The Challenge of the “Estrogen Paradox” in Pulmonary Arterial Hypertension

Keiko Yamauchi-Takihara, MD, PhD

Because of recent advances in the understanding of pulmonary arterial hypertension (PAH), several genes responsible for idiopathic PAH (IPAH) and hereditary PAH (HPAH) have been revealed, such as the bone morphogenetic protein (BMP) receptor (BMPR2, BMPR1B), activin receptor-like kinase 1 (ALK1), endoglin (ENG), Smad9 (SMAD9) and caveolin-1 (CAV1) genes. However, considering the low rate of occurrence between men and women under the age of 20 years, this female predominance suggests a potential role for estrogens in the pathogenesis of PAH.

There are several hypotheses to explain the female predominance in PAH prevalence: (1) female hormones adversely affect the pulmonary vasculature and the right ventricle; (2) male hormones exert protective effects on the pulmonary vasculature; and (3) there are other factors to which women are more likely to be sensitized than men when they are exposed to the risk factors (autoimmunity, pregnancy, anorexia, etc.). Although not all of these hypotheses have been fully evaluated, the effects of female hormone on the pathogenesis of PAH are discussed according to recent research developments in animal models and human PAH.

New Insight Into the Estrogen Paradox

Administration of estrogen has been reported to attenuate PAH in classical animal models induced by chronic hypoxia or monocrotaline administration, and to aggravate PAH in ovariectomized female animals. Based on those results, it has been concluded that estrogen exerts protective effects on the pulmonary vessels, although this does not explain the female predominance in human PAH, and this apparent contradiction between clinical epidemiology and previous animal data has given rise to the concept of the “estrogen paradox” in PAH.

In recent years, evidence has emerged to highlight the effects of estrogen in the development of PAH. West et al studied those with BMPR2 mutations and found significantly decreased transcript level of cytochrome P450 1B1 (CYP1B1; a cytochrome p450 family enzyme critical to estrogen metabolism) in affected females when compared with unaffected females with the BMPR2 mutation. In addition, Austin et al reported that single nucleotide polymorphisms of Asn453Ser (N453S) in CYP1B1 were associated with the incidence of HPAH.

Among females, there was 4-fold higher penetrance among subjects homozygous for the wild-type genotype (N/N) than for those with the N/S or S/S genotype. Consistent with those findings, the urinary estrogen metabolite levels (2-hydroxyestrone/16α-hydroxyestrone) were 2.3-fold lower in affected mutation carriers than in the unaffected mutation carriers. It is conceivable that variation in estrogen and estrogen metabolism might modify the risk for developing HPAH. In addition, an estrogen receptor (ER) binding site is demonstrated in the promoter region of the BMPR2 gene, and administration of estrogen induces direct binding between ERα and the BMPR2 promoter, resulting in reduced expression of BMPR2.

Recent studies using animal models have highlighted the adverse effects of female sex and estrogen on the development of PAH. White et al developed a mouse model overexpressing the serotonin transporter (SERT; SERT+ mice). Although PAH did not develop in male SERT+ mice, female SERT+ mice exhibited both PAH and right ventricular hypertrophy. They further performed microarray analysis of the pulmonary arteries of SERT+ mice, and found that key molecules (CEBP, CYP1B1 and FOS) were associated with the development of PAH. In addition, they demonstrated that 17β-estradiol and serotonin increased the expression of these key molecules in pulmonary artery smooth muscle cells (PASMCs). They also showed that increased CYP1B1-mediated estrogen metabolism could promote PAH in hypoxic mice and hypoxic+SU5416 (VEGF receptor antagonist) mice.

Increased susceptibility of female mice was also observed for dexfenfluramine (Dfen)-induced PAH. Dempse et al demonstrated that Dfen upregulated CYP1B1 expression in murine lung and PASMCs from PAH patients. Administration of 17β-estradiol increased the expression of both Tph1 (tryptophan hydroxylase 1); the rate-limiting enzyme in the synthesis of serotonin.

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Health Care Center, Osaka University and Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Toyonaka, Japan

Mailing address: Keiko Yamauchi-Takihara, MD, PhD, Health Care Center, Osaka University and Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 1-17 Machikaneyama Toyonaka 560-0043, Japan. E-mail: takihara@wellness.hss.osaka-u.ac.jp

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Female sex and hormones have complex effects on the pulmonary vasculature. Recent studies using sex-specific murine models of PAH and the current report by Ichimori et al bring new understanding of the adverse effects of estrogen on the development of PAH. However, the “estrogen paradox” is not yet fully understood, and further investigation into the effects of sex hormones on the pulmonary vessels and the right ventricle is necessary to discover new therapeutic targets for PAH.

**Conclusion**

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