

The Comparative Pathobiology of Atherosclerosis and Restenosis

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Percutaneous coronary interventions (PCIs) play an increasingly important role in the management of patients with coronary artery disease. However, these important procedures are complicated by restenosis in a sizeable number of patients. The pathobiology of atherosclerosis comprises a complex interaction among lipids, the endothelium, circulating and tissue inflammatory cells, platelets, and vascular smooth muscle cells. The superimposition of the mechanical and cellular consequences of PCIs on the abnormal substrate of atherosclerosis leads to a character-

istic and distinct pathobiology that initiates and perpetuates restenosis. A clear understanding of the significant differences between atherosclerosis and restenosis will provide a rational basis for developing treatment plans that always address both problems. This article reviews and contrasts the pathobiology of atherosclerosis and restenosis and compares the mechanisms and time-course of these distinct entities. ©2000 by Excerpta Medica, Inc.

Am J Cardiol 2000;86(suppl):6H-11H

Percutaneous coronary interventions (PCIs) play an increasingly important role in the management of patients with coronary artery disease. More than 800,000 procedures are currently performed in the United States each year, and this number continues to increase annually.¹ Coronary stenting accounts for >70% of all percutaneous coronary procedures.² The impetus for this rapid growth in the use of coronary artery stents has been the mounting body of evidence that supports their role in the prevention of restenosis.^{3,4} It is also apparent that the use of potent antiplatelet agents, including glycoprotein IIb/IIIa inhibitors, reduces the incidence of abrupt vessel closure and may reduce the need for repeat target vessel revascularization.⁵ Nevertheless, restenosis continues to complicate PCIs, necessitating repeat procedures in a significant number of patients. There is a need for further clarification of the mechanisms of this process to aid in the development of appropriate and specific therapies. These efforts should be considered within the context of the known benefits of global risk-factor modification after PCIs.^{6,7} This article discusses the pathobiology of atherosclerosis and restenosis and compares the time-course and mechanisms of these distinct entities.

ATHEROSCLEROSIS: AN INFLAMMATORY DISEASE

The pathobiology of atherosclerosis comprises a complex interaction among lipids, the endothelium, circulating and tissue inflammatory cells, platelets, and vascular smooth muscle cells.

Endothelial activation and dysfunction: Atherosclerosis can be characterized as an inflammatory response to endothelial injury.^{8,9} Risk factors for atherosclerosis include elevated and oxidatively modified low-density lipoprotein (LDL) cholesterol, sustained systemic arterial hypertension, diabetes, smoking, homocysteine, and possibly infectious agents. Early atherosclerotic lesions develop in a topographical pattern that strongly suggests involvement of hemodynamic forces in their pathogenesis. Certain endothelial genes exhibit differential responsiveness to mechanical stimuli, including shear stress, and modulate the atherogenic response to these aforementioned systemic risk factors.^{10,11} Endothelial activation and dysfunction, the earliest stage of atherosclerotic plaque development, includes loss of vasodilator and other local defenses that control proliferation and thrombosis. Thereafter, most of the cells in the vascular wall will participate in mounting several active responses that initiate and amplify inflammation, thrombosis, proliferation, and matrix formation.

Inflammation: On exposure to oxidized LDL, nuclear transcriptional messengers cause the formation of membrane adhesion molecules that initiate and increase adherence of inflammatory cells and platelets. The local migration of monocyte-derived tissue macrophages stimulates smooth muscle cell migration from the vascular media, cellular activation, and proliferation in response to potent cytokines and mitogens. T-lymphocytes inhibit vascular smooth muscle cell synthesis of collagen and may modulate macrophage-derived foam cell production of matrix metalloproteinases, resulting in weakening of the structure and integrity of the collagenous fibrous cap of the atherosclerotic plaque.¹²

Thrombosis: On exposure to risk factors and throughout the development of atherosclerosis, the endothelium becomes procoagulant. Altered surface heparans, decreased thrombomodulin and tissue plasminogen activator (tPA), and increased plasminogen activator inhibitor-1 (PAI-1) all contribute to this pro-

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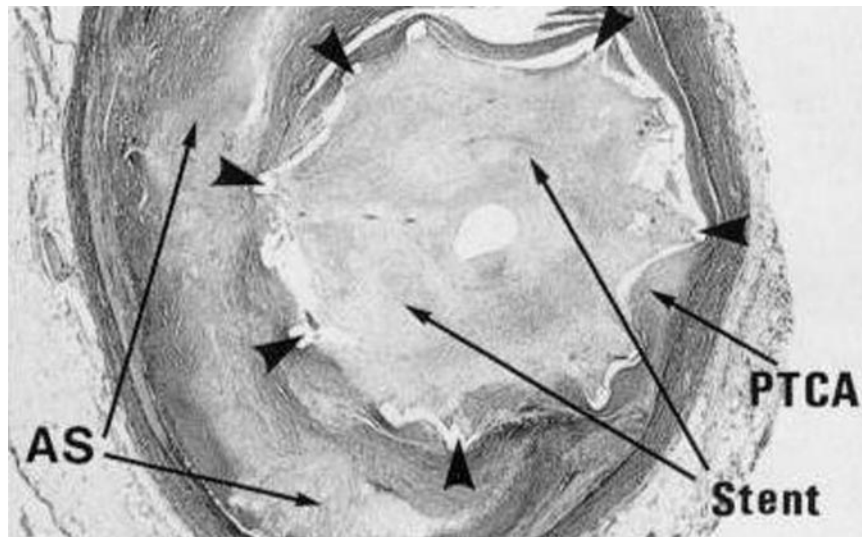


FIGURE 1. Segment of the right coronary artery 5 months after stent implantation to treat restenosis at the site of prior percutaneous transluminal coronary angioplasty (PTCA). There is exuberant formation of neointima related to the stent (Stent). The prior PTCA has also resulted in formation of neointima that is compact, rich in collagen, and compressed by the implanted stent (PTCA). The extent and histology of the displaced preexisting atherosclerotic plaque is also demonstrated (AS). (Reprinted with permission from *Circulation*.¹⁶)

cess. Activated platelets within superficial thrombi produce vascular smooth muscle cell mitogens and thrombin, which perpetuate and amplify smooth muscle cell migration and proliferation. Activated platelets also produce thromboxane A₂, a potent vasoconstrictor substance responsible for further platelet activation and aggregation, leukotrienes, and platelet-activating factor. At a later stage of endothelial erosion or plaque fissuring, circulating platelets are exposed to the thrombogenic subendothelium, including collagen and tissue factor, resulting in platelet adhesion, activation and aggregation, and local mural thrombosis.

Lipid deposition: Removal and sequestration of modified LDL cholesterol is an important protective response by macrophages after endothelial injury, but pathologic lipid accumulation by monocytes and vascular smooth-muscle cells in the subintimal space amplifies the inflammatory response and gives rise to foam cells, central elements of growing atherosclerotic plaques. Foam cells remain in plaques indefinitely. The formation of an atheroma appears to follow an evolution that includes growth and changes in the lipid pool, fibrous cap matrix, and inflammatory components. This evolution leads to a low-risk fibrous plaque and a high-risk vulnerable plaque.

Fibrous plaque: Advanced atherosclerosis is characterized by the development of a lipid core rich in foam cells and extracellular lipid, with a cellular fibrous cap of smooth muscle cells, extracellular proteoglycan and collagen matrix, and calcium deposition. This mature lesion may further progress and give rise to abluminal expansion and vascular remodeling, and then luminal stenosis, flow limitation, and regional myocardial ischemia.¹³

Vulnerable plaque: The fully developed components of any plaque may exhibit characteristics that predispose to sudden degeneration, including fissure, thrombosis, and spasm. These lesions are characterized by a large lipid pool, a thin fibrous cap, abundant inflammatory cells, diminished numbers of smooth muscle cells, and degenerate, depleted collagen. The lipid core of this mature plaque is highly thrombogenic, and rupture of the fibrous cap may precipitate thrombosis and acute partial or complete vessel occlusion.^{12,14} Inflammation, a hypocellular fibrous cap, and sparse collagen are important features of the vulnerable plaque that may predispose to rupture of the shoulder region at the site of maximal biomechanical stress.¹⁵ T-lymphocyte modulation of macrophage-derived foam cells leads to the local production of matrix metalloproteinases. These enzymes play a crucial role in the breakdown of the collagenous fibrous cap. This process is important in the genesis of acute coronary syndromes.

THE PATHOBIOLOGY OF RESTENOSIS

The superimposition of the mechanical and cellular consequences of PCIs on the abnormal substrate of atherosclerosis leads to a characteristic and distinct response to injury that can initiate and perpetuate restenosis (Figure 1).¹⁶ These important processes result in the abrupt onset of rapid but apparently self-limiting passivation, cellular proliferation, vascular remodeling, and variable luminal stenosis that progresses in a linear manner. Restenosis is not characterized by the chronic, punctuated progression that is typical of atherosclerosis, and furthermore, it is not

dependent on the concentration or composition of atherogenic plasma lipids.

Intimal injury: Intimal injury sustained at the time of coronary intervention results in variable degrees of endothelial denudation, exposure of the thrombogenic subendothelium, deep-fissuring thrombosis, and then inflammation.^{17–20} The initial responses consist of a layer of protein and platelets, followed quickly by mononuclear inflammatory cells. This is followed over weeks by smooth muscle cell proliferation, matrix deposition, and intimal growth. The degree of endothelial injury is an important predictor of vascular repair. For example, partial retention of endothelium within treated arteries may modulate cellular proliferation and reduce the extent of neointimal hyperplasia and restenosis.^{20,21} Perivascular implantation of endothelial cell grafts has been shown to reduce neointimal thickening in bovine and porcine models of carotid artery injury, supporting the critical role of endothelial cell paracrine regulation of vascular physiology.²²

The vascular injury caused by placement of a coronary artery stent differs from that of simple balloon angioplasty in at least 4 ways.²³ The struts of the stent cause focal deep vascular trauma, and the rate and duration of cellular proliferation and the contribution of mononuclear cells after stenting exceeds those of balloon injury.²⁴ Balloon angioplasty applies a transient strain to the vessel wall that is known to activate smooth muscle cells and modulate gene expression to amplify the proliferative phase of vessel repair.²⁵ These effects may be further potentiated by the prolonged mechanical strain of coronary artery stenting. The effect of residual foreign material after stent implantation includes chronic inflammation. This profound impact of an indwelling material has been clearly demonstrated in experimental systems with stents constructed from various polymer materials.²⁶

Inflammation: The inflammation described above is characterized by monocyte adherence and recruitment in response to intimal injury. At first, there are changes in the expression of activation-dependent adhesion receptors on smooth muscle cells (ICAM-1), neutrophils, and platelets (Mac-1), after exposure to the balloon-injured coronary artery plaque.²⁷ Once again, there is a significant correlation between the severity of vascular injury and the degree of inflammation and neointima formation, and a linear relation between the number of monocytes per unit area in an injured segment and the extent of arterial intimal growth.^{28,29} These important findings supporting the role of inflammation and leukocyte-mediated restenosis after intimal injury are further supported by the reduction in neointimal thickening in Mac-1 (CD11b/CD18)-deficient mice and after administration of a monoclonal antibody to this same leukocyte integrin in rabbits.^{30,31} C-reactive protein, a hepatic marker of the acute phase response, is a powerful predictor of both early and late outcome in patients undergoing single-vessel percutaneous transluminal coronary angioplasty (PTCA).³² These findings support the role of inflammation in the genesis of clinical restenosis and suggest that this pathologic process is markedly influ-

enced by the preprocedural degree of inflammatory cell activation.

Oxidative stress: Oxygen free radicals generated during vascular intimal injury increase the expression of cell adhesion molecules, activate the multifunctional transcription factor NF- κ B, and modulate the expression of many genes that control cellular proliferation.^{33,34} Preliminary trials have shown that antioxidant therapies may reduce restenosis in patients, and this effect may be achieved by improving both neointimal hyperplasia and, most importantly, constrictive vascular remodeling.^{35,36}

Adventitial scarring: An alternative, but not exclusive, theory of restenosis is supported by animal and intravascular ultrasound data suggesting that constrictive remodeling, including adventitial scarring, is responsible for luminal stenosis after nonstent coronary intervention.^{37–41} This may occur in response to adventitial injury at the time of balloon dilation, and this alternative theory is supported by the success of coronary artery stenting, a procedure that is known to induce profound neointimal thickening and smooth muscle cell proliferation, which represents the first interventional procedure able to maintain lumen caliber and reduce the incidence of restenosis.³ There is evidence that the degree of constrictive remodeling may be a function of endothelial dysfunction and collagen accumulation after balloon injury.⁴²

Thrombosis: Endothelial denudation exposes the thrombogenic constituents of the vascular subendothelium, promoting early platelet adhesion, activation, aggregation, and thrombus formation. At first, a monolayer of platelets lines the site of endothelial denudation after balloon angioplasty, whereas thick, platelet-rich mural thrombi form at the site of the struts and deep vascular injury after coronary stent implantation.

Activated and aggregating platelets produce a number of vascular smooth muscle cell mitogens, including platelet-derived growth factor (PDGF), fibroblast growth factor, epidermal growth factor, insulin-like growth factor, and transforming growth factor- β .^{8,43} Insulin-like growth factor and transforming growth factor- β also regulate extracellular matrix production and remodeling.⁴⁴ RPR101511A, an orally active PDGF-receptor tyrosine kinase inhibitor, reduces histologic intimal hyperplasia and preserves greater lumen size after PTCA in a porcine model.⁴⁵ Furthermore, preliminary data support the role of cilostazol, an antiplatelet agent, in the prevention of restenosis in patients.^{46,47} These data might support the role of platelet aggregation and mitogen elaboration in the mechanisms of smooth muscle cell migration and proliferation, and extracellular matrix production.

Thrombin, produced by activated platelets at the site of aggregation and platelet-thrombus formation, is a potent activator of circulating platelets, a chemoattractant for circulating monocytes, and directly stimulates the proliferation of vascular smooth muscle cells.^{48–50} Local and systemic delivery of low molecular weight heparin stimulates re-endothelialization

and inhibits smooth muscle cell proliferation after balloon angioplasty in rabbits.⁵¹ However, the efficacy of antithrombin agents in the prevention of smooth muscle cell proliferation and restenosis is not well defined and there is contradictory evidence from animal models.^{52–54} Clinical trials of systemic heparin and direct thrombin inhibitors have shown no effect on angiographic or clinical restenosis in patients.^{55–58}

Neointimal hyperplasia: Neointimal hyperplasia ultimately results from the migration and proliferation of vascular smooth muscle cells and their production of abundant extracellular matrix.¹⁷ This proliferative phase of vascular repair and restenosis occurs in response to injury, inflammation, platelet activation, and thrombosis, as described above. This phase is characterized by intimal migration of medial vascular smooth muscle cells, cellular proliferation, and extracellular matrix deposition and remodeling.⁴³ Several complex and redundant intracellular signals, including cyclic adenosine monophosphate, protein kinase C, protein kinase A, and calcium, mediate the effects of the aforementioned mitogens and cytokines in the activation of gene expression and the entry of the vascular smooth muscle cell into the cell cycle of proliferation.⁵⁹ Vascular smooth muscle cells of the synthetic phenotype and fibroblasts initially synthesize predominantly chondroitin sulfate and dermatan sulfate proteoglycans. As the remodeling process progresses, there is conversion of these proteoglycans to large fibrous bundles of type I collagen and elastin.⁴³

Vascular smooth muscle cell proliferation ceases once the site of injury is re-endothelialized and the normal antiproliferative actions of nitric oxide and heparin exert their influence on these activated smooth muscle cells.⁶⁰ Animal models suggest that this re-endothelialization occurs within 21–56 days, but a recent autopsy study of the tissue response to coronary stent implantation suggests that this process may take at least 3 months in humans.^{61,62}

After balloon injury and de-endothelialization in a rabbit model of restenosis, local delivery of L-arginine enhances inducible nitric oxide synthase production of nitric oxide by vascular smooth muscle cells, an effect that is accompanied by reduced monocyte binding and increased macrophage apoptosis.⁶³ This might explain why local intramural delivery of L-arginine can inhibit lesion formation after balloon angioplasty. It also highlights the role of endothelial denudation and loss of normal endothelial-cell paracrine function in neointimal hyperplasia and restenosis.⁶⁴

THE TIME COURSE OF ATHEROSCLEROSIS AND RESTENOSIS

Symptomatic atherosclerosis may take many decades to develop. The fatty streak is an inflammatory lesion of early atherosclerosis that is commonly found in the aortas of infants and children.^{65,66} The fibrous plaque is first seen in early adulthood, and the frequency and severity of the complications of this lesion of atherosclerosis correlate with the incidence and severity of a number of recognized risk factors, in-

cluding hyperlipidemia, hypertension, diabetes, smoking, and family history of atherosclerotic cardiovascular disease.⁶⁷

Atherosclerosis is commonly complicated by the consequences of acute and/or chronic limitations in organ blood flow. Plaque rupture, or endothelial denudation, with a variable amount of thrombus formation, may precipitate an acute coronary syndrome. These events occur most commonly in the fifth and sixth decades of life. This process is marked by periods of increased activity and instability, but the clinical expression is unpredictable and highly variable within any given patient population, and prolonged periods of relative quiescence are equally common. Similarly, patients with pathologically advanced disease may be entirely asymptomatic, whereas those with limited disease may have important adverse outcomes, including myocardial infarction and death from a ruptured plaque with occlusive thrombosis in a vessel that has an otherwise adequate lumen.

In contrast, the time course of restenosis after coronary intervention occurs over 3–18 months and is well described and more predictable than atherosclerosis. Acute iatrogenic mechanical injury, with or without the effects of a stent, determines the response, which is limited by recovery of normal endothelial control at the site of vascular injury. Interestingly, each intervened site in an individual patient has its own degree of response and rate of restenosis.

Serial angiography has defined the time course of restenosis after coronary angioplasty.^{68,69} The actuarial restenosis rate is 13% at 1 month, 43% at 3 months, and 53% at 1 year, with peak angiographic restenosis typically reached between the first and third months. Pathologic data from animal models and human autopsy series confirm that the site of injury is rendered quiescent and stable, in contrast to the periods of activity and instability that continue to complicate the life history of native atherosclerosis.

CONCLUSIONS

Percutaneous coronary interventions have revolutionized the effective management of ischemic syndromes in coronary artery disease and their symptoms. However, the superimposition of iatrogenic mechanical injury on coronary atherosclerosis initiates a new disease process that may complicate the patient's clinical course. Atherosclerosis is a chronic disease process that progresses over years and can be punctuated by periods of intense activity and nonlinear growth of many developing plaques at different sites and at different times. Restenosis is characterized by an abrupt onset and rapid progression with intense proliferative activity followed by stabilization and quiescence. The predominant cellular mechanisms that contribute to restenosis include thrombosis, vascular smooth muscle cell migration and proliferation, and adventitial scarring. Lipid accumulation is not characteristic of this proliferative lesion. Coronary stenting has increased the response to injury but has reduced restenosis by enlarging the lumen area.

Future efforts to reduce the sizeable number of

patients who will require repeat target vessel revascularization after PCI will include efforts to reduce platelet aggregation, thrombosis, inflammation, vascular smooth muscle cell proliferation and migration, and the sequelae of adventitial scarring. Promising new technologies include targeted medical therapies; novel stent design and material selection; and local delivery of radiation, nutrients, drugs, and genetic material. These efforts are important but will only benefit the intervened coronary segment. The rest of the coronary tree is subject to the very different pathologic processes that characterize atherosclerosis. This diffuse pathology requires an entirely different approach, including aspirin and aggressive risk-factor modification. Starting with the interventionalist, physicians need to keep these 2 very different pathologic processes in mind when initiating a treatment to better serve these patients.

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