



EDITORIAL

Oestrogen and the sexual dimorphism of pulmonary arterial hypertension: a translational challenge

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The striking female predominance in idiopathic and familial pulmonary arterial hypertension (PAH) has been well documented since the publication of the National Institutes of Health (NIH) registry in 1987 [1]. In the majority of PAH registries, females are at least twice as likely to be represented as males, with female to male ratios as high as four to one [2–6]. Notably, these sex differences are not fully explained by a differential distribution of known risk factors for PAH by sex, such as autoimmune disease or anorexigen exposure. Taken together, these epidemiological data suggest that other sex-associated factors, including sex hormones, may influence PAH pathogenesis.

Endogenous and exogenous sex hormone exposures represent a biologically plausible potential risk factor for PAH. Sex hormones determine *in utero* organ development, drive tissue-specific changes in early life and exert an evolving influence across the life span as their absolute and relative concentrations shift [7]. There can be no doubt that sex hormones, with their ability to modulate vascular tone, inflammation and remodelling, play a fundamental role in determining cardiovascular phenotypes [8]. Emerging data on the importance of sex hormones in animal models of pulmonary hypertension provide tantalising evidence that the pulmonary vascular phenotype of an organism is dependent upon these pleiotropic signalling molecules [9, 10].

In this issue of the *European Respiratory Journal*, YUAN *et al.* [11] demonstrate that monocrotaline (MCT) creates an oestrogen-deficient state in rats characterised by low plasma oestradiol (E2) and altered pulmonary expression of oestrogen receptors and enzymes responsible for E2 anabolism (reduced) and catabolism (increased). In the absence of sufficient endogenous (*i.e.* post-ovariectomy) or exogenous oestradiol, a pro-proliferative, anti-apoptotic and vasoconstrictive phenotype emerges that is mediated in part *via* reduced nitric oxide and prostacyclin, and increased endothelin. Rescue of the phenotype *via* the provision of exogenous E2 illustrates the homeostatic influence of oestrogen signalling on the pulmonary circulation of these animals. These

data add depth to a growing body of literature that explores the mechanisms by which oestrogen, as well as its metabolites [12] and receptors [13, 14], protects against pulmonary hypertension in the MCT-exposed rat.

Now we are presented with the challenge of how to translate and apply these findings to our understanding of human PAH. Study of these model systems has provided tremendous insights into the biology of oestrogen signalling in the pulmonary circulation. While this biology is critical to pulmonary vascular phenotypes in both humans and animals, the story of sex in PAH is far from complete. Current animal models can offer only limited insight into sex differences in PAH, due to the “oestrogen paradox” whereby female animals are relatively protected against the incidence of pulmonary vascular remodelling, right ventricular failure and death when challenged with hypoxia or MCT as compared to males [15]. This distinction underscores the importance of investigating determinants of sexual dimorphism in human PAH.

Epidemiological studies of PAH are challenged by the rarity of the disease, but the few that have been conducted to date suggest that exogenous hormones and reproductive events have a role in PAH. The NIH registry reported that a history of oral contraceptive use was associated with an earlier age of PAH onset (30.9 *versus* 39.9 years, $p < 0.002$) [16]. SWEENEY and VOELKEL [17] reported high rates of oral contraceptive and hormone replacement therapy use in a cohort of pre- and post-menopausal females with PAH. Though these studies did not include a comparison group of unaffected females, they do suggest that females with PAH may have a different level of exposure to exogenous oestrogens (oral contraceptives and/or hormone replacement therapy) than the general population. There is also clear evidence that pregnancy in PAH is associated with malignant, and potentially fatal, progression of PAH and right ventricle failure [18–20], though it is unknown whether this is attributable to the vascular effects of hormones or to right ventricular decompensation in the face of pregnancy-induced increases in plasma volume and cardiac output. Lastly, among patients with scleroderma, post-menopausal status is a strong predictor of PAH incidence [21] and provision of hormone replacement therapy may attenuate this risk [22].

Emerging data on PAH prognosis adds more complexity to the question of how sex-related factors influence PAH. While females represent the majority of PAH cases diagnosed, in fact they enjoy a relatively longer survival as compared to their male counterparts. Male sex is a strong predictor of death from

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PAH [23, 24], and its impact is magnified with advancing age [25], raising the interesting possibility that a dynamic hormonal milieu, defined by the relative contributions of male and female sex hormones that change over time, impacts both the pulmonary vessels and right ventricle. Whether this differential survival results from a shift to a more oestrogenic state in male menopause, confounded by prognostically favourable factors more common in females, or differential right ventricular function by sex [26] remains unknown. Alternatively females may derive a greater therapeutic benefit from approved PAH therapies, a hypothesis supported by the recent analysis of endothelin receptor antagonist clinical trials by GABLER *et al.* [27]. These demonstrations of sexual dimorphism necessitate further investigation into the impact of sex hormones on the pulmonary circulation and the right ventricle's response to increased pulmonary vascular resistance in order to enhance our understanding not only of pathogenesis but also of PAH progression and outcomes.

Inconsistencies in associations between sex and PAH, be they across species, or between disease incidence and progression, may be partly explained by evidence that complex interactions between genetic and environmental determinants govern the course of the disease. In fact, several lines of evidence implicate a sex-gene interaction in PAH pathogenesis. Female sex increases the penetrance of mutations in bone morphogenetic protein receptor II (BMPR2) in families with heritable PAH, especially after puberty [28]. In human lymphocytes BMPR2 expression is differential by sex, and modulated by oestradiol in an oestrogen receptor-dependent fashion [29]. Penetrance of BMPR2 mutations is modified by polymorphisms in CYP1B1, an oestrogen metabolising enzyme [30]. Furthermore, in the only case-control study of PAH in patients with advanced liver disease, we have shown that common single nucleotide polymorphisms in aromatase (CYP19A1) and oestrogen receptor- α (ESR1) are associated with higher oestradiol levels and a significant increase in the risk of PAH [31]. These data offer a potential pathogenetic link between sex hormones and human PAH.

Despite this wealth of provocative data in animal models and studies enrolling PAH patients, there has never been a controlled epidemiological study of the role of reproductive events or hormonal exposures in PAH incidence. The rarity of PAH (15 cases per million) has constrained epidemiological investigations to date, with clinical research largely limited to small trials, case series and disease registries [2–3], approaches that cannot identify factors associated with PAH incidence [32]. Case-control designs can efficiently be applied to the study of risk factors for rare diseases, but management of PAH in referral centres poses a significant challenge to identifying the appropriate control subjects for these cases [33].

The study of the incidence and progression of rare human diseases is inherently challenged by the tasks of assembling adequate sample sizes and biobanks of affected tissues and identifying valid control populations. Nonetheless, efforts to estimate the association between reproductive and hormonal risk factors and PAH are worthwhile, since such epidemiological evidence could illuminate long-standing questions about the marked sex differences in PAH and motivate novel therapeutic strategies. As has been applied in the study of

other rare conditions [34], collaborative studies that pool data and biospecimens from high-quality existing PAH registries and cohorts may offer a step forward towards this goal.

As we increasingly understand the complexities of sex hormone signalling in animals and models of pulmonary hypertension, we should be reminded to question the generalisability of these model systems to human PAH. Each of the animal models commonly used to study pulmonary hypertension possess unique attributes, but none are considered to be satisfactorily representative of human disease. Thus, it is critical that our study of sex differences in PAH is also approached from investigations of human populations. The discipline of translational science encourages us to frame research as a bidirectional concept, in which the knowledge generated from the bedside or the population can be translated to the benches of laboratory science, and *vice versa* [35, 36]. For example, observational epidemiological studies can generate novel designs and hypotheses that can be tested using more tractable experimental approaches in the clinical and basic sciences. It is imperative that we apply these translational philosophies to establish research collaborations across the disciplines investigating PAH sex differences. With such an approach, we will be well positioned to speed closure of the knowledge gap concerning sex and PAH pathogenesis, and to more expeditiously identify novel therapeutic targets.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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