In Response:

We appreciate the interest in our article. Dr Beckman highlights an important issue that we had not discussed, namely the statistical power associated with different methodologies for inducing flow-mediated dilatation (FMD) of the brachial artery. Using upper arm ischemia-reperfusion to induce FMD of the distal brachial artery, we were unable to demonstrate endothelial dysfunction in cigarette smokers, nor its improvement by inhibition of xanthine oxidase. In contrast, induction of FMD using ischemia of the forearm distal to the brachial artery allowed us to detect a difference in endothelial function between smokers and nonsmokers and reversal of dysfunction in smokers. As Dr Beckman points out, these results were obtained in a relatively small number of subjects (n = 10), which suggests better statistical power for the technique using lower arm occlusion. We agree with Dr Beckman that we may have been able to detect impaired FMD using upper arm ischemia if we had included more subjects, though this merely highlights the better statistical power of the lower arm approach.

Dr Beckman requested clarification of the study design and statistical power. As stated in the manuscript, our study was originally designed to examine the effects of xanthine oxidase inhibition on endothelial dysfunction and, as cited in the current article, these results have been published as analyses were completed. After the current data comparing upper and lower arm occlusion were obtained in recent analyses, we felt it was important to disseminate this information for three reasons, even if it necessitated another publication from our cohort. First, the data have important implications for the design of future studies, in terms of improved statistical power and also our demonstration of the importance of cuff location for the detection of reversal of endothelial dysfunction. Second, our results could have important implications for research participant safety. Greater statistical power using lower arm cuff placement permits fewer subjects to be exposed to experimental interventions. Also, there is about twice as much discomfort to human subjects from upper arm than forearm ischemia-reperfusion, with research subjects generally preferring lower arm occlusion. Third, there has been no clear consensus as to the best approach for stimulating brachial artery FMD, so further studies are clearly needed.

The biological reasons for the improved statistical power of a lower arm occlusion approach are unknown but intriguing. First, use of upper arm occlusion leads to ischemia of a larger volume with a greater hyperemic response. It is possible that there may be a supramaximal stimulus that tends to reduce differences between groups. Second, some dilatation after upper arm occlusion may merely reflect ischemia of the brachial artery, rather than a flow dependent response. Others have shown that the brachial artery response after upper arm ischemia reperfusion is not inhibited by L-NMMA. Third, it is notable that prolonged ischemia of the brachial artery followed by reperfusion can lead to endothelial dysfunction. Perhaps there are subtle changes in brachial artery function after briefer periods of upper arm ischemia that impact its ability to detect differences between groups or the effects of interventions. All these factors may have contributed to the inability of an upper arm occlusion approach to detect either endothelial dysfunction in smokers or its improvement with xanthine oxidase inhibition.

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Dr Beckman requested discussion of the clinical relevance of our findings in the light of his comments on statistical power. Clearly, decreased statistical power with one approach versus another would suggest that approach is suboptimal, all other factors being equal. Given that upper arm ischemia-reperfusion produces a biologically ambiguous brachial artery response, that is less able to provide mechanistic insights, it is debatable whether brachial artery responses to upper arm ischemia-reperfusion solely reflect endothelial function. This is reflected in the decreased statistical power of studies using this approach. We completely agree with Dr Beckman that larger sample sizes are an absolute requirement in studies that use only this technique to assess vascular function.

Clinical research is founded on minimization and disclosure of risks to human research participants, and how such risks relate to potential scientific or clinical benefits. Optimizing this risk-benefit equation requires that we recruit the smallest number of human subjects needed to adequately test a hypothesis, and that we use techniques that are scientifically valid and relatively innocuous. Whole arm ischemia-reperfusion causes greater discomfort, is of unclear biological relevance, and lacks statistical power. Therefore, it appears inefficient, and some might even argue unethical, to continue its use as a stimulus for measuring endothelial function in humans.

Disclosures

None.

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References

Does Cuff Location for FMD Matter in Smokers?
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