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Association of Circulating Transforming Growth Factor beta, Tumor Necrosis Factor alpha and Basic Fibroblast Growth Factor with Restenosis after Transluminal Angioplasty

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Objectives. *To assess prospectively the early time course of Transforming Growth Factor beta-1 (TGFβ-1), basic Fibroblast Growth Factor (bFGF) and Tumor Necrosis Factor alpha (TNFα) as possible contributors to restenosis development after angioplasty.*
Design. *Prospective Study.*
Methods. *The levels of the soluble forms of these factors in the early response to Percutaneous Transluminal Angioplasty (PTA) in the arteries of the lower limb were prospectively assessed. 32 patients with peripheral arterial occlusive disease (PAOD), presenting with intermittent claudication (Fontaine stage IIb) were scheduled for angioplasty treatment. Serum levels of TGFβ-1, TNFα and bFGF were assessed before intervention, 15 and 60 minutes after, 24 hours after as well as 2 and 4 weeks after intervention. We compared the distribution patterns between patients treated with balloon angioplasty and patients who required secondary stent implantation. Endpoint was the development of restenosis within 6 months after interventional treatment, defined as a lumen diameter reduction of more than 50% by ultrasound measurement compared to the result after PTA.*
Results. *The patients who later developed restenosis had significantly higher levels of TGFβ-1 at 15 minutes, 24 hours and 2 weeks after PTA ($p < 0.05$). TNFα and bFGF were only detected in a few patients and no significant change of serum levels was observed.*
Conclusion. *The results demonstrate a possible role of TGFβ-1 in the formation of restenosis after PTA.*

Keywords: Angioplasty; Restenosis; Peripheral arterial occlusive disease; Growth factors; Transforming Growth Factor beta.

Introduction

The long term benefit of percutaneous transluminal angioplasty (PTA) is severely limited by the development of restenosis. The restenosis rate varies between specific vessels, the extent of the disease and the type of endovascular treatment. Overall, restenosis occurs in approximately 30–40% after balloon dilations within 3–6 months.[1] Also primary stenting of peripheral vessels did not improve the patency rate to a satisfying level.[2] Arterial remodelling, neointimal hyperplasia, elastic recoil, scar shrinkage and thrombus formation at the site of vascular injury are discussed to be reasons for restenosis.[3]

Several growth factors have been identified and considered to play a key role in the mechanisms of restenosis formation.[4–6]

Histopathological studies of experimental angioplasty in animal models showed that the angioplasty procedure severely damages the endothelium and subendothelial structures. Endovascular ultrasound studies as well as post-mortem histopathological analysis revealed that similar damage to the arterial wall occurs after angioplasty in humans.[7,8] In the animal model the angioplasty-induced trauma leads to a local activation of inflammatory and haemostatic mechanisms which can initiate the production of signalling

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mediators such as Transforming Growth Factor β-1 (TGFβ-1), Tumor Necrosis Factor α (TNFα) and basic Fibroblast Growth Factor (bFGF). These factors can be identified in animal tissue specimens obtained after arterial injury.[4,6,9–12]

TGFβ-1, a potent regulator of wound healing and scar formation is important in the response to balloon induced arterial injury.[4] TGFβ-1 is mainly produced by smooth muscle cells (SMC) which are stimulated by the balloon induced trauma.[5] That subsequently leads to increased cellular proliferation, extracellular matrix production in the arterial wall and transformation of vascular fibroblasts to myofibroblasts.[13–15]

TNFα is another important mediator in the development of restenotic lesions.[6] It was originally regarded exclusively as a product of activated macrophages. However, in several studies, SMCs have been identified as an alternative source of this cytokine.[16] TNFα is expressed in the media as early as 6 hours after balloon catheter injury. The TNFα expression leads to a stimulatory effect on SMC migration into the intima.[9]

bFGF is synthesized by the arterial wall and acts as a potent mitogen for endothelial cells and SMCs.[17] Blocking the bFGF pathways with a neutralizing antibody prior to catheterization leads to an inhibition of SMC proliferation demonstrating that bFGF is one of the major mitogens promoting the growth of vascular SMC following denuding injury.[18]

Despite these data knowledge about angioplasty-induced arterial trauma and restenosis development in humans is still incomplete.

The aim of our study was to assess prospectively the levels of TGFβ-1, TNFα and bFGF in their soluble forms detected in the serum during the early phase after transluminal balloon angioplasty and additional stent placement. These factors were shown to contribute to restenosis formation in animal models and in-vitro studies and inhibiting their mediated pathways by selective antibodies or gene transfer was proven to reduce restenosis rate. We expected PTA to increase the expression and release of soluble growth factors into the blood. Focusing on restenosis, we intended to gain a better understanding of the complex pathophysiology of angioplasty induced vessel trauma, its consequences, and thus the delayed failure of angioplasty procedures.

Methods

Patients

Thirty-two patients (17 men, 15 women, mean age 67.3 ± 8.1 years) with PAOD and indication for interventional treatment were prospectively assessed. All patients presented with symptoms of intermittent claudication (Fontaine stage IIb). The severity of PAOD was assessed by measurement of ankle-brachial-index (ABI) at rest and treadmill test and hemodynamic and morphologic severity of the lesions were assessed non-invasively by duplex sonography (System Five, Vingmed Sounds A/S, Horten, Norway) and during angiography. Patient characteristics are listed in Tables 1 and 2.

The study was carried out according to the guidelines of the World Medical Association Declaration of Helsinki. All patients gave written informed consent and the study was approved by the Internal Review Board Committee of the Interdisciplinary Centre for Vascular Diseases of the Technical University of Munich. Patients with documented malignant diseases and/or vasculitis were excluded. All medications for concomitant diseases except coumarin derivatives were continued during the time of study participation. Medication status as well as recorded risk factors are shown in Tables 1 and 2.

Lesions

Seventeen patients (53.1%) had lesions in the iliac artery, 13 patients (40.6%) in the superficial femoral artery and 2 patients (6.3%) in the popliteal artery. The average lumen narrowing was 83.9 ± 12.2%, the average length of stenosis 2.0 ± 1.3 cm, graded on angiographic profile by the performing radiologist.

Detailed descriptions of lesions are shown in Table 3, procedural characteristics in Table 4.

Angiography and angioplasty procedures

All patients received diagnostic digital subtraction angiography of the lower limbs prior to interventional treatment. A non-ionic contrast material Iomeprol (Imeron 300, Altana Pharma GmbH, Konstanz, Germany) was used, 182.0 ± 68.3 ml per patient. Balloon angioplasty was performed in 22 patients (68.8%) in 10 patients (31.2%) secondary stenting had to be performed due to residual stenosis greater than 30% or flow limiting elastic recoil, dissection or intimal flap. As stenting devices, self expanding nitinol stents (Xpert, Abbott Vascular Devices, Abbott Park, Illinois, USA) with diameters from 5 to 8 mm and lengths from 20 to 60 mm were used. After the procedure, 18 patients (56.3%) had a three-vessel-runoff, 12 patients (37.5%) had a two-vessel-runoff and only 2 patients (6.2%) had a one-vessel-runoff.