tolerated and did not induce hypoxaemia in 12 weeks. However, there was a trend towards a decrease of forced vital capacity and diffusing capacity of the lung for carbon monoxide, while 6-min walking distance (6MWD) decreased from 320.9 m (232.96–408.84 m) to 302.9 m (205.01–400.79 m); $p<0.05$. Bosentan was not superior over the placebo in 6MWD in another double-blind, multicentre trial which included 158 patients with idiopathic pulmonary fibrosis [3]. Since the use of bosentan among patients with parenchymal lung disease has not proved to be favourable, the hypothesis that it could be beneficial for COPD subjects because they establish elevated levels of endothelin is rather weak.

While selective pulmonary vasodilation may benefit chronic obstructive pulmonary disease patients with increased pulmonary artery pressure during stress [4], this study was not designed to prove such an effect of bosentan. The pathophysiology of exercise limitation in severe chronic obstructive pulmonary disease subjects and the ventilation/perfusion ratio mismatching, which is induced by unselective pulmonary vasodilation [5], should have been taken more seriously under consideration in the study design of STOLZ *et al.* [1].

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STATEMENT OF INTEREST

None declared.

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To the Editors:

We read with interest the study by STOLZ *et al.* [1] reporting on the lack of improvement of exercise capacity caused by the dual endothelin-1 antagonist bosentan in patients with severe chronic obstructive pulmonary disease (COPD) and absence of severe pulmonary hypertension (PH) at rest. Pulmonary vasodilators, like bosentan or sildenafil, may not work in patients with COPD-related PH, a condition dominated by right ventricular diastolic dysfunction with normal cardiac output [2].

However, STOLZ *et al.* [1] acknowledged that these results may not apply to uncommon cases of severe PH associated with COPD. Thus it was suggested that PH-specific treatment first be studied in the subgroup of patients identified by CHAOUAT *et al.* [3], with severe disproportionate PH [4, 5], arbitrarily defined by a mean pulmonary arterial pressure ($\bar{P}_{pa}$) of >40 mmHg [3].

Herein, we report dramatic functional improvement with bosentan therapy in a patient with COPD and severe disproportionate PH. A 53-yr-old female with a history of obesity (body mass index 41 $kg \cdot m^{-2}$), type II diabetes, hypothyroidism and acute pulmonary embolism 3 yrs previously, was followed for severe COPD. She was a former smoker (30 pack-yrs) and her dyspnoea was functional class III. After two episodes of right cardiac failure 3 yrs previously she was receiving furosemide 80 $mg \cdot day^{-1}$. Obstructive sleep apnoea syndrome was ruled out. High-resolution computed tomography of the chest showed mild diffuse emphysema. Pulmonary function tests showed severe airflow obstruction with air trapping and hyperinflation: forced vital capacity (FVC) 2.3 L (76% predicted), total lung capacity 6.3 L (128% pred), forced expiratory volume in one second (FEV1) 0.84 L (34% pred), FEV1/FVC 37%, residual volume 4.0 L (226% pred) and carbon monoxide diffusion capacity was 87% pred. The patient had been on long-term oxygen therapy (2.5 $L \cdot min^{-1}$) for 3 yrs, with arterial oxygen tension (P_{a,O_2}) on long-term oxygen therapy of 11.0 kPa, but elevated carbon dioxide arterial tension (P_{a,CO_2}; table 1).

PH suggested by echocardiography was confirmed by right heart catheterisation, demonstrating a pulmonary artery pressure of 110/50 mmHg (mean 65 mmHg), with a transpulmonary gradient of 49 mmHg, cardiac index of 2.6 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) of 739 $dyn \cdot s \cdot cm^{-5}$ without response to inhaled NO. No chronic thromboembolic disease or other cause of PH was found. The patient had not taken anorexigens and left ventricular function was normal. Since the contribution of PH to exercise limitation was considered significant and dyspnoea gradually increased, therapy with oral bosentan was initiated at 62.5 mg *b.i.d.* for 4 weeks, then increased to 125 mg *b.i.d.* Oral anticoagulation was initiated and long-term oxygen therapy was kept unchanged.

Within 4 weeks of bosentan initiation, dyspnoea significantly decreased to functional class II. The patient was able to resume activities such as home cleaning, going shopping and going to the beach. She could climb one flight of stairs without stopping (as opposed to no more than 5–10 steps before treatment) and resumed indoor biking. However, arterial blood gas analysis showed increased P_{a,CO_2} (9.6 kPa), and nocturnal noninvasive nasal ventilation was initiated 1 yr after the diagnosis of PH. Clinical improvement persisted throughout follow-up. Bosentan was well tolerated.

The 6-min walk test distance had improved from 198 to 360 m 2 yrs after initiating bosentan therapy. Right heart cavities

TABLE 1 Patient characteristics and outcome with bosentan

Time frame	Diagnosis of PH	6 months	12 months	18 months	24 months
Oxygen therapy L·min^{-1}	2.5	2.5	2.5	2.5	2.5
Noninvasive ventilation	No	No	Started	Yes	Yes
WHO functional class	III	I/II	II	II	II
6-min walk distance m	198	306	294	294	360
Echocardiographic data					
Estimated sPAP mmHg	110	60			
Right cavities	Severe dilatation, RV/LV size ratio 1.8	Undilated	Undilated		Undilated
Right heart catheterisation					
$\bar{P}_{pa}$ mmHg	65				34
dPAP – P_{pw} mmHg	34				7
CI L·min^{-1}·m^{-2}	2.6				3.7
PVR dyn·s·cm^{-5}	739				214
Pulmonary function tests					
FVC % pred	76	75	66	69	81
FEV_1 % pred	34	27	29	28	39
P_{a,O_2} with 2.5 L·min^{-1} O_2 kPa	11.0	9.1	10.7	10.7	11.6
P_{a,CO_2} kPa	7.9	9.6	7.8	7.0	7.2
pH	7.39	7.37	7.37	7.38	7.40

PH: pulmonary hypertension; WHO: World Health Organization; sPAP: systolic pulmonary artery pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; P_{pw}: pulmonary artery wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in one second; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; RV: right ventricular; LV: left ventricular.

were no longer dilated at echocardiography, and right heart catheterisation showed that PVR decreased to 214 dyn·s·cm^{-5}, cardiac index increased to 3.7 L·min^{-1}·m^{-2} and $\bar{P}_{pa}$ was 34 mmHg. Pulmonary function tests were unchanged (table 1).

Improvement of PH was not explained by weight loss [6], or by changes in P_{a,O_2}. Interestingly, in the study by STOLZ *et al.* [1], bosentan therapy was associated with a significant decrease in P_{a,O_2}, presumably related to increased ventilation–perfusion mismatching, intrapulmonary right-to-left microshunting (itself due to quantitative perfusion augmentation or fluid retention) and/or the reduction of peripheral carotid body sensitivity with a decrease in hypoxic ventilatory response. Indeed, P_{a,CO_2} was further increased in our patient while on bosentan, leading to the initiation of noninvasive ventilation.

This observation suggests that clinical trials are warranted to evaluate the possible efficacy of pulmonary hypertension-specific therapy in patients with chronic obstructive pulmonary disease and disproportionate pulmonary hypertension and characterise possible responders [3–5]. However, detrimental effects on gas exchange should be carefully monitored.

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STATEMENT OF INTEREST

Statements of interest for V. Cottin, R. Lazor and J-F. Cordier can be found at www.erj.ersjournals.com/misc/statements.shtml

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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.