Pathophysiology of Coronary Artery Restenosis

Robert S. Schwartz, MD, Timothy D. Henry, MD

Minnesota Cardiovascular Research Institute, Minneapolis Heart Institute Foundation, Minneapolis, MN

All forms of percutaneous coronary intervention confer injury on the vessel. The arterial response to that injury is the basis for long-term outcome. The stent prevents remodeling but enhances neointimal formation, and it is this neointima that is principally responsible for in-stent restenosis. Neointima forms in response to thrombus, inflammation, intimal and medial dissections, and elastic recoil of the arterial wall when a stent is not placed. Current efforts to solve restenosis center on limiting neointimal hyperplasia through drug-eluting stents and vascular brachytherapy. This article reviews arterial injury during revascularization in both patients and animal models and discusses the nature and formation of neointimal hyperplasia.[Rev Cardiovasc Med. *2002;3(suppl 5):S4–S9*]

Key words: Coronary artery • Stents • Restenosis • Neointima • Thrombus

Injury results from coronary artery stenting and angioplasty as a very small lumen, typically less than 0.5 mm, is enlarged rapidly to 3 mm or more. The coronary artery responds to this injury over a long period, typically 3 or more months. As new stent and revascularization technologies become available, the restenosis problem within stents is high on the problem list but may at last be yielding to therapies such as brachytherapy and drug-eluting stents. Neointima is now key to in-stent restenosis. It arises from multiple pathophysiologies including thrombus, inflammation, intimal and medial dissections, and arterial-wall recoil prior to the advent of stents.[1,2]

Neointimal hyperplasia from arterial injury is of varying thickness, and the adventitia thickens also, becoming fibrotic. This latter factor frequently causes vessel shrinkage, or negative remodeling, and is a principal cause of restenosis when a stent is not present to resist the constriction.[3–5]

This article reviews restenosis and arterial injury from both patient and animal model perspectives, with special emphasis on neointimal formation.

The Coronary Artery and Injury: A Clinical Problem

Restenosis risk factors include method (stented or not), lesion location (the left anterior descending is more susceptible to restenosis), diabetes, residual stenosis, and number of stents. Many systemic drug trials have been ineffective, including trials of antiplatelet agents[6], anticoagulants[7], corticosteroids[8], angiotensin-converting enzyme inhibitors[9], statins[10], calcium channel blockers[11], and most recently oral tranilast in the Prevention of Restenosis with Tranilast and Its Outcomes (PRESTO) trial.[12,13] Other agents that have also failed include hirudin[14] and angiopeptin.[15]

The intracoronary stent improves long-term minimum luminal diameter and lowers restenosis rates.[4] However, success with coronary stents is due solely to geometric considerations through achieving larger arterial lumina, thus allowing more late loss from neointima without creating critical stenoses. A bare (non–drug-eluting) stent possesses little biologic activity against neointima and indeed stimulates neointimal thickening compared to balloon angioplasty.[16] It is only with the advent of brachytherapy, and most recently drug-eluting stents, that restenosis may finally be controlled through elimination of neointimal overgrowth and negative remodeling.

Neointimal Hyperplasia Is a Pathophysiologic Process Separate from Atherosclerosis

Antirestenosis efforts focus on neointimal reduction in these days of frequent coronary artery stenting. Coronary neointima is histopathologically distinct from most primary atherosclerosis and as such is a fundamentally different pathophysiologic process. Microscopically, the atherosclerotic lesion shows disruption and replication of the internal elastic lamina, spindle and smooth cell proliferation, interstitial fibrosis, intracellular and interstitial lipid accumulation, fibrin deposition, calcification, hemorrhage, thrombosis, capillary proliferation and macrophages.[1,17] Although many atherosclerotic lesions are endothelialized continuously with adjacent vascular endothelium, this endothelium is often completely absent or dysfunctional.

Coronary neointima is histopathologically distinct from most primary atherosclerosis.

Coronary Arterial Injury from Angioplasty and Stenting

The arterial wall sustains severe stretch injury with frequent laceration from balloon angioplasty and stenting in both animal models and in patients (Figure 1). How much neointima forms in the coronary artery undergoing revascularization? In a typical 3 mm coronary artery, the neointimal thickness corresponding to a 50% diameter restenotic lesion is about 0.75 mm. All angioplasty cases develop neointima and thus develop restenosis to varying degrees. It is only those cases with the most neointima that develop in-stent restenosis.

Angioplasty mechanisms were earlier considered to be due to "plaque compression" or movement for luminal enlargement. Subsequent histopathologic studies documented that this was rarely true. Plaque splitting occurs in more than 90% of arteries undergoing angioplasty. The splitting occurs in the plaque or

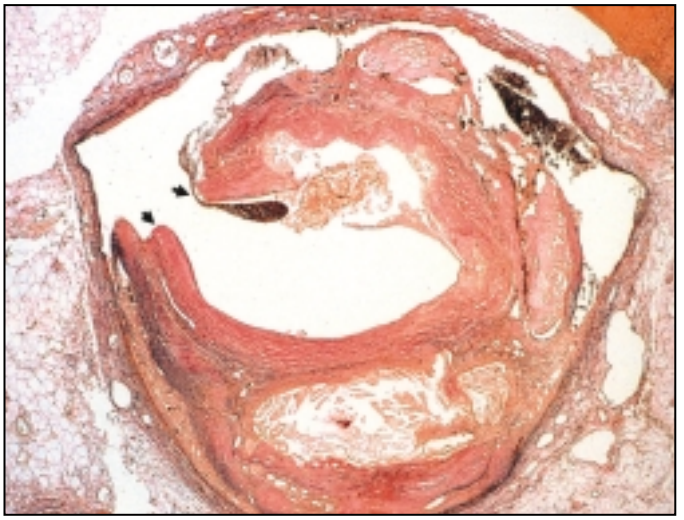


Figure 1. *Acute pathology of a patient who underwent balloon coronary angioplasty without stent placement. Note the dissection across the superior border of the artery (arrows), and laceration of the vessel at the plaque site. Elastic van Gieson stain, magnification x 10. Image courtesy Dr. William D. Edwards, Mayo Foundation.*

the media itself in eccentric lesions. The most common histopathologic finding in balloon angioplasty is plaque or intimal laceration (Figure 2). In eccentric lesions, splitting occurs most commonly at the junction between the plaque and the normal arterial wall. This site, where the highest stress concentration occurs, is expected from mechanical engineering principles to incur damage. The fracture length is quite variable, appears unpredictably, and is uncontrollable. Frequently the fracture extends through the internal elastic lamina into the media but rarely to the adventitia. Medial laceration is involved in about 80% of selective cases.[17]

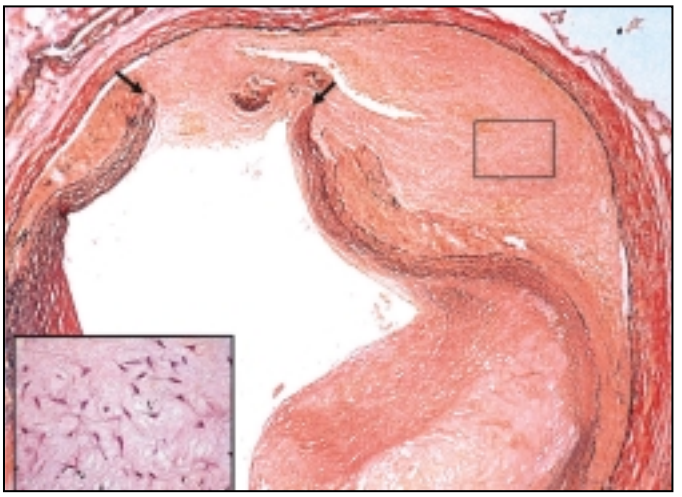


Figure 2. *Pathology of a patient 30 days following coronary angioplasty. The laceration is obvious (arrows), but has healed with neointimal hyperplasia. Remodeling has also occurred, where the vessel size is decreased due to fibrosis of the adventitia. Typical neointimal hyperplasia is seen with a highly cellular character (representative cellular neointima, inset) Elastic van Gieson stain, magnification x 10. Image courtesy of Dr. Renu Virmani, Armed Forces Institute of Pathology.*

Coronary Restenosis and Remodeling

In addition to neointimal formation, coronary arteries change size, undergoing "remodeling" following coronary angioplasty. These changes are known as negative remodeling, which is a result of adventitial thickening resulting in vessel shrinkage.[4,18,19] This is also due to arterial injury. Stenting prevents shrinking or negative remodeling, although the stent induces greater neointimal formation.[5]

Vascular Response to Injury: Histopathologic Features of Neointimal Development

The role of thrombus in vascular response to injury remains only partially understood. Hemostasis is critical for interaction with the injured vessel wall, but will be only briefly summarized here.

Thrombus formation at the arterial injury site is complex, involving both positive and negative feedback that is only poorly understood. Conceptually, rapid yet safe sealing at vascular injury sites has very stringent requirements. Evolutionarily vascular injury and sealing are fundamental for species survival. The hemostatic plug must form within minutes yet must not occlude the vessel that sustains only minor injury. The hemostatic process must remain localized, remaining only at the arterial injury site. Thrombus propagation to distal sites from the primary injury focus is potentially dangerous, and thus spatial control is critical. If an artery is completely transected, complete sealing must occur, involving assistance from other processes such as vasospasm.

Clinical diseases from failure of hemostasis overwhelmingly occur on the side of too vigorous thrombosis rather than bleeding diatheses. This concept is manifested by the high prevalence of myocardial infarction, strokes, emboli, and resulting ischemia to vital organ systems.[20,21] The hemostatic plug becomes permanent and replaced with tissue. This tissue itself is the neointimal tissue that goes on to vessel obstruction with in-stent restenosis. This histopathologic event, evolving from thrombus to neointima, has been examined in the injured porcine coronary artery. The cellular events from thrombus to neointima are summarized by the stages described below.

Stage I. Thrombotic Phase: Days 0-3—Thrombus Formation Following Injury

This stage consists of rapid thrombus formation. The initial response to arterial injury is explosive activation, adhesion, aggregation, and platelet deposition. The platelet thrombus may frequently be large and can grow large enough to occlude the vessel, as occurs in myocardial infarction. Within 24 hours, fibrin-rich thrombus accumulates around the platelet site. Two morphologic features are prominent: 1) platelet/fibrin, and 2) fibrin/red cell thrombus. The platelets are densely clumped at the injury site, with the fibrin/red cell thrombus attached to the platelet mass.

All angioplasty cases develop neointima and thus develop restenosis to varying degrees.

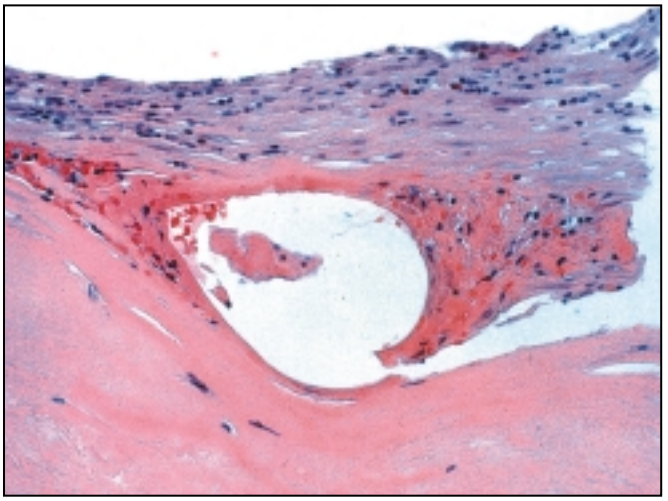


Figure 3. *Neointima forming at a stent site from a saphenous vein graft in a patient 19 weeks after stent placement. Note the high cellularity of the neointima and virtual acellularity in the vein graft itself. The cellularity consists of myofibroblasts and inflammatory cells including macrophages and lymphocytes. This image suggests the ability of such neointimal cells to migrate into regions of acellular media to heal a stent segment. The healing is occurring from the luminal side first. Hematoxylin/Eosin stain, magnification x 25. Image courtesy of Dr. Gary Roubin, Lenox Hill Hospital, New York.*

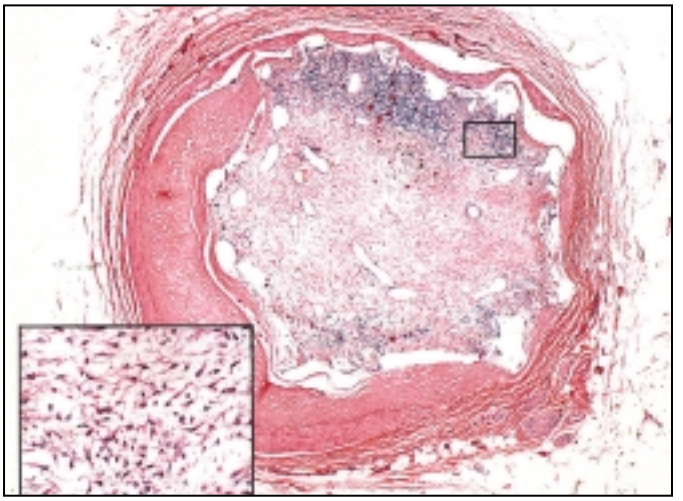


Figure 4. *Human coronary artery several months after stent placement. The artery is now totally occluded by neointimal hyperplasia, likely developing from an occluding thrombus as evidenced by the neovascularity within the neointima. Stent struts are seen around the circumference of the lumen. The neointimal hyperplasia has a significant inflammatory component (inset). Hematoxylin/Eosin stain, magnification x 10. Image courtesy of Dr. Renu Virmani, Armed Forces Institute of Pathology.*

Stage II. Recruitment Phase: Days 3-8

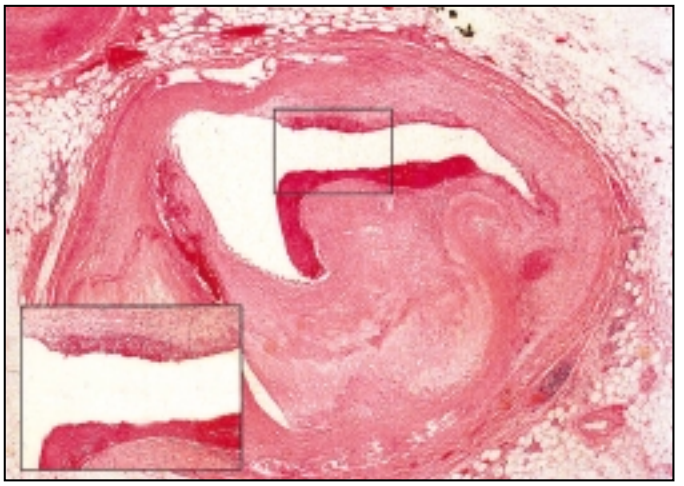
The thrombus at arterial injury sites develops an endothelial cell layer. It is unclear whether the cells are truly endothelial cells despite their histopathologic appearance. Shortly after the endothelial cells appear, an intense cellular infiltration occurs. The infiltration is principally monocytes that become macrophages as they leave the bloodstream and migrate into the subendothelial mural thrombus. Lymphocytes also are present, and both types of cells demarginate from the bloodstream. This infiltrate develops from the luminal side of the injured artery, and the cells migrate progressively deeper into the mural thrombus.

Stage III. Proliferative Phase: Day 8 to Final Healing

Actin-positive cells colonize the residual thrombus from the lumen, forming a "cap" across the top of the mural thrombus in this final stage. The cells progressively proliferate toward the injured media, resorbing thrombus until it is completely gone and replaced by neointimal cells. At this time the healing is complete. In the pig this process requires 21–40 days, depending on residual thrombus thickness.

Smooth muscle cell migration and proliferation into the degenerated thrombus increases neointimal volume, appearing greater than that of thrombus alone. The smooth muscle cells migrate from sites distant to the injury location, and the resorbing thrombus becomes a bioabsorbable "proliferation matrix" for neointimal cells to migrate and replicate. The thrombus is colonized at progressively deeper levels until neointimal healing is complete.

Figure 5. *Native coronary artery about 10 months after balloon angioplasty, showing mural thrombus accumulating on both the upper and lower luminal surfaces. Note that mature neointima has already formed beneath the thrombus. Inset: higher-power view of the neointima forming from the layered mural thrombus. This image suggests that neointima in this patient is forming from layered mural thrombus, also colonized by macrophages and lymphocytes. Hematoxylin/Eosin stain, magnification x 12.*



Histopathologic Results from Patients: Stenting

Healing progresses in the human coronary artery in a manner similar to that of the pig.[21] Figure 3 is from a surgically removed saphenous vein graft. It shows mural thrombus around the stent strut becoming colonized by inflammatory cells in a direction from the lumen toward the adventitia. Figure 4 shows a stented section from a human coronary artery several months after stent implantation. The section shows total occlusion by neointima that was likely from a thrombus. Inflammatory cells are also present. Figure 5 shows a similar process from a native human coronary artery following angioplasty. Both sides of the lumen contain mural thrombus being organized abluminally. A difference in age is apparent for these mural thrombi. The lower surface appears less organized; it probably occurred more recently than the thrombus on the upper surface. Thrombus organization is not always found in all sections. Thrombus is sufficient to cause neointima but may be found in varying degrees and may not be necessary for neointima to occur.

Several studies chronicle stent histopathology in patients. Farb and colleagues examined human stent histopathology and reported results over time from implant. Stents were examined from patients at a mean of 3 days, 4 to 11 days, and 12 to 30 days; 11 stents were examined after 30 days.[17] Results proved plaque compression by stent struts in 94% of cases. A plaque lipid core was present and the core invaded by stent struts in 26% of cases. Platelet-rich thrombi occurred on stent struts and were related to the duration of stent implant, similarly to animal models. Fibrin-containing thrombi also occurred at stent struts, especially soon after stenting. Neutrophils occurred in 79% of stents implanted for 3 days, 83% at 4 to 11 days, 72% at 12 to 30 days, and in no stents implanted for more than 30 days. Conversely, chronic inflammatory cells were mainly lymphocytes and macrophages, found around stent struts at all time points.

Medial injury occurred in about 30% of stent strut sites, and medial compression without laceration of the internal elastic lamina in 55%. In 15%, the media was completely uninjured. The mean arterial injury score when medial damage occurred was 0.73. Neointimal thickness at stent strut sites was greater at sites with medial injury than with struts contacting plaque.

Inflammation in stented coronary arteries 3 days after implant depended on underlying arterial wall morphology. Struts in contact with fibrous plaque were inflamed in only 3% of cases, compared with 44% inflamed when struts were embedded in lipid core, and in 36% of struts in damaged media. No stent less than 11 days old had neointima present. Neointima was present in 45% of patients observed between days 12 and 30 after stent implantation.

Most cardiovascular pathologists agree that stents endothelialize in humans, though this process is not necessarily complete by 1 month. Leukocytes, platelets, and fibrin are present early, and by 3 months stent coverage by endothelium is complete, with a developing neointima. At later periods (10 months), atherosclerotic plaque may occur at stent sites, manifested by foam cells and cholesterol crystals.

Human Stents Compared with Experimental Animal Models

The thrombus at stent sites in porcine restenosis models is associated with inflammatory cells.[22] Subsequent healing in the porcine model closely reflects findings in human coronary stenting soon after implantation. Vascular injury in normal stented pig arteries differs considerably from human atherosclerotic arteries. Oversized stents in normal pig arteries produce neointima through direct medial injury. Humans, by contrast, show about 60% of stent struts contacting atherosclerotic plaque rather than media. Moreover, stent struts cause medial compression and damage in about one third of cases. Experimental animal model studies suggest important relationships among inflammation,

Main Points

- All forms of percutaneous coronary revascularization impose injury on coronary arteries.
- Neointimal hyperplasia is the principal cause of in-stent restenosis and forms in proportion to the degree of injury.
- Neointima develops through processes of thrombus, deposition, inflammation, smooth muscle cell and fibroblast migration, and cellular proliferation.
- Restoration of the "healthy artery" at revascularization sites may be the signals that cease neointimal growth.

vascular injury, and neointimal growth. These results have been at least partially replicated in patients, specifically among inflammation and neointimal growth.

Conclusions

Revascularization strategies impose injury on the coronary artery. This injury is unavoidable because of the desired diameter changes to alleviate tight stenoses. The angioplasty balloon lacerates the plaque and vessel. Balloon expansion creates fissures and tissue dissections. Arterial stenting may cause fissure planes to be spread more widely than if vessel recoil were not prevented by the stent. The important common denominator appears to be injury independent of revascularization method: removal of vascular endothelium and exposure of deep tissue components to flowing blood. Potent repair mechanisms that are basic to survival of the species are triggered by these occurrences.

Morphology after coronary stent placement demonstrates thrombus formation and acute inflammation early after deployment, with subsequent neointimal growth. Inflammation early after stenting is associated with medial injury and lipid core penetration by stent struts. Medial damage and stent oversizing relative to the reference arterial lumen are associated with increased neointimal growth.

An important future goal is to understand better the vascular response to injury at both cellular and molecular levels. As brachytherapy and drug-eluting stents appear useful in solving restenosis, these therapies can also be better targeted to the neointima within stents. Results from animal models appear to mimic those of human studies, but differences must be better understood, and the implications respected. ■

References

1. Virmani R, Farb A. Pathology of in-stent restenosis. *Curr Opin Lipidol*. 1999;10:499–506.
2. Schwartz R, Holmes D, Jr, Topol E. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. *J Am Coll Cardiol*. 1992;20:1284–1293.
3. Mehran R, Mintz GS, Popma JJ, et al. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. *Am J Cardiol*. 1996;78:618–622.
4. Mintz GS, Kent KM, Pichard AD, et al. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. *Circulation*. 1997;95:1791–1798.
5. Mintz GS, Kent KM, Pichard AD, et al. Intravascular ultrasound insights into mechanisms of stenosis formation and restenosis. *Cardiol Clin*. 1997;15:17–29.
6. Webster MW, Chesebro JH, Fuster V. Platelet inhibitor therapy. Agents and clinical implications. *Hematol Oncol Clin North Am*. 1990;4:265–289.
7. Thornton MA, Gruentzig AR, Hollman J, et al. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. *Circulation*. 1984;69:721–727.
8. Pepine CJ, Hirshfeld JW, Macdonald RG, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. *Circulation*. 1990;81:1753–1761.
9. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. *Circulation*. 1992;86:100–110.
10. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *Eur Heart J*. 1999;20:58–69.
11. Corcos T, David PR, Val PG, et al. Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J*. 1985;109:926–931.
12. Holmes D, Fitzgerald P, Goldberg S, et al. The PRESTO (prevention of restenosis with tranilast and its outcomes) protocol: a double-blind, placebo-controlled trial. *Am Heart J*. 2000;139(1 pt 1):23–31.
13. Gopalan R, Goldberg S. Tranilast in the therapy of coronary artery disease. *Curr Interv Cardiol Rep*. 2000;2:149–156.
14. Serruys PW, Herrman JP, Simon R, et al. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. Helvetica Investigators. *N Engl J Med*. 1995;333:757–763.
15. Rosanio S, Tocchi M, Patterson C, Runge MS, et al. Prevention of restenosis after percutaneous coronary interventions: the medical approach. *Thromb Haemost*. 1999;82 (suppl 1):164–170.
16. Mintz G, Popma J, Pichard A, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation*. 1996;94:35–43.
17. Farb A, Sangiorgi RS, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. *Circulation*. 1999;99:44–52.
18. Schwartz RS, Topol EJ, Serruys PW, et al. Artery size, neointima, and remodeling: time for some standards. *J Am Coll Cardiol*. 1998;32:2087–2094.
19. Sangiorgi G, Taylor AJ, Farb A, et al. Histopathology of postpercutaneous transluminal coronary angioplasty remodeling in human coronary arteries. *Am Heart J*. 1999;138(4 pt 1):681–687.
20. Schwartz RS, Murphy JG, Edwards WD, et al. Restenosis occurs with internal elastic lamina laceration and is proportional to severity of vessel injury in a porcine coronary artery model. *Circulation*. 1990;4:III–656.
21. Schwartz R, Holmes DJ, Pigs, dogs, baboons, and man: lessons for stenting from animal studies. *J Interven Cardiol*. 1994;7:355–368.
23. Bayes-Genis A, Kantor B, Keelan PC, et al. Restenosis and hyperplasia: animal models. *Curr Interv Cardiol Rep*. 2000;2:303–308.