Restenosis
Another “Dysfunction” of the Endothelium

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Atherosclerosis is a chronic, systemic, and diffuse disease with focal complications in different vascular beds. The precise mechanisms by which a specific site is rendered more prone to the development of symptomatic disease and cardiovascular events are not known. Both the systemic and local manifestations of the disease can vary, depending on the stage, location, and other factors affecting the integrity of the vascular wall. Atherosclerosis, and specifically coronary atherosclerosis, can be manifested as endothelial dysfunction at the very early stage of the disease and as in-stent restenosis at the later stage. Both endothelial dysfunction and in-stent restenosis are pathophysiological processes that involve the vascular wall, may share common pathways, and may be regarded as an abnormal vascular response or healing to injury. However, the treatment effect of mechanical coronary interventions is generally confined to discrete coronary artery segments, whereas the pathological process of coronary atherosclerosis is diffuse. Coronary interventional therapy should thus constitute a part of a comprehensive strategy that includes additional therapeutic approaches, such as intensive efforts to lower lipid levels, which may halt the generalized progression of disease and reduce the risk of death or myocardial infarction.

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The ability to predict restenosis and thus the local response of the vascular wall to injury remains a major and an important target in cardiovascular disease, not only because of the potential to predict clinical events but also as a clue to the mechanism of the disease. One of the early indications that vascular reactivity may predict restenosis came from a study by Ardissino et al., who demonstrated that the presence of hyperventilation-induced abnormal coronary vasoconstriction identifies a subgroup at high risk for restenosis.

The article by Patti and colleagues in this issue of Circulation2 extends previous observations and demonstrates that impaired flow-mediated dilation (FMD) of the brachial artery independently predicts occurrence of coronary in-stent restenosis. In this study, the investigators prospectively assessed FMD in 136 patients with symptomatic coronary artery disease 30 days after stent implantation. Clinical follow-up visits, as well as noninvasive functional tests, were obtained at 3 and 6 months in all patients, and repeat angiography was performed in patients in whom myocardial ischemia or symptoms were present. FMD 1 month after the stent implantation was impaired in patients who developed in-stent restenosis during follow-up. Using univariate and multivariate statistical analysis, the authors reported that diabetes mellitus, stent diameter, and FMD <7% were the only variables associated with high risk of in-stent restenosis. The investigators concluded that impaired peripheral endothelial function as assessed by FMD is an independent predictor of in-stent restenosis.

The present study is in accord with the growing body of evidence demonstrating that the presence of coronary as well as peripheral endothelial dysfunction predicts cardiovascular events.3 However, whereas previous studies were focused on native atherosclerosis, which is a diffuse and systemic disease, the present study extends these previous observations and demonstrates that peripheral endothelial dysfunction predicts the response to local vascular injury.

The mechanism by which peripheral endothelial dysfunction may predict in-stent restenosis may be multifactorial and may include both local and systemic mechanisms. The noninvasive assessment of endothelial function, as was performed in the present study, is based on the principle that one of the hallmarks of endothelial dysfunction is abnormal endothelium-dependent vasodilatory response to chemical or physical stimuli that release nitric oxide (NO).3 However, this abnormal FMD response serves only as a marker and one of many manifestations of a syndrome that is associated with significant morbidity and mortality. In-stent restenosis represents an abnormal vascular response and repair to injury that results in excessive tissue growth and is most likely another manifestation of the same disease. The status of the vascular wall, and especially the vascular endothelium, is the key component of the response to injury. A healthy endothelium sustains an antithrombotic milieu by secretion of various factors that exert antiaggregatory effects on platelets (NO and prostaglandin I2) or have anticoagulatory (heparin and proteins C and S) or fibrinolytic (tissue plasminogen activator) properties.4 In contrast, endothelial dysfunction is characterized by a reduction in NO, prostacyclin, and tissue plasminogen activator. There is a decrease in the anticoagulatory potential of the endothelium and an increase in endothelial production of procoagulatory mediators, resulting in a vascular environment that allows thrombus formation in response to exposure of highly thrombogenic substances from ruptured or erosive plaques. In addition, platelet-derived...
mediators, such as serotonin, are more likely to induce vasoconstriction in the presence of a dysfunctional endothelium. Endothelial dysfunction is characterized by an imbalance between vasodilator substances with antiproliferative properties, such as NO, and vasoconstrictors with mitogenic properties, such as endothelin. The systemic and local milieu associated with endothelial dysfunction favors cell proliferation, intimal hyperplasia, and vasoconstriction, which may contribute to the restenosis process. Indeed, there is a local release of endothelin-1 at the site of the vascular injury, and an endothelin receptor antagonist attenuates stent restenosis. Moreover, the administration of L-arginine, the precursor of NO, inhibits lesion formation after balloon injury and coronary endothelial function. Endothelial dysfunction may also involve the vascular microcirculation, which includes the vasa vasorum, leading to vascular wall ischemia and neovascularization. Intraplaque neovascularization may lead to further enhanced influx of macrophages into the plaque as well as to intraplaque hemorrhage, contributing to the abnormal vascular repair and restenosis. Moreover, stent implantation contributes further to the vasa vasorum neovascularization at the site of the stent and thus to the inflammatory response, cell proliferation, and restenosis.

The link between endothelial function and restenosis may also be on the systemic level. The concept of endothelial dysfunction as a systemic disease may be extended from the vascular wall per se to the origin of the endothelial cells, which are the bone marrow and the endothelial progenitor cells (EPCs). The vascular wall, and the endothelium in particular, are undergoing a constant process of injury and repair in response to mechanical and chemical injuries. Emerging evidence suggests that bone marrow–derived endothelial stem cells and EPCs contribute to the repair of vascular injury and play a role in the restoration of tissue repair. The bone marrow contains vascular progenitor cells that can mobilize to the injury site and complement repair afforded by preexisting endothelium. The repair of vascular injury with EPCs is associated with normalization of endothelial function at the site of the injury. Moreover, in the setting of endothelial dysfunction, the repair of vascular injury may be impaired by 2 possible mechanisms. First, a study demonstrated that the degree of endothelial dysfunction might be correlated with the number of EPCs. Thus, one of the possible mechanisms for vascular endothelial dysfunction and potentially restenosis may be a relative deficiency of EPCs for vascular repair. Moreover, the function of these cells and their ability to participate in the vascular repair after injury has been shown to be impaired in an animal model of decreased NO activity. It may be speculated that endothelial NO activity, the hallmark of endothelial function, may be reduced at the level of the multipotential cells of subjects with systemic endothelial dysfunction and atherosclerosis. This concept is further supported by the observations that in type II diabetes, a condition that is associated with endothelial dysfunction, recruitment of EPCs to the site of tissue repair is diminished and may thereby increase the incidence of restenosis, as demonstrated in the present study. The concept that EPCs may play a role in the vascular response to injury and in the process of restenosis opens the avenue for future studies addressing the role of EPCs as a potential therapy for the repair of vascular injury.

In the present study, the use of ACE inhibitors but not statins was associated with the reduction of restenosis. Both of these drugs improve endothelial function, but their role in the prevention of restenosis is still controversial. The beneficial effect of these drugs on both endothelial function and restenosis may be dependent on the genotype of the patients as well as on the inflammatory and oxidative stress status, which was not addressed in the present article.

The observation in the present study that the lower stent diameter is associated with in-stent restenosis is well established and may be secondary to local endothelial dysfunction–mediated coronary vasoconstriction. It also highlights the lack of accuracy of coronary angiography alone for the measurement of coronary artery diameter before stent implantation and the underutilization of a more precise imaging modality, such as intravascular ultrasound, for the assessment of stent implantation.

As the authors indicated, one of the limitations of the present study is that almost all the patients received bare-metal stents. Thus, the predictive value of endothelial function for in-stent restenosis may not apply to the current growing practice of drug-eluting stents. However, it is possible that the presence of endothelial dysfunction may predict in-stent restenosis of drug-eluting stents associated with inflammation and failure of reendothelialization. Another potential limitation of the present study design is that the assessment of endothelial function was performed not only before but also 30 days after the procedure. The possibility that endothelial dysfunction was in fact induced by the local vascular injury should be entertained. This hypothesis is supported by recent observations that markers of inflammation, such as C-reactive protein, may increase after stent implantation. Thus, future studies addressing the association between endothelial function and in-stent restenosis should assess endothelial function before the procedure. Nevertheless, the present study importantly advanced the perception of endothelial dysfunction as a systemic disorder that predicts cardiovascular events and may expand and add restenosis to the diverse manifestations of this disorder. The healing of the vascular endothelium and the restoration of endothelial function early after revascularization may arise as the next therapeutic target for the prevention of restenosis and postprocedural events. Moreover, the present study supports the notion that assessment of endothelial function should be integrated into our clinical practice.

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References


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