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Oxygen Sensing in the Ductus Arteriosus: Endothelin Still a Player

To the Editor:

In a recent issue of *Circulation Research*, Hong et al[1] provided additional data in support of a mitochondrial mechanism for oxygen sensing in the ductus arteriosus. While commending the authors on the advance in this area, I find objectionable their hasty dismissal of an alternative scheme implicating endothelin in the same process. Far from being a concept exclusively originating from our work, as implied in the article, this position is espoused by diverse groups.[2]

In taking their conclusion to the fore, Hong et al[1] quoted 3 publications that warrant a comment. The first one by Michelakis et al,[3] being based on experiments with the isolated human ductus, negates a role for endothelin because the combined inhibition of its synthesis and action (with phosphoramidon and BQ123, respectively) is reportedly not followed by curtailment of the oxygen contraction. Furthermore, in the same article, oxygen does not increase the yield of the peptide. Regretfully, however, in reaching the former conclusion, the authors compared the oxygen response of an untreated vessel with that of a vessel being exposed not only to the endothelin inhibitors but also to drugs (ie, meclofenamate, L-NAME) interfering with potent endogenous relaxants, such as prostaglandin E_2 and nitric oxide. In other words, the action of endothelin inhibitors was assessed on a vessel manifesting an enhanced contractile drive for oxygen, incidentally documented by the authors themselves,[3] although using still the untreated vessel as a reference. Hardly a condition to observe an inhibition, particularly when testing, as was the case, a single, maximally effective oxygen concentration rather than a range of concentrations. On the contrary, the study of endothelin release from the human ductus poses difficulties of its own. One is dealing with a vessel intrinsically prone to constriction before surgery and being kept patent by continuous treatment with prostaglandin E_1. That is an agent which, besides relaxing the ductal muscle, can promote remodeling of the wall.[4] Not fortuitous in this context is possibly the finding that endothelin release is manyfold higher with the neonatal human ductus than with a freshly dissected ductus from the term fetal lamb.[3,5] Hence, the suspicion arises that a localized endothelin rise in response to oxygen might have been obscured by a larger pool of the compound originating from nonrelevant source(s). Admittedly, harder to explain are the data from the second article being cited in which Fineman et al[6] report the inability of an endothelin antagonist (PD-156707 in this case) to interfere with the oxygen-induced contraction of the lamb ductus both in vitro and in vivo. However, methodological differences, already underlined by us, may account for this incongruence, at least for the in vitro situation, because the same inhibitor seems effective in our hands.[7] The last article under consideration by Winters et al[8] is out of context here because it addressed the role of endothelin in pulmonary hemodynamics and, in so doing, the ductus wall was infiltrated with formalin to avoid any confounding influence from changes in the shunt. Collectively, then, the data purportedly contradicting an oxygen-sensing function for endothelin are not as firm as being portrayed by Hong et al.[1] In the end, I believe it is intrinsically unrewarding to oppose 1 scheme for oxygen sensing to the other, and an effort should instead be made to determine how the 2 mechanisms may eventually dovetail in promoting ductus closure. This is our position[2] and, in fact, while validating the endothelin function, we have found evidence of an alternative, hitherto uncharacterized, oxygen-sensing mechanism[9] that could well represent the mitochondrial function being investigated by Hong et al.[1]

Disclosures

None.

Flavio Coceani
Institute of Life Sciences
Scuola Superiore Sant'Anna
Pisa, Italy

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Correspondence to Flavio Coceani; e-mail: coceani@sssup.it
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