Effects of Percutaneous Transluminal Angioplasty and Endovascular Brachytherapy on Vascular Remodeling of Human Femoropopliteal Artery by Noninvasive Magnetic Resonance Imaging

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Background—Percutaneous transluminal angioplasty (PTA) of severely stenotic peripheral vascular lesions is hampered by a higher restenosis rate. The effects of PTA on vascular wall as well as the effects of the antirestenotic properties of endovascular brachytherapy (EVBT) remain unclear. MRI allows in vivo noninvasive assessment of the vascular effects of such treatment strategies. We sought to elucidate the vascular effect of PTA and PTA+EVBT by serial MRI.

Methods and Results—Twenty symptomatic patients with severe stenosis of the femoropopliteal artery were randomly assigned to PTA (n=10) or PTA+EVBT (n=10; 14 Gy by γ-irradiation source) and imaged by high-resolution MRI before and 24 hours and 3 months after intervention. An independent observer blinded to the procedure analyzed the MRI data. At 24 hours, cross-sectional MRI revealed that lumen area (86% and 67%) and total vessel area (47% and 34%) increased similarly in the PTA and PTA+EVBT groups, respectively. All patients showed severe splitting of the atherosclerotic plaque, resulting in an irregularly shaped lumen. At 3 months, MRI revealed a significant difference in lumen area change between the PTA and PTA+EVBT groups (40% and 106%, respectively; P=0.026) and in the total vessel area (14% and 39%, respectively; P=0.018). At 3 months, plaque disruption was still present in 50% of the patients treated with PTA+EVBT.

Conclusions—After PTA, there is deep disruption of the atherosclerotic plaques and an extensive remodeling process of the arterial wall. Luminal loss after PTA is partially due to inward vessel remodeling. Brachytherapy prevents inward remodeling and induces an increase in lumen area but partially prevents healing of disrupted vessel surface. (Circulation. 2004;110:1156-1161.)

Key Words: angioplasty, balloon • brachytherapy • magnetic resonance imaging

The mechanisms of luminal enlargement after percutaneous transluminal angioplasty (PTA) have been explained classically by a displacement of atherosclerotic plaque material into the vessel wall and remodeling mechanisms. Interestingly, Gruntzig et al speculated in one of their first reports on coronary dilatation that “the pressure of the inflated balloon compresses the atherosclerotic material in a direction perpendicular to the wall of the vessel, thereby dilating the lumen.”1 In an experimental model of angioplasty, they also first realized that dilation might result in severe mural disruption with intimal and/or medial tears. This observation was confirmed at necropsy2,3 and in coronary angioplasty of postmortem human hearts.4 Therefore, the mechanism of luminal enlargement in angioplasty may be focal damage to the arterial wall with intimal or medial splitting rather than plaque compression, as initially suggested.

In one of the first long-term follow-up studies after PTA of the femoropopliteal and iliac arteries, Gallino et al5 reported an early decay of patency during the first 6 months after angioplasty. Despite technical and therapeutic improvements, restenosis remains a major drawback of PTA of the coronary and peripheral arteries because 30% to 40% of treated patients will eventually experience recurring significant stenosis.

Two major mechanisms traditionally have been implicated in the pathogenesis of restenosis: myointimal proliferation and arterial remodeling. In the past 10 to 15 years, a large number of studies have been performed with the aim of inhibiting the process of restenosis. Intravascular radiotherapy, commonly known as endovascular brachytherapy (EVBT), is a physical approach that might reduce arterial remodeling and intima-media thickening after percutaneous
intervention, thus reducing the extent and frequency of restenosis.

Clinical care of atherosclerosis has traditionally focused on flow-limiting luminal stenoses. However, recent basic and clinical research findings have challenged this emphasis and shifted the focus away from the vessel lumen to the underlying atherosclerotic plaque.6–10 The availability of high-resolution MRI has significantly facilitated the possibility of performing in vivo studies to evaluate the effects of interventions on atherosclerosis.11 Its usefulness in studying plaque progression, stabilization, and even regression has been demonstrated in several animal models by several groups.12–14 Recently, MRI has been used to image human atherosclerotic lesions in several vascular districts, and its accuracy and reproducibility in measuring atherosclerotic plaques have been reported.15,16 Thus, MRI is a promising noninvasive technology for studying the atherosclerotic burden of arteries and the vascular response to therapeutic intervention such as PTA and EVBT.16–18

The aim of the present study was to evaluate the short- and long-term effects of PTA on severely stenotic femoropopliteal lesions as well as the effect of brachytherapy on restenosis by means of serial MRI.

Methods
Twenty consecutive patients (aged 71.4±6.5 years; 14 men) with claudication classified as Rutherford ≥3 and severe superficial femoropopliteal artery stenosis were included in the study and randomly assigned to PTA alone (n=10) or PTA+EVBT (n=10). Patients were not eligible for the study if they had nonatherosclerotic occlusive disease, vascular surgery during the preceding 6 months, uncontrolled hypertension, hemorrhagic diathesis, impaired renal function (creatinine level ≥180 mmol/L), life expectancy of <6 months, or contraindication for MRI. The local ethics committee approved the protocol, and all patients gave written informed consent.

PTA and EVBT
All patients underwent PTA with a standard (Seldinger) technique with the use of a regular angiography unit (Integris V 3000, Philips Medical Systems). No atherectomy device or stent implantation was allowed. An ipsilateral anterograde puncture of the common femoral artery and a 6F introducer sheath (Cordis Europa NV) were used in all procedures. Multiple angiographic series were obtained at femoral and popliteal levels with the use of hand injections of 10 mL of contrast material (Hexabrix). Five- or 6-mm balloon catheters were used to perform angioplasty of the stenotic lesions. The segment at which angioplasty was performed was marked with a radiopaque ruler, and movement of the table and angiographic unit was avoided to prevent parallax error. Patients were randomized to PTA alone or PTA+EVBT at the end of the standard PTA procedure.

High-dose EVBT was performed with the use of y-irradiation by a 192Ir source, as previously reported.19 In brief, a 5F closed-tip, noncentered applicator catheter (Nucletron) was advanced through the 6F sheath and placed in the balloon-treated lesion, so that the tip of catheter reached 1.5 cm distal to the distal end of the interventional length. The active source length corresponded to the interventional length plus 1 cm on the distal and proximal ends. The dose distribution was calculated by means of a computer-assisted planning system (Plato-BPS, version 13.2, Nucletron) with a 2.5-mm stopping point. The reference dose of 14 Gy was applied in a depth of 5 mm from the source (reference vessel radius of 3 mm plus reference depth of 2 mm in the center of the interventional length). Marks on a dummy wire measured the interventional length and the length of the angioplasty segment. After its definition, the dummy wire was removed. The application catheter was connected to the afterloader, and the source was advanced into the applicator. No sham procedure was performed in patients treated with PTA only; therefore, the patients and the intervention radiologist were not blinded to the procedure. In contrast, an investigator blinded to patient identity and treatment group performed the analysis of the MR images. All patients underwent treatment with aspirin 100 mg/d and statins.

MRI and Analysis
All patients were imaged by high-resolution MRI before PTA, 24 hours after PTA, and 3 months after PTA±EVBT with a whole-body 1.5-T unit (Gyrosan Intera, release 8.1; Philips Medical Systems) with a gradient strength of 30 mT/m and a slew rate of 150 mT/m per millisecond. The MRI protocol consisted of 3 steps: (1) gradient echo series to localize anatomic structures; (2) time-of-flight MR angiography to localize the stenotic lesion and provide anatomic landmarks to define exact location of the stenosis of interest; and (3) plaque imaging sequences. T2-weighted (T2W), proton density-weighted (PDW), and T1-weighted (T1W) 3-dimensional, ECG-triggered, double inversion recovery, fast spin echo (2IR-FSE) sequences were used to acquire cross-sectional vessel images. The 2IR-FSE sequence allows nulling of the signal from the flowing blood and is known as black-blood MRI. Cross-sectional images were obtained perpendicular to the long axis of the vessel beginning at the selected distance from the predefined anatomic landmark, for example, the distance between common femoral artery bifurcation to maximum stenosis (Figure 1).

The following MRI parameters were used: repetition time, 2 to 3 RR intervals for T2W and PDW and 1 RR for T1W; echo time, T2W 42 ms, PDW and T1W 9.4 ms; field of view, 9×9 cm; acquisition matrix, 256×218 (zero-filled interpolated to 512×436 to reduce the partial-volume effects in imaging pixels); 2 signal averages; in-plane resolution, 0.35×0.41 mm; slice thickness, 2.5 mm; number of slices, 10 for each sequence (no slice interpolation was used); scan
mode, 3D; echo train length, 24; bandwidth, 310 Hz per pixel; echo spacing, 9.4 ms. A chemical shift suppression pulse with volume shimming was used to suppress the signal from perivascular fat. Anterior, posterior, and lateral spatial presaturation was applied to eliminate aliasing resulting from the small field of view. All 2IR-FSE sequences were acquired by using a small, circular, superficial receive-only coil (diameter 8 cm), which was centered at the location of the stenosis of interest to optimize signal-to-noise ratio. Total patient in-room time was approximately 35 to 45 minutes.

A blinded operator (R.C.) performed the computer-assisted morphometric analysis of cross-sectional MR images consisting of measuring the vessel wall dimensions by manual tracing of vessel borders (Image Pro-Plus, Media Cybernetics). Lumen area was defined as the area encompassed by the inner boundary of the intimal surface. Total vascular area was defined by the outer vessel boundary, and vessel wall area was calculated by subtracting the lumen from the total vessel area (Figure 1). Percent area stenosis was calculated according to the following formula: 100×[(total vessel area)−(lumen area)/total vessel area)]. The mean value of 10 contiguous cross-sectional MR images centered in the lesion was computed for statistical analysis. Percent changes are reported as 100×(mean at time T2−mean at time T1)/mean at time T1. Matching of the MR images was performed with the use of vascular landmarks. All the lesions were visually evaluated for disruption. Dissection after percutaneous intervention was defined as the presence of a tear in the intimal surface separating the lesion from the underlying arterial wall.

Statistical Analysis
Data are presented as mean±1 SE. Percent changes are reported as 100×(mean at time T2−mean at time T1)/mean at time T1). Statistical analysis was performed with the use of ANOVA for repeated measures (StatView 4.1, ABACUS Inc) and Student t test. A value of P<0.05 was considered significant.

Results

Short-Term Effects
Absolute value of lumen, total vessel area, and vessel wall area before and after the interventions are given in the Table. At baseline, patient and lesion characteristics with regard to lumen area, total vessel area, and vessel wall area were similar in both treatment groups. Cross-sectional MRI before intervention revealed an average percent area stenosis of 80±2% (range, 64% to 92%), which did not differ between the treatment groups. Angiography performed at the end of the procedures (PTA or PTA+EVBT) demonstrated restoration of lumen, normalization of anterograde flow, and residual luminal diameter stenosis <50% in all patients.

Cross-sectional MRI performed at 24 hours after percutaneous intervention revealed similar enlargement of the vessel wall dimensions (Figure 2) and severe disruption of the vessel wall and splitting of the atherosclerotic plaque, resulting in an irregularly shaped lumen in both treatment groups (Figure 3). No difference in vessel wall dimensions was detected between the group of patients randomly assigned to PTA alone and those assigned to PTA+EVBT (Table). Quantitative changes in cross-sectional MR images revealed that in patients treated with PTA alone, lumen area increased by 86% compared with baseline (P=0.003), total vessel area by 47% (P=0.02), and vessel wall area by 37% (P=0.035). In patients treated with PTA+EVBT, lumen area increased by 67% (P<0.001 versus baseline), total vessel area by 34% (P=0.0008), and vessel wall area by 25% (P=0.01). At 24 hours, no significant difference was seen with regard to lumen or vessel wall area between the 2 treatment groups, confirming that brachytherapy does not have a short-term additive effect to balloon angioplasty.

Long-Term Effects
At 3-month follow-up, both PTA and PTA+EVBT treatment groups showed a significant increase in lumen area (Table). Patients treated with PTA+EVBT showed a significantly larger effect of treatment on lumen area than those treated with PTA alone (P=0.026, ANOVA for repeated measures for category lumen×treatment; Figure 4). Compared with pre-PTA, lumen area increased by 40% in the PTA group and by 106% in the PTA-EVBT group, despite similar short-term results. Interestingly, in patients treated with PTA alone, MRI at 3 months revealed a luminal area loss compared with the measurements obtained immediately after treatment (~25%). In contrast, an additional lumen increase (23%) was detected in the PTA+EVBT group at 3-month follow-up (Figure 5).

At 3 months, total vessel area was significantly larger in the PTA+EVBT group than in the PTA group (P=0.018, ANOVA for repeated measures for category vessel wall area×treatment; Figure 4). Total vessel area returned to baseline values in patients treated with PTA alone, whereas a
A further (4%) increase was seen in patients treated with PTA/H11001/EVBT (Figure 5).

The severe plaque disruptions with deep dissections seen soon after intervention were no longer visible in the PTA group at 3-month follow-up, indicating healing of the vessel wall. In contrast, in 50% of the patients treated with PTA/EVBT, some degree of dissection or splitting of the atherosclerotic plaque persisted after 3 months (Figure 3). No patient needed reintervention or showed thrombotic occlusion during the 3-month follow-up.

**Discussion**

Using MRI, we demonstrate noninvasively and in vivo that lumen gain after PTA alone or PTA plus EVBT is mainly due to 2 different vascular effects: (1) severe disruption of the atherosclerotic plaque with eventual deep dissection into the vessel wall and (2) dramatic remodeling with outward expansion (Figure 5). Shortly after intervention, lumen area almost doubled in both treatment groups, and severe disruption of the atherosclerotic plaque with dissection into the vessel wall was detected in all patients after balloon dilatation (independently of additional brachytherapy). At 3 months, no dissection was detected in patients treated with PTA alone, whereas some degree of dissection was still evident in 50% of those treated with PTA plus EVBT. Patients treated with PTA alone exhibited features of restenosis and inward (negative) remodeling at 3 months, whereas patients treated with PTA plus EVBT showed further expansion of the vessel wall, leading to additional increase in lumen size.

EVBT has recently emerged as a promising technique to reduce the incidence of restenosis after peripheral and coronary PTA. The proliferation of arterial cells occurring at the site of angioplasty plays a pivotal role in the development of restenosis, which in essence represents the end result of a wound-healing process, part of a physiological response of diseased arteries to mechanical injury, which is markedly reduced with EVBT. Delayed healing and resolution of dissection after EVBT have also been reported in the coronary circulation. In addition to delayed reendothelialization, this may explain the increased risk of late thrombosis observed in patients treated with brachytherapy. Although the exact mechanisms of the antirestenotic proper-
ties of EVBT still have not been clarified completely, the antiproliferative effects remain the most accepted.27

Our results confirm the potentially beneficial antiproliferative effect of EVBT but also reveal potential drawbacks of this therapy. In fact, in 50% of the patients, we confirmed persistent dissection at 3 months, whereas the further lumen increase encountered was due to further expansion of the vessel wall. These observations may also explain the increased incidence of arterial aneurysm after EVBT in coronary artery.28 Persistent dissection in patients with femoropopliteal obstructive disease treated with PTA plus EVBT has been also described with the use of serial intravascular ultrasound (IVUS).29 Using noninvasive imaging, we definitively demonstrate that IVUS-detected persistent dissection29 was not a result of catheter manipulation during the IVUS procedure but was most probably the result of delayed vessel healing after brachytherapy. In addition, by imaging the lesions before the catheter intervention, we demonstrate that in the short term there was no difference in the treatment between the groups, reducing a potential selection bias. One could otherwise speculate that the deep dissection is the result of a more aggressive balloon dilatation. This was not the case in our study because both groups had comparable lumen and vessel dimensions before and shortly after percutaneous intervention.

Recently, radiation-induced vasculitis has been demonstrated in experimental brachytherapy in swine arteries.30 Acute necrotizing vasculitis with fibrinoid necrosis of the wall was histologically characterized at 1 month after brachytherapy, and it was hypothesized that the vasculitis may result from radiation-induced, local overexpression of activated cytokines that results in endothelial and smooth muscle cell damage and causes vascular leakage with precipitation of fibrin.30 This mechanism may explain the weakness of the vessel wall, resulting in late expansion.

Our results highlight that a significant contributing factor to restenosis results from arterial inward remodeling. Remodeling rather than neointima formation has been related to luminal narrowing after coronary angioplasty in the pig model as well.31 Using IVUS, Mintz et al32 showed that remodeling accounted for almost 65% of the late luminal area loss after coronary angioplasty. The proliferation of smooth muscle cell contributes significantly to restenosis after angioplasty. Recent studies demonstrated that adventitial fibroblasts are also implicated in the process, not only adding to the number of proliferating cells but also contributing to the synthesis of extracellular matrix and therefore contributing to the restenosis by compressing the vessel (like scar contraction) or preventing compensatory enlargement during healing after angioplasty.33 During successful angioplasty in ad-
advanced atherosclerosis, the rigid atherosclerotic plaque is separated from the more compliant vessel wall components that are stretched, and a tear usually extends deeply into the vessel wall. The adventitial and periadventitial damage caused by stretch and tears may trigger neoadventitial formation and shrinkage (constrictive remodeling), which may cause late luminal narrowing.\(^1\)

High-resolution MRI has recently emerged as the potential leading noninvasive in vivo imaging modality for atherosclerotic vessels, providing information about the remodeling process in humans. MRI allows imaging without ionizing radiation, can be repeated serially, and permits study of the different plaque components with the use of multicontrast sequences. In addition, cross-sectional imaging provides essential information about vascular and extravascular structures, thus enabling optimal matching of the images over time with the use of anatomic markers. MRI has been proven to provide highly accurate measures of vessel wall dimensions, which can be used to perform follow-up studies with the use of plaque size as a surrogate end point. Comparing the measures in the same patient enables smaller sample sizes. IVUS is an invasive imaging methodology, which therefore limits its usefulness for serial analysis. Its usefulness has been indispensible in elucidating the coronary remodeling process during atherosclerosis progression and in interventional trials.

In conclusion, our results characterize remodeling of the vessel wall after PTA and brachytherapy and highlight the role of MRI as a noninvasive technology for the study of atherosclerosis in vivo. In addition, we confirm that plaque disruption and deep dissection into the vessel wall contribute to the short-term effect on vascular lumen.

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**References**

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