Reactive Hyperemia Revisited

To the Editor:

We read with great interest Dr Huang’s study, published in Arteriosclerosis, Thrombosis, and Vascular Biology. We are in total agreement with the authors about the clinical relevance in the periprocedural setting of the hyperemic flow velocity, measured by brachial artery Doppler ultrasound. Dr Huang suggests that reactive hyperemia increases the accuracy of the noninvasive vascular reactivity test, namely the brachial artery flow-mediated dilation, in predicting cardiovascular events after major vascular surgery, even though in his patients the strongest isolated predictor was flow-mediated dilation.

In a population of 96 vascular surgical patients, we assessed brachial artery flow-mediated dilation and reactive hyperemia with the same technique as Dr Huang’s before major vascular surgery was performed, with a Siemens ultrasound system (Sequoia), equipped with a 7.5-MHz vascular transducer. The brachial artery ultrasound was always performed in the morning, after a 6-hour fast and at least 12 hours without smoking. Patients received all medications, including statins, and remained resting in supine position 15 minutes before the beginning until the end of the examination. We acquired 2-dimensional ultrasound images of the brachial artery and pulsed Doppler signals above the antecubital crease at baseline and during a period of reactive hyperemia induced by 5-minute cuff occlusion of the upper arm, at a 250-mm Hg pressure. After at least a 10-minute rest period, for restoration of baseline conditions, we reassessed the brachial artery image and blood flow, before and 3 minutes after administration of sublingual isosorbide dinitrate (5 mg). Images of the brachial artery were recorded at baseline and during the first 2 minutes after relief of the upper-arm occlusion for assessment of the flow-mediated response and before and 3 minutes after nitrate administration. Flows were recorded at baseline and during the first 15 seconds after cuff release, for assessment of the peak reactive hyperemia. Analysis were performed offline, by the same investigator, who was blinded to clinical outcomes. He used an automated software that calculated for each phase of the examination, the mean diameter of 6 images of the brachial artery, and the vascular operation could be either aortic repair or peripheral revascularization, and this characteristic was statistically evaluated by Fisher exact test.

We detected events in 27 patients during 1-month follow-up. Although Huang et al did not report cardiac risk estimation according to some specific algorithm, we consider that our population risk profile is comparable to theirs, as the mean ages are very similar and the prevalence of coronary artery disease is the same in both populations: 38%. Moreover, if we dichotomize the flow-mediated dilation response, defining as normal FMD >8.0%, we have 67% of Huang’s patients and 70% of ours with endothelial dysfunction, almost the same. The prevalence of hypertension, history of smoking, and aspirin therapy are high in both studies. We believe that a significant difference that has to be emphasized resides in the lipid lowering therapy: 54% in Huang’s patients and 98% in ours (Table). The analysis, the nonsignificant difference in the flow-mediated dilation of the brachial artery persisted (P=0.96). Interestingly however, we found that lower hyperemic flow velocity predicted perioperative events: 81 cm/s ±20×95 cm/s ±28 (P=0.02). When we analyzed the association between hyperemic flow velocity and cardiovascular events, we found: 80 cm/s ±22×95 cm/s ±28 (P=0.09), for patients with and without events, respectively, possibly because of the lower number of events analyzed.

The lower hyperemic flow velocity observed in our patients with events could not be attributed to age, sex, diabetes, hypertension, or congestive heart failure (unpublished data, Calderaro D, Monachini MC, Vieira CLZ, Yu PC, Gualandro DM, Marques AC, Caramelli B, 2007).

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We believe that statin therapy prescribed for the majority of our patients might have altered the vascular reactivity and might have decreased the association of flow-mediated dilation to cardiovascular events, justifying at least partially why we did not reproduce this association. Mitchell et al\(^3\) have already shown that lipid lowering therapy lost its association to FMD when reactive hyperemia was considered in the stepwise regression analysis. We hypothesized that lipid lowering therapy modifies the parameter of vascular reactivity mostly related to cardiovascular risk factors from FMD to reactive hyperemia.

In addition to Dr Huang’s study, our findings indicate that hyperemic flow velocity, as a marker of the vascular shear stress and directly related to the microvascular function, should be reported and analyzed routinely whenever this vascular reactivity test is performed. Actually, more than a simple stimulus for endothelial function evaluation, reactive hyperemia provides a better understanding of the vascular biology and pathophysiology of atherosclerosis.\(^4\) Moreover, differently from Dr Huang’s findings, our data suggest that reactive hyperemia could be even a better predictor of cardiovascular events in specific populations or particular settings.

**Disclosures**

None.
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