ELSEVIER

General Review

Inflammatory Markers and Restenosis in Peripheral Percutaneous Angioplasty With Intravascular Stenting: Current Concepts

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In this article, we review the current status of inflammation linked to percutaneous transluminal angioplasty with stent implantation, especially as it relates to restenosis and its clinical implications. Common to multiple vascular diseases, including atherosclerosis, interventional restenosis is a localized inflammatory reaction. Activated smooth muscle cells respond to local inflammation and migrate from the media into the lumen of the vessel, where they proliferate and synthesize cytokines which they respond to in an autocrine manner, sustaining the progression of the lesion. The deleterious effects of proinflammatory cytokines, particularly immunomodulatory interleukins, on vascular pathophysiology and development of these maladaptive processes have been the subject of intense study. Matrix metalloproteinases and tissue inhibitors of metalloproteinases are important in many physiologic and pathologic processes and their expression is related with the classic cardiovascular risk factors as well as with inflammation. They seem to play a central role in atherosclerosis and restenosis. The primary use of drug-eluting stents has become routine clinical practice for coronary artery disease, but the use in peripheral arteries remains to be further studied, like that demonstrated in Sirolimus-coated Cordis trials. New studies to understand this complex process in peripheral arteries are warranted.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) with stent implantation is a minimally invasive technique for treatment of atherosclerotic stenosis or occlusions in peripheral vessels. Vascular inflammation is involved in the development and progression of atherosclerosis[1-5] and restenosis after balloon angioplasty.[6-9] Systematic classification of arterial intimal injuries has revealed a spectrum of vascular wall injuries, from type I (functional alterations without significant morphologic change) to type II (endothelial denudation without intimal and medial damage) to type III (endothelial denudation with intimal and medial damage).[10] Angioplasty constitutes type III vessel wall injuries, where the endothelium and the media of the vessel are damaged. The biology of in-stent restenosis (ISR) is different from that seen after balloon angioplasty.[11] After balloon angioplasty, there is thrombus formation, intimal hyperplasia development, elastic coil, and negative remodeling. Negative remodeling is a condition in which the vessel area decreases in size, often as a result of a structural change in the vessel wall. It is a major factor in restenosis following balloon angioplasty. In contrast, after stent placement, elastic coil and negative remodeling are

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eliminated,[12] and thrombus formation followed by intimal hyperplasia development are the main contributors to ISR.[13,14]

A stent is generally used if the result of balloon angioplasty is technically unsatisfactory or if there is arterial occlusion, immediate elastic recoil, dissection, or restenosis. The response of a vessel to a stent depends on the design, length, and composition of the stent, the delivery system, and the deployment technique.[15] ISR is classified on the basis of length of restenosis in relation to stented length. Four categories of ISR have been classified as follows: (1) focal ($\leq$10 mm in length), (2) diffuse (>10 mm in length), (3) proliferative (>10 mm in length and extending outside the stent), and (4) occlusion.[16] Inflammation in the vessel wall in response to balloon injury or stent implantation initiates hypertrophic neointima formation through smooth muscle cell (SMC) proliferation and constrictive vascular remodeling.[17-19] This process of neointima formation and a recurrent lumen narrowing has been referred to as manifestation of an inflammatory wound healing response expressed specifically in vascular tissue.[6] Vascular SMC proliferation and hypertrophic neointimal formation at the treated segment frequently lead to restenosis. The association between inflammatory and immune responses and clinical adverse events poststenting has yet to be defined. Interestingly, the intensity of the inflammatory process and the angiographic or clinical outcome after stenting are also influenced by genetic factors.[20] Some studies have consistently indicated that inflammatory mechanisms play a pivotal role in the process of neointimal proliferation and stent restenosis.[21,22] 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. This article reviews the current status of inflammation linked to PTA with stent implantation in peripheral arteries, especially as it relates to restenosis.

RESTENOSIS AND INFLAMMATION

Restenosis after artery stenting has long been attributed to elastic recoil immediately after balloon deflation, neointimal proliferation triggered by injury to the vessel wall, and late negative remodeling.[23] Despite the intensive studies that have been performed on restenosis, the factors that contribute to the ISR have not been completely elucidated.[15] It is known that patency rates after PTA and stent implantation also depend widely on the location of the treated lesion. Endovascular treatment of large elastic arteries, such as internal carotid artery and iliac arteries, is associated with a relatively low rate of restenosis.[24,25] In contrast, restenosis after PTA occurs frequently in the muscular conduit arteries of the femoropopliteal segment.[26] It is possible that the differences of restenosis rates may be due to differences of the extent of inflammation in response to stent implantation. Indeed, it has been shown that stent implantation in the muscular arteries of the femoropopliteal segment was associated with a more extensive vascular inflammatory response than the stenting of the elastic iliac or carotid arteries, thereby suggesting that the enhanced inflammatory response after femoropopliteal stenting might contribute to the higher rates of restenosis in this vessel area.[27]

Currently, extensive data suggested that three kinds of major factors might be contributing to intra stent restenosis (ISR), namely lesion- or procedure-related factors, patient-related factors, and genetic-related factors.[16,28,29] Chronic vascular inflammation is involved in the development of restenosis after balloon angioplasty and stent implantation.[6,7,30] After injury with the stent implantation, there is an intensive inflammatory response, with polymorphonuclear neutrophils (PMNs) and monocytes adhering to the subendothelial surface. The precise mechanism that occurs by this response is undetermined. The 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.[7] As compared with uninjured endothelium, regenerating endothelial cells show high levels of expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM); this pattern of expression appears to follow the leading edge of the regenerating endothelium. Regenerated endothelial cells removed from the leading edge continue to express ICAM but not VCAM. Expression of VCAM-1 and monocytes chemoattractant protein-1 is seen within 4 hours of injury in SMCs. SMCs on the luminal surface continue to express high levels of VCAM-1 and monocytes chemoattractant protein-1 at late time points.[31] ICAM-1 expression is intense at 1 and 2 days within medial SMCs of the wall, and administration of an antibody to ICAM-1 or lymphocyte function-associated antigen-1 reduces the intimal hyperplastic response.[32] Within 10 days, SMCs show expression for both ICAM and class II major histocompatibility complex antigens. However, by 30 days, the expression of adhesion cell molecules