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Another Piece in the Estrogen Puzzle of Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) affects predominantly women, yet women with PAH have better survival than men with PAH. Women have a more robust response to endothelin receptor antagonism, and treatment-associated improvements in right ventricular (RV) function account for survival differences between men and women with PAH (1, 2). Although female sex has been linked to the development of PAH, response to therapy, and better RV function, the role of estrogen in PAH is not completely understood (a comprehensive review of animal and human studies in this area is discussed by Hester and colleagues [3]). Higher levels of circulating 17β-estradiol (E2), the most potent estrogen, are associated with increased risk for PAH and more severe disease in both men and postmenopausal women (4–6), and variations in E2 metabolism influence the penetrance of heritable PAH (7). Although these human observations consistently demonstrate sexual dimorphism in PAH and suggest a critical role for E2 in pulmonary vascular disease, they have generated more questions than answers about the effect of E2 across the cardiopulmonary interface.

Experimental models of pulmonary hypertension (PH) have provided fundamental mechanistic insight; however, as in humans, these studies fall short in crossing the translational divide, and the estrogen puzzle of pulmonary vascular disease remains unsolved. In contrast to humans, female sex in hypoxia-induced and monocrotaline-induced PH (MCT-PH) models is protective. Endogenous and exogenous E2 has been shown to prevent, mitigate, and reverse PH in these models (8, 9). In MCT-PH, E2 is associated with increased nitric oxide and prostacyclin levels and decreased macrophage infiltration (10). In contrast, transgenic and Sugen-hypoxia (SuHx) models of PH demonstrate a female bias similar to humans, and as in humans, SuHx females have better RV function and improved survival compared with males (11–14). In the SuHx model, E2 promotes a proinflammatory and proangiogenic response but inhibits RV fibrosis, decreases collagen deposition in the myocardium, and increases proximal pulmonary artery (PA) compliance (12, 13). These studies demonstrate that E2 may have differential effects on the pulmonary vasculature as compared with the RV, but the effects of E2 on RV afterload and on the mechanics of the pulmonary vasculature have not been studied.

In this issue of the *Journal*, Philip and colleagues (pp. 371–374) describe the effect of endogenous and exogenous E2 on the prevention of SuHx PH (15). Pulmonary vascular mechanics were compared in female rats with intact cyclical endogenous E2 and ovariectomized rats with and without exogenous E2 supplementation. Rats that received continuous exogenous E2 were protected from PH with similar levels of RV systolic pressure and intermediate and distal PA impedance compared with the intact and ovariectomized rats. Exogenous E2 prevented an increase in the transpulmonary gradient, preserved distal PA distensibility, and was associated with a 60% reduction in PA wall remodeling. Treatment with a rho kinase inhibitor in the absence of continuous exogenous E2 demonstrated that SuHx-induced increases in RV afterload were driven by vasoconstriction.

This carefully executed study not only adds new knowledge in its use of pulsatile pulmonary vascular mechanics as surrogates of RV afterload but also provides critical insight into the protective role of E2 on impedance, distensibility, and remodeling in the distal PA. The distinction between biologic endogenous E2 exposure in intact animals versus exogenous E2 treatment in ovariectomized animals is an important one, as is isolating vasoconstriction. The findings of this study mirror limited observational data in humans that exogenous hormone therapy may prevent PH in postmenopausal women with systemic sclerosis (16). Similarly, higher levels of E2 in hormone therapy users have been associated with better RV function in postmenopausal women without clinical cardiovascular disease (17).

What pieces remain to solve the estrogen puzzle in PAH? Results from the preventative strategy used here will need to be replicated in rescue experiments and compared in male animals and ideally in young and aged animals. Downstream genomic effects of E2 on biomechanics and cardiopulmonary function may also differ from nongenomic vasodilatory effects. Numerous human and experimental observations implicate female sex and E2 (as well as other sex hormones, their metabolism, receptor signaling, and sex chromosomes) in the pathogenesis of PAH. This study is a strong contribution to accumulating evidence of a pleiotropic role of E2 on tissues, which may explain the observed contradictions in animal

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models and human studies to date. The biggest challenge remains bench-to-bedside and bedside-to-bench translation as hormones are tested as therapeutic targets to improve the lives of women and men living with PAH. ■

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