The estrogen paradox in pulmonary arterial hypertension

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Idiopathic pulmonary arterial hypertension (PAH) is a disabling condition characterized by PA vasoconstriction and remodeling as well as in situ thrombosis and eventual right heart failure. Idiopathic PAH occurs more frequently in females than in males. The female:male ratio is 1.64 ~ 3.88:1. Although endogenous sex hormones including estrogen have been suggested to account for the observed gender differences in PAH, a precise pathobiology for the gender differences remains uncertain. Recent studies demonstrated that estrogen exerts beneficial effects on the pulmonary vasculature. However, it seems to contradict the female predominance that is observed in idiopathic PAH.

Moreover, Sweeney and Voelkel (53) showed that early and long term estrogen exposure might be correlated with an increased risk of the development of PAH. Here we ask the question: Is estrogen a friend or a foe? According to accumulating evidence, we postulate that the different effects of estrogens on different target cells could account for this paradox, i.e., estrogens may exert beneficial effects only on the increased muscularization of vessel walls, but not on phenotypically altered endothelial cells. The effects of estrogens on the pulmonary vasculature are potent and complex yet not fully understood. A better mechanistic understanding may allow for future therapeutic interventions in patients with PAH.

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Perspectives

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Idiopathic pulmonary arterial hypertension (PAH) is a disabling condition characterized by PA vasoconstriction and remodeling as well as in situ thrombosis and eventually right heart failure (5, 30, 40). Idiopathic PAH occurs more frequently in females than in males. The female:male ratio is 1.64 ~ 3.88:1 (2, 17, 20, 35, 52).

Although endogenous sex hormones including estrogen have been suggested to account for the observed gender differences in PAH, a precise pathobiology for the gender differences remains uncertain. Recent studies demonstrated that estrogen exerts beneficial effects on the pulmonary vasculature. However, it seems to contradict the female predominance that is observed in idiopathic PAH. Moreover, Sweeney and Voelkel (49) showed that early and long term estrogen exposure might be correlated with an increased risk of the development of PAH (49). Here we ask the question: Is estrogen a friend or a foe? In this article, we describe possible mechanisms with vascular remodeling with marked proliferation of pulmonary artery smooth muscle cells (SMC) and/or endothelial cells (EC) to account for the observed estrogen effects.

Estrogen in human disease. Idiopathic PAH is widely considered to be a disease of young women, and recently severe PAH has been reported to be able to occur in postmenopausal women (51). A postmenopausal condition is the main risk factor for developing PAH in scleroderma patients (42). Interestingly, hormone replacement therapy may prevent the development of isolated pulmonary hypertension (PH) in postmenopausal patients with systemic sclerosis (4). These results suggest that the loss of estrogen associated with postmenopausal status may be a risk factor for PAH like coronary artery disease (CAD) (6, 13, 23, 55). The REVEAL registry contains a large sample of scleroderma patients and will likely shed greater light on associations between estrogen replacement and all forms of PAH, including those associated with scleroderma (2).

As mentioned above, several reports suggest that estrogen exerts benefit effect in human PAH. However, oral contraceptives have been considered to be a potential risk factor for the disease (29). Moreover, one case report described the development of familial PAH in an elderly woman after the introduction of hormone replacement therapy (34). Thus, the female predominance in PAH and the adverse effects of estrogen suggest that this hormone has the theoretical potential to negatively affect PAH. A heterogenous cohort of obese women with pulmonary hypertension reported an unusually high incidence of exogenous estrogen use (49), further complicating the interpretation of estrogen’s effects on the pulmonary vascular disease. Unfortunately, definitive epidemiological studies about the risks of exogenous estrogens in PAH are near impossible given the rare nature of the disease and its predilection for the young.

Estrogen in animal models. Estrogen exerts a beneficial effect on the pulmonary vasculature in hypoxic animal models. Female Sprague-Dawley rats exposed to chronic hypoxia have been noted to exhibit less severe PH than their male counterparts (37). Similar results have also been reported in other animals (5, 31). Interestingly, chronically hypoxic ovarietomized rats develop more severe PA remodeling and right ventricular hypertrophy than chronically hypoxic rats with intact ovaries (39). Exogenous estrogen attenuates the severity of PH in the ovarietomized animals (39). Along these lines, male mice are less resistant than females when exposed to hypoxia (48). The treatment of ovarietomized females or castrated males with estradiol increases survival. In another model, ovarietomized rats exposed to monocrotaline exhibit more severe disease than intact rats (53). This can be attenuated by the administration of the estradiol metabolite 2-ME (53). Chronic hypoxia-induced PH in male rats can also be attenuated by 2-ME (58).

English et al. (8) reported the acute administration of estrogen in an isolated PAH model to cause vasorelaxation under normoxic conditions. Along these lines, pulmonary vasoconstriction to hypoxia has thus been reported to decrease during pregnancy, when the circulating levels of estrogen are high (9, 33). Furthermore, hypoxic vasoconstriction is attenuated in lungs isolated from female sheep compared with lungs from...
Estrogens have a well-documented effect on the pulmonary vasculature. This effect is mediated through genomic and nongenomic mechanisms. Estrogen increases the prostacyclin release and enhances the production of nitric oxide (NO), the latter by the upregulation of endothelial NO synthase (eNOS) (14–16, 24, 50). This increase in prostacyclin and NO is partially the result of rapid and nongenomic mechanisms (25, 43). However, the genomic pathways also play a role in this process. Fetal pulmonary EC respond to estrogen exposure by increasing the eNOS mRNA levels and eNOS activity (28). The activation of the estrogen receptor is necessary for this response (28). In addition, estrogen downregulates the expression of endothelin-1 (ET-1), a potent vasoconstrictor and mitogen (7). Earley and Resta (7) demonstrated that chronic hypoxia increases the pulmonary preproET-1 mRNA levels in ovariectomized rats but not in rats with intact ovaries. Replacement therapy with 17β-estradiol prevents such hypoxia-mediated increases in the preproET-1 mRNA and ET-1 peptide expression. Moreover, a line of evidence suggests that estrogen inhibits rho-kinase (44). The rhoA/rho-kinase pathway recently has gained substantial interest in a variety of cardiovascular disorders, including PAH. Rho-kinase mediates vascular SMC proliferation that results in pulmonary vascular remodeling (Fig. 1).

**Estrogen and vascular remodeling with marked proliferation of SMC and/or EC.** The reason for these estrogen disparate findings in human PAH and hypoxic animal models is not clear. However, we postulate that the different effects of estrogens on different target cells could explain the findings (Fig. 1). A recent review suggests that there may be some pathogenetic differences in both the classic rodent models of mild to moderate pulmonary hypertension, namely, the chronic hypoxia and monocrotaline models, and human PAH (41). Both of these models lack clustered proliferated EC in the lumen of pulmonary arteries (32, 21). Pulmonary EC constitute a stable cell population with a very low turnover rate, and, apparently, neither severe chronic hypoxia/hypoxemia nor monocrotaline pyrrole causes the emergence of a proliferative, dysfunctional EC phenotype (38). The defining pulmonary vascular alteration in both of these models, namely, medial muscular thickening of proliferating SMC, is potentially reversible upon reexposure to normoxia or with the passage of time after monocrotaline injection (19, 22, 32). Contrastively, human PAH has two types of remodeling: pulmonary vascular disease, which develops predominantly because of increased muscularization of the vessel walls, and pulmonary vascular disease, which develops because of EC proliferation (36). The SMC shift between a proliferative and nonproliferative phenotype may be attributed to cellular plasticity, rather than due to the selective expansion of distinct cell subpopulations (27), thus suggesting that this form of vascular remodeling may be reversible. A recent study has demonstrated irreversible PAH in congenital heart disease to be strongly associated with an impaired apoptotic regulation of EC (26), with endothelial damage and with increased circulating EC counts (45), thus suggesting that vascular remodeling, which develops because of phenotypically altered EC, may be irreversible. These facts indicate that estrogen may exert beneficial effects only on the increased muscularization of vessel walls induced under hypoxic conditions and monocrotaline, but not on phenotypically altered EC, because of these beneficial effects shown only in hypoxic and monocrotaline models and hypoxic PAH (Fig. 1).

Moreover, recent reports suggested that preventing or reversing sustained constriction and neomuscularization of pulmonary arteries in the classic chronically hypoxic and monocrotaline models is not equivalent to dissolving obstructive neointimal and other complex vascular lesions that seemingly...
account for the high pulmonary vascular resistance in PAH (3, 47). The effects of estrogens should be evaluated by using more recent rodent models of neointimal lesion-associated PH rather than the classic rodent models (3).

Estrogen is an angiogenesis factor (46) that regulates the expression of the vascular endothelial growth factor (VEGF) receptor KDR (11), and the VEGF gene contains a functional estrogen response element (18). Moreover, hormone replacement therapy causes an increase in VEGF serum levels in postmenopausal females (1). Therefore, the estrogen effects may result in an exacerbation of pulmonary vascular disease that develops because of EC proliferation, because VEGF is an obligatory survival factor for EC (12) and the overexpression of VEGF is associated with EC proliferation in severe PAH (54). Thus, estrogens may exert adverse effects on phenotypically altered EC (Fig. 1).

Discussion. As mentioned above, estrogens may exert beneficial effects only on SMC, but not on phenotypically altered EC, i.e., estrogens may exert the different effects on different remodeling in PAH (Fig. 1).

Several significant factors generate confusion and opposite results in evaluating the role of estrogens in PAH. These factors include the several effects of estrogens on different receptors and opposite effects (especially on cell proliferation) exerted by several peripheral estrogen metabolites. Although the loss of reproductive hormones associated with postmenopausal status may be a risk factor for both PAH (4, 42, 51) and CAD (6, 13, 23, 55), it is unclear to what extent the postmenopausal status may be a risk factor for both PAH (4, 51) and CAD (6, 13, 23, 55). Thus, estrogens may exert adverse effects on phenotypically altered EC (Fig. 1).

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

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