Nitric Oxide and the Regulation of Arterial Elasticity: Right Idea, Wrong Vascular Bed?

To the Editor:

We read with interest the recent paper by Kinlay et al., which highlights the important relationship between arterial stiffness and cardiovascular risk. A number of other investigators have shown that aortic elasticity decreases with age, and this change is associated with increased cardiovascular mortality. In their elegant studies, the authors use the highly invasive technique of intravascular ultrasound to demonstrate, in part, that endothelium-derived nitric oxide (NO) regulates brachial artery elasticity. A major advantage of the brachial artery is its direct accessibility. However, it may not be the ideal vascular bed in which to study the involvement of endothelium-derived NO in the physiological regulation of arterial stiffness because, unlike measures of aortic stiffness, brachial artery distensibility changes little with age, despite the fact that the same authors have previously shown that aging progressively impairs endothelium-dependent vasodilatation in the human forearm vascular bed. Moreover, hypercholesterolemia, an important cause of impaired endothelial function, is not associated with reduced brachial artery distensibility. Together, these observations cast doubt on whether endothelium-derived NO regulates long-term elasticity in the brachial arterial bed. Indeed, other investigators have demonstrated that inhibition of basal NO production may actually increase radial artery distensibility. Finally, unlike indices of aortic stiffness, as yet, there is no evidence that brachial artery distensibility predicts subsequent cardiovascular risk.

There are a number of methodological considerations with regard to the work of Kinlay et al. In particular, unlike similar work in the ovine iliac bed, the present authors failed to control for changes in flow produced by infusion of N^3-monomethyl-L-arginine (L-NMMA), which is important because shear stress is believed to be a major determinant of endogenous NO production. In addition, Kinlay et al did not infuse an exogenous endothelium-dependent dilator, such as acetylcholine, to investigate whether this response could be nonspecifically inhibited by L-NMMA.

The authors conclude that future investigations should delineate whether risk factor modification, or other therapies directed at improving endothelial vasodilator function, can improve arterial elasticity over the same, relatively rapid time course with which they restore NO production. While, we would agree wholeheartedly with this statement, such investigations will, of necessity, have to involve large numbers of patients and will thus require simple, reproducible, noninvasive methodologies, unlike those employed in the current study. Noninvasive techniques such as pulse wave analysis may be more suitable for this purpose. Not only can they be used for rapid assessment of both systemic arterial and aortic stiffness in subjects, but they can also be modified to assess endothelial function noninvasively. Therefore, we believe that pulse wave analysis may provide a more suitable means of assessing endothelial function in large numbers of patients, thus answering the important question of the predictive value of endothelial function testing. Pulse wave analysis has already been included in the substudies of Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), the Edinburgh Artery Study, and Feno- fibrate Intervention and Event Lowering in Diabetes (FIELD) trial. These will address the importance of basal arterial distensibility as a predictor of risk. However, we would agree with Kinlay et al, that it is important to include the noninvasive assessment of both endothelial function and arterial stiffness in future large intervention studies.

Ian B. Wilkinson
Department of Clinical Pharmacology
Addenbrooke’s Hospital
Cambridge, England, United Kingdom

David J. Webb
Centre for Cardiovascular Science
University of Edinburgh
Edinburgh, Scotland, United Kingdom

John R. Cockcroft
Wales Heart Research Institute
University Hospital
Cardiff, Wales, United Kingdom
E-mail cockcroftjr@cf.ac.uk

Response

We agree with Wilkinson et al on the “Right Idea,” but we would like to put their concerns to bed. Our study was designed to test the hypothesis that in healthy humans, endothelium-derived nitric oxide regulated arterial elasticity. It was a “proof of principle” study that demonstrated for the first time in vivo that arterial elasticity was yet another function regulated by endothelium-derived nitric oxide. Wilkinson et al have subsequently reported similar results in sheep using pulse wave velocity (PWV)—a more indirect assessment of arterial distensibility.
Brachial artery PWV has been reported to change less with age than PWV in the aorta or lower limb arteries. However, this was irrelevant to the hypothesis and in no way detracts from the importance of our results that subsequently were confirmed by Wilkinson et al in sheep. Our group and many others have shown that endothelium-derived nitric oxide has similar important functions in coronary and peripheral arteries in vivo and in arteries from other beds ex vivo. By improving arterial elasticity, endothelium-derived nitric oxide reduces the arterial wave reflection and reduces left ventricular work and the pulse pressure within the aorta. These likely have important consequences for cardiovascular outcomes.

Although we agree with Wilkinson et al that the infusion of any substance, including L-NMMA, could potentially lead to changes in shear stress and blood flow, we disagree that this was not controlled for in our study. Our assessment of arterial elasticity was always compared with a control infusion of dextrose at the same infusion rate as the subsequent L-NMMA and nitroglycerin infusions and was equivalent to approximately 1% to 2% of brachial artery flow. Furthermore, our technique of assessing arterial elasticity is independent of blood flow, as it is a direct assessment of arterial distension (using intravascular ultrasound to image the artery wall) with simultaneous intra-arterial pressure measurements. In contrast, the assessment of distensibility using PWV is indirect and potentially affected by changes in blood flow and mean pressure that reflect changes in more distal resistance vessels. Their method relies on measuring the time taken for the arterial pressure wave to progress between two transducers placed on a 6 French catheter sitting within a 7 French sheath (approximately 2.5 mm external diameter) inserted into the iliac artery of sheep. Their demonstration that the effect of acetylcholine (a known stimulus for endothelium-derived nitric oxide) was blocked by the competitive inhibitor of nitric oxide (L-NMMA) was not unexpected and has been demonstrated by our group and others for a number of functions regulated by endothelium-derived nitric oxide. Therefore, we omitted this test in our study of humans, which was designed to examine the role in resting basal conditions.

We are unable to comment on whether their modification of the technique for measuring PWV has any value in measuring endothelial function because these data are unpublished. The assumptions required for an indirect assessment of endothelial vasodilator function would have to be remarkably robust to measure the small changes seen in even healthy people. Other noninvasive techniques that are able to directly measure arterial distension include ultrasound techniques such as wall-tracking and application tonometry. The reliance on any one technique would be a mistake in our view because they all have advantages and disadvantages.

Arterial elasticity is an important contributor to cardiovascular outcomes. While it is interesting to conduct research in sheep, species differences may exist; therefore, it is critically important to study these mechanisms in humans. Our study reminds us that therapies that improve endothelial function are likely to contribute to a reduction in adverse outcomes in patients because of their effect on elasticity as well as on other local arterial functions. It is the right idea, regardless of the vascular bed.

Scott Kinlay
Mark A. Creager
Department of Medicine
Cardiovascular Division
Brigham and Women’s Hospital
Boston, Massachusetts
E-mail skinlay@rics.bwh.harvard.edu

Nitric Oxide and the Regulation of Arterial Elasticity: Right Idea, Wrong Vascular Bed?
Ian B. Wilkinson, David J. Webb and John R. Cockcroft

Hypertension. 2002;39:e26-e27
doi: 10.1161/01.HYP.000014617.84543.CA
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/39/4/e26

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/