The long-term vascular response to coronary stenting can involve transformation of an otherwise benign neointima to one that resembles de novo atherosclerosis in an unstented vessel. The neointima may be infiltrated by foamy macrophages, undergo neovascularization, and develop unstable thin-cap fibroatheromas (TCFA) that contribute to neointimal disruption and thrombus formation in situ, similar to what is observed in the presence of a vulnerable plaque. This process is known as neoatherosclerosis and is independently associated with mean in-stent neointimal thickness (odds ratio, 2.53; 95% confidence interval, 1.96–3.27; P<0.001). When present, neoatherosclerosis leads to high rates of target lesion revascularization and stent thrombosis.

There has been growing interest in the use of intravascular optical coherence tomography (OCT) imaging to examine neointimal tissue characteristics and detect neoatherosclerosis in bare metal stents (BMS) or drug-eluting stents (DES). Several small clinical studies using this approach found that early (<6 months) after BMS implantation, the neointima was thin and homogeneous; however, after 5 years, the neointima contained lipid pools and microvessels with areas of neointimal disruption consistent with neoatherosclerosis. Similar neoatherosclerotic changes have been observed in DES neointima, although the overall lipid content is reportedly higher than what was seen in BMS. In one study of 42 patients with BMS implanted >1 year identified fragments of atherosclerotic plaques that included TCFA, foamy macrophages, and cholesterol crystals in the aspirates. Although it is not known whether or not the thrombus was retrieved from within the stent or an adjacent area, these findings add strength to the argument that in-stent neoatherosclerosis behaves the same as unstable atherosclerotic plaques.

Understanding the cellular mechanisms involved in neoatherosclerosis has led to a focus on the endothelium. A functional endothelium is key to preventing neoatherosclerosis, and this point was ably demonstrated by an experiment performed in normocholesterolemic rabbits implanted with a β-emitting stent. At 6 and 12 months, there was evidence of neoatherosclerosis with neointimal infiltration of inflammatory cells, foam cells, and calcification that occurred in the setting of poor reendothelialization. Because this model does not develop atherosclerosis in the absence of a high cholesterol diet, the in-stent lesions were determined to be neoatherosclerosis that was attributable to the lack of a functional endothelium. This is not surprising as early studies in the era of balloon angioplasty demonstrated that the regenerated endothelial cells are structurally and functionally abnormal. These cells were irregularly sized, did not align in the direction of blood flow, and were functionally impaired with abnormal endothelium-dependent vascular reactivity.
Based on these observations, it should be expected that after stent placement the regenerated endothelium would be functionally incompetent. These regenerated cells are likely to have lost many of their typical atheroprotective features and have incomplete or poorly formed cell–cell junctions that are permissive for lipid or inflammatory cell migration into the vessel wall.8,15

Several strategies have been investigated as mechanisms to restore the endothelium and, thereby, prevent neointimal thickening. The combination DES–endothelial progenitor cell capture stent has been evaluated as a mechanism to improve reendothelialization. Although a randomized trial indicates that these stents are safe and noninferior to paclitaxel-eluting stents, there are no long-term intravascular studies to determine whether or not they prevent neointimal thickening. This seems unlikely as current preclinical evidence confirms that regenerated endothelial cells originate from adjacent cells and not from endothelial progenitor cells suggesting that the main benefit of the combination stent may extend beyond restoring the endothelial monolayer.16,17 Drug-coated balloons, which avoid the proinflammatory effects of stent struts and polymers, may also be insufficient to prevent neointimal thickening. In fact, OCT performed 9 months after treatment with a drug-coated balloon for DES in-stent restenosis revealed a distinct heterogeneous pattern in the neointima with bright speckled structures consistent with macrophage infiltration and neointimal thickening.18

To address the issue of neointimal thickening, efforts need to focus on methodologies to promote reendothelialization with functional endothelial cells. The first step toward accomplishing this goal is to identify the phenotypic differences between normal and regenerated endothelium at a molecular, metabolic, and genetic level. Investigators have already started to perform gene-profiling studies comparing native and regenerated endothelial cells in preclinical models. In one study, normal and regenerated endothelial cells were isolated from hypercholesterolemic pigs 28 days after balloon angioplasty of the left anterior descending coronary artery and examined using gene expression microarrays. This experiment identified 5 genes with atherosprotective functions that were downregulated in the regenerated cells while another 9 proatherogenic genes were upregulated.19 Information derived from this and other deep phenotyping studies could be used further to identify genes or proteins that could be targeted for genetic manipulation to restore normal endothelial function. In addition, profiling studies should take into account the effects of antiproliferative drugs eluted from stents on the endothelium. This becomes an important consideration as recent work has shown that normal endothelial cells exposed to sirolimus become dysfunctional and have impaired barrier function leading to increased vascular permeability.20 The second part of the equation is to determine the best mechanism to repopulate the stent luminal surface with competent endothelial cells and prevent neointimal thickening. This could be accomplished by delivery of fully functional cells by coating a stent with an endothelial cell-specific antibody (ie, von Willebrand factor or vascular endothelial-cadherin) coupled with stop-flow infusion of genetically engineered endothelial cells (based on gene-profiling studies) that are expanded ex vivo and infused immediately after stent placement. Another plausible method is to generate a stent, such as a bioabsorbable self-expanding platform (to avoid crush injury to the cells) that is prepopulated with a layer of endothelial cells. Similarly, a modified balloon delivery system could also be used to adhere functional endothelial cells to the luminal surface. Clinical realization of these strategies will require that we continue to apply advances made in basic endothelial biology to vascular scaffold design to limit neointimal thickening and prevent this mechanism of stent failure.

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References


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