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EDITORIAL

Endothelial Nitric Oxide Production and Arterial Response to Injury

Neointima formation and arterial wall reorganization are important problems in modern cardiology. Arterial angioplasty and stenting are percutaneous procedures that provide a viable and safe alternative to surgical revascularization of the coronary, peripheral, renal, and carotid vasculature in the majority of patients. Angioplasty and stent deployment involve sudden arterial trauma to diseased segments of the vessel wall in order to reestablish luminal diameter and blood flow. In a manner analogous to atherogenesis, the cellular components of the vessel wall react to barotrauma and foreign body application with a broad array of responses. Abnormal cellular activation, proliferation, and migration can lead to adverse sequelae, including in-stent restenosis and prothrombotic phenomena. Drug-eluting stents have reduced the incidence of post-procedural complications, at least in the near term.[1,2] However, there remains an urgent need to further characterize the molecular and histologic dynamics of neointimalization so that even more effective pharmacologic means for preventing post-procedural complications can be developed and applied.

Neointimalization involves complex cellular proliferation and migration patterns, the activation of a wide range of inflammatory mediators and growth factors, and changes in extracellular matrix deposition.[3-5]

Nitric oxide is constitutively produced by normal endothelium and induces smooth muscle cell relaxation in blood vessel walls. Nitric oxide is formed from arginine by the enzyme endothelial nitric oxide synthase (eNOS). In addition to its capacity to induce and maintain vasodilatation, nitric oxide is antiatherogenic by virtue of its ability to reduce the oxidation of low-density lipoproteins, platelet aggregability, smooth muscle cell proliferation, and the expression of endothelial adhesion molecules. Adhesion molecules promote the binding and rolling of inflammatory cells (monocytes, T-lymphocytes) along stressed endothelium, and include such molecules as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Once bound, these cells can

transmigrate into the subendothelial space by following a gradient of monocyte chemoattractant protein-1 (MCP-1). Once incorporated into the subendothelial space, monocytes and T cells can create an inflammatory nidus and promote cell proliferation and migration, early events in atherogenesis and neointimalization. Experiments in a variety of animal models have shown that by inhibiting VCAM-1 and MCP-1, the development of atherosclerosis is significantly attenuated. The reduction of endothelial nitric oxide production is highly associated with accelerated atherogenesis.

In this issue of *The Journal of Applied Research*, Zhang and coworkers explore the role of nitric oxide, adhesion molecule, and MCP-1 expression in arterial wall reorganization in response to carotid artery ligation (CAL). CAL induces turbulent blood flow, a rheologic phenomenon known to induce both neointimalization and atherogenesis. When comparing wild type mice to: (1) mice with pharmacologic inhibition of eNOS with L-NAME or (2) mice with eNOS deficiency due to genetic knock out, nitric oxide emerged as an important mediator of the vessel wall's response to injury. Nitric oxide deficiency was associated with increased expression of VCAM-1 and MCP-1 as well as increased neointima formation, subendothelial inflammatory infiltrates, and cellular reorganization along the intima, media, and adventitia of the carotid artery wall. All of these changes are associated with compromised vascular function.

Clearly, neointimalization and luminal obstruction remains an important clinical sequela in a significant percentage of patients undergoing percutaneous revascularization. There is residual risk for this complication even in the setting of drug-eluting stents and when risk factors for atherosclerotic disease are well controlled and the patient is treated with appropriate anti-platelet medications. There is an urgent need to develop newer pharmacologic approaches to reversing endothelial cell dysfunction and promoting eNOS activity. Further exploration of molecular interventions against VCAM-1 and MCP-1 expression is also warranted.

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