk H. Intravascular ultrasound predictors of outcome after peripheral balloon angioplasty. Eur J Vasc Surg 1995;10:279-288.
20. Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88.
21. The SHK, Gussenhoven EJ, Zhong Y, Li W, van Egmond F, Pieterman H, van Urk H, Gerritsen GP, Borst C, Wilson RA, Bom N. The effect of balloon angioplasty on the femoral artery evaluated with intravascular ultrasound imaging. Circulation 1992;86:483-493.
22. van der Lugt A, Gussenhoven EJ, Pasterkamp G, Bom N, Posthuma DJ, Stijnen T. Interobserver reproducibility of qualitative and quantitative analysis of intravascular ultrasound images before and after peripheral balloon angioplasty. Ultrasound Med Biol 1996;22:399-404.
23. Wenguang L, Gussenhoven WJ, Bosch JG, Mastik F, Reiber JHC, Bom N. A computer-aided analysis system for the quantitative assessment of intravascular ultrasound images. Proc Comput Cardiol 1990;333-336.
24. St.Goar FG, Pinto FJ, Alderman EL, Valantine HA, Schroeder JS, Gao S-Z, Stinson EB, Popp RL. Intracoronary ultrasound in cardiac transplant recipients: In vivo evidence of "angiographically silent" intimal thickening. Circulation 1992;85:979-987.
25. Ge J, Liu F, Görge G, Haude M, Baumgart D, Erbel R. Angiographically 'silent' plaque in the left main coronary artery detected by intravascular ultrasound. Coronary Artery Disease 1995;6:805-810.
26. Pasterkamp G, Wensing PJW, Post MJ, Hillen B, Mali WPTM, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. Circulation 1995;91:1444-1449.
27. Gussenhoven EJ, van der Lugt A, Pasterkamp G, van den Berg FG, Sie LWH, Vischjager M, The SHK, Li W, Pieterman H, van Urk H. Intravascular ultrasound predictors of outcome after peripheral balloon angioplasty. Eur J Vasc Endovasc Surg 1995;10:279-288.

5 INTRAVASCULAR SONOGRAPHIC EVALUATION OF ILIAC ARTERY ANGIOPLASTY:

What is the mechanism of angioplasty and can intravascular sonography predict clinical outcome?

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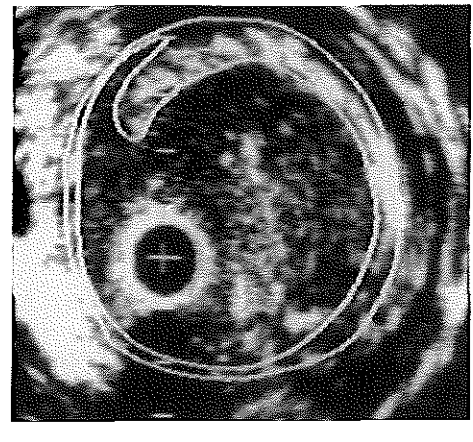

This study was supported by grants from the Netherlands Heart Foundation (900.574.002) and the Interuniversity Cardiology Institute of The Netherlands.

Am J Roentgenol 1996;166:1355-1360

ABSTRACT

Objective. The purpose of this study was to establish the arterial responses of the iliac artery after percutaneous transluminal angioplasty (PTA), using intravascular sonography, and to correlate intravascular sonography parameters with clinical outcome.

Subjects and methods. The study included 21 patients studied with intravascular sonography before and after percutaneous transluminal angioplasty of the iliac artery. Distinction was made between intravascular sonography cross sections collected from the common iliac and those from the external iliac artery. First, qualitative and quantitative intravascular sonography data obtained at the most stenotic site were compared with data derived from all corresponding cross sections of the dilated segment. Second, the predictive value of intravascular sonography parameters for the patient outcome was assessed.

Results. The free lumen and media-bounded areas seen in the common iliac artery were larger than those seen in the external iliac artery. Qualitative and quantitative effects of PTA observed with intravascular sonography on the two types of artery were not different. Vascular damage occurred in 81% of the patients. The frequency of vascular damage at the most stenotic site was slightly lower than in each dilated segment studied. The reduction in area stenosis after intervention was associated with an increase in the free lumen and media-bounded areas, whereas the plaque area reduced only slightly. The increase in the free lumen, and media-bounded areas, and decrease in the plaque area at the most stenotic site after intervention were larger than the mean values. Qualitative data seen with intravascular sonography at the most stenotic site before and after intervention were not predictive of the patient outcome. In patients with an uneventful outcome after intervention, the free lumen area measured at the most stenotic site after PTA was larger and the area stenosis was smaller than in patients with a failure.

Conclusion. This study of intravascular sonography established that although the common iliac artery is larger than the external iliac artery, the qualitative and quantitative effects of PTA in both types of arteries were similar. The size of the free lumen area and the degree of stenosis seen with intravascular sonography after percutaneous transluminal angioplasty at the most stenotic site may be predictive of a patient outcome.

INTRODUCTION

The exact mechanism by which percutaneous transluminal angioplasty (PTA) leads to successful luminal enlargement has not been definitively established. Initially, it was postulated that enlargement of the vascular lumen is due to compression and redistribution of the atheromatous plaque to the subadjacent area[1]. Overstretching of the vessel wall [2,3], splitting of the intima, rupture of the plaque [4,5], and embolization of the lesion have also been described as the ultimate result of the intervention[3,5]. Consensus on the precise contribution of each mechanism has not yet been reached.

Since the introduction of clinical Intravascular sonography, investigators have recognized the ability of this technique to provide more insight into the ultimate effect of PTA than that provided by angiography[6-8]. With intravascular sonography, morphologic features of the vascular anatomy can be obtained. A muscular artery (iliofemoral) is recognized because of the hypoechoic media, with clear definition of the internal and external elastic lamina showing bright echoes. The hypoechoic media facilitates quantitative assessment of the superimposed atherosclerotic lesion (Fig. 1).

To our knowledge, no systematic study of intravascular sonography has established the qualitative and quantitative effects encountered after PTA of the iliac artery as well as the relation between the derived parameters of intravascular sonography and the patient outcome after intervention.

The purpose of this study was to document the qualitative and quantitative effects of PTA seen with intravascular sonography in the iliac artery; investigate whether one single cross section, rather than a sequence of cross sections, obtained at the most stenotic site (i.e., the smallest free lumen area before PTA) is representative of the effect of PTA; compare the data obtained in the common iliac and external iliac artery; and assess the relation between the data from intravascular sonography and the patient outcome.

SUBJECTS AND METHODS

Study group

The study group comprised 21 patients who underwent PTA for treatment of symptomatic occlusive disease of the iliofemoral artery. Sixteen were men and five were women, and they ranged from 33 to 77 years old (mean, 61 years). Patients were referred for intermittent claudication (n=13), rest pain or night pain (n=4), and ischemic ulceration (n=4).

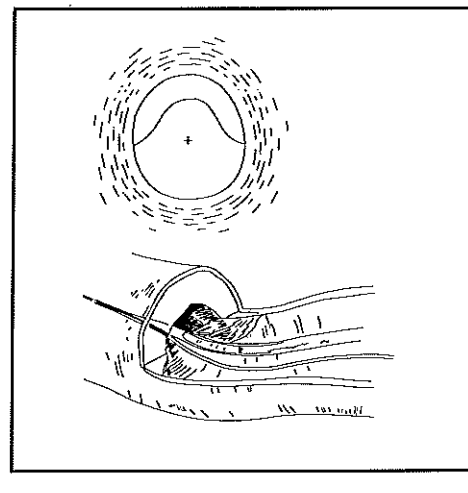

Fig. 1. Artist's rendition of an intravascular sonogram of a muscular (iliofemoral) artery with eccentric lesion.

PTA was performed because either angiography revealed a greater than 50% stenosis (n=17) or intraarterial pressure measurements revealed a pressure drop (> 15 mmHg) indicative of hemodynamic stenosis (n=4). The investigation was approved by the local Committee on Human Research at the institutions. Patients were included in the study after informed consent. The PTA procedures were preceded and followed by standard angiography, intra-arterial pressure measurements, and intravascular sonography. The balloon size was selected on the basis of the angiographic magnified uncorrected size of the artery.

Intravascular sonography

Intravascular sonography was performed using commercially available mechanical 30 MHz imaging systems with 4.3-French catheters. The catheters of the Insight system (Cardiovascular Imaging Systems, Sunnyvale, CA) house a sonographic transducer and a rotating mirror, whereas the catheters of the Princeps system (Du-MED, Rotterdam, The Netherlands) contain a sonographic transducer that is rotated externally by a motor. Details of these systems have been described previously[9]. The presence and location of obstructive lesions were first assessed by single plane angiography using a 7-French sheath in the common femoral artery. Then, the sonographic catheter was advanced over a guidewire proximally beyond the lesion. Under fluoroscopic control, images of the diseased segment were recorded during pull-back of the catheter. With a 1-cm interval the catheter was kept in position for a period of time sufficient for recording. The location of the catheter tip was compared with the radiopaque ruler and was shown on a video monitor. Care was taken to adjust the settings for time-gain compensation to yield optimal image quality. The resulting images were displayed on the video monitor by videoscanned memory and stored on a super video home system videotape.

Cross sections obtained before and after PTA by intravascular sonography were matched. The radiopaque ruler and anatomic markers such as side-branches and calcium deposits helped us match the intravascular sonography images taken before and after intervention. To distinguish between cross sections obtained in the common iliac artery and those obtained in the external iliac artery, we compared the location of the catheter tip with the angiographic records and used the visualization of large vessels such as side branch seen on intravascular sonography.

Qualitative analysis

Cross sections were assessed for lesion morphology before PTA and for vascular damage after PTA (Fig. 2). Because lesion topography can be either eccentric or concentric, we defined an eccentric lesion as a lesion seen on a cross section to involve one part of the circumference of a vessel wall while leaving the rest of the vessel free of disease (Fig. 1). A concentric lesion was defined as a lesion seen on a cross section to involve the entire circumference of the vessel wall. Morphology may include fibromuscular or fibrous lesions (echo-soft), calcification (echo-hard with shadowing), and lipid deposits (echo-poor) or a combination of any of the three. After PTA, we documented vascular damage, including

dissection, plaque rupture, and media rupture. Dissection was defined as 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; and media rupture was defined as an interruption in the internal elastic lamina and media that exposed the hyperechoic adventitia to the lumen [8].

Quantitative analysis

Quantitative measurements were performed off-line using a digital video analyzer system (International Business Machines, Boca Raton, FL)[10]. It was evident that on still-frame images dynamic information was missing. Consequently, to facilitate quantitative analyses, echo images were replayed on a separate video monitor to distinguish luminal boundaries from echoes of blood. This procedure gave us better insight into how to trace the free lumen area. Our quantitative analysis included measurement of the free lumen area and media-bounded area (Fig. 2). The 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). The media-bounded area (mm^2) was defined as the native vessel area bounded by the hypoechoic medial layer. We calculated the plaque area by subtracting the free lumen area from the media-bounded area. The area stenosis (obstruction) was calculated as the plaque area divided by the media-bounded area. Whenever there was no tunica media visible on intravascular sonography, we used the adventitia as a point of reference.

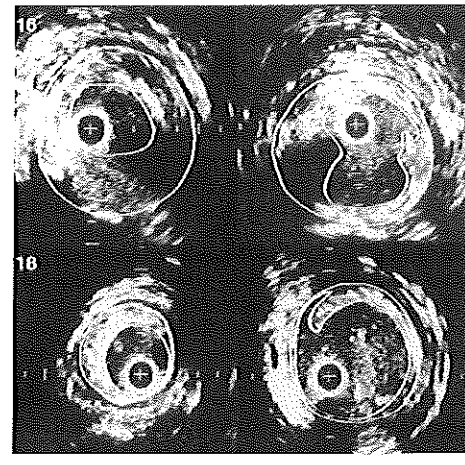

Fig. 2. Corresponding intravascular sonography cross sections obtained at the smallest free lumen area (FLA) of the common iliac artery (*level, 16 cm*) and external iliac artery (*level, 18 cm*) before (*left panel*) and after (*right panel*) percutaneous transluminal angioplasty (PTA) in a 57 year old man. Cross sections were contour-traced off-line, facilitating recognition of the FLA (*inner contour; solid arrow*) and media-bounded area (*outer contour; open arrow*). After PTA, dissection was seen at both levels. + = catheter; calibration = 1 mm.

Whenever there was extensive dropout due to calcification, dissection, or poor image quality, we could not trace the media-bounded area.

Follow-up

Patients returned for follow-up at 1 and 6 months after discharge, or they waited until an adverse event occurred. Criteria for evaluating the success of PTA have been described previously[11]. We defined success and failure with a combination of clinical and objective vascular laboratory findings. Unequivocal success of PTA was defined as improvement in the ankle-brachial index of at least 15% as a stand-

alone criterion or 10% if associated with categoric clinical improvement. In patients who received a femorodistal bypass in the same surgery (n=3) or had undergone a below-knee amputation (n=1), success was assessed with intraarterial pressure measurements after PTA (< 15 mmHg) and with duplex scanning. The ratio between the peak systolic velocity within the dilated segment and proximal to the stenosis was used to determine the diameter stenosis[12]. A peak systolic velocity ratio less than 2.5 was considered to represent a diameter stenosis that was less than 50%.

Analysis of data

First, the frequency of vascular damage (dissection, plaque rupture, and media rupture) and the quantitative effect of PTA seen at the most stenotic site before intervention were compared with data from all corresponding cross sections of the dilated segment. Results obtained in the common iliac artery were compared with data derived from the external iliac artery. Second, the relation was assessed between intravascular sonography data seen at the smallest free lumen area before and after intervention and the outcome for each patient. Differences between the groups of patients who succeeded and failed were tested with the Student's t-test for continuous data and with the chi-squared test for categoric data. All measured values were then presented as mean ± SD.

For the present study, the qualitative and quantitative analyses of the images from intravascular sonography were analyzed by two independent observers. Differences between the two observers were solved by consensus.

RESULTS

The Du-MED imaging system was used in 14 patients and the CVIS system in seven patients. Both the common iliac and external iliac artery were treated in nine patients; in six patients, only the common iliac artery, and in another six patients, only the external iliac artery was treated. The median length of the vessel segment subjected to dilatation was 6 cm (range, 4-11 cm). In 20 patients, the intravascular sonography study was completed successfully before and after PTA (14 of the common iliac artery, 14 of the external iliac artery). In one patient, who was treated for both the common iliac and external iliac artery, no intravascular sonography data were available before PTA. We had 105 corresponding cross sections from intravascular sonography available for analysis.

Qualitative analysis

As a result of angioplasty, we saw vascular damage, including dissection, plaque rupture, and media rupture on intravascular sonography in 17 of 21 (81%) patients. Vascular damage was not encountered before intervention. The frequency of vascular damage seen at the most stenotic site before PTA and in each dilated segment at both the common iliac and external iliac artery is summarized in Table 1. Overall, the frequency of vascular damage seen at the most stenotic site was slightly lower than that in each dilated segment. The frequency of vascular damage that we saw in the two types of arteries was similar, with dissection being the most common morphologic feature (Fig. 2).

Quantitative analysis

In 68 of 105 (65%) corresponding sonographic cross sections, we were able to assess both the free lumen area and media-bounded area. We used these cross sections to determine the basic quantitative mechanism related to PTA (Table 2). In the remaining 37 cross sections the media-bounded area could not be calculated because of calcification (n=14), dissection (n=4), or poor image quality (n=19). At the most stenotic site, the media-bounded area could be calculated in 21 of 28 (75%) corresponding cross sections (8 of the 14 common iliac arteries and 13 of the 14 external iliac arteries; Table 3).

Quantitative data derived from all corresponding sonographic cross sections (n=68) as well as from data obtained at the most stenotic site (n=28) before and after PTA are summarized in Tables 2 and 3. The free lumen area at the most stenotic site increased more than the mean value obtained from all cross sections (Fig. 3). The magnitude of increase in the free lumen area was larger in the external iliac artery (48%) than in the common iliac artery (28%) (Table 2, Fig. 2) With exception of area stenosis, quantitative measures of the common iliac artery were larger than those of the external iliac artery.

Table 1. Frequency of pathologic features seen with intravascular sonography after percutaneous transluminal angioplasty at the most stenotic site seen before intervention and at each dilated segment.

Artery	Frequency	
	Most stenotic site	Dilated segment
Common iliac (n=14)		
Dissection	7	9
Plaque rupture	4	5
Media rupture	2	3
Vascular damage	10	11
External iliac (n=14)		
Dissection	7	10
Plaque rupture	3	4
Media rupture	2	3
Vascular damage	9	10

n=number of arteries studied.

Table 2. Quantitative data obtained with intravascular sonography before and after percutaneous transluminal angioplasty (pta) from multiple adjacent cross sections of the common iliac artery (n=30) and the external iliac artery (n=38).

Area	Before PTA	After PTA
Free lumen area (mm^2)		
Common iliac artery	41.6 ± 16.2	53.3 ± 15.4
External iliac artery	21.9 ± 8.0	32.4 ± 9.3
Media-bounded area (mm^2)		
Common iliac artery	69.1 ± 19.6	78.8 ± 19.5
External iliac artery	38.0 ± 10.5	47.9 ± 11.0
Plaque area (mm^2)		
Common iliac artery	27.4 ± 13.3	25.5 ± 9.4
External iliac artery	16.2 ± 8.7	15.4 ± 7.4
Area stenosis (%)		
Common iliac artery	40.2 ± 17.4	32.7 ± 9.7
External iliac artery	41.9 ± 15.7	31.9 ± 12.3

Note.- Data shows mean values and SD obtained from multiple cross sections in which the free lumen area and the media-bounded area of the dilated segment could be traced.

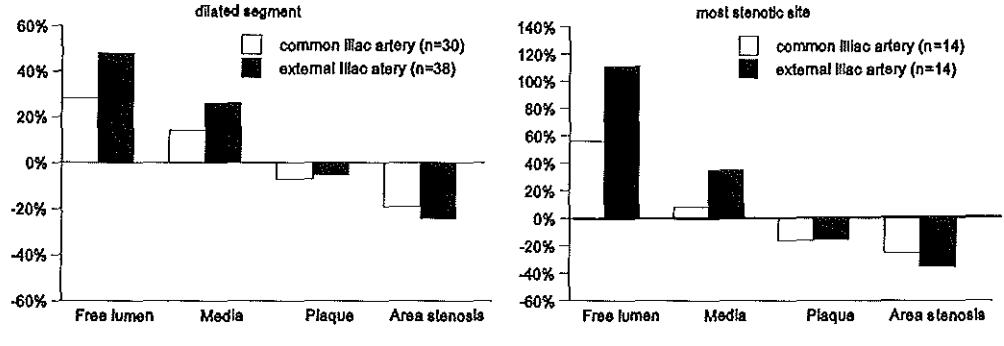

Fig. 3. Histograms show the percentage change in quantitative sonographic data obtained after percutaneous transluminal angioplasty in the common iliac and external iliac artery for cross sections obtained from the entire dilated segment (*left panel*) and at the most stenotic site (*right panel*).

Table 3. Quantitative effect of percutaneous transluminal angioplasty (PTA) assessed with intravascular sonography seen at the most stenotic site before and after intervention.

Area	Before PTA	After PTA
Free lumen area (mm^2)		
Common iliac artery (n=14)	27.9 ± 14.3	43.5 ± 10.4
External iliac artery (n=14)	15.7 ± 6.1	33.1 ± 12.0
Media-bounded area (mm^2)		
Common iliac artery (n=8)	68.2 ± 19.0	73.6 ± 17.4
External iliac artery (n=13)	35.2 ± 9.1	47.4 ± 9.4
Plaque area (mm^2)		
Common iliac artery (n=8)	34.5 ± 15.9	29.1 ± 12.8
External iliac artery (n=13)	18.8 ± 9.9	15.9 ± 6.3
Area stenosis (%)		
Common iliac artery (n=8)	51.7 ± 20.9	38.8 ± 11.3
External iliac artery (n=13)	51.5 ± 16.7	33.4 ± 10.3

Note.- Data show mean values and SD.

Follow-up

We used a combination of clinical and objective vascular laboratory findings in all 21 patients to assess their continuing success or the time of failure. The census date was 6 months. Success was scored in 12 patients (Group 1); failure in nine patients (Group 2). Based on angiographic and pressure measurements, five patients failed at the time of the intervention. Of these patients, four received a stent and one underwent a repeat PTA. In the remaining four patients who failed, failure happened within 1 month of PTA.

We found that none of the qualitative intravascular sonography parameters obtained at the most stenotic site before (topography and morphology) and after PTA (vascular damage) could predict patient outcome. In both the success and failure groups, vascular damage was seen in 72% and 75%, respectively, of the patients. Although the differences in quantitative data between the two groups were not significant, data on both free lumen area and area stenosis may be predictive of success of intervention (Table 4).

Table 4. Differences in quantitative intravascular sonographic data obtained at the site showing the smallest free lumen area after percutaneous transluminal angioplasty of the common iliac and external iliac arteries.

Artery	Patient Group	
	Group 1, Success (n=12)	Group 2, Failure (n=9)
Common iliac	(n=10)	(n=5)
Free lumen area (mm^2)	44.4 ± 11.8	33.5 ± 12.9
Media-bounded area (mm^2)	71.1 ± 15.9	83.2 ± 14.0
Area stenosis (%)	36.0 ± 7.4	48.1 ± 17.8
External iliac	(n=8)	(n=7)
Free lumen area (mm^2)	34.7 ± 14.9	22.1 ± 6.4
Media-bounded area (mm^2)	46.0 ± 18.9	42.6 ± 10.2
Area stenosis (%)	26.6 ± 12.9	41.5 ± 12.2

Note.- Data show mean values and ± SD.

DISCUSSION

Effects of PTA

This intravascular sonography study revealed that the basic mechanism by which PTA increases the free lumen area is associated with vascular damage and predominantly related to expansion of the original vessel wall. This is in agreement with others' findings[2-4]. Overall, the frequency of vascular damage seen at the most stenotic site was slightly lower than in each dilated segment. The free lumen area at the most stenotic site increased more than the mean value obtained from all cross sections. Plaque compression or embolization of the lesion as advocated by others[1,3,5] contributed to a lesser extent, but was greater at the most stenotic site.

Our study revealed vascular damage in 81% of the patients. We observed no differences in the occurrence of vascular damage in either the common iliac or the external iliac artery. Dissection, the most common feature encountered, usually occurred at the thinnest region of the lesion involved. In addition, no significant relation was found between lesion morphology and topography and the occurrence and location of dissection.

The increase in the free lumen area for the common iliac and external iliac arteries was mainly due to an increase in the media-bounded area (84%, 93%) and, to a lesser extent, to a decrease in

the plaque area (16%, 7%). In contrast, at the most stenotic site in the common iliac artery both increase in the media-bounded area and decrease in the plaque area contributed equally (50%) to the increase in the free lumen area after PTA; in the external iliac artery the contribution of the media-bounded area increase was larger (80%) than the plaque area decrease (20%). Our observation that the magnitude of increase in the free lumen area was larger in the external iliac artery (48%) than in the common iliac artery (28%) can be explained by the fact that nine patients had both arteries treated with the same balloon. The quantitative mechanism of PTA assessed in the present study agree with observations reported in coronary and femoro-popliteal arteries[6,8,13]. Conversely, Losordo et al.[7] suggested 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*[7]. The reason for these differences remains speculative. We believe that because we analyzed multiple intravascular sonography cross sections in our study, our conclusions remain well-founded.

Also, this study revealed that the size of the media-bounded area of the common iliac artery seen on intravascular sonography was twofold larger than that of the external iliac artery. However, the quantitative data on media-bounded areas reported by Losordo et al.[7] revealed no differences in these sizes. We opine that in view of endovascular interventions, one should be aware that diameters may differ for each type of artery. A point of interest is that Losordo et al.[7] could calculate in all patients the media-bounded areas. In our study, however, this calculation was feasible in only 75% of cross sections at the most stenotic site. One explanation for this discrepancy may be the sonography frequency (20 MHz) used by Losordo et al.[7], which was lower than the frequency we used (30 MHz). It is noteworthy that in our study the media-bounded area could be calculated more often in the smaller external artery (13 of 14 sites) than in the larger common iliac artery (8 of 14 sites).

Predictors of clinical outcome

The ability of intravascular sonography to predict patient outcome after PTA of the iliac artery has not yet been defined. It has been suggested that plaque morphology and vascular damage are important determinants in pathologic outcome after PTA[14,15].The results of the present study show that qualitative intravascular sonography data including echo-soft, echo-hard and echo-poor structures before PTA and as well as dissection, plaque rupture, and media rupture after intervention were not associated with patient outcome. Quantitative data on the free lumen area and area stenosis seen at the most stenotic site after PTA may be of predictive value, as was data reported for patients who underwent PTA of the superficial femoral artery [16].

Limitations

In this study, cross sections were matched based on fluoroscopy, a radiopaque ruler, and anatomic markers. It is realistic to argue that the accuracy of our matched data may not be 100%. However, our data from multiple cross

sections should serve to minimize potential mismatches. In addition, we acknowledge that the media-bounded area could not be calculated in 37 of 105 cross sections. Presumably a sonographic frequency lower than 30 MHz may effect an improvement, particularly in the larger common iliac arteries. This study is limited by the small patient cohort, and, consequently, it is hard to establish definite intravascular sonography criteria for the success of PTA, particularly for patients who had both the common iliac and the external iliac arteries treated.

Finally, using intravascular sonography for decision making during intervention, the physician should realize that quantitative analysis should be performed on-line by experienced observers.

CONCLUSION

This intravascular sonography study has shown that the common iliac artery is a larger vessel than the external iliac artery. The qualitative and quantitative effects of PTA in both types of arteries are similar. The mechanism related to the increase in the free lumen area after PTA is the result of stretching the original vessel wall; the reduction in the plaque area is minimal. Vascular damage (dissection) is a common finding. The increase of the free lumen area and the decrease in the plaque area measured at the most stenotic site exceed the measurements in all sonography cross sections. Finally, our results show that the size of the free lumen area and area stenosis seen on intravascular sonography after PTA may be predictive of patient outcome.

REFERENCES

1. Dotter CT, Judkins MP. Transluminal treatment of atherosclerotic obstruction. Description of a new technique and a preliminary report of its application. Circulation 1964;30:654-670.
2. Castaneda-Zuniga WR, Formanek A, Tadavarthy M et al. The mechanism of balloon angioplasty. Radiology 1980;135:565-571.
3. Faxon DP, Sanborn TA, Haudenschild CC. Mechanism of angioplasty and its relation to restenosis. Am J Cardiol 1987;60:5B-9B.
4. Lyon RT, Zarins VK, Lu CT, Yang CF, Glagov S. Vessel, plaque and lumen morphology after transluminal balloon angioplasty. Quantitative study in distended human arteries. Arteriosclerosis 1987;7:306-314.
5. Block PC. Mechanism of transluminal angioplasty. Am J Cardiol 1984;53:69C-71C.
6. Potkin BN, Keren G, Mintz GS, et al. Arterial responses to balloon coronary angioplasty: an intravascular ultrasound study. J Am Coll Cardiol 1992;20:942-951.
7. Losordo DW, Rosenfield K, Pieczek A, Baker K, Harding M, Isner JM. How does angioplasty work? Serial analysis of human iliac arteries using intravascular ultrasound. Circulation 1992;86:1845-1858.
8. The SHK, Gussenhoven EJ, Zhong Y, et al. The effect of balloon angioplasty on the femoral artery evaluated with intravascular ultrasound imaging. Circulation 1992;86:483-493.
9. Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88.
10. Wenguang L, Gussenhoven WJ, Bosch JG, Mastik F, Reiber JHC, Bom N. A computer-aided analysis system for the quantitative assessment of intravascular ultrasound images. Proceedings of Computers in Cardiology 1990:333-336.
11. Ahn SS, Rutherford RB, Becker GJ, et al. Reporting standards for lower extremity arterial endovascular procedures. J Vasc Surg 1993;17:1103-1107.
12. Legemate DA, Teeuwen C, Hoeneveld H, Eikelboom BC. Value of duplex scanning compared with angiography and pressure measurement in the assessment of aortoiliac arterial lesions. Br J Surg 1991;78:1003-1008.
13. van der Lugt A, Gussenhoven EJ, Stijnen T, et al. Coronary balloon angioplasty evaluated in vitro by intravascular ultrasound: a validation with histology. Am J Card 1995;76:661-666.
14. Krepel VM, van Andel GJ, van Erp WFM, Breslau PJ. Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results. Radiology 1985;156:325-328.
15. Spies JB, Bakal CW, Burke DR, et al. Standards of practice committee of the society of cardiovascular and interventional radiology. Guidelines for percutaneous transluminal angioplasty. Radiology 1990;177:619-626.
16. Gussenhoven EJ, van der Lugt A, The SHK, et al. Intravascular ultrasound predictors of outcome after peripheral balloon angioplasty. Eur J Vasc Surg 1995;10:279-288.

6 PLAQUE AREA INCREASE AND VASCULAR REMODELING CONTRIBUTE TO LUMEN AREA CHANGE FOLLOWING PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF THE FEMOROPOPLITEAL ARTERY:

An intravascular ultrasonography study

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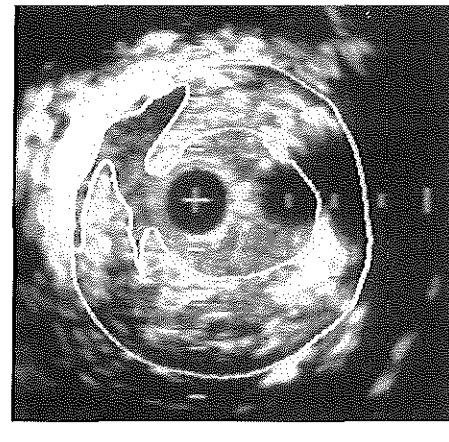

This study was supported by grants from the Netherlands Heart Foundation (91.016), the Interuniversity Cardiology Institute of the Netherlands and the Sorbo Heart Foundation

J Vasc Surg 1999;29:430-441

Plaque increase and remodeling contribute to lumen change

ABSTRACT

Objective: The aim of the study was to assess the change in lumen area (LA), plaque area (PLA) and vessel area (VA) following percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery.

Methods: This was a prospective study. Twenty patients were studied with intravascular ultrasonography (IVUS) immediately after PTA and at follow-up. Multiple corresponding IVUS cross-sections were analyzed at the segments dilated by PTA (i.e. treated sites, n=168) including the most stenotic site (n=20) and non-dilated segments (i.e. reference sites, n=77).

Results: At follow-up both PLA increase (13%) and VA decrease (9%) resulted in significant LA decrease (43%) at the most stenotic sites ($p=0.001$). At the treated sites LA decrease (15%) was smaller and caused by PLA increase (15%). At the reference sites PLA increase (15%) and VA increase (6%) resulted in slight LA decrease (3%). Analysis of IVUS cross-sections grouped according to LA change (difference ≥10%) revealed similar PLA increase in all groups: the type of vascular remodeling (VA decrease, no change or increase) determined LA change. At the treated sites lumen area change and vessel area change correlated closely ($r=0.77$, $p<0.001$). At the treated sites, significant more PLA increase was seen in IVUS cross-sections showing hard lesion or media rupture (both $p<0.05$). No relation was found between dissection and quantitative changes.

Conclusions: At the most stenotic sites, lumen narrowing was caused by plaque increase and vessel shrinkage. Both the treated sites and reference sites showed a significant PLA increase: the type of vascular remodeling determined LA change at follow-up. The extent of PLA increase was significantly larger in IVUS cross-sections showing hard lesion or media rupture.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) is one of the interventional techniques that are available for the treatment of patients with symptomatic atherosclerotic disease of the femoropopliteal artery. However, the long-term success of PTA is limited by a high incidence of restenosis (1 year patency rates: 47-81%)[1-6]. Initially, autopsy studies have shown that intimal hyperplasia is responsible for the decrease in arterial lumen after intervention[7-10]. Later, histological and intravascular ultrasonography (IVUS) studies executed in animals and human coronary arteries suggested that vascular shrinkage (defined as decrease in total arterial circumference) could be the predominant factor in the development of restenosis[11-17]. Most of these IVUS studies were performed in coronary arteries and considered one single IVUS cross-section at the most stenotic site of the artery, disregarding the changes elsewhere in the treated arterial segment [13-16]. In humans, only one IVUS study evaluated the changes at the most stenotic site and in adjacent coronary segments not subjected to intervention [17]. Kimura[17] et al. demonstrated that remodeling following coronary angioplasty was characterized by early adaptive enlargement and late constriction of the vessel wall.

The purpose of the present serial IVUS study was to evaluate the vascular response of the femoropopliteal artery following PTA, both in segments that were dilated by PTA and in the non-dilated reference segments.

METHODS

Study group

From February 1995 to February 1997, 33 symptomatic patients underwent treatment with a successful PTA (angiographic diameter stenosis <50%) of the femoropopliteal artery. Patients were studied with angiography and IVUS before and immediately after PTA. In patients with suspected restenosis on the basis of recurrent clinical symptoms (intermittent claudication, rest pain, or night pain), the angiographic and IVUS investigation was repeated. The patients with no evidence for restenosis were studied by protocol, with both angiography and IVUS within 12 to 24 months follow-up examination. The investigation was approved by the local committee on human research. The patients were included in the study after they gave informed consent.

In total 13 of 33 patients were lost to follow-up: 2 patients refused re-investigation, 4 patients underwent femoropopliteal bypass grafting, 2 patients underwent transgenual amputation and 5 patients died.

The remaining 20 patients with an angiographic and IVUS follow-up examination underwent treatment with PTA for intermittent claudication, and rest pain or night pain.

Angiography and transluminal angioplasty

Standard PTA was performed by means of an antegrade percutaneous approach with a 7F sheath. The lesions were crossed by using a guide-wire. Heparin (5000 U) was given intra-arterially. Balloon-catheter diameter (OPTA, Cordis

Europe, Roden, The Netherlands) was individually determined by the radiologist in charge and corresponded with the lumen diameter of the normal proximal or distal segment on angiography or with the vessel diameter of the minimal diseased cross-section adjacent to the stenosis on IVUS. During balloon-catheter inflation, the guide-wire was left in situ with its tip in the distal portion of the popliteal artery. Inflation pressure was increased until balloon deformity was relieved to a maximum of 12 atm. Balloon inflation was started at the distal end of the lesion and repeated as the balloon-catheter was withdrawn proximally. An overlap of 1 cm was maintained between adjacent inflations. The intervention was preceded and followed by single-plane angiography. At follow-up examination angiographic restenosis was defined as ≥50% diameter stenosis.

Intravascular ultrasonography

IVUS studies were performed with a mechanical 30 MHz imaging system with 4.3F catheter (Du-MED, Rijswijk, The Netherlands).The details of this system have been described previously[18]. The IVUS catheter was advanced distally over a guide-wire beyond the lesion. Care was taken to adjust the settings for time-gain compensation to yield optimal image quality. The IVUS images of the diseased segment subjected to PTA (i.e. treated sites) and the images of the proximal and distal adjacent non-dilated segments (i.e. reference sites), were obtained during manual pull-back of the catheter. The location of the IVUS cathetertip was systematically compared under fluoroscopic control with a radiopaque ruler to facilitate comparison of IVUS images obtained before and after intervention, and those at follow-up examination. In addition, a displacement sensing device was used that automatically documented the displacement of the IVUS cathetertip in steps of 0.01 cm. This device provided an accurate documentation of the location of the IVUS images[19]. These data were mixed with the IVUS information on the video monitor. The resulting images were stored on an S-VHS videotape.

With the displacement sensing device, the radiopaque ruler, and axial anatomic markers such as side-branches and typical shaped calcifications, the IVUS cross-sections that were obtained before and after PTA and at follow-up examination were matched. To ensure that IVUS cross-sections that were obtained at intervention corresponded with those that were obtained at follow-up examination, the cross-sections were studied side-by-side and frame-to-frame. The matched cross-sections that were obtained both from the treated sites and the proximal and distal reference sites within a 6 cm distance from the treated sites were selected with 1 cm or 2 cm interval for analysis. The IVUS cross-section that showed the most stenotic site (i.e. smallest lumen area within the treated site) before and after PTA and at follow-up examination was included in the selection.

Qualitative analysis

IVUS cross-sections that were obtained at intervention and at follow-up examination were evaluated for hard lesion (i.e. calcified) and for vascular damage, including dissection and media

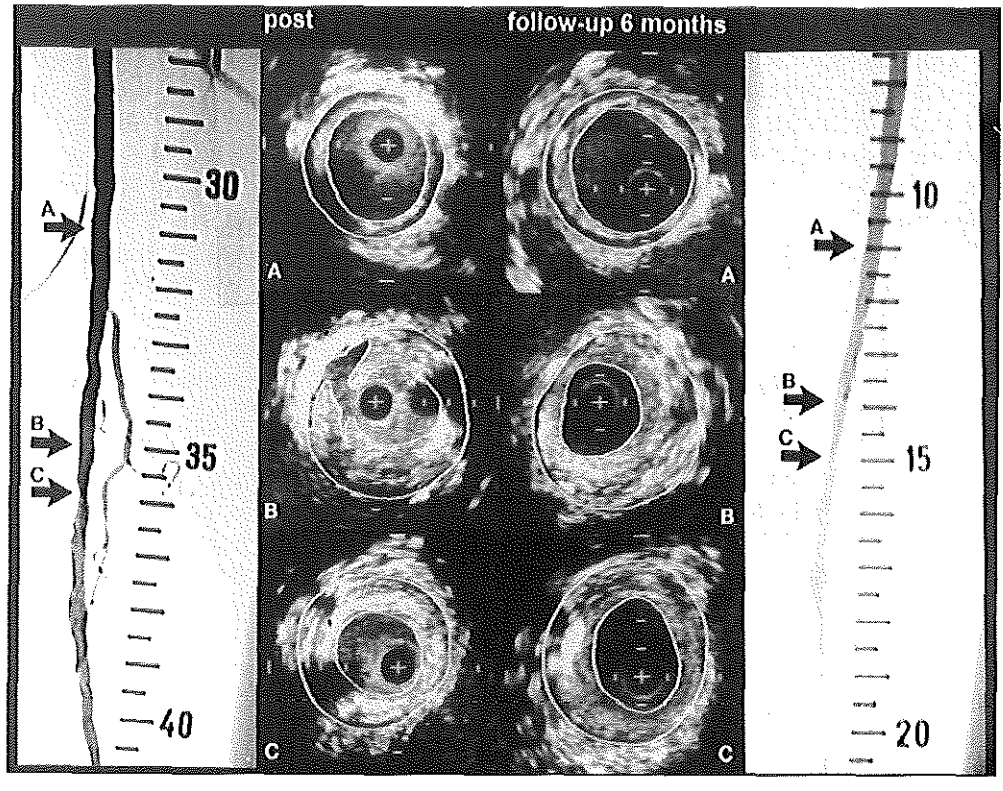

Fig. 1. Angiograms and corresponding intravascular ultrasonography cross-sections (*levels A, B, C*) obtained from a patient after percutaneous transluminal angioplasty of the femoropopliteal artery (*left*) and at 6 months follow-up examination (*right*). The ultrasonography cross-sections are contour traced off-line for lumen area (*inner contour*) and vessel area (*outer contour*). *Level A* is obtained at the proximal reference site, and *levels B* and *C* are obtained at the treated sites. Plaque area increase was seen in all levels; lumen area increase (*levels A and C*), and lumen area decrease (*level B*) was determined by the type of vessel area change. Media rupture and dissection seen after intervention (*level B, solid arrow*) were not encountered at follow-up examination. At *level C*, hard lesion (*open arrow*) was seen both at intervention and at follow-up examination. Note that the guidewire present in the *left panel* results in a dropout of 30 degrees.
+= catheter; calibration = 1 mm.

rupture (Fig. 1). Hard lesion was recognized by the presence of a bright echo structure that cast peripheral shadowing. Dissection was defined as the presence of a tear in the intimal surface that separated the lesion from the underlying arterial wall, and media rupture was defined as an interruption in the internal elastic lamina and media that exposes the hyperechoic adventitia to the arterial lumen[20]. Dissection and media rupture could be present simultaneously in one IVUS cross-section (Fig. 1).

Quantitative analysis

On IVUS, the extent of hard lesion and dissection was visually estimated and graded as an arc of the circumference with the center of the vessel as reference point (arc in steps of 30 degrees; range 0 to 360 degrees). When multiple hard lesions or dissections were seen in one IVUS cross-section the total sum was calculated[21].

For the assessment of lumen and vessel area (mm^2), a digital video analyzer system (IBM Corp. Boca Raton, Fla) was used[22]. The lumen area was defined as the area that was encompassed by the inner boundary of the intimal surface (characterized also by the presence of blood). The vessel area was defined as the area bounded by the media-adventitial border (Fig. 1). The plaque area was calculated by subtracting the lumen area from the vessel area. The percentage area stenosis (obstruction) was calculated as plaque area divided by vessel area[20]. When the image quality was inadequate or an extensive dropout due to calcification was encountered (>120 degrees of the circumference), vessel area was not assessed and these IVUS cross-sections were excluded from analysis.

Analysis of data

First, the lumen, plaque and vessel area seen after intervention and at follow-up examination were compared and the changes were calculated. A comparison was made between the data obtained at the most stenotic sites at follow-up examination, at the treated sites, and at the reference sites. Second, according to the change in lumen area at follow-up examination, IVUS cross-sections were divided into the following 3 groups, 1) lumen area decrease (≥10%), 2) lumen area unchanged (<10%), and 3) lumen area increase (≥10%). In these 3 groups, the change in plaque area and vessel area was compared in both the treated sites and reference sites. The relation between the lumen area change and the change in plaque and vessel area, respectively, was assessed. Third, the relation between the change in lumen and vessel area as result of PTA and the change in lumen, plaque and vessel area seen at follow-up examination was assessed.

Finally, the change in the extent of hard lesion and dissection seen at follow-up examination was calculated and the relation between morphologic features (i.e. hard lesion and vascular damage) and change in lumen, plaque and vessel area was assessed.

Interobserver variability

The reproducibility of IVUS parameters used in this study has been reported previously[21]. For the present study the interobserver variability on both qualitative and quantitative IVUS parameters was assessed. A total of 3 matched IVUS cross-sections of each arterial segment, chosen at the most stenotic site, at a random site in the treated segment proximal of the most stenotic site, and at the reference site were analyzed by a second independent observer (EJG).

Statistical analysis

Mean differences between quantitative IVUS data among groups were analyzed with repeated measurements analysis of variance, using the module PROC MIXED

Table 1. Patient characteristics and angiographic data.

Patients			**Ankle brachial index at rest** (mean ± SD)		
Sex (M/F)			Before PTA	71 ±	18
Age (mean ± SD)	634 ±	9.8 years	After PTA	90 ±	18
Follow-up (mean ± SD)	164 ±	9.7 months	At follow-up	84 ±	18
No. of patients		(%)	**Angiography**		(%)
Diabetes mellitus	4	-20	*Before PTA*		
Hypertension	11	-55	Stenosis	16	-80
Medication	10	-50	*Diameter stenosis*		
Hypercholesterolemia	15	-75	50% to 90%	7	-35
Medication	8	-40	≥ 90%	9	-45
Renal failure	1	-5	Occlusion	4	-20
History of smoking	17	-85	*Length of PTA (cm)*		
Indication for PTA			median range	10	(4 to 21)
Intermittent claudication	16	-80	≤5	5	-25
Rest pain/ulceration	4	-20	6 to 10	4	-20
			11 to 15	5	-25
			≥16	6	-30

SD = Standard deviation; PTA = percutaneous transluminal angioplasty.

of the SAS (Statistical Analysis Systems, SAS Institute Inc, Cary, NC) package, with compound symmetry as the assumed covariance structure. Linear regression analysis was performed to assess the strength of the following relationships: 1) between both plaque and vessel area change and lumen area change seen at follow-up examination, and 2) between the change in lumen and vessel area as a result of PTA and the change in lumen, plaque and vessel area seen at follow-up examination.

Interobserver reproducibility for the presence and absence of each qualitative parameter was expressed as unweighted

Cohen's κ statistic. To describe the agreement between the observers in the quantitative parameters, mean and standard deviations of the paired differences between the 2 observers were given. The images in which both observers agreed on the presence of these qualitative features were considered for the assessment of interobserver reproducibility of the extent of these parameters. The abovementioned repeated measurements analysis of variance was used to test whether there were systematic differences between the observers.
A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

The patient characteristics and the angiographic data are shown in Table 1. At follow-up examination (mean 16.4±9.7 months), restenosis was evidenced in 17 of the 20 patients studied. The follow-up interval for patients with and without clinical or angiographic restenosis was 14.4 ± 7.6 months and 21.3 ± 4.6 months, respectively. Fourteen patients showed clinical restenosis on the basis of recurrent symptoms: the restenosis was confirmed angiographically in 13 patients. Although there was no clinical suspicion of restenosis in the remaining 6 patients, in 3 of these patients, the angiogram revealed a diameter stenosis of ≥50%. At follow-up examination occlusions of the femoropopliteal artery were not encountered.
In 15 patients IVUS images before PTA were available. In 5 other patients, the radiologist refrained from using the IVUS catheter before intervention because the introduction of the guide-wire was difficult. In 20 patients, the IVUS images were available after PTA and at follow-up. At the treated sites, vessel area could not be assessed in 31 matched IVUS cross-sections after PTA and at follow-up examination as a result of calcification, inability to determine the media-adventitial border or a side-branch. These cross-sections therefore were excluded from analysis. For quantitative analysis 168 matched IVUS cross-sections (median 13, range 3 to 25) that were obtained at the treated sites and 77 IVUS cross-sections that were obtained at the reference sites were available.

Change in lumen, plaque and vessel area seen at follow-up examination

The results of the quantitative analysis assessed by IVUS after PTA and at follow-up examination are summarized in Table 2.
The mean lumen area measured from the matched IVUS cross-sections decreased significantly both at the most stenotic sites (43%) and at the treated sites (15%). However, at the reference sites lumen area change was negligible (-3%). A significant increase of plaque area was found at the most stenotic sites (13%), at the treated sites (15%) and at the reference sites (15%). Differences were encountered in vessel response; a significant vessel area decrease was seen at the most stenotic sites (9%), no change was seen at the treated sites (1%), and an increase in vessel area was seen at the reference sites (6%).

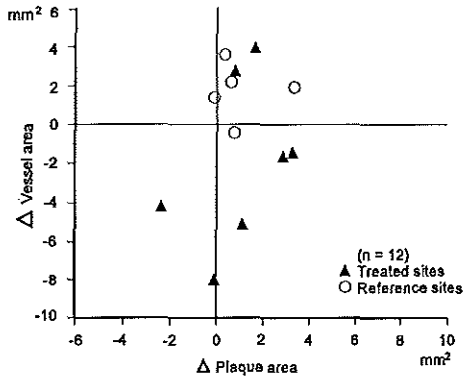

Fig. 2. Graph showing plaque and vessel area change assessed with intravascular ultrasonography, derived from an individual patient. Note that plaque area increase was combined with a wide variation of vessel area change. n=number of ultrasonography cross-sections.

Relation between both plaque and vessel area change and lumen area change at follow-up examination

During analysis of the matched IVUS cross-sections that were obtained in the individual patient from different levels, we saw that different types of vascular remodeling occurred (Figs. 1 and 2). The quantitative data grouped according to the change in lumen area are listed in Table 3.

At the treated sites no differences were encountered in plaque area increase in the 3 groups studied ($p=0.84$); the difference in vessel area change was significant ($p<0.001$). Because plaque area increase was similar in all groups, the lumen area change was determined by the vessel area change. At the reference sites, there was a significant difference between the 3 groups for both plaque and vessel area change ($p=0.03$ and $p=0.001$, respectively). Both plaque area increase and vessel area change determined the ultimate lumen size.

The relation between lumen area change and the change in plaque and vessel area at the treated and reference sites is shown in Figure 3. At the treated sites, the change in lumen area correlated more closely with the change in vessel area ($r=0.77$, $p<0.001$) than with the change in plaque area ($r=0.19$, $p=0.15$). At the reference sites, the change in lumen area correlated moderately with both the vessel area change ($r=0.40$, $p<0.001$) and the plaque area change ($r=0.47$, $p<0.001$).

Relation between the change in lumen and vessel area as a result of PTA and the change in lumen, plaque and vessel area at follow-up examination

In 15 patients, 118 matched IVUS cross-sections were obtained at the treated sites before and after PTA and at follow-up examination. The vessel area could not be assessed in 5 matched IVUS cross-sections due to calcification: 113 matched IVUS cross-sections were used to assess the relation between the change in lumen and vessel area as a result of PTA and the change in lumen, plaque and vessel area at follow-up examination. The results are shown in Figure 4. The lumen and vessel change after PTA correlated poorly with the change in lumen, plaque and vessel area seen at follow-up examination ($r=0.01$ to $r=0.36$).

Table 2. Lumen, plaque and vessel area and percentage area stenosis after percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery and at follow-up assessed with intravascular ultrasonography.

	After PTA	At follow-up	difference	% change	p value
Most stenotic site (n=20)					
LA (mm^2)	12.1 ± 4.7	6.9 ± 2.9	-5.2 ± 5.6	-43	0.001
PLA (mm^2)	19.0 ± 6.4	21.5 ± 7.4	+2.5 ± 3.2	+13	0.003
VA (mm^2)	31.1 ± 8.5	28.4 ± 6.3	-2.7 ± 5.7	-9	0.05
% S	60.9 ± 11.5	74.0 ± 14.1	+13.1 ± 13.4	+22	<0.001
Treated sites (n = 168)					
LA (mm^2)	15.6 ± 5.0	13.2 ± 5.6	-2.4 ± 5.4	-15	<0.05
PLA (mm^2)	18.9 ± 6.1	21.7 ± 7.2	+2.8 ± 3.9	+15	<0.001
VA (mm^2)	34.5 ± 8.2	34.9 ± 8.6	+0.4 ± 6.0	+1	0.05
% S	54.6 ± 10.8	61.8 ± 13.8	+7.2 ± 10.7	+13	<0.001
Reference sites (n = 77)					
LA (mm^2)	14.2 ± 5.2	13.8 ± 5.5	-0.4 ± 2.5	-3	0.2
PLA (mm^2)	13.3 ± 5.0	15.3 ± 6.1	+2.0 ± 3.0	+15	<0.001
VA (mm^2)	27.5 ± 7.4	29.1 ± 7.9	+1.6 ± 2.9	+6	<0.05
% S	48.2 ± 12.4	52.2 ± 14.2	+4.0 ± 8.5	+8	<0.001

n=number of cross-sections; % change = percentage difference between ultrasonography data after PTA and at follow-up: LA=lumen area; PLA=plaque area; VA=vessel area; %S=percentage area stenosis; + =increase; - =decrease. Values are expressed as mean ± SD.

Table 3. Change in lumen, plaque and vessel area and percentage area stenosis measured at the treated and reference sites after percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery grouped according to change in lumen area.

Treated sites (n=168)	**Lumen area decrease**	**Lumen area unchanged**	**Lumen area increase**	**p value**
	(n=87)	(n=42)	(n=39)	
Δ LA (mm^2)	-6.3 ± 4.2	-0.1 ± 0.9	+3.8 ± 2.6	
Δ PLA (mm^2)	+3.0 ± 4.3	+2.6 ± 3.4	+2.5 ± 3.7	0.84
Δ VA (mm^2)	-3.2 ± 4.5	+2.5 ± 3.3	+6.3 ± 5.3	<0.001
Δ %S	+13.9 ± 10.0	+2.5 ± 4.0	-2.8 ± 5.3	<0.001
Reference sites (n=77)	(n=20)	(n=40)	(n=17)	
Δ LA (mm^2)	-3.4 ± 2.0	-0.1 ± 1.0	+2.7 ± 1.4	
Δ PLA (mm^2)	+3.6 ± 2.9	+1.8 ± 3.2	+0.8 ± 1.9	0.03
Δ VA (mm^2)	+0.1 ± 2.4	+1.7 ± 3.0	+3.5 ± 2.3	0.001
Δ %S	+13.2 ± 8.2	+2.8 ± 5.0	-4.2 ± 4.4	<0.001

n = number of cross-sections; Δ =change; LA=lumen area; PLA=plaque area; VA=vessel area; %S=percentage area stenosis; +=increase; - =decrease. Values are expressed as mean ± SD.

Lesion morphology and vascular damage in relation to area changes

The number of IVUS cross-sections that showed a hard lesion was significantly larger at follow-up examination (n=85) than at intervention (n=74, p=0.02), and the extent of hard lesion showed a significant increase (from 51±42 degrees to 66±39 degrees, p<0.001). The number of IVUS cross-sections that showed a dissection immediately after PTA (n=65) decreased to 8 at follow-up examination (p<0.001); the extent of dissection decreased significantly from 96±57 degrees to 6±24 degrees (p<0.001). Media rupture (n=28) seen after PTA was absent at follow-up.

Analysis of the relation between the qualitative parameters involved at intervention (i.e. hard lesion, dissection and media rupture) and the quantitative changes seen at follow-up examination (in lumen, plaque and vessel area) showed a significantly larger plaque area increase in the presence of a hard lesion or a media rupture (Table 4). At the treated sites no relationship was found between lumen or vessel area change and the presence of hard lesion, dissection and media rupture.

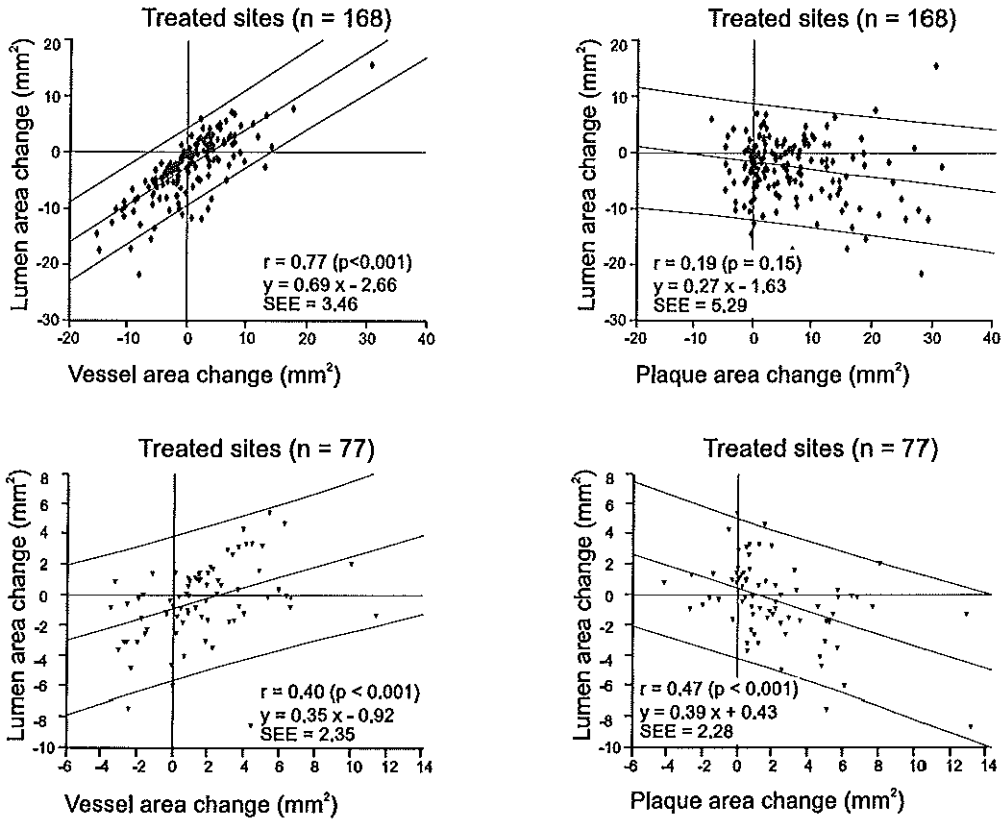

Fig. 3. Scatter plots of lumen area change versus vessel area change (*left panels*) and of the lumen area change versus plaque area change (*right panels*) assessed in matched intravascular ultrasonography cross-sections obtained at the treated sites and reference sites. SEE=standard error of the estimate.

Interobserver variability

The agreement between the 2 observers was very good for the presence of hard lesion and dissection (κ-statistics of 0.86 and 0.87, respectively) and moderate for the presence of media rupture (κ-statistic 0.54). The interobserver difference was not significant for the extent of hard lesion: the paired difference was -2±22 degrees. The interobserver difference was significant for dissection, and the paired difference was +27±30 degrees ($p<0.05$).

There was no significant interobserver difference for lumen area after PTA and at follow-up examination (+0.15±0.86 mm², and -0.32±0.69 mm², respectively) and for vessel area after PTA and at follow-up examination (-0.50 ± 1.78 mm² and +0.12±1.21 mm², respectively).

Table 4. Relation between hard lesion, dissection and media rupture obtained at intervention and change in lumen, plaque and vessel area and percentage area stenosis seen at follow-up examination with intravascular ultrasonography.

	Absent	Present	p-value
Hard lesion Treated sites	(n=100)	(n=68)	
Δ Lumen area (mm^2)	-2.5 ± 5.3	-2.2 ± 5.5	0.70
Δ Plaque area (mm^2)	+2.3 ± 3.8	+3.8 ± 4.1	0.03
Δ Vessel area (mm^2)	-0.2 ± 6.0	+1.4 ± 6.0	0.09
Δ % Area stenosis	+7.0 ± 10.5	+7.5 ± 11.0	0.75
Hard lesion Reference sites	(n=71)	(n=6)	
Δ Lumen area (mm^2)	-0.3 ± 2.6	-0.8 ± 2.1	0.52
Δ Plaque area (mm^2)	+2.0 ± 3.0	+1.7 ± 3.1	0.82
Δ Vessel area (mm^2)	+1.7 ± 3.0	+1.0 ± 1.6	0.58
Δ % Area stenosis	+4.1 ± 8.7	+3.2 ± 6.5	0.81
Dissection Treated sites	(n=103)	(n=65)	
Δ Lumen area (mm^2)	-2.4 ± 5.1	-2.4 ± 5.9	0.73
Δ Plaque area (mm^2)	+2.8 ± 3.8	+2.7 ± 4.2	0.77
Δ Vessel area (mm^2)	-0.5 ± 4.9	+0.3 ± 7.5	0.93
Δ % Area stenosis	+7.1 ± 10.8	+7.3 ± 10.7	0.93
Media rupture Treated sites	(n=140)	(n=28)	
Δ Lumen area (mm^2)	- 2.2 ± 4.8	- 3.3 ± 7.7	0.55
Δ Plaque area (mm^2)	+2.4 ± 3.5	+5.0 ± 5.2	0.04
Δ Vessel area (mm^2)	+0.2 ± 4.7	+1.7 ± 10.4	0.42
Δ % Area stenosis	+6.1 ± 10.1	+12.3 ± 12.2	0.01

n=number of cross-sections; Δ=change; +=increase; - =decrease. Values are expressed as mean ± SD.

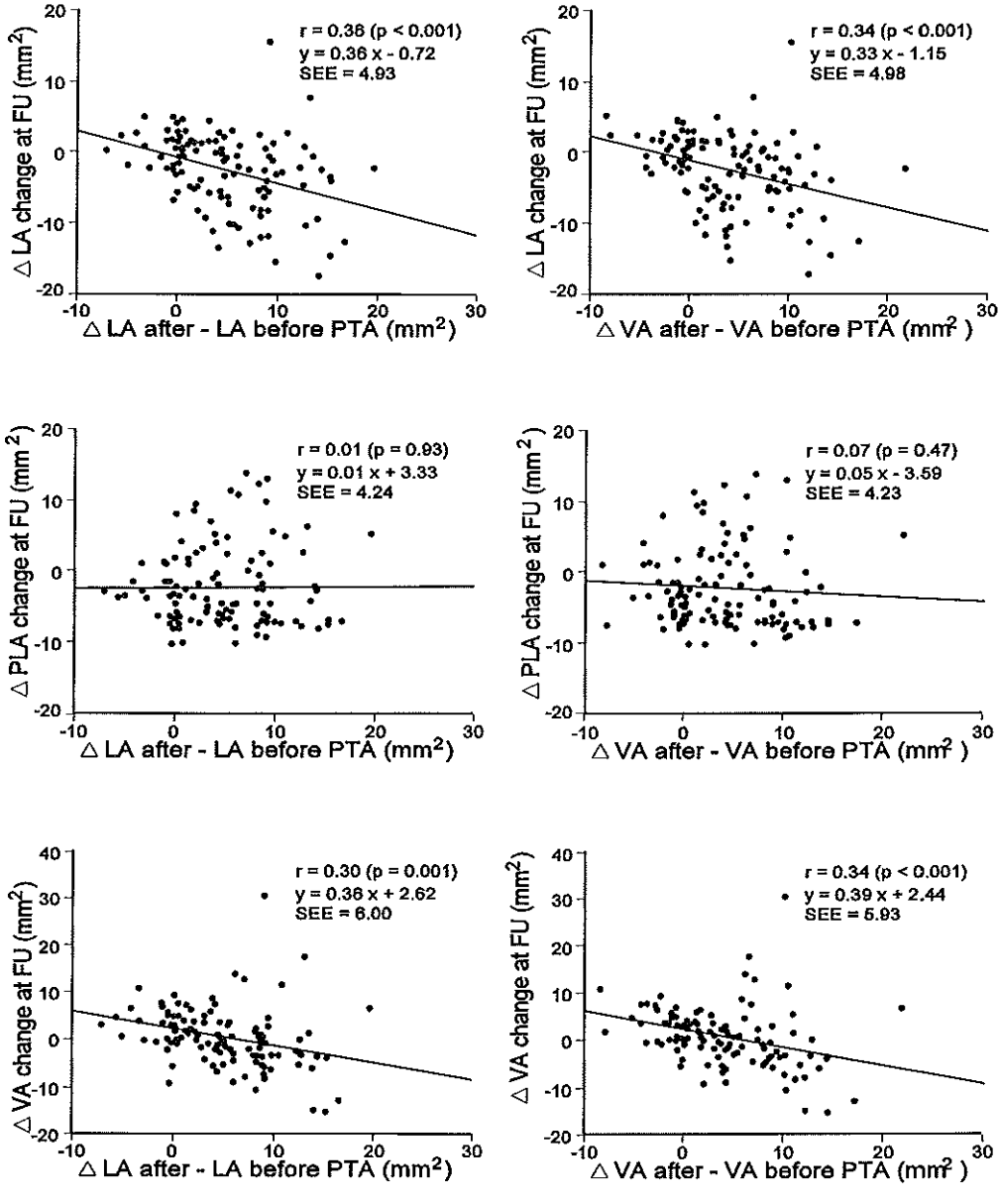

Figure 4. Scatter plots of lumen area change following percutaneous transluminal angioplasty versus lumen, plaque and vessel area change at follow-up examination (*left panels*) and of vessel area change following percutaneous transluminal angioplasty versus lumen, plaque and vessel area change at follow-up examination (*right panels*) assessed in matched intravascular ultrasonography cross-sections (n=113) obtained at the treated sites. △=change; LA=lumen area; PLA=plaque; VA=vessel area, FU= follow-up examination; PTA=percutaneous transluminal angioplasty; SEE=standard error of the estimate.

DISCUSSION

Taking into account the variation in vascular remodeling that was previously reported[23,24], the present study evaluated multiple corresponding IVUS cross-sections per vascular segment, both at the treated and the reference sites. This study demonstrated the relative influence of plaque area increase and different types of vascular remodeling (i.e. vessel decrease, no change or increase) over time on lumen area.

This study showed that at the most stenotic site the decrease in lumen area was greater than at the treated sites and the reference sites. A comparison of the mean quantitative data derived at the most stenotic sites with those at the treated sites indicated a different contribution of plaque area increase and vascular remodeling to lumen area change. At the most stenotic sites, there was an equal contribution of plaque area increase and vessel area decrease (48% and 52%, respectively) to lumen area decrease. At the treated sites, however, the change in lumen area was solely caused by plaque area increase (Table 2). The reason for the vessel area reduction at the most stenotic sites being greater remains speculative. The contribution of vessel area decrease (52%) to lumen area reduction seen at the most stenotic site was lower than seen in IVUS studies performed in coronary arteries (67-88%)[13-17]. In contrast, in the present study, an increase in vessel area was seen at the reference sites in part compensating plaque area increase and contributing to a slight decrease in lumen area (3%). The degree of lumen area decrease corresponded with the 8% reported by Kimura et al.[17]. Although the latter study reported no increase of plaque area at the reference sites at 6 months follow-up examination, in the present study, the plaque area increase was a common finding. A difference in the selection of IVUS cross-sections may account for this discrepancy.

Analysis of the IVUS cross-sections grouped by lumen area change elucidated that in the treated segment lumen area change was mainly determined by the vessel area change, while plaque area increase was similar in all 3 groups. The influence of vessel area response to lumen area change was supported by the regression analysis that showed a stronger correlation between vessel and lumen area change than between plaque and lumen area change (Fig. 3). In contrast, at the reference sites, the lumen area change correlated moderately with both the plaque and the vessel area change.

At the reference sites, an increase of plaque area should be regarded as progression of atherosclerosis, whereas, at the dilated sites, a plaque area increase might be considered as either intimal hyperplasia or as progression of atherosclerosis. We learned that the amount of plaque area increase at the dilated sites was not different in patients with a follow-up period of less then 6 months compared with patients with a follow-up of 12 to 24 months. This suggests that plaque area increase stabilized after 6 months.

In an autopsy study that was performed in coronary arteries, Nobuyoshi et al.[8] demonstrated that intimal hyperplasia was an early process following

intervention. Using IVUS, Kimura et al.[17] reported that, over a 6-month period, there was early vessel enlargement and late constriction (i.e. biphasic remodeling). From the present study, no conclusions can be drawn on the time sequence of vascular remodeling following PTA because IVUS investigation was repeated once after PTA at various follow-up intervals. However, the finding that different types of vascular remodeling within one single arterial segment were encountered may contradict the assumption that an artery may gradually lose its ability of compensatory enlargement over time. This finding supports the suggestion that vascular remodeling is a location-specific process and not a patient-specific process [24]. The suggestion that vascular remodeling is a location specific process is strengthened by the observation that the different types of remodeling were observed within the same patient, who served as their own controls, subjected to the same conditions, such as hypertension, diabetes and hypercholesterolemia. We assume that focal differences in blood flow velocity and shear stress may induce different types of vascular remodeling encountered at various levels[23, 25, 26].

Although Post et al.[27] described that acute gain of the lumen after PTA in iliac arteries of Yucatan micropigs was related with lumen area decrease caused by vascular remodeling, such a relationship was not found in the present study. At the treated sites the increase in lumen and vessel area after PTA was weakly related to the change in lumen, plaque and vessel area at follow-up examination (Fig. 4).

This study showed that the incidence rate and extent of hard lesion increased following PTA. The amount of plaque area increase was significantly related to the presence of hard lesion. Similarly, Mintz et al.[28] demonstrated that the process of accumulating atherosclerotic plaque was associated with the presence of calcified lesions. In another study, Mintz et al.[24] suggested that calcified lesions limited the adaptive vascular response to plaque accumulation. This is in contrast with our findings that showed a trend toward an increase in vessel area in the presence of hard lesion (Table 4).

At follow-up examination, dissections were smaller and less frequently present, and media ruptures were absent. The presence of media rupture was related to a larger plaque area increase at follow-up examination. This finding concurs with the relationship between intimal proliferation and the severity of vascular injury after intervention reported by others[8,10]. The observation that dissection did not provoke plaque area increase suggests that dissection is a less severe injury of the vessel wall than media rupture[29]. Media rupture and hard lesion, although related to the amount of plaque area increase, did not influence lumen area change. This underlines the statement that vessel remodeling is the main determinant of lumen area change at follow-up examination. Why the individual IVUS cross-sections responded in different ways remains to be determined.

Study limitations

It should be acknowledged that the number of patients studied is small compared to the number of patients reported in coronary artery studies[13-17]. IVUS investigations at follow-up examination were performed mainly when an adverse event had occurred. Consequently the follow-up interval showed a wide variation. Thirteen patients initially studied with IVUS were lost to follow-up; as a result, a potential selection bias in the patient population may have occurred. The assessment of IVUS parameters may be subjective. Besides, the κ statistic value of media rupture is based on a small number of incidences and should be interpreted with caution.

Despite the use of the displacement sensing device, radiopaque ruler and axial anatomic markers such as side-branches and calcifications, inaccuracies may occur in the matching of corresponding IVUS cross-sections. The inclusion of multiple IVUS cross-sections for analysis rather than one single cross-section minimized the effects of possible mismatches on the final results.

Conclusions

The present IVUS study showed a significant increase in plaque area in IVUS cross-sections derived from the most stenotic sites, the treated sites and the reference sites. In contrast, the vessel area either decreased at the most stenotic sites, or remained unchanged at the treated sites, or increased at the reference sites. Thus, in the presence of plaque area increase, the type of vascular remodeling (shrinkage vs enlargement) determined the lumen area change at follow-up examination. Analysis of the pooled quantitative IVUS data tends to obscure the different types of vascular remodeling encountered in the individual cross-sections derived from one single arterial segment. At the treated sites the extent of plaque area increase was significantly larger in IVUS cross-sections with calcified lesion or media rupture.

Finally, despite the initial angiographic success of PTA in the femoropopliteal artery, the intervention still results in a high incidence of restenosis. Because lumen narrowing was the net result of plaque area increase and vessel area decrease, future research should be aimed at eliminating both plaque growth and vascular shrinkage to increase the efficacy of PTA.

Acknowledgments

We thank T. Rijsdijk (Department of Radiology, University Hospital Rotterdam Dijkzigt) for the photographic work.

REFERENCES

1. Krepel VM, van Andel GJ, van Erp WFM, Breslau PJ. Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results. Radiology 1985;156:325-328.
2. Jeans WD, Armstrong S, Cole SEA, Horrocks M, Baird RN. Fate of patients undergoing transluminal angioplasty for lower-limb ischemia. Radiology 1990;177:559-564.
3. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty: factors influencing long-term success. Circulation 1991;83 (Suppl I):I-70-I-80.
4. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology 1992;183:767-771.
5. Matsi PJ, Manninen HI, Vanninnen RL, Suhonen MT, Oksala I, Laakso M et al. Femoropopliteal angioplasty in patients with claudication: primary and secondary patency in 140 limbs with 1-3-year follow-up. Radiology 1994;191:727-733.
6. Stanley B, Teague B, Raptis S, Taylor DJ, Berce M. Efficacy of balloon angioplasty of the superficial femoral artery and popliteal artery in the relief of leg ischemia. J Vasc Surg 1996;23:679-685.
7. Kohchi K, Takebayashi S, Block PC, Hiroki T, Nobuyoshi M. Arterial changes after percutaneous transluminal coronary angioplasty: results at autopsy. J Am Coll Cardiol.1987;10:592-599.
8. Nobuyoshi M, Kimura T, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N et al. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol 1991;17:433-439.
9. Ellis SG, Muller DWM. Arterial injury and the enigma of coronary restenosis. J Am Coll Cardiol 1992;19:275-277.
10. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267-274.
11. Kakuta T, Currier JW, Haudenschild CC, Ryan TJ, Faxon DP. Differences in compensatory enlargement, not intimal formation, account for restenosis after angioplasty in the hypercholesterolemic rabbit model. Circulation 1994;89:2809-2815.
12. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. Circulation 1994;89:2816-2821.
13. Blasini R, Mudra H, Klauss V, Regar E, Schömig A. Remodelling of coronary arteries after balloon angioplasty: In vivo documentation in patients using consecutive intravascular ultrasound. J Am Coll Cardiol 1995 ;25 (Suppl):139 A.
14. Di Mario C, Gil R, Camezind E, Ozaki Y, von Birgelen C, Umans V et al. Quantitative assessment with intracoronary ultrasound of the mechanisms of restenosis after percutaneous transluminal coronary angioplasty and directional coronary atherectomy. Am J Cardiol 1995;75:772-777.
15. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong SC et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94:35-43.
16. Luo H, Nishioka T, Eigler NL, Forrester JS, Fishbein MC, Berglund H et al. Coronary artery restenosis after balloon angioplasty in humans is associated with circumferential coronary constriction. Arterioscler Thromb Vasc Biol 1996;16:1393-1398.
17. Kimura T, Kaburagi S, Tamura T, Yokoi H, Nakagawa Y, Yokoi H et al. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. Circulation 1997;96:475-483.
18. Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88
19. Gussenhoven EJ, van der Lugt A, van Strijen M, Li W, The SHK, van Egmond FC et al. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N (eds.). Intravascular Ultrasound. Kluwer Academic Press, Dordrecht 1993:157-166.

20. The SHK, Gussenhoven EJ, Zhong Y, Wenguang L, van Egmond FC, Pieterman H et al. The effect of balloon angioplasty on the femoral artery evaluated with intravascular ultrasound imaging. Circulation 1992;86:483-493.
21. van der Lugt A, Gussenhoven EJ, Pasterkamp G, Bom N, Posthuma DJ, Stijnen T. Interobserver reproducibility of qualitative and quantitative analysis of intravascular ultrasound before and after balloon angioplasty. Ultrasound Med Biol 1996;4:399-404.
22. Wenguang L, Gussenhoven WJ, Bosch JG, Mastik F, Reiber JHC, Bom N. A computer-aided analysis system for the quantitative assessment of intravascular ultrasound images. Proc Comput Cardiol 1990:333-336.
23. Pasterkamp G, Borst C, Post MJ, Mali WPTM, Wensing PJW, Gussenhoven EJ et al. Atherosclerotic arterial remodeling in the superficial femoral artery: individual variation in local compensatory enlargement response. Circulation 1996;93:1818-1825.
24. Mintz GS, Kent KM, Picard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses: an intravascular ultrasound study. Circulation 1997;95:1791-1798.
25. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-1375.
26. Krams R, Wentzel JJ, Oomen JAF, Vinke R, Schuurbiers JCH, de Feyter PJ et al. Evaluation of endothelial shear stress and 3D geometry as factors determining the development of atherosclerosis and remodeling in human coronary arteries in vivo. Combining 3D reconstruction from angiography and IVUS (ANGUS) with computational fluid dynamics. Arterioscler Thromb Vasc Biol 1997;17:2061-2065.
27. Post MJ, de Smet BJGL, van der Helm Y, Borst C, Kuntz RE. Arterial remodeling after balloon angioplasty or stenting in an atherosclerotic experimental model. Circulation 1997;96:966-1003.
28. Mintz SM, Pichard AD, Popma JJ, Kent KM, Satler LF, Bucher TA et al. Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic and intravascular ultrasound study. J Am Coll Cardiol 1997;29:268-274.
29. Andersen HR, Mæng M, Thorwest M, Falk E. Remodelling rather than neointimal formation explains luminal narrowing after deep vessel wall injury. Insights from a procine coronary (re)stenosis model. Circulation 1996;93:1716-1724.

7 MECHANISM OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY: serial intravascular ultrasound study of femoropopliteal arteries

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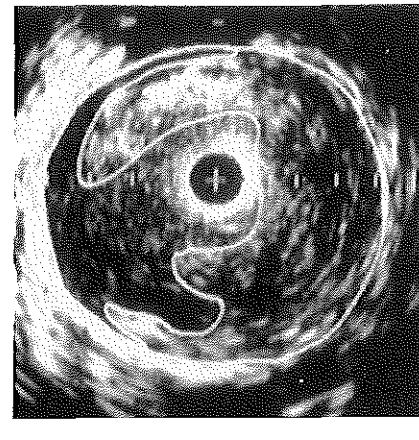

This study was supported by grants from the Sorbo Heart Foundation and the Interuniversity Cardiology Institute, the Netherlands

Submitted for publication

ABSTRACT

Purpose: To assess the difference in vascular response in restenotic and non-restenotic lesions seen 1-year following percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery using intravascular ultrasound (IVUS).

Methods: Patients (n=24) with 31 treated lesions were studied. The IVUS cross-section with the smallest lumen area at the angiographic target site before PTA and the corresponding cross-section after PTA and at follow-up were selected for analysis of lumen, plaque and vessel area. Based on lumen area distribution at follow-up a lumen area <11.0 mm^2 seen on IVUS at 1-year follow-up was considered a restenotic lesion.

Results: At follow-up 19 of the 31 lesions (61%) were restenotic. Lumen area in restenotic lesions decreased, while in non-restenotic lesions lumen area increased (-6.4±3.3 mm^2 vs 3.1±4.7 mm^2, p<0.001). Both groups showed a similar increase in plaque area (3.2±2.9 mm^2 and 3.6±3.2 mm^2, respectively, p=0.76). Whereas in the restenotic lesions vessel area decreased, in the non-restenotic lesions vessel area increased (-3.5±4.5 mm^2 and +3.8±3.9 mm^2, respectively, p=0.002), resulting in a significant difference in vessel area between both groups at follow-up (33.7±7.8 mm^2 and 47.8±8.1 mm^2, respectively, p=0.001).

Conclusions: At 1-year follow-up restenotic and non-restenotic lesions showed a similar amount of intimal hyperplasia: restenosis was determined by the type of vascular remodeling (vessel area decrease or increase).

Key words: Angioplasty; Peripheral vascular disease; Remodeling, Ultrasonics

INTRODUCTION

Despite the wide acceptance of peripheral angioplasty its results are limited by rates of restenosis ranging from 47% to 81% in 1-year[1-6]. Both experimental and clinical studies in coronary arteries have described restenosis as a healing response to vascular injury that involves both formation of neointimal hyperplasia and constriction of the vascular wall [7-17]. A previous study on femoropopliteal arteries undergoing percutaneous transluminal angioplasty (PTA) established that, besides plaque growth, vascular remodeling (constriction or enlargement) determined lumen area at follow-up[18]. In the latter study, however, no comparison was made between restenotic and non-restenotic lesions.

The purpose of this serial intravascular ultrasound (IVUS) study was to explore the mechanism of restenosis following PTA of the femoropopliteal artery by comparison of restenotic and non-restenotic lesions.

METHODS

Study group

In this multicenter study named PARIS (Peripheral Arterial Restenosis assessed with Intravascular Sonography), 3 hospitals participated. Angiographic and serial IVUS data were collected from 31 lesions in 24 patients [16 men, 8 women; median age 67 years (range 44 to 89 years)] treated with PTA for symptomatic obstructive disease of the femoropopliteal artery. Seventeen patients were excluded due to the absence of adequate IVUS follow-up for the following reasons: reintervention within 3 months due to failure of the intervention (n=6), occlusion at follow-up (n=2), lost to follow-up (n=4), logistic problems (n=3) and death (n=2). 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 gender, age, history of smoking, diabetes, hypertension (medication dependent), hypercholesterolemia (medication dependent or serum cholesterol >5.0 mmol/l) and indication of intervention (intermittent claudication, rest-/nightpain or ulceration).

Patients were studied with angiography and IVUS before and after PTA and at follow-up. In patients with suspected restenosis on the basis of recurrent clinical symptoms, the angiographic and IVUS investigation was repeated. In the remaining patients the angiographic and IVUS investigation was repeated by protocol after 12 months follow-up.

Angiography and transluminal angioplasty

Standard PTA of the femoropopliteal artery was performed by means of an antegrade percutaneous approach with a 7F introducer sheath. Balloon diameter (OPTA or Powerflex, Cordis Europe, Roden, The Netherlands) was individually determined by the radiologist in charge and was based on the lumen diameter of the normal proximal or distal reference segment on angiography and/or on the vessel diameter of a minimal diseased IVUS cross-section adjacent to the stenosis. The intervention was preceded and followed by single-plane digital subtraction angiography.

Data collected on each lesion included

the angiographic diameter stenosis before and after intervention and at follow-up, the number of open run-off vessels, the length of the dilated lesion and the balloon diameter. Angiographic diameter stenosis, visually assessed on the basis of a reduction of the diameter at the most stenotic part of the artery, compared with a nearby reference segment, was graded as <50%, 50-90%, 90-99% and 100%.
Crural run-off vessels were categorized in 2 groups (good: 2 or 3; bad: none or 1). The length of the dilated lesion, recorded using a radiopaque ruler, was categorized in 4 groups (≤5 cm, 6-10 cm, 11-15 cm, >15 cm).

Intravascular ultrasound
IVUS studies were performed before and after PTA and at follow-up using a mechanical 30 MHz imaging system with 4.3F catheter (Endosonics, Rijswijk, The Netherlands). Details of this system have been described previously[19]. The ultrasound catheter was advanced distally over a guidewire beyond the lesion. IVUS images were obtained using manual pull-back. In order to facilitate comparison of serially acquired IVUS images the location of the ultrasound cathetertip was systematically recorded under fluoroscopy with a radiopaque ruler as a reference. In addition, a displacement sensing device was used that automatically documented the displace-ment of the ultrasound cathetertip in steps of 0.01 cm[20]. These data were mixed with the ultrasound information on the videomonitor. The resulting images were stored on an S-VHS videotape.
Using the radiopaque ruler, data derived from the displacement sensing device and axial anatomic markers such as side-branches and typical shaped calcifications, the IVUS cross-sections obtained before and after PTA and at follow-up were matched. To ensure that the selected IVUS cross-sections corresponded, the cross-sections were studied side-by-side and frame-to-frame. The matched IVUS cross-sections were selected with 1 or 2 cm interval for qualitative and quantitative selection. Care was taken that the most stenotic site (i.e. smallest lumen area at the target site) before intervention was included. Analyses of the selected IVUS cross-sections were performed centrally (Erasmus Medical Center, Rotterdam).

Qualitative analysis
IVUS cross-sections obtained at intervention were evaluated for soft lesion, hard lesion (i.e. calcified) and for dissection. Soft lesion was recognized as having a homogeneous echo structure without shadowing. Hard lesion was recognized by the presence of a bright echo structure casting peripheral shadowing. Dissection was defined as the presence of a tear in the intimal surface separating the lesion from the underlying arterial wall[21].

Quantitative analysis
On IVUS, the extent of hard lesion and dissection was visually estimated and graded as an arc of the circumference with the center of the vessel as reference point (arc in steps of 30 degrees; range 0 to 360 degrees). When multiple hard lesions or dissections were seen in one IVUS cross-section the total sum was calculated[22].

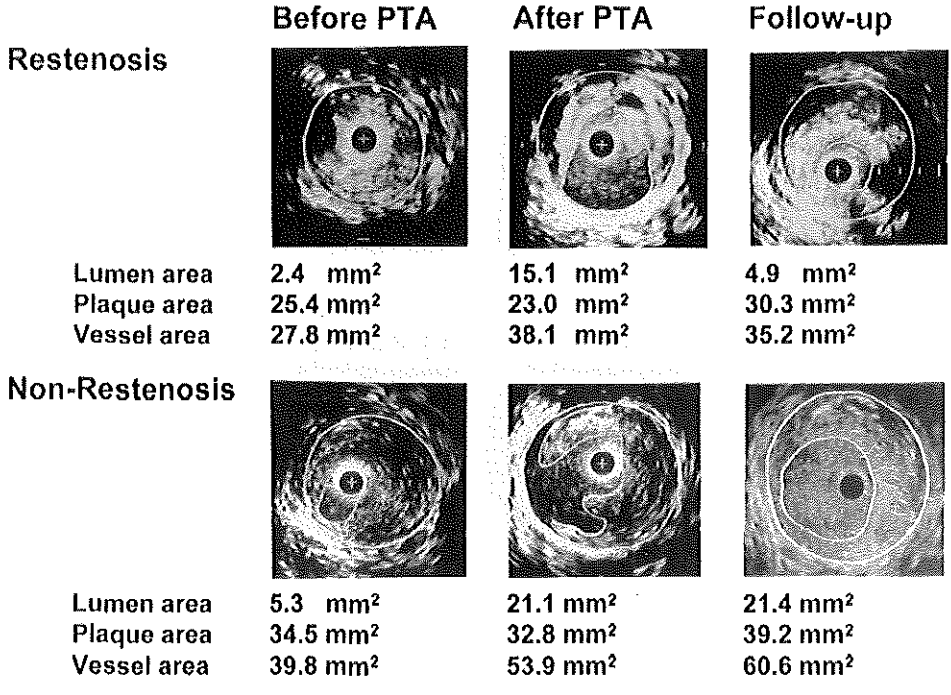

Fig. 1. Corresponding intravascular ultrasound (IVUS) cross-sections obtained before and after percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery and at 1-year follow-up in a restenotic (top panel) and non-restenotic lesion (lower panel). The IVUS cross-sections are contour-traced off-line for lumen area (inner contour) and vessel area (outer contour). Restenosis was associated with intimal hyperplasia combined with vessel shrinkage; in the non-restenotic lesion lumen area increase was associated with intimal hyperplasia compensated by vessel enlargement.

For the assessment of lumen and vessel area a digital video analyzer system (IBM Corp. Boca Raton, USA) was used[23]. The lumen area was defined as the area encompassed by the inner boundary of the intimal surface (characterized also by the presence of blood). The vessel area was defined as the area bounded by the media-adventitial border (Fig. 1). The plaque area was calculated by subtracting the lumen area from the vessel area[21]. The percentage area stenosis was calculated as the plaque area divided by the vessel area. When image quality was inadequate or extensive dropout due to calcification was encountered (>120 degrees of the circumference), vessel area could not be assessed and these IVUS cross-sections were excluded from analysis.

Analysis of data

For the present study the IVUS cross-section with the smallest lumen area at the angiographic target sites (diameter stenosis ≥50% before PTA) was

compared with the corresponding IVUS cross-section after PTA and at follow-up. First, the change in lumen, plaque and vessel area and the percentage area stenosis as result of PTA and seen at follow-up was assessed. Second, the relationship between lumen, plaque and vessel area change observed at follow-up was determined. Third, at follow-up the presence of restenosis was defined based on the distribution of the lumen area size seen with IVUS. The difference in clinical, angiographic, procedural and IVUS data between restenotic and non-restenotic lesions was assessed.

Statistical analysis

Quantitative data are expressed as mean ±SD. Continuous variables were compared using the Student's t-test and categoric data were compared using the Chi squared test. Analysis of data was performed using the module PROC MIXED of the SAS (Statistical Analysis Systems, SAS Institute Inc, Cary, NC) package with compound symmetry as the assumed covariance structure. Linear regression analysis was performed to assess the strength of the relationship between the change in lumen, plaque and vessel area seen at follow-up. The statistical significance level was set at $p<0.05$. Interobserver variability of IVUS parameters used has been reported previously[18].

RESULTS

Twenty-four patients with 31 lesions treated with an angiographic successful PTA, had a complete follow-up (mean 11.6 ± 4.0 months). The distribution of lesions treated was 1 lesion in 18 patients, 2 lesions in 5 patients, and 3 lesions in 1 patient. The median length of the lesions involved was 10 (range 2 to 21) cm. Clinical, angiographic and procedural data are listed in Table 1.

After PTA angiographic diameter stenosis was < 50% in all but one lesion; one patient with a diameter stenosis of 90-99% before PTA presented a diameter stenosis of 50-90% after PTA. At follow-up angiographic restenosis was experienced in 17 of the 31 lesions (Table 1).

In 4 patients IVUS images were not available before PTA as the radiologist refrained from using IVUS because the introduction of the guide-wire was difficult. Of the 31 target sites treated, corresponding IVUS images were available in 27 levels before PTA and in 31 levels after PTA and at follow-up. Vessel area could be assessed in 18 of the 27 target sites before PTA, in 23 of the corresponding cross-sections after PTA, and in 20 of the corresponding cross-sections at follow-up (Table 2).

Serial IVUS measurements before and after PTA

The area measurements before and after PTA and the changes are given in Table 2. As result of PTA a significant increase in lumen area and vessel area and a significant decrease in plaque area was observed. In those sites in which vessel area could be measured both before and after PTA (n=18) lumen area increase (11.2 ± 4.0 mm^2; $p<0.001$) was mainly caused by vessel area increase (9.8 ± 5.2 mm^2; 88%) ($p<0.001$) and only slightly by plaque area decrease (-1.4 ± 2.1 mm^2; 12%) ($p=0.01$).

Table 1. Clinical, angiographic and procedural data obtained in 24 patients with 31 treated lesions.

Patients (n = 24)	Sex (male/female)	16/8
	Age (median)	67 years (range 44-89 years)
	History of smoking (n)	13 (54%)
	Diabetes (n)	8 (33%)
	Hypertension (n)	9 (38%)
	Hypercholesterolemia (n)	14 (58%)
Clinical symptoms	Claudication (n)	17 (71%)
	Rest-/nightpain (n)	4 (17%)
	Ulceration (n)	3 (12%)

Angiographic and procedural data (n = 31)

		Before PTA	After PTA	Follow-up
Diameter stenosis	<50%	-	30	14
	50-90%	18	1	12
	90-99%	10	-	5
	100%	3	-	-
Run-off (n)	good	21		
	bad	1		
	unknown	9		
PTA length (n)	≤5 cm	6		
	6-10 cm	12		
	11-15 cm	8		
	>15 cm	5		
Balloon diameter (n)	5 mm	12		
	6 mm	17		
	7 mm	2		

(n) = number, PTA = percutaneous transluminal angioplasty.

Table 2. Lumen, plaque and vessel area and percentage area stenosis before and after percutaneous transluminal angioplasty (PTA) and at follow-up assessed with intravascular ultrasound at the pre-interventional target site.

	Before PTA		After PTA		Follow-up	
	(n)		(n)		(n)	
Lumen area (mm^2)	27	5.0 ± 2.3	31	14.7 ± 4.2	31	12.0 ± 6.5
Plaque area (mm^2)	18	23.8 ± 6.3	23	23.8 ± 6.2	20	26.7 ± 7.4
Vessel area (mm^2)	18	28.7 ± 6.6	23	39.2 ± 8.2	20	38.7 ± 10.3
% area stenosis	18	82.3 ± 8.4	23	60.6 ± 8.8	20	69.5 ± 28.7

	Δ Before/After			Δ After/Follow-up		
	(n)		p-value	(n)		p-value
Lumen area (mm^2)	27	+9.8 ± 4.3	<0.001	31	-2.7 ± 6.0	0.04
Plaque area (mm^2)	18	-1.4 ± 2.1	0.01	20	+3.3 ± 3.0	<0.001
Vessel area (mm^2)	18	+9.8 ± 5.2	<0.001	20	-0.9 ± 5.5	0.47
% area stenosis	18	-24.4 ± 5.3	<0.001	20	+11.0 ± 9.2	<0.001

(n) = number of cross-sections, Δ = change, + = increase, - = decrease.
Values are expressed as mean ± SD.

Serial IVUS measurements after PTA and at follow-up

The area measurements after PTA and at follow-up and the changes are given in Table 2. At follow-up a significant decrease in lumen area and a significant increase in plaque area and percentage area stenosis was observed. In those sites in which vessel area could be measured both after PTA and at follow-up (n=20) lumen area decrease (-4.2±4.9 mm^2; p=0.04) was mainly caused by plaque area increase (3.3±3.0 mm^2; 79%) (p<0.001) and only slightly by vessel area decrease (-0.9±5.5 mm^2; 21%) (p=0.47). Regression analysis showed that the change in lumen area at follow-up correlated closely with vessel area change (r=0.85, p<0.001), but did not correlate with plaque area change (r=0.10, p=0.69) (Fig. 2). There was a moderate correlation between plaque and vessel area change (r=0.45, p<0.001) (Fig. 2).

Differences between restenotic and non-restenotic lesions

Based on the distribution of the lumen area size seen at follow-up, that showed a clear division in 2 groups, a lumen area <11.0 mm^2 was considered a restenotic lesion: 19 lesions (61%) were classified as restenotic and 12 lesions (39%) as non-restenotic (Fig. 3).

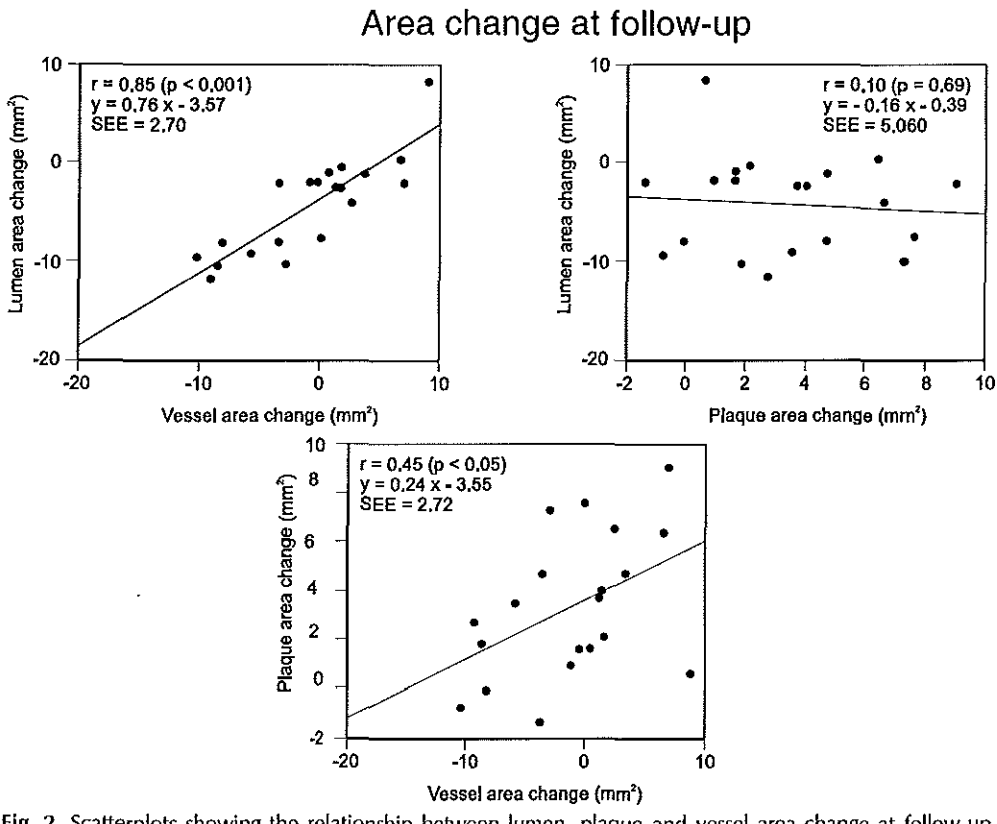

Fig. 2. Scatterplots showing the relationship between lumen, plaque and vessel area change at follow-up measured with intravascular ultrasound at the target site (n=20).

No difference was encountered in the follow-up duration of restenotic and non-restenotic lesions (10.9±3.5 months versus 12.6±4.5 months; p=0.61). Angiographic diameter stenosis was ≥50% in 13 of the 19 restenotic lesions and in 4 of the 12 non-restenotic lesions. The change in lumen area seen at intervention and at follow-up in individual restenotic and non-restenotic lesions is shown in Fig. 4. After PTA, both the restenotic and non-restenotic lesions presented an increase in lumen area. At follow-up, lumen area decreased in all restenotic lesions; in the majority of the non-restenotic lesion lumen area increased.

The differences between restenotic and non-restenotic lesions for quantitative IVUS parameters are given in Table 3. By definition restenotic lesions had a smaller lumen area at follow-up than non-restenotic lesions (7.2±2.1 mm^2 and 19.6±2.5 mm^2, respectively, p<0.001) (Fig. 3). At follow-up, both restenotic and non-restenotic lesions showed a similar plaque area increase (3.2±2.9 mm^2 and 3.6±3.2 mm^2, respectively, p=0.76). Whereas in restenotic lesions a decrease in vessel area was seen, in non-restenotic

Table 3. Differences between restenotic and non-restenotic lesions for quantitative intravascular ultrasound parameters following percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery.

		Restenosis		Non-restenosis		
		(n)		(n)		p-value
Before PTA	Lumen area (mm^2)	16	4.8 ± 2.5	11	5.4 ± 2.3	0.57
	Plaque area (mm^2)	12	22.9 ± 6.8	6	25.5 ± 5.2	0.70
	Vessel area (mm^2)	12	27.7 ± 6.9	6	30.8 ± 5.7	0.40
	% area stenosis	12	82.2 ± 9.7	6	82.7 ± 5.7	0.91
After PTA	Lumen area (mm^2)	19	13.6 ± 3.8	12	16.5 ± 4.3	0.21
	Plaque area (mm^2)	16	23.4 ± 6.8	7	24.7 ± 4.7	0.80
	Vessel area (mm^2)	16	37.1 ± 7.9	7	44.0 ± 7.1	0.18
	% area stenosis	16	62.6 ± 9.6	7	56.0 ± 4.1	0.11
Follow-up	Lumen area (mm^2)	19	7.2 ± 2.1	12	19.6 ± 2.5	<0.001
	Plaque area (mm^2)	13	25.8 ± 7.7	7	28.3 ± 7.1	0.51
	Vessel area (mm^2)	13	33.7 ± 7.8	7	47.8 ± 8.1	0.02
	% area stenosis	13	75.3 ± 6.8	7	58.6 ± 6.3	0.003
Δ Before/After	Lumen area (mm^2)	16	+8.6 ± 3.7	11	+1.6 ± 4.6	0.12
	Plaque area (mm^2)	12	-1.6 ± 2.2	6	-1.1 ± 2.3	0.77
	Vessel area (mm^2)	12	+8.2 ± 4.0	6	+13.1 ± 6.2	0.11
	% area stenosis	12	-22.8 ± 4.9	6	-27.4 ± 5.1	0.13
Δ After/Follow-up	Lumen area (mm^2)	19	-6.4 ± 3.3	12	+3.1 ± 4.7	<0.001
	Plaque area (mm^2)	13	+3.2 ± 2.9	7	+3.6 ± 3.2	0.76
	Vessel area (mm^2)	13	-3.5 ± 4.5	7	+3.8 ± 3.9	0.02
	% area stenosis	13	+15.2 ± 7.3	7	+2.6 ± 6.5	0.001

n = number of cross-sections, Δ = change, + = increase, - = decrease. Values are expressed as mean ± SD.

Table 4. Differences between restenotic and non-restenotic lesions for qualitative intravascular ultrasound parameters and balloon size used.

		Reststenosis (n=19)	Non-restenosis (n=12)	p-value
Before intervention	Hard lesion	11 (58%)	8 (67%)	0.60
	Arc of hard lesion (°)	60 ± 81	75 ± 84	0.59
After intervention	Dissection	12 (63%)	8 (67%)	0.85
	Arc of dissection (°)	60 ± 75	87 ± 93	0.97
Balloon diameter	5 mm	11	1	0.01
	6 mm	8	9	
	7 mm	0	2	

(n) = number of lesions.

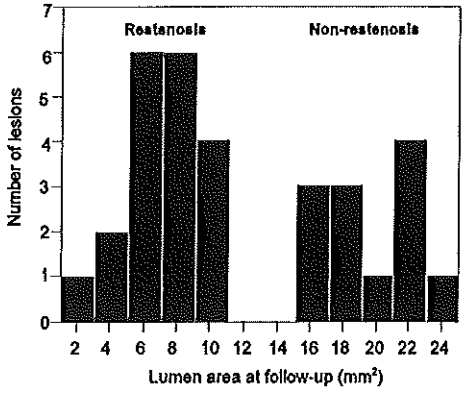

Fig. 3. Histogram of the lumen area assessed at follow-up with intravascular ultrasound at the site corresponding with the target site determined before intervention.

lesions vessel area increased (-3.5±4.5 mm^2 and +3.8±3.9 mm^2, respectively, p=0.02) resulting in a significant difference in vessel area between both groups at follow-up (33.7±7.8 mm^2 and 47.8±8.1 mm^2, p=0.001).

Qualitative IVUS parameters (hard lesion and dissection) were not related with the occurrence of restenosis (Table 4).

The use of a smaller balloon diameter was associated with a higher incidence of restenosis (p=0.01): 11 of 12 lesions dilated with a 5 mm balloon, 8 of 17 lesions dilated with a 6 mm balloon and none of the 2 lesions dilated with a 7 mm balloon developed restenosis. The severity of the clinical symptoms before intervention was related to restenosis (p=0.01). There was no difference between the restenotic and non-restenotic lesions for any other clinical or angiographic variable.

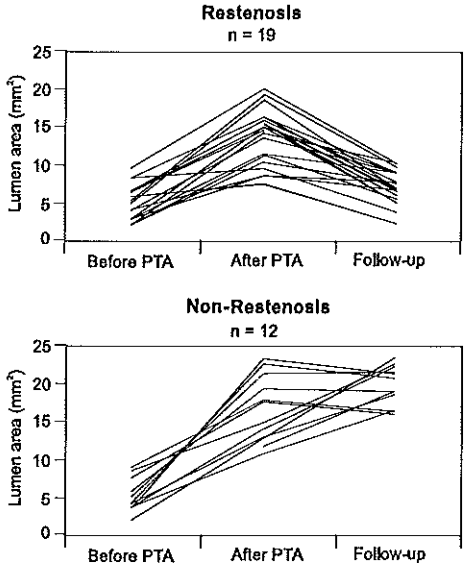

Fig. 4. Lumen area change encountered at intervention and at follow-up in the restenotic and non-restenotic lesions assessed with intravascular ultrasound.

DISCUSSION

This serial IVUS study documents the natural history of an obstructive lesion treated with PTA. For 2 reasons IVUS rather than angiography was used to define restenosis at follow-up. First, commonly in peripheral interventions, angiography grade diameter stenosis only semiquantitatively and second, there is a poor correlation between angiographic diameter stenosis and lumen size assessed with IVUS[15, 24-25].

The present IVUS study revealed a clear cut-off point at 11.0 mm^2 for lumen area distribution at follow-up: this criterion was subsequently used to distinguish restenotic from non-restenotic lesions. It may be argued that lumen area decrease at follow-up, a conditio sine qua non of a restenotic lesion, should be included in the definition. All 19 restenotic lesions defined with IVUS showed a decrease in lumen area at follow-up. Although in 5 of the 12 non-restenotic lesions a slight decrease in lumen area at follow-up was encountered, these lesions showed a lumen area that to a large extent exceeded the cut-off point of 11.0 mm^2 (Fig. 3).

Mechanism of restenosis

Overall, if the data of all IVUS cross-sections were considered, lumen area reduction seen at follow-up (lumen change) was mainly due to an increase in plaque area (79%) and to a lesser extent to vascular constriction (21%). However, the introduction of an IVUS definition for restenosis revealed that another mechanism than described above may be responsible for the restenotic process. First, regression analysis demonstrated that lumen area change was better correlated with vessel area change than with plaque area change. Second, in both restenotic and non-restenotic lesions a similar degree of plaque growth was seen at follow-up: in restenotic lesions vessel constriction was involved, in non-restenotic lesions vessel enlargement was observed. Although vessel enlargement was encountered in 22% and 31% of the coronary lesions by Mintz et al.[15] and Kimura et al.[16], these authors revealed an overall decrease in vessel area in both restenotic and non-restenotic lesions at 6 months follow-up. The extent of vessel area decrease was larger in the restenotic lesions, than in the non-restenotic lesions.

One explanation for the increase in vessel area may be the increase in vascular distensibility after PTA as the relative stiff atherosclerotic plaque has

been dissected from the underlying vessel wall. The arterial pressure may then cause more distention of the vessel wall in the subsequent hours and days. This may explain the absence of restenosis in most lesions with an increase in vessel area at follow-up. However, this may be contradicted by the fact that, in the present study the presence and extent of dissections was not significantly different between restenotic and non-restenotic lesions. Finally, different remodeling reactions to intimal hyperplasia and shear stress may explain the increase in vessel area.

Predictors of restenosis

This study revealed that there were no differences between the restenotic and non-restenotic lesions for clinical, angiographic and procedural parameters except for the balloon diameter used for PTA. Despite that similar quantitative IVUS parameters were encountered before intervention in restenotic and non-restenotic lesions, after PTA restenotic lesions tended to have a smaller lumen and vessel area, and a smaller lumen and vessel area increase than non-restenotic lesions. It is obvious that the achieved lumen size after intervention is intimately related to the balloon size used. Lumen area after PTA was smaller in procedures using a balloon diameter of 5 mm, than those using a balloon diameter of ≥6 mm (11.6 ± 3.8 mm^2 and 16.7 ± 3.6 mm^2, respectively; $p<0.001$). Given the fact that the majority (92%) of PTAs performed with a 5 mm balloon, presented a restenotic lesion at follow-up, one may wonder whether this latter balloon size should remain an option. Similarly, in 47% of the PTAs performed with a balloon size ≥6 mm a restenotic lesion was involved. Altogether, these findings support the idea that balloons with a larger diameter than currently used should be recommended for PTA in peripheral arteries. However, the balloon size used in the present study was selected based on the pre-interventional vessel size and consequently, a small vessel size can be associated with a poor outcome even though there was no significant difference in vessel area between restenotic and non-restenotic lesions before PTA.

The observation that restenotic lesions tended to have a smaller lumen area after PTA is consistent with previous studies, indicating that creation of a larger lumen after PTA is related to long-term patency[26-31]. Recent histological and animal studies have shown that a larger lumen gain resulting in more severe vascular injury may be counter-productive at follow-up because of the increased intimal hyperplasia[8,10] or increased vascular shrinkage[32]. The present study did not confirm these observations: the larger lumen area after PTA in the non-restenotic lesions was not accompanied by a larger plaque area increase or vessel area decrease at follow-up.

Study limitations

The major limitation of this study is the small number of patients with a completed IVUS follow-up (24 of the 41 patients). Secondly, due to calcification encountered at the target site the vessel area could not be measured in 9 (33%) IVUS cross-section before PTA, in 8 (26%) IVUS cross-sections after PTA, and

in 11 (35%) IVUS cross-sections at follow-up. Finally, despite the use of a radiopaque ruler, a displacement sensing device, and axial anatomic markers such as side-branches and calcifications, minimal inaccuracies may occur in matching of corresponding IVUS cross-sections.

Conclusions

The present IVUS study used lumen area at follow-up to define restenosis following angiographic successful PTA of the femoropopliteal artery. No differences were found between restenotic and non-restenotic lesions for IVUS data obtained before intervention. In the presence of a similar amount of plaque increase seen at follow-up, restenosis was determined by the type of vascular remodeling.

Acknowledgments

This study was supported by grants from the Sorbo Heart Foundation and the Interuniversity Cardiology Institute, the Netherlands. We thank T. Rijsdijk (Department of Radiology, University Hospital Rotterdam-Dijkzigt) for the photographic work.

REFERENCES

1. Krepel VM, van Andel GJ, van Erp WFM, Breslau PJ. Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results. Radiology 1985;156:325-328.
2. Jeans WD, Armstrong S, Cole SEA, Horrocks M, Baird RN. Fate of patients undergoing transluminal angioplasty for lower-limb ischemia. Radiology 1990;177:559-564.
3. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty: factors influencing long-term success. Circulation 1991;83 (Suppl I): I-70-I-80.
4. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology 1992;183:767-771.
5. Matsi PJ, Manninen HI, Vanninnen RL, Suhonen MT, Oksala I, Laakso M, Hakkarainnen T, Soimakalloi. S. Femoropopliteal angioplasty in patients with claudication: primary and secondary patency in 140 limbs with 1-3-year follow-up. Radiology 1994;191:727-733.
6. Stanley B, Teague B, Raptis S, Taylor DJ, Berce M. Efficacy of balloon angioplasty of the superficial femoral artery and popliteal artery in the relief of leg ischemia. J Vasc Surg. 1996;23:679-685.
7. Kohchi K, Takebayashi S, Block PC, Hiroki T, Nobuyoshi M. Arterial changes after percutaneous transluminal coronary angioplasty: results at autopsy. J Am Coll Cardiol.1987;10:592-599.
8. Nobuyoshi M, Kimura T, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N, Yokoi H, Kim K. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol. 1991;17:433-439.
9. Ellis SG, Muller DWM. Arterial injury and the enigma of coronary restenosis. J Am Coll Cardiol. 1992;19:275-277.
10. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol. 1992;19:267-274.
11. Kakuta T, Currier JW, Haudenschild CC, Ryan TJ, Faxon DP. Differences in compensatory enlargement, not intimal formation, account for restenosis after angioplasty in the hypercholesterolemic rabbit model. Circulation 1994;89:2809-2815.
12. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. Circulation 1994;89:2816-2821.
13. Blasini R, Mudra H, Klauss V, Regar E, Schömig A. Remodelling of coronary arteries after balloon angioplasty: In vivo documentation in patients using consecutive intravascular ultrasound. J Am Coll Cardiol. 1995 (Supplement); 139 A (Abstract).
14. Di Mario C, Gil R, Camenzind E, Ozaki Y, von Birgelen C, Umans V, de Jaegere P, de Feyter PJ, Roelandt JRTC, Serruys PW. Quantitative assessment with intracoronary ultrasound of the mechanisms of restenosis after percutaneous transluminal coronary angioplasty and directional coronary atherectomy. Am J Cardiol. 1995;75:772-777.
15. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong SC, Hong MK, Kovach JA, Leon MB. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94:35-43.
16. Kimura T, Kaburagi S, Tamura T, Yokoi H, Nakagawa Y, Yokoi H, Hamasaki N, Nosaka H, Nobuyoshi M, Mintz GS, Popma JJ, Leon MB. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. Circulation 1997;96:475-483.
17. Luo H, Nishioka T, Eigler NL, Forrester JS, Fishbein MC, Berglund H, Siegel RJ. Coronary artery restenosis after balloon angioplasty in humans is associated with circumferential coronary constriction. Arterioscler Thromb Vasc Biol. 1996;16:1393-1398.
18. van Lankeren W, Gussenhoven EJ, Honkoop J, Stijnen Th, van Overhagen H, Wittens CHA, Kranendonk SE, van Sambeek MRHM, van der Lugt A. Plaque area increase and vascular remodeling contribute to lumen area change after percutaneous transluminal angioplasty of the femoropopliteal artery: an intravascular ultrasound study. J Vasc Surg. 1999;29:430-441.
19. Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88.

20. Gussenhoven EJ, van der Lugt A, van Strijen M, Li W, The SHK, van Egmond FC, Honkoop J, Peters RJG, de Feyter P, van Urk H, Pieterman H. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N (eds.). Intravascular Ultrasound. Kluwer Academic Press, Dordrecht 1993:157-166.
21. The SHK, Gussenhoven EJ, Zhong Y, Wenguang L, van Egmond FC, Pieterman H, van Urk H, Gerritsen GP, Roelandt JRTC, Borst C, Wilson RA, Bom N. The effect of balloon angioplasty on the femoral artery evaluated with intravascular ultrasound imaging. Circulation 1992;86:483-493.
22. van der Lugt A, Gussenhoven EJ, Pasterkamp G, Bom N, Posthuma DJ, Stijnen T. Interobserver reproducibility of qualitative and quantitative analysis of intravascular ultrasound before and after balloon angioplasty. Ultrasound Med Biol. 1996;4:399-404.
23. Wenguang L, Gussenhoven WJ, Bosch JG, Mastik F, Reiber JHC, Bom N. A computer-aided analysis system for the quantitative assessment of intravascular ultrasound images. Proc Comp Cardiol. 1990: 333-336.
24. Mintz Gs, Popma JJ, Pichard AD, Kent KM, Salter LF, Chuang YC, Griffin J, Leon MB. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary vascularisation. J Am Coll Cardiol. 1996;27:1678-1687.
25. van Lankeren W, Gussenhoven EJ, van der Lugt A, Pieterman H, van Sambeek MRHM. Comparison of angiography and intravascular ultrasound before and after balloon angioplasty of the femoropopliteal artery. Cardiovasc Intervent Radiol. 1998;21:367-374.
26. Farb A, Virmani R, Atkinson JB, Anderson PG. Long-term histologic patency after percutaneous transluminal coronary angioplasty is predicted by the creation of a greater lumen area. J Am Coll Cardiol. 1994;24:1229-1235.
27. Gussenhoven EJ, van der Lugt A, Pasterkamp G, van den Berg FG, Sie LH, Vischjager M, The SHK, Li W, Pieterman H, van Urk H. Intravascular ultrasound predictors of outcome after peripheral balloon angioplasty. Eur J Vasc Endovasc Surg. 1995;10:279-288.
28. van der Lugt A, Gussenhoven EJ, Pasterkamp G, Stijnen T, Reekers JA, van den Berg FG, Tielbeek AV, Seelen JL, Pieterman H. Intravascular ultrasound predictors of restenosis after balloon angioplasty of the femoropopliteal artery. Eur J Vasc Endovasc Surg. 1998;16:110-119.
29. van der Lugt A, Gussenhoven EJ, Mali WPTM, Reekers JA, Seelen JL, Tielbeek AV, Pieterman H. Effect of balloon angioplasty in femoropopliteal arteries assessed by intravascular ultrasound. Eur J Vasc Endovasc Surg. 1997;13;549-556.
30. Vogt KJ, Rasmussen JG, Just S, Schroeder TV. Effect and outcome of balloon angioplasty and stenting of the iliac arteries evaluated by intravascular ultrasound. Eur J Vasc Endovasc Surg. 1999;17:47-55.
31. Schroeder S, Baumbach A, Haase KK, Oberhoff M, Marholdt H, Herdeg C, Athanasiadis A, Karsch K. Reduction of restenosis by vessel size adapted percutaneous transluminal coronary angioplasty using intravascular ultrasound. Am J Cardiol. 1999;83:875-879.
32. Post MJ, de Smet BJGL, van der Helm Y, Borst C, Kuntz RE. Arterial remodeling after balloon angioplasty or stenting in an atherosclerotic experimental model. Circulation 1997; 96: 996-1003.
33. Pasterkamp G, Borst C, Post MJ, Mali WPTM, Wensing PJW, Gussenhoven EJ, Hillen B. Atherosclerotic arterial remodeling in the superficial femoral artery: individual variation in local compensatory enlargement response. Circulation 1996;93:1818-1825.

8 DISCREPANCY BETWEEN STENT DEPLOYMENT AND BALLOON SIZE USED ASSESSED BY INTRAVASCULAR ULTRASOUND

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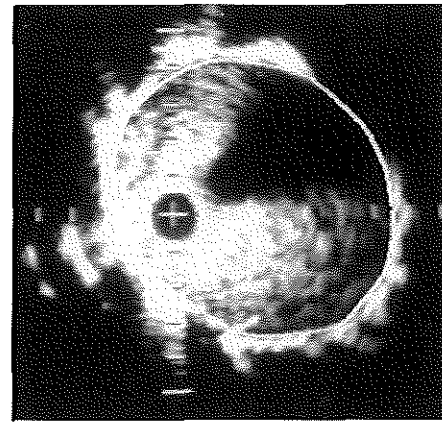

This study was supported by grants from the Netherlands Heart Foundation (93.015) the Interuniversity Cardiology Institute of the Netherlands, and the Sorbo Heart Foundation

Eur J Vasc Endovasc Surg 1998;15:57-61

SUMMARY

Objectives: This study was designed to assess discrepancy in stent deployment seen on intravascular ultrasound and its relation with the balloon size selected for stent delivery.

Design: Retrospective study.

Materials and Methods: The study group comprised 27 patients with stent (n=18) or stent-graft combination (n=9). Following angiographically optimal stent deployment was obtained (<10% residual stenosis), intravascular ultrasound was used to compare the smallest intra-stent lumen area with measurements at both stent edges, and the lumen area of the proximal and distal reference sites.

Results: In 14 of the 27 stents the intra-stent dimension was the same as the dimension of the stent edge (difference $\leq \pm 10\%$). Of the remaining stents the intra-stent dimension was smaller (difference >10%) than the proximal stent edge in seven stents (range 11-39%), smaller than the distal stent edge in three stents (range 11-20%) and smaller than both stent edges in three stents (range 12-37%). Both in patients treated with a stent or stent-graft combination, the resulting smallest intra-stent lumen area was smaller than the balloon size used (mean difference 32% and 42%, respectively) and smaller than the mean lumen area of the reference sites (mean difference 25% and 23%, respectively).

Conclusions: This intravascular ultrasound study shows a discrepancy between intra-stent lumen area, the area of the stent edges and the balloon size used.

Key words: Intravascular ultrasound; Stent; Diameter; Stenosis; Aneurysm.

INTRODUCTION

To improve the immediate and long-term results of vascular interventions stent deployment is used in different vascular sites[1-3]. In the coronary intravascular ultrasound has revealed that stents may be incompletely deployed despite optimal angiographic results, and consequently interventional strategies have been modified[2,4-8]. The present study describes stent deployment in non-coronary sites assessed with intravascular ultrasound, and examines the relation with the balloon size used.

SUBJECTS AND METHODS

The study included 27 patients (17 men and 10 women, median age 65 (range 36-86) years) successfully treated with a stent (n=18) or a combined stent-graft (n=9) placement. Success was defined as a residual diameter stenosis <10% with a smooth lumen of the stented segment and without an endoleak to the aneurysm. Balloon-expandable stents were used (Palmaz; Johnson and Johnson, Interventional Systems, NJ, U.S.A.). The subclavian artery (n=4), the common iliac artery (n=10), and the superficial femoral artery (n=13) were treated. Patients were scheduled for intervention based on angiographic data (diameter stenosis >50% or aneurysm). Indications for stenting were suboptimal balloon angioplasty (n=15), elective (n=1), and a dissection larger than the initial lesion (n=2). Stent-graft combinations (Palmaz stent + ePTFE graft) were used to treat peripheral arterial aneurysm (n=6) and false aneurysm at graft anastomoses (n=3)
Dilatations were performed with a compliant balloon (OPTA, Cordis, Europe BV). The size of the balloon and stent were selected on the basis of pre-deployment intravascular ultrasound. For this purpose the diameter of the original vessel wall (media-to-media) at the location of the diseased stenotic segment was used, or the diameter of the normal lumen where the stent-graft would be anchored. Inflation time and pressure were left to the discretion of the interventionalist based on fluoroscopy and angiography.

Intravascular ultrasound

Intravascular ultrasound studies were performed with a mechanical system containing a rotating single ultrasound element (30 MHz; Endosonics, Rijswijk, the Netherlands) using a 4.3-French flexible catheter ('Princeps'). Before and immediately after intervention the ultrasound catheter was advanced distally and cross-sections were obtained during pull-back of the catheter. The resulting images together with their unique frame number were displayed on a monitor via a video-scanned memory and stored on an S-VHS video system. Cross-sectional area measurements were performed off-line using a computer-based analysis system[9]. Measurements included (1) *before intervention* assessment of reference vessel area (bounded by the media) in those cross-sections used to determine balloon size and stent size; and (1) *after intervention* assessment of the area at the two stent edges (entry and exit), the smallest area within each stent (intra-stent dimension), and the mean lumen area of the proximal and distal reference segment.
The reference segments were, by definition, within 1-2 cm of the stented

segment showing the largest lumen area without sidebranches. Stent deployment was reviewed for:

1. Comparison between the lumen area measured at the deployed stent edges and within each stent. The difference between stent area measured at the edges and within the stent (smallest area) was calculated and expressed as a percentage of the smallest area within the stent. A relative stent area at the stent edge of >110% indicates a larger edge; a relative stent dimension at the edge of 90-110% indicates no difference. The cut-off point of 10% was used to correct for intraobserver differences in measurements.
2. Comparison between balloon area and vessel area in those ultrasound cross-sections obtained before intervention on which the size of the balloon used was based. Balloon area was derived from specifications provided by the manufacturer.
3. Comparison between balloon area used and the smallest stent area.
4. Comparison between the smallest stent area and the reference lumen area (mean of proximal and distal reference area) seen after intervention. A distinction was made between data derived from stents and stent-grafts, as well as between data derived from the subclavian, common iliac and femoral arteries.
5. Apposition of the stent to the vessel wall (without protrusion of the struts within the lumen).
6. Stent symmetry at the stent edges and within the stent, which was calculated by dividing minimum and maximum diameter.

To assess intraobserver variability of lumen, vessel and stent areas, the cross-sections selected were analyzed blinded by the same observer with an interval of 2 months.

Statistical analysis

All values are given as mean ± standard deviation (SD). Differences in area measurement were examined with the Student's *t*-test. In order to describe the intraobserver agreement in measurements of the area, mean ± SD of the paired differences between the measurements were given. The Student's *t*-test was used to determine whether there were systematic intraobserver differences. The degree of intraobserver variation is presented with a coefficient of variation defined as the SD of the paired difference divided by the mean of the absolute value. A p-value <0.05 was considered statistically significant.

RESULTS

The mean length of stents used was 3.0 cm (range 1.0-4.5 cm); the mean pressure to implant the stent against the arterial wall was 11 ± 1 atm.

All intravascular ultrasound studies were completed successfully. Table 1 summarizes the quantitative data obtained.

TABLE 1. Balloon size and intravascular ultrasound measurements (mean ± SD) through the implanted stent and adjacent vessel segments in the study population.

		Stenosis (n = 18)	Aneurysm (n = 9)
Balloon size (mm^2)		46.8 ± 26.4	93.1 ± 59.6
Before intervention			
Reference vessel area (mm^2)		53.7 ± 31.9	84.4 ± 51.3
After intervention			
Stent area (mm^2)	smallest	32.0 ± 21.4	54.2 ± 35.9
	largest	38.9 ± 24.2	72.4 ± 44.3
Reference lumen area (mm^2)	mean	42.8 ± 30.6	70.8 ± 48.3

1. Comparing the intra-stent lumen area and the lumen area of the stent edges individually in each stent, it was found that in 14 stents the areas were in the same order. In the remaining 13 stents either the area of the proximal stent edge (n=7; range 11-39%) or of the distal stent edge (n=3; range 11-20%) was larger than both the intra-stent area and opposite stent edge area (Fig. 1). In three stents the intra-stent area was smaller than the area of both stent edges (range 12-37%).
2. The balloon size selected in patients treated for a stenosis was smaller (13%) than the reference vessel area seen on ultrasound before intervention; in patients treated for an aneurysm the balloon size selected was larger (10%) than the reference vessel area seen on ultrasound.
3. The balloon size used exceeded the resulting intra-stent lumen area. Mean difference between balloon size and smallest intra-stent area was 32% for patients treated for a stenosis and 42% for patients treated for an aneurysm. The difference between the balloon size and smallest intra-stent area was significant for the common iliac (44%) and superficial femoral artery (37%), but not for the subclavian artery (11%) (Fig. 2).
4. Comparing the smallest intra-stent area and the lumen area of the reference segment, a mean difference of 25% was seen for patients treated with a stent, and 23% for patients treated with acombined stent-graft. Individually, the difference between smallest intra-stent area and reference lumen area was less than 10% in seven patients; between 10% and 20% in three patients and between 20% and 56% in 17 patients.

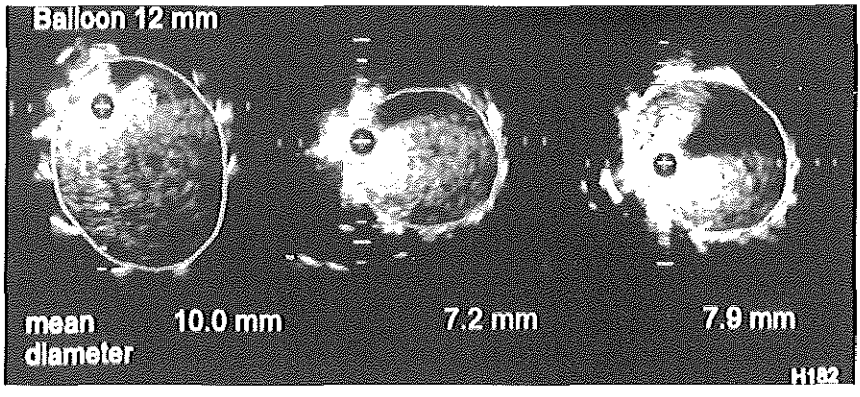

Fig. 1: Intravascular ultrasound cross-sections of the iliac artery after stent-graft placement for an aneurysm using a 12 mm balloon. Diameters of the proximal stent edge (A), intra-stent (B) and distal stent edge (C) are smaller than the balloon diameter used. + = catheter; calibration =1 mm.

5. Complete stent-opposition with the struts touching the arterial wall was seen in all patients.
6. Data on the symmetry index indicate well deployed circular stents: an index of ≥0.7 was found in 100% of the stents, and an index of ≥0.8 was found in 95% of the stents, respectively.

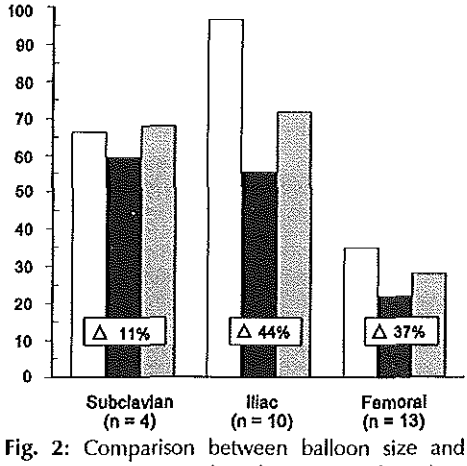

Fig. 2: Comparison between balloon size and stent areas measured with intravascular ultrasound. (□) Balloon size; (■) smallest stent;(◻) largest stent, (Δ) difference between balloon size and smallest stent area.

Of the intraobserver differences, none were statistically significant. The coefficient of variation of the vessel area assessed before intervention was 5%; for lumen and stent area assessed after intervention it was 7% and 6%, respectively.

DISCUSSION

Endovascular treatment offers a minimally invasive therapy that is effective in most circulatory beds for an increasing array of pathology[10]. The use of stent and stent-graft combinations to improve long-term patency of endovascular interventions is being investigated[10]. Because angiography alone is insufficient to adequately monitor endovascular procedures, the comprehensive insight into vessel and stent geometry provided by intravascular ultrasound has played an important role in developing the concept of optimized stent deployment[11]. Despite good angiographic appearance the use of intravascular ultrasound in coronary

arteries has resulted in a significant increase in intra-stent dimensions[2-4]. Dilatation with low-compliant high-pressure oversized balloon has been advocated[5-8].

The present observational intravascular ultrasound study compared the balloon size used with the immediate outcome following stent or stent-graft implantation.

The results show that well-opposed stents can vary in lumen dimensions despite the use of adequately sized balloons. As expected, a good agreement was found between balloon size used and the reference vessel area seen prior to intervention. Irrespective of treated pathology, we found that in 14 of 27 stents a uniform expansion of the stent was achieved; a funnel-like shape was observed in 10 stents, while in three stents both stent edges were larger than the dimension seen within the stent. Moreover, a discrepancy was observed between balloon area and resulting stent area in patients treated for both a stenosis (difference 32%) and for an aneurysm (difference 42%). If, however, diameters were used, the difference between balloon and stent was 18% in patients treated with a stent and 23% in patients treated with a stent-graft combination. These observations concur with others reporting that the balloon diameter used for coronary artery application is larger than the resulting intra-stent diameter (difference 9-25%)[3,4,6-8]. Inadequate stent expansion may be caused by a balloon that is too small for the artery, by compression of the stent by the plaque,[3] or by plaque resistance[8]. Because discrepancy in stent expansion in the present study occurred in patients treated for both stenosis and aneurysm, we postulate that inability to expand the stent to a diameter equal to the balloon diameter is due to either the type of balloon used or the nature of the stent. It is noteworthy that we found a similar under-expansion of the stent using a non-compliant balloon (Powerflex, Cordis Europe BV) (unpublished observations). This suggests that the balloon type used may not influence the outcome of stent deployment. It should be mentioned that, in the present study, the angiographic diameter stenosis (<10%) can not be compared with the area stenosis shown by intravascular ultrasound. If ultrasound diameter stenosis for stent and stent-graft combination was calculated, data (12% and 11%, respectively) were in the same order as the angiographic data. The individual differences seen between intra-stent diameter and reference lumen diameter were, however, indicative for a residual stenosis of >10% in 17 patients (between 10-20% stenosis in 11 patients and between 20-33% in six patients). The significance of this finding for clinical outcome is, however, not addressed in this study.

It is noteworthy that only stents in the subclavian artery reached the dimensions of the balloon size used. We assume this to be due to the oblique position of the ultrasound cathetertip within the arterial wall lumen, as such a position results in an elliptic cross-sectional image in which the lumen area appears to be larger than the actual lumen area. This assumption is supported by the finding that the mean minimal intra-stent diameter seen within the subclavian artery stent (7.8 mm) was

13% smaller than the balloon diameter (9 mm).
Finally, it should be noted that for the present study the nominal size of the balloon was used. However, if its diameter was corrected for the pressure used, the mean expected balloon size increased 11%. This implies an even greater discrepancy between the balloon size used and the resulting intra-stent dimensions.

Limitation
This study was not designed as an outcome study to test whether these criteria predict clinical results after stent insertion. The study compares the ultrasonically assessed reference vessel area and stent area on the one hand, and the manufacturer's specified balloon diameters on the other. The balloon diameter specified by the manufacturer is determined under *in vitro* conditions. Both vessel wall and obstructing plaque, as well as the stent itself, may influence balloon expansion[9].

CONCLUSION
This intravascular ultrasound study shows a discrepancy between the intra-stent lumen dimensions, the dimension of the stent edges and the balloon size used both in patients treated for a stenosis or an aneurysm. This discrepancy is not seen angiographically. Selection of larger balloon size and/or higher pressures than currently used might be warranted in future clinical applications.

REFERENCES

1. Bolz KD, Hatlinghus S, Wiseth R, Myhre HO, Gronningsaeter A: Angiographic and intravascular ultrasonographic findings after endovascular stent implantation. Acta Radiologica 1994;35,6:590-596.
2. Mudra H, Volker K, Blasini R, Kroetz M, Rieber J, Regar E, Theisen K. Ultrasound guidance of Palmaz-Schatz intracoronary stenting with a combined intravascular ultrasound balloon catheter. Circulation 1994;90:1252-1261
3. Goldberg SL, Colombo A, Nakamura S, Almagor Y, Maiello L, Tobis JM. Benefit of intracoronary ultrasound in the deployment of Palmaz-Schatz stents. J Am Coll Cardiol 1994; 24: 996-1003.
4. Nakamura S, Colombo A, Gaglione A, Almagor Y, Goldberg SL, Maiello L, Finci L, Tobis JM. Intracoronary ultrasound observations during stent implantation. Circulation 1994;89:2026-2034.
5. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676-1688.
6. Kiemeneij F, Laarman GJ, Slagboom T. Mode of deployment of coronary Palmaz-Schatz stents after implantation with the stent delivery system: An intravascular ultrasound study. Am Heart J 1995;129:638-644.
7. Kiemeneij F, Laarman GJ, Slagboom T. Percutaneous transradial coronary Palmaz-Schatz stent implantation, guided by intravascular ultrasound. Cathet Cardiovasc Diagn 1995;34:133-136.
8. Bermejo J, Botas J, Garcia EJ, Elizaga J, Soriano J, Abeytua M, Sarnago F, Delcán JL. Mechanisms of residual lumen stenosis after high pressure stent implantation: a QCA and IVUS study. Circulation 1996;94-8:I 1158.
9. Wenguang L, Gussenhoven WJ, Zhong Y, The SHK, Di Mario C, Madretsma S, van Egmond F, de Feyter P, Pieterman H, van Urk H, Rijsterborgh H, Bom N. Validation of quantitative analysis of intravascular ultrasound images. Int J Card Imaging 1991; 6: 247-253.
10. Bergeron P, Pinot JJ, Poyen V, Benichou H, Khanoyan P, Rudony P, Wang Y, Chiarandini S, El Hussein R, Rieu R, Larroude L, Pelissier R. Long-term results with the Palmaz stent in the superficial femoral artery. J Endovasc Surg 1995;2:161-167.
11. von Birgelen C, Gil R, Ruygrok P, Prati F, Di Mario C, van der Giessen WJ, de Feyter PJ, Serruys PW. Optimized expansion of the wallstent compared with the Palmaz-Schatz stent: On-line observations with two- and three-dimensional intracoronary ultrasound after angiographic guidance. Am Heart J 1996;137:1067-1075.

9 STENT REMODELING CONTRIBUTES TO FEMOROPOPLITEAL ARTERY RESTENOSIS:
An intravascular ultrasound study

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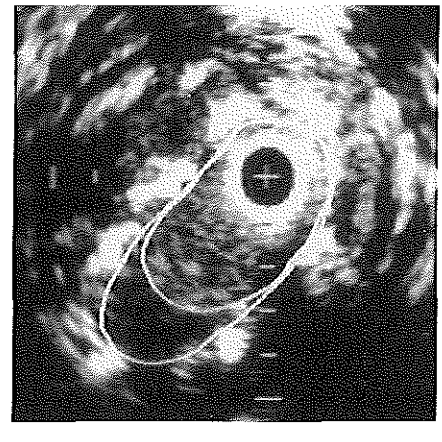

This study was supported by grants from the Netherlands Heart Foundation (91.016) and the Interuniversity Cardiology Institute of The Netherlands.

J Vasc Surg 1997;25:753-756

ABSTRACT

This case report describes the status of femoropopliteal artery stents after intervention documented with intravascular ultrasound compared with the changes seen at follow-up. To treat an extensive dissection following balloon angioplasty, a 57-year-old man received 7 adjacent Palmaz stents. At 5 months follow-up, an angiographic and intravascular ultrasound examination revealed four distinct stenotic lesions (≥50%) at stent junctions. Intravascular ultrasound images obtained during the initial stent placement were compared with the corresponding images obtained at follow-up. A distinction was made between changes seen at stent junctions and stent edges (n=8), those seen within each stent (n=7), and those in the nonstented sections proximally and distally (n=3). Intravascular ultrasound established that both intimal hyperplasia and stent area reduction (stent remodeling) resulted in lumen area reduction. The extent of the changes seen at the stent junctions were greater than those seen within the stents: lumen area reduction, 67% vs 23%; stent area reduction, 26% vs 11%; and intimal hyperplasia, 10.8 vs 3.3 mm^2; respectively. Changes in the non-stented sections were minimal (<2%). The stent edge seen at the adductor canal showed elliptical deformation.

Thus, there is a higher risk of restenosis at stent junctions. In addition to intimal hyperplasia, stent remodeling contributes to restenosis.

INTRODUCTION

Stents were developed to improve instant and long-term results of balloon angioplasty. Recently, it has been shown that geometric arterial remodeling (decrease of total arterial cross-sectional area) may be the dominant factor contributing to restenosis following balloon angioplasty[1]. It is assumed that stents may reduce restenosis by eliminating this geometric remodeling[2]. This assumption is supported by serial intravascular ultrasound analysis after stent placement in coronary arteries, showing that late recoil of the Palmaz-Schatz stent rarely occurred and, when it did, late stent recoil was minimal. The dominant mechanism of late lumen loss was intimal hyperplasia[3]. The present report describes the changes encountered in the restenosis process after stent placement in the femoropopliteal artery.

CASE REPORT

A 57-year-old man underwent percutaneous transluminal angioplasty (PTA) of the left femoropopliteal artery for treatment of intermittent claudication. Two short, subtotal stenoses (≥90%) in the proximal and distal third of the thigh were dilated using a 6-mm balloon (OPTA, Cordis Europe, Roden, the Netherlands). Because the stenoses persisted, an additional PTA was preformed. This second procedure was complicated by an extensive 22 cm long dissection evidenced by angiographic examination. It was decided that the dissection would be treated with Palmaz stents (P394, Johnson & Johnson Interventional Systems, Warren, NJ). After stent placement, an intravascular ultrasound scan was performed using a commercially available mechanical 30 MHz imaging system (Endosonics, Rijswijk, the Netherlands). Details of this system have been described previously[4]. The ultrasound catheter was advanced over a guidewire distally. Under fluoroscopic control, the location of the cathetertip was compared with a radiopaque ruler.

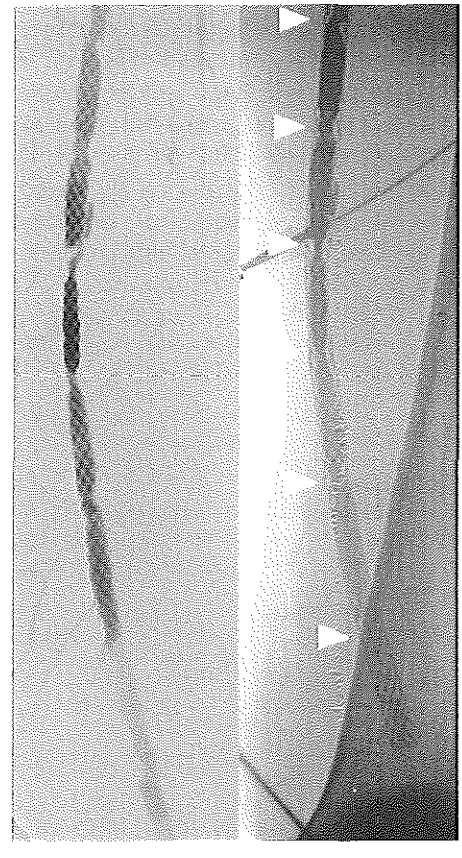

Fig. 1. Angiogram of the left superficial femoral artery obtained at 5 months follow-up. Arrowhead = Stent junctions.

During pull-back, a displacement sensing device was used to document the position of the ultrasound catheter

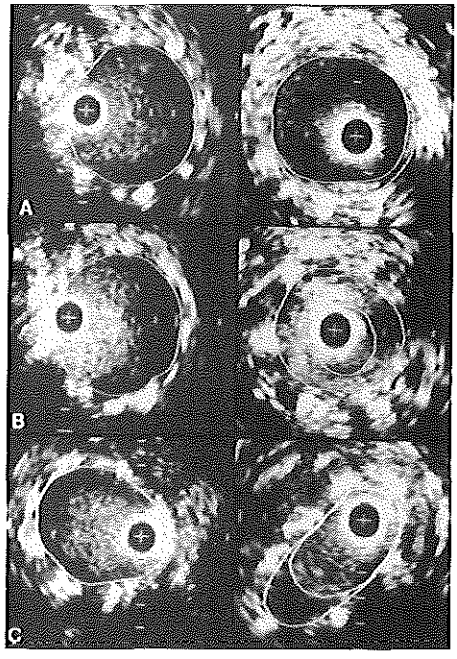

Fig. 2. Matched intravascular ultrasound cross-sections of the femoropopliteal artery obtained after stent deployment (*left panels*) and at 5 months follow-up (*right panels*). The lumen area (*inner contour*) and stent area (*outer contour*) display the quantitative results. **A**, In-stent changes were minimal. **B**, Intimal hyperplasia and stent area reduction (remodeling) were the predominant mechanisms responsible for restenosis seen at the stent junctions. **C**, Distally remodeling of the stent in the region of the adductor canal hiatus.
+ = Catheter; calibration, 1 mm.

automatically on the video monitor[5]. The images were stored on an S-VHS videotape. For quantitative analysis a digital video analysis system was used[6]. Analysis included measurement of stent area (area within the stent), and stent diameter. To repair the entire dissection seven stents were placed with overlap, which resulted in a stented segment of 22 cm. Angiographic and intravascular ultrasound examination following stent placement showed a satisfactory result. On intravascular ultrasound the mean stent diameter seen was 5.9 mm (range, 4.8 - 6.3 mm). After the procedure the patient was prescribed 80 mg aspirin daily.

Five months after undergoing PTA the patient was referred for recurrent symptoms of disabling claudication. Duplex scanning showed multiple stenoses in the stented area. The angiogram showed 4 distinct stenotic sites located at the stent junctions with diameter stenosis of ≥50% (Fig. 1). Intravascular ultrasound was repeated, and the images were analyzed for lumen area and diameter, stent area, lesion area, and percentage area stenosis. Lesion area was calculated by subtracting lumen area from stent area. The percentage area stenosis was calculated as lesion area divided by stent area. The stenotic lesions were confirmed by intravascular ultrasound imaging; lumen diameter in these stenoses ranged from 2.5 - 3.1 mm. Segment-to-segment comparisons were made of the intravascular ultrasound images obtained immediately after the first intervention and at 5 months follow-up to reveal the changes that occurred. A distinction was made between measurements at the stent junctions and stent edges ('junctions'), inside the stents ('in-stent'), and in the nonstented reference sections proximally and distally. Quantitative data on lumen area, stent area, lesion area, and percentage area stenosis seen on intravascular ultrasound are listed in Table 1.

Table 1. Quantitative intravascular ultrasound data obtained from femoropopliteal artery stents immediately after placement and at 5 months follow-up.

	Junctions (n=8)				In-stent (n=7)			
	mean	range			mean	range		
Post intervention								
Stent area (mm²)	26.5	17.9	to	31.1	26.6	21.6	to	28.7
At follow-up								
Lumen area (mm²)	8.8	5.0	to	15.2	20.5	16.5	to	23.1
Stent area (mm²)	19.6	12.4	to	21.6	23.8	19.9	to	27.4
Lesion area (mm²)	10.8	4.7	to	20.2	3.3	0.7	to	6.0
Area stenosis (%)	53.0	2.8	to	77.0	14.0	3.0	to	25.0

n = number of cross-sections.

Both intimal hyperplasia (lesion area) and geometric remodeling of the stent (stent area reduction) were common findings responsible for lumen area reduction. The extent of lumen area reduction, intimal hyperplasia, and stent area reduction was more severe at the stent junctions compared with the changes seen inside the stent (Fig. 2). At the most stenotic site seen angiographically, intimal hyperplasia (57%) and stent area reduction (43%) contributed to lumen area reduction evidenced on intravascular ultrasound. The degree of intimal hyperplasia and stent area reduction seen at the most proximal stent edge was in the same order as seen at the stent junctions. At the most distal stent edge, near the adductor canal hiatus, intimal hyperplasia was minimal and the stent showed a distinct elliptical deformation (Fig. 2). The changes seen in the nonstented reference sections were minimal (<2%).

DISCUSSION

It is reported that the placement of Palmaz stents in the iliac arteries is a satisfactory alternative to surgery, whereas placement in the femoropopliteal artery is still controversial[7,8]. Serial intravascular ultrasound studies have shown that the mechanism related to restenosis after angiographically successful placement of stents in coronary arteries is progressive intimal hyper-plasia[3]. Recently, Khosla et al.[9] investigated with quantitative angiographic examination the mechanisms of restenosis after renal artery stenting. They reported that, in addition to tissue growth, significant stent recoil contributed to the late lumen loss (stent area reduction range, 25-41%). The present study revealed, both

angiographically and on intravascular ultrasound examination, that restenosis occurred at the junctions from one stent to the other. On intravascular ultrasound examination, lumen area reduction was 67% at stent junctions and 23% inside the stents. The mechanisms that are related to restenosis evidenced with intravascular ultrasound included intimal hyperplasia and stent area reduction. The decrease in stent area was larger at the stent junctions (26%) than seen within the stent (11%). Similarly, the extent of intimal hyperplasia at stent junctions was larger (10.8 mm^2) than that evidenced inside the stent (3.3 mm^2). We assume that stent remodeling may be caused by mechanical forces as a result of stent articulation at the junctions. The large amount of intimal hyperplasia at the junctions may be explained by the reaction of the vessel wall to these forces. It is noteworthy that changes seen in the nonstented reference sections were minimal. It was found that the stent placed in the vicinity of the adductor canal hiatus showed an elliptical shape at 5 months follow-up. It has been postulated that the femoropopliteal artery undergoes external compression in the region of the adductor canal hiatus[10, 11]. A stent placed at this location may be subjected to external pressure and consequently deform. This observation is validated by an in vitro study showing that Palmaz stents can exhibit permanent plastic deformation under pressure and that the stents may undergo eccentric narrowing[12].
The present study shows that, in addition to intimal hyperplasia, stent remodeling contributes to restenosis. This remodeling consists of a decrease in stent circumference seen at the stent junctions, and elliptical deformation at the adductor canal. This case report provides evidence that there is a higher risk of restenosis at stent junctions. For this reason, surgeons should consider using one long stent rather than multiple stents for treatment of extensive dissection.

REFERENCES

1. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty; a study in the normal rabbit and the hypercholesterolemic Yucatan micropig. Circulation 1994;89:2816-21.
2. Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, Chin Wong S, et al. Endovascular stents reduce restenosis by eliminating geometric arterial remodeling: A serial intravascular ultrasound study. J Am Coll Cardiol 1995;25:36A.
3. Painter JA, Mintz GS, Chiu Wong S, Popma JJ, Pichard AD, Kent KM, et al. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. Am J Cardiol 1995;75:398-400.
4. Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88.
5. Gussenhoven EJ, van der Lugt A, van Strijen M, Li W, The SHK, van Egmond FC, et al. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N, eds. Intravascular Ultrasound. Dordrecht: Kluwer Academic Press, 1993:157-66.
6. Wenguang L, Gussenhoven WJ, Zhong Y, The SHK, Di Mario C, Madretsma S, et al. Validation of quantitative analysis of intravascular ultrasound images. Int J Card Imaging 1991;6:247-53.
7. Henry M, Amor M, Ethevenot G, Henry I, Amicabile C, Beron R, et al. Palmaz stent placement in iliac and femoropopliteal arteries: Primary and secondary patency in 310 patients with 2-4 years follow-up. Radiology 1995;197:167-74.
8. White GH, Liew SC, Waugh RC, Stephen MS, Harris JP, Kidd J, et al. Early outcome and intermediate follow-up of vascular stents in the femoral and popliteal arteries without long-term anticoagulation. J Vasc Surg 1995;21:270-9; discussion 279-81.
9. Khosla S, Shaw D, McCarthy N, Collins TJ, Jenkins JS, White CJ, et al. Mechanism of restenosis following stenting of renal arteries with nonarticulated Palmaz Stents. J Am Coll Cardiol 1996;27:111A.
10. Scholten FG, Warnars GA, Mali WP, van Leeuwen MS. Femoropopliteal occlusions and the adductor canal hiatus, Duplex study. Eur J Vasc Surg 1993;7:680-3.
11. The SHK, Wilson RA, Gussenhoven EJ, Pieterman H, Bom K, Roelandt JRTC, et al. Extrinsic compression of the superficial femoral artery at the adductor canal: evaluation with intravascular sonography. Am J Roentgenology 1992;159:117-20.
12. Lossef SV, Lutz RJ, Mundorf J, Barth KH. Comparison of mechanical deformation properties of metallic stents with use of stress-strain analysis. J Vasc Interv Radiol 1994;5:341-9.

10 MEMOTHERM IN-STENT RESTENOSIS DUE TO INTIMAL HYPERPLASIA: An intravascular ultrasound study

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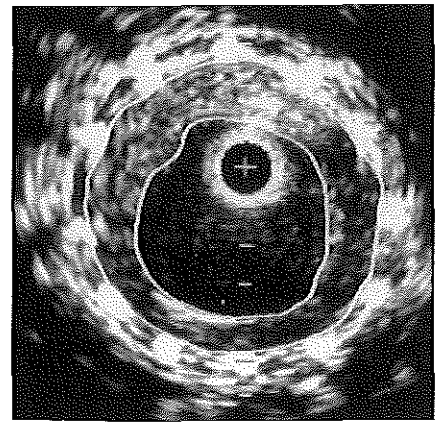


This study was supported by grants from the Netherlands Heart Foundation (91.016), the Interuniversity Cardiology Institute of the Netherlands and the Sorbo Heart Foundation

J Ang Vasc Surg 1998;4:54-58

ABSTRACT

In a previous serial intravascular ultrasound study we established that lumen area reduction in Palmaz stents placed in the superficial femoral artery was the result of both intimal hyperplasia and stent area reduction; a higher degree of restenosis was found at stent junctions. In the present study the changes seen on intravascular ultrasound immediately after placement of 2 Memotherm stents and at 11 months follow-up in a patient with a subtotal stenosis of the superficial femoral artery, were documented. Restenosis occurred at the stent junction and was the result of intimal hyperplasia. The degree of intimal hyperplasia at the stent junction (26.9 mm^2) was larger than seen at the stent edges (21.2 mm^2) and inside the stents (12.0 mm^2), and resulted in a percentage area stenosis of 80%, 57% and 37%, respectively. Stent/vessel area enlargement was evidenced at the stent junction (9%), at the stent edges (16%), and in the adjacent reference segments proximally and distally (9%).

This intravascular ultrasound study showed that restenosis in Memotherm stents occurred at the stent junction. Intimal hyperplasia was the sole factor contributing to restenosis.

INTRODUCTION

Use of stents within coronary and peripheral vessels continues to increase exponentially. It is assumed that stents may reduce restenosis by eliminating the important factor contributing to restenosis following balloon angioplasty: arterial remodeling (decrease of total arterial cross-sectional area)[1,2]. This assumption is supported by serial intravascular ultrasound analysis after stent placement in coronary arteries[3], showing that late recoil of the Palmaz stent rarely occurred and, when it did, late stent recoil was minimal. The dominant mechanism of late lumen loss was intimal hyperplasia. In a previous study we established that both intimal hyperplasia and stent area reduction contributed to restenosis in Palmaz stents placed in the femoropopliteal artery[4]. The present study with intravascular ultrasound describes the development of restenosis following Memotherm stent placement in the superficial femoral artery.

CASE REPORT

A 46-year-old man underwent percutaneous transluminal angioplasty (PTA) of the left superficial femoral artery for treatment of intermittent claudi-cation. Angiography and intravascular ultrasound (IVUS) revealed a 5 cm long subtotal stenosis (≥90%) in the distal third of the superficial femoral artery, that was dilated with a 4 mm balloon (OPTA, Cordis Europe, Roden, the Netherlands). In order to obtain additional lumen gain and preserve luminal patency, Memotherm stents (Angiomed, BARD, Karlsruhe, Germany) were implanted and adjunctively dilated with a 6-mm balloon

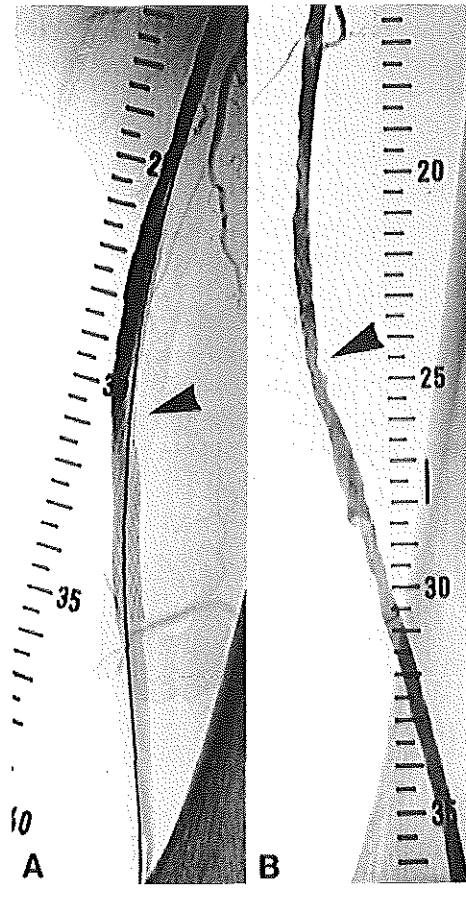


Fig. 1. Angiogram of the left superficial femoral artery obtained after stent placement (A) and at 11 months follow-up (B). Arrowhead = stent junction.

(OPTA, Cordis Europe, Roden, the Netherlands). Two stents (4 and 7 cm length, 7 mm in diameter) were placed with a one centimeter overlap, resulting in a stented segment of 10 cm. Following stent placement, intravascular ultrasound was performed using a commercially available mechanical 30 MHz imaging system (Endosonics, Rijswijk, the Netherlands). Details of this system have

been described previously[5]. The ultrasound catheter was advanced over a guidewire distally. Under fluoroscopic control, the location of the cathetertip was registered with a radiopaque ruler. During pull-back, a displacement sensing device was used to document the position of the ultrasound catheter automatically on the video monitor[6]. The intravascular ultrasound images were stored on an S-VHS videotape. For quantitative analysis a digital video analysis system was used[7]. Analysis included assessment of stent diameter and area measurements.

Angiography and intravascular ultrasound following stent placement showed a satisfactory result (Figs. 1 and 2). On intravascular ultrasound the mean stent diameter was 6.5 mm (range 6.2 - 6.8 mm). After the procedure the patient received 80 mg aspirin daily.

Eleven months after PTA the patient was referred for recurrent symptoms of disabling claudication. Duplex scanning showed a significant stenosis in the stented area. The angiogram showed a distinct stenotic site

located at the stent junction with a diameter stenosis of 70% (Fig. 1). To reveal the quantitative changes that occurred, intravascular ultrasound images obtained immediately after the first intervention were compared with corresponding images at 11 months follow-up. Images were analyzed for lumen area, stent/vessel area, stent diameter, plaque area, and percentage area stenosis. Vessel area was measured in the non-stented segments instead of stent area. Plaque area was calculated by subtracting lumen area from stent/vessel area. The percentage area stenosis was calculated as plaque area divided by stent/vessel area. A distinction was made between measurements at the stent junction, stent edges, inside the stents ('in-stent'), and in the adjacent non-stented reference sections proximally and distally.

The mean stent diameter seen on IVUS was 6.5 mm (range 6.0 - 7.4 mm).

Table 1. Changes in quantitative intravascular ultrasound data obtained immediately after Memotherm stent placement in the superficial femoral artery and at 11 months follow-up.

	Junction (n=1)	**Edge** (n=2)	**In-stent** (n=6)	**Reference** (n=4)
Lumen area	- 78%	- 50%	- 40%	- 6%
Stent/vessel area	+ 0.09	+ 16%	- 3%	+ 9%
Area stenosis	+ 0.8	+ 57%	+ 37%	+ 23%
Plaque area	+ 26.9 mm^2	+ 21.2 mm^2	+ 12.0 mm^2	+ 4.3 mm^2

n= number of cross-sections; - = decrease; + = increase.

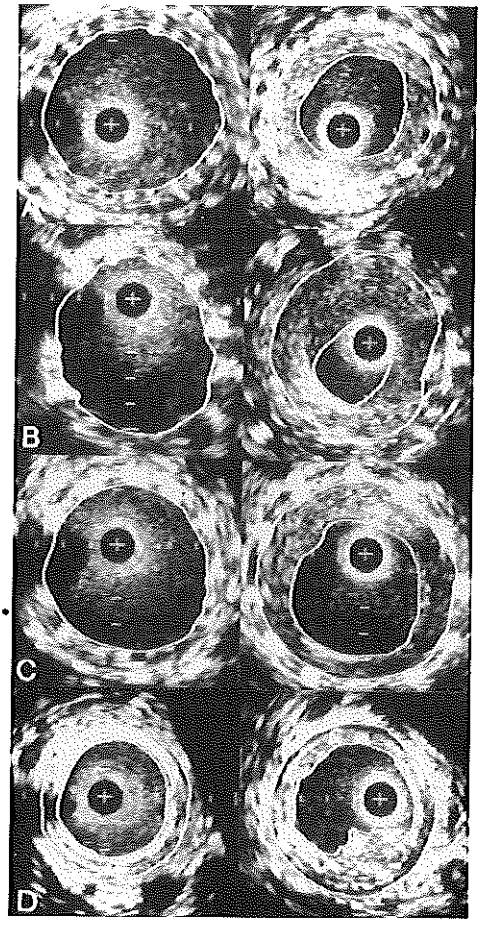


Fig. 2. Matched intravascular ultrasound cross-sections of the superficial femoral artery obtained immediately after stent deployment (*left panels*) and at 11 months follow-up (*right panels*). The lumen area (inner contour) and stent area (outer contour) are responsible for the quantitative results. **A,** Some intimal hyperplasia is seen in the stent. **B,** Intimal hyperplasia is the dominant mechanism responsible for restenosis seen at the stent junction. Besides, stent area enlarged. **C,** At the stent edge, intimal hyperplasia and stent area enlargement are seen. **D,** At the reference segment, vessel area enlargement is evident.
+ = catheter; calibration = 1 mm.

Quantitative changes seen on intravascular ultrasound in lumen area, stent/vessel area, percentage area stenosis, and plaque area between data obtained after intervention and at 11 months follow-up are given in Table 1. At the most stenotic site seen angiographically, intravascular ultrasound revealed that intimal hyperplasia was solely responsible for lumen area reduction. The extent of intimal hyperplasia was largest at the stent junction (26.9 mm^2) compared with the changes seen at the edges (21.2 mm^2) and inside the stent (12.0 mm^2) (Fig. 2). Besides intimal hyperplasia, a distinct stent area enlargement was evidenced both at the most stenotic site (9%) and at the stent edges (16%). Similarly, vessel area of the reference segments increased 9%, while intimal hyperplasia at this site was minimal (4.3 mm^2; 36%).

DISCUSSION

The use of endovascular stents has shown to improve the initial technical success of peripheral balloon angioplasty by minimizing flow disturbances[8]. Despite short-term (6 months) clinical benefit maintained in most patients, a high incidence of restenosis and reocclusion is reported in patients with long-segment superficial femoral artery disease[8]. However, the mechanism of restenosis within stents placed in a diversity of vascular sites seems to vary. The development of restenosis following renal artery stenting evidenced with quantitative angiography is attributed to intimal hyperplasia and significant stent recoil[9]. Intravascular ultrasound studies have shown that the mechanism related to restenosis in stents placed in coronary

arteries is progressive intimal hyperplasia[3]. In contrast, stent compression was identified as the principal cause of restenosis in stents placed in the superficial femoral arteries and in dialysis conduits[10]. Recently, van Lankeren et al.[4] established that in addition to intimal hyperplasia, stent compression contributed to restenosis, particularly at stent junctions.

The present study with intravascular ultrasound established that the major cause of restenosis in Memotherm stents was intimal hyperplasia. The extent of intimal hyperplasia was larger at the stent junction (26.9 mm^2) than at the stent edges (21.2 mm^2) and in the stent (12.0 mm^2). The large amount of intimal hyperplasia at the junction may be explained by the reaction to mechanical forces of stent articulation at the stent junction.

Whereas stent compression (i.e. stent area decrease) was documented in balloon expandable stents, in the present study stent area enlargement was seen, predominantly at the stent edges (16%). This finding may be related to the temperature induced pre-determined size of the Memotherm stent. It is noteworthy, however, that the mean stent diameter on IVUS, both after initial stent placement (6.5 mm) and at follow-up (6.5 mm), was smaller than the predetermined size (7.0 mm).

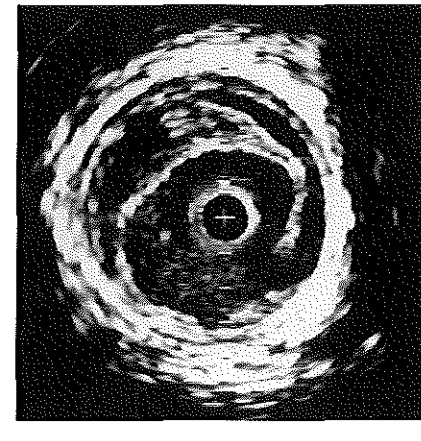
In this study we did not encounter compression of the Memotherm stent in the region of the adductor canal hiatus as previously reported in Palmaz stents[4]. It is noteworthy that whereas stent area increased, vessel area of the reference site proximally and distally to the stent also increased (9%) which compensated for the increase in plaque area at the reference segments. To our knowledge, this finding has not been described previously.

The present study showed a controversial reaction with regard to restenosis in Memotherm and Palmaz stent. Intimal hyperplasia solely contributed to restenosis in Memotherm stents and there was a higher risk of restenosis at the stent junction. For this reason, the use of one long stent rather than multiple stents should be considered.

REFERENCES

1. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty; a study in the normal rabbit and the hypercholesterolemic Yucatan micropig. Circulation 1994;89:2816-21.
2. Mintz GS, Pichard AD, Kent KM, et al. Endovascular stents reduce restenosis by eliminating geometric arterial remodeling: A serial intravascular ultrasound study. J Am Coll Cardiol 1995;25:36A.
3. Painter JA, Mintz GS, Chiu Wong S, et al. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. Am J Cardiol 1995;75:398-400.
4. van Lankeren W, Gussenhoven EJ, van Kindts MJ, et al. Stent remodeling contributes to femoropopliteal artery stenosis: An intravascular ultrasound study. J Vasc Surg 1997;25:753-6.
5. Bom N, Hoff ten H, Lancée CT, et al. Early and recent intraluminal ultrasound devices. Int J Cardiac Imaging 1989;4:79-88.
6. Gussenhoven EJ, van der Lugt A, van Strijen M, et al. Displacement sensing device enabling accurate documentation of catheter tip position. In: Roelandt J, Gussenhoven EJ, Bom N, eds. Intravascular Ultrasound. Dordrecht: Kluwer Academic Press, 1993:157-66.
7. Wenguang L, Gussenhoven WJ, Zhong Y, et al. Validation of quantitative analysis of intravascular ultrasound images. Int J Card Imaging 1991;6:247-53.
8. Gray BH, Sullivan TM, Childs M, et al. High incidence of restenosis/reocclusion of stents in the percutaneous treatment of long-segment superficial femoral artery disease after suboptimal angioplasty. J Vasc Surg 1997;25:74-83.
9. Khosla S, Shaw D, McCarthy N, et al. Mechanism of restenosis following stenting of renal arteries with nonarticulated Palmaz Stents. J Am Coll Cardiol 1996;27:111A.
10. Rosenfield K, Schainfeld R, Pieczek A, et al. Restenosis of endovascular stents from stent compression. J Am Coll Cardiol 1997;29:328-38.

11 SUMMARY SAMENVATTING



Summary

Summary

Restenosis following vascular intervention is considered the major drawback in the treatment of obstructive atherosclerotic disease. As indicated in **chapter 1**, the problem of restenosis has been extensively described in the literature. Histologic and intravascular ultrasound (IVUS) studies performed in animals and humans gave us information about the nature of the stenotic process. Subsequently, longitudinal IVUS studies, performed at two points in time provided an improved insight in the morphologic and quantitative changes following vascular intervention, and the mechanism of restenosis. The IVUS studies described in this thesis were performed in vitro and in a clinical setting in order to address the following questions:

1. What patterns of vascular remodeling are encountered in atherosclerotic coronary arteries studied in vitro?
2. What is the effect of balloon angioplasty of the iliac artery as assessed with IVUS both in vitro and in vivo?
3. What is the level of agreement between angiographically and with IVUS obtained morphologic and quantitative parameters before and after balloon angioplasty of the femoropopliteal artery?
4. Which factors are responsible for the change in lumen area, seen in a longitudinal study, following balloon angioplasty of the femoropopliteal artery?
5. Can IVUS improve our understanding of the long-term effects of peripheral balloon angioplasty and stent placement?

Chapter 2 explores the phenomenon of atherosclerosis and associated vascular remodeling. In this in vitro study, IVUS was used to investigate the nature of remodeling in human coronary arteries. Using regression analysis a positive relationship was found between vessel and plaque areas both at the target site and the reference site. These findings were in accordance with the study of Glagov et al. However, when the vessel area at the target site was compared with the vessel area at the reference site, it was found that both enlargement and reduction (i.e. shrinkage) of the vessel area could occur. In other words, regression analysis was unable to discern shrinkage of the vessel area as the cause of lumen area narrowing at the target site. It was concluded that an adequate method to analyze the relationship between the progression of atherosclerosis and vessel remodeling should entail a longitudinal prospective IVUS study (vide infra chapter 6).

Chapter 3 presents an in vitro study on 40 human iliac artery specimens. Data acquired with IVUS before and after balloon angioplasty were compared with their histologic counterparts. Following intervention morphologic and quantitative changes documented at the most stenotic site were compared with data derived from all corresponding IVUS cross-sections of the dilated vascular specimen. This study showed that the sensitivity of IVUS to detect a dissection was high (74%), but was moderate for media rupture (59%). Dissections occurred, unrelated to plaque calcification, at the thinnest region of the plaque. Following balloon angioplasty, the

quantitative changes seen at the most stenotic site were greater than the overall data derived from all corresponding cross-sections. Lumen area increase was solely caused by vessel stretch.

Chapter 4 presents a comparison between morphologic and quantitative data derived angiographically and with IVUS, before and after balloon angioplasty of the femoropopliteal artery. IVUS detected more lesions, calcified lesions and vascular damage than angiography. The sensitivity of angiography was good for the presence of lesions (84%), moderate for eccentric lesions (53%) and for vascular damage (52%), and poor for calcified lesions (30%). Compared to IVUS, the presence of a lesion and the degree of stenosis were underestimated angiographically. More importantly, quantitative IVUS analysis comparing different groups of angiographic diameter before PTA revealed that the decrease in lumen area was the net result of a decrease in vessel area and, to a lesser extent, to an increase in plaque area. This observation supports other IVUS studies reporting that vessel wall shrinkage or failure to enlarge vessel area in combination with plaque area increase, contribute to lumen narrowing in the femoropopliteal artery. Therapeutical consequences of this finding are merely speculative. In the measurements taken before PTA a good agreement was found between angiographic diameter stenosis and lumen size demonstrated on IVUS, but such agreement was not seen after PTA. This finding may be related to the vascular damage after PTA, which allows contrast filling of the dissection clefts, distorting the luminal silhouette of the angiogram. This may be the underlying reason why angiographic diameter stenosis assessed after PTA is not predictive for outcome of the intervention.

Chapter 5 presents a clinical study with IVUS in order to document the arterial response of the iliac artery following balloon angioplasty. Twenty one patients who underwent PTA for treatment of symptomatic obstructive disease of the iliofemoral artery were studied before and immediately after balloon angioplasty. A distinction was made between IVUS images obtained from the common iliac and those from the external iliac artery. First, analogous to the previous in vitro study (chapter 3), the morphologic and quantitative changes seen after intervention at the most stenotic site were compared with data derived from all corresponding IVUS cross-sections of the dilated segment. Second, the predictive value of IVUS parameters for the patient outcome was assessed. This study established that although the common iliac artery is larger than the external iliac artery, the morphologic and quantitative effects of balloon angioplasty are similar in both types of artery. Vascular damage was documented in 81% of the patients. Dissection, the most common feature encountered, usually occurred at the thinnest region of the lesion involved. In addition no significant relation was found between morphology or topography and the occurrence or location of dissection. The frequency of vascular damage at the most stenotic site was only slightly less than in each dilated segment (79% and 88%, respectively).

Similarly as seen in the vitro study of the iliac artery (chapter 3), lumen area increase after intervention was associated with vessel area increase, whereas plaque area decreased slightly. The changes seen at the most stenotic site were larger than those at the dilated segment. Finally, both the size of the lumen area and the degree of area stenosis seen at the most stenotic site after intervention seen with IVUS tended to be predictive of patient outcome.

Chapter 6 presents a prospective study on 20 patients using IVUS to document the change in lumen area immediately after balloon angioplasty of the femoropopliteal artery and at follow-up. For this purpose, multiple corresponding IVUS cross-sections of the dilated vascular segment (i.e. the treated site) including the most stenotic site and non-dilated segment (i.e. the reference site) were analyzed. This study revealed that, at the most stenotic site, lumen narrowing at follow-up was caused by plaque increase (48%) and vessel shrinkage (52%). It is worth mentioning that the extent of plaque area increase seen at the most stenotic site was similar to that seen in the cross-sections derived from the treated site and reference site (13% and 15%, respectively). Vessel area did not change at the treated site (+1%) and increased slightly at the reference site (6%). Analysis of IVUS cross-sections grouped according to lumen area change revealed a similar increase in plaque area in all groups: the type of vascular remodeling (vessel area decrease, no change in vessel area, or vessel area increase) determined lumen area change. At the treated site there was a close correlation between lumen area change and vessel area change. The extent of plaque area increase was significantly larger in IVUS cross-sections showing a hard lesion or a media rupture. No relation was found between dissection and quantitative changes seen at follow-up. Because lumen narrowing was the net result of plaque area increase and vessel area decrease, it was concluded that future research should be aimed at eliminating both plaque growth and vascular shrinkage.

In **Chapter 7** the difference in vascular response in the treated lesions showing restenosis (i.e. restenotic lesions) and in the treated lesions showing no restenosis (i.e. non-restenotic lesions) seen 1-year following PTA of the femoropopliteal artery was demonstrated using IVUS. In this study 31 stenotic lesions of the femoropopliteal artery derived from 24 patients were successfully treated with PTA. The IVUS cross-section with the smallest lumen area at the angiographic target site before PTA and the corresponding cross-section after PTA and at follow-up were selected for analysis of lumen, plaque and vessel area. Based on the lumen area distribution at follow-up a lumen area <11.0 mm^2 seen on IVUS at 1-year follow-up was considered a restenotic lesion. It was found that at follow-up 19 of the 31 lesions (61%) were restenotic. Comparison of mean quantitative data showed that lumen area in restenotic lesions decreased, while in non-restenotic lesions lumen area increased. Both groups showed a similar increase in plaque area. Whereas in the restenotic lesions vessel area decreased, in the non-

restenotic lesions vessel area increased, resulting in a significant difference in vessel area between both groups at follow-up. The use of smaller balloons was associated with a significant higher incidence of restenosis: 11 of 12 lesions dilated with a 5 mm balloon and 8 of 17 lesions dilated with a 6 mm balloon presented restenosis. The 2 lesions dilated with a 7 mm balloon did not develop restenosis. It was concluded that at 1-year follow-up restenotic and non-restenotic lesions showed a similar amount of plaque increase and restenosis was determined by the type of vascular remodeling (vessel area decrease or increase).

Chapter 8 addresses the role of IVUS in the evaluation of peripheral stent placement. In this retrospective study, 27 patients treated with a balloon expandable stent for a stenosis or a stent-graft for an aneurysm combination were investigated with IVUS. After angiographic optimal stent placement, the smallest intra-stent lumen area seen with IVUS was compared with the area measurements of both stent edges, and the lumen areas of the proximal and distal reference sites. In 13 of the 27 stents the intra-stent dimension was smaller than the proximal and/or distal stent edge (difference >10%) both in patients treated for stenosis or an aneurysm. In all stents and stent-graft combinations IVUS showed that the smallest intra-stent lumen area was smaller than the balloon size used and smaller than the mean lumen area of the reference site. The observed discrepancy between the expansion of the stent and the balloon size used might warrant the selection of larger balloons and/or higher inflation pressures than currently used.

Chapter 9 discusses the ability of IVUS to document the changes that occur 5 months after placement of balloon expandable stents in the femoropopliteal artery. In this case report, a male patient who received 7 adjacent Palmaz stents to treat an extensive dissection following balloon angioplasty developed restenosis at 5 months follow-up. At follow-up angiography and IVUS revealed 4 significant stenoses at the stent junctions. IVUS images obtained immediately after stent placement were compared with the corresponding IVUS images at follow-up: lumen area decrease, stent area decrease and intimal hyperplasia were greater at the stent junctions than within the stents. The changes in the adjacent non-stented vascular segments were minimal. Moreover, the stent in the adductor canal showed elliptical deformation. This IVUS study demonstrated that both stent area decrease (remodeling of the stent) and intimal hyperplasia result in lumen area decrease.

Similarly, **chapter 10** discusses the changes seen with IVUS that occurred 11 months after placement of self-expandable Memotherm stents. This male patient was treated with 2 Memotherm stents for severe stenosis (≥90% diameter stenosis) of the femoropopliteal artery. At 11 months the patient was referred for recurrent symptoms of disabling intermittent claudication. Both angiography and IVUS demonstrated restenosis at the stent junction. The degree of intimal hyperplasia seen at the stent junction

was larger than at the stent edges and within the stent. Stent area increase was seen both at the stent junction and at the stent edges. Besides, vessel area increase was seen in the adjacent non-stented reference vascular segments. Thus, in the presence of stent enlargement IVUS revealed that restenosis seen at the junction of the 2 Memotherm stents occurred solely due to intimal hyperplasia.

In summary, the IVUS studies in this thesis contributed to the knowledge on the effect of peripheral vascular interventions and the mechanism related to lumen decrease following these procedures. Knowledge and understanding of the mechanism of the restenosis process based on IVUS is essential for the development of new therapeutic strategies for obstructive disease of peripheral arteries.

Samenvatting

Een van de grootste problemen in de behandeling van atherosclerotische vaatziekte is het opnieuw optreden van vaatvernauwing (restenose) na een aanvankelijk succesvolle behandeling. In **hoofdstuk 1** komt duidelijk naar voren dat er op het gebied van restenose zeer veel gepubliceerd is. Inmiddels is er gebaseerd op onderzoek van histologische coupes en intravasculaire echografie (IVUS) in mens en dier veel duidelijk geworden over de aard van het restenose proces. Het inzicht in dit proces is verder verbeterd doordat er vervolgens longitudinale IVUS studies zijn uitgevoerd. Met deze studies, uitgevoerd op twee verschillende tijdstippen waren we in staat om de morfologische en kwantitatieve veranderingen vast te stellen, die plaatsvonden direct na een vasculaire behandeling en het mechanisme van de daaropvolgende restenose.

De IVUS studies, behandeld in dit proefschrift, werden uitgevoerd in-vitro en in-vivo om antwoord te geven op de volgend vragen:

1. Welk aspect heeft vaatwand remodellering in atherosclerotische coronaire vaten?
2. Wat is het effect van ballondilatatie op de arteria iliaca?
3. In hoeverre Samenvatting komen morfologische en kwantitatieve parameters verkregen met angiografie en IVUS voor en na ballondilatatie van de arteria femoralis superficialis en arteria poplitea met elkaar overeen?
4. Welke factoren zijn verantwoordelijk voor de veranderingen van het lumenoppervlak een jaar na ballondilatatie van de arteria femoralis superficialis en arteria poplitea?
5. Kan IVUS een beter inzicht geven in de lange termijn effecten van ballondilatatie en stentplaatsing in perifere bloedvaten?

In **hoofdstuk 2** wordt het fenomeen atherosclerose met daarmee samenhangende vaatwand remodellering beschreven. In deze in-vitro studie werd IVUS gebruikt om de aard van het remodelleren van coronaire vaten te onderzoeken. Door middel van regressie analyse werd aangetoond dat er een positieve relatie bleek te zijn tussen vaat- en plaqueoppervlak zowel ter plaatse van de vernauwing als ter hoogte van het referentiesegment. Deze resultaten stemden overeen met de onderzoeksresultaten van Glagov et al. Door het vaatoppervlak ter plaatse van de vernauwing te vergelijken met dat van het referentiesegment bleek dat er zowel een vergroting als een verkleining (krimp) van het vaatoppervlak kon plaatsvinden. Met andere woorden, regressie analyse was niet in staat om krimp van vaatwand te onderscheiden als oorzaak van lumen vernauwing. Geconcludeerd werd dat de relatie tussen het voortschrijden van atherosclerose en vaatwand remodellering beter geanalyseerd kan worden in een longitudinaal prospectief studiemodel door middel van IVUS (vide infra Hoofdstuk 6).

Hoofdstuk 3 beschrijft een in-vitro studie in 40 segmenten van de arteria iliaca waarin IVUS-beelden, verkregen voor en na ballondilatatie, werden vergeleken met histologische coupes.

Aansluitend aan de interventie werden de morfologische en kwantitatieve veranderingen ter plaatse van de dwarsdoorsnede met het nauwste lumen vergeleken met de gegevens van alle corresponderende dwarsdoorsneden van het totale gedilateerde vaatsegment. Deze studie liet een hoge sensitiviteit zien van IVUS om een dissectie aan te tonen (74%), maar een matige sensitiviteit om een mediaruptuur vast te stellen (59%). Dissecties werden voornamelijk aangetroffen op het dunste deel van de lesie en waren niet gerelateerd aan de samenstelling van de lesie. Na ballondilatatie waren de kwantitatieve veranderingen ter plaatse van het nauwste lumen groter dan berekend over het totale gedilateerde vaattraject. Vergroting van het lumenoppervlak werd voornamelijk veroorzaakt door oprekking van de vaatwand.

In **hoofdstuk 4** worden morfologische en kwantitatieve gegevens verkregen door middel van angiografie en IVUS voor en na ballondilatatie van stenotische lesies in de arteria femoralis superficialis en arteria poplitea met elkaar vergeleken. IVUS detecteerde een groter aantal lesies, meer verkalkte atherosclerotische lesies en meer vaatschade dan angiografie. De sensitiviteit van angiografie was goed voor het vaststellen van de aanwezigheid van een lesie (84%), matig voor het vaststellen van een eccentrische lesie (53%) en van vaatschade (52%) en laag voor het vaststellen van verkalking (30%). In vergelijking met IVUS, onderschatte angiografie de aanwezigheid van een lesie en de stenosegraad van de lesie. Voorafgaand aan ballondilatatie werden verschillende groepen angiografische diameter stenose met elkaar vergeleken. De kwantitatieve IVUS analyse liet zien dat de afname in lumenoppervlak het resultaat was van een verkleining van vaatoppervlak en, in mindere mate veroorzaakt werd door een vergroting van plaqueoppervlak. Deze bevinding ondersteunt andere IVUS studies, die vaatwandkrimp of het falen van de vaatwand om compensatoir te vergroten in combinatie met vergroting van het plaqueoppervlak aanmerken als oorzaak van lumenverkleining in arteriën. Therapeutische consequenties van deze bevindingen zijn voornamelijk speculatief. Voorafgaande aan ballondilatatie bleek er een goede overeenkomst te zijn tussen de angiografische diameterstenose en de grootte van het lumen vastgesteld met IVUS: deze overeenkomst wordt echter niet gezien na ballondilatatie. Dit zou verklaard kunnen worden door het ontstaan van vaatschade tijdens de ballondilatatie, waarbij er vulling met contrastmiddel van de vaatwandscheuren kan plaatsvinden wat een verstoring van het angiografische lumensilhouet geeft. Ook kan dit een reden zijn waarom angiografische diameterstenose niet voorspellend is voor de lange termijn resultaten van interventies.

In **hoofdstuk 5** wordt een klinisch IVUS studie beschreven die de vaatwandreactie op ballondilatatie van de arteria iliaca bestudeert. Vijfentwintig patiënten, die behandeld werden met ballondilatatie vanwege symptomatisch obstruerend vaatlijden van de arteria iliaca werden onderzocht met IVUS voor en onmiddellijk na de interventie. Er werd een onderscheid gemaakt tussen IVUS

beelden afkomstig van de arteria iliaca communis en de arteria iliaca externa. Ten eerste werden, analoog aan de in-vitro studie (Hoofdstuk 3), de morfologische en kwantitatieve veranderingen ter plaatse van de dwarsdoorsnede met het nauwste lumen na de ballondilatatie vergeleken met de gegevens van alle corresponderende dwarsdoorsneden van het totale gedilateerde vaatsegment. Ten tweede werd de voorspellende waarde voor IVUS parameters voor de lange termijn resultaten bepaald. Deze studie heeft aangetoond dat, hoewel de arteria iliaca communis een groter bloedvat is dan de arteria iliaca externa, in beide type vaten de morfologische en kwantitatieve effecten van de ballondilatatie hetzelfde waren. Vaatschade ontstond in 81% van de patiënten. Dissecties, het meest voorkomende type vaatschade, werden voornamelijk aangetroffen op het dunste deel van de betrokken lesie. Er werd geen significante relatie aangetoond tussen de morfologie en topografie van de lesie en het voorkomen of de locatie van de dissectie. De incidentie van vaatschade was ter plaatse van de dwarsdoorsnede met het nauwste lumen iets lager dan wanneer het hele gedilateerde segment in ogenschouw werd genomen (respectievelijk 79% en 88%). De toename in lumenoppervlak van arteria iliaca tijdens ballondilatatie, voornamelijk geassocieerd met toename in vaatoppervlak, terwijl plaque oppervlak maar gering afnam, was overeenkomstig met de resultaten van de in-vitro studie (Hoofdstuk 3). De veranderingen ter plaatse van de dwarsdoorsnede met het nauwste lumen waren groter dan in het totale gedilateerde segment. Tot slot vertoonde de grootte van het lumenoppervlak en de mate van oppervlakte stenose een voorspellende trend wat betreft de lange termijn resultaten van de patiënt.

Hoofdstuk 6 presenteert een klinische studie van 20 patiënten waarin IVUS werd gebruikt om de veranderingen van lumenoppervlak tussen het moment vlak na ballondilatatie van de arteria femoralis superficialis en een jaar later te documenteren. Voor dit doel werden er multipele corresponderende IVUS dwarsdoorsneden van het totale gedilateerde vaatsegment (het behandelde gebied) inclusief de dwarsdoorsnede met het nauwste lumen en van een niet gedilateerd vaatsegment (het referentie gebied) geanalyseerd. Deze studie liet zien dat ter plaatse van de dwarsdoorsnede met het nauwste lumen, lumen verkleining bij follow-up veroorzaakt werd door plaque toename (48%) in combinatie met vaatwandkrimp (52%). Opvallend was dat de plaque toename ter plaatse van de dwarsdoorsnede met het nauwste lumen (15%) vergelijkbaar was met die van het behandelde gebied en het referentie gebied dat niet gedilateerd was (respectievelijk 13% en 15%). Het vaatoppervlak veranderde nauwelijks in het behandelde gebied (+1%) en vergrootte enigszins in het referentie gebied (6%). Analyse van IVUS dwarsdoorsneden die gegroepeerd waren naar lumen verandering liet een vergelijkbare toename van plaque-oppervlak zien voor alle drie de groepen. Het type van vaatwand remodelleren (vaatoppervlak afname, geen verandering of toename) bepaalde de verandering in

het lumenoppervlak. In het behandelde gebied bestond er een nauwe correlatie tussen verandering van lumenoppervlak en verandering van vaatoppervlak en er was een significant grotere toename van plaqueoppervlak in IVUS dwarsdoorsneden die een plaque verkalking of een media ruptuur lieten zien. Er werd geen relatie aangetoond tussen de aanwezigheid van dissectie en kwantitatieve veranderingen gezien bij follow-up. Doordat lumen vernauwing volgend op ballondilatatie het resultaat was van zowel toename in plaqueoppervlak als afname van vaatoppervlak, kan onderzoek zich in de toekomst het beste richten op het elimineren van plaquegroei en vaatwandkrimp.

In **hoofstuk 7** worden, 1 jaar na ballondilatatie van de arteria femoralis superficialis en arteria poplitea, de verschillen tussen behandelde lesies die restenose vertoonde (restenotische lesies) en die geen restenosis vertoonde (niet-restenotische lesies) geëvalueerd met IVUS. In deze studie werden 31 stenotisch lesies, afkomstig van 24 patiënten succesvol behandeld door middel van ballondilatatie. De IVUS dwarsdoorsnede met het nauwste lumen ter plaatse van de angiografische stenose voor ballondilatatie en de corresponderende IVUS dwarsdoorsnede na ballondilatatie en die verkregen na 1 jaar follow-up werden geselecteerd en geanalyseerd voor lumen, plaque en vaatoppervlak. Gebaseerd op de distributie van de grootte van het lumenoppervlak gezien met IVUS na 1 jaar follow-up werd een lumenoppervlak van minder dan 11.0 mm^2 geclassificeerd als een restenotische lesie. Bij follow-up bleek dat 19 van de 31 lesies (61%) beschouwd konden worden als een restenotische lesie. In de groep van restenotische lesies werd het lumenoppervlak kleiner, terwijl in de groep van niet-restenotisch lesies het lumenoppervlak vergrootte. Beide groepen vertoonden een identieke toename van plaqueoppervlak. In de restenotische lesies vond vaatwandkrimp plaats en in de niet-restenotische lesies zagen we een toename van de oppervlakte van de vaatwand, hetgeen resulteerde in een significant verschillend vaatoppervlak tussen beide groepen bij follow-up. Tevens was het voorkomen van restenose groter bij gebruik van een kleine dilatatieballon: 11 van de 12 lesies die gedilateerd waren met een 5mm ballon en 8 van de 17 lesies die gedilateerd waren met een 6 mm ballon vertoonden restenose. Geconcludeerd werd dat bij een follow-up van 1 jaar restenotische en niet-restenotische lesies dezelfde toename in plaque vertoonden en dat restenose werd bepaald door het type van vaatwand remodellering (af- of toename van het vaatoppervlak).

In **hoofdstuk 8** wordt de rol van IVUS bij de evaluatie van stentplaatsing in perifere bloedvaten behandeld. In deze retrospectieve studie werden 27 patiënten, die behandeld werden met een ballonexpandeerbare stent voor de behandeling van een stenose of een stent/vaatprothesecombinatie voor de behandeling van een aneurysma geëvalueerd met IVUS. Na angiografisch optimale stentplaatsing werd het kleinste lumenoppervlak gezien met IVUS in de stent vergeleken met de oppervlak metingen van beide stentranden en de

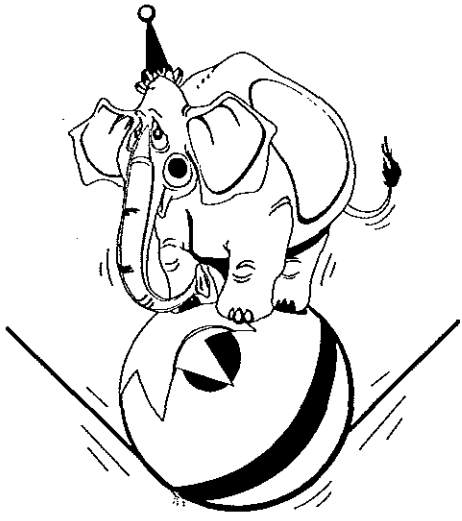
lumenoppervlakken van de proximale en distale referentiesegmenten. In 13 van de 27 stents waren de afmetingen in de stent kleiner (verschill>10%) dan de proximale en/of distale stentrand, zowel bij patiënten die behandeld werden voor een stenose als voor een aneurysma. IVUS toonde aan dat in alle stents en stent/prothesecombinaties het kleinste lumenoppervlak in de stent kleiner was dan de gebruikte ballon grootte en kleiner was dan het gemiddelde lumenoppervlak van het referentiesegment. De discrepantie tussen de stentontplooiing en de gebruikte ballongrootte zou de keuze van een grotere ballon en/of een hogere inflatiedruk dan momenteel gebruikt, kunnen rechtvaardigen.

In **hoofdstuk 9** worden de mogelijkheden van IVUS besproken om veranderingen te documenteren die plaatsvinden 5 maanden na plaatsing van een ballonexpandeerbare stent in de arteria femoralis superficialis. Een mannelijke patiënt onderging een ballondilatatie waarbij een grote dissectie ontstond, die werd behandeld met 7 aaneengesloten Palmaz stents. De patiënt ontwikkelde 5 maanden later klachten die wezen op mogelijke restenose. Angiografie en IVUS lieten 4 significante stenoses zien, gelokaliseerd op de stentovergangen. IVUS-beelden, verkregen onmiddellijk na de stentplaatsing, werden vergeleken met de corresponderende IVUS-beelden bij follow-up. Het lumenoppervlak en het stentoppervlak nam af en de hoeveelheid intimahyperplasie was groter op de stentovergangen dan binnen in de stents. In de aangrenzende referentiesegmenten waren de veranderingen minimaal. Bovendien was de stent die in het traject van het kanaal van Hunter was geplaatst ellipsvormig gedeformeerd. Deze IVUS studie liet zien dat restenose zowel door afname van het stent oppervlak, als door intimahyperplasie wordt veroorzaakt.

Hoofdstuk 10 laat een met hoofstuk 9 vergelijkbare studie zien waarbij de veranderingen worden besproken, die IVUS liet zien 11 maanden na plaatsing van zelfexpandeerbare Memotherm stents. Deze mannelijke patiënt werd behandeld met 2 Memotherm stents voor een ernstige stenose (≥90% diameter stenose) van de arteria femoralis superficialis. Na 11 maanden werd de patiënt opnieuw onderzocht vanwege invaliderende claudicatio intermittens. Zowel angiografie als IVUS lieten restenose op de stentovergang zien. De hoeveelheid intimahyperplasie was op de stentovergang groter dan bij de stentranden en binnen in de stent. Toename van het stentoppervlak werd gezien zowel op de stentovergang als op de stentranden. Ook werd er een toename van het vaatoppervlak gezien in de aangrenzende referentiesegmenten. In deze studie maakte IVUS duidelijk dat in de aanwezigheid van stentvergroting de restenose bij de overgang van de 2 Memotherm stents alleen werd veroorzaakt door intimahyperplasie.

Samengevat hebben de IVUS studies in dit proefschrift bijgedragen aan de kennis omtrent het effect van vasculaire interventies in perifere bloedvaten en omtrent het mechanisme van de lumen afname die volgt op deze procedures. Met name de kennis over het mechanisme van het restenoseproces is essentieel voor de ontwikkeling van nieuwe therapeutische strategieën voor obstruerend vaatlijden van de perifere bloedvaten.

DANKWOORD



DANKWOORD

Dit proefschrift is tot stand gekomen door de bijdrage van een groot aantal mensen. Met name wil ik bedanken:

Dr. E.J. Gussenhoven, voor de geboden kans om op haar afdeling onderzoek te doen en voor de gedegen wijze waarop dit onderzoek en het eruit voortgekomen proefschrift zijn begeleid.

Prof.Dr. G.P. Krestin, voor de bereidheid om als promotor op te treden en voor het gestelde vertrouwen om op zijn afdeling tot radioloog opgeleid te worden.

Prof.Dr. H. van Urk, voor de vruchtbare samenwerking van intravasculaire echografie en de afdeling vaatchirurgie.

Prof.Dr.Ir. N. Bom en zijn afdeling experimentele echocardiografie, die de technische uitvoering van het onderzoek mogelijk maakten.

Prof.Dr. M.G.M Hunink voor het beoordelen van het manuscript.

Jan Honkoop, voor zijn op ervaring gebaseerde rustige en deskundige technische begeleiding tijdens de klinische studies.

Aad van der Lugt, Aran Hartlooper, Jeroen van Essen, Trude Leertouwer en Tjebbe Hagenaars, voor de wetenschappelijke en emotionele bijdrage als paranimfen en geliefde collega's.

Laraine Visser, for her ever lasting patience to revise the manuscripts and for contributing to our English education with humourous and stylish remarks.

Andries Zwamborn, voor zijn enthousiaste bijdrage aan de opmaak van dit proefschrift en zijn wijze raadgevingen in de aanloop naar de promotie.

Alle medewerkers van de afdeling experimentele cardiologie en de afdeling radiologie, die allen op hun eigen manier hebben meegeholpen aan het onderzoek.

Alle mede-auteurs van de in dit proefschrift opgenomen artikelen, voor hun inbreng, kritiek en structurele discussies.

Mijn vrienden en familie, zonder wiens steun en vertrouwen niets mogelijk is.

Dankwoord

LIST OF PUBLICATIONS

List of Publications

Articles

W. van Lankeren, E. J. Gussenhoven, A. van der Lugt, M. Vischjager, P. Khajehi, H. Pieterman, P.G. Gerritsen. Intravascular sonographic evaluation of iliac artery angioplasty: what is the mechanism of angioplasty and can intravascular sonography predict clinical outcome?
AJR 1996;166:1355-1360.

W. van Lankeren, E. J. Gussenhoven, M.J. van Kints, A. van der Lugt, H. van Urk. Stent remodeling contributes to femoropopliteal artery restenosis: an intravascular ultrasound study.
J Vasc Surg 1997;25:753-6.

E. J. Gussenhoven, J.H. Geselschap, W. van Lankeren, D.J. Posthuma, A. van der Lugt. Remodeling of atherosclerotic coronary arteries assessed with intravascular ultrasound in vitro.
Am J Cardiol 1997;79:699-702.

W. van Lankeren, E. J. Gussenhoven, A. van der Lugt, H. Pieterman, M.R.H.M. van Sambeek. Comparison of angiography and intravascular ultrasound before and after balloon angioplasty of the femoropopliteal artery.
Cardiovasc Intervent Radiol. 1998;21:367-374.

M.R.H.M. van Sambeek, A. Qureshi, W. van Lankeren, A. van der Lugt, J. Honkoop, E. J. Gussenhoven. Discrepancy between stent deployment and balloon size used assessed by intravascular ultrasound.
Eur J Vasc Endovasc Surg 1998;15:57-61.

T.C. Leertouwer, E.J. Gussenhoven, W. van Lankeren, H. van Overhagen, M.R.H.M. van Sambeek. Memotherm in-stent restenosis due to intimal hyperplasia: an intravascular ultrasound study.
J Ang Vasc Surg. 1998;4:54-58.

M.R.H.M. van Sambeek, E. J. Gussenhoven, W. van Lankeren, H van Urk. Pre-operative assessment with intravascular ultrasound for peripheral endografts.
Cardiovascular interventions Online 1998;1:36.

W. van Lankeren, E. J. Gussenhoven, A. Qureshi, A. van der Lugt. Intravascular ultrasound and histology in in vitro assessement of iliac artery angioplasty.
Cardiovasc Intervent Radiol. 1999;22:50-55.

W. van Lankeren, E.J. Gussenhoven, J. Honkoop, Th. Stijnen, H.van Overhagen, C.H.A. Wittens, S.E. Kranendonk, M.R.H.M. van Sambeek, A.van der Lugt. Plaque area increase and vascular remodeling contribute to lumen change after percutaneous transluminal angioplasty of the femoropopliteal artery: an intravascular ultrasound study.
J Vasc Surg. 1999;29:430-441.

W. van Lankeren, E.J. Gussenhoven, Th. Stijnen, J.L. Seelen, A. J. van Seijen, L.C. van Dijk, M. R.H.M. van Sambeek, A. van der Lugt. Mechanism of restenosis after percutaneous transluminal angioplasty: serial intravascular ultrasound study of femoropopliteal arteries.
Submitted 1999.

T.C. Leertouwer, E.J. Gussenhoven, W. van Lankeren, H. van Overhagen. Response of renal and femoropopliteal arteries to Palmaz stent implantation assessed with intravascular ultrasound.
J Endovasc Surg 1999:6;359-364.

Book
M.R.H.M. van Sambeek, E. J. Gussenhoven, A. van der Lugt, W. van Lankeren. Is the use of intravascular ultrasound essential for femoropopliteal balloon angioplasty and stenting?
In : R.M. Greenhalgh (ed), Indications in vascular and endovascular surgery. W.B. Saunders Company Ltd, London 1998:317-326.

Abstracts
W. van Lankeren, E. J. Gussenhoven, A. van der Lugt, M.J. van Kints, N.A.J.J. du Bois, M.R.H.M. van Sambeek, A. Qureshi. Serial intravascular ultrasound following balloon angioplasty in the femoropopliteal artery: Remodeling or intimal hyperplasia?
Nederlandse Vereniging voor Heelkunde, Najaarsvergadering, Programma en Samenvattingen:39.

W. van Lankeren , E. J. Gussenhoven, A. van der Lugt, M.J. van Kints, N.A.J.J. du Bois, M.R.H.M. van Sambeek, A. Qureshi. Serial intravascular ultrasound following balloon angioplasty in the femoropopliteal artery: Remodeling or intimal hyperplasia?
European Radiology 1997;7:S-203.

W. van Lankeren, E. J. Gussenhoven, A. van der Lugt, J. Honkoop, A. Qureshi, M.J. van Kints, N.A.J.J. du Bois, M.R.H.M. van Sambeek. Does vascular remodeling contribute to restenosis? A serial intravascular ultrasound study.
12th Symposium on Echocardiology and 9th Meeting of the International Cardiac Doppler Society. Rotterdam. The Thoraxcentre Journal. June 1997;18.

E. J. Gussenhoven, W. van Lankeren, M.J. van Kints, A. van der Lugt, M.R.H.M. van Sambeek, N.A.J.J. du Bois. Stent area reduction contributes to femoropopliteal artery restenosis: An intravascular ultrasound study.
J Endovasc Surg 1997;4:I-1-I-13.

M.R.H.M. van Sambeek, E. J. Gussenhoven, A. Qureshi, W. van Lankeren, A. van der Lugt, J. Honkoop, M.J. van Kints. Discrepantie tussen stent afmeting en de gebruikte ballon geëvalueerd middels intravasculaire echographie.
Nederlandse Vereniging voor Vaatchirurgie, Voorjaarsvergadering 1997, Programma. Utrecht, april 1997.

M.R.H.M. van Sambeek, E. J. Gussenhoven, W. van Lankeren, M.J. van Kints, A. van der Lugt, N.A.J.J. du Bois, H. van Urk. Stent diameterverkleining draagt bij aan de restenose in femoropopliteale traject: een intravasculare echographie studie.
Nederlandse Vereniging voor Vaatchirurgie, Voorjaarsvergadering 1997, Programma. Utrecht, april 1997.

M.T.C. Hoedt, M.R.H.M. van Sambeek, E.J. Gussenhoven, W. van Lankeren, H. van Urk. Discrepancy between stent deployment and balloon size used, in-stent intimal hyperplasia and stent remodeling: What have we learned from IVUS. International Endovascular Symposium 1997. Abstracts:95.

E. J. Gussenhoven EJ, J.A. van Essen, W. van Lankeren, A. van der Lugt, A. Hartlooper, L. Wenguang. Can intravascular ultrasound be used to assess effect of antisclerotic agents? J Molec Cell Cardiol 1998;30:A186.

H. van Urk, M.R.H.M. van Sambeek, E. J. Gussenhoven, A. van der Lugt, W. van Lankeren. Femoropopliteal balloon angioplasty and stenting: What have we learned from IVUS. International Society for endovascular Surgery. European Summer Symposium. Abstracts 1998:13.

T. Hagenaars, W. van Lankeren, J. Honkoop, H. van Overhagen, A.J. van Seyen, J.L. Seelen, E.J. Gussenhoven. Intimal hyperplasia and the type of vascular remodeling determined lumen area change following balloon angioplasty of the femoropopliteal artery: an intravascular ultrasound study.
Echocardiography 1998;15:S49

W. van Lankeren, E.J. Gussenhoven, J.L. Seelen, A.J. van Seyen, L.C. van Dijk, A. van der Lugt. Restenosis after percutaneous transluminal angioplasty: a serial intravascular ultrasound study in femoropopliteal arteries.
De vierde Nederlandse Radiologendagen, Veldhoven. Memorad 1999;4.

E.J. Gussenhoven, J.A. van Essen, J. Honkoop, A.J. van Seyen, J.L. Seelen. W. van Lankeren, Plaque area increase and vascular remodeling contribute to lumen change after percutaneous transluminal angioplasty of the femoropopliteal artery: an intravascular ultrasound study.
J Am Coll Cardiol 1999;34:292A

T. Hagenaars, E. Gussenhoven, J. Honkoop, L van Dijk, G. Gerritsen, W. van Lankeren. Plaque dissection following balloon angioplasty of the femoropopliteal artery does not provoke plaque growth and vascular remodeling: an serial intravascular ultrasound study. Eur J Echocardiography. Abstract Supplement, December 1999;S42

Posters

A. van der Lugt, E. J. Gussenhoven, R.J. van Suylen, W. van Lankeren, H. van Overhagen. Validation of intravascular ultrasound images by comparison with histologic sections.
Radiology 1997;205 P:562.

List of publications

W. van Lankeren, E. J. Gussenhoven, A. van der Lugt, J. Honkoop, H. van Overhagen, C.H.A. Wittens, S.E. Kranendonk, M.R.H.M. van Sambeek. Intimal hyperplasia and vascular remodeling contribute to lumen change following balloon angioplasty of the femoropopliteal artery: a serial intravascular ultrasound study.
Current concepts in the therapy of coronary heart disease. The second update on experimental results and clinical interventions 1998. Abstracts.

Lectures
'PTA en re-stenose'.
Vaatdag '98, perifeer stenoserend vaatlijden. Hilversum, april 1998.

'Mechanisme van PTA en re-stenose'
Endovascular Forum: 'Basic Principles and Advanced Techniques'. Zeist, december 1999

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