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From the authors:

We are pleased by the great interest in our recently published manuscript [1].

In their letter, V. Cottin and co-workers describe the clinical course of a patient with chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and disproportional pulmonary hypertension, who showed considerable benefit from oral bosentan. The authors noted an improvement in 6-min walking test distance of >160 m 2 yrs after initiating bosentan therapy, but also reported a marked increase in carbon dioxide arterial tension levels. Indeed, the case report of V. Cottin and colleagues seems to illustrate the fact that patients with COPD and disproportional pulmonary hypertension could well improve on selective pulmonary vasodilators, despite disadvantageous effects on gas exchange. Nevertheless, with regard to the case report of V. Cottin and colleagues, we believe that the contribution of bilevel positive airway pressure (BiPAP) therapy for possible alveolar hypoventilation (body mass index 41 $kg \cdot m^2$) and residual previous pulmonary embolism might need to be considered in the context of clinical improvement. A further argument supporting the hypothesis that pulmonary hypertension in V. Cottin and colleagues' case report was not solely related to COPD, was the fact that no major abnormalities were evidenced by computed tomography scan and diffusion capacity was well preserved, uncommon findings in advanced emphysema. Moreover, haemodynamics in pulmonary arterial hypertension usually improve only marginally in most patients treated with pulmonary vasodilators, even when their clinical response to therapy is excellent [2]. In contrast, pulmonary hypertension in patients with adipositas hypoventilation syndrome is largely reversible on BiPAP ventilation, a feature also observed in this case (mean pulmonary artery pressure decreased from 65 mmHg to 34 mmHg under ventilation). We fully agree with V. Cottin and colleagues that randomised, controlled trials are the only reliable way to evaluate the efficacy of a drug with regard to a particular patient population.

The comments of C. Jardim and R. Souza merely summarise the limitations of our randomised, double-blind, placebo-controlled study, which have already been extensively mentioned in the original manuscript [1]. It should be noted that a similar study [3], in which right heart catheterisation at rest and during exercise was performed, also failed to show an improvement in stroke volume or exercise capacity following a 3-month treatment period with sildenafil. The absence of a treatment response was independent of the presence of pulmonary hypertension [3]. C. Jardim and R. Souza also ask for subgroup analyses. However, it is well known that investigators need to exercise caution when drawing conclusions from subgroup analyses as they have a proclivity to detect spurious effects [4]. We are not aware of a pathophysiological denominator between COPD-related pulmonary hypertension and hepatosplenic schistosomiasis, as cited in the letter by C. Jardim and R. Souza.

It is well known that pulmonary hypertension considerably aggravates during exercise in patients with severe COPD. Until now it has been unclear to what extent pulmonary hypertension limits exercise tolerance in severe COPD, given that pulmonary hypertension and the resulting right ventricular dysfunction could account for both muscle fatigue and hypoxia. Therefore, considering the patient profile of COPD and the general efficacy and established ease of use of oral endothelin (ET)-1 antagonists in patients with pulmonary arterial hypertension, it would be appropriate to consider whether the use of ET-1 receptor antagonist may find a valuable place in the therapy of pulmonary hypertension associated with COPD [5]. There are several similarities between patients with COPD and those with primary pulmonary hypertension: fibromuscular intimal thickening with a diffuse increase in smooth muscle cells within the intima [6]; low bronchoalveolar levels of vascular endothelial growth factor [7]; activation of phospholipase A2 [8]; and both epithelial and endothelial increased cell proliferation [9]. It is important to note that increased lipid peroxidation is a feature of all forms of pulmonary hypertension, including that seen in COPD [10], and endothelial nitric oxide production is decreased in COPD [11]. There is also evidence that ET_A and ET_B receptor expression is increased in the pulmonary arteries of patients with COPD [12], contrasting with heart failure in which the ET receptor expression is reduced [13] where ET-1 antagonists fail to affect the disease. Thus, although ET-1 levels do not correlate with survival in patients with COPD [14], and in contrast to the statements by A.K. Boutou and co-workers, there are strong pathobiological associations between the pulmonary vascular changes of COPD and ET-1 [5]. Moreover, prior to this trial, the efficacy of newer pulmonary vasodilators in patients with COPD was described in one case series, which showed a beneficial effect of pulmonary vasodilator therapy [15]. It is worth noting that the latter was an open label study rather than a placebo-controlled trial [15]. A.K. Boutou and colleagues also argue that bosentan has not proved to be favourable in patients with interstitial lung disease and therefore the hypothesis that it could be beneficial in patients with COPD is ''rather weak''. However, the study cited by A.K. Boutou and co-workers explicitly excluded patients with pulmonary arterial hypertension [16]. We might also add that the pathophysiology of COPD and idiopathic pulmonary fibrosis differs.

In summary, at the current time, there is evidence suggesting that patients with pulmonary hypertension due to severe chronic obstructive pulmonary disease will not benefit from pulmonary vasodilator therapy as evidence by our study [1] and by the study of RIETEMA *et al.* [3]. Whether patients suffering from ''disproportional'' pulmonary hypertension and chronic obstructive pulmonary disease might benefit from therapy remains to be proved in a randomised, placebo-controlled trial addressing this question.

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STATEMENT OF INTEREST

A statement of interest for D. Stolz can be found at www.erj.ersjournals.com/misc/statements.shtml

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Regional variations in pulmonary endarterectomy rates within the UK

To the Editors:

We were very interested in the paper by TOSHNER *et al.* [1] which highlights regional variations in pulmonary endarterectomy (PEA) rates for the UK population. The authors explore the reasons for this variability. Understandably they dismiss the possibility of differences due to variability in incidence or management. Their analysis looks at the PEA rate rather than the referral rate. This reduces, but does not abolish, the varying threshold for referral by designated centres as a cause. However, they conclude that the differences shown in the paper, are in a large part, due to the distance of patients from nationally designated centres for the management of pulmonary hypertension.

The one region that does not fit with this explanation is Scotland (UK) where there is a national centre for the management of pulmonary hypertension (the Scottish Pulmonary Vascular Unit (SPVU), Glasgow, UK) but the PEA rate appears to be similar to that seen in regions not served by pulmonary hypertension centres. In order to understand the reasons for the Scottish results, we have analysed the data on chronic thromboembolic pulmonary hypertension (CTEPH) patients seen by the SPVU between 2000 and 2008 (table 1).

These data show a number of possible additional reasons for the low Scottish rate seen in the TOSHNER *et al.* [1] study. The first is that the period 2000–2006 was early in the existence of the SPVU when its referral base was building rapidly. PEA incidence in our patients has increased dramatically over the last 8 yrs leading to a three-fold increase in the number of patients with CTEPH referred to our unit between the two epochs analysed in table 1. This occurred in parallel with an