Endothelial Recovery
The Next Target in Restenosis Prevention

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In this world there are only two tragedies. One is not getting what one wants and the other is getting it.
—Oscar Wilde

By most accounts, the field of interventional cardiology appears to have achieved one of its most elusive milestones, the virtual eradication of restenosis. In the present issue of Circulation, however, Hedman and colleagues report the results of a pilot study of gene therapy with vascular endothelial growth factor (VEGF) for restenosis prevention. Are these authors attempting to develop a treatment for a disease that no longer exists? Or is it possible that the mounting exuberance anticipating the release of drug-eluting stents is ignoring a major liability of these otherwise promising therapies?

AUGMENTED SMC PROLIFERATION

As a result, intense effort has been successful in reducing neointimal lesion formation. In both of which have been shown to reduce the incidence of restenosis after primary coronary stenting. In both cases, a strategy targeting proliferating VSMCs at the site of injury has been successful in reducing neointimal lesion formation. The early success of these interventions, however, has exposed a potential liability of an indiscriminate antiproliferative approach for restenosis prevention.

The fate of the endothelium in humans after radiation or drug-eluting stent is uncertain at present, but evidence exists to suggest that endothelial recovery may be perturbed. The initial applications of intravascular brachytherapy were complicated by a significant incidence of stent thrombosis occurring up to 9 months after the revascularization procedure. Subsequently, the incidence of late thrombosis was shown to be reduced by extending the duration of dual antiplatelet therapy for 6 to 12 months. These findings imply that endothelial recovery was inhibited by the antiproliferative approach, which, although intended to prevent VSMC proliferation, also may have inhibited proliferation of endothelial cells (ECs). This possibility is substantiated by studies in animals that reveal protracted deendothelialization in irradiated arteries. The apparent inhibition of reendothelialization, manifest as late stent thrombosis, observed after brachytherapy has only been rarely documented after implantation of rapamycin- or paclitaxel-eluting stents, but this may be a reflection of the fact that prolonged dual antiplatelet therapy is standard treatment after deployment of these devices. Moreover, recent data have revealed direct inhibition of reendothelialization by paclitaxel and inhibition of EC proliferation by rapamycin.

The extent and duration of inhibition of endothelial recovery that result from intravascular radiation or antiproliferative drug-eluting stents, as well as the long-term consequences, remain to be defined at this time; however, the impairment of functional endothelial recovery resulting from these therapies may have undesirable long-term consequences.

In this context, we and others have considered an alternative hypothesis: that stents that develop intimal thickening, as well as a portion of restenosis lesions that originate in nonstented arteries after PTCA, may result, in part, from belated reendothelialization. Previous studies carried out in a variety of animal species have repeatedly shown that exten-
sive endothelial denudation of the artery wall promotes neointimal thickening. Because it is difficult to achieve extensive EC denudation without injuring the underlying media, it has been difficult to establish with certainty that the loss of endothelial integrity per se constitutes the sole and/or primary basis for neointimal thickening. Nevertheless, at least 4 studies in the rat model of arterial balloon injury have clearly established an inverse relationship between endothelial integrity and SMC proliferation.

Data on the relationship between endothelial integrity and neointimal thickening in human arteries, though limited, are consistent with the results of animal experiments. Davies et al harvested coronary arteries from explanted hearts of 6 transplant recipients and found that the severity and extent of EC defects varied directly with the severity and extent of intimal disease. Schwarcz et al found foci of EC defects varied directly with the severity and extent of intimal disease. Schwarcz et al found foci of EC defects varied directly with the severity and extent of intimal disease. Schwarcz et al found foci of EC defects varied directly with the severity and extent of intimal disease. Schwarcz et al found foci of EC defects varied directly with the severity and extent of intimal disease.

These studies support the notion that certain functions of the endothelium—including barrier regulation of permeability, thrombogenicity, and leukocyte adherence, as well as production of growth-inhibitory molecules—are critical to prevention of luminal narrowing by neointimal thickening. This significance of the antithrombotic function of the endothelium has been highlighted most recently by the finding that selective inhibition of the tissue factor pathway by a gene therapy approach effectively inhibits restenosis. The role of the endothelium in excluding leukocyte trafficking has been underscored by studies suggesting significant participation of inflammatory cells in the pathogenesis of neointimal lesions.

Advances in vascular biology and molecular medicine have opened the door to a new era in the prevention of restenosis, providing genetic interventions to modulate the response to injury in the vessel wall. Early investigations into the realm of cardiovascular gene therapy focused on the ability of angiogenic cytokines to accelerate reendothelialization, improve endothelial function, and significantly reduce intimal proliferation in models of balloon-induced arterial injury. Capitalizing on the advent of stent technology capable of drug delivery, we have recently shown that gene-eluting stents coated with phVEGF-2 naked plasmid DNA accelerate reendothelialization and inhibit neointimal proliferation in a hypercholesterolemic rabbit iliac angioplasty model.

In the present issue of Circulation, Hedman et al report the provocative results of a phase II, randomized, placebo-controlled, double-blind study designed to test the feasibility, tolerability, and efficacy of VEGF gene therapy to prevent restenosis after coronary stenting. Thus, another step toward ameliorating, rather than perturbing, the biology of the artery wall as a restenosis prevention strategy has been taken.

The overall restenosis rate in this study was surprisingly low at 6%, virtually precluding the detection of a difference among treatment groups. This might be related to the low-risk profile of the patient population, large reference lumen diameter, and moderate percentage diameter stenoses. Nevertheless, the results establish feasibility and provide safety data about the use of both naked DNA and adenovirus encoding for VEGF. The safety data are especially important in the wake of recent reports suggesting that angiogenic cytokines can accelerate atherogenesis in certain animal models. Celletti et al reported increased fatty streak formation and plaque vascularity after VEGF administration in hyperlipidemic animal models. In contrast, the present report by Hedman et al adds to a growing literature substantiating the safety and potential efficacy of angiogenic agents, administered as recombinant proteins or as gene therapy, in patients with advanced atherosclerosis (reviewed in Losordo and Kawamoto). This apparent discrepancy may be explained by the differing role of angiogenesis in nascent atherosclerosis in the animal models versus the established disease in patients. In the animals, the earliest stage of atheroma formation can be influenced by modulating angiogenesis. In patients with well-established disease, there is currently no evidence that this is the case.

The “endothelial injury/dysfunction” concept and its pathophysiological relationship to atherosclerosis have been propelled by identification of measurable deficiencies in endothelium-dependent functions such as NO production in human atherosclerotic arteries and acceleration of atheroma formation after chemically or mechanically induced endothelial dysfunction. Delinquent reendothelialization has a permissive, if not facilitatory, impact on SMC proliferation, a relationship that has been attributed to certain endothelial functions, including barrier regulation of permeability, production of growth-inhibitory molecules, thrombogenicity, and leukocyte adherence, all of which may be critical in the prevention of intimal/neointimal proliferation. This concept has led to the development of new strategies directed to provide endothelial protection in veins used for bypass surgery; to accelerate reendothelialization after balloon-induced arterial injury; and to facilitate endothelialization of prosthetic conduits or endovascular stents. The capabilities of certain cytokines to serve as mitogens for ECs in vitro suggest that such molecules might be exploited to accelerate reendothelialization after the injury induced by natural plaque rupture or mechanical endovascular devices. VEGF has the capability of modulating qualitative aspects of EC biology that could be contributory to the maintenance and repair of the endothelium, as evidenced by the finding of the fms-like tyrosine kinase receptor in the mature (quiescent) endothelium of adult organs. Consistent with this notion, VEGF directly increases NO release by ECs, confirming VEGF’s role as a determinant of endothelial maintenance and repair, a feature that is critical for inhibition of SMC proliferation and/or neointimal thickening by the restored endothelium.

As physicians, we are obliged to embrace strategies that offer the highest clinical benefit, while minimizing safety concerns. The rates of restenosis reported with the use of cytostatic and cytotoxic drug-eluting stents are impressive and promise to enhance the outcomes of coronary interventions. However, amid the enthusiasm that has been triggered by the release of these data, we should consider a new
therapeutic target—enhanced endothelial recovery. Extensive data suggest that this may be an effective stand-alone strategy for restenosis prevention, serving to inhibit smooth muscle proliferation and perhaps also deter inflammatory cell invasion. The latter phenomenon, although relatively understudied, appears to be a significant component of neointimal lesions, which can be inhibited by targeting leukocytes themselves or by restoring endothelial barrier function.

An intact endothelium appears to be nature’s means of preventing intimal lesion formation. The study by Hedman et al unveils a strategy designed to recapitulate nature, rather than thwart it, enhancing endothelial function as a primary strategy for restenosis prevention. As cardiologists, vascular biologists, and physicians, we must now consider an alternative to the “antitumor” approach to restenosis prevention and seek to restore the normal biology of the vessel wall rather than perpetuate its disruption.

References


Key Words: Editorials | gene therapy | restenosis | endothelium | angioplasty
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_Circulation_. 2003;107:2635-2637
doi: 10.1161/01.CIR.0000071083.31270.C3
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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