Simply say yes to NO? Nitric oxide (NO) sensor-based assessment of coronary endothelial function

Joerg Herrmann1, Lilach Lerman2, and Amir Lerman1*

1Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and College of Medicine, Rochester, MN 55905, USA; and 2Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic and College of Medicine, Rochester, MN, USA

Online publish-ahead-of-print 24 August 2010

This editorial refers to ‘First evaluation of real-time nitric oxide (NO) oxide changes in the coronary circulation in patients with non-ischaemic dilated cardiomyopathy using a catheter-type sensor’1, by S. Takarada et al., on page 2862

In 1980 Furchgott and Zawadzki published their observation on how removal of the endothelium abolishes acetylcholine-induced relaxation of vascular smooth muscle cells, which ignited a passionate search for an endothelium-derived vasorelaxing factor.1 Yet who would have thought in the beginning that the search was for a gas! Seven years later, Ignarro and co-workers identified nitric oxide (NO) as the endothelium-derived vasorelaxing factor.2 In the same decade, Murad’s laboratory pointed out that NO activates the cytosolic (soluble) isoenzyme form of guanylate cyclase which increases cGMP synthesis and leads to the activation of cGMP-dependent protein kinase and ultimately reduces intracellular calcium concentration and elicits vascular smooth muscle relaxation.3 Closing the loop on endothelium-dependent vasorelaxation with these findings and discovering ‘nitric oxide as a signaling molecule in the cardiovascular system’, Robert Furchgott, Louis Ignarro, and Ferid Murad were awarded the Nobel Prize in Physiology/Medicine in 1998.

NO’s role in the physiology and pathology of the cardiovascular system is quite manifold and extends beyond its anatomical boundaries (Figure 1). In synoptic terms, NO is a multifunctional molecule that exerts anti-atherosclerotic properties in the vasculature and contributes to primarily the diastolic function of the myocardium.4,5 Abnormalities in the endogenous NO system have been found in various pathological conditions of the cardiovascular system including hypertension, atherosclerosis, and cardiomyopathies.6–7 While important, direct measurements of NO have been challenged by its rapid metabolism owing to the rapid interaction with dissolved oxygen, haemoglobin, oxyhaemoglobin, reactive oxygen species, or thiol compounds such as albumin or glutathione, once released into the circulation from its production site. For practical purposes, NO has therefore remained below the radar in today’s cardiovascular environment as much as it had been before its cardiovascular discovery more than two decades ago.

Very recently, major strides have been made towards successful measurements of NO directly by an electrochemical electrode (sensor) after conversion of nitrite back to NO.10 Applying this technique, Takarada et al. have presented first-in-man data on ‘real-time NO changes in the coronary circulation in patients with non-ischaemic dilated cardiomyopathy’ (DCM).11 In patients medically stabilized after hospital admission for congestive heart failure, and in control patients with normal cardiac function and coronary arteries, they measured epicardial coronary artery diameter and average peak flow velocity (APV) changes with intracoronary Doppler in the proximal left anterior descending coronary artery in response to infusion of acetylcholine with and without the nitric oxide synthase inhibitor N⁰-monomethyl-L-arginine (L-NMMA). The coronary sinus was engaged with a 4F catheter, upon which the NO sensor was mounted, and changes in NO levels were recorded relative to the pre-acetylcholine baseline. Most certainly, Takarada et al. should be congratulated on their innovative approach to address the challenging role of NO in coronary physiology in humans.

The findings obtained by this technique are remarkable because they recapitulate the original link between acetylcholine, the endothelium, NO, and vasoreactivity. As expected, in control group acetylcholine induced a dose-dependent increase in coronary artery diameter that was completely blunted by L-NMMA, confirming the physiological role of the endogenous NO pathway. In the presence of a dilating epicardial vasculature, the acetylcholine-induced increase in APV reflects an increase in coronary blood flow due to a reduction in tone of the resistance vessels. The fact that this response was nearly but still not completely suppressed by L-NMMA indicates that NO and presumably
the endothelium is the major but not the only determinant of acetylcholine-induced vasomotor changes of the myocardial microvasculature. Coronary sinus NO levels increased with acetylcholine stimulation, but, relative to the APV response, showed a remarkable latency in time to rise and time to peak of 50–60 s and 2.5 min, respectively. While this constellation can indicate acetylcholine-induced release of NO from the endothelium, it does not rule out the possibility of flow-induced release of NO.

In the DCM population, Takarada et al. were able to confirm impairment of acetylcholine-induced vasodilatation mainly on the level of the epicardial rather than the myocardial vasculature. Acetylcholine did not induce a change in coronary artery diameter, and the increase in APV was much smaller than in the control group. Intriguingly, the APV response, rather than NO, seemed to be the most sensitive parameter to distinguish DCM from the control group. While the study was not designed to detect baseline differences in NO levels between cases and controls, the absence of a significant difference in stimulated levels with the lowest dose of acetylcholine argues against any difference. Yet the difference in relative changes in NO became apparent between cases and controls even before coronary artery diameter changes in the framework of the dose escalation design of the current study.

Pertinent for the interpretation of the current study results is the fact that coronary sinus samples do not allow adequate distinction between coronary and myocardial generation of NO. This is of particular interest for the case group, as alternations in the expression of isoforms of NO synthase have been described in DCM. Furthermore, clinical screening processes may be inherently inadequate to exclude processes that may present as DCM, such as viral myocarditis. Under these conditions, upregulation of inducible nitric oxide synthase (iNOS) and the consequent increase in NO production would be a confounder. Nevertheless, the similarities in the release kinetics, albeit at a lower level, suggest a similar release (trigger) mechanism and source for NO in both the case and the control group.

The authors studied a unique group of patients with DCM. Conceptually, to remain focused on the vascular aspects, it would have been of interest to study patients without overt heart disease, differentiated only by the presence or absence of coronary endothelial dysfunction. Assessment of changes in radial NO levels relative to brachial artery vasoreactivity would also be of interest. Future modifications in catheter design may facilitate this exploration and may even allow sensing NO changes in the coronary arteries directly.
Finally, measurements by the NO sensor were correlated with nitrite level measurements by the Griess reaction in an internal control effort. However, the weak correlation observed between the two techniques limits the confidence in the validity of the sensor-based approach, as acknowledged by the authors. Hence, while this is an important first step to real-time NO recording in the human cardiovascular system, further validation studies of the current technique are clearly warranted. Until then, we cannot ‘simply say yes’ to NO-based coronary endothelial function assessment.

Conflict of interest: none declared.

Acknowledgements

This work was supported by the National Institute of Health (grants HL-92954, HL085307, and HL77131).

References