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A randomized, controlled trial of bosentan in severe COPD

Daiana Stolz MD[1,2], Helmut Rasch MD[3], Andre Linka MD[4], Marcello Di Valentino MD[5], Anja Meyer[1], Martin Brutsche MD/PhD[1], and Michael Tamm MD[1]

[1]Clinic of Pneumology and Pulmonary Cell Research, University Hospital Basel, Switzerland;
[2] Harvard School of Public Health, Boston, Massachusetts, USA;
[3] Division for Nuclear Medicine, University Hospital Basel, Switzerland;
[4] Cardiology, Hospital Winterthur, Switzerland;
[5] Cardiology, University Hospital Basel, Switzerland;

Correspondence to:
Daiana Stolz, MD, Clinic of Pulmonary Medicine and Respiratory Cell Research
University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
Phone: +41 (61) 265 5185 Fax: +41 (61) 265 4587
E-mail: dstolz@uhbs.ch

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ABSTRACT

Introduction: Pulmonary hypertension during exercise is common in severe COPD. We hypothesized that the use of the endothelin-receptor antagonist bosentan can improve cardiopulmonary hemodynamics during exercise, thus increasing exercise tolerance in patients with severe COPD.

Methods: In this 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 endpoint was change in the 6-minute walking distance. Secondary endpoints included changes in health-related quality of life, lung-function, cardiac hemodynamics, maximal oxygen uptake, and pulmonary perfusion patterns.

Results: As compared to placebo, patients treated with bosentan during 12 weeks showed no significant improvement in exercise capacity as measured by 6-minute walking distance (331 m [123] versus 329 [94], p=0.474). There was no change in lung-function, pulmonary arterial pressure, maximal oxygen uptake, and regional pulmonary perfusion pattern (p=ns). In contrast, arterial oxygen pressure dropped (p=0.029), alveolar-arterial gradient increased (p=0.029), and quality of life deteriorated significantly in patients' assigned bosentan (p=0.039).

Conclusions: The oral administration of the endothelin receptor antagonist bosentan not only failed to improve exercise capacity but also deteriorated hypoxemia and functional status in severe COPD patients without severe pulmonary hypertension at rest.

INTRODUCTION

Pulmonary hypertension at rest and during exercise is a very frequent complication in the natural history of chronic obstructive lung disease (COPD) [1, 2]. Correspondingly, this condition has been reported in 20 to 91% of patients with severe COPD and/or emphysema [3, 4]. The presence of pulmonary hypertension is commonly associated with more frequent use of health care 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, pulmonary arterial hypertension is generally of moderate severity, but the range of mean pulmonary artery pressures varies substantially [7]. Moderate and severe pulmonary hypertension are present in 9.8% and 3.7% of the patients undergoing right-heart catheterization before lung-volume reduction surgery, respectively [7]. Despite many uncertainties, studies indicate that 35% of all patients with severe COPD have pulmonary artery pressures of more than 20mmHg at rest [8]. In addition, pulmonary pressures during exercise are greater than predicted by the pulmonary vascular resistance equation in COPD, suggesting active pulmonary vasoconstriction on exertion [9]. Hence, of those patients without pulmonary hypertension at rest, a further 52% are estimated to develop pulmonary hypertension during exercise [5].

There are many pathological similarities between idiopathic pulmonary hypertension related to COPD and pulmonary arterial hypertension. Alike idiopathic pulmonary arterial hypertension, 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 pulmonary arterial hypertension [11]. Endothelin-1 is a potent vasoconstrictor released by

endothelial cells that 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 and HIV-related pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, Eisenmenger syndrome and portopulmonary hypertension [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, we undertook a randomized, double-blind, placebo-controlled study comparing bosentan with placebo over a 12- week's period in patients with severe or very severe COPD without severe pulmonary hypertension at rest.

METHODS

The study was a prospective, randomized, 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 March 2007 at the University Hospital Basel, Switzerland. The study protocol was reviewed and approved by the local ethics committee and registered in the Current Controlled Trials Database (ISRCTN98252311). Written informed consent was obtained from all participants before inclusion in the study.

Patients

We recruited ambulatory patients 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 optimized therapy with short and long-acting $ß_2$-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 co-morbidity resulting in reduced life expectancy; severe mental disorder preventing appropriate judgment concerning study participation; insufficient technical quality in the echocardiographic evaluation; or known intolerance or formal contra-indication for the use of bosentan.

Thirty patients were randomly assigned 62·5 mg bosentan twice daily for the first 2 weeks followed by the target dose (125 mg twice daily) unless drug-related adverse events arose (e.g., increase in liver enzymes), or matching doses of placebo. Randomization was computer generated using the Almedica Drug Labelling System, with a block size of six and a 2/1 randomization ratio (bosentan/placebo).

Outcome Measurements

Patients were assessed on outpatient basis after 24 hours and at 2, 4, 8, and 12 weeks of treatment. The primary endpoint was exercise capacity at week 12 and was measured by the distance a patient could walk in 6 min (6MWT) [19]. Secondary measures of efficacy included maximal oxygen uptake [VO_2 max] on cardiopulmonary exercise testing; cardiopulmonary performance as measured by Doppler-echocardiography; lung function parameters as measured by bodyplethysmography; and perfusion pattern on thorax SPECT (at baseline and week 12). Secondary measures of efficacy also included Borg dyspnea index, which was obtained immediately after completion of the 6MWT, and health-related quality of

life (SF-36). Safety was appraised by the number of adverse events and laboratory assessment.

Procedures

6 Minute Walk-Test and Cardiopulmonary Exercise Testing

The 6 MWT was performed according to the ATS 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, heart rate, oxygen-pulse, minute-ventilation, oxygen uptake (VO_2), and peripheral oxygen saturation were monitored and registered real-time during exercise.

Echocardiography

Cardiac morphological and functional parameters were assessed by comprehensive 2-dimensional (2D) and Doppler echocardiography by a single investigator (GE Vivid FiVe - GEMS, Milwaukee, Wisconsin, US) [20]. Echocardiography data were digitally stored and independently analyzed by two investigators blinded to the patients' clinical data. Pulmonary vascular resistance (PVR) in Wood units (WU) and Tissue Doppler imaging (TDI) of the mitral and tricuspid annulus were assessed as described [21].

Lung Function Testing

Pulmonary function was evaluated with bodyplethysmography and carbon-monoxide diffusion capacity (Jaeger; Wuerzburg, Germany); all testing was performed according to the European Respiratory Society standards [22].

Single Photon Emission Computer Tomography and Quantitative Perfusion Scintigraphy (SPECT) 99m-Tc-Nanocoll

Perfusion scintigraphy was performed using 100 MBq ^{99m}Tc -MAA (TechneScan LyoMAA; Mallinckrodt Medical) by i.v. injection. Each examination consists of a planar data set followed by a 3-D SPECT combined with a low dose computertomography scan. A Siemens Dual Head SPECT-CT camera (SYMBIA T_2) was used for all nuclear imaging. The SPECT and fused images were independently reviewed by two nuclear medicine attendings blinded to the patients' clinical data using a 3-D 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 analyzed slice by slice for the extent and severity of morphological and perfusion abnormalities.

Statistical analysis

Power and sample size was calculated using the 6-minutes walking distance before and after treatment as the primary outcome variable. Assumptions were based on the results of the only study performed on a similar population (open label trial) [23]. Considering an improvement in the 6-minutes walking distance from 351 meters (49) to 433 meter (52) after treatment, 8 patients would be needed in each study arm to achieve a significance level of <0.05 with a power of 0.85 performing a 2-sided Student's t-test. Taking into account the small size and open label character of the published study, we decided to duplicate 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 meters change in the 6-minutes walking distance at a significance levels of <0.05 performing a 2-sided Student's t-test.

The results are presented as the mean (SD) for all variables that were normally distributed, and as the median (25th to 75th percentile) for variables that were not normally distributed. We calculated the significance of the differences from baseline to week 12 between treatment

groups for all parameters using a linear mixed effect model. The proportion of patients who withdrew because of side-effects was analyzed with Fisher's exact test. The primary endpoint statistical analysis was done on an intention-to-treat basis. All p values were two-tailed. Analysis was performed using the Statistical Package for Social Sciences (version 15 for Windows; SPSS; Chicago, IL) or R (http://www.r-project.org).

RESULTS

Thirty patients were included in the study; 20 were assigned bosentan and 10 placebo (Figure 1). All patients remained in the study until the last patient had completed the week 12 assessments, unless they dropped out due to side effects. Of those randomized, 10% (1 patient) in the placebo group and 30% (6 patients) in the bosentan group discontinued 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 (2), dyspnea (2), drowsiness and lower extremity edema refractory to medical therapy (1), and subjective cervical swelling combined with constipation (1). One patient in the placebo group developed dyspnea after the presumptive increase in medication dosage at 2 weeks, thus requiring a lower maintenance dosage up to 12 weeks. Lower extremity edema warranting diuretic therapy was observed in 4 patients receiving bosentan and in 1 patients receiving placebo. In two cases, the bosentan dosage had to be halved after 8 weeks due to reversible elevation of liver enzymes.

Overall, treatment groups were well matched with respect to baseline characteristics (Table 1). All patients were in WHO 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 (≥ 45%) in all cases.

Primary End-Point: 6-Minute Walking Distance

Changes from baseline to the week 12 in the 6-minute walking distance were similar across treatment groups (p= 0.474) (Figure 2). The mean distance walked in 6 minutes decreased by 10 m in patients given bosentan (from 339 meters [81] at baseline to 329 meters [94] at week 12, p=0.040), and remained unchanged in those given placebo (331 meters [116] at baseline and 331 meters [123] at week 12, p=0.100).

Table 1. Demographic and hemodynamic characteristics at baseline

	Placebo n = 10	Bosentan n = 20	p-value
Demographic variables			
Age, years	65 (7.9)	69.5 (8.8)	0.184
Male gender	7 (70%)	11 (55%)	0.694
Weight, kg	76.9 (16.4)	66.3 (14.0)	0.075
Height, centimeters	165 (6.1)	166.9 (6.9)	0.464
Body mass index	28.1 (4.7)	24.0 (5.9)	0.064
Pack-years	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 edema	2 (20%)	5 (25%)	1
Physical examination			
Wheezing	2 (20%)	8 (40%)	0.420
Rales	1 (10%)	1 (5%)	1
GOLD stages			
III (30%pred < FEV1% ≤ 50% predicted)	6 (60%)	11 (55%)	1
IV (FEV1%≤< 30% predicted)	4 (40%)	9 (45%)	
Exercise tolerance			
6-minute walking distance, meters	331 (116)	339 (81)	0.817
Borg dyspnea 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 diuretics use	3 (30%)	5 (25%)	1
Short ß$_2$-agonists	10 (100%)	20 (100%)	1
Long-acting ß$_2$-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	18 (3)	20 (5)	0.291
Peripheral O_2-saturation, %	92 (4%)	93 (4%)	0.510
Heart rate, beats/min	90 (12)	88 (15)	0.759
Systolic blood-pressure, mm Hg	142 (19)	129 (16)	0.069
Diastolic blood-pressure, mm Hg	87 (7)	78 (9)	0.009
Echocardiography			
Pulmonary hypertension at rest (≥ 30mmHg)*	6 (60%)	14 (70%)	0.584
Median estimated systolic PAP at rest, mmHg*	37 [20-42]	32 [(29-38]	0.779
Left ventricular ejection fraction, %	57 (9)	61 (10)	0.321

Definition of abbreviations: Kg, kilograms; GOLD, Global Initiative for Chronic Obstructive Lung Disease. Numbers represent absolute numbers (percentage), mean (standard deviation), median [interquartile range]. *Estimated pulmonary pressures without adding central venous pressure.

Secondary End-Points

No significant treatment group 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 evidenced solely a significant increase in pulmonary vascular resistance in patients randomized to placebo (p=0.006). There was no change in the Borg dyspnea index (p=0.932). Conversely, arterial partial pressure of oxygen decreased significantly in patients assigned bosentan as compared to those assigned placebo (p=0.029). In the bosentan group, mean arterial partial pressure of oxygen was 65.2 mmHg (10.5) at baseline, 58.8 mmHg (8.6) at 4 weeks, and 60.7 mmHg (7.5) at 12 weeks. The corresponding values for the placebo group were 66.1 mmHg (15.1), 64.4 mmHg (6.9), and 65.7 mmHg (10.9), respectively. The decrease in arterial oxygen pressure was associated with a significant increased in alveolar-arterial gradient in the group treated with bosentan as compared to patients receiving placebo (Figure 3). Health-related quality of life, particularly the global physical health domain in the Short-Form-36 Health Survey, deteriorated in patients given bosentan as compared to those given placebo (Table 4). Hematological 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 the 12 weeks therapy with bosentan (Figure 4A-B and Figure 5). As compared to baseline, mean change in perfusion of the right lung at 12 weeks was 0.88% (2.7) for the placebo group and 0.07 (1.7) for the bosentan group (p=0.381). The respective values for the left lung were -0.66% (2.7) and -0.142% (1.7) (p=0.576).

Table 2. Lung function testing and cardiopulmonary exercise test parameters

	Placebo		Bosentan		p-value
	Baseline n = 10	12 weeks n = 9	Baseline n = 20	12 weeks n = 14	
Bodyplethysmography					
Total lung capacity post-BD, liter	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, liter	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, liter	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
Heart rate rest, beats/min	85 (13.3)	87 (16)	91.9 (15)	91 (11)	0.474
Heart rate max, beats/min	115 (20)	115 (14)	108 (21)	114 (21)	0.626
Heart rate max, %	75 (13)	75 (8)	72 (15)	76 (15)	0.489
O_2 pulse at rest, ml/beat	3.81 (1.60)	3.27 (1.68)	3.07 (0.77)	3.41 (1.38)	0.088
O_2 pulse max, ml/beat	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, liters	13.6 (3.6)	13.8 (5.0)	14.0 (2.8)	15.4 (4.8)	0.498
Minute ventilation max, liters	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
VO_2 at rest, ml/min/kg	4.1 (1.0)	4.9 (1.9)	4.3 (0.8)	3.5 (1.7)	0.288
VO_2 max, ml/min/kg	13.4 (2.4)	13.9 (2.8)	13.8 (3.0)	13.4 (3.4)	0.113
VO_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

Definition of abbreviations: BD, bronchodilator; O_2, oxygen; max, peak exercise; VO_2, maximal oxygen uptake. PAP, pulmonary arterial pressure; RV, right ventricle. Numbers represent mean (standard deviation).

Table 3. Cardiopulmonary hemodynamics at baseline and after therapy

	Placebo		Bosentan		p-value
	Baseline n = 10	**12 weeks n = 9**	**Baseline n = 20**	**12 weeks n = 14**	
Cardiopulmonary hemodynamics					
Systolic PAP, mmHg*	37 [20-42]	33 [29-39]	32 [29-38]	30 [26-34]	0.288
RV Fractional area change (FAC), %	34.2 (11.8)	43.9 (7.9)	42.7 (11.0)	50.5 (6.8)	0.935
Tricuspid annular motion (TAM), mm	24.4 (2.7)	22.5 (2.4)	21.0 (4.5)	22.7 (3.6)	0.059
Early diastolic velocity RV (E), cm/s	0.44 (0.09)	0.40 (0.08)	0.44 (0.11)	0.41 (0.12)	0.512
Late diastolic velocity RV (A)	0.46 (0.12)	0.46 (0.09)	0.44 (0.13)	0.39 (0.07)	0.338
Early diastolic/late diastolic velocity RV(E/A)	1.00 (0.30)	0.88 (0.15)	0.99 (0.23)	1.07 (0.33)	0.142
Tissue Doppler Imaging					
Early diastolic velocity (E'), cm/s	0.08 (0.03)	0.08 (0.03)	0.08 (0.04)	0.09 (0.03)	0.346
Late diastolic velocity (A'), cm/s	0.14 (0.05)	0.15 (0.02)	0.14 (0.05)	0.15 (0.05)	0.890
Systolic velocity (S'), cm/s	0.12 (0.04)	0.12 (0.02)	0.12 (.03)	0.12 (0.03)	0.961
Pulmonary vascular resistance, $(dyne*sec)/cm^5$	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

Numbers represent median [interquartile range] or mean (standard deviation). *Estimated pulmonary pressures without adding central venous pressure

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 n = 10	12 weeks n = 9	Baseline n = 20	12 weeks n = 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

Numbers represent mean (standard deviation).

DISCUSSION

Our 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 endpoint studied, including cardiopulmonary hemodynamics 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 pulmonary hypertension at rest, therapy with bosentan is not beneficial and results in relevant functional status deterioration.

The current study is the first to report the results of a randomized, 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 pO_2 [9, 27]. Moreover, clinical results of long-term treatment with calcium-channel blockers in COPD have been disappointing, showing that both pulmonary hemodynamics 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 case series [23].

In this placebo-controlled trial, therapy with the pulmonary vasodilator bosentan proved ineffective in improving exercise tolerance in patients with severe COPD without severe pulmonary hypertension 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 pulmonary hypertension [14, 28]. However, in contrast to pulmonary hypertension related to COPD, patients with idiopathic pulmonary hypertension demonstrate preponderantly right ventricular dysfunction leading to decreased cardiac index and major cardiovascular limitation in exercise testing. As yet, it was unclear, as to what extent right ventricular dysfunction during exercise limits exercise tolerance in severe COPD [24]. In this study, patients with COPD presented well preserved right ventricular function at rest, with in particular TAM (tricuspidal annular motion) above values known to worsen prognosis. Thereby, cardiopulmonary exercise testing profile was typical of a major ventilatory limitation (maximum respiratory quotient < 1 and maximum ventilation approximately equal to maximal minute ventilation). Hence, it remains questionable whether

improvement in right ventricular function during exercise can enhance exercise tolerance at all in patients with severe COPD without manifest right ventricular dysfunction in the resting state.

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

Interestingly, we observed a statistically significant increase of pulmonary vascular resistance, as assessed by echocardiography, in patients randomized to the placebo group. Considering the slow progression of mean pulmonary arterial pressures, pulmonary vascular resistance 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, we believe that this finding most likely represents an artefact. In any case, the clinical impact of an increase in pulmonary vascular resistance is suggested to be limited in the context of unchanged exercise capacity and maximal oxygen uptake.

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. Herein, we have evaluated COPD patients by single photon emission computer tomography and quantitative perfusion scintigraphy (SPECT), which appraise concomitantly parenchyma morphology and changes in regional and global perfusion patterns. As compared to the placebo group, patients with COPD receiving bosentan developed hypoxemia as assessed by blood gases analysis and pulsoxymetry. 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]. We found no evidence of change in qualitative pulmonary perfusion patterns in patients receiving bosentan in SPECT, e.i. there was no redistribution of blood flow within pulmonary regions. Therefore, we hypothesize that the decrease in arterial oxygen pressure could be attributed to a quantitative perfusion augmentation [2, 9]. The marked initial decrease in arterial oxygen partial pressures at 4 weeks, followed by a secondary increase at 12 weeks, suggests a consequential adjustment to the vasodilator effect in patients given bosentan. Fluid retention could have been another possible cause of decrease in oxygen arterial pressure and widening in alveolar-arterial gradient in patients treated with bosentan. Although body weight remained unchanged during the 3 months study period, patients on bosentan did require more often prescription of diuretic due to low extremity edema. Hence, fluid retention might have caused or aggravated hypoxemia in the 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 study and the respiratory rate remained unchanged during drug treatment in our 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. Of note, the decline of 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 hypoxemia associated with vasodilator therapy. The well known placebo effect in participants of a clinical trial was also evident in our trial 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 from the study due to side-effects of the medication. Although the drop-out rate was not statistically significant in comparing both randomized groups, patients treated with bosentan reported increased dyspnea, drowsiness and required more often diuretics due to peripheral edema. These observations corroborate the unfavorable effect of this class of drugs in patients with COPD. Accordingly, a preliminary report suggests that sildenafil, another pulmonary vasodilator, which selectively inhibits cGMP specific phosphodiesterase type 5, is equally ineffective in improving exercise capacity in patients with COPD [35].

Several limitations of this study need to be mentioned. First, we conducted a single centre study and included a relatively small number of patients. However, due to the well-defined findings of our 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 ß-error. Additionally, a major weakness of this study is that no invasive assessment of pulmonary arterial pressures, e.i. cardiac catheterization including exercise testing, has been performed. By refraining from catheterization, we could neither reliably measure pulmonary pressures at rest nor prove the extent of pulmonary hypertension during exercise. 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 this study are rather illustrative and might not stand the test of invasive confirmation. Finally, the patients included in this trial did not have severe pulmonary hypertension at rest. Therefore, our results are only generalizable to the majority of patients with severe COPD, who usually only present with mild to moderate pulmonary hypertension during exercise [7], and may not apply to the uncommon cases of disproportional pulmonary hypertension 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 pulmonary hypertension or in those selected COPD patients with clearly documented cardiovascular limitation to exercise capacity.

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

Acknowledgment

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Figure Legends:

Figure 1. Trial Design

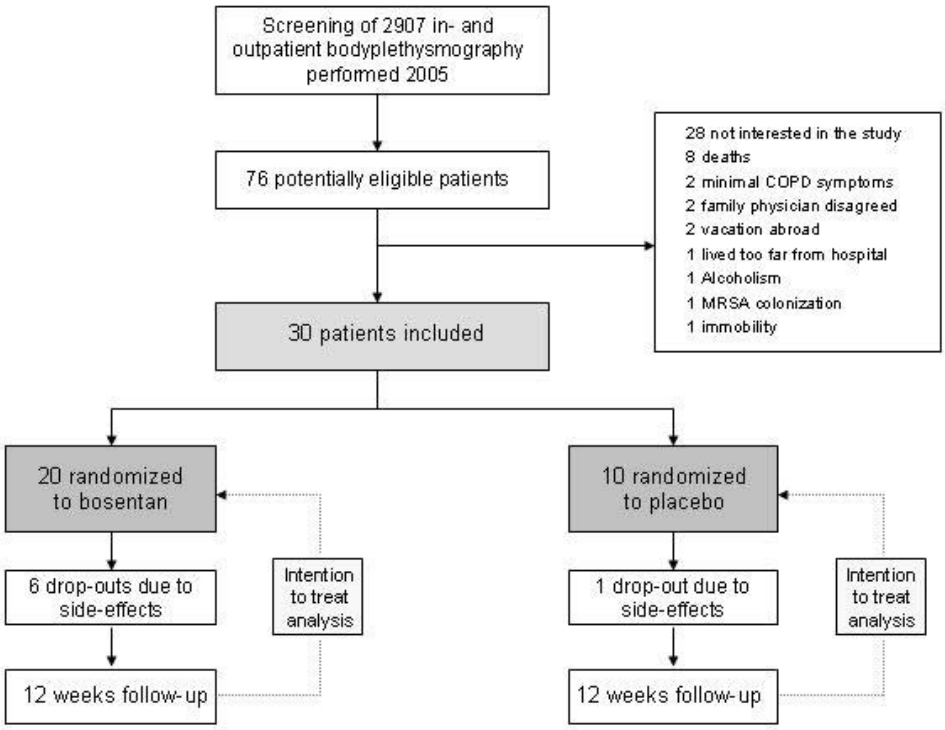


Figure 2. Individual patient data showing the 6-minute walking distance at baseline and at 12 weeks in patients assigned placebo (n=10) and in patients assigned bosentan (n=20). The changes in the 6-minute walking distance were similar across treatment groups (p= 0.474). The mean distance walked in 6 minutes decreased by 10 m in patients given bosentan (from 339 meters [81] at baseline to 329 meters [94] at week 12, p=0.040), and remained unchanged in those given placebo (331 meters [116] at baseline and 331 meters [123] at week 12, p=0.100).

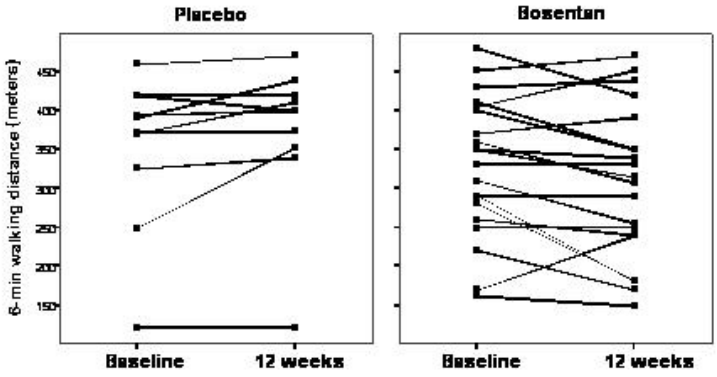


Figure 3. Alveolar-arterial gradient at baseline, at 4 weeks and at 12 weeks in patients assigned placebo and in patients assigned bosentan. The alveolar-arterial gradient increased significantly in patients assigned bosentan as compared to those assigned placebo (p=0.029). In the bosentan group, median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

Figure 3

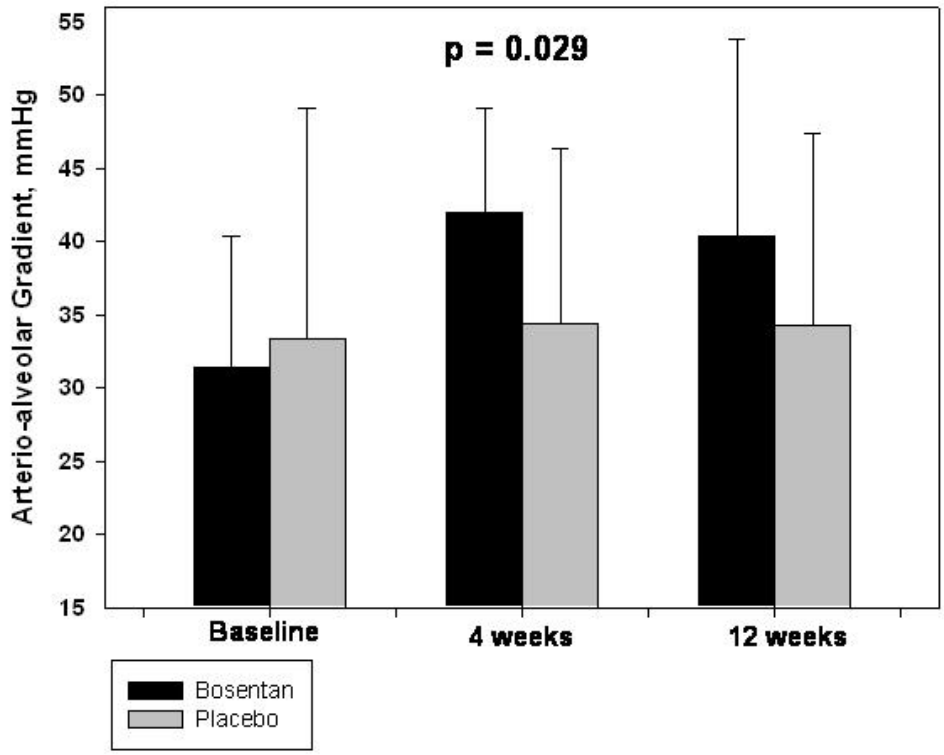


Figure 4A. Transversal thoracic-CT scan image showing emphysematous changes in the right anterior upper lobe.

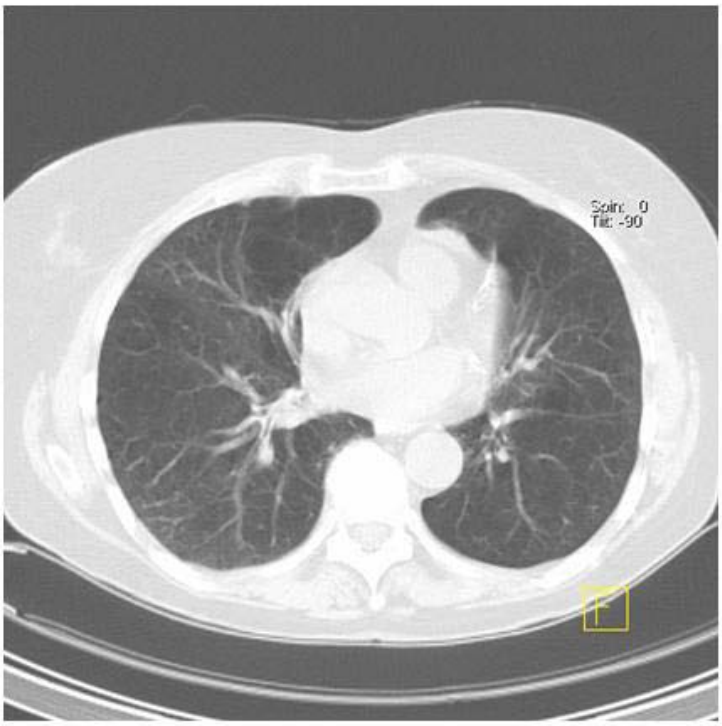


Figure 4B. Transversal fusion image combining thoracic-CT scan image and perfusion signal. Color-coded areas denote perfusion of lung parenchyma (yellow= high perfusion areas, blue= low perfusion areas, black= no perfusion).

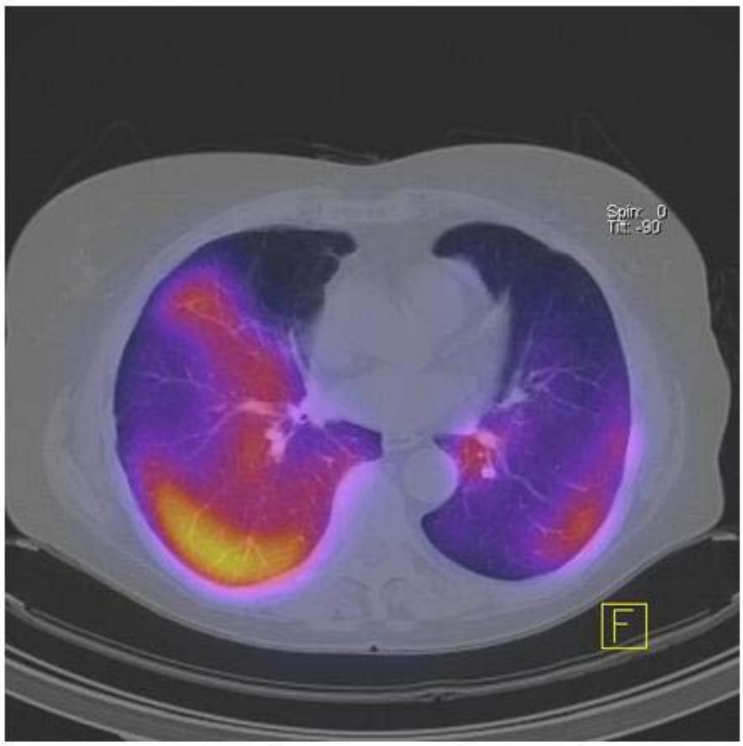
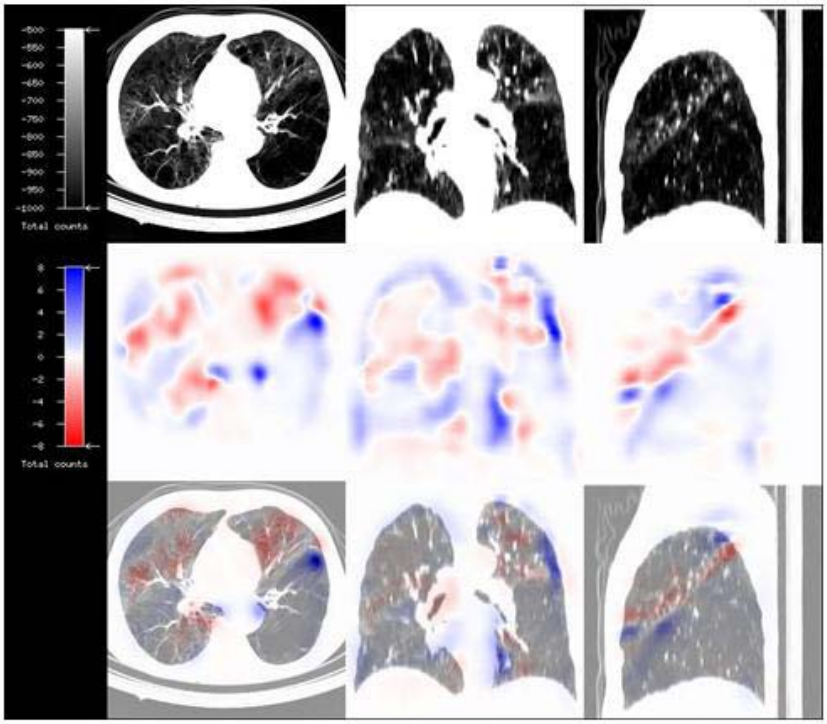


Figure 5. Transversal, coronal, and sagital thoracic-CT scan images showing the pulmonary morphology (first row); perfusion signal showing the perfusion difference (expressed as standard deviation) between baseline and 12 weeks (blue = decreased perfusion at 12 weeks as compared to baseline, red = increased perfusion at 12 weeks as compared to baseline, second row); and fusion thoracic-CT and perfusion signal images combining morphology and perfusion in one image (third row).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