



# Sildenafil treatment in COPD does not affect stroke volume or exercise capacity

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**ABSTRACT:** In chronic obstructive pulmonary disease (COPD) patients, stroke volume response to exercise is impaired. The aim of the present study was to investigate whether 3 months of sildenafil treatment improves stroke volume and, if so, whether this improvement is related to the pulmonary artery pressure and translated into an improved exercise capacity.

A total of 15 stable COPD patients (Global Initiative for Chronic Obstructive Lung Disease stage II–IV) underwent right heart catheterisation at rest and during exercise. Stroke volume was assessed by magnetic resonance imaging (MRI) at rest and during submaximal exercise in the supine position and compared with eight age-matched controls. Additionally, a cardiopulmonary exercise test and a 6-min walking distance test were performed. Exercise tests and MRI were repeated after 12 weeks of oral therapy with 50 mg sildenafil three times daily.

Stroke volume in COPD patients was significantly lower than in healthy controls ( $62 \pm 12$  versus  $81 \pm 22$  mL at rest and  $70 \pm 15$  versus  $101 \pm 28$  mL during exercise). Pulmonary hypertension (PH) was diagnosed in nine patients and was absent in six. Treatment with sildenafil had no effect on stroke volume or exercise capacity. Although the stroke volume was lower in COPD patients with associated PH in comparison with non-PH patients, there was no difference in treatment response between both groups.

In the present group of 15 chronic obstructive pulmonary disease patients, a reduced stroke volume was found at rest and during exercise. Neither stroke volume nor exercise capacity were improved by 3 months of sildenafil therapy.

**KEYWORDS:** Chronic obstructive pulmonary disease, magnetic resonance imaging, pulmonary hypertension, sildenafil, stroke volume

Several studies have shown that stroke volume (SV) in chronic obstructive pulmonary disease (COPD) patients may be reduced at rest and frequently fails to increase during exercise [1–5]. Since cardiac output is proportionally related to tissue oxygen delivery, impaired SV response (when not compensated by an increased cardiac frequency) may contribute to reduced exercise capacity in COPD.

The inability of the right ventricle (RV) to increase SV during exercise is considered to be partly caused by an inadequate pulmonary vascular vasodilator response to an increased flow, resulting in a sudden increase in right ventricular afterload [6, 7]. An alternative explanation is intrinsic right ventricular dysfunction, independent of afterload.

Sildenafil has been proposed as a drug that may reduce pulmonary vascular resistance (PVR) and improve right ventricular function in COPD. PVR reduction occurs by augmenting intracellular

levels of the nitric oxide (NO) second messenger cyclic GMP, which causes opening of the calcium-sensitive potassium ion channels. This causes a reduction in intracellular calcium ion levels, which leads to vasodilatation [8]. Sildenafil might also increase coronary perfusion, which might be important in hypertrophied RV, thus improving cardiac function [9]. In addition, a recent study showed that sildenafil caused an increased contractility in hypertrophied RVs of rats [10]. However, these results have yet to be confirmed in humans. Thus, sildenafil may improve cardiac function in COPD patients by both decreasing RV afterload and improving RV function. If sildenafil is associated with an improvement in RV function, this may result in an increased exercise capacity. It was recently reported by HOLVERDA *et al.* [11] that SV response during submaximal exercise on a recumbent bicycle can be assessed noninvasively using magnetic resonance imaging (MRI). In the present study, the effects of 3 months of oral

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sildenafil treatment on SV response, measured at submaximal exercise capacity, and the exercise capacity in a group of COPD patients with and without pulmonary hypertension (PH) are reported. The first aim of the present report was to assess whether SV at rest or during exercise was lower in COPD patients in comparison with controls. The second aim was to assess the effects of sildenafil treatment on the exercise SV response and on exercise capacity in the COPD group. Finally, the association between pulmonary artery pressure and treatment response was explored.

## MATERIAL AND METHODS

### Subjects

A total of 15 patients with stable COPD were included in the present study. Inclusion criteria were moderate-to-severe COPD according to Global Initiative for Chronic Obstructive Lung Disease guidelines [12], and patients had to be without exacerbation or hospital admission in the previous 4 months. Exclusion criteria were a history of systemic hypertension, left-sided heart failure or pulmonary embolism. All patients had optimal bronchodilator therapy. In total, 10 patients were ex-smokers and five were current smokers. Patients were also excluded if they were using cardiac drugs (angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, calcium channel blockers, nitrates or other vasodilators). As a control group, eight sex- and age-matched healthy subjects were included. The study was approved by the medical ethics committee of the VU University Medical Center (Amsterdam, the Netherlands) and written informed consent was obtained from all patients.

### Study design

At baseline, right heart catheterisation was performed. In order to assess the effect of sildenafil on SV and exercise capacity, an MRI, a 6-min walk distance (6MWD) test and a cardiopulmonary exercise test (CPET) were performed. The 6MWD and CPET were performed on 2 separate days. The control group underwent an MRI in the same way as the study group. After the baseline measurements, 50 mg sildenafil was administered three times daily. Blood pressure was monitored for the first hours after sildenafil intake.

After 1 month, patients were phoned and all side-effects of sildenafil were recorded. After a treatment period of 3 months with sildenafil, the maximal workload was again determined during CPET and 6MWD. The SV response was assessed with MRI performed at the same workload as the initial measurement.

### Lung function testing

Standard spirometry, determination of transfer factor of the lung for carbon monoxide and measurement of RV and total lung capacity were performed according to the European Respiratory Society/American Thoracic Society (ATS) guidelines [13–15]. The lung function test was repeated after 3 months in order to confirm the stability of the lung function over the study period and to assess possible effects of sildenafil on the lung function.

### CPET

The CPET was a physician-supervised, standardised, progressively increasing work rate to maximum tolerance on an electromagnetically braked cycle ergometer (Lode, Groningen, the Netherlands). The load was increased until spontaneous

interruption of exercise, while ECG and breath-to-breath respiratory gas exchange were recorded (Vmax 229; SensorMedics, Yorba Linda, CA, USA). Minute ventilation ( $V'E$ ), oxygen uptake ( $V'O_2$ ), carbon dioxide output ( $V'CO_2$ ) and respiratory exchange ratio were calculated. Peak  $V'O_2$  was defined as the highest  $V'O_2$  measured during the last minute of symptom-limited exercise. Ventilatory efficiency was assessed by calculation of the slope of the increase in  $V'E$  with respect to  $CO_2$  output ( $V'E/V'CO_2$ ). The anaerobic threshold (AT) was assessed by the V-slope method (*i.e.* the  $V'O_2$  level at which  $V'CO_2$  began to increase). The ventilatory reserve was calculated by forced expiratory volume in one second multiplied by 37.5. Arterial blood gases were analysed during maximal exercise testing.

### 6MWD test

The 6MWD test was performed according to ATS guidelines [16]. Immediately after the 6MWD test, the Borg dyspnoea score was obtained.

### Right heart catheterisation

Right heart catheterisation was performed with patients breathing room air. A flow-directed balloon-tipped 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp., Irvine, CA, USA) was inserted in the internal jugular vein. Measurements at the end of expiration were recorded. Cardiac output was determined by the direct Fick method.  $V'O_2$  was measured for 5 min during catheterisation (Vmax 229; SensorMedics). Arterial and mixed venous blood gases were obtained from the radial and pulmonary arteries, respectively. Subsequently, patients inhaled NO for 5 min at a concentration of 20 ppm (flow rate 15 L·min<sup>-1</sup>) mixed with room air (Nodomo; Drägers, Lübeck, Germany). Patients inhaled and exhaled nasally through a tight face mask. Finally, subjects were asked to cycle on a recumbent bicycle (Lode). Work rate was increased to 40% of maximal workload as previously determined during maximal exercise testing. After reaching a haemodynamically steady state, haemodynamic measurements and blood sampling were repeated.

### Measurement of exercise-induced SV response by MRI

Magnetic resonance images and flow measurements were acquired with a 1.5-T Siemens Sonata whole body system (Siemens Medical Solutions, Erlangen, Germany) as previously described [17], with the exception that no breath-holds were used and temporal resolution was increased to 35 ms for flow quantification. SV was determined in both patients and controls by assessing the flow in the aorta. For the exercise measurements, the number of time phases in the cardiac cycle and the velocity sensitivity were adjusted to the increased cardiac frequency. The MRI exercise protocol consisted of a 3-min period of cycling in supine position on the same recumbent bicycle (Lode) used during invasive haemodynamic measurements after right heart catheterisation. Work rate was increased to 40% of maximal workload in the first minute as previously determined during maximal exercise testing. After 3 months, MRI was repeated at the same workload.

### Estimation of changes in pulmonary artery pressure with MRI

In order to measure any possible effect of sildenafil on pulmonary artery pressure ( $P_{pa}$ ) the acceleration time/ejection

time ratio [18] and the left ventricular septal bowing (LVSB) [19] were measured. The acceleration time is the time from onset of forward flow to the moment of maximum flow velocity in the main pulmonary artery, as measured by velocity-encoded cine MRI. The LVSB is the extent of septal bowing in the direction of the left ventricle at the beginning of early diastole. These measurements were repeated after 3 months of sildenafil treatment.

### Statistical analysis

Data are presented as mean  $\pm$  SD. A p-value  $<0.05$  was considered to be significant. A Wilcoxon paired rank test was used to compare SV and MRI estimates of  $\bar{P}_{pa}$  between rest and exercise and between baseline measurements and sildenafil treatment. A Mann–Whitney U-test was used to compare MRI measurements in COPD patients and healthy controls. Pearson correlation analysis was used to assess the relationship between SV, determined using MRI, and right heart catheterisation and between the SV response before and after treatment with sildenafil.

## RESULTS

### Patient characteristics

Pulmonary function characteristics of the 15 COPD patients before and after treatment with sildenafil are reported in table 1. Lung function remained stable over the treatment period. The results of the haemodynamic measurements during right heart catheterisation are presented in table 2. Mean  $\bar{P}_{pa}$  ( $\bar{P}_{pa}$ ) and cardiac output increased significantly during exercise in all patients. Nine patients were diagnosed with COPD-associated PH, which is defined as a  $\bar{P}_{pa} \geq 25$  mmHg with a pulmonary capillary wedge pressure  $<15$  mmHg at rest, or a  $\bar{P}_{pa} \geq 30$  mmHg during exercise [20]. Five patients showed PH at rest ( $33 \pm 7$  mmHg). In all patients, PVR failed to decrease during submaximal exercise. Both

arterial and mixed venous oxygen saturation decreased significantly during submaximal exercise. NO inhalation decreased  $\bar{P}_{pa}$  by  $14 \pm 8\%$ , whereas cardiac output and systemic arterial pressure remained unchanged.

### SV response during exercise measured with MRI

The SV measured during right heart catheterisation was first compared with the SV measured using MRI and a good correlation between the two measurements was found ( $R^2=0.88$ ;  $p<0.001$ ) showing the validity of the MRI to measure SV.

Table 3 shows the results of cardiac MRI at rest and during exercise at baseline and after treatment. SV, cardiac frequency and cardiac output increased significantly from rest to exercise. In comparison with COPD patients, the control subjects showed a significantly higher SV both at rest ( $62 \pm 12$  versus  $81 \pm 22$  mL) and during exercise ( $70 \pm 15$  versus  $101 \pm 28$  mL;  $p<0.05$ ).

The SV did not change after 3 months of sildenafil treatment. Figure 1 shows the individual SV responses (SV during exercise minus SV at rest) of all patients before and after 3 months of treatment. As shown in figure 2, the SV response after treatment remained similar to that before treatment ( $R^2=0.66$ ;  $p<0.001$ ). A subgroup analysis of the nine COPD patients with abnormally increased  $\bar{P}_{pa}$  showed a lower SV response to exercise compared with the COPD patients with a normal pressure ( $4.3 \pm 5.7$  versus  $13.1 \pm 6.4$  mL $\cdot$ beat $^{-1}$ ), although this did not reach significance. In the COPD patients with associated PH, the SV response changed from  $4.3 \pm 5.7$  to  $3.3 \pm 5.4$  mL $\cdot$ beat $^{-1}$  ( $p=0.2$ ) after 3 months of treatment, which was not different from the non-PH group ( $13.1 \pm 6.4$  to  $13.2 \pm 6.7$  mL $\cdot$ beat $^{-1}$ ;  $p=0.3$ ).

### Estimation of $\bar{P}_{pa}$ with MRI

The acceleration time/ejection time ratio and the LVSB did not change after treatment with sildenafil ( $0.32 \pm 0.02$  to  $0.32 \pm 0.03$  and  $0.31 \pm 0.13$  to  $0.31 \pm 0.15$  cm, respectively).

### CPET and 6MWD test

Table 4 presents the CPET parameters and 6MWD before and after treatment. At baseline,  $56 \pm 28$  W (37%) with a peak  $V_{O_2}$

**TABLE 1** General characteristics and lung function data

	COPD		Healthy controls
	At baseline	After sildenafil treatment	
Subjects n	15		8
Male/female n	9/6		5/3
Age yrs	$65 \pm 2^{\#}$		$66 \pm 3$
Smoking pack-yrs	$61 \pm 11^{\#}$		
BMI kg $\cdot$ m $^{-2}$	$24 \pm 4^{\#}$		$23 \pm 2$
VC % pred	$100 \pm 26$	$99 \pm 19$	$118 \pm 22$
FEV $_1$ % pred	$49 \pm 24$	$46 \pm 18$	$109 \pm 16$
FEV $_1$ /VC % pred	$38 \pm 16$	$37 \pm 17$	$72 \pm 6$
TLC % pred	$125 \pm 16$	$124 \pm 17$	$103 \pm 9$
DL $_{CO}$ % pred	$48 \pm 16$	$46 \pm 17$	$94 \pm 12$

Data are presented as mean  $\pm$  SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; VC: vital capacity; % pred: % predicted; FEV $_1$ : forced expiratory volume in one second; TLC: total lung capacity; DL $_{CO}$ : diffusing capacity of the lung for carbon monoxide. #: data after sildenafil treatment were not significantly different to baseline data.

**TABLE 2** Haemodynamic response to submaximal exercise and nitric oxide (NO) inhalation

	Rest	Exercise	NO
$\bar{P}_{pa}$ mmHg	$22 \pm 9$	$32 \pm 11^*$	$19 \pm 10^*$
$P_{cwp}$ mmHg	$11 \pm 2$	$14 \pm 2$	$11 \pm 2$
$P_{syst}$ mmHg	$97 \pm 14$	$113 \pm 19^*$	$96 \pm 14$
PVR dyn $\cdot$ s $\cdot$ cm $^{-5}$	$259 \pm 166$	$288 \pm 174$	$23 \pm 126$
Cardiac output L $\cdot$ min $^{-1}$	$5.4 \pm 1.7$	$7.5 \pm 2.3$	$5.4 \pm 1.6$
Cardiac frequency beats $\cdot$ min $^{-1}$	$80 \pm 14$	$96 \pm 14^*$	$81 \pm 10$
Sa $_a$ O $_2$ %	$92 \pm 4$	$88 \pm 6^*$	$93 \pm 4$
SV $_v$ O $_2$ %	$67 \pm 6$	$51 \pm 8^*$	$68 \pm 5$

Data are presented as mean  $\pm$  SD.  $\bar{P}_{pa}$ : mean pulmonary artery pressure;  $P_{cwp}$ : pulmonary capillary wedge pressure;  $P_{syst}$ : mean systemic artery pressure; PVR: pulmonary vascular resistance; Sa $_a$ O $_2$ : arterial oxygen saturation; SV $_v$ O $_2$ : mixed venous oxygen saturation. \*:  $p<0.05$  versus rest.

**TABLE 3** Stroke volume (SV) at rest and during exercise measured using magnetic resonance imaging before and after treatment with sildenafil

	Healthy controls <sup>#</sup>		COPD patients <sup>†</sup>			
	Rest	Exercise	Before treatment with sildenafil		After 3-month treatment with sildenafil	
			Rest	Exercise	Rest	Exercise
Cardiac frequency beats·min <sup>-1</sup>	71±8	96±12 <sup>+</sup>	78±13*	94±15 <sup>+</sup>	79±10	99±8 <sup>+</sup>
SV mL·beat <sup>-1</sup>	81±22	101±28 <sup>+</sup>	62±12*	70±15* <sup>+</sup>	64±12	73±21 <sup>+</sup>
Cardiac output L·min <sup>-1</sup>	5.7±1.5	9.6±2.6 <sup>+</sup>	5.1±1.4	6.7±2.0* <sup>+</sup>	5.3±1.4	7.3±2.2 <sup>+</sup>

Data are presented as mean ± sd. COPD: chronic obstructive pulmonary disease. <sup>#</sup>: n=8; <sup>†</sup>: n=15. \*: p<0.05 versus healthy controls; <sup>+</sup>: p<0.05 versus rest in same treatment.

of  $12.1 \pm 3.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $44 \pm 11\%$ ) were reached. AT was reached in seven patients. The blood pH and CO<sub>2</sub> tension did not really change from rest to maximal exercise from 7.42 to 7.37 and  $39 \pm 6$  to  $42 \pm 8$  mmHg, respectively. The ventilatory reserve was  $38 \pm 18\%$  at maximal exercise. Five out of the 15 patients reached a peak exercise ventilation  $>70\%$ . A ventilatory reserve  $<15\%$  is considered indicative of ventilatory exercise limitation. This was observed in one patient who reached a peak exercise ventilation of 99%. No statistically significant differences in the maximal exercise capacity and 6MWD were reached after treatment with sildenafil.

### Side-effects

Reported side-effects after sildenafil intake were headache (seven cases), facial flushing (two cases) and muscle pain (two cases). No major side-effects were experienced and all patients completed the study.

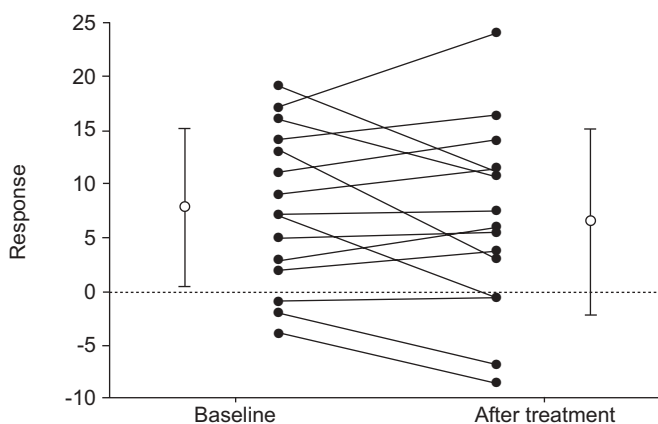
### DISCUSSION

The present study is the first in COPD to assess the effects of sildenafil on SV response during submaximal exercise and maximal exercise capacity. A 3-month treatment period did not improve SV or exercise capacity (assessed by 6MWD test and CPET). In addition, sildenafil did not alter arterial oxygenation at rest or during maximal exercise.

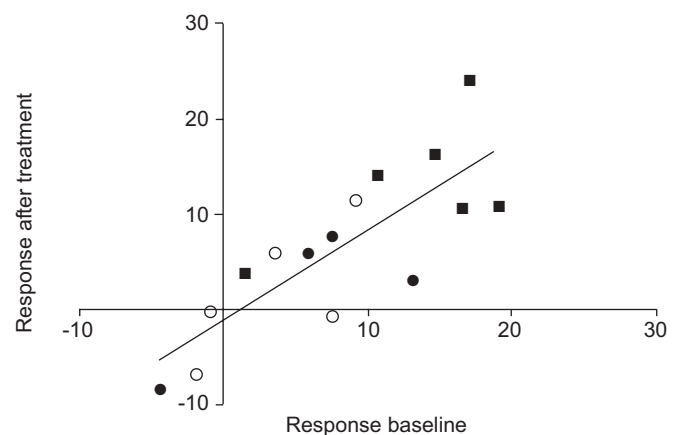
At rest, SV was lower in COPD patients compared with healthy controls. This difference was even more pronounced during exercise. During exercise there was a rapid increase in  $P_{pa}$  even in patients with normal resting pressures. The findings of a reduced SV response during exercise together with an increase in  $P_{pa}$  are consistent with those of previous studies [3, 5, 21] and fit with the idea that this reduced SV during exercise is caused by an increased afterload.

There are many possible causes of the steep increase in  $P_{pa}$  during exercise in COPD. First, loss of recruitment capacity of the pulmonary vascular bed due to remodelling of the pulmonary vessels and a reduced capillary bed will lead to an increase in  $P_{pa}$  if cardiac output augments. Secondly, exercise might even increase PVR further due to mechanic compression of the alveolar vessels, secondary to hyperinflation and endothelial dysfunction of the alveolar vessels, leading to an impaired release of the vasodilator NO [22]. The latter supports the finding that  $P_{pa}$  decreases after inhalation of NO, providing a rationale for the present study, since sildenafil is a well-recognised alternative to stimulate NO-mediated vasodilatation.

In the present study, neither an improved SV nor an increased exercise capacity following a 3-month treatment period was



**FIGURE 1.** Individual stroke volume (SV) response before and after 3 months of treatment with sildenafil. ●: SV response, calculated as SV during exercise minus SV at rest; ○: mean SV response. Whiskers represent sd.



**FIGURE 2.** Stroke volume response during exercise before and after 3 months of treatment with sildenafil. ○: chronic obstructive pulmonary disease (COPD) with pulmonary hypertension (PH) at rest; ●: PH during submaximal exercise; ■: COPD without PH.  $R^2=0.66$ ,  $p<0.001$ .

**TABLE 4** Maximal cardiopulmonary exercise testing in chronic obstructive pulmonary disease patients before and after treatment with sildenafil

	Baseline	After 3-month treatment with sildenafil
<b>Workload max W</b>	56±28 (37±17)	56±22 (39±27)
<b>Peak <math>\dot{V}O_2</math> mL·kg<sup>-1</sup>·min<sup>-1</sup></b>	12.1±3.6 (44±11)	12.4±3.8 (46±13)
<b>Cardiac frequency max beats·min<sup>-1</sup></b>	122±19 (79±11)	124±14 (81±7)
<b>Peak <math>O_2</math>- pulse mL·beat<sup>-1</sup></b>	7.1±2 (50±18)	7.4±1.4 (53±20)
<b><math>\dot{V}E</math> max L·min<sup>-1</sup></b>	38±14 (67±16)	39±15 (65±15)
<b><math>\dot{V}E/\dot{V}CO_2</math></b>		
Slope	46±27	40±17
At nadir	51±18	46±15
<b><math>\Delta\dot{V}O_2/\Delta</math>workload</b>	8.4±1.6	8.9±1.9
<b><math>P_{a,O_2}</math> mmHg</b>		
At rest	74±13	72±14
During exercise	64±17	64±19
<b><math>P_{a,CO_2}</math> mmHg</b>		
At rest	39±6	36±12
During exercise	42±8	41±6
<b><math>S_{a,O_2}</math> %</b>		
At rest	95±2	94±2
During exercise	89±6	88±6
<b>6MWD m</b>	385±135	396±116
<b>Borg score</b>	6.4±1.7	6.6±2.2

Data are presented as mean±SD (% of predicted±SD) or mean±SD. Max: maximum;  $\dot{V}O_2$ : oxygen uptake;  $\dot{V}E$ : minute ventilation;  $\dot{V}CO_2$ : carbon dioxide production;  $\Delta\dot{V}O_2/\Delta$ workload: increase in  $\dot{V}O_2$  with respect to increase in work rate;  $P_{a,O_2}$ : arterial oxygen tension;  $P_{a,CO_2}$ : carbon dioxide arterial tension;  $S_{a,O_2}$ : arterial oxygen saturation; 6MWD: 6-min walk distance.

found with sildenafil. All the parameters of the exercise test remained unchanged. The absence of a treatment response was independent of the presence of PH. Although no clinical data of the long-term effects of sildenafil on pulmonary haemodynamics in COPD exists, the effects of sildenafil under hypoxic conditions have been studied [23–25]. FAORO *et al.* [24] showed that although sildenafil improved peak  $\dot{V}O_2$  in healthy subjects after acute exposure to hypoxia, it did not affect peak  $\dot{V}O_2$  nor maximal workload after 2 weeks of exposure to hypoxia, indicating that the effects of sildenafil under chronic and acute hypoxic conditions are different. In addition, ALDASHEV *et al.* [25] did not find improvement of cardiac output or oxygen saturation after a 12-week course of sildenafil in individuals living at high altitude; however, in contrast to the study of FARAO *et al.* [24], exercise capacity measured by the 6MWD test was improved.

Several factors may explain the absence of effect in the present study. First, an increased  $P_{pa}$  may play only a minor role in the impaired SV response to exercise. Reduced venous return (due to the increase of intrinsic positive end-expiratory pressure), disturbed diastolic filling of the left ventricle or an intrinsic impairment of RV function may be more important determinants in COPD patients [26–28].

A second possible explanation is that sildenafil may not lead to effective reduction of  $P_{pa}$  during exercise in COPD. This may be prevented by the presence of intimal fibrosis and the influence of mechanic compression of the alveolar vessels secondary to hyperinflation.

Finally, a decreased SV and an attenuated SV response may reflect severe deconditioning in these patients. Although the nature of this impairment remains largely unknown, it has been observed that in deconditioned healthy subjects, SV at rest is lowered and SV response is impaired during exercise [29].

A limitation of the present study is that a small number of patients had significant PH measured at rest. However, these patients did not show a more favourable response than the non-PH patients, as presented in figure 2. Nevertheless, it cannot be excluded that some COPD patients with more advanced PH and more pronounced endothelial dysfunction could benefit from sildenafil therapy. Therefore, a large trial is required to confirm the results found in the present study. In addition, right heart catheterisation was not repeated after 3 months of treatment. However, based on the close relation between SV measured by right heart catheterisation and MRI at baseline, the present authors believe that MRI is a valid method to study SV in these patients.

### Conclusion

In the present study of 15 chronic obstructive pulmonary disease patients, it was demonstrated that stroke volume was reduced in chronic obstructive pulmonary disease patients in comparison with healthy controls. However, 3 months of vasodilator therapy with sildenafil neither improved stroke volume nor exercise capacity. Although stroke volume was lower in the chronic obstructive pulmonary disease patients with associated pulmonary hypertension in comparison with

the nonpulmonary hypertension patients, there was no difference in treatment response.

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