New Approaches to the Evaluation of Coronary Endothelial Function

— Direct Measurement of Intra-Arterial NO Concentration In Vivo —

Shuichi Hamasaki, MD; Chuwa Tei, MD

Nitric oxide (NO) is released by endothelial cells in response to hemodynamic forces (eg, shear stress, axial strain) and has vasodilator and anti-atherogenic properties. Endothelial dysfunction is associated with diminished bioavailability of NO and poor prognosis in patients with traditional cardiovascular risk factors. Rather than directly measuring NO concentrations, most previous studies have measured vasodilator activity as a proxy, including assessment of flow-mediated dilation (FMD) and response to intracoronary injection of acetylcholine (ACh).

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In this issue of the Journal, Kume et al1 demonstrate the utility of a catheter-type NO sensor for evaluating the bioavailability of NO and detecting the early stages of endothelial dysfunction in high-fat-diet-induced obese dogs. They have already demonstrated the validity of this catheter-type NO sensor for in vivo measurement of NO in the coronary circulation;2–4 and in the present study, the investigators report that a high-fat diet resulted in a significant reduction in intra-arterial NO concentrations, but not in the ACh-induced coronary flow response. These findings suggest that in the early stages of coronary endothelial dysfunction other endothelium-derived relaxing factors, such as prostacyclin and endothelium-derived hyperpolarizing factors (EDHF), may contribute to the maintenance of coronary flow after injection of ACh. Furthermore, ACh-induced coronary flow may not be a good proxy for reduced NO bioavailability and coronary endothelial dysfunction.

The authors also demonstrated that while fasting plasma insulin levels increased, fasting plasma glucose levels remained constant in their dog model of obesity, which indicates that insulin resistance accompanied the decrease in NO production. Cardillo et al suggested that insulin stimulates both endothelin and NO activity in the skeletal muscle circulation and that an imbalance between the release of these 2 substances may be involved in the pathophysiology of atherosclerosis in insulin-resistant states associated with endothelial dysfunction. In fact, insulin-mediated production of endothelin may increase in the context of insulin resistance and thereby induce the vasoconstriction associated with endothelial dysfunction. Therefore, endothelin may affect vascular tone after injection of ACh in patients with insulin resistance through direct or indirect effects, which may complicate interpretation of the significance of ACh-induced vasomotion.

Assessment of vasomotion after intracoronary injection of ACh or by FMD is commonly used to evaluate coronary endothelial function. However, evaluation of vascular endothelial function based on these 2 methods depends on the normal function of vascular smooth muscle. If both the basal tone and the response of vascular smooth muscle during the procedure are impaired, the utility of this measure is poor. Furthermore, the data are influenced by multiple endothelium-derived vasodilators other than NO and by vasoconstrictors and neural control of the vascular smooth muscle. The compensatory vasodilator effect among NO, EDHF (hydrogen peroxide), and adenosine to maintain coronary blood flow has also been reported during coronary ischemia–reperfusion injury in vivo. Thus, FMD and vasomotion after ACh injection may not be adequate parameters of NO bioavailability and endothelial function.

NO is immediately oxidized or inactivated in the blood stream after its release from vascular endothelial cells. However, Rassaf et al suggest that NO can be transported in its bioactive form for significant distances along the vascular bed and may therefore exert remote effects. If this supposition proves true, then direct measurement of plasma NO concentration is necessary to characterize the kinetics and physiological role of NO and to evaluate endothelial function.

An inhibitor of NO synthase (L-NMMA) has been used to distinguish whether an impaired coronary flow response to ACh is related to NO or to other types of oxidative stress. In a previous study, Mochizuki et al showed that direct exposure to either ACh or L-NMMA solution did not cause any significant change in the baseline current assessed by a NO sensor. The NO sensor also showed no noticeable change in the baseline current with and without solution mixing, which suggests that it was not affected by fluid motion. Thus, the NO sensor only measures the current, reflecting the change in plasma concentration of NO induced by ACh and L-NMMA infusions. Additional refinements in technology and technique are required in order to allow measurement of the absolute concentration of NO in the
circulation. Furthermore, local plasma NO concentrations may differ in areas of impaired oxygenation, such as in regions of coronary ischemia, or may vary with the location of the NO catheter within the blood vessel. However, these concerns do not diminish the importance of Kume et al’s study.

Their technique may have other applications; for example, patients with septic shock could be evaluated for increased production of NO, which would offer opportunities to directly treat vasomotor abnormalities.

In conclusion, rapid advances in technology are now allowing direct measurement of plasma NO concentrations, which will provide a powerful tool for the characterization of NO physiology and pathophysiology and may identify greater opportunities for therapeutic modulation in humans.

References