A randomised, controlled trial of bosentan in severe COPD

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ABSTRACT: Pulmonary hypertension during exercise is common in severe chronic obstructive pulmonary disease (COPD). It was hypothesised that the use of the endothelin-receptor antagonist bosentan can improve cardiopulmonary haemodynamics during exercise, thus increasing exercise tolerance in patients with severe COPD.

In the present double-blind, placebo-controlled study, 30 patients with severe or very severe COPD were randomly assigned in a 2:1 ratio to receive either bosentan or placebo for 12 weeks. The primary end-point was change in the 6-min walking distance. Secondary end-points included changes in health-related quality of life, lung function, cardiac haemodynamics, maximal oxygen uptake and pulmonary perfusion patterns.

Compared with placebo, patients treated with bosentan during 12 weeks showed no significant improvement in exercise capacity as measured by the 6-min walking distance (mean $\pm$ SD 331 $\pm$ 123 versus 329 $\pm$ 94 m). There was no change in lung function, pulmonary arterial pressure, maximal oxygen uptake or regional pulmonary perfusion pattern. In contrast, arterial oxygen pressure dropped, the alveolar–arterial gradient increased and quality of life deteriorated significantly in patients assigned bosentan.

The oral administration of the endothelin receptor antagonist bosentan not only failed to improve exercise capacity but also deteriorated hypoxaemia and functional status in severe chronic obstructive pulmonary disease patients without severe pulmonary hypertension at rest.

Pulmonary hypertension (PH) at rest and during exercise is a very frequent complication in the natural history of chronic obstructive pulmonary disease (COPD) [1, 2]. Correspondingly, this condition has been reported in 20–91% of patients with severe COPD and/or emphysema [3, 4]. The presence of PH is commonly associated with more frequent use of healthcare resources and worse clinical outcome [5]. Remarkably, pulmonary artery pressure has been suggested to be the single best predictor of mortality in COPD [6].

In COPD, PH is generally of moderate severity, but the range of mean pulmonary artery pressures varies substantially [7]. Moderate and severe PH are present in 9.8 and 3.7%, respectively, of the patients undergoing right heart catheterisation before lung volume reduction surgery [7]. Despite many uncertainties, studies indicate that 35% of all patients with severe COPD have pulmonary artery pressures of >20 mmHg at rest [8]. In addition, pulmonary pressures during exercise are greater than predicted by the pulmonary vascular resistance (PVR) equation in COPD, suggesting active pulmonary vasoconstriction on exertion [9]. Hence, of those patients without PH at rest, a further 52% are estimated to develop PH during exercise [5].

There are many pathological similarities between idiopathic pulmonary arterial hypertension (PAH) and PH related to COPD. Like idiopathic PAH, pulmonary arteries in patients with COPD show evidence of fibromuscular intimal thickening with a diffuse increase in smooth muscle cells within the intima [10]. In addition, the expression of endothelin-1 in pulmonary arteries is increased in all forms of PAH [11]. Endothelin-1 is a potent vasoconstrictor released by endothelial cells, which also exerts a mitogenic effect on arterial smooth muscle cells. Elevated endothelin-1 plasma levels are described in patients with severe COPD [12] and endothelial dysfunction has been demonstrated at both ends of the COPD spectrum [13].

The oral endothelin-1 receptor antagonist bosentan has been established as a safe and effective treatment in patients with idiopathic, scleroderma

Screening of 2907 in- and outpatients who underwent body plethysmography in 2005

↓

77 potentially eligible patients →

Not interested in the study (n=28)
Deaths (n=8)
Minimal COPD symptoms (n=2)
Family physician disagreed (n=2)
Vacation abroad (n=2)
Lived too far from hospital (n=2)
Alcoholism (n=1)
MRSA colonisation (n=1)
Immobility (n=1)

↓

30 patients included

20 randomised to bosentan ⇠ Intention-to-treat analysis ⇢ 10 randomised to placebo

Drop-outs due to side-effects (n=6)   Drop-out due to side-effects (n=1)

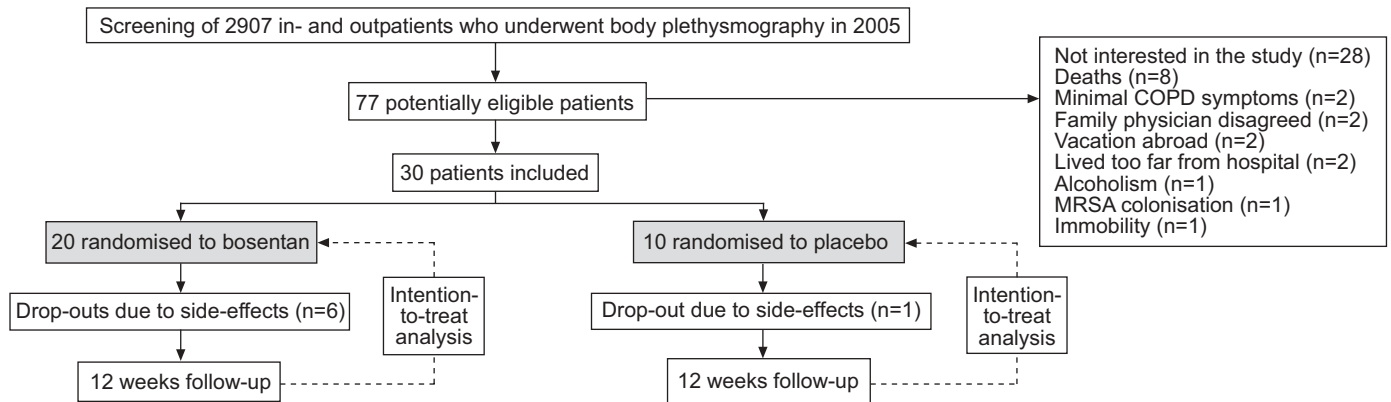12 weeks follow-up   12 weeks follow-up

FIGURE 1. Flow diagram showing the trial design. COPD: chronic obstructive pulmonary disease; MRSA: methicillin-resistant *Staphylococcus aureus*.

and HIV-related PAH, chronic thromboembolic PH, Eisenmenger syndrome and porto-PH [14–18]. Therefore, it appears rational to consider whether the use of this class of drug might decrease pulmonary pressures and improve both right ventricular function and oxygen delivery during exercise, thereby increasing exercise tolerance in severe COPD. To test this hypothesis, a randomised, double-blind, placebo-controlled study was carried out to compare bosentan with placebo over a 12-week period in patients with severe or very severe COPD without severe PH at rest.

MATERIALS AND METHODS

The study was a prospective, randomised, single-centre, double-blind trial comparing bosentan with placebo in regard to exercise tolerance in patients with severe or very severe COPD. The trial was conducted from March 2006 through to March 2007 at the University Hospital Basel (Basel, Switzerland). The study protocol was reviewed and approved by the local ethics committee (Ethikkommission Beider, Basel) and registered in the Current Controlled Trials Database (ISRCTN98252311). Written informed consent was obtained from all participants before inclusion in the study.

Patients

Ambulatory patients were recruited who had symptomatic, severe or very severe COPD and/or emphysema (in classes III–IV according to the Global Initiative for Chronic Obstructive Lung Disease classification), despite optimised therapy with short- and long-acting β_2-agonists, long-acting anticholinergics and inhaled steroids. Patients were excluded if they had: significant exacerbation of COPD within the last month; decompensate right or left heart failure; significant comorbidity resulting in reduced life expectancy; a severe mental disorder preventing appropriate judgement concerning study participation; insufficient technical quality in the echocardiographic evaluation; or known intolerance or formal contraindication for the use of bosentan.

In total, 30 patients were randomly assigned 62.5 mg bosentan twice daily for the first 2 weeks followed by the target dose of 125 mg twice daily, unless drug-related adverse events arose (*e.g.* increase in liver enzymes), or matching doses of placebo. Randomisation was computer-generated using the Almedica Drug Labelling System (Dorset, UK), with a block size of six and a 2:1 randomisation ratio (bosentan:placebo).

Outcome measurements

Patients were assessed on an outpatient basis after 24 h and at 2, 4, 8 and 12 weeks of treatment. The primary end-point was exercise capacity at week 12 and was measured by the 6-min walking test (6MWT) [19]. Secondary measures of efficacy included: maximal oxygen uptake ($V'O_2,max$) on cardiopulmonary exercise testing; cardiopulmonary performance as measured by Doppler echocardiography; lung function parameters as measured by body plethysmography; and perfusion pattern on thorax single photon emission computed tomography (CT) and quantitative perfusion scintigraphy (SPECT; at baseline and week 12). Secondary measures of efficacy also included the Borg dyspnoea index, which was obtained immediately after completion of the 6MWT, and health-related quality of life, as assessed by the Short-Form-36 Health Survey (SF-36). Safety was appraised by the number of adverse events and laboratory assessment.

Procedures

6MWT and cardiopulmonary exercise testing

The 6MWT was performed according to the American Thoracic Society guidelines [19]. Cardiopulmonary exercise testing was performed using a telemetric mobile device (Oxycon Mobile® software v. 4.6; VIASYS Healthcare GmbH, Würzburg, Germany). Respiratory quotient, cardiac frequency, oxygen pulse, minute ventilation, $V'O_2$ and peripheral oxygen saturation were monitored and registered at real time during exercise.

Echocardiography

Cardiac morphological and functional parameters were assessed by comprehensive two-dimensional and Doppler echocardiography using a single investigator (GE Vivid FiVe; GEMS, Milwaukee, WI, USA) [20]. Echocardiography data were digitally stored and independently analysed by two investigators blinded to the patients' clinical data. PVR in Wood units and tissue doppler imaging of the mitral and tricuspid annulus were assessed as described previously [21].

Lung function testing

Pulmonary function was evaluated by body plethysmography and the carbon monoxide diffusion capacity (Jaeger, Wuerzburg, Germany). All testing was performed according to the European Respiratory Society standards [22].

SPECT 99m-Tc-Nanocoll

Perfusion scintigraphy was performed using 100 $MBq^{99m}Tc$-MAA (TechneScan LyoMAA; Mallinckrodt Medical, Hazelwood, MO, USA) by intravenous injection. Each examination consisted of a planar data set followed by a three-dimensional (3D) SPECT combined with a low dose CT scan. A Siemens Dual Head SPECT-CT camera (SYMBIA T_2; Siemens, Malvern, PA, USA) was used for all nuclear imaging. The SPECT and fused images were independently reviewed by two nuclear medicine investigators blinded to the patients' clinical data using a 3D workstation. The regional perfusion difference between baseline and 12 weeks, expressed in percentage, was calculated by subtracting the starting data set and the data obtained after the treatment. Images were qualitatively analysed, slice by slice for the extent and severity of morphological and perfusion abnormalities.

Statistical analysis

Power and sample size was calculated using the 6MWT before and after treatment as the primary outcome variable. Assumptions were based on the results of the only previous study performed in a similar population (an open-label trial) [23]. Considering a mean±SD improvement in the 6MWT from $351±49$ to $433±52$ m after treatment, eight patients were required in each study arm to achieve a significance level of $p<0.05$ with a power of 0.85 performing a two-sided unpaired t-test. Taking into account the small size and open label character of the published study, the present authors decided to double the size of the active treatment arm. Considering a 25% dropout rate after assignment to the study medication, 30 inclusions were planned. The sample size of 30 patients provided the study with a calculated power of 0.93 to detect a 50-m change in the 6MWT at a significance level of $p<0.05$ performing a two-sided unpaired t-test.

The results are presented as the mean±SD for all variables that were normally distributed, and as the median (interquartile range) for variables that were not normally distributed. The significance of the differences from baseline to week 12 between the treatment groups were calculated for all parameters using a linear, mixed effect model. The proportion of patients who withdrew because of side-effects was analysed using Fisher's exact test. The primary end-point statistical analysis was carried out on an intention-to-treat basis. All p-values were two-tailed.

RESULTS

In total, 30 patients were included in the study; 20 were assigned bosentan and 10 were assigned placebo (fig. 1). All patients remained in the study until the last patient had completed the assessments at week 12, unless the patients dropped out due to side-effects. Of those randomised, one (10%) patient in the placebo group and six (30%) in the bosentan group discontinued the study agent due to adverse events (p=0.372). An acute exacerbation of COPD requiring intensive care admission led to study withdrawal in the placebo group. Reasons for treatment discontinuation in the bosentan group were: drowsiness (n=2); dyspnoea (n=2); drowsiness and lower extremity oedema refractory to medical therapy (n=1); and subjective cervical swelling combined with constipation (n=1). One patient in the placebo group developed dyspnoea after the presumptive increase in medication dosage at 2 weeks, thus requiring a

lower maintenance dosage up to 12 weeks. Lower extremity oedema warranting diuretic therapy was observed in four patients receiving bosentan and in one patient receiving placebo. In two cases, the bosentan dosage had to be halved after 8 weeks due to reversible elevation of liver enzymes.

TABLE 1	Demographic and haemodynamic characteristics at baseline		
	Placebo	Bosentan	p-value
Subjects n	10	20	
Demographic variables			
Age yrs	65±7.9	69.5±8.8	0.184
Male	7 (70)	11 (55)	0.694
Weight kg	76.9±16.4	66.3±14.0	0.075
Height cm	165±6.1	166.9±6.9	0.464
Body mass index	28.1±4.7	24.0±5.9	0.064
Pack-yrs	80±38	38±21	0.001
Ex-smoker	8 (80)	18 (90)	0.584
Current smoker	2 (20)	2 (10)	0.584
Symptoms			
Dizziness	4 (40)	4 (20)	0.384
Peripheral oedema	2 (20)	5 (25)	1
Physical examination			
Wheezing	2 (20)	8 (40)	0.420
Rales	1 (10)	1 (5)	1
GOLD stages			
III[#]	6 (60)	11 (55)	1
IV[¶]	4 (40)	9 (45)	
Exercise tolerance			
6-min walking distance m	331±116	339±81	0.817
Borg dyspnoea index levels	5.3±2.4	5.1±2.1	0.084
Regular medication use			
Long-term oxygen therapy	3 (30)	8 (40)	0.702
Chronic diuretic use	3 (30)	5 (25)	1
Short-acting β_2-agonists	10 (100)	20 (100)	1
Long-acting β_2-agonists	10 (100)	20 (100)	1
Long-acting-anticholinergics	10 (100)	20 (100)	1
Inhaled steroids	10 (100)	20 (100)	1
Vital signs			
Respiratory frequency breaths·min^{-1}	18±3	20±5	0.291
Peripheral O_2 saturation %	92 (4)	93 (4)	0.510
fC beats·min^{-1}	90±12	88±15	0.759
Systolic blood pressure mmHg	142±19	129±16	0.069
Diastolic blood pressure mmHg	87±7	78±9	0.009
Echocardiography			
Pulmonary hypertension at rest ⩾30 mmHg[+]	6 (60)	14 (70)	0.584
Median estimated systolic P_{pa} at rest mmHg[+]	37 (20–42)	32 (29–38)	0.779
Left ventricular ejection fraction %	57±9	61±10	0.321

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; fC: cardiac frequency; P_{pa}: pulmonary arterial pressue. [#]: 30% predicted less than forced expiratory volume in one second ⩽50% pred; [¶]: forced expiratory volume in one second ⩽30% pred; [+]: estimated pulmonary pressures without adding central venous pressure.
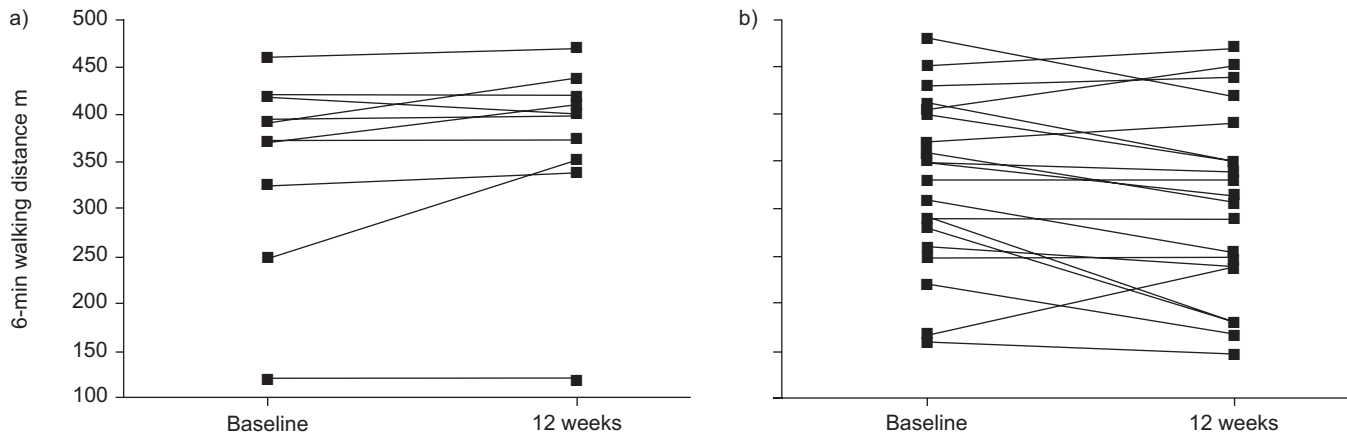
FIGURE 2. Individual patient data showing the 6-min walking distance at baseline and at 12 weeks in patients assigned a) placebo (n=10) and b) bosentan (n=20). The changes in the 6-min walking distance were similar across both treatment groups (p=0.474). The mean±SD distance walked in 6 min decreased by 10 m in patients assigned bosentan (from 339±81 m at baseline to 329±94 m at week 12, p=0.040), and remained unchanged in those given placebo (331±116 m at baseline and 331±123 m at week 12, p=0.100).

Overall, treatment groups were well matched with respect to baseline characteristics (table 1). All patients were in the World Health Organization functional class III or IV at baseline. Use of concomitant medication (including long-term oxygen therapy and diuretics) did not differ between groups. The only significant differences between groups were the higher cigarette consumption in patients assigned placebo (p=0.001) and the lower diastolic blood pressure in patients assigned bosentan (p=0.009). Left ventricular ejection fraction was preserved ($\geq$45%) in all cases.

Primary end-point: 6MWT
Changes from baseline to week 12 in the 6MWT were similar across treatment groups (p= 0.474; fig. 2). The mean±SD distance walked in 6 min decreased by 10 m in patients assigned bosentan (from 339±81 at baseline to 329±94 m at week 12; p=0.040), and remained unchanged in those assigned placebo (331±116 at baseline and 331±123 m at week 12; p=0.100).

Secondary end-points
In the treatment groups, no significant differences were observed in the change from baseline to week 12 in lung function or cardiopulmonary exercise testing parameters (table 2). Cardiopulmonary performance as assessed by echocardiography displayed a significant increase in PVR only in patients randomised to placebo (p=0.006; table 3). There was no change in the Borg dyspnoea index (p=0.932). Conversely, arterial partial pressure of oxygen (P_{O_2}) decreased significantly in patients assigned bosentan compared with those assigned placebo (p=0.029). In the bosentan group, mean±SD arterial P_{O_2} was 65.2±10.5, 58.8±8.6 and 60.7±7.5 mmHg at baseline, 4 weeks and 12 weeks, respectively. The corresponding values for the placebo group were 66.1±15.1, 64.4±6.9 and 65.7±10.9 mmHg, respectively. The decrease in arterial oxygen pressure was associated with a significant increase in alveolar–arterial gradient in the group treated with bosentan compared with patients receiving placebo (fig. 3). Health-related quality of life, particularly the global physical health domain in the SF-36, deteriorated in patients' assigned bosentan compared with those assigned placebo

(table 4). Haematological and hepatic laboratorial assessments did not reveal any relevant toxicity of bosentan (data not shown). Circulating brain-natriuretic peptide remained similar in both treatment groups (p=0.979). The regional perfusion pattern on the thoracic SPECT-CT did not change after 12 weeks therapy with bosentan (figs 4 and 5). Compared with baseline, mean±SD change in perfusion of the right lung at 12 weeks was 0.88±2.7 and 0.07±1.7% for the placebo and bosentan group, respectively (p=0.381). The respective values for the left lung were -0.66±2.7 and -0.142±1.7% (p=0.576).

DISCUSSION
The current results show that oral administration of a dual endothelin-receptor antagonist failed to improve exercise capacity in patients with severe COPD. Furthermore, bosentan did not positively affect any secondary end-point studied, including cardiopulmonary haemodynamics at rest as assessed by echocardiography. Finally, and most importantly, therapy with bosentan was associated with a significant decrease in arterial oxygen pressure and health-related quality of life. Hence, in patients with severe COPD without severe PH at rest, therapy with bosentan was not beneficial and resulted in relevant functional status deterioration.

The present study is the first to report the results of a randomised, placebo-controlled trial using an endothelin-receptor antagonist in patients with severe COPD [24]. Unselective vasodilators (i.e. calcium-channel blockers) have been previously evaluated in several clinical studies. The acute administration of nifedipine is suggested to reduce pulmonary pressures and increase cardiac output both at rest and during exercise [9, 25]. However, nifedipine inhibits hypoxic pulmonary vasoconstriction [26], leading to worsening of the ventilation–perfusion relationship and to lower arterial P_{O_2} [9, 27]. Moreover, clinical results of long-term treatment with calcium-channel blockers in COPD have been disappointing, showing that both pulmonary haemodynamics and clinical status either deteriorated or remained unchanged after treatment. The efficacy of newer pulmonary vasodilators in patients with COPD has only been described in one case series [23].

TABLE 2	Lung function testing and cardiopulmonary exercise test parameters				
	Placebo		Bosentan		p-value
	Baseline	12 weeks	Baseline	12 weeks	
Subjects n	10	9	20	17	
Body plethysmography					
Total lung capacity post-BD L	6.89 ± 0.91	6.70 ± 1.08	7.23 ± 1.45	7.32 ± 1.30	0.372
Total lung capacity post-BD %	120 ± 22	114 ± 14	126 ± 15	124 ± 14	0.927
Residual volume post-BD L	3.80 ± 1.07	3.46 ± 0.69	4.18 ± 1.11	4.40 ± 0.97	0.095
Residual volume post-BD %	174 ± 68	151 ± 28	184 ± 51	188 ± 38	0.094
FEV_1 post-BD L	1.05 ± 0.39	1.07 ± 0.38	0.92 ± 0.27	0.86 ± 0.26	0.379
FEV_1 post-BD %	41 ± 14	42 ± 14	38 ± 13	35 ± 12	0.482
FEV_1/VC post-BD %	35 ± 8	35 ± 11	32 ± 10	31 ± 9	0.320
Diffusion capacity %	44 ± 13	42 ± 13	37 ± 18	35 ± 18	0.842
Cardiopulmonary exercise testing					
Respiratory quotient rest	0.86 ± 0.07	0.89 ± 0.11	0.85 ± 0.11	0.85 ± 0.07	0.282
Respiratory quotient max	0.88 ± 0.04	0.86 ± 0.06	0.85 ± 0.07	0.80 ± 0.06	0.056
f_C rest beats·min^{-1}	85 ± 13.3	87 ± 16	91.9 ± 15	91 ± 11	0.474
f_C max beats·min^{-1}	115 ± 20	115 ± 14	108 ± 21	114 ± 21	0.626
f_C max %	75 ± 13	75 ± 8	72 ± 15	76 ± 15	0.489
O_2 pulse at rest mL·beat^{-1}	3.81 ± 1.60	3.27 ± 1.68	3.07 ± 0.77	3.41 ± 1.38	0.088
O_2 pulse max mL·beat^{-1}	9.02 ± 2.91	9.98 ± 3.11	8.69 ± 4.56	7.90 ± 3.02	0.156
O_2 pulse max %	75 ± 15	75 ± 18	93 ± 52	82 ± 31	0.293
Minute ventilation rest L	13.6 ± 3.6	13.8 ± 5.0	14.0 ± 2.8	15.4 ± 4.8	0.498
Minute ventilation max L	34.6 ± 10.7	36.0 ± 12.2	31.4 ± 9.1	30.3 ± 7.2	0.114
Minute ventilation max %	47 ± 13	48 ± 14	45 ± 15	43 ± 15	0.276
$V'O_2$ at rest mL·min·kg^{-1}	4.1 ± 1.0	4.9 ± 1.9	4.3 ± 0.8	3.5 ± 1.7	0.288
$V'O_2$ max mL·min·kg^{-1}	13.4 ± 2.4	13.9 ± 2.8	13.8 ± 3.0	13.4 ± 3.4	0.113
$V'O_2$ max %	63 ± 11	64 ± 15	54 ± 12	50 ± 12	0.304
O_2 saturation at rest %	92 ± 4	93 ± 2	93 ± 3	91 ± 4	0.035
O_2 saturation at max %	77 ± 17	84 ± 5	83 ± 6	79 ± 13	0.842

Data are presented as mean$\pm$SD, unless otherwise stated. BD: bronchodilator; FEV_1: forced expiratory volume in one second; VC: vital capacity; f_C: cardiac frequency; $V'O_2$: maximal oxygen uptake.

In the present placebo-controlled trial, therapy with the pulmonary vasodilator bosentan proved ineffective in improving exercise tolerance in patients with severe COPD without severe PH at rest. Conversely, bosentan has been beneficial in improving exercise capacity, cardiac index, right ventricular systolic function, and left ventricular early diastolic filling in patients with idiopathic PH [14, 28]. However, in contrast to PH related to COPD, patients with idiopathic PH demonstrate preponderant right ventricular dysfunction leading to decreased cardiac index and major cardiovascular limitation in exercise testing. To date, it is unclear to what extent right ventricular dysfunction during exercise limits exercise tolerance in severe COPD [24]. In the present study, patients with COPD presented well-preserved right ventricular function at rest with tricuspidal annular motion values, in particular, above those known to worsen prognosis. Cardiopulmonary exercise testing profile was typical of a major ventilatory limitation (maximum respiratory quotient less than one and maximum ventilation approximately equal to maximal minute ventilation). Therefore, it remains questionable whether improvement in right ventricular function during exercise can enhance exercise tolerance at all in patients with severe COPD without manifesting right ventricular dysfunction in the resting state.

In contrast to previous reports on echocardiographic assessment in idiopathic PH and PH associated with connective tissue disease [28], the present authors failed to notice any relevant change in cardiopulmonary haemodynamics at rest in patients with COPD receiving bosentan. Echocardiography has been put forward as a useful tool in patients with suspected PH if right heart catheterisation is not feasible or warranted [29]. However, it might be imprecise in determining actual pressures compared with invasive evaluation in a portion of patients and its inherent limitations in COPD have been extensively described previously [30]. Furthermore, haemodynamics in the resting state improve only marginally in most patients even when their clinical response to therapy appears to be excellent [31]. Thus, resting haemodynamics might not necessarily reflect changes occurring with exercise [31].

Interestingly, a statistically significant increase of pulmonary vascular resistance, as assessed by echocardiography, was observed in patients randomised to the placebo group.

TABLE 3	Cardiopulmonary haemodynamics at baseline and after therapy				
	Placebo		Bosentan		p-value
	Baseline	12 weeks	Baseline	12 weeks	
Subjects n	10	9	20	14	
Cardiopulmonary haemodynamics					
Systolic P_{pa} mmHg[#]	37 (20–42)	33 (29–39)	32 (29–38)	30 (26–34)	0.288
RV fractional area change %	34.2±11.8	43.9±7.9	42.7±11.0	50.5±6.8	0.935
Tricuspid annular motion mm	24.4±2.7	22.5±2.4	21.0±4.5	22.7±3.6	0.059
Early diastolic velocity RV cm·s^{-1}	0.44±0.09	0.40±0.08	0.44±0.11	0.41±0.12	0.512
Late diastolic velocity RV	0.46±0.12	0.46±0.09	0.44±0.13	0.39±0.07	0.338
Early diastolic/late diastolic velocity RV	1.00±0.30	0.88±0.15	0.99±0.23	1.07±0.33	0.142
Tissue doppler imaging					
Early diastolic velocity cm·s^{-1}	0.08±0.03	0.08±0.03	0.08±0.04	0.09±0.03	0.346
Late diastolic velocity cm·s^{-1}	0.14±0.05	0.15±0.02	0.14±0.05	0.15±0.05	0.890
Systolic velocity cm·s^{-1}	0.12±0.04	0.12±0.02	0.12±0.03	0.12±0.03	0.961
Pulmonary vascular resistance (dyne × s)·cm^5	145±28	182±23	158±30	154±45	0.006
Cardiac index L·min·m^2	3.3±0.79	3.39±0.58	2.45±0.41	2.66±0.65	0.296

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. P_{pa}: pulmonary arterial pressure; RV: right ventricle [#]: estimated pulmonary pressures without adding central venous pressure.

Considering the slow progression of mean pulmonary arterial pressures, PVR would be expected to remain unchanged within 12 weeks in COPD patients during the stable state of the disease. Therefore, taking into account the limitations of echocardiography in this patient population, the present authors believe that this finding most likely represents an artefact. In any case, the clinical impact of an increase in PVR is suggested to be limited in the context of unchanged exercise capacity and $V'_{O_2,max}$.
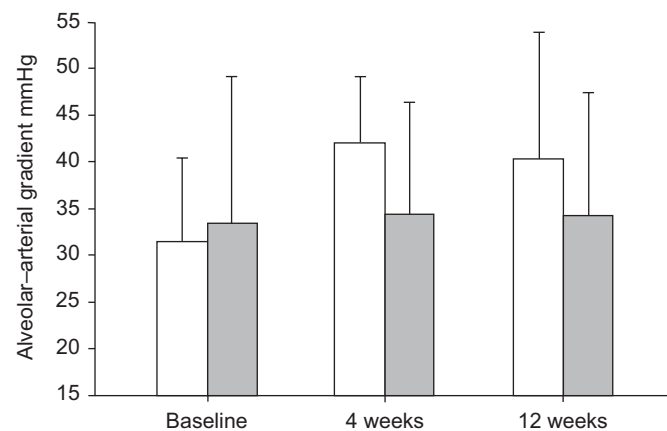

FIGURE 3. Alveolar–arterial gradient at baseline, 4 weeks and 12 weeks in patients assigned bosentan (□) and placebo (■). The alveolar–arterial gradient increased significantly in patients assigned bosentan compared with those assigned placebo (p=0.029). In the bosentan group, median (interquartile range) alveolar–arterial gradient was 31.4 (28.1–37.1), 42.0 (37.4–44.5) and 40.4 (31.5–44.9) mmHg at baseline, 4 weeks and 12 weeks, respectively. The corresponding values for the placebo group were 33.4 (32.5–48.2), 34.4 (29.3–41.3), and 34.3 (20.9–42.8) mmHg, respectively.

Hypoxic pulmonary vasoconstriction has been suggested to be a factor leading to increased right ventricular diastolic pressures and impaired exercise capacity in COPD [24]. Accordingly, inhaled nitric oxide, a selective pulmonary vasodilator, has been reported to improve gas exchange during exercise and increase exercise tolerance in patients with COPD [32]. The pulmonary vasodilator bosentan could have potentially improved exercise tolerance by inhibiting exercised-induced hypoxic vasoconstriction in selected parts of the emphysematous lung. The present study has evaluated COPD patients using SPECT, which concomitantly appraises parenchyma morphology and changes in regional and global perfusion patterns. Compared with the placebo group, patients with COPD receiving bosentan developed hypoxaemia as assessed by blood gas analysis and pulse oxymetry. The decrease in arterial oxygen pressures was associated with a significant widening of alveolar–arterial gradient, thus suggesting that bosentan enhances ventilation–perfusion mismatching or intrapulmonary right-to-left microshunting [2]. No evidence of change was found in qualitative pulmonary perfusion patterns by SPECT in patients receiving bosentan, i.e. there was no redistribution of blood flow within pulmonary regions. Therefore, it is hypothesised that the decrease in arterial oxygen pressure could be attributed to a quantitative perfusion augmentation [2, 9]. The marked initial decrease in arterial P_{O_2} at 4 weeks, followed by a secondary increase at 12 weeks, suggests a consequential adjustment to the vasodilator effect in patients assigned bosentan. In patients treated with bosentan, fluid retention could have been another possible cause of decrease in oxygen arterial pressure and widening in alveolar–arterial gradient. Although body weight remained unchanged during the 3-month study period, patients receiving bosentan more often required prescription of a diuretic due to low extremity oedema. Hence, fluid retention might have caused or aggravated hypoxaemia in the

TABLE 4	Health-related life quality as assessed by the Short-Form-36 Health Survey (SF-36) at baseline and after therapy				
	Placebo		Bosentan		p-value
	Baseline	12 weeks	Baseline	12 weeks	
Subjects n	10	9	20	14	
Physical functioning	43.3±28.1	55.6±20.1	27.5±15.3	23.2±19.9	0.067
Role limitations due to physical health	23.0±38.1	53.1±47.1	16.3±33.7	7.1±26.7	0.082
Body pain	70.8±32.6	80.8±29.2	78.3±28.0	70.2±31.7	0.413
General health perceptions	50.5±20.0	62.4±19.0	43.2±20.9	39.1±20.4	0.018
Vitality	47.8±20.0	50.0±25.2	36.4±19.3	34.6±18.5	0.571
Social functioning	70.0±36.4	89.1±15.6	58.1±32.0	57.1±28.5	0.230
Role limitations due to emotional problems	63.3±45.7	79.2±35.4	43.3±49.7	59.5±49.2	0.970
Mental health	76.0±19.2	87.1±13.5	66.6±15.0	64.9±17.0	0.023
Total physical health	47.4±23.2	61.1±21.5	38.5±14.8	34.9±18.3	0.032
Total mental health	61.6±23.4	68.9±21.4	50.6±20.7	51.1±20.8	0.263
Total SF-36 Score	56.2±21.3	66.9±19.6	46.1±17.6	44.5±18.7	0.039

Data are presented as mean±SD, unless otherwise stated.

group of patients treated with bosentan. Finally, the antagonism of endothelin-1 receptors might lead to a reduction of the peripheral carotid body sensitivity to arterial hypoxia, thus decreasing the ventilatory response to hypoxia [33]. However, a decrease in respiratory rate does not explain the increase in alveolar–arterial gradient observed in the present study and the respiratory rate remained unchanged during drug treatment in the patients. Moreover, more recent data suggest that circulating endothelin does not play an important role in peripheral chemoreceptor activation by acute hypoxia [34].

In contrast to patients receiving placebo, health-related quality of life deteriorated significantly in the bosentan group. It is noteworthy that the decline in quality of life was driven by the physical health domain of the SF-36. The enhanced perception of physical limitation and symptoms is suggested to reflect hypoxaemia associated with vasodilator therapy. The well-known placebo effect in participants of a clinical trial was also evident in the present study, as noted by the improvement in mental and physical health domains in the placebo group. In addition, more patients in the bosentan group dropped out of the study due to side-effects of the medication. Although the dropout rate was not statistically significant in comparing both randomised groups, patients treated with bosentan reported increased dyspnoea, drowsiness and more often required diuretics due to peripheral oedema. These observations corroborate the unfavourable effect of this class of drugs in patients with COPD. Accordingly, a preliminary report
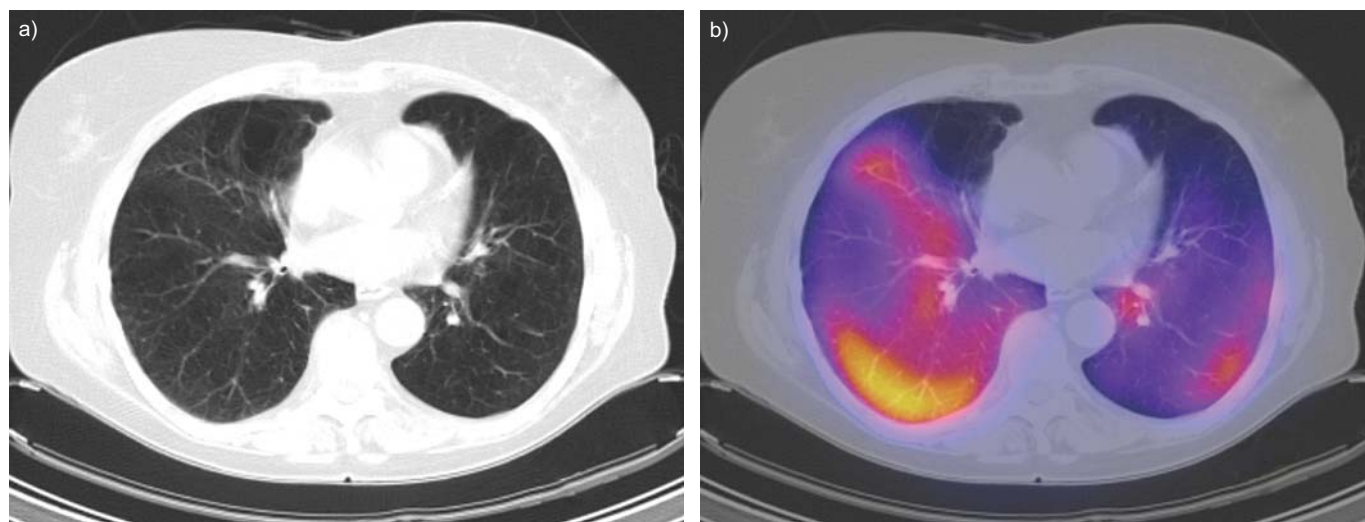

FIGURE 4. a) Transversal thoracic-computed tomography (CT) scan showing emphysematous changes in the right anterior upper lobe. b) Transversal fusion image combining a thoracic CT scan and perfusion signal. Colour-coded areas denote perfusion of lung parenchyma (yellow: high-perfusion areas; blue: low-perfusion areas; red: intermediate perfusion; black: no perfusion).
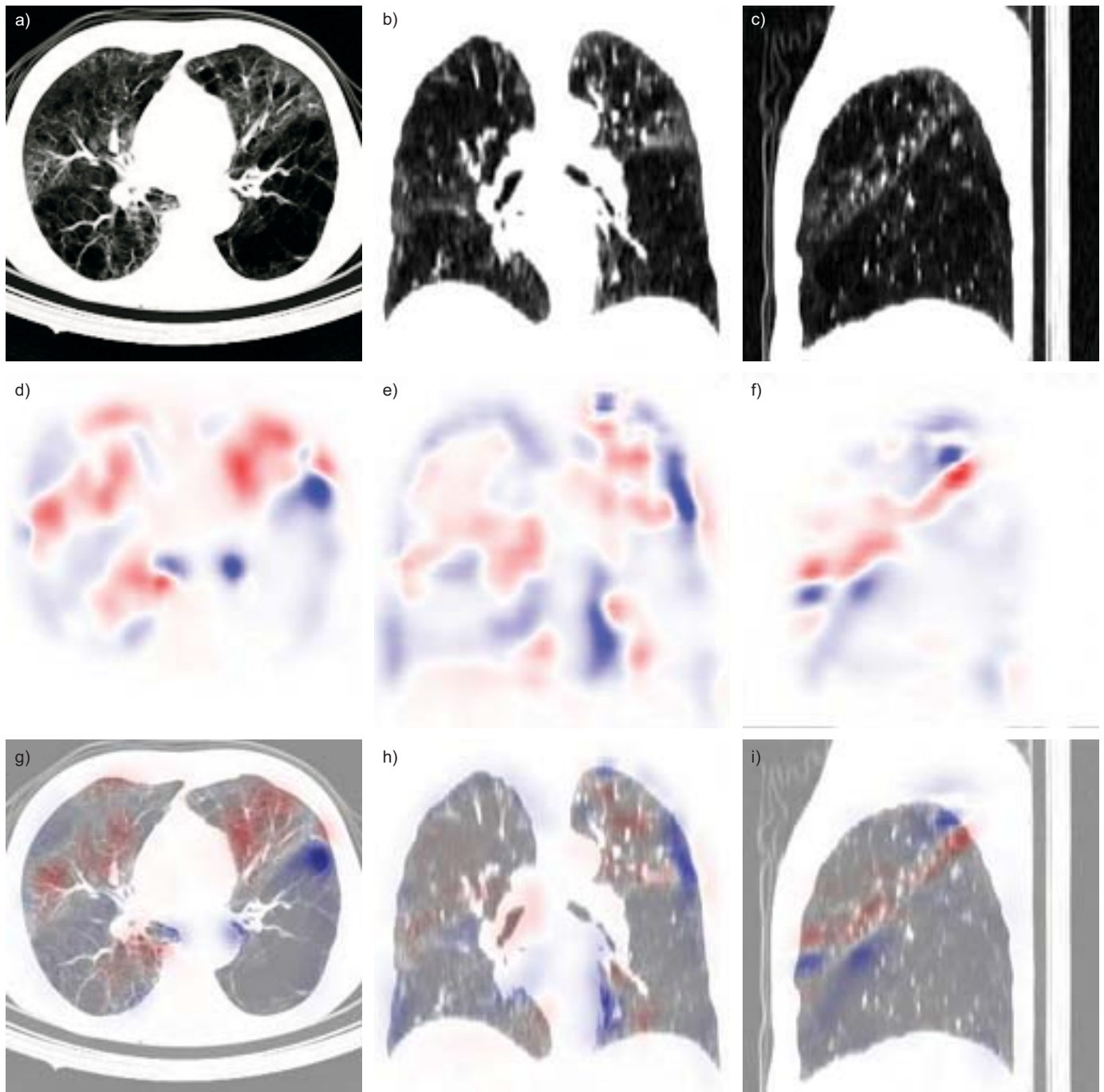
FIGURE 5. Transversal, coronal and sagital thoracic computed tomography (CT) scans showing a–c) the pulmonary morphology, d–f) the perfusion signal showing the perfusion difference between baseline and 12 weeks (blue: decreased perfusion at 12 weeks compared with baseline; red: increased perfusion at 12 weeks compared with baseline), and g–i) fusion thoracic CT and perfusion signal images combining morphology and perfusion.

suggests that sildenafil, another pulmonary vasodilator, which selectively inhibits cGMP-specific phosphodiesterase 5, is equally ineffective in improving exercise capacity in patients with COPD [35].

Several limitations of the present study need to be mentioned. First, a single-centre study was conducted, which included a relatively small number of patients. However, due to the well-defined findings of the study, it seems unlikely that contradicting results would be found by investigating a larger population. Moreover, the sample size of the study provided enough power to allow statistically significant inferences about the detrimental effect of bosentan in several domains, thus excluding, by definition, a type II or β-error. Additionally, a major weakness of the study was that no invasive assessment of pulmonary arterial pressures, *i.e.* cardiac catheterisation including exercise testing, was performed. By refraining from catheterisation, pulmonary pressures at rest could not be

reliably measured and the extent of PH during exercise could not be proved. Considering the very weak correlation between echocardiographic estimates of pulmonary artery pressures and right heart catheterisation, as well as the poor test characteristics (*e.g.* sensitivity and specificity) of echocardiographic assessments in patients with severe COPD [30], the echocardiographic estimations of pressure, flow and resistance reported in the present study are rather illustrative and might not stand the test of invasive confirmation. Finally, the patients included in this trial did not have severe PH at rest. Therefore, the current results are only generalisable to the majority of patients with severe COPD, who usually only present with mild-to-moderate PH during exercise [7], and may not apply to the uncommon cases of disproportional PH associated with COPD. In this context, these findings do not rule out that bosentan (or other endothelin-receptor antagonists) may be efficacious in patients with less severe airflow obstruction, more severe PH or in the selected COPD patients with clearly documented cardiovascular limitation to exercise capacity.

In conclusion, the current findings suggest that therapy with the dual endothelin-receptor antagonist bosentan is not beneficial and results in relevant functional status deterioration in patients with chronic obstructive pulmonary disease without severe pulmonary hypertension at rest.

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