ARTERIAL REMODELING AFTER PERIPHERAL VASCULAR INTERVENTION AS DOCUMENTED WITH INTRAVASCULAR ULTRASOUND

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Vaatwand remodelleren na perifere vasculaire interventies gezien met intravasculaire echografie

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CHAPTER 1

Introduction

INTRODUCTION

For patients with symptomatic obstructive disease of peripheral arteries, Dotter and Judkins [1] introduced the percutaneous approach of treatment in 1964, using coaxial catheters to enlarge the obstructed lumen. In 1974 Grüntzig and Hopff [2] improved this technique by introducing dilatation balloon catheters. Since then, percutaneous transluminal angioplasty (PTA) has been considered the most important technique to treat patients with obstructive vascular disease. However, the long-term results of PTA in femoropopliteal arteries are disappointing with 1-year restenosis rates of 47% to 81%.[3-5]

For objective evaluation of the location and severity of obstructive vascular disease different imaging techniques are available. The most important of these imaging techniques is angiography, which displays a silhouette of the lumen. This imaging technique is considered the gold standard, but has the disadvantage of being an invasive imaging technique. External ultrasound is a non-invasive imaging technique which, in addition to information on lumen dimensions, gives information on vessel wall thickness of superficially located arteries. Over the past decade, intravascular ultrasound (IVUS) has become an acknowledged technique for imaging coronary and peripheral arteries.[6,7] The advantage of IVUS, as compared to angiography or external ultrasound, is that this technique provides a cross-sectional view of the vessel with information on lumen, vessel and plaque area at high resolution. Serial IVUS studies have shown that, following successful intervention, vascular remodeling (vascular shrinkage) is an important factor in the development of restenosis in addition to plaque growth.[8,9] As a consequence, treatment modalities should be developed that potentially might reduce vascular shrinkage in addition to other ways of treatment that may inhibit plaque growth.

The aim of the IVUS studies presented in this thesis was to provide insight in new alternative treatment modalities including endografts, intravascular radiation (i.e. endovascular brachytherapy) and statin therapy on the outcome of peripheral intervention in patients with obstructive disease of the femoropopliteal artery.

Endografts

To eliminate vascular shrinkage after successful vascular intervention, stents have been introduced. The use of stents resulted in a reduction in restenosis rate in coronary arteries.[10] However, stents used in femoropopliteal arteries did not improve restenosis rates; both plaque growth and stent area reduction resulted in lumen area reduction, particularly at stent edges and stent junctions.[11,12] In order to diminish the vascular response to mechanical intervention, a polytetrafluoroethylene (ePTFE) endograft was developed. This endograft covers the damaged arterial wall with an endoprosthesis after vascular intervention. **Chapters 2 and 3** present the IVUS findings in patients that were treated with this endograft 6 months and 2 years after endograft placement, respectively. Long-term clinical follow-up data of all patients treated with this ePTFE endograft are presented in **Chapter 4.**

Endovascular brachytherapy

To diminish the vascular response to intervention (PTA), endovascular brachytherapy (EBT) was introduced. The effective use of EBT to prevent plaque growth in animal models after balloon arterial injury has been demonstrated in preclinical studies using histology as the gold standard.[13,14] Similarly, there is clinical and angiographic evidence that EBT reduces restenosis following percutaneous transluminal coronary angioplasty with or without stent placement in coronary arteries.[15-18] **Chapter 5** describes a randomized IVUS study aimed at determining the precise effect of endovascular radiation as an adjunct to PTA in femoropopliteal arteries at 6-months follow-up.

Statin therapy

In the early 1990s the newest class of cholesterol-lowering drugs, HMG-CoA reductase inhibitors (i.e. statins), became available for primary and secondary prevention of cardiovascular disease.[19,20] Clinical studies using angiography and external ultrasound have shown that statin therapy may reduce the progression of atherosclerosis or even induce regression.[21,22] However, the benefits of statin therapy on the primary and secondary prevention of cardiovascular disease cannot be solely attributed to the reduction in cholesterol levels and the reduction in progression of atherosclerosis. More

recent studies reported that statin therapy may exert a direct antiproliferative effect on the arterial wall [23] and may enhance endothelial function.[24] Before performing our first IVUS study to assess the effect of statin therapy, some validation studies were needed in order to test a newly developed automated contour analysis system. With this system three-dimensional (3-D) reconstructions of cross-sectional IVUS images can be obtained providing data on plaque, lumen and vessel volumes. Before this automated contour analysis system was used in a clinical setting, the reproducibility of volume measurements obtained with the system was determined (**Chapter 6**). **Chapter 7** presents a study to assess the reproducibility of circumferential arc and length measurements of calcified lesions seen with IVUS and the changes observed at 1-year follow-up. **Chapter 8** presents a study using the automated contour analysis system to assess the progression of atherosclerosis and vascular remodeling of femoropopliteal arteries at 1-year follow-up. **Chapters 9 and 10** present longitudinal IVUS studies conducted to assess the effect of 1-year treatment with statin therapy on both plaque growth and vascular remodeling in femoropopliteal arteries not treated with PTA (**Chapter 9**) and in femoropopliteal arteries subjected to PTA (**Chapter 10**). In **Chapter 11** the rationale and design of a future randomized IVUS study aimed at assessing the dose-dependent effect of statin therapy on both plaque growth and vascular remodeling is described. Finally, **Chapters 12 and 13** present the summary of this thesis.

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CHAPTER 2

Vascular Response in the Femoropopliteal Segment After Implantation of An ePTFE Balloon-expandable Endovascular Graft:

An intravascular ultrasound study

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ABSTRACT

Purpose: To use intravascular ultrasound (IVUS) to document changes in vascular dimensions after placement of a balloon-expandable endograft.

Methods: Thirteen patients (9 men; mean age 62 years, range 47-75) treated with an investigational polytetrafluoroethylene endograft for obstructive disease of the femoropopliteal segment were studied with IVUS immediately after endograft implantation and at follow-up. Corresponding IVUS cross sections were analyzed for changes in lumen, vessel, and plaque areas seen inside the endograft, in the anastomotic segment, and in the remote arterial segment.

Results: A mean 6-month (range 1.5-9) follow-up was completed in 12 patients. Matched IVUS cross sections derived from within the endograft (n=12) and at the endograft edges (n=23) showed no change in lumen area (LA) in 17, reduction in 11, and dilatation in 7. Median changes within the endograft (+3%) were not significant (p=0.28) and no neo-intima was found. Cross sections obtained at the anastomotic segment revealed a significant increase in LA (85%, p<0.001), which was associated with a significant increase in both vessel area (VA) (42%, p<0.001) and plaque area (PLA) (15%, p=0.003). In the remote arterial segment, the change in LA was minimal (6%, p=0.07), as were changes in the VA (9%, p=0.04) and PLA (10%, p=0.07).

Conclusions: Following endograft placement, luminal changes within the endograft, at the endograft edges, and at the remote arterial segments were minimal. Intimal hyperplasia was not observed in the endograft. The distinct LA increase at the anastomotic segments was determined by the extent of VA and PLA change.

INTRODUCTION

The long-term results of balloon angioplasty in femoropopliteal arteries are disappointing, with 1-year patency rates ranging from 47% to 81%.[1-6] Intravascular ultrasound (IVUS) studies performed in coronary arteries have shown that vascular remodeling is an important factor in the development of restenosis, in addition to intimal hyperplasia.[7-9] By eliminating this geometrical remodeling, stents have reduced restenosis in coronary vessels.[10] However, stents used in the femoropopliteal arteries did not improve patency rates. Both intimal hyperplasia and stent area reduction resulted in lumen area (LA) reduction, particularly at stent edges and stent junctions.[11,12] To diminish the vascular response to intervention, a polytetrafluoroethylene (ePTFE) endograft was developed that covers the damaged arterial wall with an endoprosthesis. The aim of this study was to use angiography and IVUS to assess the vascular response following endovascular graft placement in the femoropopliteal segment.

METHODS

From October 1996 to August 1997, 13 patients (9 men; mean age 62 years, range 47-75) with obstructive disease of the femoropopliteal segment were selected for treatment with an endovascular graft. Patients were known to have disabling claudication (n=12) or critical ischemia (n=1). Five patients had a stenotic lesion (5.2-cm mean length) and 8 had an occlusion (7.5-cm mean length). The lesion length was estimated from the angiograms. Four patients underwent previous vascular interventions (3 balloon angioplasties and 1 femoropopliteal bypass). The preoperative mean ankle-brachial index was 0.7 at rest and 0.42 after exercise. Patients were included in the study after giving informed consent for the procedure and the invasive follow-up study.

The endograft used was a balloon-expandable thin-walled ePTFE graft (Enduring, W.L. Gore & Associates, Flagstaff, AZ, USA) with a 4-mm outer diameter (Figure 1). The graft wall contains ring-shaped ePTFE reinforcements that are integrated in the material. It can be custom cut in any length, and depending on the diameter of the balloon used, the graft can be expanded from 4 to 7 mm (inner diameter). This maneuver fixes the graft to the arterial wall over its entire length and provides a proper seal. The rings are compression resistant, comparable to self-expandable stents.

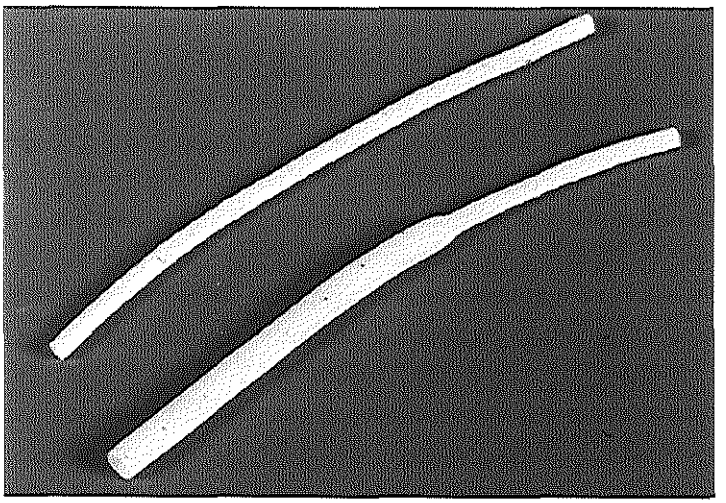

Figure 1. Samples of the enduring vascular graft (lower example partially dilated).

Procedures were performed in the operating theater under fluoroscopic, angiographic, and IVUS guidance. IVUS examinations used a 4.3-F motor-driven imaging catheter with a 30-MHz transducer (Endosonics, Rijswijk, The Netherlands). The IVUS transducer was advanced beyond the diseased arterial segment, and cross-sectional images were obtained during manual pullback of the catheter. The catheter position was documented using a displacement-sensing device[13] and fluoroscopy, with a radiopaque ruler as reference. Images were stored on an S-VHS videotape. Arterial access was gained through a surgical cutdown of the common or superficial femoral artery. In 5 patients with a stenosis and in 5 of the 8 patients with an occlusion, a hydrophilic guidewire was positioned beyond the lesion. Predilation with a 5- to 7-mm balloon was performed to facilitate passage of a 14-F sheath. In the 3 remaining occlusion patients, remote endarterectomy with a MollRing Cutter (Avatar, Inc., Portola Valley, CA, USA) was necessary before the guidewire was advanced.[14,15] The endograft was cut to match the length of the entire predilated segment, or in the case of a remote endarterectomy, with a 1-cm overlap. The endograft was mounted on a dilation balloon catheter and positioned in the femoropopliteal segment under fluoroscopic guidance. The sheath was retracted and the endograft expanded. Care was taken that the adjacent arterial segments were not dilated.

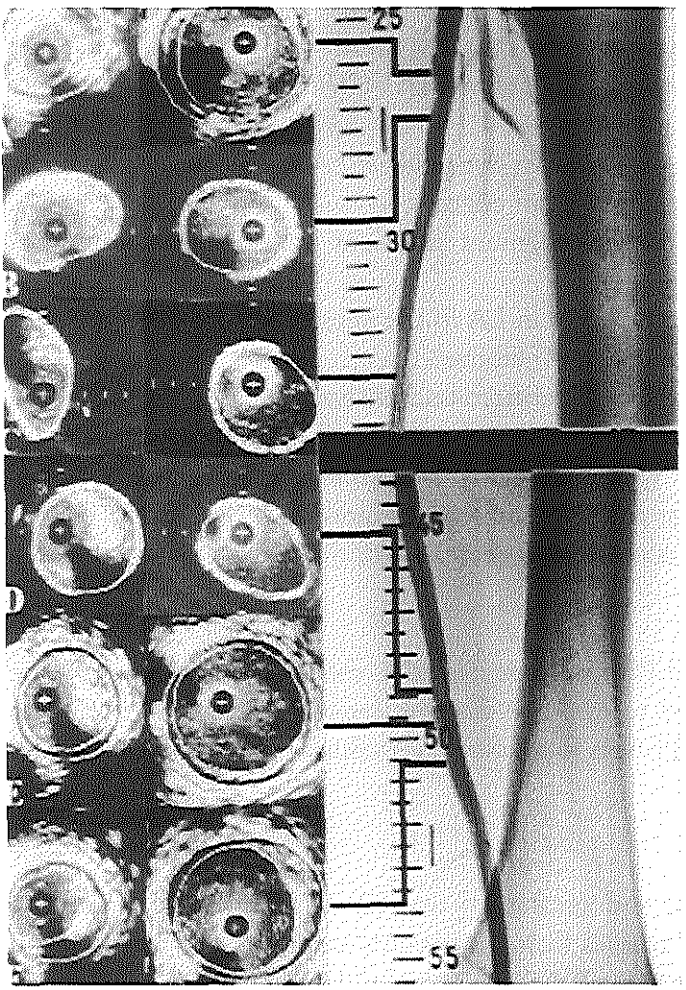

Figure 2. Matched intravascular ultrasound cross sections of a femoropopliteal segment after endograft placement (left panel) and at follow-up (middle panel) paired with the corresponding follow-up angiogram (right panel). Note the absence of plaque inside the endograft. A distinct dilatation seen at the anastomotic segments (A, E, F) was absent within the endograft (B, proximal edge; C, inside endograft; and D, distal edge). The angiogram showed dilatation in the anastomotic segments, but the change was less prominent.

Imaging protocols

The follow-up protocol included single plane angiography and IVUS imaging 6 months after intervention. In cases of graft occlusion, a control angiogram and IVUS were performed after successful fibrinolysis. The single plane angiograms obtained after placement of the endograft and at follow-up were compared by a radiologist blinded to the IVUS results. By visual inspection, the change in the endograft lumen, the adjacent arterial segments (i.e., anastomotic segment), and the remote arterial segment (>2 cm) was defined as no change, reduction, or dilatation.

IVUS cross sections obtained after endograft placement and at follow-up were

matched precisely using the radiopaque ruler and catheter displacement-sensing device.[13] The following IVUS images were selected from each patient for quantitative analysis:

1. the site within the endograft with the smallest LA;
2. the proximal and distal endograft edges;
3. 0.5 cm from the arterial segment adjacent to the endograft (i.e., anastomotic segment);
4. the site with the largest change in LA in the anastomotic segment; and
5. 2 cm remote from the site in (4) (above).

The selected cross sections were digitized and analyzed for LA, VA, and PLA. If no intimal hyperplasia was evident in the endograft or at the edges (PLA=0), LA was equal to VA. The matched IVUS cross sections were grouped according to the change in LA at follow-up and classified as no change (difference <10%), reduction (>10% decrease), or dilatation (>10% increase).

Statistical analysis

Changes in LA, VA, and PLA were expressed as median values (ranges). The 1-sample t test was used to evaluate the null hypothesis that there was no change in LA, VA, and PLA in follow-up. A p value of <0.05 was considered statistically significant.

RESULTS

The mean length of the endograft used was 20 cm (range 13 to 34). The angiographic and IVUS studies from 12 patients were acquired after a mean 6-month follow-up (range 1.5-9.0). One endograft, which had been implanted subintimally, occluded within 1 week due to a dissection distal to the graft; imaging follow-up was not available in this patient. In 8 patients, the endografts remained patent during follow-up (minimum 6 months), but the other 4 endografts occluded at 1.5, 2, 4, and 7 months. These were successfully recanalized using thrombolysis; 2 remained patent, but the other 2 reoccluded after 3 and 5 months.

From the 12 endografts, 20 (8 proximal, 12 distal) anastomotic segments and 10 remote arterial segments were available for angiographic analysis. Compared to the postimplantation angiogram, the follow-up image showed no change in the endograft lumen, at the edges of the endograft, or in the arterial segments

Table 1 Differences at Follow-up in the Lumen, Vessel, and Plaque Areas at 4 Endograft Locations as Assessed by IVUS*

Locations	n	Lumen Area	Vessel Area	Plaque Area
Inside endograft	12	3% (p=0.28) (-22% to 45%)	–	–
No lumen change	4	0% (-5% to 5%)	–	–
Reduction	3	-18% (-22% to -14%)	–	–
Dilatation	5	22% (12% to 45%)	–	–
Endograft edge	23	-6% (p=0.19) (-26% to 63%)	–	–
No lumen change	13	-5% (-9% to 6%)	–	–
Reduction	8	-18% (-26% to -12%)	–	–
Dilatation	2	38% (13% to 63%)	–	–
Anastomotic segment	22	85% (p<0.001) (-56% to 339%)	42% (p<0.001) (-16% to 130%)	15% (p<0.001) (-11% to 158%)
No lumen change	1	7%	2%	-8%
Reduction	4	-41% (-56% to -28%)	7% (-16% to 27%)	69% (17% to 156%)
Dilatation	17	100% (29% to 339%)	49% (21% to 130%)	13% (-11% to 158%)
Remote arterial segment	10	6% (p=0.07) (-9% to 53%)	9% (p=0.04) (-6% to 46%)	10% (p=0.07) (-17% to 65%)
No lumen change	6	2% (-9% to 9%)	4% (-6% to 31%)	10% (-3% to 65%)
Reduction	0	–	–	–
Dilatation	4	28% (13% to 53%)	19% (-3% to 46%)	10% (-17% to 58%)

* Values are expressed as median (range); n = number of cross sections analyzed

Table 2 Differences at Follow-up in the Lumen, Vessel, and Plaque Areas at the Endograft Edges and Adjacent Arterial Segments as Assessed by IVUS*

Locations	n	Lumen Area	Vessel Area	Plaque Area
Proximal endograft edge	11	-6% (-26% to 13%)	–	–
No lumen change	8	-4% (-9% to 6%)	–	–
Reduction	2	-20% (-26% to -14%)	–	–
Dilatation	1	13%	–	–
Distal endograft edge	12	-10% (-22% to 63%)	–	–
No lumen change	5	-5% (-7% to 1%)	–	–
Reduction	6	-18% (-22% to -12%)	–	–
Dilatation	1	63%	–	–
Proximal anastomotic segment	10	93% (-56% to 339%)	41% (-16% to 100%)	26% (-10% to 156%)
No lumen change	1	7%	2%	-8%
Reduction	2	-51% (-56% to -45%)	5% (-16% to 27%)	87% (17% to 156%)
Dilatation	7	100% (75% to 339%)	48% (32% to 100%)	10% (-10% to 56%)
Distal anastomotic segment	12	82% (-38% to 188%)	45% (-13% to 130%)	25% (-11% to 158%)
No lumen change	0	–	–	–
Reduction	2	-33% (-28% to -38%)	7% (-13% to 27%)	69% (56% to 82%)
Dilatation	10	90% (29% to 188%)	54% (21% to 130%)	18% (-11% to 158%)

* Values are expressed as median (range); n= number of cross sections analyzed

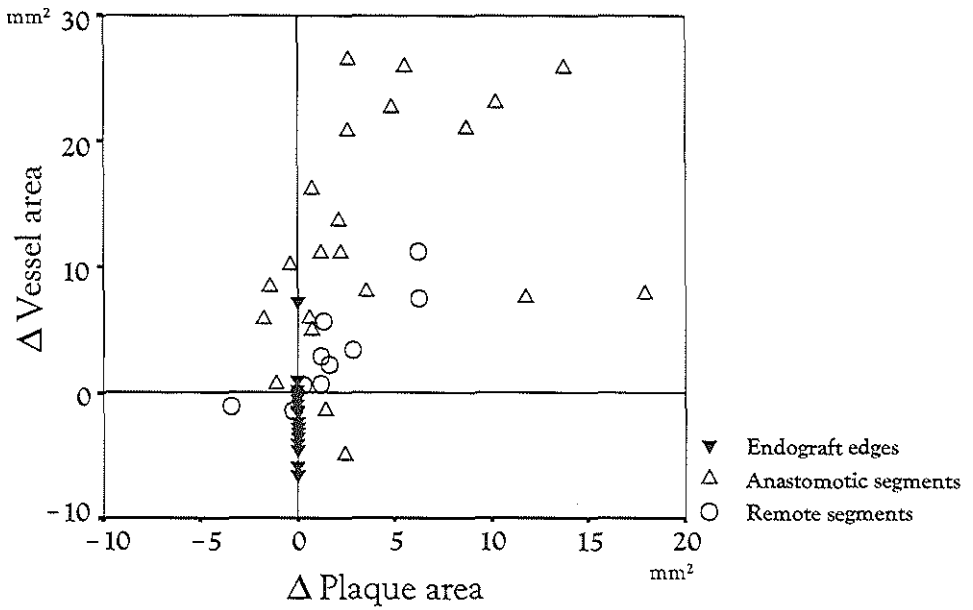

Figure 3. Changes in plaque and vessel area measurements at different locations within the endograft. Remodeling produced minimal change at the endograft edge and increases in plaque and vessel areas in the majority of the anastomotic segments. At the remote arterial segments, the changes were less prominent.

remote from the endograft. Of the 20 anastomotic segments studied, no lumen change was encountered in 9, a reduction in 2 (<1 cm), and an increase in 9 (<2 cm) (Figure 2). No change in LA was observed in the remote arterial segments.

Changes in LA, VA, and PLA assessed with IVUS are summarized in Tables 1 and 2 and Figure 3. LA change was minimal both inside the endograft (3%, p=0.28) and at the endograft edge (-6%, p=0.19). No hyperplasia was seen within the endografts or at the endograft edges (Figure 2). LA showed no change (n=17), a reduction (n=11), or a dilatation (n=7) (Table 1). Changes encountered in LA at the proximal and distal endograft edge were comparable (Table 2). In 1 patient, the reoccluded endovascular graft was excised after 8 months; histology (Figure 4) confirmed the absence of plaque, which is consistent with the IVUS findings.

Of the anastomotic sites studied, 10 proximal and 12 distal anastomotic segments were available for IVUS analysis. The LA increase (85%, p<0.001)

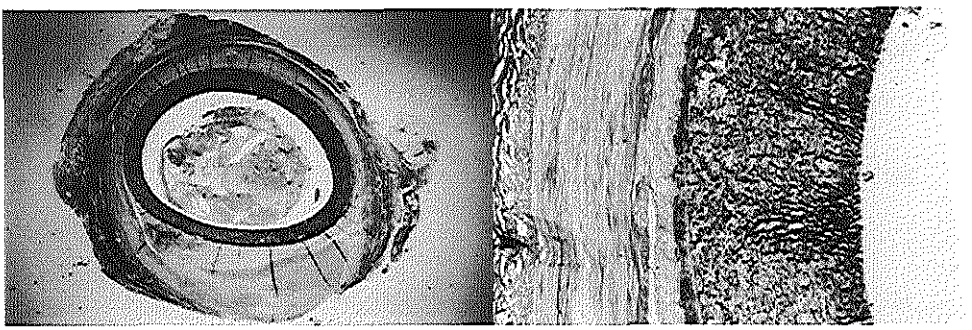

Figure 4. Histology sections (Milligan's trichrome stain) of an ePTFE endograft (left: in situ; right: magnified 325) excised 8 months after deployment. No neointima was observed within the endograft.

was associated with an increase in both VA (42%, $p<0.001$) and PLA (15%, $p=0.003$) (Table 1, Figure 2). The increase in PLA was overcompensated by the increase in VA. Individual cross sections showed no change in LA in 1, a reduction in 4, and a dilatation in 17. No significant differences were observed between the proximal and distal anastomotic segment (Table 2).
Of the 10 remote arterial segments available for IVUS analysis, the minimal change in LA (6%) was associated with an increase in both VA (9%) and PLA (10%) (Table 1). Individual cross sections showed no change in LA in 6 and a dilatation in 4 others.

DISCUSSION

Endografts of many types are being investigated for treatment of both occlusive and aneurysmal disease.[16-21] We employed arteriography and IVUS imaging to evaluate a new ePTFE balloon-expandable endograft in patients with obstructive femoropopliteal disease. On both the angiogram and the IVUS images, there were only minimal luminal changes within the endograft and at the remote arterial segments. Distinct changes in LA were encountered at the anastomotic segments, however. The greater incidence of dilatation seen with IVUS at this level was probably due to the quantitative nature of the cross-sectional analysis compared to the subjective visual assessment of the angiographic images.
In this study, the lumen changes seen on IVUS both within the endograft (3%) and at the endograft edges (-6%) were small. Intimal hyperplasia (PLA increase) and VA reduction (shrinkage), both of which are important

parameters in the development of postangioplasty restenosis, were likewise minimal.[7-9,22] Similarly, the changes in LA in the arterial segments remote from the endograft were modest (6%) and associated with minor increases in VA (9%) and PLA (10%). These data are in accordance with those of van Lankeren et al.,[22] who reported a 3% LA change and associated increases in both VA (6%) and PLA (15%) in cross sections not subjected to balloon dilation.

The changes at the anastomotic segments adjacent to the endograft were significant for all area measurements, a remarkable finding for an arterial segment that has not been dilated. Although the mechanism for this local dilatation at the anastomosis is unclear, there are hypotheses that may explain the findings.

First, the patency of a prosthetic vascular graft may be determined, in part, by the healing properties of the graft and the development of intimal hyperplasia at the anastomotic segment.[23-25] Development of intimal hyperplasia is related to low mean and oscillating shear stress.[26,27] Compared to an end-to-side anastomosis, wall shear stress distribution in endovascular end-to-end anastomosis may prevent turbulent flow and consequently intimal hyperplasia. Hasson et al.[28] described an increase in arterial diameter in a "para-anastomotic hypercompliant" zone distal to an end-to-end anastomosis. They suggested that this zone might be associated with a local high stress induced by compliance mismatch in a direct graft-to-artery anastomosis.[29-31] This phenomenon may explain our findings related to the increase of lumen and vessel areas, but not plaque.

Secondly, dilatation seen at the anastomotic segment might be explained by flow obstruction from the 14-F delivery sheath used during endograft implantation. At follow-up, the angiogram and IVUS were obtained using a 7-F sheath. The higher arterial pressure could be responsible for the increase in both LA and VA. The fact that this phenomenon was not encountered within the endograft and in the arterial segments remote from the endograft, however, does not support this argument.

Thirdly, covering endothelial cells with an endograft may lead to local tissue hypoxia by interrupting the interaction between blood and the vessel wall. Vascular endothelial growth factor (VEGF) expression is upregulated by hypoxia in normal tissues that become ischemic, and receptors to VEGF are also upregulated in hypoxic tissues. Hence, local tissue ischemia may lead to

angiogenesis, necessitating remodeling without sprouting.[32] Growth factors or other mediators may play a role in the findings described in our study, although no objective evidence exists.

Based on our observations, vascular remodeling may compensate for intimal hyperplasia at the anastomotic segment of an e-PTFE endograft. However, the small number of patients available for analysis limits our ability to make definitive conclusions in this regard. Only 10 remote arterial segments were available for angiographic and IVUS analysis because the sheath hampered visualization of the proximal remote arterial segment. Another limitation of this study was the visually estimated angiographic analysis, whereas the IVUS cross sections were analyzed quantitatively.

Compared to angiography, we have shown that IVUS is more sensitive in demonstrating luminal changes at follow-up. Minimal changes in LA were found within the endograft, at the endograft edges, and in the remote arterial segments. Distinct LA increases encountered at the anastomotic segments were associated with increases in VA and PLA. Endografts may prove useful in long segment obstructions in the femoropopliteal segment.

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CHAPTER 3

Intravascular Ultrasound Evidence for Stabilization of Compensatory Enlargement of the Femoropopliteal Segment Following Endograft Placement

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ABSTRACT

Purpose: To document whether the vasodilatory response seen at the anastomotic segment 6 months after placement of a balloon-expandable endograft is progressive between 6 and 24 months follow-up.

Methods: Patients (n=12; median age 65 years, range 47 to 75) treated with an investigational polytetrafluorethylene (ePTFE) endograft for obstructive disease of the femoropopliteal artery, were studied with intravascular ultrasound (IVUS) immediately after placement and at 6 and 24 months follow-up. Matched IVUS cross-sections derived from the endograft and the anastomotic segment were analyzed for changes in lumen (LA), vessel (VA) and plaque area (PLA).

Results: In total 5 patients had a complete follow-up with IVUS at 8 (first follow-up period) and 25 months (second follow-up period). Matched IVUS cross-sections derived from the endograft showed no significant change in LA during both follow-up periods (-8% and +1%, respectively). There was no evidence for intimal hyperplasia or endograft recoil. During both follow-up periods IVUS cross-sections derived from the anastomotic segment revealed a significant increase in LA (+37% and +8%, respectively) and VA (+26% and +6% respectively). The change in PLA during both follow-up periods was not significant (+13% and +3%, respectively).

Conclusions: The ePTFE endograft seems to inhibit both intimal hyperplasia and constrictive remodeling. The vascular dilatory response seen at the anastomotic segment at 8 months follow-up tends to stabilize at 25 months follow-up. Therefore, this endovascular anastomosis acts as an "ideal" end-to-end anastomosis.

INTRODUCTION

Recently, a polytetrafluorethylene (ePTFE) endograft was developed to cover the damaged arterial wall after vascular intervention. In a previous intravascular ultrasound (IVUS) study on femoropopliteal arteries undergoing ePTFE endograft placement we established that at 6 months follow-up lumen area change within the endograft and at the endograft edges was minimal and intimal hyperplasia was not observed.[1] In contrast, the arterial segment adjacent to the endograft (i.e. anastomotic segment) revealed a distinct increase in lumen area, which was due to a vasodilatory response. The purpose of the present IVUS study is to document whether this vasodilatory response seen at the anastomotic segment is progressive between 6 and 24 months follow-up.

METHODS

Patients

This is a follow-up study of 12 patients in whom the short-term results have been previously reported.[1] Patients with disabling claudication (n=11) or critical ischemia (n=1) were treated with an ePTFE endovascular graft of the femoropopliteal artery. A high-grade stenosis (mean length 5.2 cm) was involved in 5 patients and an occlusion (mean length 7.5 cm) in 7 patients. There were 9 men and 3 women, with median age of 65 (range 47-75) years. At baseline patients were studied with IVUS immediately after endograft placement. A per-protocol follow-up IVUS investigation was performed after 6 and 24 months. Patients were included in the present study after giving informed consent for the procedure and the invasive follow-up study.

Endovascular graft

The characteristics of the endograft used have been described before.[1] Briefly, the endograft is a balloon expandable ePTFE thin-walled graft (ENDURING™, W.L. Gore & Associates, Flagstaff, AZ, USA) with an outer diameter of 4 mm; it can be custom cut in any desired length. The graft wall contains ring-shaped ePTFE reinforcements that are integrated in the material. The rings are compression resistant comparable to self-expandable stents. Depending on the diameter of the balloon used, the graft can be expanded from 4 to 7 mm inner diameter. This maneuver fixes the graft to the arterial wall over its entire length and provides proper seal. In 9 patients pre-dilatation

with a balloon (5–7 mm) was performed to allow passage of a 14 French sheath which included the endograft. In the 3 remaining patients, a remote endarterectomy with a MollRing CutterTM (Vascular Architects, Inc., Portola Valley, CA, USA) was performed first.[2,3]

Intravascular ultrasound

The IVUS studies were performed using a single rotating ultrasound element (30 MHz) on a guidewire-tipped 4.3F catheter (Endosonics, Rijswijk, The Netherlands, 0.035"). The IVUS catheter was advanced beyond the endograft and cross-sectional images were obtained during manual pullback of the catheter. The information on the location of the cathetertip was documented using a catheter displacement sensing device and fluoroscopy, with a radiopaque ruler as reference.[4] This information on the cathetertip position was mixed with the IVUS images on the monitor and the resulting images were stored on an S-VHS videotape.

Follow-up

The follow-up protocol included IVUS at 6 and 24 months follow-up. In case of graft occlusion, the IVUS investigation was performed after successful fibrinolysis. The IVUS cross-sections obtained after endograft placement and at follow-up were matched using the information derived from the radiopaque ruler and the catheter displacement sensing device. The following matched IVUS cross-sections were selected for quantitative analysis (Figure 1): (1) from the endograft, the proximal and distal edge and the site showing the smallest lumen area following endograft placement; (2) from the anastomotic segment, 2–4 cross-sections with an interval of 0.5 to 1 cm. Subsequently, these matched IVUS cross-sections were digitized and analyzed for lumen area (LA), vessel area (VA) and plaque area (PLA). A comparison was made between area measurements obtained immediately after endograft placement and at 6 months follow-up (first follow-up period) and at 6 to 24 months follow-up (second follow-up period).

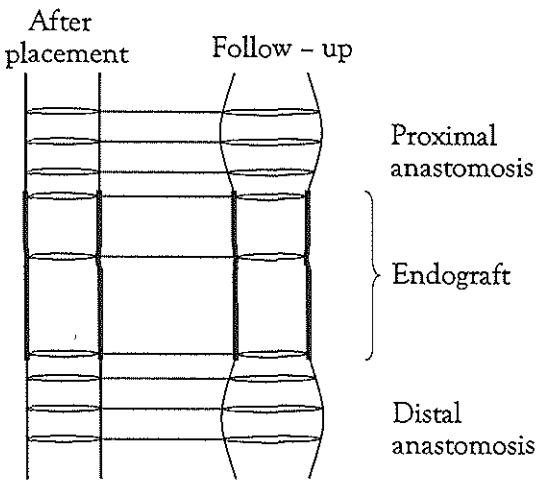

Figure 1. Schematic drawing showing the ePTFE endograft and the proximal and distal anastomotic segments immediately after endograft placement and at follow-up. Intravascular ultrasound measurements are performed on corresponding intravascular ultrasound cross-sections obtained from the endograft and the anastomotic segments.

Statistical analysis

Results are given as mean ± standard deviation, or as median and range. Comparison of the area measurements obtained at baseline and at both follow-up periods was performed by means of the Student's t-test for paired observations. A p-value <0.05 was considered statistically significant.

RESULTS

Clinical events and follow-up characteristics of the 12 patients included in the study are listed in Table 1. Occlusions of the endograft experienced during the first follow-up period (n=4) were successfully treated with fibrinolysis. One stenotic lesion (>50% diameter stenosis) observed distal to the endograft was additionally treated with PTA. During the second follow-up period fibrinolysis was successful in 1 patient, unsuccessful in 2 patients and not performed in 2 other patients. The occlusion of the endograft was compensated by collateral flow in 1 patient and bypass surgery was required in 3 patients. There were 5 patients (4 men and 1 woman) with a complete IVUS follow-up at 8 (range 7-9) and 25 (range 23-26) months. The remaining 7 patients were excluded during the second follow-up period; in 2 patients fibrinolysis was unsuccessful, in 2 patients fibrinolysis was not performed, in 1 patient the IVUS equipment

failed at 25 months follow-up and 2 patients were lost to follow-up.
In the endograft and at the endograft edges lumen area did not change during both follow-up periods (Table 2, Figure 2). Intimal hyperplasia inside the endograft and at the endograft edges was not observed.

Table 1 Clinical events and follow-up characteristics of 12 patients treated with an experimental polytetrafluorethylene endograft.

Patient	Remote endarterectomy used at baseline	Occlusion during 1st follow-up period	Occlusion during 2nd follow-up period	IVUS investigation at 25 months follow-up	Clinical status at 25 months follow-up
1	-	-	-	+	Enduring patent
2	-	-	-	+	Enduring patent
3	-	+	-	+	Enduring patent
4	+	-	-	+	Enduring patent
5	+	-	-	+	Enduring patent
6	+	-	-	-	Enduring patent
7	-	++	+	-	Enduring patent
8	-	++	+**	-	Enduring occluded
9	-	++	+*	-	Bypass surgery
10	-	-	+**	-	Bypass surgery
11	-	-	+*	-	Bypass surgery
12	-	-	-	-	Lost to follow-up

IVUS = intravascular ultrasound; - = no; + = yes; + + = twice; * = fibrinolysis not successful, ** = fibrinolysis not performed.

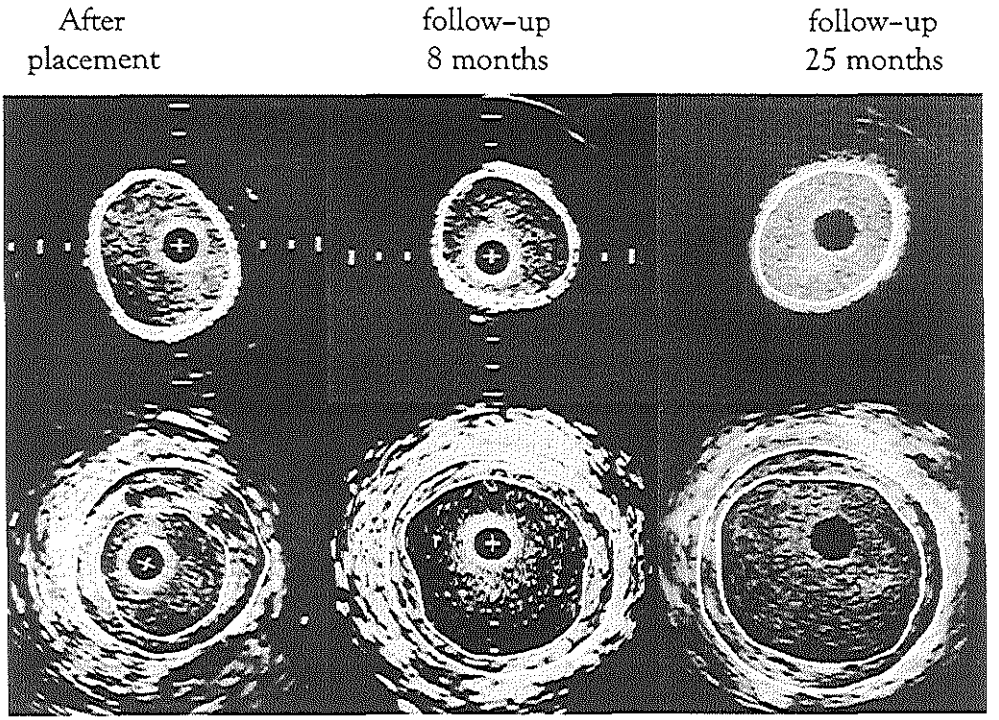

Figure 2. Corresponding intravascular ultrasound cross-sections obtained after endograft placement, and at 8 and 25 months follow-up from the distal endograft edge (upper panel) and anastomotic segment (lower panel) of a patient treated with an ePTFE endograft. The inner contour displays the lumen area (endograft) and the outer contour the vessel area. The endograft did not change at follow-up. At the anastomotic segment an increase in both lumen and vessel area was seen at 8 months follow-up, which tended to stabilize at 25 months follow-up. Plaque area increase encountered in both follow-up periods was similar. (+ = catheter; calibration = 1 mm).

There were 8 anastomotic segments (3 proximal and 5 distal) available for analysis. During the first follow-up period there was a significant increase in LA (37%) and VA (26%) at the anastomotic segments; the increase in PLA (13%) was not significant (Table 2, Figures 2–4). Similarly, during the second follow-up period there was a significant increase in LA (8%) and VA (6%) at the anastomotic segments; the increase in PLA (3%) was not significant. In 1 patient a distinct stenosis observed at the distal anastoosis was treated with percutaneous transluminal angioplasty.

DISCUSSION

In the present study we compared changes in vessel dimensions encountered 6 and 24 months following endograft placement of the femoropopliteal artery. It was found that inside the endograft and at the endograft edges the change in LA encountered during both follow-up periods was minimal and not significant. More important, there was no evidence of endograft recoil or intimal hyperplasia; these latter observations concur with the results of van Sambeek et al.[1] At the anastomoses, however, there was a significant increase in LA and VA associated with no significant change in PLA during both follow-up periods. The extent of LA and VA increase declined from 37% and 26%, respectively during the first follow-up period to 8% and 6%, respectively during the second follow-up period (Table 2). The following issues encountered in the present study deserve specific comment.

Table 2 Data on lumen, vessel and plaque area derived from the endograft (n=5) and the anastomoses proximal and distal of the endograft (n=8), after placement and at 8 and 25 months follow-up seen with intravascular ultrasound.

	Area	After placement (mm^2)	8 months follow-up (mm^2)	25 months follow-up (mm^2)	Δ_1 (mm^2)	Δ_2 (mm^2)
Endograft	Lumen	22.1 ± 5.2	20.3 ± 5.0	20.6 ± 4.0	↓ 1.8 ± 2.9 (-8%)	↑ 0.2 ± 2.0 (1%)
Anastomoses	Lumen	15.4 ± 4.8	21.2 ± 5.5	23.0 ± 5.7	↑ 5.7 ± 4.9 (37%)*	↑ 1.8 ± 1.8 (8%)*
	Vessel	30.5 ± 4.7	38.4 ± 5.0	40.7 ± 4.6	↑ 7.9 ± 5.1 (26%)*	↑ 2.3 ± 2.5 (6%)*
	Plaque	15.2 ± 2.0	17.3 ± 4.8	17.8 ± 4.3	↑ 2.0 ± 4.5 (13%)	↑ 0.5 ± 1.6 (3%)

Values are mean ± SD; Δ_1 = difference at first follow-up; Δ_2 = difference at second follow-up; ↓ = decrease; ↑ = increase; * = $p < 0.05$.

Endograft

In the present study there was no evidence for endograft recoil or intimal hyperplasia inside the endograft and at the endograft edges. This is a remarkable finding since previous IVUS studies in femoropopliteal arteries demonstrated that both intimal hyperplasia and stent area reduction (especially at stent edges and stent junctions) resulted in lumen area reduction.[5,6]

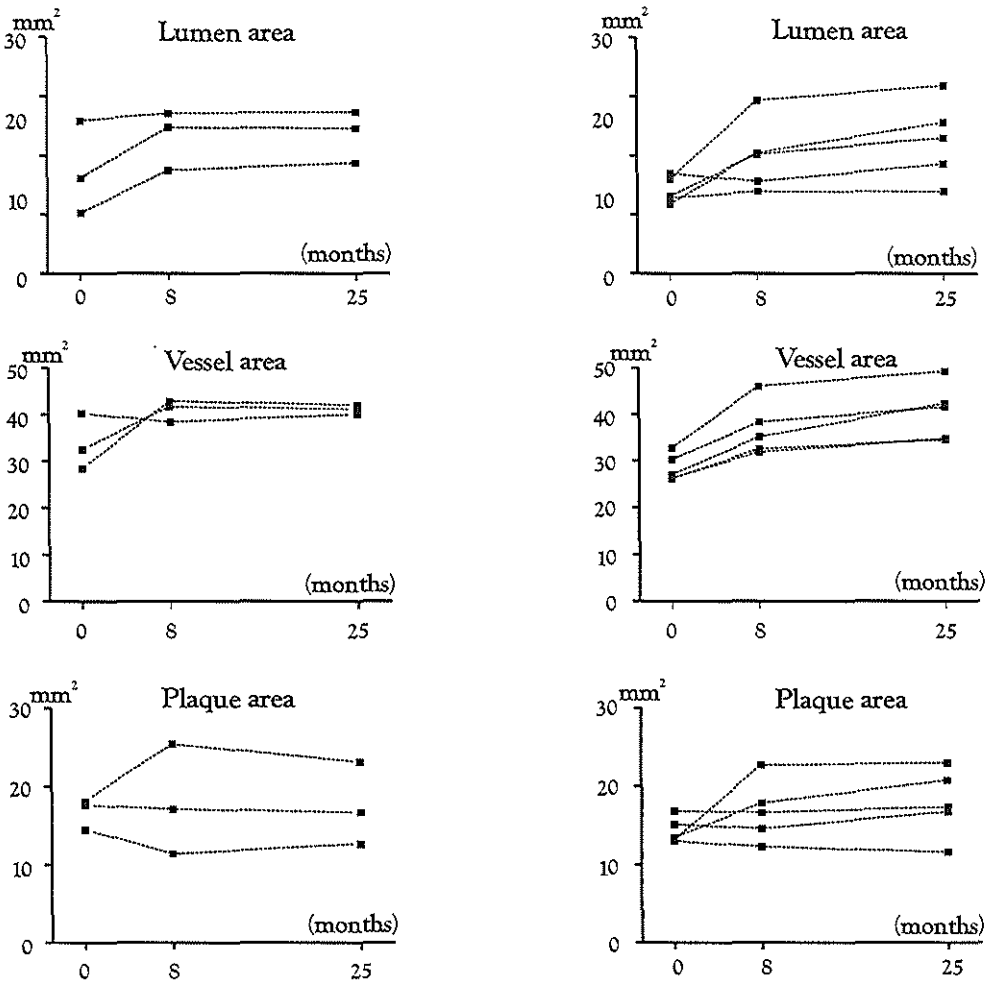

Figure 3. Longitudinal changes seen with intravascular ultrasound in the lumen, vessel and plaque area encountered after endograft placement and at 8 and 25 months follow-up in the proximal (left, n=3) and distal (right, n=5) anastomotic segment adjacent to the endograft. Values are mean ± SD.

Although the use of this new ePTFE endograft seems to overcome the problem of in-stent restenosis, acute occlusion of the endograft was observed in 4 patients during the first follow-up period and in 5 patients during the second follow-up period (Table 1). Except for 1 patient presenting with a small LA proximal to the endograft, no IVUS characteristics (i.e. lumen area of the graft and the proximal and distal anastomosis) predictive for the occurrence of the occlusions were found. It is worth mentioning that in 3 patients in whom the remote endarterectomy was used before placement of the endograft, no acute occlusion was observed. In 2 other patients in whom the endograft was placed across the knee the endograft occluded during both follow-up periods (Table 1; patient nos. 7 and 8). Although reasons for the acute occlusions remain speculative, endograft placement in vascular segments proximal to the knee in combination with remote endarterectomy before implantation of the endograft might limit the problem of acute occlusion of the endograft.

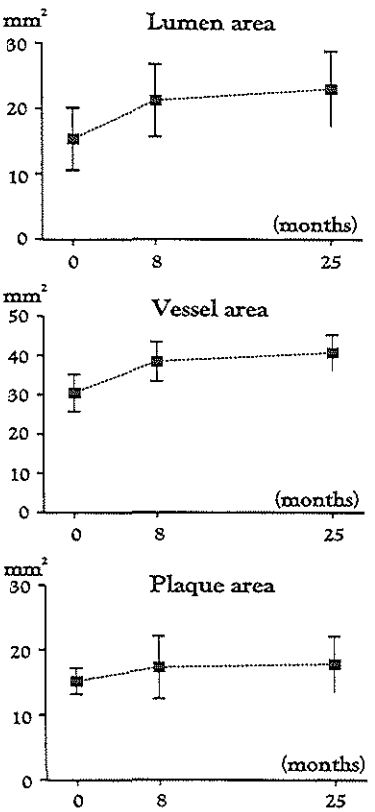

Figure 4. Mean changes seen with intravascular ultrasound in lumen, vessel and plaque area encountered after endograft placement and at 8 and 25 months follow-up in the proximal and distal anastomotic segment (n=8). Values are mean ± SD.

Anastomotic segment

Results from the present study suggest that the local vasodilatory response at the anastomotic segment seen during the first follow-up period tends to stabilize during the second follow-up period. Previously, van Sambeek et al.[1] hypothesized that the vasodilatory process could be explained by: (1) hypercompliance due to local high shear stress, (2) increased arterial pressure at follow-up due to the use of a 7 French sheath compared to a 14 French sheath used during endograft placement, and (3) local tissue hypoxia resulting in neovascularization. Given the

present study results, the hypotheses presented by van Sambeek et al.[1] might be reconsidered:

First: Hypercompliance due to local high shear stress. Hasson et al.[7] postulated that a "para-anastomotic hypercompliant" zone distal to end-to-end anastomosis could be associated with local high stress induced by compliance mismatch in a direct graft to artery anastomosis. This might explain the increase of LA and VA seen at the anastomotic segment. However, dilatation was encountered at both the proximal and distal anastomotic segments which is a counter-argument for this hypothesis.

Second: Increased arterial pressure at follow-up. Difference in arterial pressure at implantation of the endograft (using a 14 French delivery sheath) and at follow-up study (using a 7 French sheath) could be responsible for the dilatation at the anastomotic segment. However, the observation that the vasodilatory response was a local process and that the increase in LA and VA was significant at both follow-up periods suggests that the higher arterial pressure is not responsible for the vasodilatory response.

Third: Local tissue hypoxia resulting in neovascularization. Covering the arterial wall with an endograft may lead to local tissue hypoxia by discontinuation of the interaction between blood and vessel wall. Hypoxia may induce vasodilatation mediated by a local interplay of growth factors, adhesive proteins and other mediators.[8-10] In brief, local hypoxia may stimulate vascular endothelial growth factor (VEGF) dependent signaling by upregulation of the expression of VEGF,[10] a VEGF ligand and a specific signaling receptor.[8] VEGF, in turn, has been shown to stimulate dilatation of coronary microvessels; a mechanism which is mediated by nitric oxide (NO).[9] Since the local vasodilatory response is encountered both at the proximal and distal anastomosis and tends to stabilize at 25 months follow-up, we believe an NO-dependent mechanism of dilatation might be at the basis of the local vasodilatory process.

In addition to the 3 hypotheses presented by van Sambeek et al.[1], we opine that a multicellular inflammatory reaction triggered directly by PTFE could be responsible for the local vasodilatory response. There is evidence that PTFE activates alterations in expression of several surface adhesion molecules on granulocytes, monocytes and platelets such as b2-integrins and intercellular adhesion molecule (ICAM-1).[11-13]

However, the extent to which this inflammatory response can cause a dilatation is not yet fully understood.

Limitation

The main limitation of the present study is the small number of patients available for analysis. However, our study population has provided some additional insight into the progression of the vasodilatory process encountered at the anastomotic segment after endograft placement.

CONCLUSIONS

This longitudinal IVUS study suggests that the ePTFE endograft inhibits plaque growth and constrictive remodeling. The vascular dilatory response at the anastomotic segment seen at 8 months follow-up tends to stabilize at 25 months follow-up. This endovascular anastomosis acts as an "ideal" end-to-end anastomosis, jeopardized by the unexplained acute occlusions. Momentarily, these acute occlusions are subject to further investigation.

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CHAPTER 4

Longterm Follow-up of ePTFE Balloon-expandable Endografts in Femoropopliteal Arteries

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Submitted for publication.

ABSTRACT

Purpose: To evaluate the longterm clinical outcome of patients treated with an polytetrafluoroethylene (ePTFE) endograft for long-segment obstructive and occlusive disease of the femoropopliteal artery.

Methods: 89 patients (median age 69 years, range 43 to 81) were treated with an ePTFE (mean length 29 cm) endograft for obstructive disease of the femoropopliteal artery. The follow-up protocol included Doppler scanning, duplex scanning or angiography of the endograft. Primary and secondary patency rates of the ePTFE endograft after 6, 12, 24 and 36 months follow-up, respectively, were analyzed.

Results: At baseline, patients presented with disabling claudication (n=73) or critical ischemia (n=16). A high-grade stenosis (mean length 9 cm) was involved in 7 patients and an occlusion (mean length 19 cm) in 82 patients. At the end of the study, the endograft was patent in 52 patients (median 17 months [range 7 to 50]), occluded in 35 patients (median 7 months [range 0 to 40]) and 2 patients had deceased of no vascular cause (6.5 and 7 months, both with a patent endograft). At follow-up, the primary and secondary patency rates of the ePTFE endograft were 71% and 83% at 6 months, 57% and 69% at 1 year, 45% and 49% at 2 years and 30% and 44% at 3 years, respectively.

Conclusions: The success of this new ePTFE endograft is limited. Therefore, refinements of the endograft are necessary if this new, minimal invasive, technique wants to compete with conventional bypass surgery.

INTRODUCTION

One of the major complications of percutaneous transluminal angioplasty (PTA) for obstructive arterial disease is the occurrence of restenosis, which is the net result of both intimal hyperplasia and vascular remodeling.[1-4] To prevent the development of intimal hyperplasia and vascular remodeling after vascular interventions, stents have been introduced. However, the benefits of stents in femoropopliteal arteries are still controversial.[5-8] Both intimal hyperplasia and stent area reduction have been observed to result in lumen area reduction, especially at stent edges and stent junctions.[9,10] In order to prevent these important factors from contributing restenosis, a polytetrafluorethylene (ePTFE) endograft was developed to cover the damaged arterial wall immediately after vascular intervention. In previous studies using intravascular ultrasound we established that the ePTFE endograft applied in femoropopliteal arteries inhibits intimal hyperplasia and constrictive vascular remodeling.[11,12] Furthermore, at the anastomotic segments adjacent to the endograft a local dilatory response was observed at 6-months follow-up, which tended to stabilize at 2-years follow-up. However, these positive findings were jeopardized by the occurrence of acute occlusions of the endograft. The aim of the present descriptive international multicenter study was to evaluate the longterm clinical outcome of patients that received an ePTFE endograft.

MATERIALS AND METHODS

Patients

From October 1996 to August 2000, 89 patients (68 men; median age 69 years (range 43-81 years) with long-segment obstructive disease of the femoropopliteal artery were treated with an ePTFE endograft. The study was conducted at the following institutions (with the number of patients enrolled in parentheses): St. Antonius Hospital, Nieuwegein (41); Erasmus University Medical Center Rotterdam (32); Catharina Hospital, Eindhoven (11); University Hospital Leuven (4). The investigation was approved by the local committee on Human Research in each hospital. Patients were included in the study after giving informed consent.

Endograft

The endograft used was a balloon-expandable thin-walled ePTFE graft (Enduring™ vascular graft, W.L. Gore & Associates, Flagstaff, AZ, USA) with a 4-mm outer diameter. The graft wall contains ring-shaped ePTFE reinforcements that are integrated in the material (no metal parts). The rings are compression resistant comparable to self-expandable stents (Figure 1). Gold markers are incorporated in the graft to allow visualization under fluoroscopy. The graft can be cut in any desired length and, depending on the balloon-size used, the graft can be expanded to a maximum inner diameter of 7 mm, with a recoil of (10%). This maneuver fixes the graft to the arterial wall providing proper seal over its entire length.

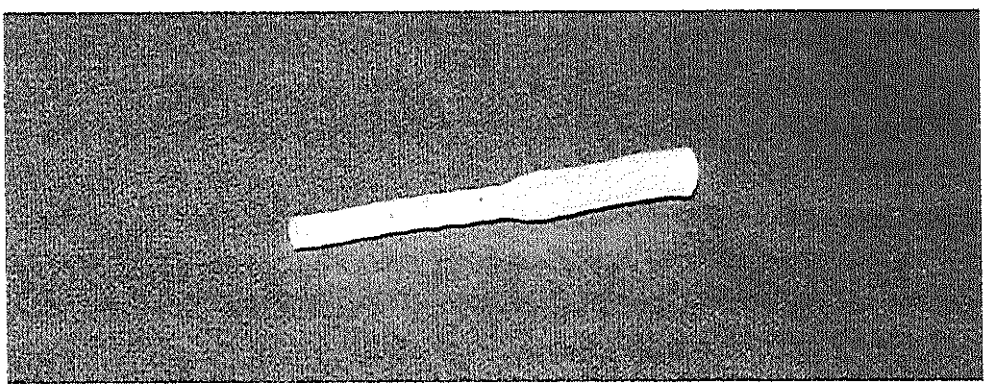

Figure 1. Sample of a partially dilated polytetrafluoroethylene (ePTFE) endograft.

Operative technique

All procedures were performed in the operating theater under fluoroscopic and angiographic guidance. Arterial access was gained through a surgical cutdown of the common or superficial femoral artery. Initially, in the first 10 patients a hydrophilic guidewire was placed beyond the lesion and predilatation with a 5 to 7 mm balloon was performed to facilitate passage of a 14-F sheath. Subsequently, it was decided to modify the procedure. In the remaining 79 patients, remote endarterectomy with a MollRing Cutter™ (Vascular Architects, Inc., Portola Valley, CA, USA) was performed before placement of a guidewire (Figure 2). Thereafter, the endograft was mounted on a balloon catheter with a pressure of 2 atmospheres and positioned in the femoropopliteal

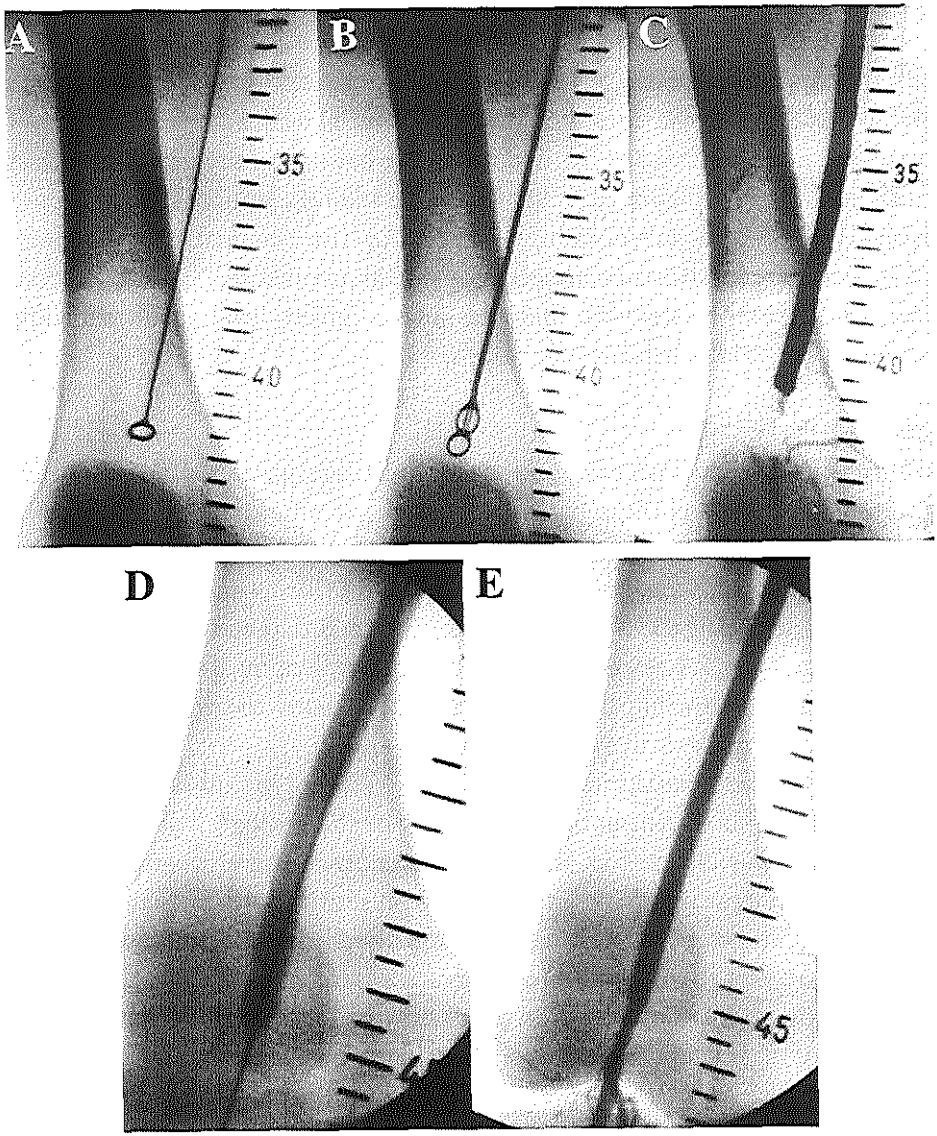

Figure 2. Angiographic images of a patient during polytetrafluoroethylene (ePTFE) endograft placement. Frames A and B show the Mollring Cutter at the proximal popliteal artery performing the remote endarterectomy. (A) closed position of the Mollring Cutter and (B) open position of the Mollring Cutter. Frame C shows the femoropopliteal artery after the remote endarterectomy. Note the distal occlusion due to the presence of a plaque dissection after remote endarterectomy. Frame D shows an expanded dilatation balloon, fixing the ePTFE endograft to the arterial wall. Frame E shows a control angiogram immediately after endograft placement, showing a good appositioned and widely patent endograft.

segment under fluoroscopic guidance. To cover the entire treated segment of the femoropopliteal artery, care was taken to position the endograft with 1 cm overlap distally over the untreated (normal) arterial wall. After retraction of the sheath the endograft was expanded using the balloon catheter with a pressure of 12 atmospheres (Figure 2). The proximal end of the endograft was cut to the desired length and subsequently sutured to the femoral artery using an end-to-end anastomosis or an end-to-side anastomosis.
After endograft placement patients were given oral anti-coagulants, platelet-aggregation-inhibitors or both.

Data collection

Baseline data collected on each patient included age, gender, diabetes mellitus, hypertension, hypercholesterolemia, history of smoking, angina pectoris, myocardial infarction, cerebrovascular accident or transient ischemic attack, pulmonary disorders and vascular intervention prior to endograft placement. Data collected during the operating procedure included operating time, length of pre-dilatation PTA or remote endarterectomy, length of lesion/endograft, balloon-size (diameter) and type of anastomosis used to suture the proximal part of the endograft to the arterial wall.
Depending on the institution the follow-up protocol included regular duplex scanning, Doppler scanning or angiography of the endograft. Early failure of the endograft was defined as an acute occlusion of the endograft within 30 days after the operating procedure. Patients presenting with an acute occlusion of the endograft were treated with fibrinolysis. In case fibrinolysis was not performed or was unsuccessful, conservative treatment was given or bypass surgery or lower-limb amputation was performed depending on the clinical condition of the leg. Primary and secondary patency rates of the ePTFE endograft at 1, 6, 12, 18, 24 and 36 months follow-up were analyzed with SPSS (version 9.0). The primary assisted patency rate was not calculated because intervention before graft occlusion rarely was performed.

RESULTS

Baseline patient characteristics and presenting symptoms are shown in Table 1. Patients presented with disabling claudication (n=73) or critical ischemia (n=16).

A high-grade stenosis (mean length 9 cm) was involved in 7 patients and an occlusion (mean length 19 cm) in 82 patients. Characteristics of the operating procedure and follow-up data are shown in Table 2.

Table 1 Patient characteristics and presenting symptoms of 89 patients treated with an ePTFE endograft.

Patient characteristics	
Age (years) (mean ± SD)	67.2 ± 8.8
Sex (male:female)	68:21
Diabetes Mellitus	23 (26%)
Hypercholesterolemia	34 (38%)
Hypertension	43 (48%)
Pulmonary disease	10 (11%)
History of smoking	52 (58%)
History of angina pectoris	16 (18%)
M.I.	17 (19%)
T.I.A./C.V.A.	12 (13%)
Prior vascular intervention	55 (62%)
Presenting symptoms	
Stenosis:occlusion	7:82
Length of stenosis (cm)	9.3 ± 6.1
Length of occlusion (cm)	18.9 ± 7.3
Run-off vessels (1:2:3) (n=73)	9:19:45
Rutherford classification (2:3:4)	73:7:9

M.I. = myocardial infarction;
T.I.A. = transient ischemic attack;
C.V.A. = cerebrovascular accident.

Table 2 Characteristics of the operating procedure and follow-up data of 89 patients treated with an ePTFE endograft.

Operating procedure		
Operating time (minutes) (median [range])	180 [75 - 290]	
Endarterectomy used	79 (89%)	
Length of endograft (cm)	29 ± 6	
Balloonsize proximal (5 : 6 : 7)	2 : 53 : 24	(10 missing)
distal (5 : 6 : 7)	6 : 55 : 18	(10 missing)
Follow-up		
Antithrombotics		
Oral anticoagulants (Coumadin)	29	
Platelet-agregation-inhibitors (Aspirin)	44	
Both	12	
No data	4	
Additional treatment		
PTA/stent proximal anastomosis	9	
PTA endograft	3	
PTA/stent distal anastomosis	19	
Current status (February 2001)		
Patent (months) (median [range])	52	(17 [7 - 50])
Occluded (months) (median [range])	35	(7 [0 - 40])
Deceased (months)	2	6.5 and 7

PTA = percutaneous transluminal angioplasty

The median duration of the operating procedure was 180 minutes. The ePTFE endograft (29 ± 6 cm) was sutured to the proximal femoral artery using an end-to-end anastomosis or an end-to-side anastomosis. Antithrombotic therapy was started immediately after endograft placement; 29 patients received Coumadin, 44 patients Aspirin and 12 patients received both.

Graft patency

Figure 3 presents the fate of the 89 patients treated with an ePTFE endograft.

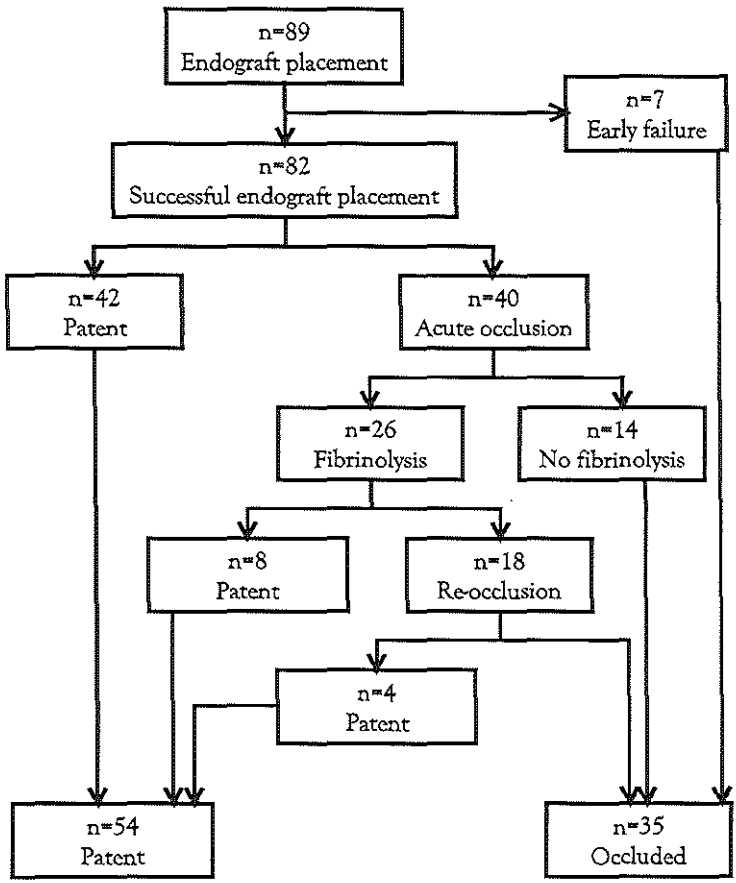

Figure 3. The fate of 89 patients that received a polytetrafluoroethylene (ePTFE) endograft.

Early failure of the endograft was encountered in 7 of the 89 patients. In 42 patients the endograft remained patent during the entire follow-up period. The other 40 patients presented with an acute occlusion later at follow-up. These patients were either treated conservatively (n=5), with femoropopliteal bypass surgery (n=9) or fibrinolysis was performed successfully (n=26).

Table 3 Primary patency rates of 89 patients treated with an ePTFE endograft.

Time interval (months)	Patients at risk	Events (occlusion)	Withdrawn			Interval patency	Cumulative primary patency (%)
			Permanent occlusion	Time	Death		
1	89	7	0	0	0	0.923	92.3
6	82	19	7	0	0	0.768	70.9
12	57	11	8	15	2	0.807	57.2
18	33	6	10	14	0	0.818	46.8
24	24	1	6	3	0	0.958	44.9
36	9	3	3	12	0	0.667	29.9
>36	8		1				
Totals	89	47	35	44	2		

Subsequently, re-occlusion of the endograft was encountered in 18 of the 26 patients treated successfully with fibrinolysis. In 4 of these patients a repeat fibrinolysis was performed successfully. The remaining 14 patients were treated conservatively (n=4), with femoropopliteal bypass surgery (n=8) or with lower-limb amputation (n=2).

Table 4 Secondary patency rates of 89 patients treated with an ePTFE endograft.

Time interval (months)	Patients at risk	Permanent occlusion	Withdrawn		Interval patency	Cumulative secondary patency (%)
			Time	Death		
1	89	7	0	0	0.923	92.3
6	82	8	0	0	0.902	83.3
12	57	10	15	2	0.825	68.7
18	33	6	14	0	0.818	56.2
24	24	3	3	0	0.875	49.2
36	9	1	12	0	0.889	43.7
Totals	89	35	44	2		

At the end of the study the endograft was patent in 52 patients (median 17 months [range 7 to 50]), occluded in 35 patients (median 7 months [range 0 to 40]) and 2 patients had deceased of no vascular cause (6.5 and 7 months, both with a patent endograft) (Table 2). In the present study no independent risk factors for the acute occlusions were encountered.
Tables 3, 4 and 5 present the primary and secondary patency rates of the ePTFE endograft. Figure 4 shows the Kaplan-Meier plot of the primary and secondary patency data of the 89 patients treated with an ePTFE endograft.

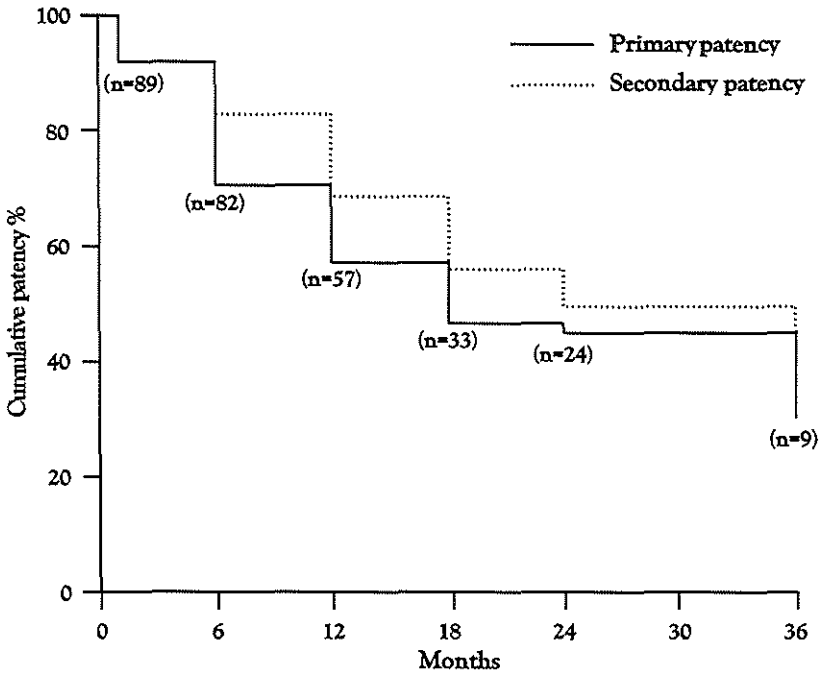

Figure 4. Kaplan-Meier plot of the primary and secondary patency of 89 patients that received a polytetrafluoroethylene (ePTFE) endograft. n = number of patients at risk.

The primary patency rate was 92% at 1-month, 71% at 6-months, 57% at 12 months, 47% at 18-months, 45% at 24-months and 30% at 36-months follow-up, respectively (Table 3). The secondary patency rate was 92% at 1-month, 83% at 6-months, 69% at 12 months, 56% at 18-months, 49% at 24-months and 44% at 36-months follow-up, respectively (Table 4).

DISCUSSION

For patients with long-segment obstructive disease of the femoropopliteal artery, femoropopliteal bypass surgery is the most common treatment modality. However, conventional surgical femoropopliteal bypass surgery is associated with various problems and/or complications such as the need for multiple incisions and the associated risk of wound infection, haematoma or haemorrhage, neuralgia around the knee joint and graft infection.[13-15] Recently, the endobypass technique has emerged as a promising technique to provide a less invasive alternative to supragenicular bypass surgery in the treatment of long-segment femoropopliteal obstuctive disease.[16-21] Encouraged by this endobypass technique, a new ePTFE endograft with ring-shaped ePTFE reinforcements that are integrated in the material was developed. Previous intravascular ultrasound studies using this completely supported ePTFE endograft have shown that endograft recoil and plaque growth were not encountered at 6-months[11] and 2-years follow-up.[12] Furthermore, at the anastomotic segments adjacent to the endograft, an unexplained local vasodilatory response was observed at 6-months follow-up, which tended to stabilize at 2-years follow-up. However, these positive findings seen after placement of the ePTFE endograft were jeopardized by the occurrence of acute early and late occlusions of the endograft. In the present study, the longterm clinical follow-up data of 89 patients treated with an ePTFE endograft were reported.

Experience with endografts

In the present study early failure of the endograft was observed in 7 of the 89 patients (8%). At the end of the study the endograft was patent in 54 of the 89 patients (61%) and occluded in 35 patients (39%). In addition, in 10 of the 54 patients (19%) with a patent endograft at the end of the study, an acute occlusion of the endograft during follow-up was successfully treated with fibrinolysis.

Early failure of the endograft used for treatment of long-segment femoropopliteal obstructive disease in 4 other studies (9% to 14%) was similar as observed in the present study.[18-21] In these studies an endograft was used that required a stent at the distal anastomosis to provide proper seal of the endograft to the arterial wall and a surgical procedure to attach the proximal

anastomosis of the endograft. In contrast, in our study an endograft with ring-shaped reinforcements was used, making stent-placement at the distal anastomosis unnecessary in order to achieve proper seal of the endograft.

Table 5 Primary and secondary patency rates and the number of acute occlusions in patients treated with endografts or conventional bypass surgery.

	Endograft					Bypass
	Present study	Diethrich[18]	Spoelstra[19]	Stockx[20]	Ho[21]	Abbott[15]
Primary patency						
6 months	71%	76%	80%	<50%	85%	88%
1 year	57%	72%	73%	-	70%	75%
2 years	45%	-	-	-	61%	63%
3 years	30%	-	-	-	-	59%
Secondary patency						
6 months	83%	86%	90%	-	93%	-
1 year	69%	84%	86%	-	78%	88%
2 years	49%	-	-	-	70%	80%
3 years	44%	-	-	-	-	78%
Acute occlusions						
	40/89 (45%)	15/50 (30%)	11/55 (20%)	(>50%)	5/14 (36%)	55/231 (24%)

Primary and secondary patency rates and the percentage of patients that presented with an acute occlusion of the endograft during follow-up in the present study and the studies reported by others are shown in Table 5.[18-21] The primary and secondary patency rates at 6-months follow-up in our study were similar to those reported by Diethrich et al.[18] and Spoelstra et al.[19] However, the patency rates at 1-year follow-up in those 2 studies were better than the patency rates in our study. The study reported by Stockx et al.[20] using the same

technique as described by Spoelstra et al[19] could not duplicate Spoelstra's favourable results. Despite a similar initial technical success rate of 98%, more than 50% of the endografts occluded within 6-months. Recently, Ho et al.[21] reported on a study of 14 patients treated with an endograft after remote endarterectomy of the femoropopliteal artery (Table 5). Overall, the reported primary and secondary patency rates were similar to those reported without additional endarterectomy by Diethrich et al.[18] and Spoelstra et al.[19]: 85% and 93%, respectively, at 6-months follow-up, 70% and 78%, respectively, at 1-year follow-up and 61% and 70%, respectively, at 2-years follow-up. The authors believed that deploying an endograft after remote endarterectomy should decrease the risk of an acute occlusion at follow-up. However, in 5 of the 14 patients an endograft occlusion was encountered. It was suggested that completely supported endografts might increase patency rates. However, the use of an ePTFE endograft with ring-shaped reinforcements integrated in the ePTFE endograft as tested in the present study did not improve primary and secondary patency rates. Furthermore, in the present study no differences were encountered between patients in whom remote endarterectomy before endograft placement was performed and patients in whom remote endarterectomy was not performed. Thus, remote endarterectomy may not be considered as obligatory strategy before endograft placement.

Despite the enthusiastic reports of some authors, the use of endografts for treatment of long-segment femoropopliteal obstructive disease is still premature. The number of acute occlusions encountered in the present study and studies by others[18-21] are high, compared to approximately 24% acute occlusions encountered after conventional prosthetic above-knee femoropopliteal bypass grafting at 3-years follow-up (Table 5).[15] Furthermore, patency rates for conventional prosthetic above-knee femoropopliteal bypass grafting are still superior (Table 5); primary and secondary patency rates are 75% and 88% at 1-year, 63% and 80% at 2-years, and 59% and 75% at 3-years follow-up, respectively.[15]

Reasons why acute occlusions are more common after endograft placement than after conventional bypass surgery remain unknown. In the present study there was no difference in primary and secondary patency rates between patients treated with Aspirin and patients treated with Coumadin. We opine that the use of heparin-coated endografts or a different antithrombotic

strategy after endograft placement, for example, the use of Plavix, may decrease the number of acute occlusions. It is beyond dispute that the acute occlusions deserve further investigation.

CONCLUSIONS

Endovascular endograft placement could be an attractive, minimal invasive, alternative for conventional bypass surgery in treatment of patients with long-segment obstructive or occlusive disease of the femoropopliteal artery. However, as long as the problem of the high number of acute occlusions has not been solved, this new endograft used in the present study can not be considered as an improved treatment modality.

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CHAPTER 5

Gamma Radiation Induces Positive Vascular Remodeling After Balloon Angioplasty:
A prospective, randomized intravascular ultrasound study

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Submitted for publication

ABSTRACT

Background: Endovascular brachytherapy (EBT) has shown to prevent restenosis after percutaneous transluminal coronary angioplasty (PTCA) in both animal and clinical studies. However, as yet, the effect of EBT on plaque growth and vascular remodeling in peripheral arteries is unknown.

Objective: This intravascular ultrasound (IVUS) study evaluates the effect of EBT on the extent of plaque growth and vascular remodeling after PTA of the femoropopliteal artery.

Methods: Twenty-four patients with obstructive disease of the femoropopliteal artery underwent standard PTA. Patients were randomized to receive additional gamma-radiation after PTA. IVUS investigation was performed immediately after PTA and at 6-months follow-up. A comparison was made between patients without EBT (n=16) and with EBT (n=8) in the change in both quantitative data (lumen, vessel and plaque area) and qualitative data (calcified lesion and dissection) seen with IVUS at 6-months follow-up.

Results: At follow-up, IVUS revealed a significant difference in lumen area change between patients without EBT and patients with EBT (-9% and +23%, respectively): this difference was due to a significant difference in vessel area change (+2% and +19%, respectively). In both groups of patients a similar increase in plaque area (+12% and +16%, respectively) was encountered. Qualitative IVUS data showed no change in the extent and number of calcified lesions in both groups of patients. However, dissections encountered immediately after PTA were absent at follow-up in patients without EBT, whereas in 4 of the 8 patients with EBT a persistent dissection was encountered.

Conclusion: This randomized IVUS study showed that gamma-radiation after PTA has a positive effect on lumen dimensions at 6-months follow-up by inducing positive vascular remodeling; gamma-radiation seemed not to affect plaque growth. In addition, gamma radiation has effect on the healing process of dissections after PTA.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) is in common use for revascularisation of obstructive disease of femoropopliteal arteries. However, restenosis continues to be the main problem of this intervention with reported restenosis rates in up to 80% of patients at 1-year follow-up.[1-4] Intravascular ultrasound (IVUS) studies have shown that the restenosis process following PTA was the result of both plaque growth (i.e. intimal proliferation) and vascular constriction.[5-9]

To diminish the vascular response to intervention, endovascular brachytherapy (EBT) has been proposed. The effective use of EBT to prevent intimal proliferation in animal models after balloon arterial injury has been demonstrated in preclinical studies using histology as gold standard.[10-13] Similarly, there is angiographic and clinical evidence that EBT reduces restenosis following both PTA[14-19] and stent placement of coronary arteries.[18,20-25] However, as yet, the effect of EBT on vascular remodeling is unknown. The aim of the present randomized study was to determine the effect of EBT on the extent of plaque growth and vascular remodeling 6 months after PTA of the femoropopliteal artery using IVUS.

METHODS

Study group

In this multicenter trial, named VARA (VAscular RAdiotherapy), 4 hospitals participated. Between September 1998 and August 2000, 38 patients (24 men; median age 65 (range 44-85) years) with disabling claudication were recruited. Entry criteria included angiographically proven femoropopliteal arterial stenosis (>50% diameter stenosis) or occlusion, lesion length <10 cm, patients aged 40 to 85 years and no inflow obstruction or significant stenosis in the iliac artery. Exclusion criteria included impaired renal function (serum creatinine >160 μmol/l), acute ischemia, pregnancy and life expectancy less than 12 months (Table 1). The study was approved by the local Committee on Human Research. Patients were included in the study after having given informed consent.

Table 1 Inclusion and exclusion criteria of the VARA (VAscular RAdiotherapy) trial.

Inclusions
● Patients aged 40 to 85 years
● Symptomatic femoropopliteal arterial disease eligible for PTA
● Single lesion < 10 cm
● Reference lumen diameter of 4 to 8 mm
● Written informed consent
Exclusions
● Life expectancy < 12 months
● Renal insufficiency (serum creatinine > 160 (μmol/l)
● History of radiation therapy
● Obstructive disease of the iliac artery
● Single vessel run-off
● PTA > 11 cm

PTA = percutaneous transluminal angioplasty.

Procedure

All patients underwent a standard PTA procedure. Heparin (5000 IU intravenously) was given at the onset of the procedure and additional Heparin (5000 IU intravenously) was given in case of EBT because of the delay between the two interventions. Following intervention patients received standard oral anticoagulation (Ascal 100 mg daily) for 6 months. Patients were randomized to PTA only or to PTA with additional EBT using a minimization method (permuted blocks stratified by center, stenosis/occlusion and lesion length).

Intravascular ultrasound

Intravascular ultrasound was performed following angiographic successful PTA (diameter stenosis <50%). A guidewire-tipped 4.3F catheter (Jomed, Ulestraten, The Netherlands; 0.035") containing a single rotating ultrasound element (30 MHz) was used. Antegradely through a 7F sheath in the ipsilateral femoral artery the IVUS catheter was advanced over a guidewire beyond the lesion. The guidewire was then removed and a manual pull-back of the IVUS catheter was performed. The location of the IVUS cathetertip was documented using fluoroscopy, a radiopaque ruler and a displacement sensing device.[26] The latter device documents the location of the cathetertip in relation to the patella in steps of 0.01 cm during the pull-back maneuver.[26] The cathetertip position was documented together with the IVUS images on the monitor and the resulting images were stored on an S-VHS videotape for off-line analysis.

Radiation therapy

Immediately after the IVUS study was performed, radiation was given in those patients randomized for EBT using a 5F over-the-wire delivery catheter. Radiation was performed in the department of radiotherapy under supervision of a radiotherapist. A specially designed EBT centering catheter (Nucletron, Veenendaal, the Netherlands) was used which ensures optimal dose distribution over the vessel wall. The catheter was connected with a computerized afterloader, microSelectron HDR with an iridium-192 radioactive source. Dose distribution was calculated on the basis of the post-PTA angiographic lumen diameter at the level of the target lesion and the length of the dilated segment with an additional 1 cm at both the proximal and distal ends. The actual length of irradiation equalled the length of the dilated segment (maximal 11 cm) plus 1.5 cm proximal and distal, so that the 100% isodose reaches 1 cm beyond the proximal and distal ends: this was performed using a standard procedure. The prescribed dosage must be applied to the adventitia. Distance from the source axis to the adventitia was defined as the radius of the dilated vessel lumen plus 2 mm. In practice this means that this distance corresponded with the diameter of the EBT catheter balloon divided by 2 and plus 2 mm.

A dose of 14 Gy was delivered at the prescribed points along the length of the dilated segment at a previously defined distance from the source axis.

Actual irradiation was applied by the 192-iridium source which was computer-guided to traverse the entire dilated segment in 5 mm steps moving from distal to proximal. After treatment, the catheter was removed after emptying the EBT centring balloon.

Follow-up

The follow-up protocol included single plane angiography and IVUS imaging 6 months after intervention. The angiograms obtained at follow-up were scored for lumen diameter stenosis by an independent radiologist blinded to EBT data. Angiographic restenosis of the vascular segment subjected to PTA was defined as >50% diameter stenosis. If a >50% diameter stenosis was involved at the reference segment (i.e. the segment proximal or distal to the dilated vascular segment) it was considered as a de novo stenosis.
The IVUS procedure was performed in the same manner as described before. With the information of the displacement sensing device, the radiopaque ruler and anatomic markers such as side-branches and typical shaped calcifications, the IVUS cross-sections obtained immediately after PTA and at follow-up were matched. To ensure that the IVUS cross-sections obtained after intervention corresponded with those that were obtained at follow-up examination, the cross-sections were studied side-by-side and frame-to-frame. Matched IVUS cross-sections obtained from the *treated site* and from the non-dilated *reference site* were selected with 1 cm interval for analysis. In addition, from patients who received EBT, one IVUS cross-section located at the proximal and one at the distal junction between the treated and reference site (i.e. *junction site*) were selected for analysis. These junction sites included a 1 cm non-dilated segment which received EBT.

Quantitative analysis

For the assessment of lumen, vessel and plaque area seen on IVUS a digital video analyzer system (IBM Corp. Boca Raton, USA) was used.[27] 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 encompassed by the media-adventitia border. The plaque area was calculated by subtracting the lumen area from the vessel area.

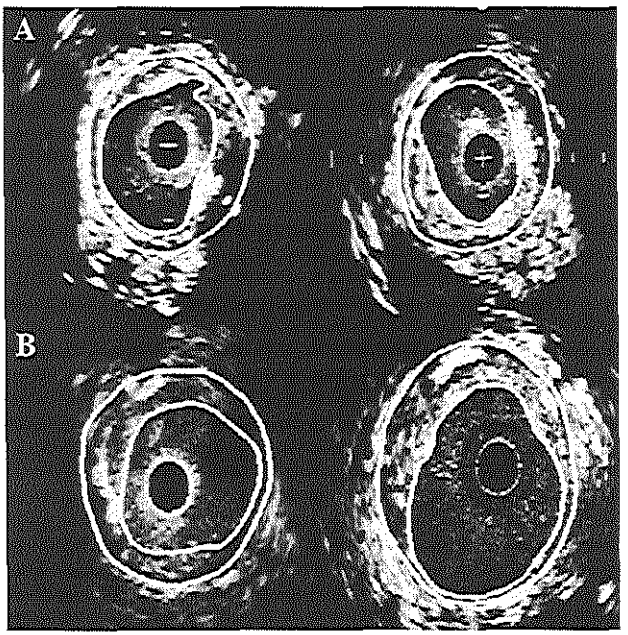

Figure 1. Corresponding intravascular ultrasound cross-sections obtained after percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery (left) and at 6-months follow-up (right) from a patient without endovascular brachytherapy (EBT) (A) and a patient with EBT (B). At follow-up, the patient without EBT (A) showed a decrease in both lumen and vessel area, whereas the patient with EBT (B) showed an increase in both lumen and vessel area. Plaque area increase encountered in both patients (A and B) was similar.
Calibration = 1 mm; + = catheter; ⇑ = increase; ⇓ = decrease

When image quality was inadequate or extensive dropout due to calcification (>120 degrees of the circumference) was encountered, the analysis of vessel area could not be performed and these IVUS cross-sections were excluded.

Qualitative analysis

IVUS cross-sections obtained after intervention and at follow-up were evaluated for hard lesion (i.e. calcified) and dissection. Calcified lesions were recognized by the presence of a bright echo structure casting peripheral shadowing. For the present study a calcified lesion was present if its arc was >30 degrees of the circumference. Dissection was defined as the presence of a tear in the intimal surface separating the lesion from the underlying arterial wall.[28]

Analysis of data

First, lumen, vessel and plaque area measurements from each individual patient were averaged over the number of IVUS cross-sections acquired. Second, the averaged area measurements seen immediately after intervention and at 6-months follow-up were compared and the changes were calculated. First, a comparison was made between patients without EBT and with additional EBT after PTA in lumen, vessel and plaque area change seen at the treated site and at the reference site. Second, a comparison was made between the change in lumen, vessel and plaque area seen at the treated site, the reference site and the junction site in patients with EBT. Finally, the relation between morphologic features (i.e. calcified lesion and dissection) and the use of additional EBT was assessed. Observers were not aware of any patient characteristics or of the use/non-use of EBT.

Statistical analysis

Results are given as mean ± SD. To analyze differences between both groups of patients, the Student's t-test was used. Differences between both groups of patients for non-parametric data were analyzed using the Mann-Whitney test. The statistical significance level was set at $p<0.05$. The reproducibility of IVUS parameters used in this study has been reported previously.[29]

RESULTS

A complete IVUS follow-up (7.4 ±1.6 months) was obtained in 24 (17 men, 7 women) of the 38 patients. The remaining 14 patients were excluded from the study for the following reasons: in 1 patient (randomized for EBT) additional PTA was necessary after IVUS investigation resulting in a treated segment too long for EBT; 2 patients presented with restenosis within 5-months follow-up (1 with and 1 without EBT); 5 patients were lost to follow-up (2 without and 3 with EBT); 3 patients died (no vascular cause; 1 without and 2 with EBT); and in 3 patients IVUS investigation was not performed at follow-up due to failure of the IVUS equipment (n=1; with EBT), the presence of an iatrogene dissection due to the arterial puncture (n=1; with EBT) and occlusion of the artery (n=1; with EBT).

Of the 24 patients with a complete follow-up 8 patients received additional EBT. Table 2 presents demographic features, presenting symptoms, data on the

Table 2 Baseline patient characteristics, procedural data and follow-up data obtained in patients without endovascular brachytherapy (EBT) and with EBT.

	Without EBT (n=16)	With EBT (n=8)	p-value
Patient characteristics			
Men/women	11/5	6/2	0.76
Age (mean ± SD) (years)	65.9 ± 9.9	60.0 ± 9.8	0.18
Diabetes mellitus	3 (19%)	2 (25%)	0.74
Systemic hypertension	7 (44%)	5 (63%)	0.41
Hypercholesterolemia	4 (25%)	5 (63%)	0.08
Cigarette smoking	10 (63%)	7 (88%)	0.17
Fontaine classification (2B/3/4)	6/6/4	6/1/1	0.13
Stenosis/occlusion	10/6	5/3	1.00
Lesion length (cm)	3.4 ± 2.9	5.2 ± 3.3	0.18
Procedure			
Balloon diameter used (4/5/6)	1/6/9	0/4/4	0.89
PTA length (cm)	7.1 ± 3.6	8.6 ± 2.7	0.33
Follow-up			
Clinical restenosis	3 (19%)	1 (13%)	0.71
Angiographic stenosis	5 (31%)	3 (38%)	0.76
- restenosis	5	0	0.08
- de novo stenosis	0	3	0.01

SD = Standard Deviation; PTA = percutaneous transluminal angioplasty

procedure and follow-up data. With regard to patient characteristics and the procedural data, no significant difference between patients without EBT and

with EBT was seen. Angiographic, duplex and Doppler values at baseline were similar. In 38% of both groups of patients a total occlusion was involved. The remaining patients presented with a stenosis. At follow-up, restenosis was observed only in patients without EBT (n=5). This difference between patients without and with EBT in the occurrence of restenosis was not significant (p=0.08).

Change in quantitative IVUS data

In total, 441 IVUS cross-sections (without EBT n=275; with EBT n=166) were analyzed for the change in lumen, vessel and plaque area at 6-months follow-up; 180 (8 ± 3 per patient) from the treated site, 245 (10 ±3 per patient) from the reference site and 16 from the junction site (2 per patient).

Table 3 summarizes the quantitative IVUS data derived from the treated and reference site in patients without EBT and with EBT. Immediately after PTA no significant difference in lumen, vessel and plaque area was encountered between both groups of patients at the treated site and the reference site. At follow-up, at the treated site a significant difference between both groups of patients was observed in the change in lumen and vessel area (Figure 1); in patients without EBT a decrease in lumen area of 9% and an increase in vessel area of 2% was encountered, while in patients with EBT an increase in lumen and vessel area of 23% and 19%, respectively, was seen. Plaque area increase in both groups of patients was similar (12% and 16%, respectively). At the reference segment no significant differences between both groups of patients in lumen, vessel and plaque area were encountered (Table 3).

Table 4 summarizes the quantitative IVUS data derived from the treated, junction and reference site acquired in patients with EBT. The changes in lumen, vessel and plaque area at the junction site were smaller (12%, 10% and 7%, respectively) than the changes observed at the treated site (23%, 19% and 16%, respectively). The dimensions of the reference site remained unchanged (-2%, 0% and 1%, respectively) (Table 4).

IVUS data confirmed that the restenotic lesion seen with angiography in patients without EBT was located at the treated site. In patients with EBT, the de novo stenosis was seen proximal to the junction site at 1 cm, 1.5 cm and 3.5 cm distance, respectively.

Table 3 Quantitative intravascular ultrasound data from the treated and reference site obtained immediately after percutaneous transluminal angioplasty (PTA) and at follow-up in patients without endovascular brachytherapy (EBT) and with EBT.

	EBT	After PTA (mm^2)	Follow-up (mm^2)	Change (mm^2)
Treated site				
Lumen area	–	18.3 ± 6.9	16.6 ± 7.4	-1.6 ± 5.1 (-9%)
	+	18.8 ± 6.1	23.1 ± 7.7	4.3 ± 6.8 (23%)
		(p = 0.86)	(p = 0.06)	(p = 0.03)
Vessel area	–	36.4 ± 12.9	37.3 ± 12.9	0.8 ± 5.5 (2%)
	+	36.8 ± 8.6	43.7 ± 12.2	6.9 ± 8.7 (19%)
		(p = 0.94)	(p = 0.26)	(p = 0.05)
Plaque area	–	18.3 ± 8.8	20.6 ± 8.6	2.2 ± 4.0 (12%)
	+	17.9 ± 6.4	20.7 ± 7.3	2.8 ± 6.0 (16%)
		(p = 0.91)	(p = 0.98)	(p = 0.80)
Reference site				
Lumen area	–	16.8 ± 6.4	18.1 ± 6.6	1.3 ± 3.3 (8%)
	+	16.6 ± 5.0	16.3 ± 5.0	-0.3 ± 3.2 (-2%)
		(p = 0.95)	(p = 0.50)	(p = 0.26)
Vessel area	–	30.5 ± 9.8	32.5 ± 9.8	2.0 ± 3.5 (7%)
	+	31.6 ± 5.6	31.5 ± 5.6	-0.1 ± 3.7 (0%)
		(p = 0.78)	(p = 0.80)	(p = 0.20)
Plaque area	–	13.7 ± 6.0	14.4 ± 5.7	0.7 ± 2.3 (5%)
	+	14.8 ± 3.8	15.0 ± 3.6	0.2 ± 2.9 (1%)
		(p = 0.64)	(p = 0.78)	(p = 0.66)

Values are mean ± standard deviation; – = without EBT; + = with EBT.

Table 4 Quantitative intravascular ultrasound data from the treated site, the junction site and the reference site obtained immediately after percutaneous transluminal angioplasty (PTA) and at follow-up in patients with endovascular brachytherapy (n=8).

	Segment	After PTA (mm^2)	Follow-up (mm^2)	Change (mm^2)
Lumen area	Treated	18.8 ± 6.1	23.1 ± 7.7	4.3 ± 6.8 (23%)
	Junction	17.2 ± 4.8	19.2 ± 5.5	2.0 ± 5.7 (12%)
	Reference	16.6 ± 5.0	16.3 ± 5.0	-0.3 ± 3.2 (-2%)
Vessel area	Treated	36.8 ± 8.6	43.7 ± 12.2	6.9 ± 8.7 (19%
	Junction	32.4 ±8.2	35.6 ± 8.7	3.1 ± 7.0 (10%)
	Reference	31.6 ± 5.6	31.5 ± 5.6	-0.1 ± 3.7 (0%)
Plaque area	Treated	17.9 ± 6.4	20.7 ± 7.3	2.8 ± 6.0 (16%)
	Junction	15.3 ± 6.5	16.4 ± 5.4	1.1 ± 4.2 (7%)
	Reference	14.8 ± 3.8	15.0 ± 3.6	0.2 ± 2.9 (1%)

Values are mean ± standard deviation.

Change in qualitative IVUS data

The number of IVUS cross-sections showing a calcified lesion was 93 (34%) immediately after PTA and 101 (37%) at follow-up in patients without EBT and 45 (27%) and 44 (27%), respectively, in patients with EBT.

All patients without EBT and 7 of the 8 patients with EBT presented a dissection immediately after PTA. In patients without EBT dissections observed after PTA (n=43) were absent at follow-up. Four of the patients with EBT presented with a persistent dissection at follow-up (Figure 2). The mean arc of the dissections (n=6) in these patients decreased from 65° ± 29° immediately after PTA to 35°±12° at follow-up (p=0.04).

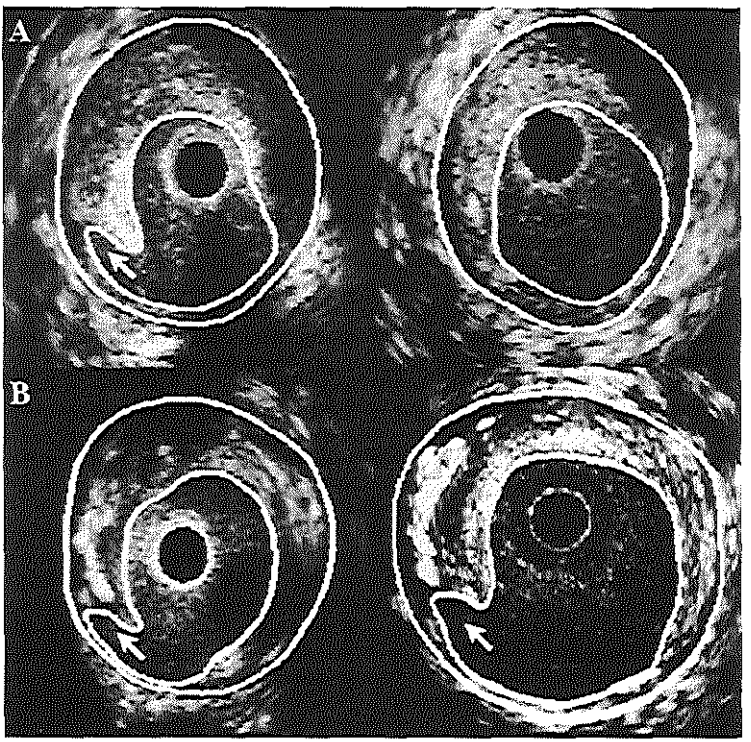

Figure 2. Corresponding intravascular ultrasound cross-sections obtained after percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery (left) and at 6-months follow-up (right) from a patient without endovascular brachytherapy (EBT) (A) and a patient with EBT (B). Immediately after PTA a small dissection (arrows) was present in both patients. At follow-up, no dissection was encountered in the patient without EBT, whereas in the patient with EBT a persistent dissection (arrow) was seen.
Calibration = 1 mm; + = catheter.

DISCUSSION

Endovascular brachytherapy has recently emerged as a promising technique to reduce the incidence of restenosis after vascular intervention. Clinical studies have shown that radiation therapy in addition to PTCA or stent placement in coronary arteries is successful, with restenosis rates of 8% to 22%[15,18-21] at 6-months follow-up (39%-54% in patients without EBT) and 33% at 3-years follow-up (64% in patients without EBT).[21] Furthermore, coronary studies

using radiation therapy in addition to PTCA for treatment of in-stent restenosis showed restenosis rates of 19% to 28% in patients with EBT, compared to 44% to 58% in patients without EBT at 6-months follow-up.[23-25] Until now, two studies have reported on the use of gamma-radiation in femoropopliteal arteries. The first group, represented by Minar et al.[30] documented a restenosis rate of 40% at 1-year follow-up; in this study 10 patients with long-segment lesions (mean 16 cm) were included. The second group, represented by Liermann et al.[31] studied 40 patients with in-stent restenosis. These patients treated with PTA and additional EBT showed a clinical restenosis rate of 16% at follow-up (4 months to 7.5 years). The present study represents the first randomized study in which the effects of gamma radiation on both plaque growth and vascular remodeling after PTA of the femoropopliteal artery has been studied using IVUS. This study revealed a significant difference between patients without EBT and with EBT in lumen area change at 6-months follow-up at the treated site; in patients without EBT lumen area decreased with 9%, whereas in patients with EBT an increase in lumen area of 23% was observed (Table 3). This difference in lumen area change at follow-up was the result of a difference in vessel area change; in patients without EBT vessel area remained unchanged (+2%), whereas in patients with EBT a vessel area increase of 19% was observed. Overall, both groups of patients showed a similar increase in plaque area (12% and 16%, respectively). Changes observed at the junction site were similar to the changes at the treated site in patients with EBT (Table 4). In other words, EBT appeared to have a beneficial effect on lumen size due to its effect on the mode of vascular remodeling rather than on the degree of plaque growth.
Some issues encountered in the present study deserve further discussion.

Lumen gain at 6-months follow-up

The observation that lumen gain following gamma-radiation of the femoropopliteal artery seen at 6-months follow-up was the result of positive vascular remodeling confirms the effects of EBT evidenced with IVUS in coronary arteries.[16,32,33] In two of these studies[16,32] beta-radiation was used as adjunct to PTCA and in one study[33] gamma-radiation was used in untreated coronary segments. These studies showed an increase in vessel dimension in the presence of an increase in plaque dimension resulting in no change to a

small increase in lumen dimension. Furthermore, in the study described by Ahmed et al.[33] both patients without and with EBT were studied and results of their study were similar to the results seen in our study; patients without EBT showed a decrease in vessel dimension, whereas in patients with EBT an increase in vessel dimension was encountered. Both groups of patients showed a similar increase in plaque dimension. The reason why these observations were not documented in animal studies and in clinical studies using angiography, is that the latter technique only displays a silhouette of the lumen, without any information on plaque dimensions. The importance of IVUS in this respect is that IVUS is the only available imaging technique to document both plaque growth and vascular remodeling.

The "edge effect" of radiation

Although the mean lumen area at the junction site in patients with EBT increased by 12% at 6-months follow-up (Table 4), late lumen loss at 1 cm and 1.5 cm proximal to the junction site was observed in 2 of the 3 patients with an angiographic de novo stenosis. IVUS data showed that the decrease in lumen area at the stenotic lesion resulted from a decrease in vessel area (i.e. vascular shrinkage). Whether this late lumen loss was due to the "edge effect" of radiation therapy or a coincidental finding remains speculative. However, in a study performed by Kozuma et al.[32] in coronary arteries using beta-radiation after PTCA, similar results were encountered; vessel volume at the non-dilated edges in patients with EBT decreased, whereas vessel volume at the non-dilated edges in patients without EBT remained unchanged. Plaque volume increase in both groups of patients was similar. In contrast, in two other IVUS studies in stented coronary arteries using gamma-[33] or beta-radiation[34] the "edge effect" was not encountered. Reasons why these results differ from the results of the present study and the study performed by Kozuma et al.[32] remain speculative, but may be due to the use of stents. Further investigation of the "edge effect" of EBT may be warranted.

Persistent dissections after radiation

Although qualitative IVUS data showed no change in the extent and number of calcified lesions in both groups of patients, dissections encountered immediately after PTA were absent at follow-up in patients without EBT,

whereas in 4 of the 8 (50%) patients with EBT a persistent dissection was encountered. Similar results were seen in an IVUS study performed by Kay et al.[35] in coronary arteries using beta-radiation. In their study a persistent dissection was encountered in 8 of the 16 patients (50%) with EBT at 6-months follow-up.
Results of their study raised the question whether persistent dissections in patients with EBT represent permanent dissections to the vessel wall or merely retardation in the healing process. Since the arc of the persistent dissections in the present study decreased from 65° to 35°, one may conclude that EBT seems to slow the normal healing process of the artery. However, whether this retardation in the healing process influences lumen dimensions in the longterm needs further investigation.

Limitations

The major limitation of the present study is the small number of patients with a completed IVUS follow-up (24 of the 38 patients). Consequently, a potential selection bias in the patient population may have occurred.

CONCLUSION

This randomized IVUS study in femoropopliteal arteries showed that gamma-radiation after PTA 1) has a positive effect on lumen dimensions at 6-months follow-up by inducing positive vascular remodeling, 2) seems not to reduce plaque growth, and 3) appears to delay the healing process of dissections after PTA.

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CHAPTER 6

Reproducibility of Volumetric Quantification in Intravascular Ultrasound Images

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ABSTRACT

The reproducibility of volume measurements in intravascular ultrasound (IVUS) images derived from separate pull-back manoeuvres remains to be elucidated. Patients (n=23) were imaged with IVUS prior to (first series) and following percutaneous transluminal angioplasty (PTA) (second series). In 15 patients, one matched vascular segment (3-4 cm in length), not subjected to PTA, was used for analysis of lumen, vessel and plaque volume using an automated contour analysis system. Volume measurements assessed by two independent observers and in the two separate series were compared. Interobserver differences in volume measurements were small (≤0.4%), with low coefficients of variation (≤1.7%) and high correlation coefficients (r=1.00). Differences in volume measurements obtained in the two separate series were small (≤2.6%), with low coefficients of variation (≤8.6%) and high correlation coefficients (r=0.97-0.99). In conclusion, volume measurements derived from IVUS images are highly reproducible. Therefore, IVUS may be used to monitor the progression/regression of atherosclerotic plaque volume in a longitudinal study.

INTRODUCTION

The beneficial effect of statins on the secondary prevention of cardiovascular disease has been shown in studies with clinical endpoints[1-2] and in studies with surrogate endpoints using angiography and external ultrasound.[3-4] However, angiography displays a planar view giving information on vessel lumen diameter only, whereas external ultrasound gives information on arterial wall thickness only. In contrast, intravascular ultrasound (IVUS) provides a cross-sectional view of the vessel with information on lumen, vessel and plaque area.[5-7] Recently, the reduction of plaque area by statins in segments with angiographically silent atherosclerotic plaques in patients with elevated serum cholesterol has been demonstrated by IVUS.[8] Nowadays, the use of an automated contour analysis system, which creates a three-dimensional (3-D) reconstruction of cross-sectional IVUS images, allows assessment of atherosclerotic plaque volume.[9-12]

To use the automated contour analysis system in a clinical setting to establish the effect of lipid-lowering drugs on plaque volume, the reproducibility of volume measurements by two observers and from two separate pull-back manoeuvres obtained from femoropopliteal arterial segments was determined.

METHODS

Study group

The study group comprised 23 patients: 14 men, 9 women; age range 48-88 (median 71) y. Patients were selected from an existing study group with symptomatic femoropopliteal artery disease eligible for percutaneous transluminal angioplasty (PTA), who were studied with IVUS during intervention. The investigation was approved by the local committee on human research. Patients were included in the study after giving written informed consent. The patient selection was based on: (1) the availability of IVUS images prior to and following intervention; (2) the use of a displacement sensing device to document the location of the IVUS catheter; and (3) the presence of a side-branch together with a moderately diseased vascular segment 3-4 cm in length not subjected to PTA.

Intravascular ultrasound

The IVUS studies were performed using a mechanical system based on a single ultrasound element (30 MHz); the tomographic image is produced by a rotating element mounted on a guidewire-tipped 4.3F catheter (Du-MED, Rotterdam, The Netherlands, 0.035"=0.89 mm).

IVUS images were obtained prior to (first series) and following PTA (second series) using the following procedure. The ultrasound catheter was introduced antegradely through a sheath into the femoropopliteal artery. Following catheter tip advancement distally across the symptomatic lesion, the catheter position was documented using fluoroscopy and a radiopaque ruler as reference. Then the catheter was pulled back manually. If possible, the guidewire was removed first to avoid drop-out. A displacement-sensing device was used to document the location (i.e., position) of the catheter tip in steps of 0.1 mm. This device consists of a small, sterile, disposable sensing unit. The movement of the catheter activates a rotating wheel that converts the linear movement into an electronic pulse train signal so that the advancement or withdrawal of the catheter is digitized and wirelessly registered by a sterilizable unit to which the sensing unit is mounted.[13] The information on the position of the catheter tip was combined with the IVUS information on the monitor. To avoid the time-consuming process of manual selection of IVUS images required for automated analysis, a computerized position registry device with audio feedback enabling automatic selection of IVUS images was used. Based on the position information from the displacement-sensing device, the position of the IVUS catheter tip was translated into a digital audio signal, which was stored on the audio channel of the videotape using a time-code generator and a special video recorder.

Automated analysis system

The automatic contour detection is based on the minimum-cost algorithm, as described previously.[9] The analysis program uses the Microsoft Windows operating system on a Pentium (100 MHz) personal computer with 32 Mbytes of internal RAM. In short, a maximum of 200 IVUS cross-sections was stored per vessel segment using a framegrabber (DT-3852; resolution 800 × 600 × 8 bits). The analysis procedure can be divided into three steps (Figure 1). First, a sequence of IVUS images was digitized, and two perpendicular planes,

parallel to the longitudinal axis of the vessel, were selected to reconstruct longitudinal views. The user was able to optimize the angle and location of the perpendicular planes within the arterial lumen. Second, the program defined the contours of lumen boundary and vessel boundary (media-adventitia border) on these longitudinal planes by applying a minimum cost algorithm. In brief, a matrix was yielded from the digitized images, producing low values (costs) for large changes in echo intensity. Through this matrix, the algorithm determined a path with the smallest accumulated cost, which represents the boundaries (contours) of the arterial structures. Third, the longitudinal contour information was transformed to the cross-sections defining four guiding points on the two perpendicular planes. These points were used to facilitate automated contour detection of lumen and vessel boundary on each individual cross-section. During all steps, the user could interactively modify the contours of lumen and vessel boundary that were detected by the automated analysis system. The results were presented in a graph containing the measurements of each individual cross-section (Figure 1).[9]
Lumen, vessel and plaque volumes were calculated as:

$$Volume = \sum_{i=1}^{n} A_i \times H$$

where A is the area, H is the interval between two cross-sections (slice thickness) and n is the number of IVUS images acquired.
To select IVUS images for analysis, two methods were applied: (1) using the information on the audio channel, IVUS images were automatically selected and digitized at 0.2-mm intervals. The automated selection of IVUS images is limited to eight images per second. In case of missing images at 0.2-mm interval (caused by a too fast pull-back manoeuvre), the next image at a 0.2-mm interval was selected. At the end of the analysis, the volume was determined by adjusting the slice thickness for the number of missing cross-sections; (2) using the displacement-sensing device information on the video screen, IVUS images were manually selected at 0.2-mm intervals and subsequently digitized. If cross-sections were missing, the gap was filled with neighbouring images. Selection of these neighbouring images was performed during the selection procedure.

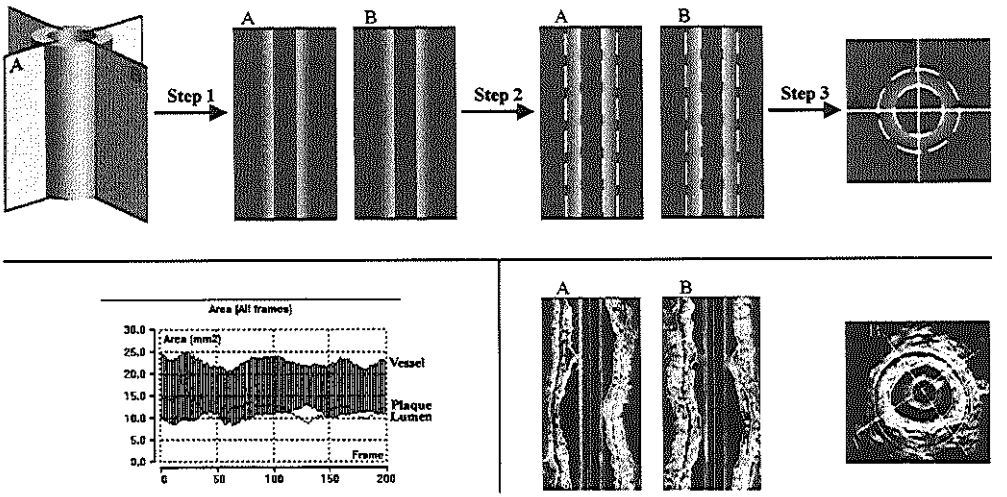


Figure 1. Automatic contour detection of intravascular ultrasound (IVUS) images. Upper panel: two perpendicular planes are used to reconstruct two longitudinal sections (A and B) from the digitized IVUS images (step 1). Automatic contour detection of the intimal leading edge and the external boundary of the vessel is performed on these longitudinal sections (step 2). The longitudinal contours are represented as individual edge points in the cross-sectional images. These points define center and range of the final contour detection process on the cross-sectional images (step 3). Lower left panel presents a standard display of lumen, vessel and plaque area measurements derived from a femoropopliteal artery. Lower right panel: the two reconstructed longitudinal sections (A and B) correspond to the perpendicular planes seen in the cross-section.

Analysis

Vascular segments obtained from the two separate pull-back manoeuvres were matched using side-branches (Figure 2). Subsequently, for each patient, one vascular segment (3-4 cm in length) not subjected to PTA was selected for the following analyses: (1) assessment of lumen, vessel and plaque volume in the first and second series following automatic and manual selection of IVUS cross-sections; (2) assessment of lumen, vessel and plaque volume in the first and second series by a second independent observer using the automatically acquired series of IVUS cross-sections. Volume measurements in IVUS images assessed by the two observers, in the automatically and manually selected images and in the first and second series, were subsequently compared.

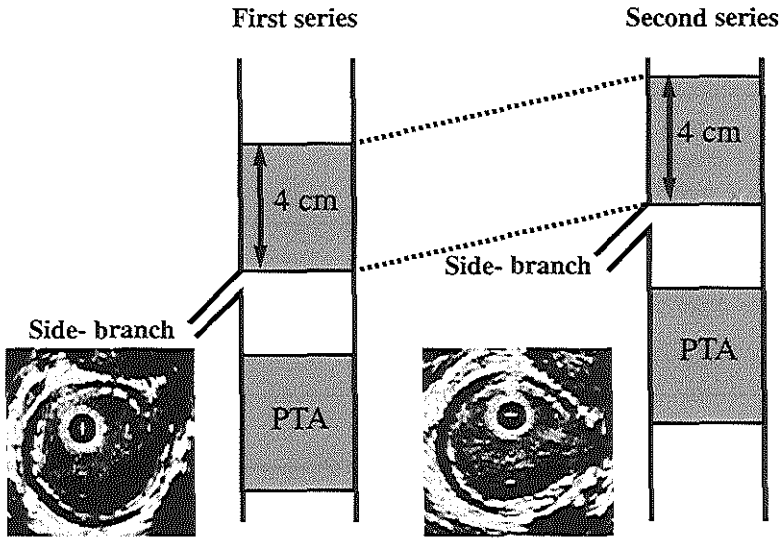


Figure 2. Schematic drawing showing how corresponding vascular segments obtained from two separate pull-back manoeuvres are matched using side-branches and the information derived from the displacement sensing device. The two intravascular ultrasound (IVUS) images represent matched cross-sections showing the side-branch.

Statistical analysis

Results are given as mean ± standard deviation (SD), or as a median and range. To compare the volume measurements, mean and SD of the paired differences were calculated. Systematic differences were analyzed with the Student's t-test for paired observations. The degree of variation was presented as a coefficient of variation, defined as the SD of the paired difference divided by the mean of the absolute value. Differences in volumes were plotted against the mean of the volume measurements. Linear regression analysis was performed to assess the strength of the relation between the volume measurements. A p-value < 0.05 was considered statistically significant.

RESULTS

For the present study, one corresponding vascular segment was used for analysis in 15 of the 23 patients; in the eight remaining patients, the analysis could not be performed due to extensive calcification (>30° of the lumen circumference) (n=4) and the presence of a guide-wire and/or

Table 1 Interobserver reproducibility on lumen, vessel and plaque volume assessed in the two separate pull-back manoeuvres (n=30).

	First observer (mm^3)	Second observer (mm^3)	Δ± SD (mm^3)	Δ (%)	p-value	Coefficient of Variation (%)	r
Lumen volume	804.31	800.95	−3.36 ± 3.38	−0.4	0.00	0.4	1.00
Vessel volume	1287.50	1285.20	−2.30 ± 8.16	−0.2	0.13	0.6	1.00
Plaque volume	483.19	484.25	1.06 ± 8.45	0.2	0.50	1.7	1.00

Δ = mean difference; SD = standard deviation

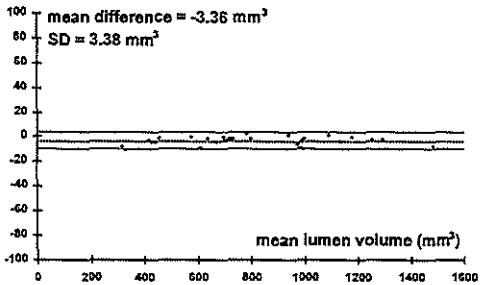
a too fast pull-back manoeuvre of the IVUS catheter, resulting in low image quality (n=4). The median length of the vascular segment selected for automated contour analysis of each patient was 3.7 (range 3.0–4.0) cm. The selected vascular segments had a maximum area stenosis of 45% (median) (range 36–75%).

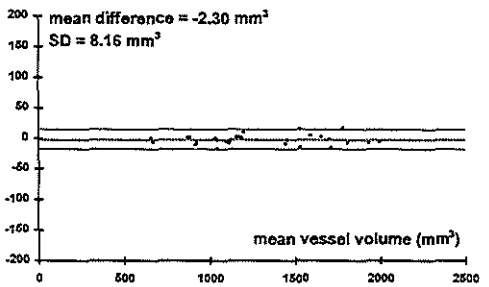
The number of IVUS cross-sections selected manually per segment was determined by the length of the segment, and ranged from 151 to 200 (median 194) in the two separate pull-back manoeuvres.

Table 2 Data on lumen, vessel and plaque volume assessed in automatically and manually selected intravascular ultrasound images (n=30).

	Auto-mated (mm^3)	Manual (mm^3)	Δ± SD (mm^3)	Δ (%)	p-value	Coefficient of variation (%)	r
Lumen volume	804.31	803.75	−0.56±11.26	0.0	0.79	1.4	1.00
Vessel volume	1287.50	1284.98	−2.52±13.95	−0.2	0.33	1.1	1.00
Plaque volume	483.19	481.23	−1.96±9.29	−0.4	0.26	1.9	1.00

Δ = mean difference; SD = standard deviation





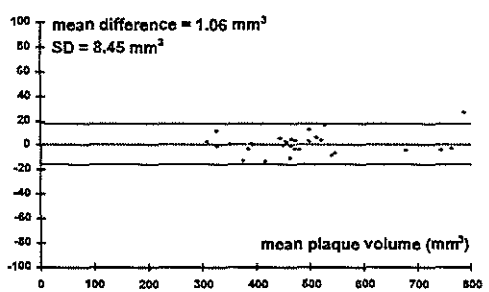
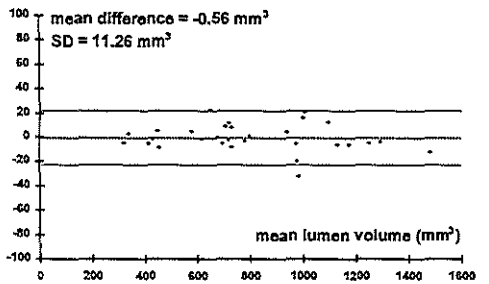
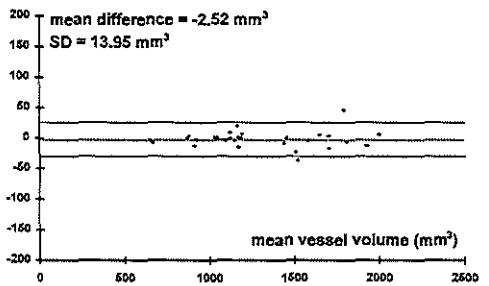


Figure 3. Interobserver difference in lumen, vessel and plaque volume assessed in the two separate pull-back manoeuvres (n=30).





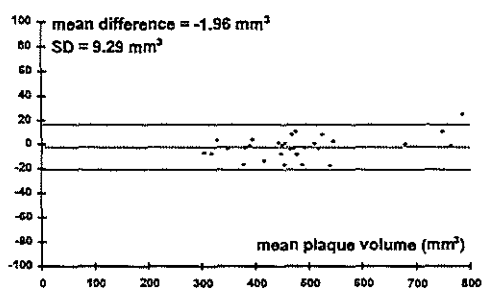


Figure 4. Difference in lumen, vessel and plaque volume assessed in automatically and manually selected intravascular ultrasound images (n=30).

The number of cross-sections selected automatically per segment ranged from 40 to 197 (median 157) in the first series, and from 47 to 195 (median 151) in the second series. The number of missing images using automated selection was 0 to 130 (median 16) in the first series, and 0 to 153 (median 12) in the second series. The interobserver differences in volume measurements were minimal (0.2-0.4%) and not significant (Table 1, Figure 3); the coefficient of variation was small (≤1.7%) and correlation coefficients were high (r=1.0 for all).

Table 3 Inter-exam reproducibility on lumen, vessel and plaque volume assessed by the first observer.

	First series (mm^3)	Second series (mm^3)	Δ ±SD (mm^3)	Δ (%)	p-value	Coefficient of Variation (%)	r
Automatic selection (n=15)							
Lumen volume	79391	81472	20.81 ± 68.58	26	26	85	99
Vessel volume	127572	129928	23.55 ± 79.59	19	27	62	98
Plaque volume	48182	48455	2.73 ± 26.90	6	70	56	98
Manual selection (n=15)							
Lumen volume	79647	81103	14.56 ± 68.81	-1.8	43	86	98
Vessel volume	127419	129577	21.58 ± 86.15	-1.7	35	67	98
Plaque volume	47772	48473	7.01 ± 30.77	-1.5	39	64	97

Δ = mean difference; SD = standard deviation

Table 2 and Figure 4 summarize the differences in lumen, vessel and plaque volumes assessed in the automatically and manually selected IVUS cross-sections. Differences in volume measurements were minimal (0.0-0.4%) and not significant; the coefficient of variation was small (≤1.9%) and correlation coefficients were high (r=1.0 for all).

Results of lumen, vessel and plaque volumes assessed in the two separate pull-back manoeuvres (i.e., interexam reproducibility) are summarized in Table 3 and Figure 5. Results of the volume measurements in the automatically and manually selected IVUS images were given separately. Differences in the volume measurements were minimal (0.6-2.6%) and not significant; the coefficient of variation was small (≤8.6%) and correlation coefficients were high (r=0.97-0.99).

DISCUSSION

Serial IVUS studies have been used to study the mechanism of vascular intervention[14-16] and restenosis.[17-19] In addition, it may permit assessment of the progression or regression of atherosclerosis and the effects of pharmacological agents on this process.[8] In these studies, single or multiple IVUS cross-sections with a given interval were manually analyzed. The main problem in these studies is to find the same location during the next catheter passage following a certain time interval. Initially, the IVUS cross-sections were matched using anatomic markers such as side-branches and calcium and/or using the position of the ultrasound catheter documented under fluoroscopic control. To facilitate matching of IVUS images, a motorized pull-back device for coronary application[20] and a displacement-sensing device for peripheral application[13,21] were developed.

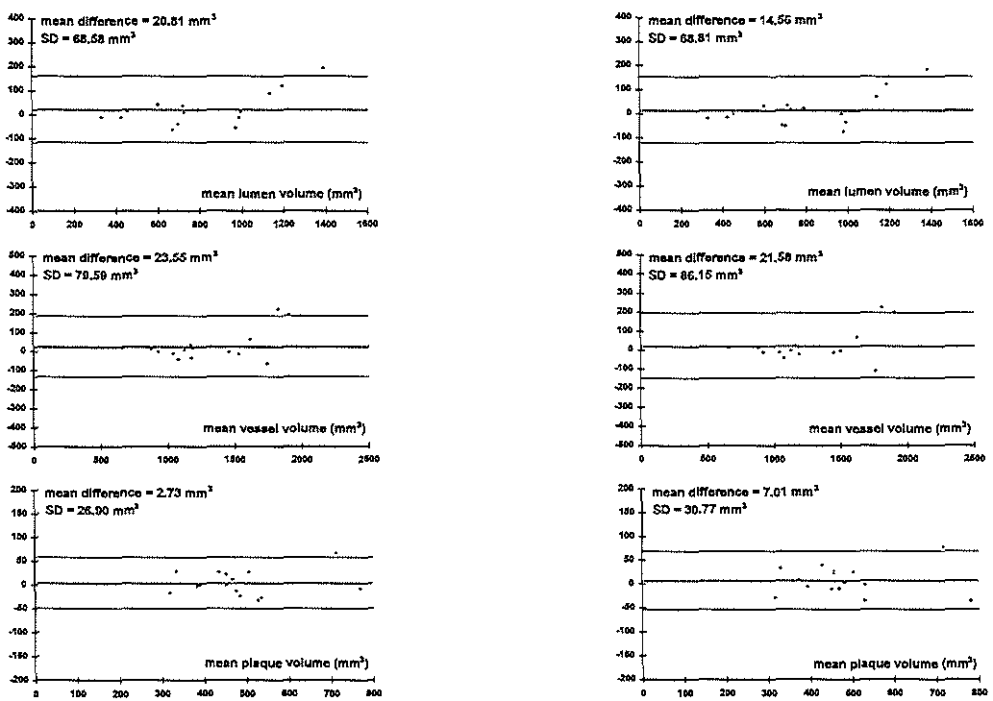


Figure 5. Interexamination difference in lumen, vessel and plaque volume assessed by the first observer. The left panels represent data following automatic selection of intravascular ultrasound (IVUS) images. The right panels represent data following manual selection of IVUS images.

These systems allow accurate documentation of IVUS cross-sections in relation to any given side-branch. To enable volume measurements, which might be more reproducible in serial IVUS studies than area measurements, an automated contour analysis system was developed.
The present study was aimed at the reproducibility of volume measurements obtained using the automated analysis system, as well as the agreement of volume measurements, in IVUS images acquired from two separate pull-back manoeuvres. This study demonstrated that: (1) the automated contour detection system results in volume measurements with a high degree of interobserver agreement, (2) automatic selection of IVUS images is feasible and (3) there is good agreement in volume measurements in IVUS images acquired from two separate pull-back manoeuvres.

Interobserver reproducibility

Previous studies performed in coronary[10,22] and peripheral arteries[12,23] have shown that automated contour analysis has two main advantages over manual contour tracing: (1) the reduction in analysis time, and (2) the improvement in interobserver reproducibility of area measurements [the coefficient of variation improved from 17.2% to 11.3% for lumen area and from 10.5% to 5.7% for vessel area].[12,23] The present study showed that measurement of volumes rather than areas further improved the interobserver reproducibility; the coefficient of variation was 0.4% and 0.6% for lumen and vessel volume, respectively. This reflects an averaging of the differences of the area measurements. The same phenomenon was observed in coronary arteries.[11,24]
The interobserver difference of lumen and vessel area was 0.8% ± 7.3% and 0.2% ± 4.4%, respectively, whereas the interobserver difference of lumen and vessel volume was 0.7% ± 2.7% and 0.2% ± 0.7%, respectively.[24]
It should be acknowledged that the accuracy of volume measurements obtained in coronary arteries may be hampered by curvature of the vessel, the vessel distensibility and by cardiac movement.[25] In the absence of vessel curvature in femoropopliteal arteries, the problem of nonuniform rotational distortion of the catheter is not encountered in femoropopliteal arteries. To overcome the problem of vessel distensibility and cardiac movement, von Birgelen et al.[11] introduced ECG-gated IVUS image acquisition for volume measurements. However, we did not observe the characteristic sawtooth artifacts seen in 3-D

reconstructions of nongated images from coronary arteries in femoropopliteal arteries (Figure 1). In addition, given the high reproducibility of the volume measurements in femoropopliteal arteries, it is unlikely that ECG-gated image acquisition is required.
The reproducibility of the plaque volume in the present study was lower than for lumen and vessel volume (coefficient of variation 1.7% vs. 0.4% and 0.6%, respectively). This reflects the combined variability of lumen and vessel volume, a common observation reported in other studies.[11,26]

Automatic and manual selection of IVUS cross-sections

To avoid the time-consuming process of manual selection of IVUS images, in the present study, a computerized position registry device with audio feedback was used. Depending on the speed of the pull-back of the IVUS catheter, both automatic and manual selection resulted in a certain number of missing images. The following solution was applied to overcome this problem: for automatic selection of IVUS cross-sections, the slice thickness was adjusted, and for manual selection of IVUS cross-sections, the neighbouring image was used. Although the latter solution is better than the first, no significant differences in volume measurements were found between the automatically and manually selected images, whereas the coefficients of variation were low. This suggests that (1) automatic selection is reliable, and (2) the interval between IVUS cross-sections selected for analysis might be increased.

Interexamination reproducibility

This study showed for the first time that volume measurements are reproducible in IVUS images that were acquired from two separate pull-back manoeuvres. This high reproducibility is the summation of very low observer variability, the absence of significant vessel distensibility and the absence of significant catheter movement. Although no difference was found between automatically and manually selected images (Table 3, Figure 5), a slow pull-back, without missing images at the interval of 0.2 mm, might increase the agreement between the assessed volumes.

Clinical implication

The results of this study suggest that IVUS has the potential to image the same vascular segment during follow-up and to assess changes in lumen, vessel and plaque volume in a longitudinal study. This permits assessment of progression and regression of atherosclerosis and the influence of pharmacological agents on the atherosclerotic plaque.[26] Furthermore, measurement of lumen, vessel and plaque volume may be used as a basis for dosimetry for subsequent radiation treatment approaches.

Limitations

It should be acknowledged that patients were selected from an existing study. In eight patients, no suitable vascular segment was available for analysis. Therefore, the ultimate quality of future IVUS studies may benefit from a slow pull-back manoeuvre and removal of the guide-wire.

Secondly, at present, the automated system is limited in the length of the vessel segment (4.0 cm) that can be analyzed at once. Increasing the interval between IVUS images to be grabbed may extend the vessel length to be studied.

Finally, the automated contour analysis system is not a true 3-D acquisition system, but one that gives a "stacked coins" geometry of the vessel segment. However, in the straight femoropopliteal artery, the distortion will be small. To obtain a real 3-D reconstruction in a curved coronary artery the ANGUS method, a combination of X-ray angiographic and IVUS data may be used.[27]

SUMMARY

This study indicates that lumen, vessel and plaque volume in peripheral arteries can be assessed with low differences between observers and separate acquisitions of IVUS images. Therefore, in the future, IVUS may be used to monitor the progression/regression of atherosclerotic plaque volume in a longitudinal study.

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CHAPTER 7

Reproducibility of Calcified Lesion Quantification:
A longitudinal intravascular ultrasound study

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ABSTRACT

In view of a prospective intravascular ultrasound (IVUS) study, the reproducibility of the extent of the calcified lesion in IVUS images derived from separate pull-back maneuvers was assessed. Patients (n=34) were imaged with IVUS before and after percutaneous transluminal angioplasty (PTA) and at 1-y follow-up. In the presence of a calcified lesion, the largest arc and the length of the matched calcified lesions was assessed. Interobserver differences in arc measurements were low (≤0.7%), with low coefficients of variation (≤ 5.8%). Similarly, interexamination differences in arc and length measurements were small (≤1.1%), with low coefficients of variation (≤3.2%). At follow-up, a nonsignificant increase in both the arc (1.9%) and length (1.7%) of the calcified lesion was observed. This study showed that measurements of the calcified lesion are highly reproducible; changes seen at 1-y follow-up were not significant. We conclude that IVUS may be used to monitor the effect of medical intervention on the extent of the calcified lesion in a longitudinal study.

INTRODUCTION

Previous studies have suggested good correlation between IVUS and histologic findings regarding the identification of calcified and noncalcified lesions.[1-3] Clinical IVUS studies were aimed at identifying whether or not calcified lesions were associated with restenosis[4-7] and with intimal hyperplasia and vascular remodeling.[8] In view of a prospective IVUS study on the effect of medical intervention on the progression and composition of the atherosclerotic lesion, the present study was designed to determine: (1) the reproducibility of the extent of the calcified lesion derived from separate pull-back maneuvers, and (2) to assess the progression of the extent of the calcified lesion seen at 1-y follow-up.

METHODS

Study group

The study group consisted of 34 patients (23 men, 11 women; ages 43 to 88, median 68, y). Patients were selected from an existing study group with symptomatic femoropopliteal artery disease eligible for percutaneous transluminal angioplasty (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 of restenosis were studied by protocol with angiography and IVUS at 1-y follow-up.[8] The investigation was approved by the local committee on Human Research. Patients were included in the study after giving written informed consent. The patient selection was based on: (1) the availability of data from a displacement sensing device to document the location of the IVUS catheter, (2) the availability of corresponding IVUS images before and after intervention (group I), and (3) the availability of corresponding IVUS images after intervention and at 1-y follow-up (group II).

Intravascular ultrasound

The IVUS studies were performed using a mechanical system based on a single US element (30 MHz); the tomographic image is produced by a rotating element mounted on a guidewire-tipped 4.3 F catheter (Endosonics, Rijswijk,

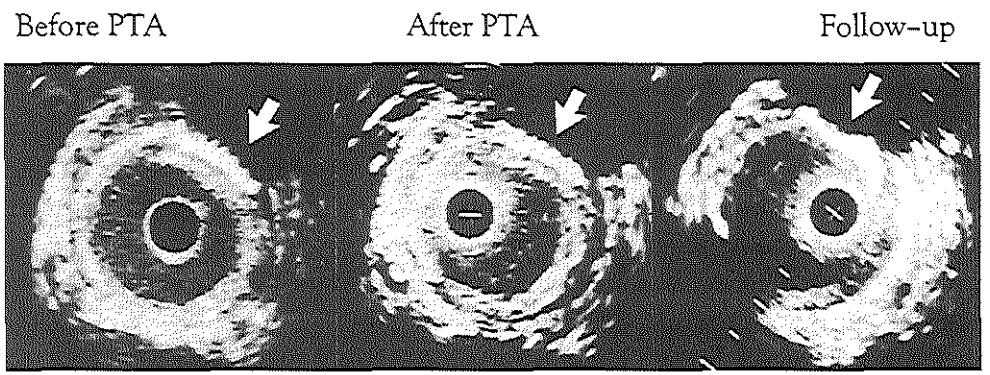

Figure 1. Corresponding calcified lesion seen with intravascular US before (left) and after (middle) percutaneous transluminal angioplasty of the femoropopliteal artery and at 1-y follow-up (right). Calcified lesions are characterized by the presence of a bright echo together with acoustic shadowing of the underlying structures (arrows). + = catheter; calibration = 1 mm.

The Netherlands, 0.035" = 0.89 mm). IVUS images were obtained before and immediately after PTA using the following procedure; through a 7-F sheath in the femoropopliteal artery, the IVUS catheter was introduced antegradely over a guidewire, distal to the symptomatic lesion. The information on the location (i.e., position) of the cathetertip was documented using a radiopaque ruler and a displacement sensing device. The catheter was pulled back manually. If possible, the guidewire was removed first to avoid dropout. The displacement sensing device was used to document the location of the catheter tip in relation to the patella in steps of 0.1 mm during the pull-back maneuver.[9] This displacement-sensing device consists of a small, sterile disposable sensing unit. The movement of the catheter activates a rotating wheel that converts the linear movement into an electronic pulse train signal so that the advancement or withdrawal of the catheter is digitized and registered by a sterilizable unit to which the sensing unit is mounted. The information on the position of the catheter tip was combined with the IVUS information on the monitor and stored on an S-VHS videotape. After 1-y follow-up, the IVUS study was repeated. The procedure was performed in the same manner as described before. Using the radiopaque ruler as reference, care was taken to image both the vascular segment not subjected to PTA (i.e., nondilated vascular segment) and the vascular segment subjected to PTA (i.e., dilated vascular segment).

With the information of the radiopaque ruler, the displacement-sensing device and anatomic markers such as side-branches, the IVUS series of the nondilated and the dilated segment obtained before and after PTA and at 1-y follow-up were matched. These matched IVUS series were subsequently analyzed for the absence or presence of calcified lesions (Figure 1).

Measurement of the calcified lesion

Calcified lesions were easily identified by US imaging and were characterized by the presence of a bright echo together with acoustic shadowing of the underlying structures (Figure 1). In the presence of a calcified lesion (≥ 30°), both the arc of calcium and the length of the lesion involved were assessed. The arc of the calcified lesion was measured from the IVUS cross-section showing the largest arc of calcium within the selected lesion using a protractor. The protractor was centered in the vessel circumference defined by the hyperechoic adventitia (Figure 2).

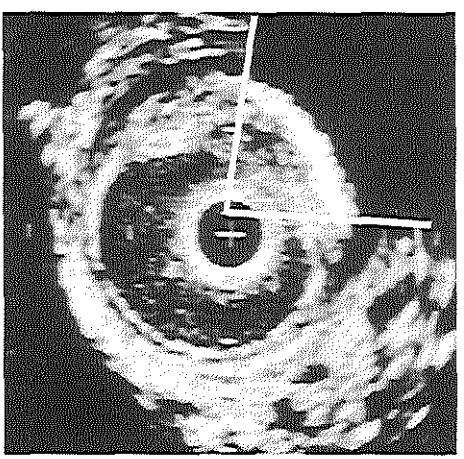

Figure 2. An intravascular US image showing how the largest arc of the calcified lesion was measured using a protractor (two lines) centered in the vessel circumference. + = catheter; calibration = 1 mm.

In the presence of acoustic shadowing of the vessel circumference caused by lesion calcification, extrapolation of the circumference of the vessel area was applied. If necessary, neighboring IVUS cross-sections were used to define the vessel area in the IVUS cross-section showing the largest arc of calcium. The length of the calcified lesion was measured using the information derived

from the displacement-sensing device. Lesion length was measured as the distance between the first and last IVUS image showing the calcified lesion.

Analysis

1 Assessment of the arc of the calcified lesions obtained before PTA, after PTA and at 1-y follow-up by two independent observers (T. Hagenaars and E. J. Gussenhoven).
2 Assessment of the length of the calcified lesions obtained before PTA, after PTA and at 1-y follow-up by the first observer.

A comparison was made between: (1) the arc of the calcified lesions assessed by the two observers (i.e., interobserver difference), (2) the arc and length of the calcified lesions seen before and after PTA (i.e., interexamination difference) both in the nondilated and dilated vascular segment, and (3) the arc and length of the calcified lesions seen after PTA and at 1-y follow-up.

Statistical analysis

Results are given as mean ± standard deviation (SD), or as median and range. To compare the measurements of the arc and length of the calcified lesions, mean and SD of the paired differences were calculated. Systematic differences were analyzed with the Student's t-test for paired observations. The degree of variation was presented as 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

All 34 IVUS studies were completed successfully and complications as result of the IVUS procedure were not encountered. Reviewing the IVUS records, 11 patients were excluded from the study for the following reasons: absence of a calcified lesion (n=4), diffuse mediasclerosis of the vessel limiting length measurements of the calcified lesion (n=4), and the presence of a guidewire that hampered analysis of the calcified lesion (n=3). In the remaining 23 patients, a multitude of calcified lesions was selected for analysis. In group I (n=19), there were 54 calcified lesions (median 2; range 1 to 5 per patient) matched from the IVUS records obtained before and after PTA. From the remaining 4 of the 23 patients, IVUS records before PTA were not available

(n=2), the displacement-sensing device was not used (n=1), or the presence of a guidewire hampered analysis (n=1). In group II (n=12) there were 33 calcified lesions (median 2; range 1 to 5 per patient) matched from the IVUS records obtained after PTA and at 1-y follow-up. From the remaining 11 of the 23 patients, IVUS records at follow-up were not available (n=10) or the displacement-sensing device was not used (n=1).

Table 1 Interobserver reproducibility of the arc of the calcified lesion assessed with intravascular US before and after percutaneous transluminal angioplasty (PTA) and at 1-y follow-up in 23 patients.

	Observer						
	first (°)	second (°)	Δ ± SD (°)	Δ (%)	*p*-value	Coefficient of variation (%)	r
Before PTA (n=54)	118	119	0.9 ± 5.1	0.7	0.23	4.3	0.997
After PTA (n=67)	110	110	0.1 ± 4.5	0.1	0.81	4.1	0.997
Follow-up (n=33)	102	103	0.2 ± 5.9	0.2	0.82	5.8	0.992
Total (n =154)	111	112	0.4 ± 5.0	0.4	0.31	4.5	0.997

n = number of calcified lesions, Δ = mean difference, SD = standard deviation.

The total number of IVUS cross-sections presenting with a calcified lesion analyzed after PTA was 67; of these, 20 were matched with both the IVUS cross-sections obtained before PTA (n=54) (group I) and the IVUS cross-sections obtained at follow-up (n=33) (group II). The calcified lesions analyzed presented a median arc of 98° (range 41 to 360°) and a median length of 88 (range 26 to 931) mm.

The interobserver differences in measurement of the arc of the calcified lesions were minimal (≤0.7%) and not significant; the coefficients of variation were small (≤5.8%) and the correlation coefficients were high (r≥0.992) (Table 1). Table 2 summarizes the interexamination differences in the arc and length of the matched calcified lesions obtained before and after PTA.

Table 2 Interexamination reproducibility on the arc and length of the calcified lesion assessed with intravascular US before and after percutaneous transluminal angioplasty in 19 patients.

	Series			Δ		Coefficient	
	first	second	Δ ± SD	(%)	*p*-value	of variation (%)	r
Non-dilated segment (n=29)							
Arc (°)	111	110	-1.2 ± 3.6	1.1	0.07	3.2	0.998
Length (mm)	115	116	0.7 ± 3.3	0.6	0.27	2.8	0.999
Dilated segment (n=25)							
Arc (°)	126	120	-6.2 ± 11	-4.9	0.01	8.8	0.989
Length (mm)	133	135	1.4 ± 5.3	1.1	0.19	3.9	0.999

n = number of calcified lesions, Δ= mean difference, SD = standard deviation.

The numbers of individual matched calcified lesions obtained from the nondilated and the dilated vascular segments were 29 and 25, respectively. The differences in both the arc and length of the calcified lesions acquired from the nondilated vascular segments were minimal (≤1.1%) and not significant; the coefficients of variation were small (≤3.2%) and the correlation coefficients were high (r≥0.998). Similarly, the difference in the length of the calcified lesions acquired from the dilated vascular segments was minimal (1.1%) and not significant. However, a significant difference (-4.9%) in the arc of the calcified lesions was encountered at the dilated vascular segments.

Table 3 presents measurements of the arc and length of the calcified lesions obtained after PTA and at 1-y follow-up. A nonsignificant increase in both the arc (1.9%) and length (1.7%) of the calcified lesions was observed.

Table 3 Difference in the arc and length of calcified lesions (n=33) assessed with intravascular US after percutaneous transluminal angioplasty (PTA) and at 1-y follow-up in 12 patients.

	After PTA	At Follow-up	Δ ± SD	Δ (%)	*p*-value
Arc (°)	101 ± 20	103 ± 20	1.9 ± 10.4	1.9	0.54
Length (mm)	100 ± 48	102 ± 47	1.7 ± 5.8	1.7	0.34

Δ = mean difference, SD = standard deviation.

DISCUSSION

Previous studies have suggested good correlation between IVUS and histologic findings regarding the identification of calcified and noncalcified lesions.[1-3] From a previous study, we learned that the sensitivity of angiography as compared to IVUS was poor for calcified lesions (30%)[10]; therefore, angiography should not be used to assess progression of calcium in a longitudinal follow-up study. Because thickness of lesion calcification cannot be measured, the arc and length should be regarded as the "best" possible measurement.[11] The present IVUS study aimed to document the reproducibility of the extent of the calcified lesion, as well as the progression of the extent of the calcified lesion seen at 1-y follow-up. The following issues should be addressed.

Reproducibility

The results of the current study indicated that the reproducibility of both arc and length measurements assessed by independent observers and from separate pull-back maneuvers was high, showing small differences (<1.1%), low coefficients of variation (<5.8%) and high correlation coefficients (>0.992). In vascular segments that were subjected to PTA, however, the interexamination difference encountered in the arc of the calcified lesion was significant (-4.9%; p=0.01). This may be explained by the fact that, as a result of balloon angioplasty, the vessel circumference after intervention is larger than the preintervention vessel circumference.

As a consequence, the arc of the calcified lesion measured after intervention was significantly smaller (-6.2°) than the arc measured before intervention. Our study results on the interobserver variability of arc measurements of the calcified lesion concur with others. Fitzgerald et al.[4] and van der Lugt et al.[12] reported close agreement for the interobserver variability of arc measurements of the calcified lesion.

In the present study, we used the vessel circumference to center the protractor to quantitate the arc of the calcified lesion. Other approaches have been advocated as well: either the protractor was centered on the imaging catheter[4,13] or centered on the lumen.[14] These latter studies aimed to relate the extent of the calcified lesion obtained from one single pull-back maneuver to predict future cardiac events or to define risk factors leading to lesion calcification. However, the position of the imaging catheter may be different at each pull-back maneuver and the center of the lumen may be more liable to change at follow-up compared to the center of the vessel circumference. In view of future longitudinal IVUS studies, we believe that the center of the vessel circumference should be used for analysis of the arc of the calcified lesion.

To measure the length of the calcified lesion, we used a validated displacement-sensing device.[9] Results from the present study indicate that this system reproducibly measures the length of the calcified lesion (interexamination differences ≤ 1.1%). For coronary application, Mintz et al.[13] used a motorized pull-back device, using the number of seconds or the number of frames of the videotape in which the calcification appeared to determine the lesion length; however, they did not report on the reproducibility of this procedure. It is worth mentioning that the errors in calcium length measurements using pull-back techniques in coronary arteries may include: (1) angulation of the catheter tip in relation to the imaged calcification, (2) catheter-induced deformation or straightening of the natural coronary artery tortuosity, and (3) beam thickness.[11] The results of the present study indicate that these problems are not encountered in straight peripheral arteries.

Change at follow-up

This study showed a nonsignificant increase in both the arc and length of the calcified lesion at 1-y follow-up. Recently, van Lankeren et al.[8] reported that the extent of the calcified lesion significantly increased from 51° to 66° at 16 months follow-up. The reason why the results from the latter study differ from the present study may be due to the difference in follow-up duration and to the difference in arc measurements; van Lankeren et al.[8] graded the extent of the calcified lesion in steps of 30° by visual estimation.

Clinical implication

One may argue whether or not a future study using a larger study population and/or a longer follow-up might achieve a statistically significant increase in the extent of the calcified lesion. Moreover, because IVUS is a costly and invasive procedure, future IVUS studies aimed at monitoring the effect of medical intervention on the progression of atherosclerosis should be executed in conjunction with regular interventional procedures.

CONCLUSION

This IVUS study showed that measurements of the extent of the calcified lesion are highly reproducible; the changes seen at 1-y follow-up were not significant. We conclude that IVUS may be used in a longitudinal study to monitor the effect of medical intervention on the composition of the atherosclerotic lesion.

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CHAPTER 8

Progression of Atherosclerosis at One-Year Follow-Up seen with Volumetric Intravascular Ultrasound in Femoropopliteal Arteries

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ABSTRACT

Volume measurements derived from intravascular ultrasound (IVUS) images assessed with an automated contour analysis system are accurate and reproducible. However, it is unknown to what extent plaque volume may change at follow-up. Therefore, the purpose of this longitudinal study is to examine whether IVUS is a sensitive means to identify progression of atherosclerosis and its derived primary end point plaque volume at 1-year follow-up. Patients (n=11) undergoing percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery were studied with IVUS immediately after PTA in the same session and at 1-year follow-up. Matched well-identified vascular segments (3 to 4 cm in length), not subjected to PTA, imaged at baseline and after 1-year follow-up, were used for calculation of the longitudinal change in lumen, vessel and plaque volume, and mean plaque thickness. The median length of the selected vascular segments was 4 cm. At follow-up (12 ± 2 months) a nonsignificant increase in lumen volume (2.3 ± 11%), vessel volume (2.0 ± 7.0%), and plaque volume (3.0 ± 5.1%) was seen; the mean plaque thickness increase was 2.2 ± 5.6%. In conclusion, progression of atherosclerosis implies changes in plaque and vessel volume, resulting in lumen volume change. This observation has important implications for future clinical trials aimed at monitoring the effect of pharmacologic agents on the progression and/or regression of atherosclerosis.

INTRODUCTION

Intravascular ultrasound (IVUS) is an acknowledged technique to assess the different components of the diseased vessel wall and to measure the change in lumen, vessel, and plaque area as result of vascular intervention.[1-7] Serial IVUS studies have shown that following successful vascular intervention, plaque growth and the mode of vessel area change (compensatory enlargement or vascular shrinkage) determined the change in lumen area at follow-up.[8-12] To document progression and/or regression of atherosclerotic plaque volume in a longitudinal study, an automated contour analysis system was developed; this system creates a 3-dimensional reconstruction from a multitude of IVUS cross-sectional images.[13] Validation studies have shown that volume measurements obtained with this analysis system were accurate with low interobserver variability[14-17] and were highly reproducible.[18] The present study examines whether IVUS is the means to sensitively identify progression of atherosclerosis at 1-year follow-up.

METHODS

The study group consisted of 16 patients (12 men, 4 women; aged 43 to 80 years [median 71]). Patients were selected from an existing study group with symptomatic femoropopliteal artery disease. At baseline, these patients were studied with IVUS before and after percutaneous transluminal angioplasty (PTA). A per-protocol follow-up IVUS investigation was performed after 1 year.[12] The investigation was approved by the local committee on Human Research. Patients were included in the study after they gave informed consent. Patient selection was based on an angiographically successful intervention (diameter stenosis <50%) and on the availability of a vascular segment not subjected to PTA (≥3 cm length together with a side-branch) imaged with IVUS immediately after intervention in the same session.

Intravascular ultrasound

The IVUS studies were performed using a single rotating ultrasound element (30 MHz) on a guidewire-tipped 4.3Fr catheter (Endosonics, Rijswijk, The Netherlands, 0.035 in). The following procedure was applied: the IVUS catheter was introduced antegradely over a guidewire through a 7Fr sheath in the femoropopliteal artery, distal to the lesion. The information on the

location (i.e., position) of the catheter tip was documented using a radiopaque ruler and a displacement sensing device.[19] The latter device was used to document the location of the catheter tip in relation to the patella in steps of 0.1 mm during the pull-back maneuver. The information on the catheter tip position was mixed with the IVUS images on the monitor and translated into a digital audiosignal, which was stored on the audiochannel of the videotape using a timecode generator and a special videorecorder. This enabled automated selection of IVUS images required for the longitudinal reconstruction. For the purpose of this study care was taken that vascular segments not subjected to PTA, proximal to the treated site, were recorded for analysis. To avoid dropout due to the guidewire, the IVUS images were recorded after the guidewire was removed. After 1-year follow-up, the IVUS study was repeated. The procedure was performed in the same manner as described previously. Vascular segments imaged after PTA and at follow-up were matched with the use of side-branches and the information of the displacement sensing device

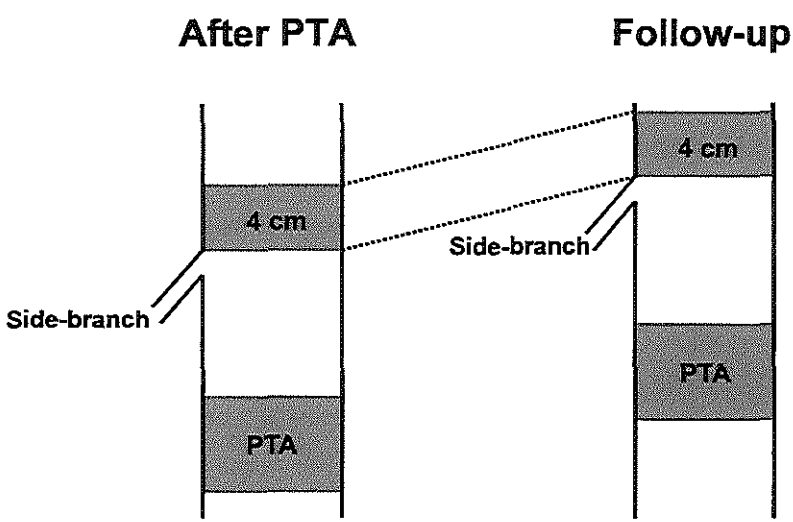

Figure 1. Schematic drawing showing how corresponding vascular segments obtained immediately after intervention and at follow-up are matched using side-branches and the information from the displacement sensing device.

(Figure 1). From each patient the most proximal located vascular segment (3 to 4 cm in length) that had not been subjected to PTA was selected for automated analysis.

Automated analysis system

An automated contour analysis system, which created a longitudinal reconstruction of a multitude of cross-sectional IVUS images, was used to assess volume measurements of lumen, vessel, and plaque. The automated contour detection was based on the minimum-cost algorithm, as described previously.[13] In brief, a matrix was yielded from the digitized images, producing low values (costs) for large changes in echo intensity. Through this matrix, the algorithm determined a path with the smallest accumulated cost that represents the boundaries (contours) of the arterial structures. The analysis program uses the Microsoft Windows operating system on a Pentium (100 MHz) personal computer with 32 Mbytes of internal RAM. Using a framegrabber (DT-3852; resolution 800 × 600 × 8 bits) a maximum of 200 IVUS cross sections was stored per vascular segment. The analysis procedure could be divided in 3 steps (Figure 2). First, a sequence of IVUS images was selected and digitized at 0.2-mm intervals. Two perpendicular planes, parallel to the longitudinal axis of the vessel, were selected to reconstruct longitudinal views. Second, the program defined the contours of lumen and vessel boundaries on these longitudinal planes by applying the algorithm. Third, the longitudinal contour information was transformed to the cross sections by defining 4 guiding points. By applying the algorithm and the information of the 4 guiding points, lumen and vessel boundaries on each cross section were detected. During all steps, the user could interactively refine the analysis. The results were presented in a graph containing the measurements of each cross section.[13] Lumen, vessel, and plaque volumes were calculated as:

$$Volume = \sum_{i=1}^{n} A_i \times H$$

where A is the area, H is the interval between the 2 cross sections, and n is the number of acquired IVUS images. In addition, the mean plaque thickness (i.e., intima-media thickness) of each vascular segment was determined.

Reproducibility of volume measurements

The reproducibility of volume measurements using the automated contour analysis system was determined in a previous study.[18] Briefly, 15 patients were imaged with IVUS before and after PTA of the femoropopliteal artery. From each patient, 1 vascular segment of 3 to 4 cm (median 3.7), which was not subjected to PTA, was selected for measurements of lumen, vessel, and plaque volume. The analysis was performed by 2 independent observers.

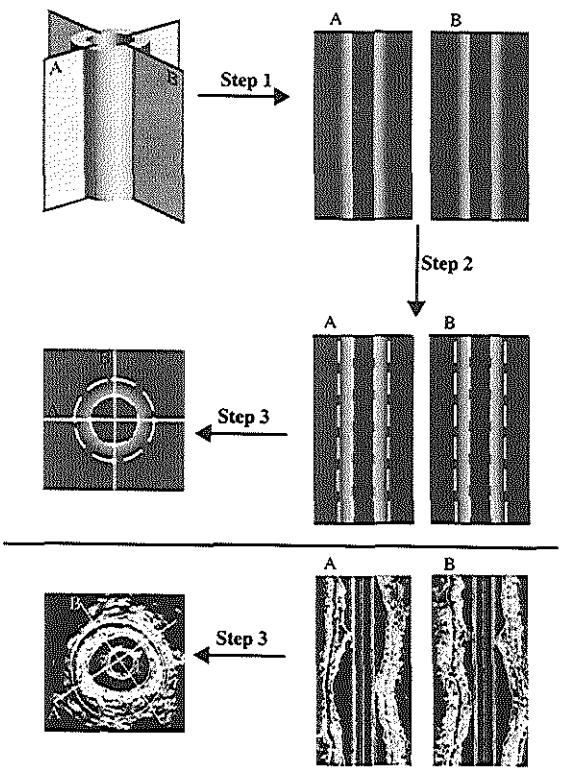

Figure 2. Automatic contour detection of IVUS images. Upper panel: 2 perpendicular planes are used to reconstruct 2 longitudinal sections (A and B) from the digitized IVUS images (Step 1). Automatic contour detection of the intimal leading edge and the external boundary of the vessel is performed on these longitudinal sections (Step 2). The longitudinal contours are represented as individual edge points in the cross-sectional images. These points define center and range of the final contour detection process on the cross-sectional IVUS images (Step 3). Lower panel: the 2 reconstructed longitudinal sections (A and B) correspond to the perpendicular planes seen in the cross section.

The results showed that the interobserver differences in volume measurements of lumen, vessel, and plaque were small (0.2% to 0.4%), with low coefficients of variation (0.4% to 1.7%) and high correlation coefficients (r = 1.00 for all). Similarly, volume measurements obtained in the 2 separate pull-back maneuvers were small (0.6% to 2.6%), with low coefficients of variation (5.6%

to 8.6%) and high correlation coefficients (r = 0.97 to 0.99).

Data analysis

First, a comparison was made between lumen, vessel and plaque volume, and mean plaque thickness assessed at baseline and after 1-year follow-up. Because the length of the vascular segments used for analysis was not uniform, the change in volume was given in cubed millimeters per centimeter and as a percentage of the volume measurements after intervention. Second, a comparison was made between the change in plaque volume and mean plaque thickness.

Results are given as mean ± SD or as median and range. The volumes seen immediately after intervention and at follow-up were compared with Student's t test for paired observations. A p value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up period was 12 ± 2 months. Vascular segments initially selected after intervention could in all instances be matched with the vascular segments obtained at follow-up using side-branches and the information of the displacement sensing device. The IVUS quality of the vascular segment selected was adequate to document lumen, vessel, and plaque volume in 11 of the 16 patients; in the 5 remaining patients the analysis of lumen volume (n=1), vessel volume (n=3), or both (n=1) could not be performed due to low image quality at follow-up (n=1), progression of calcified lesions (n=3), and subintimal introduction of the guidewire (n=1). The side-branch of the selected vascular segments was situated proximally (n=6) or distally (n=3); in 2 patients the vascular segment was interposed between 2 side-branches. The median distance between the segment subjected to PTA and the selected vascular segment used for analysis was 8 cm (range 1 to 17). The median length of the vascular segments selected for analysis was 4 cm (range 3.2 to 4). The selected vascular segments had a maximum area stenosis of 44% (median) (range 31% to 63%).

Table 1 summarizes the measurements of lumen, vessel and plaque volume, and mean plaque thickness of each patient after intervention and at 1-year follow-up. Changes in lumen, vessel and plaque volume, and mean plaque

thickness seen with IVUS in the individual matched vascular segments after intervention and at follow-up are summarized in Table 2. The mean increase in plaque volume of 3.7 ± 7.1 mm^3/cm (3.0 ± 5.1%; p=0.12) was associated with an increase in vessel volume of 3.9 ± 27 mm^3/cm (2.0 ± 7.0%; p=0.64), resulting in an increase in lumen volume of 0.2 ± 23 mm^3/cm (2.3 ± 11%; p=0.98). At follow-up the mean plaque thickness increased to 0.02 ± 0.08 mm (2.2 ± 5.6%; p=0.34).

Table 1 Lumen, Vessel and Plaque Volume and Mean Plaque Thickness Seen in Matched Vascular Segments *

Vascular Segment	Lumen volume		Vessel volume		Plaque volume		Plaque thickness	
	After PTA (mm^3/cm)	Follow-up (mm^3/cm)	After PTA (mm^3/cm)	Follow-up (mm^3/cm)	After PTA (mm^3/cm)	Follow-up (mm^3/cm)	After PTA (mm)	Follow-up (mm)
1	262	263	358	370	96	108	0.98	1.09
2	230	261	323	359	93	99	1.00	1.00
3	106	137	226	258	120	121	1.69	1.55
4	171	177	301	305	430	129	1.54	1.50
5	322	348	478	519	156	171	1.40	1.47
6	187	177	289	285	102	108	1.18	1.28
7	249	245	392	386	143	141	1.44	1.44
8	241	246	408	411	166	165	1.69	1.65
9	404	363	528	487	125	124	1.04	1.08
10	313	282	502	465	189	183	1.68	1.70
11	263	252	476	479	213	227	2.01	2.16
Mean ± SD	250 ± 80	250 ± 69	389 ± 99	393 ± 88	139 ± 39	143 ± 39	1.42 ± 0.34	1.45 ± 0.33

*From 11 patients studied with IVUS after intervention and at 1-year follow-up.

The comparison between the change in plaque volume and mean plaque thickness in the individual vascular segments is shown in Figure 3 and Table 2.
It was discovered that the location of the vascular segments selected for analysis (distance to the segment subjected to PTA) and the position of the side-branch

Table 2 Changes in Lumen, Vessel and Plaque Volume and Mean Plaque Thickness Seen in Matched Vascular Segments*

Vascular Segment	ΔLumen volume		ΔVessel volume		ΔPlaque volume		ΔPlaque thickness	
	(mm^3/cm)	%	(mm^3/cm)	%	(mm^3/cm)	%	(mm)	%
1	0.7	0.3	12	3.4	11	12	0.11	11
2	31	13	37	11	6.0	6.4	0.01	0.5
3	31	29	32	14	0.7	0.5	-0.14	-8.2
4	5.9	3.5	4.1	1.4	-1.8	-1.4	-0.05	-2.9
5	26	8.2	41	8.6	15	9.4	0.07	5.1
6	-10	-5.4	-4.0	-1.4	6.2	6.1	0.10	8.1
7	-4.7	-1.9	-6.9	-1.8	-2.2	-1.5	-0.004	-0.3
8	4.9	2.0	3.3	0.8	-1.6	-0.9	-0.03	-2.0
9	-41	-10	-41	-7.7	-0.3	-0.3	0.04	4.3
10	-30	-9.7	-37	-7.3	-6.1	-3.2	0.02	1.1
11	-11	-4.3	2.6	0.6	14	6.6	0.15	7.4
Mean ± SD	0.2 ± 23 (p=0.98)	2.3 ± 11	3.9 ± 27 (p=0.64)	2.0 ± 7.0	3.7 ± 7.1 (p=0.12)	3.0 ± 5.1	0.02 ± 0.08 (p=0.34)	2.2 ± 5.6

*From 11 patients studied with IVUS after intervention and at 1-year follow-up.
Δ = Change; − = Decrease

in relation to the selected vascular segment had no influence on the changes in lumen, vessel and plaque volume, and mean plaque thickness seen at follow-up.

DISCUSSION

The present IVUS study is the first in which vascular segments obtained at baseline were matched with the vascular segments at 1-year follow-up using side-branches, to document the change in lumen, vessel and plaque volume, and mean plaque thickness.

By combining the IVUS procedure with angiography at baseline and at follow-up, the additional burden to the patient was small. The advantage of using the automated contour analysis system to determine volume measurements from a multitude of IVUS cross sections, rather than using manual analysis to assess area measurements from single IVUS cross sections, was improved interobserver reproducibility.[18] From coronary artery studies, we learned that the accuracy of volume measurements may be hampered by the vessel distensibility, cardiac movement, and curvature of the vessel.[16] However, in the relatively straight femoropopliteal artery used in the present study the problem of vessel distensibility and cardiac movement was not observed in the longitudinal reconstructions of the IVUS cross-sectional images (Figure 2). Based on these findings, we postulate that the femoropopliteal artery will be suitable for progression and/or regression studies using IVUS together with the automated contour analysis system. The following issues encountered in the present study deserve specific comment.

Volume change at 1-year follow-up

The present longitudinal IVUS study revealed that at follow-up the plaque volume increase (3.0 ± 5.1%) was associated with an increase in vessel volume (2.0 ± 7.0%), resulting in an increase in lumen volume (2.3 ± 11%) (see Tables 1 and 2). Although these changes were not statistically significant, the increase in plaque volume should be regarded as progression of atherosclerosis, whereas the increase in vessel volume might be explained by the Glagov effect.[20]

Recently, van Lankeren et al[12] reported an increase in both the plaque (15%) and vessel (6%) areas of femoropopliteal arteries after 16 months of follow-up, resulting in a decrease in lumen area (−3%). Similarly, Takagi et al[21] reported

that at 3-year follow-up, plaque area (41%) and vessel area (9%) increased in the coronary arteries, resulting in a decrease in lumen area (-9%). The difference between plaque volume change encountered in the present study and plaque area change reported by others may be attributed to the difference in patient selection, selection of individual cross sections, and the difference in follow-up duration.

Plaque volume versus mean plaque thickness

Although the mean change in plaque volume (3.0 ± 5.1%) was of the same order as the mean change in mean plaque thickness (2.2 ± 5.6%), individually, the 2 parameters were different (see Table 2; Figure 3). The difference can be explained by the change in mean plaque thickness, which is intimately related to changes in both plaque and vessel volume. In other words, in the presence

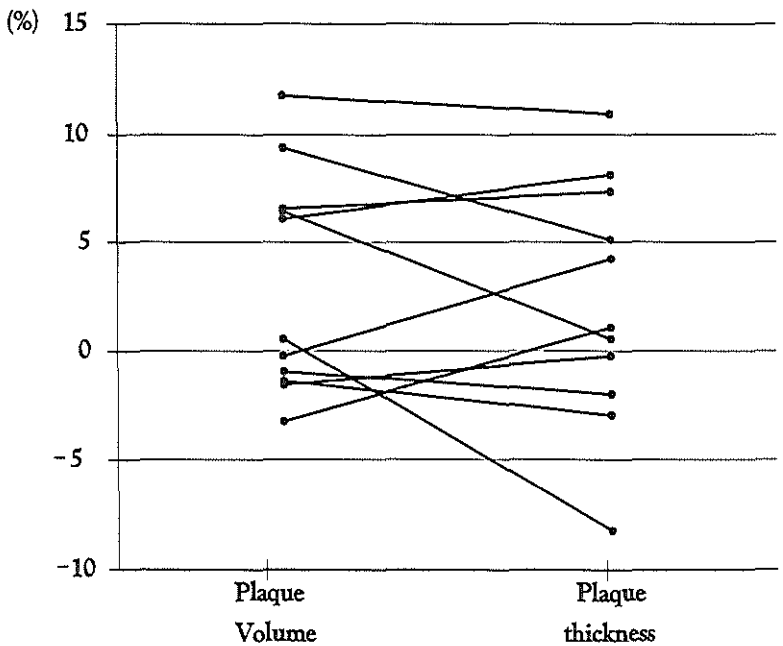

Figure 3. The relation between the change in plaque volume (left) and mean plaque thickness (right) seen at follow-up in the patients. The 2 measurements from each patient are connected by a line, showing the discrepancy between the change in plaque volume and mean plaque thickness.

of no change in plaque volume and an increase or decrease in vessel volume, plaque thickness measurements may either underestimate or overestimate the change in plaque seen at follow-up. With these findings in mind, one should reconsider the value of intima-media thickness measurements derived from external ultrasound, used to document the progression of atherosclerosis.[22-26] De Groot et al[26] established that the intima-media thickness did not change after 2-year follow-up in the control group. In contrast, in the present study an increase in plaque volume (3%) and vessel volume (2%) were evidenced at 1-year follow-up; in addition, the mean plaque thickness increased by 2.2%. The difference between plaque thickness change seen in the control group reported by de Groot et al[26] and that in the present study may be because external ultrasound provided data on the far wall of an arterial segment only, whereas IVUS has the potential to image the total arterial segment. The strong advantage of IVUS compared with intima-media thickness measurements is embedded in that IVUS has the potential to sensitively observe the impact of arterial remodeling on the lumen and plaque change.

Clinical implications

The results of this study support the idea, dating from 1989, that IVUS can be used to grade the effect of pharmacologic interventions on the progression and/or regresssion of atherosclerosis.[27,28] Because the potential of IVUS to sensitively observe arterial remodeling has been established,[8-12] we believe that the results of progression and/or regression studies using intima-media thickness measurements from external ultrasound should be reconsidered. Indeed, in the presence of an increase in plaque and vessel volume seen at follow-up, intima-media thickness measurements may reveal no change. With these findings in mind, we believe that volumetric IVUS studies are excellently suited to establish the basic mechanism associated with progression and/or regression of atherosclerotic plaque and the influence of pharmacologic agents on these processes.

Study limitations

In 5 of the 16 patients in whom a vascular segment was selected after intervention, the quality of the vascular segment at follow-up hampered analysis. Second, currently, the automated contour analysis system is restricted

in the length of the vascular segment (4 cm) that can be analyzed. Increasing the capacity of storing IVUS images may overcome this problem. Another solution might be to increase the interval (0.2 mm) between the stored IVUS images. Third, determination of the factors that may affect an increase or decrease in vessel and plaque volume at follow-up needs further investigation. It should be stressed that the automated contour analysis system cannot be used in vascular segments containing a dissection as a result of intervention.[29] Fourth, we must bear in mind that thus far no correlation has yet been established between change in volumetric IVUS parameters and future vascular events. Finally, contrary to intima-media thickness measurements obtained with external ultrasound, IVUS is an expensive and invasive procedure, and is, for ethical reasons, less fit for investigation of control groups without disease and largescale epidemiologic-oriented population studies.

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CHAPTER 9

Early Experience with Intravascular Ultrasound in Evaluating the Effect of Statins on Femoropopliteal Arterial Disease:

Hypothesis-generating observations in humans

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ABSTRACT

The purpose of this study was to compare the vascular response seen with intravascular ultrasound (IVUS) at 1-year follow-up between statin-treated and non-statin-treated patients. Patients (n=10) undergoing percutaneous transluminal angioplasty (PTA) of the femoropopliteal artery were studied with IVUS immediately after PTA and at 1-year follow-up. In nondilated matched vascular segments the change in lumen, vessel and plaque volume was assessed. In balloon-dilated matched vascular segments, the change in lumen, vessel and plaque area was assessed. A comparison was made between statin-treated (n=5) and non-statin-treated patients (n=5) in lumen, vessel and plaque changes. At follow-up, both statin-treated and non-statin-treated patients showed a similar increase in plaque volume at the nondilated segment (+4% and +2%, respectively). In statin-treated patients the plaque volume increase was compensated by an increase in vessel volume (+2%), resulting in an increase in lumen volume (+1%). In non-statin-treated patients, on the other hand, the increase in plaque volume was associated with a decrease in vessel volume (-2%), resulting in a decrease in lumen volume (-4%). At the balloon-dilated segment a similar trend in changes of lumen, vessel and plaque was encountered. Differences between both groups of patients were not statistically significant. Despite the nonsignificant nature of the observation, this small retrospective IVUS study may generate the hypothesis that statin therapy may contribute to superior long-term lumen dimensions by inducing positive vascular remodeling both in nondilated and balloon-dilated vascular segments.

INTRODUCTION

Over the past decade, intravascular ultrasound (IVUS) has become an acknowledged technique to document immediate and long-term changes in lumen, vessel and plaque area following a vascular intervention.[1-4] Encouraged by these results, an automated contour analysis system was developed to assess lumen, vessel and plaque volume derived from IVUS images.[5-8] In a previous study we established that this analysis system is a sensitive means to identify progression of atherosclerosis at 1-year follow-up.[9] The scope of the present retrospective observational IVUS study was to determine the difference between statin-treated and non-statin-treated patients in progression of atherosclerosis seen at 1-year follow-up.

METHODS

The study group comprised 16 patients (12 men, 4 women), with an age range of 43 to 80 (median 71) years. Patients were selected from an existing study group with symptomatic femoropopliteal artery disease. At baseline session these patients were studied with IVUS immediately after percutaneous transluminal angioplasty (PTA). A per protocol follow-up investigation was performed after 1 year. The local Committee on Human Research approved the investigation. Patients were included in the study after they gave informed consent. The patient selection was based on: (1) an angiographically successful PTA (angiographic diameter stenosis <50%), (2) the availability of IVUS images immediately after PTA and at 1-year follow-up, and (3) the use of a displacement sensing device. Data collected on each patient included age, gender, systemic hypertension, diabetes, cigarette smoking, indication for intervention (Fontaine classification 2B [claudication], 3 [rest pain] and 4 [ulceration]) and total cholesterol levels during the follow-up period.

Intravascular ultrasound

The IVUS studies were performed using a single rotating ultrasound element (30 MHz) on a guidewire-tipped 4.3F catheter (Endosonics, Rijswijk, The Netherlands, 0.035"). Briefly, the following procedure was applied: Through a 7F sheath in the femoropopliteal artery the IVUS catheter was introduced antegradely over a guidewire, distal to the lesion. After the guidewire was removed to avoid dropout, the ultrasound catheter was pulled back manually.

A displacement sensing device was used to document the location (i.e. position) of the cathetertip in steps of 0.1 mm during the pullback maneuver.[10] The information on the cathetertip location was (1) combined with the IVUS images on the monitor and (2) translated into a digital audiosignal that was stored on the audiochannel of the videotape using a timecode generator and a special videorecorder. This digital audiosignal enabled automatic selection of the IVUS images required for volume measurements. Using the information on the cathetertip and anatomic markers such as side branches and typical shaped calcifications, the IVUS cross sections obtained after PTA and at follow-up were matched.

From each patient 1 or 2 vascular segments (3- to 4-cm length) not subjected to PTA *(i.e. nondilated segments)* were selected for *volume* measurements of lumen, vessel and plaque using an automated contour analysis system. Vascular segments subjected to PTA *(i.e. balloon-dilated segments)* could not be analyzed using the automated contour analysis system due to an irregular-shaped lumen circumference caused by a dissection as result of the vascular intervention.[7] For this reason, the change in vascular dimensions in the balloon-dilated segments was assessed in individual matched IVUS cross sections selected with 1 cm interval. These cross sections were subsequently manually analyzed for lumen, vessel and plaque *area*.

Automated contour analysis

The automated contour analysis program uses the Microsoft Windows operating system on a Pentium (100 MHz) personal computer with 32 Mbytes of internal RAM. Using a framegrabber (DT-3852; resolution 800 × 600 × 8 bits), a maximum of 200 IVUS cross sections was stored per vascular segment. The analysis procedure could be divided in 3 steps (Figure 1). First, a sequence of IVUS images was selected at 0.2 mm interval using the information provided by the displacement sensing device and was subsequently digitized. Two perpendicular planes, parallel to the longitudinal axis of the vessel, were selected to reconstruct longitudinal views. Second, the program defined the contours of both lumen and vessel boundaries on these longitudinal planes by applying a minimum cost algorithm, as described previously.[5] Third, the longitudinal contour information was transformed to the cross sections by defining 4 guiding points. By applying the algorithm and the information of

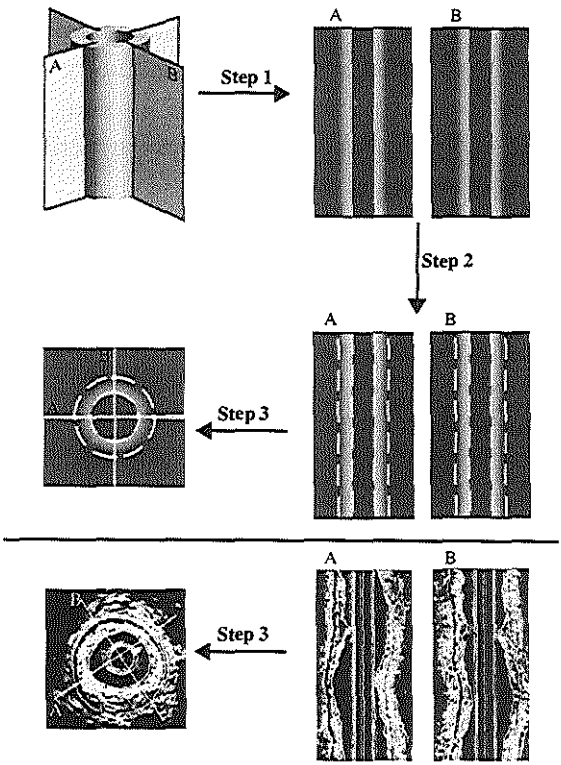

Figure 1. Automatic contour detection of intravascular ultrasound (IVUS) images. Upper panel: Two perpendicular planes are used to reconstruct 2 longitudinal sections (A and B) from the digitized IVUS images (Step 1). Automatic contour detection of the intimal leading edge and the external boundary of the vessel is performed on these longitudinal sections (Step 2). The longitudinal contours are represented as individual edge points in the cross-sectional images. These points define center and range of the final contour detection process on the cross-sectional IVUS images (Step 3). Lower panel: the 2 reconstructed longitudinal sections (A and B) correspond to the perpendicular planes seen in the cross-section.

the 4 guiding points, lumen and vessel boundary on each individual cross-section was detected. During all steps, the user could interactively modify the contours of lumen and vessel boundary that were detected by the automated contour analysis system. Lumen, vessel and plaque volume were calculated as:

$$Volume = \sum_{i=1}^{n} A_i \times H$$

where A is the area, H is the interval between 2 cross sections (slice thickness) and n is the number of IVUS images acquired.

Manual analysis

For the assessment of lumen, vessel and plaque area, a digital video analyzer system (IBM, Boca Raton, FL, USA) was used.[11] When image quality was inadequate or extensive dropout due to calcification was encountered, the analysis of vessel area could not be performed and these IVUS cross sections were excluded from the study.

Reproducibility

The reproducibility of volume and area measurements was established in previous studies [8,12] The interobserver difference for lumen, vessel and plaque volume measurements using the displacement sensing device was ≤0.4%, with low coefficients of variation (≤1.7%) and high correlation coefficients (r=1.00 for all).[8] The interobserver difference for lumen, vessel and plaque area was ≤0.9%, with coefficients of variation ≤14% and correlation coefficients ≥0.93.[12]

Statical analysis

Volume measurements of the nondilated segment from each individual patient were summed when 2 vascular segments were analyzed. Because the length of the nondilated segments was not uniform, the change in volume was given in mm^3/cm and as a percentage of the volume measurements after PTA. Similarly, area measurements from the balloon-dilated segment were averaged over the number of IVUS cross sections acquired from each individual patient. Results are given as mean and standard deviation. For comparison of changes in volume and area measurements seen in statin-treated and non-statin-treated patients the Student's t-test was used. A p value <0.05 was considered statistically significant.

RESULTS

The IVUS quality of the vascular segment selected was adequate to document lumen, vessel and plaque volume in 11 of the 16 patients; in the 5 remaining patients the analysis of lumen volume (n=1), vessel volume (n=3), or both (n=1) could not be performed due to low image quality at follow-up (n=1), progression of calcified lesion (n=3), and subintimal introduction of the guidewire (n=1), respectively.

Table 1 Characteristics of the study population

	Statin-treated patients (n=5)	Non-statin-treated patients (n=5)	p value
Gender, male	4	5	0.37
Age, mean (±SD), years	70.8 ± 8.4	64.8 ± 12.9	0.41
Diabetes Mellitus	2	3	0.58
Systemic hypertension	3	1	0.24
Cigarette smoking	3	5	0.14
Cessation of cigarette smoking	0	0	n.a.
Fontaine classification, 2B/3/4	4/1/0	4/0/1	0.88
Follow-up, mean (±SD), months	13.0 ± 0.9	11.1 ± 2.9	0.21
Cholesterol, mean (±SD), mmol/L	5.5 ± 1.4	5.6 ± 1.4	0.91

SD = Standard Deviation; n = number of patients; n.a. = not applicable

Because one patient received Gemfibrozil (lipid-lowering medication) periodically during the follow-up period, this patient was excluded from the study. Of the remaining 10 patients, 5 patients were treated with statin (Group 1) during the entire follow-up period: 4 with Simvastatin 10 mg (n=3) or 20 mg (n=1), and 1 patient with Pravastatin 20 mg. Five other patients were not treated with statin (Group 2). No significant differences were encountered between both groups of patients with regard to demographic features, presenting symptoms and mean follow-up duration (Table 1). Total cholesterol levels obtained 3 ± 2 months after the initial PTA and IVUS study, in all statin-treated patients and in 3 of the 5 non-statin-treated patients, showed no difference; 4.0-7.5 mmol/l and 4.3-7.0 mmol/l, respectively.
In total 16 matched nondilated segments (14 proximal, 2 distal) were analyzed: 2 segments in 6 patients and 1 segment in 4 patients.

Table 2 Quantitative data on lumen, vessel and plaque volume and area seen with intravascular ultrasound immediately after percutaneous transluminal angioplasty (PTA) and at 1-year follow-up in statin-treated patients (+) and in non-statin-treated patients (-).

	Statin	After PTA	Follow-up	Change
Nondilated segment (mm^3/cm)				
Lumen volume	+	267 ± 82	269 ± 64	+1.9 ± 26 (+1%)
	-	247 ± 46	237 ± 44	-9.8 ± 18 (-4%)
Vessel volume	+	389 ± 92	395 ± 78	+6.2 ± 30 (+2%)
	-	402 ± 91	395 ± 85	-6.8 ± 18 (-2%)
Plaque volume	+	123 ± 23	127 ± 28	+4.3 ± 6.1 (+4%)
	-	155 ± 51	158 ± 52	+3.1 ± 9.4 (+2%)
Volume stenosis	+	32%	32%	+0%
	-	39%	40%	+1%
Balloon-dilated segment (mm^2)				
Lumen area	+	25 ± 5.6	23 ± 6.5*	-1.8 ± 2.6 (-7%)
	-	17 ± 5.2	13 ± 1.6*	-3.9 ± 3.7 (-23%)
Vessel area	+	43 ± 5.9	45 ± 6.4	+1.5 ± 2.0 (+4%)
	-	42 ± 14	40 ± 12	-1.2 ± 2.2 (-3%)
Plaque area	+	19 ± 1.9	22 ± 3.4	+3.3 ± 1.8 (+18%)
	-	25 ± 9.3	28 ± 11	+2.7 ± 1.8 (+11%)
Area stenosis	+	44%	49%	+5%
	-	60%	70%	+10%

Differences were not statistically significant except * ($p<0.05$)

The median length of the nondilated segments analyzed in each individual patient was 6.9 (range 3.6-8.0) cm. The median distance between the nondilated and balloon-dilated segment was 7 (range 3-19) cm.

In total 63 (median 6, range 3–14) of the 97 matched IVUS cross sections from the balloon-dilated segment were manually analyzed for lumen, vessel and plaque area. In the remaining 34 cross sections, the vessel area could not be analyzed due to extensive calcification, causing drop-out.
Table 2 summarizes the quantitative data on lumen, vessel and plaque volume and area seen immediately after PTA and at 1-year follow-up. At baseline no significant difference was encountered between both groups of patients. At follow-up there was a significant difference between both groups of patients in lumen area at the balloon-dilated segment. At follow-up, both statin-treated and non-statin-treated patients showed a similar increase in plaque volume at the nondilated segment (+4% and +2%, respectively). In statin-treated patients the plaque volume increase was compensated for by an increase in vessel volume (+2%), resulting in an increase in lumen volume (-1%). In non-statin-treated patients, on the other hand, the increase in plaque volume was associated with a decrease in vessel volume (-2%), resulting in a decrease in lumen volume (-4%). At the balloon-dilated segment a similar difference between both groups of patients was encountered. In statin-treated patients the extent of plaque area increase was similar to that seen in non-treated patients (+18% and +11%, respectively). In statin-treated patients the plaque area increase was partially compensated for by an increase in vessel area (+4%), whereas in non-statin-treated patients a decrease in vessel area (-3%) was encountered. The resulting decrease in lumen area was 7% in statin-treated patients and 23% in non-statin-treated patients. All differences in volume and area changes between Group 1 and 2 were not significant.

DISCUSSION

The conventional concept of progression/regression of atherosclerotic plaque is that statin therapy reduces the progression of atherosclerosis or even induces regression.[13-16] Current findings, although obtained from a small set of data, suggest an alternative pathway for the beneficial effect of statin therapy on lumen size. Surprisingly, in statin treated patients the extent of plaque volume and area increase was similar to that seen in non-statin-treated patients. Positive vascular remodeling seen in statin-treated patients and negative vascular remodeling in non-statin-treated patients determined the lumen change at 1-year follow-up (Figure 2, Table 2).

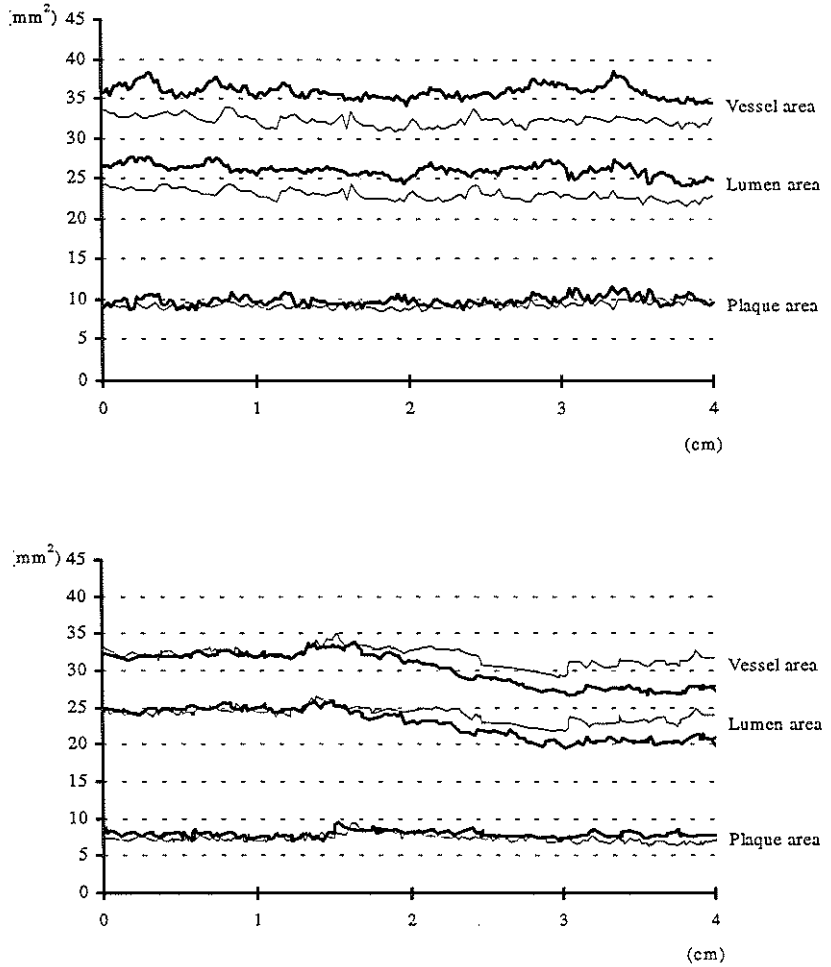

Figure 2. Standard display of the information on lumen, vessel and plaque area immediately after PTA (fine lines) and at 1-year follow-up (thick lines) derived from a nondilated segment using an automated contour analysis system. The upper panel represents a vascular segment derived from a statin-treated patient (Group 1): plaque area remained unchanged while the vessel area increased resulting in an increase in lumen area. The lower panel represents a vascular segment derived from a non-statin-treated patient (Group 2): plaque area remained unchanged while the vessel area decreased, resulting in a decrease in lumen area.

Thus one may hypothesize that statin therapy might have a beneficial effect on lumen size due to its effect on the mode of vascular remodeling rather than on the degree of plaque growth. With these findings in mind one should

reconsider the value of angiography [13,14] and external ultrasound[15,16] studies used to document the beneficial effect of statin therapy on the progression of atherosclerosis. Although these latter studies could not provide insight into the change in atherosclerotic plaque volume or area, the general consensus was that the effect of statin was related to the degree of plaque growth.

To date, two IVUS studies have reported on the effect of statin therapy in nondilated vascular segments using area measurements.[17,18] In a 3-year follow-up study in 18 coronary arteries not subjected to vascular intervention, Takagi et al.[17] revealed an increase in lumen area (10%) due to a decrease in plaque area (-7%) and no change in vessel area (0%) in statin-treated patients. Reasons why the latter results differ from ours remain speculative, but may be related to the difference in follow-up duration and/or to the use of a different vascular region. Recently, Hamasaki et al.[18] established that the effect of statin therapy on lumen size was the result of an increase in vessel area rather than a decrease in plaque area, supporting the possible mechanism of action of statin hypothesized in the present study.

Limitations

The main limitations of this study are the small number of patients examined, the retrospective and observational protocol, the short period of exposure to statin therapy (1 year), and the fact that the patients were treated with different statins. Second, it should be acknowledged that in 5 of the 16 patients in whom a nondilated segment was selected after intervention, the quality of the vascular segment at follow-up hampered the analysis. Finally, because IVUS is a costly and invasive procedure, prospective IVUS studies should be carried out in patients undergoing vascular intervention.

Future implications

This small retrospective IVUS study may generate the hypothesis that statin therapy contributes to superior long-term lumen dimensions by inducing positive vascular remodeling. A prospective IVUS study should include measurements of both the nondilated and balloon-dilated vascular segments. Analysis of the nondilated segment will elucidate the effect of statin therapy on the progression of atherosclerosis, without the side-effects of an intervention. Analysis of the balloon-dilated segment will reveal the beneficial effect of statin on the prevention of restenosis.

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CHAPTER 10

Effect of Simvastatin on Restenosis after Percutaneous Transluminal Angioplasty of Femoropopliteal Arterial Obstruction

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INTRODUCTION

Clinical studies using angiography have shown that HMG-CoA reductase inhibitors (statins) may reduce restenosis after coronary angioplasty.[1-3] However, the precise effect of statin therapy on the mechanism of restenosis after vascular intervention remains to be elucidated. The purpose of the present retrospective observational intravascular ultrasound (IVUS) study was to evaluate whether simvastatin therapy limits lumen area reduction 1 year after percutaneous transluminal angioplasty (PTA) by reducing reactive plaque growth, reducing reactive vasoconstriction, or both.

METHODS

The study group comprised 24 patients (16 men, 8 women); age range 44 to 89 years (median 72) with obstructive femoropopliteal artery disease treated successfully with PTA (angiographic diameter stenosis <50%). The study group consisted of a subset of patients retrospectively selected from the Peripheral Arterial Restenosis assessed with Intravascular Sonography (PARIS) study[4] based on the availability of IVUS images immediately after PTA and at 1-year follow-up. The study was approved by the Medical Ethics Committee. Patients were included in the study after they gave informed consent. Data collected on each patient included gender, age, diabetes, hypertension, history of smoking, and indication for intervention (intermittent claudication, pain at rest or night pain, and ulceration). Data on clinical and angiographic restenosis were collected at follow-up. Clinical restenosis was based on recurrent symptoms; angiographic restenosis was defined as a diameter stenosis of ≥50%.

The IVUS studies were performed immediately after PTA and at 1-year follow-up using the following procedure: the IVUS catheter was advanced distally through a 7Fr sheath in the femoropopliteal artery over a guidewire beyond the lesion. The IVUS catheter consisted of a single rotating ultrasound element (30 MHz) on a guidewire-tipped 4.3Fr catheter (Endosonics, Rijswijk, The Netherlands, 0.035 in). After the guidewire was removed to avoid drop-out, the ultrasound catheter was pulled back manually. The information on the location of the catheter tip was documented using a radiopaque ruler and a displacement sensing device. The latter device documents the location of the catheter tip in relation to the patella in steps of 0.01 cm during the

pull-back maneuver.[5] The information on the catheter tip position was correlated with the IVUS images on the monitor and the resulting images were stored on S-VHS videotape. With the information of the displacement sensing device, the radiopaque ruler, and anatomic markers such as side branches and typical-shaped calcifications, the IVUS cross sections obtained after PTA and at follow-up were matched. To ensure that the IVUS cross sections that were obtained after intervention corresponded with those that were obtained at follow-up examination, the cross sections were studied side-by-side and frame-to-frame. Matched IVUS cross sections obtained from the treated sites, including the most stenotic site (i.e., the cross section showing the smallest lumen area) after PTA, were selected with 1-cm intervals for analysis.

A digital video analyzer system (IBM Corp., Boca Raton, Florida) was used to assess the lumen, vessel, and plaque area.[6] Observers were blinded to patient characteristics and their use of simvastatin. The lumen area was defined as the area that was encompassed by the inner boundary of the intimal surface (also characterized by the presence of blood). The vessel area was defined as the area bounded by the media-adventitia border. The plaque area was calculated by subtracting the lumen area from the vessel area. When image quality was inadequate or there was extensive dropout due to calcification (>120° of the circumference), the analysis of vessel area could not be performed and these IVUS cross sections were excluded.

Lumen, vessel, and plaque area measurements from each patient were averaged over the number of IVUS cross sections acquired. Subsequently, the differences of the averaged area measurements at baseline and at 1-year follow-up were calculated. A comparison was made between patients who received and did not receive simvastatin in the absolute change of lumen, vessel, and plaque area seen at the treated site and at the most stenotic site by means of Student's t test. A p value of <0.05 was considered statistically significant. Results are given as mean and SD. The reproducibility of IVUS parameters used in this study has been reported previously.[4]

RESULTS

There were no complications as result of the IVUS procedure. Seven of the 24 patients were excluded from the study: 3 patients (who did not receive simvastatin) had angiographic restenosis within 6 months after PTA; in 2 patients the image quality was too low for analysis; and 2 patient were excluded because gemfibrozil or pravastatin was used during the follow-up period. IVUS images obtained after intervention and at 1-year follow-up were adequate for analysis in the remaining 17 patients. Patients given simvastatin (n=6) were treated during the entire follow-up period with 10 mg (n=4) or 20 mg (n=2) simvastatin; the remaining 11 patients were not treated with simvastatin.

At baseline no significant difference between patients who received and did not receive simvastatin, with regard to demographic features or presenting symptoms, was seen (Table 1). At follow-up, no clinical or angiographic restenosis was evident in patients who received simvastatin; in patients who did not receive simvastatin there was evidence for both clinical restenosis (n=4) and angiographic restenosis (n=8) (Table 1).

The length of the lesion treated with PTA (median 9.5 cm, range 4 to 21) did not differ among the 2 groups of patients (11 ± 6 and 9 ± 4 cm, respectively, p=0.53). In total 183 IVUS cross sections from the treated site were matched: in 147 of these IVUS cross sections (median 8, range 3 to 15) lumen, vessel, and plaque area could be analyzed. Fourteen of these 147 cross sections were derived from the most stenotic site (4 patients on simvastatin and 10 patients not on simvastatin). The remaining 36 cross sections (20%) were excluded from the study because of extensive dropout due to calcification.

Table 2 summarizes the quantitative data on lumen, vessel, and plaque area acquired in patients who received and did not receive simvastatin. Immediately after PTA no significant difference in lumen, vessel, and plaque area was encountered between both groups of patients. At the treated site, a significant difference between both groups of patients in lumen area and a borderline significant difference in vessel area change was seen at follow-up; in patients given simvastatin a lumen area decrease (-4%) and a vessel area increase (4%) was seen, whereas in patients not given simvastatin, lumen and vessel area decreased (-25% and -2%, respectively) (Figure 1).

Table 1 Patient Characteristics and Clinical and Follow-Up Data Obtained in Patients Who Received and Did Not Receive Simvastatin

	Patients who receiced simvastatin (n=6)	Patients who did not receive simvastatin (n=11)	p-value
Men / women	3/3	6/5	0.87
Age (mean±SD) (yrs)	71.1 ± 7.5	70.6 ± 9.3	0.85
Diabetes Mellitus (n [%])	2 (33 %)	5 (45 %)	0.46
Systemic hypertension	2 (33 %)	3 (27 %)	0.81
Cigarette smoking	3 (50 %)	7 (64 %)	0.61
Fontaine classification, 1/2B/3/4	0/5/1/0	1/6/1/3	0.41
Follow-up			
Follow-up (mean ± SD) (mo)	13.5 ± 1.3	12.6 ± 2.3	0.36
Clinical restenosis	0 (0 %)	4 (36 %)	0.10
Angiographic restenosis	0 (0 %)	8 (73 %)	0.002
Total-cholesterol (mean ± SD) (mmol/l)	5.7 ± 1.2 (n=6)	6.4 ± 0.8 (n=5)	0.31

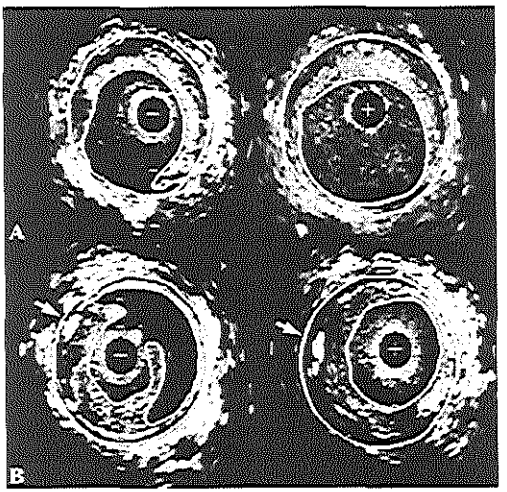
There was no difference in plaque area change in both groups of patients at follow-up.

Similarly, at the most stenotic site, a significant difference between both groups of patients in lumen and vessel area change was seen at follow-up; in patients given simvastatin, the lumen and vessel area increased, whereas in patients not given simvastatin, the lumen and vessel area decreased. There was no difference in plaque area change in both groups of patients at follow-up.

Table 2 Mean change in lumen, vessel and plaque area seen with intravascular ultrasound at one-year follow-up in patients treated with (+) and without (–) simvastatin

	Statin	After PTA (mm^2)	Follow-up (mm^2)	Change (mm^2)
Treated sites (n=17)				
Lumen area	+	22.7 ± 6.3	21.8 ± 6.3	-0.9 ± 3.6 (-4%)
	–	18.3 ± 7.4	13.7 ± 6.6	-4.6 ± 2.5 (-25%)
		(p=0.24)	(p=0.03)*	(p=0.03)*
Vessel area	+	41.2 ± 6.5	42.9 ± 6.7	1.7 ± 3.2 (4%)
	–	41.7 ± 12.9	40.7 ± 13.2	-1.0 ± 2.3 (-2%)
		(p=0.94)	(p=0.70)	(p=0.06)
Plaque area	+	18.5 ± 1.7	21.2 ± 3.3	2.6 ±1.8 (14%)
	–	23.4 ± 7.3	27.0 ± 8.1	3.6 ± 2.4 (15%)
		(p=0.13)	(p=0.12)	(p=0.39)
Most stenotic sites (n=14)				
Lumen area	+	17.3 ± 3.2	19.3 ± 3.4	2.0 ± 1.8 (12%)
	–	12.3 ± 5.8	10.9 ± 5.9	-1.4 ± 2.2 (-11%)
		(p=0.14)	(p=0.02)*	(p=0.02)*
Vessel area	+	41.4 ± 10.8	46.2 ± 12.3	4.8 ± 1.5 (12%)
	–	37.9 ± 12.6	36.9 ± 12.7	-0.9 ± 2.1 (-2%)
		(p=0.63)	(p=0.24)	(p=0.001)*
Plaque area	+	24.2 ± 7.7	27.0 ± 9.3	2.8 ± 2.5 (12%)
	–	25.6 ± 10.6	26.0 ± 10.5	0.4 ± 2.2 (2%)
		(p=0.81)	(p=0.87)	(p=0.10)

* Significant difference between patients treated with and without simvastatin.



	Change
Lumen area:	⇑ 4.8 mm^2
Vessel area:	⇑ 8.1 mm^2
Plaque area:	⇑ 3.3 mm^2
Lumen area:	⇓ 3.1 mm^2
Vessel area:	⇑ 0.7 mm^2
Plaque area:	⇑ 3.7 mm^2

Calibration = 1 mm; + = catheter
⇑ = increase; ⇓ = decrease

Figure 1. Corresponding intravascular ultrasound cross sections obtained after PTA of the femoropopliteal artery (left) and at 1-year follow-up (right) from a patient who received simvastatin (A) and a patient who did not receive simvastatin (B). Note the calcified spot in the corresponding images from the patient who did not receive simvastatin (arrow). At follow-up, the patient who received simvastatin (A) had an increase in lumen and vessel area, whereas the patient who did not receive simvastatin (B) had a decrease in lumen area and a negligible increase in vessel area. The increase in plaque area in both patients was similar.

DISCUSSION

The present retrospective observational IVUS study revealed a significant difference between patients who received and did not receive simvastatin in lumen area reduction at 1-year follow-up: −4% in patients who received simvastatin and −25% in patients who did not receive simvastatin (Table 2). Overall, both groups of patients showed an identical increase in plaque area. Surprisingly, the increase in plaque area was associated with an increase in vessel area in patients given simvastatin and a decrease in vessel area in patients not given simvastatin. In other words, the use of simvastatin appeared to have a beneficial effect on lumen size due to its effect on the mode of vascular remodeling rather than on the degree of plaque growth. Angiographic records confirmed the difference between both groups of patients in lumen area reduction; patients given simvastatin showed no angiographic restenosis,

whereas 8 patients who did not receive simvastatin had angiographic restenosis. The importance of IVUS in this respect is that vessel area measurement is unique to IVUS and has no angiographic equivalent.

In summary, this retrospective observational IVUS study showed that plaque growth at 1-year follow-up is a general response after PTA regardless of the use of simvastatin; simvastatin has the potential to induce positive vascular remodeling, thereby reducing the occurrence of restenosis.

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CHAPTER 11

Rationale and Design for the Saris Trial; Effect of Statin on Atherosclerosis and Vascular Remodeling Assessed with Intravascular Sonography

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ABSTRACT

The SARIS study (effect of Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography) is a prospective randomized multicenter trial designed to assess the dose dependent effect of statin therapy on the vascular anatomy and endothelial function. Participating centers will include 50 patients with normal to mildly elevated cholesterol levels eligible for balloon angioplasty and/or stent placement of the common iliac artery. Patients will be randomized to 1-year treatment with either low-dose (10 mg) or high-dose (80 mg) atorvastatin. The primary objective of this study is the use of intravascular ultrasound (IVUS) to document the dose dependent effect of atorvastatin on plaque volume and vascular remodeling seen at 1-year follow-up. The secondary objective is the use of dobutamine stress echocardiography (DSE) to assess the dose dependent effect of atorvastatin on myocardial coronary flow reserve (MCFR) at 6-months and 1-year follow-up. The design of the present study is noteworthy in respect that: (1) IVUS is the only available technique to sensitively measure the effect of statin therapy on both plaque growth and vascular remodeling, and (2) DSE is a non-invasive test to objectively quantify the effect of statin therapy on the functionality of the coronary artery.

INTRODUCTION

The beneficial effect of HMG-CoA reductase inhibitors (statins) on the primary and secondary prevention of cardiovascular disease has been shown in studies with both hard endpoints and with surrogate endpoints using external ultrasound and angiography.[1-4] However, angiographic studies are not capable to reveal the precise mechanism how statin acts, as angiography merely shows a silhouette of the lumen. Studies using intravascular ultrasound (IVUS) have documented that the lumen dimension is not only influenced by plaque growth, but is also influenced by vascular remodeling ("shrinkage" vs. "enlargement").[5-10]

In addition, recent studies have reported that besides the positive effects of statin therapy on the vascular anatomy, statin therapy may exert a direct positive effect on the endothelial function of diseased arteries.[11,12] Myocardial coronary flow reserve (MCFR) is known to be a functional test of the coronary artery and is determined by local nitric oxide production of the endothelium. Nitric oxide induces vasodilatation, which is impaired in patients with coronary artery disease.[13-15] Dobutamine stress echocardiography (DSE) can assess MCFR during dobutamine infusion as an improved Doppler velocity value using pulsed-wave Doppler tissue sampling (PW-DTS).[16-18]

This study addresses the dose-dependent effect of statin therapy on the vascular anatomy using IVUS and on the endothelial function using DSE.

STUDY DESIGN

The SARIS study (effect of Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography) is a prospective randomized multicenter trial designed to assess the dose dependent effect of atorvastatin on atherosclerosis and vascular remodeling. The primary objective of this study is the use of IVUS to document the dose dependent effect of statin on plaque volume and vascular remodeling and on the extent of in-stent intimal hyperplasia in the absence of vascular remodeling seen at 1-year follow-up. The secondary objective is the use of DSE to assess the dose dependent effect of atorvastatin on MCFR evaluated during dobutamine infusion, compared to baseline value.

Table 1 Inclusion and exclusion criteria of the SARIS trail (effect of Statin on Atherosclerosis and vascular Remodeling assessed with Intravascular Sonography).

INCLUSIONS
■ Symptomatic iliac arterial disease eligible for PTA and/or stent-placement in the common iliac artery
■ Serum total cholesterol 5-8 mmol/l
■ Serum LDL ≥3 mmol/l
■ Written informed consent
EXCLUSIONS
■ Endocrine disorders (Diabetes Mellitus)
■ Use of lipid-lowering drugs within the last year
■ Uncontrolled hypertension (DBP >110 mmHg, SBP >180 mmHg)
■ Use of drugs known to be associated with rhabdomyolysis when used in conjunction with statins (e.g. cyclosporin, erythromycin, azole anti-fungal drugs and niacin)
■ History of serious adverse drug reactions, hypersensitivity or allergy to statins
■ Significant active liver disease (>3x upper limit of normal)
■ Renal insufficiency (serum creatinine >160 mol/l) or micro-albumin in urine
■ Concurrent therapy with long-term immunosuppressants
■ History of alcoholism, drug abuse or other emotional or intellectual problems likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements

PTA = percutaneous transluminal angioplasty; LDL = low-density lipoprotein; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Participants

This is a multicenter study in association with the Erasmus Medical Center Rotterdam, Leiden University Medical Center, University Medical Center Utrecht, St. Elisabeth Hospital Tilburg, Twee Steden Hospital Tilburg and

St. Franciscus Hospital Rotterdam. The participating centers will recruit 50 consecutive patients (male and female) with symptomatic obstructive vascular disease eligible for percutaneous transluminal angioplasty (PTA) and/or stent placement in the common iliac artery. Patients with normal to mildly elevated cholesterol levels will be included; total cholesterol levels between 5 and 8 mmol/l and low-density lipoprotein (LDL) levels ≥3 mmol/l. In- and exclusion criteria are listed in Table 1.

Medication and randomization

Patients will be randomized to 1-year treatment with either low dose (10 mg) or high dose (80 mg) atorvastatin daily. The dosage remains fixed during the follow-up duration unless clinically important adverse reactions occur. Randomization will be performed in permuted blocks stratified by center. Observers responsible for analysis of IVUS and DSE data will be blinded for patient characteristics, including treatment with either 10 mg or 80 mg atorvastatin.

METHODS

Intravascular ultrasound

The IVUS studies will be performed using a single rotating ultrasound element (30 MHz) on a 0.035" guidewire-tipped 4.3F catheter (Endosonics, Rijswijk, The Netherlands). Briefly, the following procedure will be applied. After angiographic successful PTA and/or stent placement, the IVUS catheter will be advanced retrogradely over the guidewire to the aortic bifurcation. After the guidewire is removed to avoid drop-out of a catheter segment, the ultrasound catheter will be pulled back manually. A displacement sensing device will be used to document the location (i.e. position) of the cathetertip in relation to the aortic bifurcation in steps of 0.1 mm during the pull-back maneuver.[19] The information on the cathetertip position will be: (1) combined with the IVUS images on the monitor, and (2) translated into a digital audiosignal that will be stored on the audiochannel of the videotape using a timecode generator and a special videorecorder. This digital audiosignal enables automatic selection of the IVUS images required for volume measurements.

After 1-year follow-up, the angiographic and IVUS study will be repeated using the procedure as described above. Vascular segments seen with IVUS (including the stent, adjacent reference segments and external iliac artery) obtained at intervention and at 1-year follow-up, will be matched. These matched vascular segments will be used to assess the volume of lumen, vessel/stent and plaque using an automated contour analysis system.
In our previous study the reproducibility of serial volume measurements using this system has been established.[19] This study showed that matching of vascular segments using side-branches and the information of the displacement sensing device is highly reliable and reproducible. The interobserver difference for lumen, vessel and plaque volume was ≤0.4%, with low coefficients of variation (≤1.7%) and high correlation coefficients (r=1.00 for all).

Follow-up

Recently, we completed a longitudinal study to examine whether IVUS is a sensitive means to identify progression of atherosclerosis and its derived primary endpoint plaque volume at 1-year follow-up.[10] This study showed that (1) vascular segments obtained at baseline could in all instances be reliably matched with the vascular segments obtained at follow-up, and (2) progression of atherosclerosis implies a change in both plaque and vessel volume, resulting in lumen volume change.

Analysis of data

Analysis will include assessment of the change in lumen, vessel/stent and plaque volume seen after 1-year of lipid-lowering treatment in both groups of patients. A comparison will be made between patients treated with 10 mg and 80 mg atorvastatin using the Student's t-test.

Dobutamine stress echocardiography

All echocardiograms will be performed with the SystemFive imaging system (Vingmed, General electric) equipped with a 1.8 MHz transducer using second harmonic imaging to optimize endocardial border visualization. Standard parasternal long- and short-axis views will be obtained as well as apical long-axis 2- and 4-chamber views. The left ventricle will be divided into 6 walls (septum anterior, septum posterior, posterior, inferior, anterior and

lateral wall) and 16 segments. Wall motion of each segment will be scored as normokinesia, mild-hypokinesia, severe-hypokinesia, akinesia or dyskinesia. After baseline echocardiography, dobutamine infusion will be started with 5 μg/kg/min for 5 minutes followed by 10 μg/kg/min for 5 minutes. Dobutamine will then be increased by 10 μg/kg/min every 3 minutes until test end-point (target heart rate or signs or symptoms of ischemia occur). In patients not achieving the target heart rate atropin (up to 2 mg) will be injected intravenously. Images will be acquired continuously and recorded on tape at the end of every dose-step.

Pulsed-wave Doppler tissue sampling

PW-DTS will be performed using a 3.7 MHz probe, with a pulse repetition frequency of 4.5-6.0 KHz. The temporal resolution of PW-DTS is 4±3 ms. A sample volume of 4 mm^3 will be used. The continuous measurement of velocity of the 16 segments will be sampled in apical views during a minimum of 5 consecutive beats in order to minimize the variability induced by respiration. Measurements will be performed at rest, low-dose dobutamine and at peak stress. The depth of the sample volume of every wall will be kept constant during DSE. After stopping dobutamine infusion the measurements will be repeated at 3-min. interval. Measurements will be stopped if baseline velocities are recorded or after a 30-minutes period.

Analysis of data

All the measurements will be performed off-line using a software system of VingMed. The velocity values (cm/s) will be obtained on calibrated still frames by automatically measuring the distance between the zero baselines and the peak Doppler profile of ejection phase, early and late diastole in reference to both the electrocardiogram and phonocardiogram. Analysis will include the change in velocity values, evidenced at 6 and 12 months follow-up. A comparison will be made between patients with 10 mg and 80 mg atorvastatin using the Student's t-test.

DISCUSSION

This prospective randomized study has 2 objectives. First, to assess the dose-dependent effect of statin on the progression of atherosclerosis and vascular remodeling using IVUS. Second, to assess the dose-dependent effect of statin on MCFR using DSE.

To date, 3 IVUS studies have reported on the effect of statin on the vascular wall.[20-22] These IVUS studies had in common to report a positive effect of statin on lumen area. In 1997 Takagi et al.[20] reported that the increase in lumen area in coronary arteries was due to a decrease in plaque area with no change in vessel area. Subsequently, Hamasaki et al.[21] showed that patients with coronary artery disease adequately treated with statin therapy had a larger vessel area than patients not adequately treated with statin therapy. This latter observation concurs with our study performed in peripheral arteries[22] showing that the increase in lumen area as result of statin therapy was due to a positive effect on vascular remodeling. Moreover, we found that irrespective of the use of statin during 1-year following PTA of the femoropopliteal artery plaque growth is a universal response.

The design of the present study is noteworthy in respect that IVUS is the only available technique to sensitively measure the impact of arterial remodeling on lumen dimensions. In addition, in this study DSE will be used to assess the dose-dependent effect of statin on MCFR. DSE can assess MCFR during dobutamine infusion as an improved velocity value using PW-DTS. Recently, studies showed that MCFR in patients with hypercholesterolemia improved after statin therapy.[23,24] In these studies positron emission tomography and single photon computed tomography were used in combination with a perfusion marker [13N-ammonia] during dipyridomole and dobutamine stimulation. Stress echocardiography can be used as a more widely available and less expensive alternative for nuclear scanning.[25-27]

It is noteworthy that PW-DTS is a non-invasive test to objectively quantify the effect of statin therapy on the functionality of the coronary artery.

APPENDIX

Participating centers and principal investigators

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CHAPTER 12

Summary

In the last decade several new treatment modalities have emerged for the management of patients with obstructive disease of the femoropopliteal artery. This thesis addresses the effect of endografts, endovascular brachytherapy and statin therapy on plaque growth, and especially vascular remodeling, at follow-up using intravascular ultrasound (IVUS).
In addition, the role of intravascular ultrasound as research tool is discussed.

Endografts

Chapter 2 presents an IVUS study in which 12 patients with long-segment obstructive femoropopliteal artery disease were treated with a newly developed polytetrafluoroethylene (ePTFE) endograft. Intravascular ultrasound investigation was performed immediately after endograft placement and at 6-months follow-up. Corresponding IVUS images obtained from inside the endograft, the anastomotic segment and a reference segment were subsequently analyzed for the change in area measurements. At 6-months follow-up, the change in lumen area inside the endograft (+3%) and in the reference segment (+6%) were minimal; however, a distinct increase in lumen area of 85% was observed at the anastomotic segment. This increase in lumen area was associated with an increase in vessel area of 42%, overcompensating the increase in plaque area of 15%. The study shows that vascular remodeling can compensate for plaque growth at the anastomotic segment of an ePTFE endograft.

Chapter 3 presents the long-term results after implantation of an ePTFE endograft. In this study, repeat IVUS investigation was performed at 2-years follow-up in 5 of the 12 patients that were treated with the ePTFE endograft. The change in area measurements between 6-months and 2-years follow-up was analyzed and subsequently compared with the change in area measurements at 6-months follow-up. During the second follow-up period, the change in lumen area inside the endograft was minimal (+1%) and similar to the lumen area change at 6-months follow-up. At the anastomotic segment an increase in lumen area of 8% was observed during the second follow-up period, associated with an increase in vessel area of 6% and no change in plaque area. Although still significant, these changes were much smaller than the changes observed at 6-months follow-up. This study shows that 1) the ePTFE endograft appears to inhibit plaque growth and constrictive vascular

remodeling, and 2) the vasodilatory response at the anastomotic segment tends to stabilize in the long term.

Chapter 4 presents a multicenter study to evaluate the long-term clinical outcome of 89 patients who were treated for long-segment obstructive and occlusive disease of the femoreopopliteal artery with an ePTFE endograft (mean length 29 cm); a high-grade stenosis (mean length 9 cm) was involved in 7 patients and an occlusion (mean length 19 cm) was involved in 82 patients. Early failure of the endograft was encountered in 7 of the 89 patients: these patients presented with an acute occlusion of the endograft within 30 days after the operating procedure and were subsequently treated with femoropopliteal bypass surgery. In 42 patients the endograft remained patent during the entire follow-up period. The remaining 40 patients presented with a late acute occlusion of the endograft (median 7 months). These patients were either treated with femoropopliteal bypass surgery (n=9), conservatively (n=5) or fibrinolysis was performed successfully (n=26). Eighteen of the 26 patients treated successfully with fibrinolysis presented with a re-occlusion at a later stage. In 4 of these 18 patients repeat fibrinolysis was performed successfully. The remaining 14 patients were treated with femoropopliteal bypass surgery (n=8), lower-limb amputation (n=2) or conservatively (n=4). The primary and secondary patency rates of the ePTFE endograft were 71% and 83% at 6-months follow-up, 57% and 69% at 1-year follow-up, 45% and 49% at 2-years follow-up and 30% and 44% at 3-years follow-up, respectively. This study shows that the success of the ePTFE endograft is limited by the occurrence of acute occlusions. Therefore, refinements of the endograft are necessary if this new, minimal invasive, technique wants to compete with conventional bypass surgery.

Endovascular brachytherapy

Chapter 5 describes a randomized IVUS study in which 24 patients with obstructive femoropopliteal artery disease were treated with percutaneous transluminal angioplasty (PTA) without or with additional endovascular brachytherapy (EBT). Intravascular ultrasound investigation was performed immediately after PTA and at 6-months follow-up. Corresponding IVUS images obtained from both the treated and the untreated (i.e. reference) site were analyzed for the change in lumen area, vessel area and plaque area at

6-months follow-up; a comparison was made between patients without additional EBT (n=16) and with additional EBT (n=8). At 6-months follow-up, IVUS measurements of the reference site revealed no significant difference in the change in lumen, vessel and plaque area between both groups of patients. In contrast, IVUS measurements of the treated site revealed a statistically significant difference (p=0.03) in lumen area change between patients without EBT and those with EBT (-9% and +23%, respectively): this was due to a significant difference (p=0.05) in vessel area change (+2% and +19%, respectively). In both groups of patients a similar increase in plaque area (+12% and +16%, respectively) was encountered. This study shows that EBT as adjunct therapy immediately after PTA in femoropopliteal arteries has a positive effect on lumen dimensions at 6-months follow-up by inducing positive vascular remodeling.

Intravascular ultrasound as research tool

Since the introduction of IVUS as a research tool in the late 1980s, it was suggested that IVUS could be used to grade the effect of pharmacologic interventions on the progression/regression of atherosclerosis. However, to investigate both local and diffuse effects of pharmacologic interventions on plaque growth and vascular remodeling, volumetric IVUS measurements were thought necessary. In order to acquire such measurements an automated contour analysis system, which creates three-dimensional (3-D) reconstructions of cross-sectional IVUS images, has been developed.

In addition, to grade the effect of pharmacologic interventions on the composition of the atherosclerotic plaque, especially the calcified lesion, a sensitive method for calcified lesion quantification in IVUS images was developed.

Chapter 6 presents an IVUS study aimed at determining the reproducibility of volume measurements in IVUS images acquired by two observers (i.e. interobserver reproducibility) and derived from two separate pull-back maneuvers (i.e. interexamination reproducibility). For this study, the automated contour analysis system was used to generate 3-D reconstructions of cross-sectional IVUS images. A total of 15 patients was included in the study and from each patient one matched vascular segment (3-4 cm in length), not subjected to intervention, was used for analysis of lumen, vessel and plaque

volume. The results show that volume measurements derived from IVUS images are highly reproducible; the interobserver differences in volume measurements were ≤0.4%, with low coefficients of variation (≤1.7%) and high correlation coefficients (r=1.00). Similarly, interexamination differences were ≤2.6%, with low coefficients of variation (≤8.6%) and high correlation coefficients (r=0.97–0.99). Therefore, IVUS may be used to monitor the progression/regression of atherosclerotic plaque volume in a longitudinal study.

Chapter 7 describes a longitudinal IVUS study aimed at determining the reproducibility of circumferential arc and length measurements of calcified lesions in IVUS images. In addition, the change in circumferential arc and length measurements at 1-year follow-up was determined. For the purpose of this study, 34 patients were imaged with IVUS before and after PTA and at 1-year follow-up. The interobserver and interexamination differences in circumferential arc and length measurements were low (≤1.1%), with low coefficients of variation (≤5.8%). At 1-year follow-up, a non-significant increase in both the circumferential arc (1.9%) and length (1.7%) of the calcified lesion was observed. This study shows that measurements of the circumferential arc and length of the calcified lesion are highly reproducible; changes seen at 1-year follow-up are not significant. It was concluded that IVUS may be used to monitor the effect of medical intervention on the extent of the calcified lesion in a longitudinal study.

Chapter 8 presents an IVUS study in which the natural progression of atherosclerosis at 1-year follow-up was examined using volume measurements obtained with the automated contour analysis system. For the purpose of this study 11 patients were imaged with IVUS at baseline and at 1-year follow-up and subsequently analyzed for the change in lumen, vessel and plaque volume. At follow-up, a non-significant increase in lumen volume (2.3%), vessel volume (2%) and plaque volume (3%) was encountered. This study shows that progression of atherosclerosis implies changes in both vessel and plaque volume, resulting in lumen volume change. With these findings in mind, we believe that volumetric IVUS studies are excellently suited to establish the basic mechanism associated with progression/regression of atherosclerotic plaque and vascular remodeling and the influence of pharmacologic agents on these processes.

Statin therapy

Chapter 9 describes a retrospective non-randomized study in 10 patients, in which 3-D IVUS was used to document the effect of 1-year treatment with statin therapy on vascular segments of the femoropopliteal artery not subjected to PTA. Patients were imaged with IVUS at baseline and at 1-year follow-up and subsequently analyzed for the change in lumen, vessel and plaque volume. A comparison was made between the change in volume measurements seen in patients with statin therapy (n=5) and patients without statin therapy (n=5). At follow-up, both groups of patients showed a similar increase in plaque volume (+4% and +2%, respectively). In patients with statin therapy the plaque volume increase was compensated by an increase in vessel volume (+2%), resulting in an increase in lumen volume (+1%). In contrast, in patients without statin therapy, the increase in plaque volume was associated with a decrease in vessel volume (-2%), resulting in a decrease in lumen volume (-4%). Despite the non-significant nature of this retrospective observation, this small IVUS study generates the hypothesis that statin therapy may contribute to superior long-term lumen dimensions by inducing positive vascular remodeling.

Chapter 10 presents an IVUS study aimed at determining the effect of 1-year treatment with statin therapy in 17 patients with obstructive femoropopliteal artery disease. Intravascular ultrasound investigation was performed immediately after PTA and at 1-year follow-up. Corresponding IVUS images obtained from the treated site were analyzed for the change in lumen, vessel and plaque area at 1-year follow-up; a comparison was made between patients with statin therapy (n=6) and without statin therapy (n=11). In this study area measurements, rather than volume measurements, were performed since the automated contour analysis system is unable to determine lumen dimensions after PTA, due to the presence of dissections. After PTA no difference in lumen, vessel and plaque area between both groups of patients was encountered. However, at follow-up a significant difference between both groups of patients in lumen area change and a borderline significant difference in vessel area change was seen; in patients with statin therapy a lumen area decrease (-4%) and a vessel area increase (+4%) was seen, whereas in patients without statin therapy, lumen and vessel area decreased (-25% and -2%, respectively). There was no difference in plaque area change at follow-up (14% and 15%, respectively). This IVUS study shows that plaque growth is a

universal response after PTA regardless of the use of statin therapy; statin therapy has the potential to induce positive vascular remodeling, thereby reducing the occurrence of restenosis.

Chaper 11 describes a prospective randomized IVUS study designed to assess the dose-dependent effect of statin therapy on both plaque growth and vascular remodeling. Recently, this study was canceled due to a patient intake that was too slow. The original study design was as follows: 50 patients with symptomatic obstructive vascular disease eligible for PTA and/or stent placement in the common iliac artery would be included. Patients would be randomized to 1-year treatment with either 10 mg atorvastatin or 80 mg atorvastatin daily. Intravascular ultrasound investigation would be performed immediately after successful PTA and/or stent placement in the common iliac artery and at 1-year follow-up. Both the treated common iliac artery and the untreated external iliac artery would be documented using IVUS. Analysis of the common iliac artery would reveal the dose-dependent effect of statin therapy on the prevention of restenosis. Analysis of the external iliac artery would elucidate the dose-dependent effect of statin therapy on the progression of atherosclerosis and vascular remodeling, without the side-effects of an intervention.

In conclusion, the IVUS studies in this thesis contributed to the knowledge and understanding of the mechanism of action of several new treatment modalities for patients with obstructive disease of the femoropopliteal artery. The studies showed that vascular remodeling, besides plaque growth, is an important factor that determines the change in lumen dimension at follow-up.

CHAPTER 13

Samenvatting

In het afgelopen decennium zijn verschillende nieuwe methodes ontwikkeld voor de behandeling van patiënten met obstructief vaatlijden van de arteria femoralis superficialis. Dit proefschrift beschrijft de effecten van endografts, endovasculaire bestraling en behandeling met een statine op de progressie van atherosclerose, en in het bijzonder op veranderingen van de vaatwand, zoals gedocumenteerd met intravasculaire echografie (IVUS).
Bovendien is de rol van IVUS voor het uitvoeren van wetenschappelijk onderzoek van door atherosclerose aangetaste bloedvaten beschreven.

Endografts

Hoofdstuk 2 beschrijft een IVUS-studie waarin 12 patiënten met obstructief vaatlijden van een lang segment van de arteria femoralis superficialis behandeld werden met een nieuw ontworpen polytetrafluoroethylene (ePTFE) endograft. Deze patiënten werden onderzocht met IVUS direct na het plaatsen van de endograft en na 6 maanden follow-up. Corresponderende IVUS-beelden verkregen van de endograft, het overgangsgebied naar het oorspronkelijke bloedvat en een referentie vaatsegment werden geanalyseerd om te bepalen in hoeverre veranderingen hadden plaatsgevonden in lumen-, vaatwand- en plaque-oppervlak na 6 maanden. Het bleek dat de veranderingen in lumen-oppervlak zowel in de endograft (+3%) als in het referentie segment (+6%) minimaal waren. Daarentegen werd een duidelijke toename van het lumen-oppervlak (+85%) gezien in het overgangsgebied. Deze toename was het netto resultaat van een toename in het vaatwand-oppervlak (+42%), terwijl de toename in het oppervlak van de atherosclerotische plaque (+15%) gering was. Deze studie toont aan dat ondanks toename van een atherosclerotische plaque in het overgangsgebied van een ePTFE endograft, het lumen toe kan nemen door het optreden van, wat genoemd wordt, "positief vaatwand remodelleren".
Hoofdstuk 3 beschrijft de lange termijn resultaten na plaatsing van een ePTFE endograft. In deze studie was het mogelijk de IVUS-procedure 2 jaar na plaatsing van de endograft in 5 van de 12 patiënten te herhalen. De veranderingen in oppervlakte metingen tussen 6 maanden en 2 jaar follow-up werden geanalyseerd en vervolgens vergeleken met de veranderingen die waren opgetreden na de eerste 6 maanden follow-up. In de endograft zelf was de verandering van het lumen-oppervlak tijdens de tweede follow-up periode minimaal (+1%), net zoals gezien werd na de eerste follow-up periode.

Daarentegen werd in het overgangsgebied naar het oorspronkelijke bloedvat een toename in het lumen-oppervlak gezien (+8%), gepaard gaande met een toename in het vaatwand-oppervlak (+6%) terwijl het oppervlak van de atherosclerotische plaque niet was veranderd. Deze veranderingen in lumen- en vaatwand-oppervlak waren veel kleiner dan de veranderingen die waren opgetreden na de eerste 6 maanden follow-up. Deze studie laat zien dat na het plaatsen van een ePTFE endograft 1) geen plaquegroei plaatsvindt binnen de endograft en de vaatkrimp, die traditioneel gezien wordt als mede oorzaak van een restenose, niet optreedt, en 2) plaquegroei en vaatwand remodelleren in het overgangsgebied van endograft naar oorspronkelijk bloedvat, gezien na de eerste 6 maanden follow-up, zich lijkt te stabiliseren op de lange termijn.
Hoofdstuk 4 beschrijft een multicenter studie naar de klinische lange termijn resultaten van ePTFE endograft-plaatsing. In totaal waren 89 patiënten met obstructief vaatlijden van een lang segment van de arteria femoralis superficialis behandeld met een ePTFE endograft (gemiddelde lengte 29 cm); 7 patiënten werden behandeld voor een hoog-gradige stenose van het bloedvat (gemiddelde lengte 9 cm) en 82 patiënten werden behandeld voor een occlusie van het bloedvat (gemiddelde lengte 19 cm). Vroeg falen van de endograft werd gezien in 7 van de 89 behandelde patiënten: bij deze patiënten was een acute occlusie van de endograft opgetreden binnen 30 dagen na plaatsing. Deze 7 patiënten werden vervolgens behandeld met bypass-chirurgie. Bij 42 patiënten bleef de endograft open gedurende de gehele follow-up periode. Bij de resterende 40 patiënten trad een late acute occlusie van de endograft op (mediaan 7 maanden). Deze patiënten werden behandeld met bypass-chirurgie (n=9), werden conservatief vervolgd (n=5) of werden succesvol behandeld met fibrinolyse (n=26). In 18 van de 26 patiënten die succesvol behandeld werden met fibrinolyse trad in een later stadium her-occlusie van de endograft op. Vier van deze 18 patiënten werden opnieuw succesvol behandeld met fibrinolyse. De overige 14 patiënten werden behandeld met bypass-chirurgie (n=8), onderbeens-amputatie (n=2) of er werd een conservatief beleid gevolgd (n=4). De primaire en secundaire doorgankelijkheids-percentages na ePTFE endograft plaatsing waren respectievelijk 71% en 83% na 6 maanden follow-up, 57% en 69% na 1 jaar follow-up, 45% en 49% na 2 jaar follow-up en 30% en 44% na 3 jaar follow-up. Deze studie toont aan dat het succes van ePTFE endograft plaatsing beperkt is door het optreden van acute occlusies van

de endograft. Er kan gesteld worden dat verbeteringen van de endograft noodzakelijk zijn als deze nieuwe, minimaal-invasieve, techniek wil concurreren met conventionele bypass chirurgie.

Endovasculaire bestraling

Hoofdstuk 5 beschrijft een gerandomiseerde IVUS-studie waarin 24 patiënten met obstructief vaatlijden van de arteria femoralis superficialis behandeld werden middels een Dotterprocedure met of zonder endovasculaire bestraling (Endovasculaire BrachyTherapie, EBT). Deze patiënten werden onderzocht met IVUS direct na de Dotterprocedure en na 6 maanden follow-up. Corresponderende IVUS-beelden verkregen van zowel het behandelde als een onbehandeld vaatsegment werden geanalyseerd met betrekking tot de veranderingen in het oppervlak van lumen, vaatwand en atherosclerotische plaque die na 6 maanden hadden plaatsgevonden. Vervolgens werd er een vergelijking gemaakt tussen patiënten zonder EBT (n=16) en patiënten met EBT (n=8). In het onbehandelde vaatsegment werden na 6 maanden follow-up met IVUS geen verschillen gezien tussen de 2 groepen patiënten in de veranderingen die plaatsvonden in het lumen-, vaatwand- en plaque-oppervlak. Daarentegen werd in het behandelde vaatsegment een statistisch significant verschil gevonden tussen patiënten zonder en met EBT in de verandering van het lumen-oppervlak (-9% en +23%, respectievelijk): Dit verschil was het resultaat van een significant verschil in de verandering van het vaatwand-oppervlak (+2% en +19%, respectievelijk). In beide groepen patiënten was de toename van de atherosclerotische plaque even groot (+12% en +16%, respectievelijk). Deze studie toont dat EBT direct na een Dotterprocedure in de arteria femoralis superficialis een positief effect heeft op lumen dimensies na 6 maanden door het induceren van positief vaatwand remodelleren.

Intravasculaire echografie voor wetenschappelijk onderzoek

Na de introductie van IVUS eind jaren '80, werd geopperd dat deze techniek gebruikt kon worden om het effect van een farmacologische behandeling op de progressie/regressie van atherosclerotische plaques te onderzoeken. Echter, om zowel lokale als diffuse effecten van een farmacologische behandeling te onderzoeken werd aangenomen dat volume-metingen noodzakelijk waren. Om

volume-metingen mogelijk te maken werd een automatisch contour-analyse systeem ontwikkeld, waarmee een drie-dimensionale (3-D) reconstructie van het bloedvat gemaakt kon worden. Om bovendien het effect van een farmacologische behandeling op de compositie van de atherosclerotische plaque, met name de hoeveelheid kalk, te onderzoeken, werd een methode ontwikkeld om de hoeveelheid kalk in IVUS-beelden te kwantificeren en in de tijd te vervolgen.

Hoofdstuk 6 beschrijft een IVUS-studie waarin de reproduceerbaarheid van lumen-, vaatwand- en plaque-volume, verkregen met het automatische contour-analyse systeem, werd onderzocht. Voor deze studie werden de analyses uitgevoerd 1) door twee onderzoekers om de interobserver reproduceerbaarheid van volume-metingen te bepalen en 2) in twee series IVUS-beelden om de reproduceerbaarheid van de metingen binnen hetzelfde bloedvat te bepalen. Van 15 met IVUS onderzochte patiënten werd een corresponderend onbehandeld vaatsegment (3 tot 4 cm lang) gebruikt voor de analyse van lumen-, vaatwand- en plaque-volume. De resultaten van deze IVUS-studie lieten zien dat volume-metingen reproduceerbaar zij. De verschillen in volume-metingen verkregen door de twee onderzoekers waren ≤0,4%, met lage variatiecoëfficiënten (≤1,7%) en hoge correlatiecoëfficiënten (r=1,00). De verschillen in volume-metingen verkregen in hetzelfde bloedvat waren ≤2,6%, met lage variatiecoëfficiënten (≤8,6%) en hoge correlatiecoëfficiënten (r=0,97-0,99). De resultaten geven aan dat volume metingen verkregen met het automatisch contour-analyse systeem reproduceerbaar zijn en daarom gebruikt zouden kunnen worden om de effecten van een farmacologische behandeling op de vaatwand te onderzoeken in een longitudinale studie.

Hoofdstuk 7 beschrijft een IVUS-studie waarin de reproduceerbaarheid van metingen van de hoeveelheid kalk in IVUS-beelden werd onderzocht. Daarnaast werd onderzocht in hoeverre de uitgebreidheid van kalk veranderde na 1 jaar follow-up. IVUS-beelden van 34 patiënten onderzocht voor en direct na Dotterbehandeling en na 1 jaar follow-up werden gebruikt voor analyse. Voor deze studie werden de analyses uitgevoerd 1) door twee onderzoekers om de interobserver reproduceerbaarheid van kalkmetingen te bepalen en 2) in twee series IVUS-beelden om de reproduceerbaarheid van kalkmetingen binnen hetzelfde bloedvat te bepalen. De verschillen in metingen

van de cirkelboog en lengte van de kalk in de axiale vaatrichting verkregen door twee onderzoekers en in twee IVUS-series van hetzelfde bloedvat waren klein (≤1,1%), met lage variatiecoëfficiënten (≤5,8%). Na 1 jaar werd een niet-significante toename gezien in zowel de cirkelboog (1,9%) en de lengte (1,7%) van kalk. Deze studie toont dat metingen van de cirkelboog en lengte van kalk in IVUS-beelden reproduceerbaar zijn; veranderingen na 1 jaar zijn niet significant. Er werd geconcludeerd dat IVUS gebruikt kan worden om het effect van een medische interventie op de hoeveelheid kalk te onderzoeken in een longitudinale studie.

Hoofdstuk 8 presenteert een IVUS-studie die de progressie van atherosclerose na 1 jaar beschrijft met behulp van volume-metingen verkregen met het automatisch contour-analyse systeem. In deze studie werden de IVUS-beelden van 11 patiënten verkregen na een Dotterbehandeling en na 1 jaar follow-up geanalyseerd om de veranderingen in het volume van lumen, vaatwand en atherosclerotische plaque vast te stellen. Na 1 jaar werd een niet-significante toename in lumen-volume (2,3%), vaatwand-volume (2%) en plaque-volume (3%) gezien. Deze studie toont aan dat progressie van atherosclerose gepaard gaat met een toename van omvang van de vaatwand, wat resulteert in een verandering in lumen-volume. Met deze resultaten in het achterhoofd, kan gesteld worden dat volumetrische IVUS-studies bij uitstek geschikt zijn om het basale mechanisme van zowel de progressie en regressie van de atherosclerotische plaque als van vaatwand-remodelleren te documenteren en eveneens geschikt zijn om de invloed van farmacologische behandeling op deze processen te doorgronden.

Statine behandeling

Hoofdstuk 9 beschrijft een retrospectieve studie waarin bij 10 patiënten 3-D-IVUS gebruikt werd om het effect van 1 jaar behandeling met een statine op onbehandelde vaatsegmenten van de arteria femoralis superficialis te documenteren. De patiënten waren onderzocht met IVUS direct na een Dotterbehandeling en na 1 jaar follow-up. De verkregen IVUS-beelden van de niet-geDotterde vaatsegmenten werden geanalyseerd om de veranderingen in volume van lumen, vaatwand en atherosclerotische plaque te meten. De veranderingen die optraden in patiënten *met* statine behandeling (n=5) en in patiënten *zonder* statine behandeling (n=5) werden met elkaar vergeleken. Na

1 jaar follow-up bleek dat de toename in plaque-volume in patiënten met en zonder statine behandeling vergelijkbaar was (+4% en +2%, respectievelijk). In patiënten *met* statine behandeling werd deze toename in plaque-volume gecompenseerd door een toename in vaatwand-volume (+2%), waardoor het lumen-volume groter werd (+1%). Daarentegen werd er in patiënten *zonder* statine behandeling een afname in vaatwand-volume (-2%) gezien, waardoor het lumen-volume kleiner werd (-4%). Alhoewel de verschillen tussen beide groepen patiënten statistisch niet significant waren, genereert deze kleine retrospectieve IVUS-studie de hypothese dat statine behandeling bijdraagt aan betere lange termijn lumen-dimensies door het induceren van positief vaatwand-remodelleren.

Hoofdstuk 10 beschrijft een IVUS-studie naar het effect van 1 jaar statine behandeling in 17 patiënten na een Dotterbehandeling voor obstructief vaatlijden van de arteria femoralis superficialis. In deze studie werden oppervlakte-metingen verricht in plaats van volume-metingen, omdat het automatische contour-analyse systeem niet in staat is lumen-dimensies te bepalen in de aanwezigheid van een dissectie die het gevolg is van de Dotterbehandeling. De IVUS-onderzoeken waren verricht direct na de Dotterbehandeling en na 1 jaar follow-up. Corresponderende IVUS-beelden van het geDotterde vaatsegment werden geanalyseerd voor de veranderingen in het oppervlak van lumen, vaatwand en atherosclerotische plaque na 1 jaar follow-up; de veranderingen gezien in patiënten *met* statine behandeling (n=6) en patiënten *zonder* statine behandeling (n=11) werden met elkaar vergeleken. Na de Dotterbehandeling waren er geen verschillen in het oppervlak van lumen, vaatwand en plaque tussen beide groepen patiënten. Echter, na 1 jaar werd er een significant verschil in de verandering van het lumen-oppervlak en een borderline significant verschil in de verandering van het vaatwand-oppervlak gezien; in patiënten met statine behandeling werd een afname in het lumen-oppervlak (-4%) en een toename in het vaatwand-oppervlak (+4%) gezien. Daarentegen werd in patiënten *zonder* statine behandeling een afname in zowel het lumen-oppervlak als het vaatwand-oppervlak gezien (-25% en -2%, respectievelijk). Er werd geen verschil gezien tussen beide groepen patiënten in de verandering van het plaque-oppervlak (+14% en +15%, respectievelijk). Deze IVUS-studie toont

aan dat plaquegroei een universele response is na een Dotterbehandeling, ongeacht een behandeling met statines; statine behandeling heeft de potentie om positief vaatwand-remodelleren te stimuleren en heeft daardoor invloed op het voorkomen van restenose.
Hoofdstuk 11 beschrijft een prospectief gerandomiseerde IVUS-studie die ontworpen was om het dosis-afhankelijke effect van statine behandeling op zowel plaquegroei als vaatwand-remodelleren te onderzoeken. Onlangs is deze studie gestopt, omdat de intake van patiënten voor deze studie te gering was. Het originele ontwerp van de studie was als volgt: 50 patiënten met symptomatisch obstructief vaatlijden in aanmerking komend voor een Dotterbehandeling en/of stentplaatsing van de arteria iliaca communis zouden geincludeerd worden. Patiënten zouden gerandomiseerd worden voor 1 jaar behandeling met ofwel 10 mg Atorvastatine, ofwel 80 mg Atorvastatine. Intravasculaire echografie onderzoeken zouden gedaan worden direct na een succesvolle Dotterbehandeling en/of stentplaatsing en na 1 jaar follow-up. Zowel de behandelde arteria iliaca communis als de onbehandelde arteria iliaca externa zouden met IVUS worden onderzocht. Onderzoek van de arteria iliaca communis zou het dosis-afhankelijke effect van statine behandeling ter preventie van restenose onthullen. Onderzoek van de arteria iliaca externa zou het dosis-afhankelijke effect van statine behandeling op de progressie van atherosclerose en vaatwand-remodelleren onthullen, zonder de bijeffecten van de vasculaire interventie.

Samenvattend kan gesteld worden dat de IVUS-studies die in dit proefschrift zijn beschreven hebben bijgedragen aan de kennis van verschillende nieuwe behandelingsmethodes voor patiënten met obstructief vaatlijden van de arteria femoralis superficialis. De studies tonen aan dat bij follow-up vaatwand-remodelleren, naast plaquegroei, een belangrijke factor is voor de verandering in lumen-dimensies.

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