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Sex matters in pulmonary arterial hypertension

To the Editor:

It has been known for a while that female sex is a risk factor for pulmonary arterial hypertension (PAH), but that women with the condition survive better than men [1–3]. Further light has been shed on this paradox by the excellent meta-analysis recently reported by VENTETUOLO *et al.* [4] in the *European Respiratory Journal*. The authors showed that female patients with idiopathic or connective tissue-associated PAH have higher cardiac output and lower pulmonary vascular resistance. The average differences in male patients were small, but sufficient to translate into a 5–8% difference in mortality. What could be the explanation of this?

Population studies have shown that female lungs differ from those of men. Women have smaller lungs, decreased maximal expiratory flow rates and lower lung diffusing capacities [5]. These sex-related differences in the respiratory system persist after adjustment for body dimensions, which has been referred to as a ''dysanapsis'', or unequal growth of the lung parenchyma and bronchial tree with respect to body size. However, smaller lungs at any given body size do not affect gas exchange [6] and, if anything, would increase rather than decrease pulmonary vascular resistance. The control of breathing is also different in women, with progesterone-dependent, increased peripheral chemosensitivity [7], which results in in slightly but significantly lower arterial partial pressure of carbon dioxide [8]. However, hypocapnia has been shown to be a predictor or poor survival in PAH [9]. As the prognostic impact of sex on PAH was lost after the age of 45 years, VENTETUOLO *et al.* [4] understandably thought of possible anti-remodelling effects of oestrogens or pro-remodelling effects of testosterone.

We previously reported exercise stress echocardiographic measurements of higher resistive vessel distensibility in healthy women compared with men, which limits the increase in pulmonary artery pressures as flow increases [10]. The difference smoothened out after the age of 45 years, very much like in the study by VENTETUOLO *et al.* [4]. This adds argument in favour of oestrogen.

The fascinating aspect of the study by VENTUOLO *et al.* [4] is that beneficial effects of oestrogen seem to persist in the extensively remodelled pulmonary resistive vessels of PAH patients. Whether this is mechanically similar can be tested by exercise stress measurements of the pulmonary circulation and recalculation of resistive vessel distensibility from a curvilinear fit of four or five pressure–flow coordinates [11]. This can be performed noninvasively.

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Pre-menopausal women with pulmonary arterial hypertension survive better than men
http://ow.ly/vGL7M

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