Endothelial dysfunction after right coronary artery remodeling: a new pathogenetic role of eNOS uncoupling?

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LU ET AL. (2) reported in the Journal of Applied Physiology by using a swine model of pulmonary artery banding-induced right ventricular hypertrophy (RVH) that the outward remodeling of the right coronary artery (RCA) induces reactive oxygen species (ROS) generation, an increase in basal vascular tone, and endothelial dysfunction, stemming from endothelial nitric oxide synthase (eNOS) uncoupling. This sophisticated study provides new insights in the vascular consequences of RVH. However, they did not investigate eNOS uncoupling by measuring eNOS-dependent ROS generation, NOS activity, and/or the eNOS monomer/dimer ratio (1). In addition, they did not measure levels of tetrahydrobiopterin (BH₄), dihydrobiopterin, and/or their ratio in the RCA tissue to confirm BH₄ oxidation (3). This study also demonstrated an improvement of endothelial function after administration of BH₄ and stated that this effect points to eNOS uncoupling. However, BH₄ has, besides its eNOS cofactor role, a broad spectrum of pleiotropic effects such as significant direct antioxidant (i.e., superoxide scavenging) effect, which was not investigated by, e.g., administration of BH₄. In addition, the authors measured, very elegantly by using three independent methods, the total ROS production. Unfortunately, they did not use NOS inhibitors such as L-NAME or L-NMMA to determine the amount of eNOS uncoupling-induced ROS generation. Therefore, an improvement of endothelial function by administration of BH₄ is not sufficient to argue that eNOS uncoupling is involved.

The source of ROS generation in the pathogenesis of pulmonary artery banding-induced remodeling and endothelial dysfunction is intriguing. The authors mentioned that they used Western blot and chemiluminescence analysis to support the important pathogenetic role of NADPH oxidases in the pathogenesis of RVH-induced RCA remodeling. However, no data of chemiluminescence analysis (except total O₂⁻ production) are provided in this manuscript.

Overall, Lu et al. (2) described very appealingly that RVH-induced RCA remodeling induced total O₂⁻ generation and endothelial dysfunction and have paved the way for further research to tackle endothelial dysfunction in patients with RVH. Nevertheless, no direct evidence is provided for a pathogenetic role of eNOS uncoupling.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES