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REBUTTAL FROM DR. ROBERTSON

Two words came to mind as I read my opponent’s side of the argument: “smoke” and “mirrors.” To quote my esteemed opponents; “our strongest argument comes from the freshly isolated PASMC model.” While I do not regard these arguments as “ugly,” they may have more than a few unsightly blemishes! The observation that enzymatically dispersed PASMCs contract in hypoxia in no way negates a primary role for an endothelium-dependent Ca\(^{2+}\) sensitization in the intact artery or in the whole animal. To infer that the PASMC is the sole repository for the mechanism(s) of HPV as it can constrict hypoxia, with complete disregard to the myriad of cellular changes that likely occur during its rather traumatic isolation, is one inference too far!

I must also take issue with my opponent’s argument that HPV “cannot be explained by a mechanism involved in the vasoconstriction to prostanoids or phenylephrine.” I must admit to finding this argument rather baffling. Could not the specificity, with respect to HPV, be attributed to an endothelium-derived constrictor factor released locally within the lung, and/or one that acts solely within the pulmonary circulation rather than in the signal transduction pathway it activates?

It is interesting that my opponents state that “methodological differences can be debated in the isolated PA model.” Indeed they can and since my opponents state that “in our hands, rat resistance PAs can have full HPV” (1), this seems like a suitable point to debate some methodological differences! In their work, the PAs were ~74 μm in diameter and had a resting tension of 700 mg (~6.9 mN). With a generous allowance of between 1 and 2 mm vessel length, for an artery of this diameter, the equivalent transmural pressure would probably lie between ~500 and ~1,000 mmHg compared with other laboratories (2–9). Moreover, the resultant constrictor responses in this report were, perhaps unsurprisingly, given the “resting” conditions, rather small (~100 mg or ~1 mN) compared with those reported by other investigators using small PAs (~30 mN; Refs. 2, 4, 6, 7).

In the laboratories in which I have had the privilege to work, a pulmonary artery with a resting tension of 7 mN and a subsequent constrictor response of 1 mN would have been a candidate for life support measures!

Finally, HPV (like a Ferrari) is multifactorial. It requires a spark (the mitochondria and increases in cytosolic Ca\(^{2+}\)), fuel (glucose for glycolysis), and an accelerator (Rho kinase). But one thing is missing in this Ferrari...oh yes, the driver—something to put the pedal to the metal when it’s really needed. . .now I wonder what that could be?

REFERENCES

REBUTTAL FROM DRS. ROCHEFORT AND MICHELAKIS

Opening his argument, our opponent calls you, the readers, to a gambling exercise; admittedly a safe bet. Because in one of his reviews on the subject, only four papers found the endothelium to be nonessential for HPV, compared to the 15 that found it to be essential (1), he asks you to bet your money on his side of the argument. However, even in Las Vegas you get in trouble if you play safe bets, but with weighted dice! To support their side of the story in that review, the authors listed (in Table 1 of that review) apparently all the papers that were studying sustained HPV (more than 20 min of hypoxia) (1). We do not understand the basis on which 20 min was used as the cutoff between acute and “sustained HPV.” But, even using this rule, several papers were omitted from that table and argument, which, interestingly, strongly suggest a nonessential role of the endothelium. For example, Wang et al. (3) studied...
isolated lamb pulmonary arteries: even up to 120 min of hypoxia, caused the same constriction in the vessels with and without endothelium. In fact, the endothelium-denuded vessels had a faster constriction to hypoxia. Jane Madden’s work [including the paper that we discussed in our argument and in our Fig. 1A (2)] is also not included in the 4/15 argument. We could improve the odds more by adding papers from our group (published before and after that review), but lucky you, you are scientists and not gamblers.

Nevertheless, this Point:Counterpoint series proves to be much easier to settle than expected. For example, our opponent alerts you to the fact that we would try to downgrade the importance of endothelial-derived factors by presenting them as modulators of HPV. But we do not really have to. He has done this for us, in the “gambler’s guide to HPV,” that he offered you (2). The conclusion of this review reads: “media
tors derived from the pulmonary vascular endothelium exert a powerful modulating influence on the response of the pulmonary circulation to hypoxia.” We could not agree more.

In his current argument, our opponent concludes: “It is, therefore, possible that the activation of Rho kinase during sustained HPV represents the bridge between physiological HPV . . . and the pathophysiological consequences of chronic hypoxia.”

REFERENCES