Restenosis after percutaneous angioplasty: the role of vascular inflammation

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Abstract: Restenosis after endovascular treatment of atherosclerotic lesions in the peripheral, cerebrovascular, and coronary circulation is the major drawback of this minimally invasive technique. Although certain advances have been made during recent years to improve patency rates after percutaneous angioplasty, restenosis remains a challenging clinical problem. Understanding factors that contribute to the pathophysiology of late lumen loss is an effective strategy to improving patients' postangioplasty outcome. Vascular inflammation after balloon angioplasty or stent implantation has been identified as a cornerstone of the restenotic process, and several markers of inflammation have been referred to as potential predictors of outcome. This article reviews recent findings on the issue of inflammation and restenosis after percutaneous angioplasty with special attention given to the role of inflammatory parameters as markers for the restenosis risk in the peripheral vessel area.

Keywords: percutaneous transluminal angioplasty, restenosis, inflammation

Introduction

Percutaneous transluminal angioplasty (PTA) is a minimally invasive revascularization procedure for treatment of atherosclerotic lesions in the peripheral, cerebrovascular, and coronary vessel area. Late clinical failure after primarily successful interventions due to recurrent stenosis (restenosis) occurring in up to 60% of the patients within the first 12 months remains the major drawback of percutaneous angioplasty and limits a widespread application of this minimally invasive technique (Gallino et al 1984; Krepel et al 1985; Maca et al 1996; Minar et al 1998; Cejna et al 2001; Exner et al 2001; Schillinger et al 2001). As competitive surgical approaches yield better long-term results, the indications for endovascular revascularisation are a matter of debate (Diegeler et al 2002). Furthermore, with increasing numbers of procedures performed, late sequelae due to recurrent stenoses and the need for costly reinterventions become more frequent. Understanding the factors that contribute to the pathophysiology of late lumen loss is the foundation to develop effective strategies for improvement of patients' postangioplasty outcome. Endovascular brachytherapy (Minar et al 1998, 2000) and the upcoming drug eluting stents (Sousa et al 2001; Suzuki et al 2001; Morice et al 2002) are suggested to reduce the rate of intermediate term restenosis in the peripheral as well as in the coronary vessel area, but selection criteria for patients who are candidates for these expensive procedures with limited availability are indeterminate. Once identified, reliable predictors of the restenosis risk could facilitate the targeted use of measures for prevention of restenosis and help to save healthcare resources.

Accumulating data indicate that insights gained from the link between inflammation and restenosis can yield predictive and prognostic information of considerable clinical utility. Inflammation in the vessel wall in response to balloon

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injury or stent implantation initiates hypertrophic neointima formation through vascular smooth muscle cell (VSMC) proliferation and constrictive vascular remodelling (O'Brian and Schwartz 1994; Ross 1999; Orford et al 2000). This process of neointima formation and recurrent lumen narrowing has been referred to as manifestation of an inflammatory wound healing response expressed specifically in vascular tissue (Forrester et al 1991). The present article reviews recent findings on the issue of inflammation and restenosis with special attention to the peripheral vessel area.

Pathophysiology of inflammation and restenosis

Chronic vascular inflammation is involved in the development of restenosis after balloon angioplasty and stent implantation (Forrester et al 1991; Belch et al 1997; Serrano et al 1997; Kamijikkoku et al 1998; Kornowski et al 1998; Tsakiris et al 1999; Yutani et al 1999; Lusis 2000; Cippolone et al 2001; Glass and Witztum 2001; Schillinger et al 2001, 2002a; Libby et al 2002). Broadly, restenosis can be considered to be a form of hypertrophic wound healing resulting from an interaction between monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall. A triggering event for the vascular inflammatory process is shear stress during balloon inflation or stent implantation and vascular injury, which stimulate the production of proinflammatory molecules and activation of circulating monocytes (Serrano et al 1997). Expression of selectins and adhesion molecules mediate the binding of circulating monocytes and penetration of these cells into the vascular wall (Ross 1999; Lusis 2000; Glass and Witztum 2001; Libby et al 2002). The magnitude of monocyte activation and adherence to the vascular wall was suggested to promote late lumen loss (Pietersma et al 1995; Mickelson et al 1996). The first step in adhesion of inflammatory cells at the dilated or stented segment, the "rolling" of leucocytes, is mediated by selectins, which bind to carbohydrate ligands on leukocytes. The E-selectin serum level, for example, has been demonstrated to closely correlate with the restenosis risk (Belch et al 1997). The firm adhesion of monocytes and T cells to the arterial wall is then mediated via cell adhesion molecules (CAMs); CAMs have also been shown to be associated with the restenotic process (Kamijikkoku et al 1998; Tsakiris et al 1999). Once adherent to the endothelium, the monocytes penetrate into the intima and through the media to the adventitia (Wilcox et al 2001). Monocyte chemotactic protein-1 (MCP 1) appears responsible for monocyte recruitment and direct transmigration into the vascular wall at the treated lesion, and higher serum levels of this chemokine indicate a higher restenosis risk (Cipollone et al 2001). Once resident in the arterial wall, the blood-derived inflammatory cells participate in and perpetuate a local inflammatory response. Inflammatory molecules as well as shear stress during the endovascular procedure stimulate the immigration of VSMCs from the medial layer of the arterial wall past the internal elastic lamina and into the intimal or subendothelial space. Recruitment and proliferation of myofibroblasts and synthesis of extracellular matrix proteins are key factors of hypertrophic neointima formation and restenosis (Wilcox et al 2001). This phase of lesion progression is markedly influenced by interactions between monocyte/macrophages and T cells, which results in the acquisition of many features of a chronic inflammatory state.

Predictive value of inflammatory markers and acute phase proteins

Acute phase reactants are related to atherosclerosis in the peripheral, coronary, and extracranial brain arteries (Heinrich et al 1995; Tschöpl et al 1997; Blum et al 1998; Buffon et al 1999; Schillinger et al 2002b, 2003a, 2003b). These circulating markers of inflammation reflect the activity of the disease associated with accumulation of macrophages and proliferation of endothelial cells and vascular smooth muscle cells (Haverkate et al 1997). The plasma proteins, C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen are sensitive, specific, and fast reacting markers of acute phase reaction (Pepys and Baltz 1983; Young et al 1991; Ernst 1993) and provide an indirect measure of a cytokine dependent inflammatory process of the arterial wall (Pepys 1995; Kuller et al 1996). Balloon injury and stent implantation in the peripheral vessel area have been demonstrated to induce a vascular inflammatory response at the dilated vessel segment, which is measurable by the postintervention course of serum acute phase parameters like CRP, SAA, or fibrinogen (Schillinger et al 2002c), and the severity of arterial injury during balloon injury or stent placement correlated with increased inflammation (Virmani and Farb 1999).

It is well known that patency rates after percutaneous transluminal angioplasty and stent implantation widely depend on the location of the treated lesion. Endovascular treatment of large elastic arteries like the internal carotid

artery and the iliac arteries is associated with a relatively low rate of recurrence (Bosch et al 1997; Tetteroo et al 1998; Dormandy and Rutherford 2000; Ahmadi et al 2001). In contrast, in the muscular conduit arteries of the femoropopliteal segment restenosis after PTA more frequently occurs (Adar et al 1989; Jeans et al 1990; Matsi et al 1994; Dormandy and Rutherford 2000). Thus, it seemed reasonable to speculate that these differences of restenosis rates may be due to differences of the extent of inflammation in response to endovascular treatment. Indeed, it could be shown that stent implantation in the muscular arteries of the femoropopliteal segment was associated with a more extensive vascular inflammatory response than stenting of the elastic iliac or carotid arteries, suggesting that the enhanced inflammatory response after femoropopliteal stenting might contribute to the higher rates of restenosis in this vessel area (Schillinger et al 2002d). Nevertheless, the predictive value of acute phase reactants remained to be demonstrated.

Recently, several studies evaluated the prognostic impact of inflammatory laboratory parameters and the potential clinical relevance to predict the individual's restenosis risk. It was consistently shown that elevated baseline values and postintervention levels of these inflammatory parameters were associated with an increased risk for restenosis after peripheral, coronary, and carotid angioplasty (Tschöpl et al 1997; Blum et al 1998; Buffon et al 1999; Schillinger et al 2001, 2002a, 2002b, 2003a, 2003b). Elevated CRP levels are an indicator of increased cardiovascular risk in healthy individuals as well as in patients with atherosclerosis (Berk et al 1990; Liuzzo et al 1994; Heinrich et al 1995; Kuller et al 1996; Mendall et al 1996; Haverkate et al 1997). Low level chronic inflammatory activity in the vascular tissue is suggested to cause a CRP elevation in patients with atherosclerosis (Mendall et al 1996), reflecting the activity of the disease. Higher peri-procedure CRP values are thus thought to indicate a higher activity of the disease and an increased susceptibility for hypertrophic vascular remodeling and excessive neointima formation after percutaneous angioplasty. However, it remains indeterminate whether acute phase reactants are only indicators of an increased risk for restenosis or causally contribute to its occurrence. One mechanism of a causal role could be the activation of the complement system, local vascular inflammatory reactions, and subsequent tissue damage (Torzewski et al 1998). Furthermore, CRP at concentrations known to predict adverse vascular events decreases nitric oxide synthesis and inhibits angiogenesis (Verma et al 2002); both factors are markedly involved in the pathogenesis of vascular disease.

The crucial question remains, whether acute phase reactants like CRP will be clinically useful to predict the individual's risk for restenosis. Currently, clear cut-off levels of CRP indicating an increased restenosis risk are lacking, and routine application of these inflammatory parameters therefore seems not to be justified.

Inflammatory and antiinflammatory genes: involvement in restenosis?

Recent research has focused on the potential implications of genetic variability on the pathophysiology of vascular disease (Jukema et al 2000; Kastrati et al 2000; Bauters et al 2001; Roguin et al 2001). Traditional risk factors for recurrent lumen narrowing after percutaneous angioplasty – like local hemodynamics or technical success – account for only a minor proportion of the restenosis risk, and genetic predisposition seems to markedly influence the individual's susceptibility for this process (Exner et al 2001). In particular, genes encoding for inflammatory or anti-inflammatory proteins are suggested to play a pivotal role in the pathophysiology of lesion recurrence. Several candidate genes have been investigated so far. Briefly, genetic variability may be found in most of the genes encoding for the inflammatory parameters mentioned above: interleukins, selectins, CAMs etc. Variable expression of almost all of these factors may influence the extent of vascular inflammation in response to percutaneous angioplasty, and thus the occurrence of restenosis. However, results of most observational studies demonstrating an association between a genetic characteristic and the restenosis risk have to be interpreted cautiously – type II errors or false positive findings are likely to occur in small patient series.

Exemplary, two specific gene polymorphisms may be discussed that are potentially involved in the patho-physiology of restenosis in the peripheral vessel area: the heme oxygenase 1 (HO-1) genotype, as an antiinflammatory factor; and the interleukin 6 (IL-6) genotype, as an inflammatory polymorphism. Heme oxygenase-1 (HO-1) is a novel vascular protective factor with potent antiinflammatory and antioxidant effects and the ability to inhibit the proliferation of smooth muscle cells (Maines 1988; Tenhunen et al 1989; Duckers et al 2001; Ishikawa et al 2001; Tulis et al 2001). Development of restenosis in large

measure involves these very factors that are inhibited by HO-1: inflammation in the vessel wall, constrictive vascular remodeling, and hypertrophic neointima formation through smooth muscle cell proliferation.

HO-1 is up-regulated by balloon angioplasty. However, humans differ quantitatively in their ability to mount a HO-1 response. There is a length polymorphism in the form of a $(GT)_n$ dinucleotide repeat in the 5′-flanking region of the human HO-1 gene that modulates the quantitative level of HO-1 activity in response to a given stimulus (Kimpara et al 1997; Yamada et al 2000). The HO-1 promoter genotype was associated with the postintervention inflammatory response and the occurrence of restenosis after femoropopliteal PTA (Exner et al 2001, Schillinger et al 2002e, 2004). Patients with a certain genotype of the HO-1 gene promoter exhibited a lower postintervention inflammatory response and a lower restenosis rate at 6 months compared with non-carriers of this genetic variant. This suggested that a stronger HO-1 response is protective against restenosis. Modulation of the postintervention vascular inflammatory response seemed to be an underlying mechanism of the protective effect of HO-1 up-regulation after balloon angioplasty.

Interleukin 6, on the other hand, represents a key factor in the vascular inflammatory cascade after balloon injury that is directly involved in the regulation of the acute phase response. A functional polymorphism in the IL-6 gene promoter has been demonstrated to modulate the cytokine expression in response to vascular injury (Brull et al 2001). Consistently, this IL-6 promoter polymorphism was associated with the 12 months restenosis risk after femoropopliteal PTA in a larger patient series (Exner et al 2004), indicating a potential involvement of pro-inflammatory genes in the restenotic process. Nevertheless, future research will have to focus on more complex gene–gene and gene–environment interactions, since restenosis likely is a polygenetic process and may not be explained by a single genetic polymorphism.

Potential clinical implications

Some experimental data indicate that modulation or suppression of the inflammatory response after endovascular treatment may exert beneficial effects on outcome. Statins are known to exert potent antiinflammatory properties and have been demonstrated to reduce inflammation and progression of atherosclerosis. In this context, it has been recently demonstrated that a statin (pitavastatin) has the ability to inhibit neointimal hyperplasia after stenting in a procine coronary model mainly through a reduction of inflammatory reactions (Yokoyama 2004). Furthermore, in patients with persistently high CRP levels after successful coronary artery stent implantation, oral immunosuppressive therapy with prednisone resulted in a striking reduction of clinical events and angiographic restenosis rate (Versaci et al 2002). In contrast to these conventional pharmacological approaches, various gene therapeutic approaches also seemed promising. In hypercholesterolemic rabbits, local adenovirus-mediated I kappa B alpha gene transfer had the potential to reduce intimal hyperplasia after stent placement (Breuss et al 2002; Cejna et al 2002). Similarly, pre-treatment with recombinant antibodies against leukocyte P-selectin glycoprotein ligand-1, a key factor of inflammation and activation of platelets, in a porcine coronary stent model reduced neointimal proliferation and in-stent restenosis (Tanguay et al 2004). Another experimentally successful gene-therapeutic approach to inhibit inflammation and reduce restenosis was the recently described inhibition of early growth response factor 1 in hypercholesterolemic rabbits after carotid balloon injury (Ohtani et al 2004).

Conclusion

Evidence from experimental, animal, and clinical studies support the hypothesis that vascular inflammation is a key factor in the restenotic process. The extent of vascular inflammation in response to percutaneous angioplasty predicts the restenosis risk, although currently inflammatory markers are not of clinical utility in this context. Variability in genes encoding for vascular inflammatory and antiinflammatory genes is worth further examination with regard to the pathophysiology of recurrent lumen narrowing.

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