Restenosis Following Arterial Reconstruction

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Each year more than 3 million patients undergo some form of arterial reconstruction and roughly one third will fail within months to years from a process termed restenosis. Restenosis, simply defined, is a recurrent blockage at the site of earlier vascular reconstruction, typically for atherosclerotic occlusive disease. While classically applied to recurrent blockages after angioplasty, the term has also been used to describe stenoses developing in virtually all forms of arterial reconstruction (e.g. bypass grafts, anastomoses, endarterectomy, stenting, atherectomy, etc.). Decades of research have produced an in-depth understanding of the structural basis of restenosis and the cellular and molecular events regulating specific contributing events. Unfortunately, clinical applications of experimental therapies have met with limited success in preventing restenosis in human beings.

The structural changes underlying restenosis include accumulation of new tissue within the artery wall and shrinkage of the artery wall at sites of reconstruction. These processes have been termed intimal hyperplasia and artery wall remodeling, respectively. The cellular and molecular basis of intimal hyperplasia has been explored in a number of animal models. The most extensively characterized model is the rat carotid balloon injury, as popularized by the Seattle group. They have defined four distinct stages or "waves" leading to neointima formation in normal arteries. These include: 1.) an initial wave of medial smooth muscle cell replication [24-72 hours]; 2.) migration of medial smooth muscle cells from the media across the internal elastic lamina to form a new intimal layer or "neointima" [4-7 days]; 3.) a second wave of replication in smooth muscle cells within the neointima [1-4 weeks]; and 4.) smooth muscle cell production of extracellular matrix material to further expand neointimal mass. This sequence of events begins within hours and concludes within 6 to 12 weeks at which point the neointima remains stable or regresses (Figure 1).

Each stage of intimal hyperplasia is regulated by unique but overlapping molecular events dominated by growth factors, cytokines, and proteases. For example, the first wave of replication is dependent upon basic fibroblast growth factor (bFGF) released from damaged cells while the second wave of replication (Stage 3) is not bFGF-dependent but driven by a separate set of growth factors. Cell migration (Stage 2) is stimulated in part by platelet-derived growth factor (PDGF A and B chains) and dependent upon matrix-degrading proteases (eg, MMPs) while Stage 4 is dominated by production of extracellular matrix molecules including collagen-I and various proteoglycans (eg, versican) and glycosaminoglycans (eg, hyaluronan). For a detailed review of intimal hyperplasia and its contribution to restenosis please refer to Schwartz SM. The intima: A new soil. Circ Res. 1999;85;877-9 and Schwartz SM, deBlois D, O'Brien ER. The intima. Soil for atherosclerosis and restenosis. Circ Res. 1995;77:445-65.

Despite extensive characterization of the mechanisms underlying intimal hyperplasia, experimental strategies to inhibiting neointima formation have generally failed to prevent restenosis in clinical practice. For instance, heparin derivatives and ACE inhibitors effectively limited intimal hyperplasia in rats and rabbits after balloon injury but both failed to prevent restenosis after coronary artery angioplasty in human beings. A number
of drugs and devices have met a similar fate, prompting reappraisal of experimental models and concepts of restenosis. Disparate results may be explained by one of three general problems. First, smooth muscle cell growth leading to intimal hyperplasia may be regulated differently in human beings than in non-primate species. This has been documented for heparin, which is quite effective at inhibiting mitogen-stimulated replication (eg, in response to PDGF-B) of rat cells in culture but not of baboon or human cells. This could explain why heparin reduced neointima formation after balloon injury in rats but not in baboons and why heparin failed to prevent restenosis in human angioplasty trials. Second, and probably more important than species differences per se, human atherosclerosis is very difficult to model. Few species develop lesions that truly depict the range of pathology present in atherosclerotic human arteries undergoing reconstruction. Thus, the contribution of the plaque to the process of restenosis is not well defined. Third, and in my opinion the most important reason that strategies targeting intimal hyperplasia have largely failed to prevent restenosis, is that other processes (eg, remodeling) contribute more to restenosis than accumulating neointimal mass.

Arterial remodeling has emerged over the past decade as the leading structural determinant of lumen narrowing after angioplasty. Remodeling refers to geometric redistribution of cells and matrix independent of net change in wall mass or cross-sectional area. Thus, cells and matrix reorganize to either increase wall diameter while decreasing wall thickness or to decrease wall diameter while increasing wall thickness. The concept of artery wall remodeling is not new. Physiologists have for decades championed remodeling as the pathological underpinning of hypertension, showing that resistance vessels in hypertensives undergo inward remodeling with reduced vessel diameter and wall thickening. Evidence implicating remodeling in restenosis is quite strong. Data from clinical trials of coronary stenting versus angioplasty alone showed that stents reduced the incidence of restenosis by ~15%. The metal stent scaffolding prevents the surrounding wall from remodeling inward so late lumen narrowing is due entirely to intimal hyperplasia. Stents reduced restenosis slightly despite the fact that stents lead to more neointima formation than angioplasty alone. Thus, stents maintain more of the initial gain in lumen diameter from angioplasty by preventing acute recoil and subsequent inward or constrictive remodeling. This provides more space to accommodate an exaggerated intimal hyperplasia response without substantially re-narrowing the lumen. Further evidence that remodeling contributes to restenosis came from animal models and then from clinical trials employing intravascular ultrasound (IVUS). IVUS allowed for artery wall cross-sectional imaging in human beings so that wall area and geometry could be documented immediately after angioplasty then repeatedly at the same location over time. This strategy demonstrated that lumen narrowing after angioplasty was caused primarily by changes in wall geometry (inward remodeling) rather than increases in wall mass (intimal hyperplasia). A number of investigators have confirmed this observation, estimating that remodeling accounts for 60-80% of the decrease in lumen area after angioplasty (Figure 2).

The cellular and molecular mechanisms of remodeling are yet to be defined. However, data are accumulating that suggest wall constriction at sites of reconstruction is in many ways analogous to wound healing in other tissues. Damage caused by angioplasty initiates a healing response that culminates in cell and matrix turnover and matrix remodeling and maturation that results in tissue shrinkage analogous to wound contraction. Research has thus focused on smooth muscle cell-matrix interactions, particularly the attachment of cells to matrix via cell-surface integrins (matrix receptors), and on matrix degradation and turnover by cell proteases such as the family of MMPs also implicated in aneurysm formation. The composition of new matrix elaborated at sites of injury may also influence smooth muscle cell behavior promoting or inhibiting
tissue shrinkage. Our own work suggests that specific matrix molecules such as the glycosaminoglycan hyaluronan can accelerate the reorganization and shrinkage of collagen matrix by smooth muscle cells. Investigations are underway in a number of laboratories to test the efficacy of integrin antagonists, protease inhibitors, and other agents likely to impact the remodeling process and thus improve restenosis.

**Figure 1. Traditional View: Restenosis from Intimal Hyperplasia.**

Angioplasty of a stenotic atherosclerotic artery acutely increases lumen area (black) by fracturing the atherosclerotic plaque (green) and stretching/tearing surrounding media (pink) and adventitia (orange). Injury induces smooth muscle cell replication, migration and matrix production, giving rise to neointima (yellow). Accumulation of excessive neointima leads to lumen encroachment and restenosis.

**Figure 2. Contemporary View: Restenosis from Inward Remodeling.**

Angioplasty of a stenotic atherosclerotic artery acutely increases lumen area (black) by fracturing the atherosclerotic plaque (green) and stretching/tearing surrounding media (pink) and adventitia (orange). Injury induces smooth muscle cell replication, migration and matrix production, giving rise to neointima (yellow). However, restructuring of new and existing cells and matrix within the artery wall results in tissue shrinkage and a change in wall geometry, independent of new wall mass. If the decrease in wall diameter is substantial, lumen encroachment occurs independent of neointima formation.
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For information on restenosis and other cardiovascular diseases use the search engine at http://www.theheart.org.