OPEN ACCESS Freely available online

PLOS ONE

Acute Effects of Aerosolized Iloprost in COPD Related Pulmonary Hypertension - A Randomized Controlled Crossover Trial

Lucas Boeck, Michael Tamm, Peter Grendelmeier, Daiana Stolz*

Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital Basel, Basel, Switzerland

Abstract

Background: Inhaled iloprost potentially improves hemodynamics and gas exchange in patients with chronic obstructive pulmonary disease (COPD) and secondary pulmonary hypertension (PH).

Objectives: To evaluate acute effects of aerosolized iloprost in patients with COPD-associated PH.

Methods: A randomized, double blind, crossover study was conducted in 16 COPD patients with invasively confirmed PH in a single tertiary care center. Each patient received a single dose of 10 μg iloprost (low dose), 20 μg iloprost (high dose) and placebo during distinct study-visits. The primary end-point of the study was exercise capacity as assessed by the six minute walking distance.

Results: Both iloprost doses failed to improve six-minute walking distance ($p = 0.36$). Low dose iloprost (estimated difference of the means −1.0%, $p = 0.035$) as well as high dose iloprost (−2.2%, $p < 0.001$) significantly impaired oxygenation at rest. Peak oxygen consumption and carbon dioxide production differed significantly over the three study days ($p = 0.002$ and $p = 0.003$, accordingly). As compared to placebo, low dose iloprost was associated with reduced peak oxygen consumption (−76 ml/min, $p = 0.002$), elevated partial pressure of carbon dioxide (0.27 kPa, $p = 0.040$) and impaired ventilation during exercise (−3.0l/min, $p < 0.001$).

Conclusions: Improvement of the exercise capacity after iloprost inhalation in patients with COPD-associated mild to moderate PH is very unlikely.

Trial Registration: Controlled-Trials.com ISRCTN61661881

Citation: Boeck L, Tamm M, Grendelmeier P, Stolz D (2012) Acute Effects of Aerosolized Iloprost in COPD Related Pulmonary Hypertension - A Randomized Controlled Crossover Trial. PLoS ONE 7(12): e52248. doi:10.1371/journal.pone.0052248

Editor: Lynette Kay Rogers, The Ohio State Unversity, United States of America

Received April 23, 2012; **Accepted** November 16, 2012; **Published** December 27, 2012

Funding: DS was supported by a grant from the Swiss National Foundation (PP00P3_128412/1). The trial was supported by an unrestricted grant from Bayer Schering. Additional funding was granted by the Clinic of Pulmonary Medicine, University Hospital Basel, Switzerland. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: DS was supported by a grant from the Swiss National Foundation (PP00P3_128412/1). The trial was supported by an unrestricted grant from Bayer Schering. Additional funding was granted by the Clinic of Pulmonary Medicine, University Hospital Basel, Switzerland. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: dstolz@uhbs.ch

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. The increasing prevalence of COPD demands substantial progress to prevent and control the enormous burden of disease. COPD patients with secondary pulmonary hypertension (PH) have more severe disease, more frequent exacerbations, more rapid decline of functional capacity and worse outcome [2,3,4]. Thus, cardiovascular disease mechanisms are gaining importance as potential treatment targets in COPD [5,6,7].

So far, only a few trials investigated pulmonary vasodilators in COPD patients [8,9,10,11]. Unfortunately, pulmonary vasodilators mostly caused an impaired gas exchange and did not improve exercise capacity in COPD. Hereby it is conceivable that non-selective (ventilation-independent) pulmonary vasodilatation and inhibition of hypoxic vasoconstriction increases ventilation/perfusion (V/Q) mismatch and intrapulmonary shunting. Drug application by inhalation might overcome this flaw. Inhaled medications facilitate access to alveolar units, which receive the greatest proportion of ventilation, hence redirecting pulmonary blood flow advantageously to these areas while lowering pulmonary pressures. Two inhaled vasodilators, namely nitric oxide and prostacyclin, have shown to improve oxygenation and pulmonary artery pressure (PAP) in high V/Q mismatch states [12,13]. Although nitric oxide has shown beneficial aspects in COPD, its use is inconvenient and the safety of this approach has been considered questionable [14,15,16]. In contrast, prostacyclin, one of the most powerful pulmonary vasodilators, might play a central role in the development of secondary PH in COPD [17,18]. The selective vasodilative properties of inhaled iloprost, a prostacyclin

analogue, were previously investigated in interstitial lung disease [19]. Recently, an open-label study reported an improvement in 6 minute walking distance after iloprost inhalation in COPD patients [20]. Importantly, V/Q matching improved after iloprost administration. However, to our knowledge, inhaled prostacyclins have not been investigated in a randomized trial in COPD patients.

The aim of this study was to evaluate whether inhaled iloprost improves exercise capacity in COPD patients with pulmonary hypertension in a randomized, double-blind fashion.

Methods

The study was designed as a prospective, randomized, double-blind, single center, cross-over trial comparing two doses of inhaled iloprost (10 μg iloprost = low dose iloprost and 20 μg iloprost = high dose iloprost) and placebo in 16 patients with COPD-associated PH (a detailed description of the methods is provided by the supporting information – Supporting information S1, Protocol S1, CONSORT checklist S1). The trial was conducted from October 2009 to September 2010 at the University Hospital Basel. The study protocol was reviewed and approved by the Institutional Review Board (EKBB 190/2009) and registered as the OPTION trial (On demand prostacyclin inhalation in obstructive pulmonary disease and pulmonary hypertension; ISRCTN61661881). Written informed consent was obtained from all participants before study inclusion.

Patients

Patients with a smoking history of more than 20 pack-years and confirmed COPD, as specified by the global initiative of chronic obstructive lung disease (GOLD) guidelines [21], were considered for eligibility according to a screening algorithm (**Figure 1**). Patients were included if 1) COPD was confirmed by lung function, 2) age was above 40 years, 3) the mean pulmonary artery pressure (mPAP) at rest was $\geq$ 30 mmHg and/or mPAP during exercise was $\geq$ 45 mmHg, 4) COPD management adhered to GOLD guidelines. Patients were excluded if 1) severe mental disorder prevented appropriate judgment concerning study participation, 2) life expectancy was severely restricted (less than 6 months), 3) COPD exacerbated within the last 4 weeks or changes in COPD management occurred within less than 3 months, 4) there were significant signs of left heart failure, 5) the patient had a history of pulmonary embolism, 6) PH was explained by another cause than COPD, including hypoventilation syndrome and/or sleep apnea syndrome, 7) the patient was pregnant or breastfeeding. In patients with insufficient COPD management, therapy was optimized according to GOLD guidelines and study inclusion postponed by 3 months. One patient declining right heart catheterization with estimated systolic pulmonary artery pressure on echocardiography of 65 mmHg in addition to the central venous pressure was included in the study.

Study Procedures

Formulas for inhalation were randomized by an automated computer-generated randomization scheme and assigned to specific study days. The patient as well as the study personnel, who administered the inhalation and performed all tests, was blinded to the medication allocation. A nurse and a physician, responsible for preparation of the medication, were the only persons aware of the randomization code during the trial. They were not involved in other study functions. Every patient received 10 μg iloprost (low dose iloprost), 20 μg iloprost (high dose iloprost) or placebo (normal saline) on three different study days. Iloprost (Ventavis®) was diluted in normal saline to achieve a 2 ml solution. The three solutions were not visually distinguishable. Approximately 15 minutes before inhalation of the study medication a short acting beta-2 agonist (200 μg salbutamol; Ventolin®) was inhaled via a spacer. Placebo and iloprost was inhaled through an ultrasonic nebulizer system (Multisonic® infracontrol; Schill, Probstzella, Germany) [22].

Pulmonary function testing. Dynamic and static pulmonary function parameters were evaluated by body plethysmography. Carbon monoxide diffusing capacity (DLCO) was measured. All tests were performed according to the European Respiratory Society standards [23].

Echocardiography. Transthoracic two-dimensional and Doppler echocardiography were carried out by an ultrasound instrument (Philips, iE33) and performed in all patients for screening. Two-dimensional and Doppler imaging was performed in standard parasternal and apical views. Systolic pulmonary artery pressures (sPAP) were estimated from the systolic transtricuspid pressure gradient by means of the modified Bernoulli equation (tricuspid pressure gradient = 4×[maximal velocity of tricuspid regurgitant jet]^2). Tricuspid annular plane systolic excursion (TAPSE) was estimated by two-dimensional echo guided M-mode recordings from the apical four-chamber view. According to the ESC/ERS guidelines, patients with possible or likely echocardiographic PH criteria, preserved systolic and absence of significant diastolic dysfunction were referred for right heart catheterization [24].

Right heart catheterization. Standard right heart catheterization measurements were taken without sedation from the right atrium, right ventricle and pulmonary artery at the end of expiration. Cardiac output was determined by the thermodilution method, whereas cardiac index is corrected for body surface area. Patients with normal or slightly elevated pulmonary pressures at rest were further evaluated during exercise.

Mobile cardiopulmonary exercise testing. The mobile cardiopulmonary exercise test was performed exactly 10 minutes after iloprost or placebo inhalation as described previously [25,26]. Exercise parameters were measured using a telemetric mobile cardiopulmonary exercise test device (Oxycon Mobile® software v. 4.6, VIASYS Healthcare GmbH, Würzburg, Germany). This device consists of an EKG-triggered belt, an oxygen sensor, a facemask with a dead space $<$30 ml, a flow sensor, a sensor unit to measure oxygen and carbon dioxide, a data storage unit and a data transfer unit with integrated long-range telemetry, allowing real-time monitoring of the data. Heart rate, oxygen saturation, respiratory rate, tidal volume, oxygen consumption (VO2) and carbon dioxide production (VCO2) were continuously registered. Out of those parameters ventilation (VE), ventilatory reserve, O2 pulse, and ventilatory equivalents (VE/VO2, VE/CO2) were calculated. Before the exercise test there was a resting phase of several minutes. Measures at rest were obtained during a steady state after inhalation before exercise start. 10 minutes after inhalation of iloprost/placebo a six-minute walking test (6MWT) with the mobile exercise equipment was performed according to the American Thoracic Society guidelines [27]. At all times patients had the opportunity to slow the pace, to stop temporarily and to discontinue the test. During the test patients were not encouraged to walk faster or to continue walking. Exercise measures were obtained at peak oxygen uptake. Except for oxygen saturation, where minimal values, and heart rate where maximal values during exercise were analyzed. After test measures were acquired 6 minutes after exercise stop. Walking distance, perceived dyspnea as well as complications/side effects were recorded after the tests.

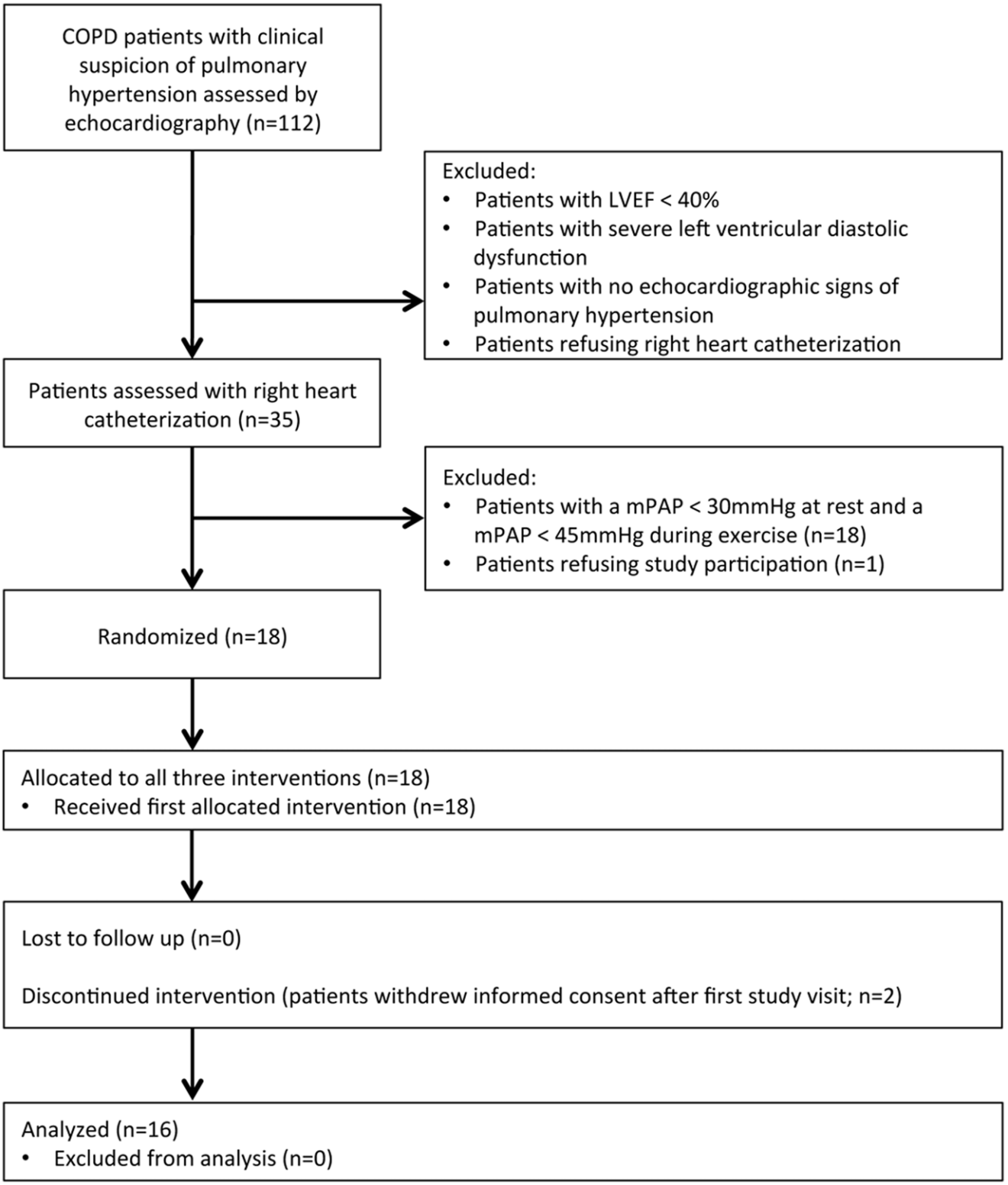

Figure 1. Screening, enrollment and interventions of the study participants. COPD denotes chronic obstructive pulmonary disease, CVP central venous pressure, LVEF left ventricular ejection fraction, mPAP mean pulmonary artery pressure, PH pulmonary hypertension, sPAP systolic pulmonary artery pressure, 6MWT six-minute walking distance.
doi:10.1371/journal.pone.0052248.g001

Table 1. Population characteristics; discrete variables are expressed as counts (%) and continuous variables as mean ± standard deviation.

N	16
Age, years	73.2±6.7
Male gender (%)	10 (62.5%)
BMI	26.7±4.3
Smoked pack years	50±29
Exacerbation within the last year	1.2±1.4
MMRC	3.8±1.1
FEV_1, liters	1.1±0.5
FEV_1, % predicted	51.3±31.4
FEV_1/FVC	44.2±16.8
TLC, liters	6.4±2.3
TLC, % predicted	107.2±29.7
RV/TLC	55.3±9.2
DLCO, % predicted	39.5±15.6
sPAP (excluding CVP), mmHg	43.9±12.8
LVEF, %	59.5±5.8
TAPSE, mm	21.2±2.7
pH	7.42±0.03
pO2, kPa	8.53±1.78
pCO2, kPa	5.66±1.15
Bicarbonate	26.6±3.5
mPAP at rest, mmHg	31.3±7.3
PCWP at rest, mmHg	12.8±5.6
CI at rest, L min^{-1} m^2	3.11±0.55
PVR at rest, dyn s cm^{-5}	266.5±123.5
mPAP exerc., mmHg	51.8±8.6
PCWP exerc., mmHg	23.6±9.1
CI exerc., L min^{-1} m^2	5.3±1.3
PVR exerc., dyn s cm^{-5}	245.9±72.6

BMI denotes body mass index, CI cardiac index, DLCOcarbon monoxide diffusing capacity, FEV_1 forced expiratory volume in one second, FVC forced vital capacity, LVEF left ventricular ejection fraction, MMRC medical research council dyspnea scale, mPAP mean pulmonary artery pressure, pCO_2 partial pressure of carbon dioxide after exercise, PCWP pulmonary capillary wedge pressure, pO_2 partial pressure of oxygen, PVR pulmonary vascular resistance, RV residual volume, spa systolic pulmonary artery pressure (estimated), TAPSE tricuspid annular plane systolic excursion, TLC total lung capacity.
doi:10.1371/journal.pone.0052248.t001

Six-Minute walk test. The 6MWT without cardiopulmonary exercise equipment was performed in patients who did not tolerate the facemask and/or strongly required oxygen during exercise. Inhalation, resting and the 6MWT was carried out identically. Heart rate and oxygen saturation were monitored continuously throughout the test. Walking distance, perceived dyspnea and complications/side effects were recorded after the test. 6MWTs were performed with a steady amount of oxygen at each of the three tests.

Arterial blood gas analysis. Immediately after each exercise test a standard arterial puncture to obtain a specimen for blood gas analysis was performed.

Power Calculation

Power was calculated using the 6MWT distance before and after treatment as the primary outcome variable. Assuming a standard deviation of the difference before and after treatment of 50 m, there is a power >80% to detect a mean difference of 40 m with a sample size of 16 subjects by a two sided paired t-test (alpha = 0.05).

Table 2. Comorbidities of 16 patients with COPD and PH.

Comorbidities	
Arterial Hypertension	11 (69%)
Coronary artery disease	4 (25%)
Renal comorbidity	4 (25%)
Hypertensive heart disease	3 (19%)
Peripheral artery disease	3 (19%)
Alcohol abuse	3 (19%)
Current smoker	1 (6%)
Diabetes mellitus	1 (6%)
Malignancy	1 (6%)
Hepatic comorbidity	1 (6%)
Osteoporosis	1 (6%)

doi:10.1371/journal.pone.0052248.t002

Data Analysis

Discrete variables are expressed as counts (percentages) and continuous variables as mean ± standard deviation (SD). Parameters were analyzed by mixed-effects models, including treatment and period as fixed effects and subject as random effect. Results are presented as differences of means between placebo and iloprost with corresponding 95% confidence intervals and p-values. All tests were two tailed; $p<0.05$ was defined as significant. Data were analyzed using statistical software (Statistical Package for Social Sciences, IBM SPSS statistics 19, Chicago IL; R Development Core Team, version 2.9.2, Vienna).

Results

Sixteen patients (10 men, 6 women) were included in the study (**Figure 1**). All patients had confirmed COPD and had a mean of 50 pack years ±29 smoked (mean ± standard deviation). Most patients had severe (25%) or very severe COPD (38%). Signs of emphysema were evident in 87%, air trapping in 100% and hyperinflation in 38%. At rest, 5 patients (31%) were hypoxemic and 5 patients (31%) hypercapnic. Demographic, pulmonary and hemodynamic characteristics of the study population are presented in **Table 1**. Included patients had a considerable number of comorbidities (**Table 2**). All patients received, at least, agents recommended by the global initiative of obstructive lung disease. 6 patients (38%) received nocturnal or long-term oxygen therapy.

One patient fulfilling all inclusion criteria and included in the study withdrew informed consent before the first study visit. Two further patients withdrew informed consent after the first study visit. One of them experienced severe dyspnea after inhalation of the first study medication and denied to undergo any further study procedure. Retrospectively, the episode leading to study interruption followed placebo inhalation. Comprehensive mobile cardiopulmonary exercise testing, including the measures of a six-minute walk test (6MWT), was performed in 13 patients. Three patients were evaluated by standard 6MWTs. Four patients refused repeated arterial punctures and two arterial punctures were not achieved in a timely manner (21% and 4% of all arterial punctures, accordingly). Side-effects included exhaustion, dyspnea,

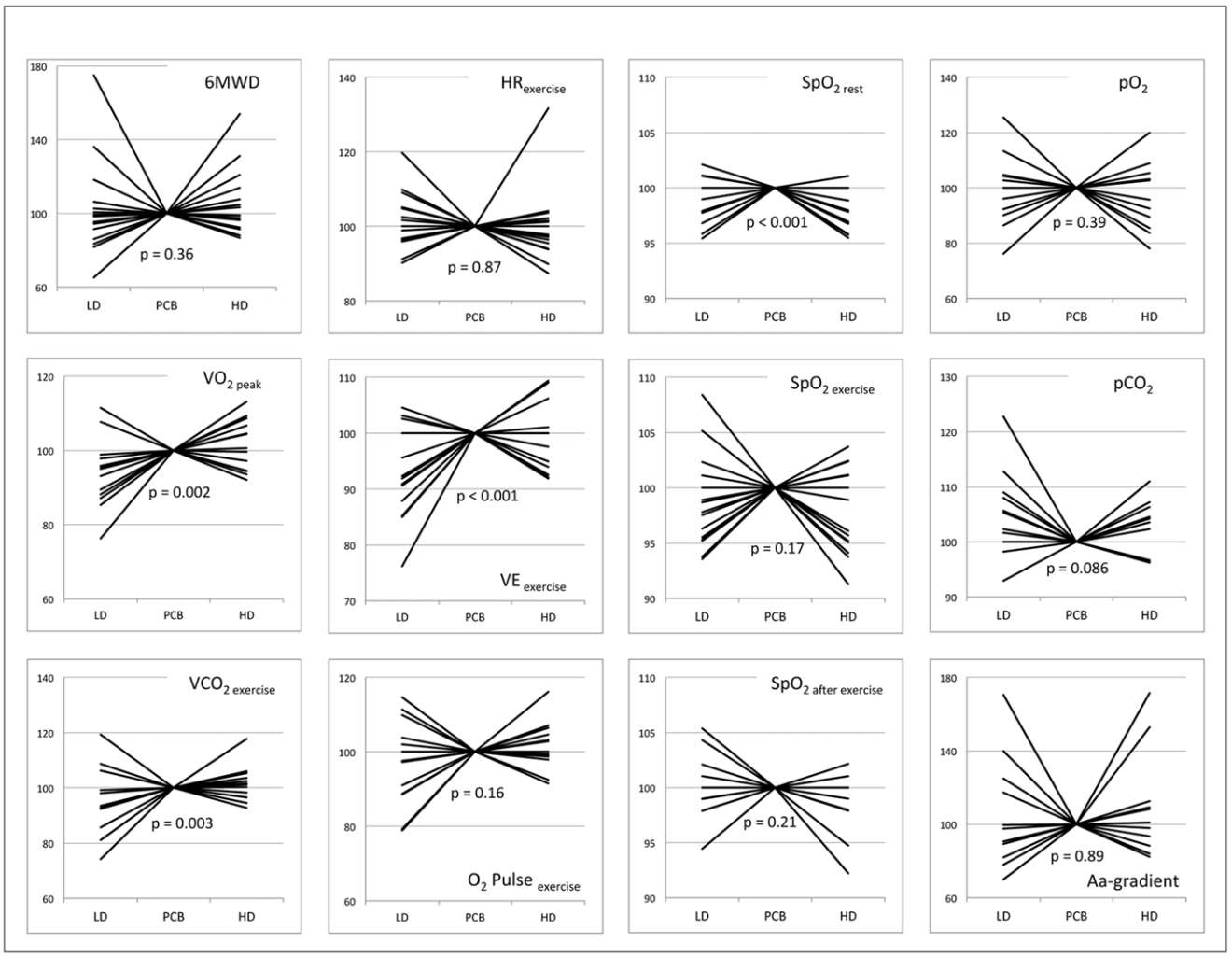

Figure 2. Improvement/worsening (in %) of outcome parameters in individual subjects after low dose iloprost inhalation (LD), high dose iloprost inhalation (HD) and placebo (PCB). Parameters after placebo inhalation were considered 100%. Aa-gradient denotes alveolar-arterial oxygen gradient, HR heart rate, pCO_2 partial pressure of carbon dioxide after exercise, pO_2 partial pressure of oxygen, SpO_2 oxygen saturation, VCO_2 carbon dioxide production, VE minute ventilation, VO_2 oxygen consumption, 6MWD six-minute walking distance.
doi:10.1371/journal.pone.0052248.g002

leg weakness and headache (n = 1), and dizziness (n = 1) after low dose iloprost. Unspecific weakness was reported following the low dose iloprost (n = 2) and placebo (n = 2) inhalation.

Iloprost inhalation did not affect 6-minute walking distance (p = 0.36; **Table 3**; **Figure 2**). There was a modest trend to a lower walking distance after low dose iloprost inhalation (estimated difference of the means as compared to placebo (EDOM): −12.4 m, 95% confidence interval (95% CI): −32.7–7.9 m, p = 0.22). High dose iloprost inhalation was similar to placebo in regard to walking distance (p = 0.98). Peak oxygen consumption ($VO_{2\ peak}$) during the 6MWT differed significantly over the three study groups (p = 0.002). $VO_{2\ peak}$ was clearly reduced after low dose iloprost inhalation as compared to placebo (EDOM: −76 ml/min, 95% CI: −122–−31 ml/min, p = 0.002). Noteworthy, inhalation of high dose iloprost seemed not to influence $VO_{2\ peak}$ (p = 0.92). A similar effect on carbon dioxide production during exercise ($VCO_{2\ exercise}$) was observed. Low dose iloprost impaired $VCO_{2\ exercise}$ (EDOM: −70 ml/min, 95% CI: −115–−26 ml/min, p = 0.004) whereas high dose iloprost did not alter $VCO_{2\ exercise}$ (p = 0.90). Oxygen saturation after iloprost inhalation at rest ($SpO_{2\ rest}$) was significantly different across the study groups (p<0.001). Low dose iloprost (EDOM: −1.0%, 95% CI: −1.9–−0.1%, p = 0.035) as well as high dose iloprost (EDOM: −2.2%, 95% CI: −3.1 −1.2%, p<0.001) significantly diminished $SpO_{2\ rest}$. Minimal oxygen saturation ($SpO_{2\ exercise}$) during the 6MWT was similar after placebo and iloprost inhalation (p = 0.17). However, there was a non-significant trend to a lower $SpO_{2\ exercise}$ after high dose iloprost inhalation (EDOM: −1.7%, 95% CI: −3.4–0.1%; p = 0.064). Oxygen saturation after exercise was similar in patients with low dose iloprost (p = 0.55) and declined in patients with high dose iloprost (EDOM: −2.4%, 95% CI: −3.4–0.0%; p = 0.047), as compared to placebo. Neither the partial pressure of oxygen nor the alveolar-arterial oxygen gradient was affected by treatment (p = 0.39 and 0.89, accordingly). The partial pressure of carbon dioxide after exercise was elevated in the low dose iloprost group (EDOM: 0.27 kPa, 95% CI: 0.01–0.52 kPa; p = 0.040). Ventilation during exercise ($VE_{exercise}$) differed in the three study groups (p<0.001). Low dose iloprost inhalation significantly impaired $VE_{exercise}$ (EDOM: −3.0l/min, 95% CI: −4.5–−1.5l/min, p<0.001), whereas high dose iloprost did not influence ventilation (p = 0.4). O_2 pulse during the 6MWT was similar after iloprost and placebo inhalation (p = 0.16). Perceived

Table 3. Outcome parameters after inhalation of placebo, low and high dose iloprost; * denotes significant changes as compared to placebo ($p<0.05$); rest: after inhalation at rest before exercise, exercise: during exercise, peak: peak during exercise, after exercise: at rest after exercise; Aa-gradient denotes alveolar-arterial oxygen gradient, bpm beats per minute, n number of patients providing all three measures, pCO_2 partial pressure of carbon dioxide after exercise, pO_2 partial pressure of oxygen, SD standard deviation, SpO_2 oxygen saturation, VE minute ventilation, VCO_2 carbon dioxide production, VO_2 oxygen consumption, 6MWD six-minute walking distance.

	n	Placebo (mean ± SD)	Iloprost 10 μg (mean ± SD)	Iloprost 20 μg (mean ± SD)
6 MWD, m	16	299±150	293±143	301±135
$VO_{2\ rest}$, ml/min	13	301±117	288±73	317±107
$VO_{2\ peak}$, ml/min	13	1018±351	946±301*	1024±333
$VO_{2\ peak}$, ml/min/kg	13	14.3±4.7	13.5±3.9*	14.3±4.4
$VO_{2\ peak}$, % pred.	13	63.9±20.2	60.5±20.9*	64.7±21.2
$VCO_{2\ rest}$, ml/min	13	245±113	241±79	255±88
$VCO_{2\ exercise}$, ml/min	13	903±393	842±359*	912±391
$SpO_{2\ rest}$, %	16	93.3±3.7	92.4±4.3*	91.4±3.7*
$SpO_{2\ exercise}$, %	16	84.1±4.8	83.0±5.0	82.6±6.0
$SpO_{2\ after\ exercise}$, %	16	95.1±2.7	95.0±3.5	94.1±3.9*
Heart rate $_{rest}$, bpm	16	82±16	84±15	84±17
Heart rate $_{exercise}$, bpm	16	109±18	110±21	109±22
Heart rate $_{after\ exercise}$, bpm	16	86±15	87±13	87±15
VE $_{rest}$, l/min	13	11.4±2.8	11.9±3.2	12.2±4.1
VE $_{exercise}$, l/min	13	35.9±18.0	33.3±17.3*	35.5±18.3
VE $_{after\ exercise}$, l/min	13	16.0±3.0	15.8±3.7	14.2±4.4
VR $_{exercise}$, %	13	16.1±11.4	24.0±12.8*	19.1±11.5
O_2 Pulse $_{exercise}$, ml	13	9.4±3.0	9.1±2.6	9.5±2.9
O_2 Pulse $_{exercise}$, % pred.	13	95.8±28.3	92.7±27.6	96.7±30.0
$VE/VO_{2\ exercise}$	13	33.1±7.8	32.2±7.5	33.0±9.0
$VE/VCO_{2\ exercise}$	13	38.5±8.5	37.5±6.9	38.0±8.2
pO_2, kPa	10	7.84±2.20	7.68±1.75	6.98±1.32
pCO_2, kPa	10	5.86±1.39	5.88±1.01*	6.13±1.47
Aa-gradient, kPa	10	4.28±2.17	4.51±1.68	4.82±1.51
BORG-scale	16	4.0±1.6	4.0±1.7	4.3±1.9

doi:10.1371/journal.pone.0052248.t003

exertion (BORG-scale) after the 6MWT did not differ according to the intervention ($p = 0.74$).

Discussion

Herein we report three main findings. First, iloprost inhalation failed to improve six minute walking distance in COPD-associated PH. Second, peak oxygen consumption was not affected or declined after iloprost inhalation. Third, oxygenation at rest deteriorated following both iloprost inhalations.

The present study is the first randomized, placebo-controlled trial investigating aerosolized iloprost in patients with COPD-related PH. Against our hypothesis, inhaled iloprost did not improve exercise capacity. Low dose iloprost even impaired peak oxygen consumption during the 6MWT. However, impaired oxygen uptake did not translate into a reduced walking distance.

Multiple factors cause exercise intolerance in COPD. Ventilatory components (expiratory flow limitation, dynamic hyperinflation, respiratory muscle dysfunction), gas exchange (hypoxemia, hypercapnia) as well as peripheral factors (locomotor muscle dysfunction, deconditioning) increase energy demands and decrease energy supplies, consequently leading to dyspnea and exercise limitation [28]. In COPD-associated PH hemodynamics and cardiac output are further elements of poor exercise tolerance. Reasons for the absent exercise improvement are that the key limiting factor was not addressed, the key limiting factor was insufficiently addressed or a simultaneous deterioration of another exercise limiting component.

A small number of other vasodilators were investigated in COPD so far. Nifedipine caused de-oxygenation in patients with COPD, most likely due to inhibition of hypoxic vasoconstriction [29,30]. Bosentan, an endothelin-receptor antagonist worsened oxygenation and quality of life in patients with severe COPD [10]. Moreover, three months of sildenafil did not improve exercise capacity in a similar cohort of COPD patients [11]. In a recent study, sildenafil deteriorated oxygenation due to impaired V/Q distributions at rest [31]. Still, there was a trend to a higher V/Q imbalance during exercise. Nevertheless, a beneficial effect of pulmonary vasodilators on hemodynamics is also in COPD-related PH likely [31,32]. Probably, most drugs lack selective vasodilative properties and consequently inhibit hypoxic vasoconstriction. Iloprost, a rather large molecule with a short half-life,

administered via inhalation, is one of the most selective pulmonary vasodilators available yet. However, similar flaws of inhaled iloprost limit its utilization in COPD.

Iloprost inhalation clearly impaired oxygenation at rest, both at low and high dose. An enhanced perfusion, similar to the effect reached by other pulmonary vasodilators, most likely caused a worsening of V/Q mismatch. It is unclear, whether selectivity of inhaled iloprost is insufficient or vasodilation *per se* causes impaired V/Q matching in COPD patients at rest. Although not statistically significant, there was a dose dependent decrease in oxygen saturation during exercise. Six minutes after exercise, once more at rest, oxygen saturation was clearly diminished after high dose iloprost inhalation. Thus, it is likely that the effect of iloprost on oxygenation is more pronounced at rest. A similar phenomenon was observed after sildenafil administration [31]. Noteworthy, beneficial effects of sildenafil on hemodynamics were similar at rest and during exercise.

Besides V/Q mismatch, other mechanisms impairing oxygenation and exercise capacity are conceivable. The major factor limiting exercise capacity in most COPD patients is ventilation. A minor effect of iloprost on airways could potentially aggravate air trapping, dynamic hyperinflation and compromise exercise tolerance. In accordance, decreased minute ventilation was observed after low dose iloprost inhalation. Our results are in line with results of a previous study, which suggest a significantly lower minute ventilation after iloprost inhalation [20]. The elevated carbon dioxide levels following iloprost inhalation might either reflect an effect on the ventilatory pump or an impairment of the respiratory drive. Previously, it was reported that iloprost attenuates cerebral blood flow, which might alter ventilatory control [33].

In the current trial, the subgroup of COPD patients who improved in walking distance also improved in peak oxygen consumption. These three patients were characterized by a more restricted diffusion capacity, more dyspnea and a more severe right cardiac strain, while left cardiac function was preserved (data not shown). Thus, patients with a more severe hemodynamic and right cardiac compromise might still benefit. Presumably, ventilatory factors were the main determinants of exercise intolerance in this population. This is also in line with a recent study, suggesting that only COPD patients with severe PH (mPAP$\geq$40 mmHg) are limited by hemodynamics [34]. Moreover, the deleterious effects of iloprost on gas exchange and potentially on ventilation have further precluded an exercise improvement.

A few limitations of the study need to be mentioned. Obtained results are restricted to acute effects of the investigated iloprost dose. Whether other or repeated medication doses would have yielded another outcome is not known. However, our results already prove a clinically relevant deterioration of oxygenation at rest following single iloprost inhalation. Thus, a) indicating that there is a measurable (detrimental) effect of inhaled iloprost in this population; and b) questioning the appropriateness of a long-term trial in respect of short-term safety. The fact that all patients receiving continuous open-label iloprost inhalation following the study end, discontinued therapy within four weeks due to side-effects and/or lack of subjective clinical benefit, supports this notion. Despite careful patient evaluation we cannot rule out that other causes of PH contributed to elevated pulmonary pressures. A considerable number of patients had cardiac comorbidities and six patients had slightly elevated pulmonary capillary wedge pressures (PCWP$\geq$15 mmHg). Since left ventricular pressures were not measured it remains uncertain whether this reflects a true elevation [35]. Importantly, all patients had a preserved systolic function. However, a minor cardiac dysfunction at rest might have become more relevant during exercise. Three patients did not achieve current criteria for pulmonary hypertension (mPAP$>$25 mmHg). Mean pulmonary pressures during exercise in these patients were 49, 58 and 62 mmHg, respectively. Due to a significant number of missing arterial blood gases (25%) interpretation is limited.

In summary, inhaled iloprost failed to improve exercise capacity in patients with COPD-related PH. Negative effects of inhaled iloprost on oxygenation limit applicability in COPD. Up to date inhaled iloprost cannot be recommended in patients with COPD.

Supporting Information

Checklist S1 CONSORT Checklist.
(DOC)

Protocol S1 Trial Protocol.
(DOC)

Supporting Information S1 A detailed description of the methods.
(DOC)

Acknowledgments

We acknowledge the following people for their invaluable help: A. Schötzau (Schötzau AG) and C. Schindler (Swiss Tropical and Public Health Institute, University Basel, Basel, Switzerland) for statistical advice; M. Leo, G. Lüdin, G. Novicic, D. Wissler (Lung function lab, Clinic of Respiratory Medicine, University Hospital Basel, Basel, Switzerland) for cardiopulmonary assessments; A. Jochmann and A. Meyer (Clinic of Respiratory Medicine, University Hospital Basel, Basel, Switzerland) for randomization and preparation of the study medication; E. Seelig and M. Brinkert for data administration and manuscript preparation.

Author Contributions

Conceived and designed the experiments: LB MT PG DS. Performed the experiments: LB DS. Analyzed the data: LB MT PG DS. Wrote the paper: LB DS. Contributed to and approved the final draft of the manuscript: LB MT PG DS.

References

1. Mannino DM (2002) COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest 121: 121S–126S.
2. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E (1999) Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159: 158–164.
3. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, et al. (1995) Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 107: 1193–1198.
4. Sims MW, Margolis DJ, Localio AR, Panettieri RA, Kawut SM, et al. (2009) Impact of pulmonary artery pressure on exercise function in severe COPD. Chest 136: 412–419.
5. Bogaard HJ, Dekker BM, Arntzen BW, Woltjer HH, van Keimpema AR, et al. (1998) The haemodynamic response to exercise in chronic obstructive pulmonary disease: assessment by impedance cardiography. Eur Respir J 12: 374–379.
6. Sabit R, Bolton CE, Fraser AG, Edwards JM, Edwards PH, et al. (2010) Sub-clinical left and right ventricular dysfunction in patients with COPD. Respiratory medicine 104: 1171–1178.
7. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, et al. (2010) Percent emphysema, airflow obstruction, and impaired left ventricular filling. The New England journal of medicine 362: 217–227.

8. Melot C, Hallemans R, Naeije R, Mols P, Lejeune P (1984) Deleterious effect of nifedipine on pulmonary gas exchange in chronic obstructive pulmonary disease. Am Rev Respir Dis 130: 612–616.
9. Agusti AG, Barbera JA, Roca J, Wagner PD, Guitart R, et al. (1990) Hypoxic pulmonary vasoconstriction and gas exchange during exercise in chronic obstructive pulmonary disease. Chest 97: 268–275.
10. Stolz D, Rasch H, Linka A, Di Valentino M, Meyer A, et al. (2008) A randomised, controlled trial of bosentan in severe COPD. Eur Respir J 32: 619–628.
11. Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, et al. (2008) Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Respir J 31: 759–764.
12. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, et al. (1996) Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. American journal of respiratory and critical care medicine 153: 991–996.
13. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, et al. (1996) Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. American journal of respiratory and critical care medicine 154: 1671–1677.
14. Vonbank K, Ziesche R, Higenbottam TW, Stiebellehner L, Petkov V, et al. (2003) Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. Thorax 58: 289–293.
15. Adnot S, Kouyoumdjian C, Defouilloy C, Andrivet P, Sediame S, et al. (1993) Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. The American review of respiratory disease 148: 310–316.
16. Roger N, Barbera JA, Roca J, Rovira I, Gomez FP, et al. (1997) Nitric oxide inhalation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 156: 800–806.
17. Lee JD, Taraseviciene-Stewart L, Keith R, Geraci MW, Voelkel NF (2005) The expression of prostacyclin synthase is decreased in the small pulmonary arteries from patients with emphysema. Chest 128: 575S.
18. Nana-Sinkam SP, Lee JD, Stearman R, Sakao S, Sotto-Santiago S, et al. (2006) Prostacyclin synthase in smoking-related lung disease. Proceedings of the American Thoracic Society 3: 517.
19. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, et al. (1999) Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. American journal of respiratory and critical care medicine 160: 600–607.
20. Dernaika TA, Beavin M, Kinasewitz GT (2010) Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Respiration; international review of thoracic diseases 79: 377–382.
21. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, et al. (2007) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American journal of respiratory and critical care medicine 176: 532–555.
22. Gessler T, Schmehl T, Hoeper MM, Rose F, Ghofrani HA, et al. (2001) Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J 17: 14–19.
23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, et al. (1993) Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. The European respiratory journal Supplement 16: 5–40.
24. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et al. (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology 34: 1219–1263.
25. Attinger A, Tuller C, Souren T, Tamm M, Schindler C, et al. (2006) Feasibility of mobile cardiopulmonary exercise testing. Swiss Med Wkly 136: 13–18.
26. Tueller C, Kern L, Azzola A, Baty F, Condrau S, et al. (2010) Six-minute walk test enhanced by mobile telemetric cardiopulmonary monitoring. Respiration; international review of thoracic diseases 80: 410–418.
27. (2002) ATS statement: guidelines for the six-minute walk test. American journal of respiratory and critical care medicine 166: 111–117.
28. Aliverti A, Macklem PT (2008) Last Word on Point:Counterpoint: The major limitation to exercise performance in COPD is 1) inadequate energy supply to the respiratory and locomotor muscles, 2) lower limb muscle dysfunction, 3) dynamic hyperinflation. Journal of applied physiology 105: 763.
29. Simonneau G, Escourrou P, Duroux P, Lockhart A (1981) Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. The New England journal of medicine 304: 1582–1585.
30. Kalra L, Bone MF (1993) Effect of nifedipine on physiologic shunting and oxygenation in chronic obstructive pulmonary disease. The American journal of medicine 94: 419–423.
31. Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, et al. (2010) Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. American journal of respiratory and critical care medicine 181: 270–278.
32. Alp S, Skrygan M, Schmidt WE, Bastian A (2006) Sildenafil improves hemodynamic parameters in COPD–an investigation of six patients. Pulm Pharmacol Ther 19: 386–390.
33. Rosengarten B, Schermuly RT, Voswinckel R, Kohstall MG, Olschewski H, et al. (2006) Sildenafil improves dynamic vascular function in the brain: studies in patients with pulmonary hypertension. Cerebrovascular diseases 21: 194–200.
34. Boerrigter BG, Bogaard HJ, Trip P, Groepenhoff H, Rietema H, et al. (2012) Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. Chest.
35. Halpern SD, Taichman DB (2009) Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 136: 37–43.