PH, and that E_2 induces right ventricle–pulmonary vasculature uncoupling: despite more severe PAH, females had significantly reduced right ventricular hypertrophy, and ovariectomy exacerbated the increase in right ventricular mass, an effect that was reversed by exogenous E_2 [2, 7]. Therefore, MCT-PH may not be the best model for studying the complexities of oestrogen pharmacology in human PAH.

The concept that E_2 deficiency is involved in MCT-PH may be correct; but this concept may be incorrect in human PAH. Monocrotaline is a toxin that, in male rats, reduces plasma testosterone levels by 50%, and gonadal toxicity could be the reason for reduced E_2 levels. Furthermore, in the YUAN *et al.* [1] study, animals were not synchronised for oestrous cycle, and this may also have contributed to differences in plasma E_2 levels. It is noteworthy that recent clinical data suggest that female sex and increased, rather than decreased, E_2 levels and P450 Cyp19 (aromatase) activity are associated with greater risk of developing portopulmonary PAH [8].

Oestradiol may exert beneficial effects on the right ventricle, yet may exacerbate PAH and pulmonary vascular lesions. The question of whether oestradiol is good, bad, or both in human PAH requires further investigation. We view E_2 as a double-edged sword in human PAH.

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From the authors:

We thank S.P. Tofovic and E.K. Jackson for their interest in our study [1]. It is well known that pulmonary arterial hypertension (PAH) is a female-predominant disease [2–4], and this seems to indicate that oestrogens may be predisposing factors. However, this contrasts with the fact that females with PAH have preserved right ventricle function and survival compared with males with PAH [2–5], suggesting that oestrogens could be protective of PAH. So, oestrogens may be viewed as a double-edged sword in PAH. To explore the role of oestrogens in PAH, we observed the effect of endogenous and exogenous E_2 (17β-oestradiol) in rats with monocrotaline (MCT)-induced pulmonary hypertension (PH) [1]. Our results suggested similar protective roles of endogenous and exogenous E_2 in pulmonary vascular remodelling and right ventricular hypertrophy in MCT-induced PH rats, which is similar to the effect of E_2 reported in the study of UMAR *et al.* [6]. E_2 therapy has been shown to rescue both pulmonary vasculopathy and right ventricle function in rats with PH. Thus, our results do not support the opinion expressed by S.P.Tofovic and E.K. Jackson that E_2 may have opposite roles in the pulmonary vasculature and the right ventricle.

In the study described by S.P. Tofovic and E.K. Jackson, 2-methoxyoestradiol (2ME) attenuated the development of PH in rats and was decisively more potent than E_2 in increasing prostacyclin and nitric oxide release, inhibiting endothelin-1 synthesis in endothelial cells, and inhibiting growth of systemic and pulmonary vascular smooth muscle cells. We do not exclude the possibility that the beneficial effects of oestradiol in MCT-induced PH are mediated, at least in part, by 2ME. Therefore, it is a good suggestion by S.P. Tofovic and E.K. Jackson that the effects of E_2 and its metabolites are studied in other animal models of PH, which may further confirm the overall effects of E_2.

We have conducted a cohort study at our centre in which serum concentrations of oestradiol were measured in 120 adult fertile female patients with incident idiopathic PAH and 120 age- and sex-matched healthy female controls. Serum oestradiol concentrations were significantly decreased in PAH patients compared with controls (median (interquartile range): 184.6 (111.9–351.3) *versus* 271.4 (158.4–497.6) $pmol \cdot L^{-1}$; $p<0.001$). The same trend of was observed in serum oestradiol concentrations in 42 female patients with idiopathic PAH and 42 female controls studied in the follicular phase (median (interquartile range): 166.2 (114.1–223.6) *versus* 195.4 (144.2–287.7) $pmol \cdot L^{-1}$; $p=0.03$) (fig. 1). The data indicated that serum oestradiol concentrations were

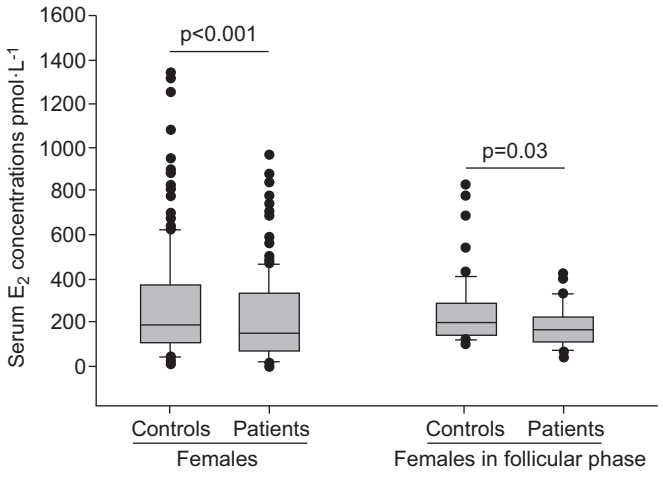

FIGURE 1. Serum concentrations of oestradiol in female patients with idiopathic pulmonary arterial hypertension (PAH) and in control subjects. The panel indicates that serum oestradiol (E_2) concentrations were significantly lower in female idiopathic PAH patients than in controls. Patients: n=120; in follicular phase, n=42. Controls: n=120; in follicular phase, n=42. p-values are for the comparisons with concentrations in the control group. Boxes represent the 25th to 75th percentiles and the line in box the median.

decreased in these female patients with idiopathic PAH (unpublished results).

S.P. Tofovic and E.K. Jackson have also pointed out that in our study, animals were not synchronised for the oestrous cycle. The reason for not considering the oestrous cycle in our animal model was that we employed a large dose of oestrogen and ovariectomy to demonstrate the effect of oestrogen in the pathogenesis of PH. The difference in oestradiol concentrations induced by these methods is of greater magnitude than that induced by the menstrual cycle or oestrous cycle. Interestingly, our study implied that aromatase protein was decreased in the lungs of MCT-induced PH rats [1]. This result differed from a previous report showing that aromatase activity is associated with a greater risk of developing portopulmonary hypertension [7]. A possible explanation is that this MCT-induced PH animal model may be not suitable for patients with portopulmonary hypertension. We plan to measure plasma concentrations of oestradiol and its metabolic enzymes in other animal models of PH and in patients with various forms of PAH to better understand the puzzle.

Oestrogen and its metabolites are increasingly being implicated in the pathogenesis of PAH. The precise mechanisms explaining why females are at greater risk and have better survival remain elusive. Unravelling these mysteries may help to understand the biological processes of PAH, gain insight into the epidemiological trends observed in PAH, and provide novel therapeutic targets.

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