LETTERS TO THE EDITOR

Reactive Hyperemia as a Test of Endothelial or Microvascular Function?

We would like to compliment Binggeli et al. (1) on their challenging study investigating the improvement in the cutaneous vascular response to reactive hyperemia following statin therapy in hypercholesterolemic patients. We recently published similar findings regarding the reactive hyperemia test in young, healthy control subjects. Unfortunately, we were not aware of each other’s work at the time of publication (2). The two main goals of our study were: to characterize the reactive hyperemic response in the cutaneous circulation to varying periods of occlusion (between 3 and 15 min), and to examine the role of nitric oxide (NO) in the reactive hyperemic response in the skin. In addition, we attempted to improve and standardize the analysis of reactive hyperemia with the goal of decreasing the variability in the measured response to possibly improve the clinical utility of this test. Similar to the findings of Binggeli et al. (1), we (2) found that the vascular response to reactive hyperemia was extremely variable, even in the young healthy population. Despite our improvement in the analysis technique, we still observed within-subject coefficients of variation ranging from 6% to 11% and, more importantly, between-subject coefficients of variation ranging from 19% to 74% (2). Furthermore, we also found, using microdialysis and laser-Doppler flowmetry, that NO does not contribute to either the peak or total (area under the curve) reactive hyperemic response (2). In our opinion, these findings significantly limit the clinical utility of using the reactive hyperemic response in the skin as a test of endothelial function in a given individual. However, it is recognized that periodic evaluation of the reactive hyperemic response across a treatment period within an individual may provide some important information regarding improvement in microvascular function.

We agree with Dr. Celermajer in his accompanying Editorial Comment (3) in pointing out that there is a need for a noninvasive method to assess endothelial function in humans and that testing of microvascular function may not correlate with endothelial function. In this context, we published a study that investigated the local hyperemic response to heating a small area of skin (4). In this study, we found that there are at least two separate mechanisms in the “thermal hyperemia” response: 1) an initial peak that is axon reflex-mediated, and 2) a sustained plateau phase that is dependent on NO (4).

Evaluation of the thermal hyperemia response as described in our study, therefore, may be a better tool to independently assess both endothelial and microvascular function than reactive hyperemia. Using this technique, we were able to demonstrate diminished thermal hyperemia responses in healthy older subjects (>65 years old) in comparison to younger subjects (5). Thus, using our standardized local heating protocol may prove valuable in providing a noninvasive and reliable test of endothelial function, although, clearly, more work needs to be done to explore this possibility. We would like to encourage other investigators to test the efficacy of the thermal hyperemia test of endothelial function as discussed in our study in various patient populations and across treatments.

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doi:10.1016/j.jacc.2004.03.005

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REPLY

Drs. Minson and Wong support our findings that the hyperemic skin blood flow is not nitric oxide (NO) dependent. They showed that NO is responsible neither for the development nor the maintenance of the hyperemic response after arterial occlusion. This is true for reactive hyperemia after short occlusion as well as after more prolonged arterial occlusion of 15 min (1).

We also believe that normalization of the laser-Doppler-flux is important to minimize the influence of the number of blood vessels under the probe. The data of Wong et al. (1) and our data were normalized in a slightly different way. Normalization to the maximum level achieved during infusion of sodium nitroprusside and local heating as done by Wong et al. (1) assumes that the maximum vasodilatory effect is not largely affected by cardiovascular risk factors as shown in conductance arteries using different techniques. Our method normalizes to baseline. In the microvascularity, baseline as well as peak laser-Doppler-flux are at least in part dependent on the presence of risk factors (2,3). Therefore, both of the approaches have some advantages and disadvantages. We are aware that despite correcting for different sites, the intra-individual variability is considerably high. However, the decreased hyperemic responses of smokers and patients with hypercholesterolemia are in line with endothelial dysfunction measured using more invasive techniques, suggesting a common phenomenon. A better reproducibility of the method would allow one to detect smaller differences and, therefore, local heating as nicely investigated by Minson et al. (4) may be advantageous. The