

Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

Noninvasive Assessment of Subclinical Atherosclerosis in Children and Adolescents

To the Editor:

Standards relating to the assessment of subclinical atherosclerosis in children are important, especially given the large variation that exists in the “normative” data being published. This variability can, at least in part, be ascribed to variability and inconsistency in the application of the technique.

Unfortunately, the Statement recently published in *Hypertension*¹ ignores a large and established literature related to improving methods of assessment of flow-mediated dilation (FMD). For example, literature developed across the past decade and summarized by Pyke and Tschakovsky² has focused on appropriate assessment and quantification of the stimulus responsible for FMD. Ignoring the shear stress stimulus to FMD when comparing responses between subjects or within subjects before and after interventions is akin to comparing responses to a drug without taking account of the dose administered. Carefully performed physiological studies have demonstrated that the shear rate (area under the curve) between cuff deflation and the peak diameter time point represents the best estimate of stimulus to FMD, not the maximal velocity recorded at or around 15 seconds. This necessitates continuous assessment of velocity after cuff deflation. It is surprising that these issues pertaining to stimulus quantification and normalization were not addressed in the Recommendations section.

The guidelines also leave “wriggle room” on the question of the method of diameter analysis, which we think is unwarranted. It is generally acknowledged that edge detection and wall tracking significantly improve diameter analysis compared with manual caliper placement or “wall tracing.”³ Moreover, edge-detection software allows largely automated and operator-independent assessment in a technique that is otherwise open to experimenter bias. Finally, continuous edge detection allows for accurate determination of true peak diameters and time-to-peak diameter, whereas assessment at arbitrary time points can lead to misleading “peak” data, which, in turn, can alter study conclusions.⁴ Manual caliper placement at arbitrary time points should be strongly discouraged in our view for all of these reasons. User-independent automated edge-detection software and continuous postdeflation diameter assessment should be considered mandatory if the technique is to become more reliable and reproducible and make the jump to clinical “prime time.”

Finally, the Statement suggests using a distal cuff position for FMD assessment, because imaging the brachial artery is challenging when using a proximal cuff position. The major reason for distal cuff placement is, in fact, physiological. FMD is considered a surrogate for endothelial and largely NO-dependent function. Dilator responses of arteries that are within the ischemic territory during cuff inflation are not as NO dependent as those of arteries upstream from the cuff.⁵

We applaud the publication of guidelines to standardize FMD and other imaging approaches. However, we would like to draw some attention to issues pertaining to the physiology and integrity of the technique. We have raised a couple of examples here. There are many other examples of studies aimed at enhancing the reliability and validity of the technique that are already published in high-profile and -impact peer-reviewed journals of integrative physiology.

Sources of Funding

D.J.G. receives funding support from the Australian Research Council and the National Heart Foundation of Australia.

Disclosures

None.

Dick H.J. Thijssen

Research Institute for Sport and Exercise Science
Liverpool John Moore's University
Liverpool, United Kingdom
Department of Physiology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands

N. Timothy Cable

Research Institute for Sport and Exercise Science
Liverpool John Moore's University
Liverpool, United Kingdom

Daniel J. Green

Research Institute for Sport and Exercise Science
Liverpool John Moore's University
Liverpool, United Kingdom
School of Sport Science, Exercise and Health
University of Western Australia
Crawley, Western Australia, Australia

1. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, Jacobson M, Mahoney L, Mietus-Snyder M, Rocchini A, Steinberger J, McCrindle B. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. *Hypertension*. 2009;54:919–950.
2. Pyke KE, Tschakovsky ME. The relationship between shear stress and flow-mediated dilatation: implications for the assessment of endothelial function. *J Physiol*. 2005;568:357–369.
3. Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, Puddey IB, Beilin LJ, Burke V, Mori TA, Green D. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. *J Appl Physiol*. 2001;91:929–937.
4. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension*. 2008;51:203–210.
5. Green D. Point: flow-mediated dilation does reflect nitric oxide-mediated endothelial function. *J Appl Physiol*. 2005;99:1233–1234; discussion 1237–1238.