Does Helium Act on Vascular Endothelial Function in Humans?

To the Editor:

Smit *et al.*[1] have demonstrated intriguing results that preconditioning with helium can preserve acetylcholine-induced vasodilator responses in the human forearm exposed to ischemia–reperfusion. This study seems to have many questions regarding the mechanisms of helium's action, whereas we would congratulate their impressive results. First, Smit *et al.* used a nonselective nitric oxide synthase inhibitor, NG-monomethyl-L-arginine, to document that the acetylcholine-induced enhancement of forearm blood flow is due to the activation of endothelial nitric oxide synthase.[1–3] However, they failed to show that the inhibition by NG-monomethyl-L-arginine in the control condition, as well as that with the effect of helium-preconditioning.[1] Therefore, it is quite difficult to conclude that nitric oxide, derived from endothelial enzyme, is a source of acetylcholine-induced vasodilator effects in their study. Second, it is unclear that the dosage of NG-monomethyl-L-arginine, used by Smit *et al.*, is comparable with those are sufficiently effective to inhibit acetylcholine-induced vasodilation in humans (32–64 μmol/min or 5 mg/min).[1–3] Third, Smit *et al.* did not evaluate roles of oxygen-derived free radicals including superoxide, which should modify vasodilator function in several pathological conditions including ischemia–reperfusion.[4–6] Indeed, it is possible to obtain endothelial cells from patients using J-wires to determine the degree of oxidative stress.[4] Fourth, it is possible that deflation of a blood pressure cuff placed on the arm to a pressure of 200 mmHg for 20 min induces flow-mediated dilation, which is mediated by endothelium-derived nitric oxide.[7] This possibility has to be ruled out because this dilation may play a role in the protective effects of helium on forearm blood flow after ischemia–reperfusion.[7] Therefore, further studies are needed to clarify the mechanistic insight into helium's protective effects on the vascular function exposed toward ischemia–reperfusion.

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In Reply:

We thank Kinoshita *et al.* for their valuable comments on our article regarding helium preconditioning in human endothelium.[1] Kinoshita *et al.* state that there still remain questions regarding the underlying mechanism of the observed endothelial protection after helium-induced late and early preconditioning. In our experiments,[1] we have shown significant endothelial dysfunction after 20 min of forearm ischemia induced by inflating a blood pressure cuff. This endothelial dysfunction was prevented by helium early and late preconditioning. The experiments using the nonselective nitric oxide synthase inhibitor, NG-monomethyl-L-arginine, during helium preconditioning were performed to investigate whether endothelial nitric oxide synthase is crucially involved in the mechanism of the observed helium preconditioning. Because co-infusion of NG-monomethyl-L-arginine did not block the protective effect of helium, we concluded that endothelial nitric oxide synthase is not a central mediator of helium-induced preconditioning in this model. In contrast to the reference[2] cited by Kinoshita *et al.*, we did not use NG-monomethyl-L-arginine as vasoconstrictive agent during acetylcholine infusion. Therefore, it is correct that we cannot conclude that nitric oxide derived from endothelium is the source of the acetylcholine-induced vasodilatory effect. The dosage of NG-monomethyl-L-arginine, we used equates to that, maximally reduces basal forearm blood flow in healthy volunteers without a possible systemic effect.[3] Unfortunately, we were unable to directly obtain endothelial cells from our volunteers to measure oxidative stress in those cells. The last comment raised by the authors pertained to reactive

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hyperemia directly after release of the blood pressure cuff. As stated in our article, we did not measure reactive hyperemia but performed our measurements in all groups after 20 min of reperfusion. It is, therefore, unlikely that reactive hyperemia caused the observed differences between groups. We agree that further studies are needed to clarify more the mechanisms of helium preconditioning in human endothelium.

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Differentiating Inspiratory and Expiratory Valve Malfunctions

To the Editor:

We appreciate Dr. Kodali's recent review of capnography outside the operating room environment.[1]

Two small yet important details would benefit from further clarification. Figure 2C is purported to display the malfunction of an inspiratory valve in an anesthesia breathing circuit. Unlike a stuck, open expiratory valve, an inspiratory valve that remains open during expiration shows the end-tidal carbon dioxide baseline *returning to zero*.

The best way to understand this is to consider taking the circle system breathing circuit and removing the inspiratory valve entirely from the circuit. During expiration, one half of the exhaled carbon dioxide-rich gas will "exhale" into the inspiratory limb of the breathing circuit. With the next inhalation, roughly the first half of the inspired breath will contain this exhaled gas, and the last part of inspiration will be fresh gas from the absorber and the fresh gas flow, *i.e.*, carbon dioxide-free gas, which allows the capnogram to return to the zero baseline. Compared with the normal capnogram, with a competent inspiratory valve, the inspiratory downstroke will sluggishly return to a zero baseline (or a B angle greater than 90 degrees) as appropriately depicted in the cartoon in figure 2C. This subtle difference that occurs with the baseline returning to zero helps elucidate the difference between malfunctioning inspiratory and expiratory valves or exhausted carbon dioxide absorbent.

The second point is that in figure 3 A–D, the apparent presence of inspired carbon dioxide is an abnormal finding, and suggests that in this sedation case, there is evidence of rebreathing in the microenvironment around the face, which may occur as a result of draping. The normal inspired carbon dioxide during sedation is expected to be zero.

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Reference

1. Kodali BS: Capnography outside the operating rooms. Anesthesiology 2013; 118:192–201

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In Reply:

I thank the authors Giordano, Gravenstein, and Rice for their valuable comments on the subject of "Capnography Outside the Operating Rooms."[1] Due to the limitations of word count for "Clinical Concepts Commentary," a detailed account of each capnogram was not provided. Given the wider scope of electronic accessibility, the intention of the article was to provide a comprehensive review of the use of capnography outside operating rooms not only to anesthesiologists and certified registered nurse anesthetists, but also to physicians in other specialties and nurses who provide sedation. Therefore, the article was scripted to provide a concise physiologic background and clinical applications of capnography.

Giordano *et al.* raised important comments regarding capnograms 2C and 3A–D of the article.[1] Analysis of capnograms 2C and 3A–D in the aforementioned article is a little more complex than the explanation provided by Giordano *et al.* Regarding 2C, they state that the inspiratory downstroke will sluggishly return to a zero baseline (or a β angle >90 degrees) during inspiratory valve malfunction. This may be true in the typical circumstance described by Giordano *et al.*, where an assumption is made that half of the expiratory gases will enter the inspiratory limb. However in reality, the quantity of expiratory gases entering the inspiratory limb is dependent on the resistance to the flow of expiratory gases in each limb of the circuit. The resistance in turn is dependent on the design of the valves, extent of malfunction of the inspiratory valve, fresh gas flows, and the length of the circuit. In addition, the carbon dioxide concentration across the inspiratory limb is also dependent on turbulent *versus* laminar flow of expiratory gases and mixing of carbon dioxide–free fresh gases with expiratory gases in the inspiratory limb (expiratory gases do