Response to Reactive Oxygen Species and Angiotensin II Response in Human Omental Arteries: What About Tachyphylaxis?

In response to the letter by Verdonk and Danser1 concerning our study, “Mechanisms of Enhanced Vascular Reactivity in Preeclampsia,” we did control experiments to verify that human omental arteries remain responsive to repeated angiotensin II dose-response challenges, so tachyphylaxis or rapid internalization of angiotensin II receptors cannot explain the inhibition we observed with superoxide dismutase/catalase or RhoA kinase inhibitor. Verdonk and Danser1 state that angiotensin II–induced tachyphylaxis does not allow for 2 angiotensin II concentration-response curves in a row in the same vessel; however, the enhanced vessel reactivity to angiotensin II in response to ROS or activated neutrophils in our study was a second angiotensin II dose response. If Verdonk and Danser1 were correct, we should not have seen a response, but rather we saw an enhanced response, so there was no tachyphylaxis and there were sufficient receptors to respond to angiotensin II. As an additional control, we sometimes changed the order of treatments, for example, doing the inhibitor treatment first, followed by angiotensin II. In addition, we were very careful to thoroughly rinse the vessels between each treatment, allowing them time to equilibrate and to recharge their intracellular calcium stores with KCl treatment. Failure to respond to a second dose-response challenge of angiotensin II may be attributed to depletion of intracellular calcium rather than tachyphylaxis or depletion of receptors.

With regard to inhibition of vascular response with superoxide dismutase/catalase, enhanced response to angiotensin II was inhibited not only in normal pregnant arteries treated with an ROS-generating solution but also in untreated preeclamptic arteries and in normal pregnant arteries perfused with activated neutrophils where the ROS was generated within the vessel lumen. It is important to point out that superoxide, whether generated by hypoxanthine plus xanthine oxidase or by activated neutrophils, quickly and spontaneously dismutates to hydrogen peroxide, which is the signaling molecule.2 Although superoxide does not cross the cell membrane, hydrogen peroxide does and, so, enters the extracellular space where superoxide dismutase/catalase can quench it. Verdonk and Danser1 also cite an earlier study in which they were not able to show that superoxide mediates the action of angiotensin II in coronary arteries; however, many studies, in addition to ours, have shown that ROS are involved in mediating the action of angiotensin II.3–6 Coronary arteries respond quite differently to vasoconstrictive hormones than systemic arteries involved in determining total peripheral vascular resistance, such as omental arteries used in our study, so the discrepancy may relate to the vascular bed studied.

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Disclosures
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