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Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study

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Aims Exercise oscillatory breathing (EOB) is a ventilatory abnormality that occurs in ~20% of heart failure (HF) patients and carries a very unfavourable prognosis. Pulmonary vasoconstriction has been suggested to be involved in this disorder. We hypothesized that modulation of pulmonary vascular hypertone by oversignalling of the nitric oxide pathway with phosphodiesterase 5 (PDE5) inhibition might be beneficial. Accordingly, we performed a 1-year pilot trial with sildenafil in patients with HF and EOB.

Methods and results Among 122 HF cases, 32 presented with EOB during cardiopulmonary exercise testing (CPX) and were randomized to receive placebo ($n = 16$) or sildenafil ($n = 16$) at the dose of 50 mg three times a day, in addition to their current antifailure treatment. CPX-derived variables and pulmonary haemodynamics were assessed at 6 and 12 months. Sildenafil reversed EOB in 87% of patients at 6 months and 93% at 1 year, respectively ($P < 0.01$). This effect was accompanied by an improvement in functional performance (peak VO_2; from 9.6 to 12.4 and 13.2 mL/min/kg; $P < 0.01$) and exercise ventilation efficiency (ventilation to CO_2 production slope; from 41.1 to 32.7 and 31.5; $P < 0.01$). Chronic treatment with PDE5 inhibition significantly decreased pulmonary capillary wedge pressure (from 21 to 14 and 14 mmHg), mean pulmonary artery pressure (PAP; from 34.8 to 23 and 24 mmHg), and pulmonary vascular resistance (PVR; from 360 to 270 and 266 dyne/s/cm^5) compared with placebo ($P < 0.01$ for each comparison). On exploratory analysis, there was a correlation between PAP and PVR and the decrease in EOB in the treatment group. Placebo did not alter any of the aforementioned variables.

Conclusions PDE5 inhibition in HF patients with EOB offers the dual advantage of improving functional capacity and modulating the EOB pattern. PAP and PVR reduction seem to underlie the correction of the breathing disorder. Whether reversal of this unfavourable prognostic signal can affect survival remains unconfirmed at the moment.

Keywords Exercise oscillatory breathing • PDE5 inhibition • Pulmonary pressure

Introduction

Exercise oscillatory breathing (EOB) is an abnormal ventilatory manifestation typical of some patients presenting with heart failure (HF).[1] According to recent reports, its prevalence varies between 18 and 33% of cases of systolic HF with left-sided pulmonary hypertension (PH),[2–8] and a similar rate has also been observed in diastolic HF.[9] This subset of HF patients carries a very unfavourable prognosis.[2–8]

The pathophysiology is quite complex, and the main putative mechanisms and sustaining pathways for EOB include an increased pulmonary capillary pressure,[10] pulmonary vasoconstriction,[11]

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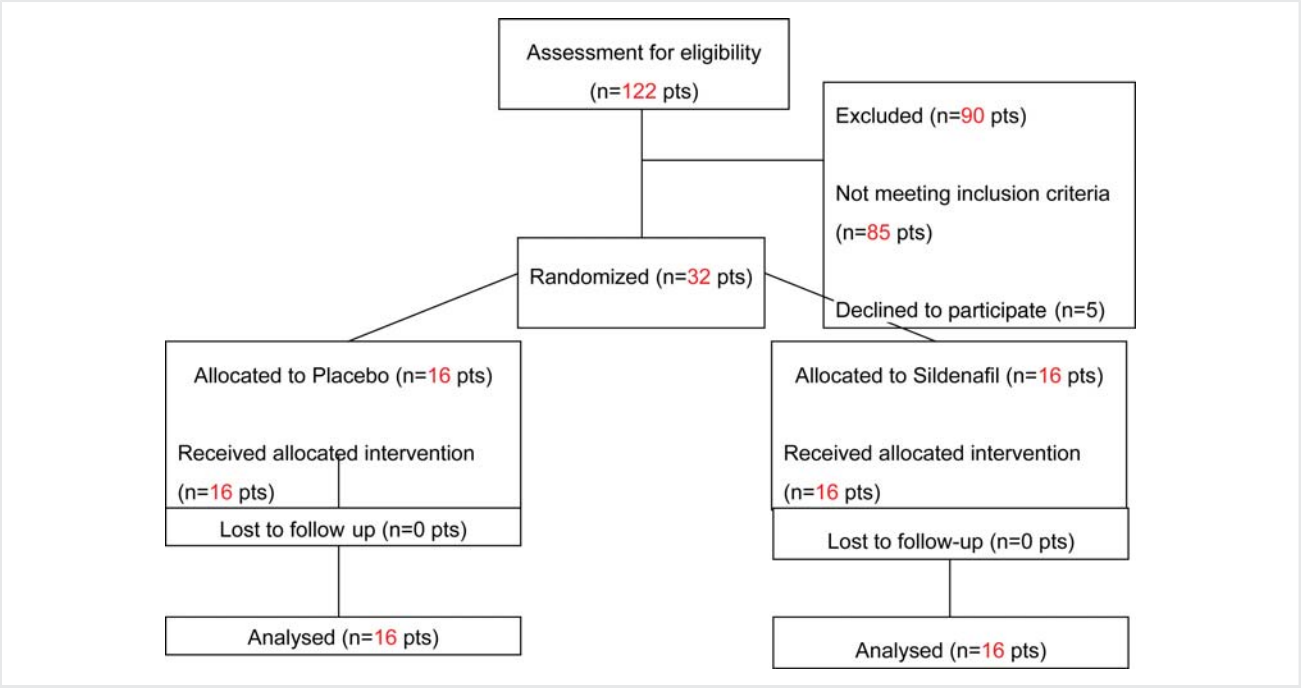

Figure 1 Flow diagram showing progress through the phases of the trial from enrolment to follow-up and data analysis.

some degree of circulatory blood flow fluctuations in the pulmonary arterial system,[12] and instability of the ventilatory control with demodulation of central and peripheral controllers of ventilatory drive.[13,14]

Although EOB recognition and targeting appear to be important clinical endpoints, attempts to identify effective therapeutic approaches are limited. This may be due to the relatively recent attention given to this abnormal ventilatory pattern and, as a consequence, a true appreciation in daily clinical practice is missing.

Phosphodiesterase 5 (PDE5) inhibition is quite a new therapeutic strategy for overexpressing nitric oxide (NO) signalling by increasing cyclic guanylyl monophosphate (cGMP) availability through inhibition of its breakdown.[15]

Sildenafil is a highly selective PDE5 inhibitor that reduces the excessive pulmonary vascular tone and improves diffusion capacity in patients with HF and left-sided PH.[16–22] Compared with other pulmonary vasodilators, it is well tolerated and possesses some attractive pharmacological properties that, at least in theory, might favour a modulatory activity on EOB, such as a peculiar pulmonary and intrapulmonary selectivity that prevents any significant pulmonary mismatching and O_2 desaturation.[23]

According to these premises, the primary aim of our study was to test the hypothesis that chronic administration of sildenafil can reverse EOB in human HF with mild to moderate PH through the well documented activity on pulmonary arterial vasomotion. An additional aim was to identify whether this effect may have an impact on relevant clinical correlates such as functional status and quality of life (QOL) in this subset of high risk HF patients.

Methods

Patient population

Of 122 stable HF patients with mild to moderate PH [mean pulmonary arterial pressure (PAP) within 25–35 mmHg] referred for cardiac evaluation to the Cardiopulmonary Laboratory at San Paolo Hospital, University of Milano, 37 (30%) presented with EOB. Five of them did not consent to participate in the study. Thus 32 patients comprised the final study population. A flow diagram of the study progress through the phases of the trial is reported in *Figure 1*. HF aetiology was either ischaemic, idiopathic, or hypertensive cardiomyopathy. All subjects were in a stable clinical condition, as there were no cardiovascular events in the previous 3 months or a need to increase or change therapy due to worsening of clinical status and symptoms in the last month. None presented with significant renal insufficiency (serum creatinine concentration $<$1.5 mg/dL). All had a left ventricular ejection fraction (LVEF) $<$45%.

Eligibility criteria were: consent to participate in the study after detailed information about possible benefits and risks; negative exercise stress test prior to study initiation; and forced expiratory volume in 1 s/forced vital capacity ratio $>$70%. Exclusion criteria were: female gender; inability to complete a maximal exercise test; a systolic blood pressure at rest $>$140 or $<$110 mmHg; therapy with nitrate preparations; a history of sildenafil intolerance; significant lung or valvular diseases; neuromuscular disorders; or peripheral vascular disease. All patients were symptomatic during exercise and limited by breathlessness and/or muscle fatigue; their present drug HF treatment was adherent to current guidelines.[24] Sleep breathing disorders, although frequently associated with EOB, were not included as enrolment criteria nor were they specifically investigated. Nonetheless, it is noteworthy that seven patients in the placebo group and five in the sildenafil group had been evaluated for sleep apnoea events before

study enrolment. All subjects except two in the placebo group exhibited an apnoea–hypopnoea index (AHI) >30 events/h due to occurrence of central sleep apnoea and were actually treated with continuous positive airway pressure (CPAP).

Patients gave their written consent to participate in the study and none was excluded after enrolment. The local Ethic Committee approved the trial.

Study protocol

This was a 1-year double-blind, randomized, placebo-controlled study. Patients were randomly assigned, in a 1:1 ratio, to receive placebo (16 patients) or the PDE5 inhibitor sildenafil, 50 mg three times a day (16 patients). For evaluations at baseline and at 6 and 12 months, patients underwent medical review, routine laboratory work, chest X-ray, haemodynamic and ultrasound measurements, and pulmonary function tests. They attended the Cardiopulmonary Clinic for physical examination, symptom and electrocardiogram (ECG) recording, compliance assessment (pill count method), and active drug or placebo supply (by a nurse who was unaware of the study aims and design) for the trial duration on a monthly basis.

Haemodynamic measurements

Circulatory measurements were performed in the morning, in the fasting state, in the supine position, without premedication. A 7 French thermodilution balloon-tipped catheter was inserted

Table 1 Baseline patient characteristics

	Placebo group ($n = 16$)	Sildenafil group ($n = 16$)
Demographics		
Age, years	68.0 ± 6.0	66.0 ± 8.0
BMI, kg/m^2	29.2 ± 8.0	29.6 ± 7.0
Gender, men/women, *n*	16/0	16/0
Race (Caucasian/others)	16/0	16/0
NYHA functional class, III/IV, *n* (%)	15 (94)/1 (6)	14 (87)/2 (13)
LVEF, %	28.0 ± 7.0	29.0 ± 8.0
Dilated cardiomyopathy, *n*	8	9
Ischaemic cardiomyopathy, *n*	7	5
Hypertensive cardiomyopathy, *n*	1	2
Chronic atrial fibrillation, *n*	4	3
Haemodynamics		
HR, b.p.m.	73.0 ± 2.0	69.0 ± 4.0
Mean blood pressure, mmHg	78.0 ± 6.0	77.0 ± 5.4
WPP, mmHg	20.0 ± 4.8	21.0 ± 3.0
Mean PAP, mmHg	34.0 ± 3.0	34.8 ± 4.0
PVR, dynes/cm^{-5}	354.0 ± 46.0	360.0 ± 53.0
SVR, dynes/cm^{-5}	1970.0 ± 260.0	1983.0 ± 254.0
PVR/SVR	0.190 ± 0.04	0.181 ± 0.05
Cardiac output, L/min	3.8 ± 1.2	3.9 ± 1.6
CPX variables		
Peak VO_2, mL/min/kg	10.4 ± 5.2	9.6 ± 6.1
VO_2 at AT, mL/min/kg	6.3 ± 4.0	6.0 ± 5.0
VE/VCO_2 slope	39.0 ± 4.2	41.1 ± 4.9
EOB, yes/no	16/0	16/0
Quality of life		
Breathlessness	24.0 ± 4.9	25.7 ± 4.8
Fatigue	22.7 ± 5.7	24.0 ± 4.9
Emotional function	31.9 ± 7.4	31.5 ± 7.0
Therapies		
Beta-blockers, *n* (%)	12 (75)	13 (81)
ACE inhibitors, *n* (%)	11 (69)	13 (81)
AT1 blockers, *n* (%)	5 (31)	3 (19)
Antialdosterone agents, *n* (%)	7 (44)	9 (56)
Digitalis, *n* (%)	1 (6)	2 (12)
Cardiac resynchronization therapy, *n* (%)	8 (58)	9 (56)

ACE, angiotensin-converting enzyme; AT, anaerobic threshold; AT1, angiotensin II type 1 receptor; BMI, body mass index; CPX, cardiopulmonary exercise testing; EOB, exercise oscillatory breathing; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; VE/VCO_2, ventilation to carbon dioxide; VO_2, oxygen consumption; WPP, wedge pulmonary pressure.

percutaneously, under local anaesthesia, into an antecubital vein and floated to the right atrium then advanced to the right ventricule, to the pulmonary artery, and to the wedge position. Pressure transducers were balanced against atmospheric pressure, and the zero reference levels for recordings were 5 cm below the sternal angle. Mean pressures were obtained by electronic damping.

Mean PAP and wedge pulmonary pressure (WPP) were recorded. Systemic vascular resistance (SVR) and pulmonary vascular resistance

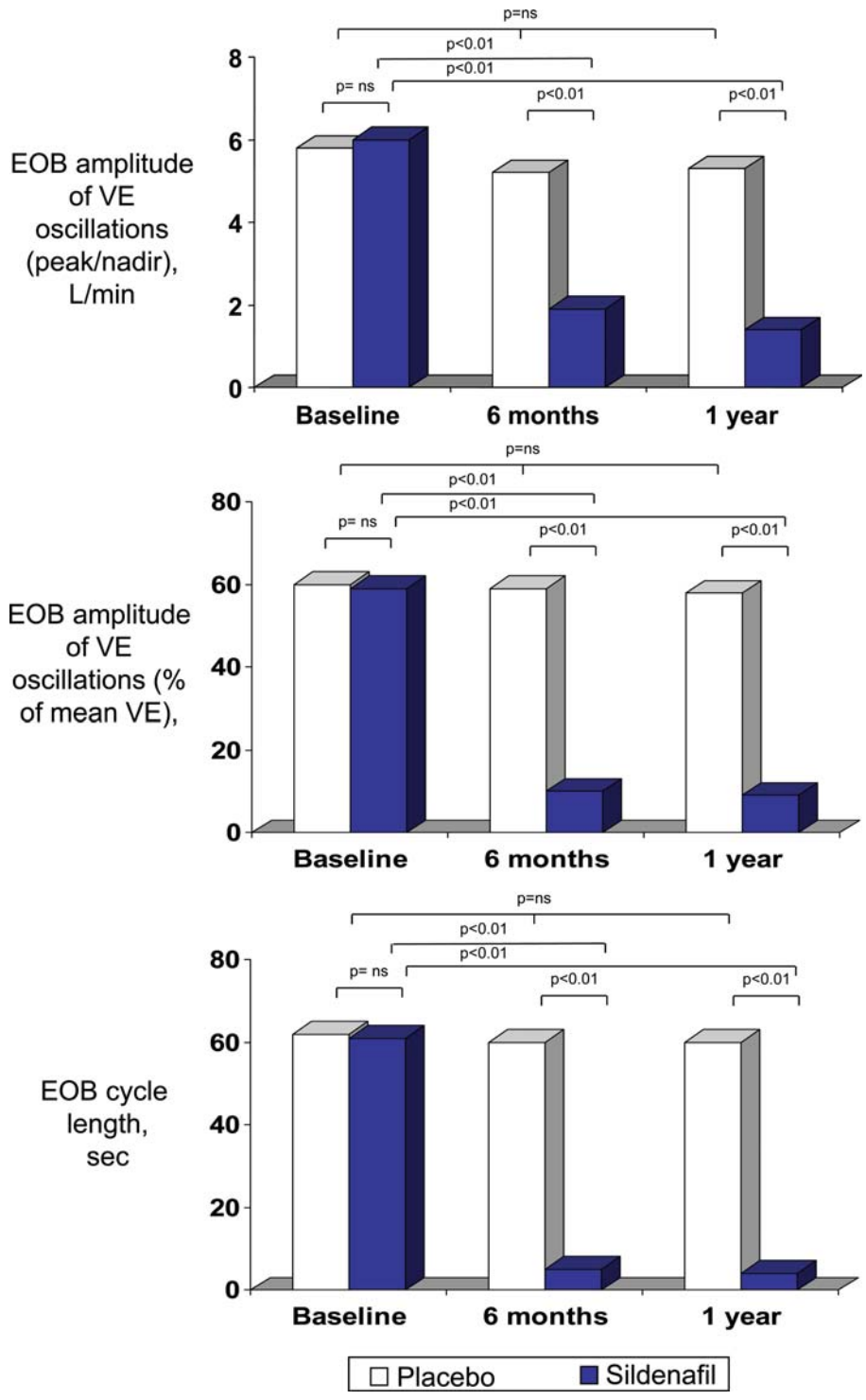

Figure 2 Changes over time in minute ventilation (VE) cycle amplitude as absolute values, percentage values, and cycle length. EOB, exercise oscillatory breathing.

(PVR) were calculated using standard formulae. Heart rate and cardiac output (CO) by thermodilution were also recorded.

Cardiopulmonary exercise testing (CPX)

Patients performed a progressively increasing (personalized ramp protocol) work rate CPX to maximal tolerance on an electromagnetically braked cycle ergometer (Carnival 906900, Lode, The Netherlands) in the upright position. Ventilatory expired gas analysis (Cardiopulmonary Metabolic Cart, Sensormedics Vmax Spectra) was performed at rest (3 min), throughout exercise, and during 3 min of recovery. A 12-lead ECG (Corina, GE Medical Systems) and cuff blood pressure were recorded. Respiratory gas was sampled continuously from a mouthpiece, oxygen consumption (VO_2) at peak exercise and at anaerobic threshold (AT), carbon dioxide output (VCO_2), minute ventilation (VE), and other exercise variables were calculated by computer breath by breath and averaged over 10 s intervals. Test termination criteria consisted of symptoms (i.e. dyspnoea and/or fatigue), ventricular tachycardia, >2 mm of horizontal or downsloping ST-segment depression, and drop in systolic blood pressure >20 mmHg during progressive exercise.

Exercise oscillatory breathing definition

EOB was assessed with the criteria previously reported by Leite *et al.*[2] Specifically, EOB was defined as: (i) oscillations of $\geq 60\%$ of entire exercise data at an amplitude $>15\%$ of resting values; (ii) minimal average amplitude of ventilatory oscillations of 5 L (peak value minus the average of two in-between consecutive nadirs); and (iii) a regular oscillation as defined by an SD of three consecutive cycle lengths (time between two consecutive nadirs) within 20% of the average.

Quality of life

Breathlessness, fatigue, and emotional function of daily living were assessed using a 16 question chronic HF questionnaire with answers scored from 1 (worst) to 7 (best).[25]

Statistical analysis

Randomization was performed on the basis of computer-generated random numbers. Differences in patient baseline frequencies were compared using Fisher's exact test analysis. Student's *t*-test for independent sample was used for testing differences in quantitative baseline variables. For abnormally distributed data, Mann–Whitney U-test or Wilcoxon test were used.

Repeated measures analysis of variance (ANOVA) and Neman–Keuls multiple comparison procedure were used to test differences between groups and differences between pre- and post-treatment.

Pearson product–moment correlation was used to assess the relationship between the 6 months and 1 year change in resting PVR and WPP and change in EOB amplitude in the subjects receiving sildenafil.

Values are expressed as mean values $\pm$ SD. A *P*-value of <0.05 was considered significant. Statistical analyses were performed by means of the STATA 7.0 package (Stata Corp, LP, College Station, TX, USA).

Results

Thirty-two patients with stable systolic HF, New York Heart Association (NYHA) class III–IV, and moderate left-sided PH were randomly assigned to receive placebo ($n = 16$) or sildenafil ($n = 16$) three times daily for 1 year. As regards baseline characteristics, no statistical differences were detected between the two treatment arms (*Table 1*). In particular, the two groups were homogeneous for age, sex, body mass index, aetiology of HF, haemodynamics, CPX-derived variables, and therapy distribution.

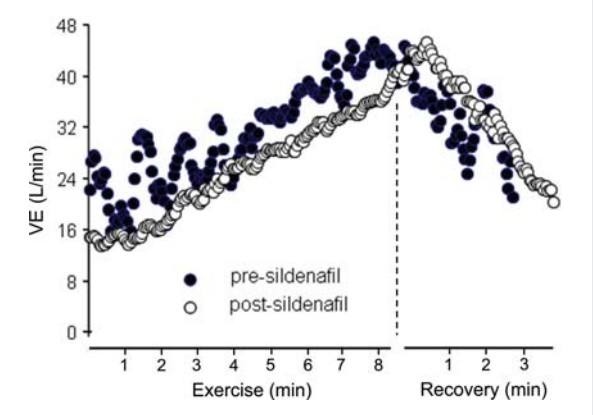

Figure 3 Example of sildenafil-induced reversal in exercise oscillatory breathing (EOB) at 1-year follow-up. According to criteria used for EOB definition, this case shows pre-sildenafil oscillations of $\geq 60\%$ of the whole exercise data as well as a minimal average amplitude of ventilatory oscillations of 5 L (peak value minus the average of two in-between consecutive nadirs) and a regular oscillatory pattern as defined by an SD of three consecutive cycle lengths (time between two consecutive nadirs) within 20% of the average. VE, minute ventilation.

Exercise oscillatory breathing changes

PDE5 inhibition promoted EOB pattern reversal toward a normal linear ventilatory response in 87% ($n = 14$) and 93% ($n = 15$) of patients at 6 and 12 months, respectively. In the placebo group, EOB reversed to a normal ventilatory pattern in just two patients. In responders, sildenafil induced a significant reduction in the amplitude of oscillations of VE (both absolute and as a percentage of mean VE) and in the cycle length ($P < 0.01$ for all; *Figure 2*).

Figure 3 reports a representative case of pre-treatment EOB and its disappearance after treatment.

Haemodynamic measurements

Compared with baseline, sildenafil did not significantly change resting heart rate, mean blood pressure, and SVR. Conversely, patients receiving sildenafil showed a significant decrease in mean PAP ($34 \pm 6\%$ and $31 \pm 7\%$ at 6 and 12 months; $P < 0.01$), WPP ($34 \pm 5\%$ and $34 \pm 5\%$ at 6 and 12 months; $P < 0.01$), transpulmonary gradient ($40 \pm 6\%$ and $35 \pm 4\%$; $P < 0.01$), PVR ($25 \pm 6\%$ and $24 \pm 6\%$; $P < 0.01$), and PVR/SVR ($17 \pm 3\%$ and $22 \pm 4\%$ at 6 and 12 months; $P < 0.01$), indicating a selective effect on pulmonary vasomotor tone (*Table 2*). In addition, sildenafil induced a mild but significant rise in CO at both 6 and 12 months ($11 \pm 3\%$ and $13 \pm 2\%$ at 6 and 12 months; $P < 0.01$). The changes observed were not different between 6 and 12 months. (*Table 2*).

Cardiopulmonary exercise testing data and quality of life assessment

In both groups all cardiopulmonary tests were terminated for symptom limitation (dyspnoea in 60% and fatigue in 40% of cases). In the sildenafil group, CPX data at 6 and 12 months (*Table 2*) showed a significant increase vs. baseline in peak VO_2

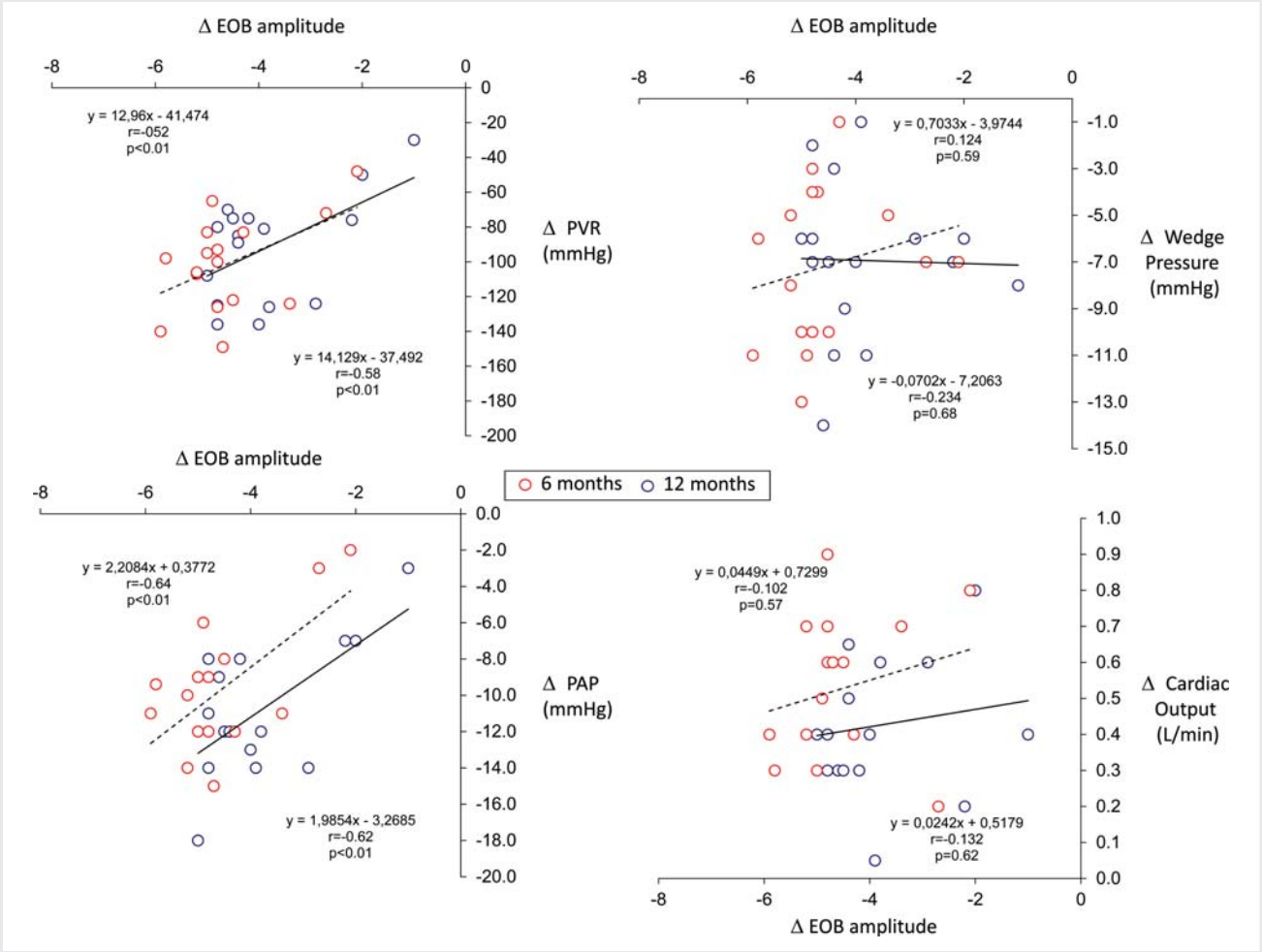

Figure 4 Plots of correlation between changes in exercise oscillatory breathing (EOB) oscillatory amplitude and changes in haemodynamic variables [pulmonary vascular resistance (PVR), mean pulmonary artery pressure (PAP), cardiac output, and wedge pulmonary pressure] at 6 (red circles) and 12 (blue circles) months.

($29 \pm 5\%$ and $37 \pm 5\%$; $P < 0.01$) and VO_2 AT ($28 \pm 6\%$ and $26 \pm 5\%$; $P < 0.01$) and a decrease in VE/VCO_2 slope ($23 \pm 6\%$ and $21 \pm 5\%$; $P < 0.01$). QOL assessment documented a significant and sustained sildenafil-mediated improvement in breathlessness, fatigue, and emotional function. Changes observed were not different between 6 and 12 months.

Correlation analyses

Changes in EOB amplitude significantly correlated with changes in PVR ($r = -0.52$, $P < 0.01$ and $r = -0.58$, $P < 0.01$ at 6 and 12 months, respectively) and mean PAP ($r = -0.64$, $P < 0.01$ and $r = -0.62$, $P < 0.01$ at 6 and 12 months, respectively), whereas no significant correlation was found with changes in CO ($r = -0.102$, $P = 0.57$ and $r = -0.132$, $P = 0.62$ at 6 and 12 months, respectively) and WPP ($r = -0.124$ $P = 0.59$ and $r = 0.234$, $P = 0.68$ at 6 and 12 months, respectively)

Safety and tolerability

Sildenafil was well tolerated by all patients. Minor adverse reactions consisted of flushing in five cases and headache in three cases, which disappeared in a few days after drug initiation. One case of diarrhoea was observed in the placebo group. No cardiac-related events occurred during the study, and three subjects in the placebo group and one in the sildenafil group were admitted to hospital for paroxysmal atrial fibrillation. Five patients in the placebo group and one in the sildenafil group required up-titration of loop diuretic during the trial, whereas two patients in the placebo group and four in the sildenafil group underwent down-titration of loop diuretic. Concomitant drugs for HF were not changed during the follow-up. There were no deaths during the follow-up.

Discussion

A large majority of sildenafil-treated patients showed a very significant reduction in the amplitude and the cycle length of the exercise oscillations of ventilation and improvement in gas exchange kinetics, suggesting that these respiratory abnormalities may be specific targets of PDE5 inhibition. The drug selectivity and the association of PAP and PVR reduction with EOB

Table 2 Haemodynamics, cardiopulmonary exercise testing, and quality of life data at baseline and at 6 and 12 months treatment with placebo or sildenafil

	Placebo group ($n = 16$)			Sildenafil group ($n = 16$)		
	Baseline	6 months	12 months	Baseline	6 months	12 months
Haemodynamics						
HR, b.p.m.	73.0 ± 2.0	71.0 ± 4.0	72.0 ± 3.0	69.0 ± 4.0	73.0 ± 3.8	72.0 ± 5.0
Mean blood pressure, mmHg	78.0 ± 6.0	75.0 ± 7.0	76.0 ± 7.0	77.0 ± 5.4	73.0 ± 6.0	74.0 ± 5.0
WPP, mmHg	20.0 ± 4.8	19.2 ± 5.0	19.9 ± 6.0	21.0 ± 3.0	14.0 ± 3.0*§	14.0 ± 4.0*§
Mean PAP, mmHg	34.0 ± 3.0	33.0 ± 5.0	35.0 ± 4.0	34.8 ± 4.0	23.3 ± 6.9*§	24.2 ± 6.2*§
Transpulmonay gradient, mmHg	14.7 ± 4.3	13.5 ± 4.8	14.1 ± 3.0	15.2 ± 3.9	9.1 ± 5.6*§	9.9 ± 5.5*§
PVR, dynes/cm^{-5}	354.0 ± 46.0	360.0 ± 48.0	358.0 ± 45.0	360.0 ± 53.0	270.0 ± 45.0*§	266.0 ± 49.0*§
SVR, dynes/cm^{-5}	1970.0 ± 260.	1950.0 ± 243.0	1954.0 ± 261.0	1983.0 ± 254.0	1990.0 ± 270.0	1980.0 ± 260.0
PVR/SVR	0.19 ± 0.04	0.18 ± 0.05	0.18 ± 0.03	0.181 ± 0.05	0.15 ± 0.05*§	0.14 ± 0.03*§
Cardiac output, L/min	3.7 ± 1.2	3.6 ± 1.2	3.7 ± 1.4	3.6 ± 1.6	4.0 ± 1.6 *§	4.1 ± 1.6*§
CPX variables						
Peak VO_2, mL/min/kg	10.4 ± 5.2	11.0 ± 4.3	10.6 ± 4.6	9.6 ± 6.1	12.4 ± 5.7*§	13.2 ± 5.4*§
VO_2 at AT, mL/min/kg	6.3 ± 4.0	6.2 ± 3.2	6.0 ± 3.8	6.0 ± 5.0	7.7 ± 3.0*§	7.6 ± 3.2*§
VE/VCO_2 slope	39.0 ± 4.2	38.5 ± 3.6	39.2 ± 4.3	41.1 ± 4.9	32.7 ± 4.2*§	31.5 ± 4.0*§
Quality of life						
Breathlessness	24.0 ± 4.9	23.0 ± 4.0	24.2 ± 6.0	25.7 ± 4.8	15.6 ± 5.8*§	16.2 ± 5.5*§
Fatigue	22.7 ± 5.7	21.0 ± 6.0	23 ± 6.2	24.0 ± 4.9	18.5 ± 6.0*§	19.0 ± 6.0*§
Emotional function	31.9 ± 7.4	31.4 ± 6.0	31.0 ± 7.3	31.5 ± 7.0	26.0 ± 6.9*§	25.5 ± 6.2*§

*$P < 0.01$ vs. baseline value; §$P < 0.01$ vs. corresponding value in the placebo group.
Abbreviations are as in Table 1.

modulation and reversal over time may be consistent with a pathophysiological role for the disordered pulmonary haemodynamics.

These observations add to the growing quest for therapeutic approaches aimed at targeting the unfavourable consequences of left-sided PH on the lung vasculature.[26] Oversignalling of the NO pathway by PDE5 inhibition appears to be even more appropriate in this high risk subgroup of HF patients who would enjoy the double advantage of an EOB modulation and, like those without EOB,[17,19,27] of an improvement in functional capacity and QOL.

Pathophysiological and clinical relevance of exercise oscillatory breathing

Ventilation increase during exercise is essential for maintaining adequate oxygenation and eliminating the progressive CO_2 output. The increase in ventilation is almost linear, with two deflection points that reflect the transition from a predominant aerobic to progressively increasing anaerobic metabolism, and the final rapid increase in respiratory rate due to ventilatory compensation to acidosis. It is certainly impressive how this physiology may be importantly deranged in the presence of EOB, when a continuous vacillation in the ventilatory and gas exchange kinetics occurs. This may *per se* explain the consistently reported increase in risk for cardiac events.[2–8]

Mechanisms stimulating EOB occurrence remain unclear, but two major pathogenetic hypotheses have been advanced. The haemodynamic hypothesis recognizes an increase in left atrial and pulmonary capillary pressures, pulmonary vasoconstriction,[10,11] as well as a reduction in CO (i.e. increased circulatory time) causing fluctuations in pulmonary blood flow, as major substrates for EOB.[12] The ventilatory hypothesis highlights a most important pathogenetic role for instability of central and peripheral neural control of ventilation.[13,14] These theories integrate with each other in agreement with the concept of multiple pathophysiological pathways as mutual triggers of the abnormal ventilatory pattern during exercise.

Reversal of EOB with sildenafil was associated with an improvement of other prognostic determinants assessed during maximal exercise with gas exchange analysis, such as peak VO_2 and the VE/VCO_2 slope. A better QOL seems, therefore, attributable to the overall improvement in these variables.

Mechanistic explanations for sildenafil efficacy

In this study we focused on the effects of sildenafil on pulmonary haemodynamics as a major putative mechanism for the reversal of EOB. This thinking was based on the rationale that an impaired regulation of pulmonary vascular tone is typical in patients with HF and left-sided PH, and studies have consistently shown that the pharmacological activity of PDE5 inhibition is primarily exerted in the lung microcirculation.[16–22]

The observed reduction over time in WPP, PVR, and PAP is in keeping with a causative role in the modulation of EOB. Experimental reports have suggested that an important causal pathway is that the elevated pulmonary pressures stimulate intrapulmonary

J receptors located in close proximity to pulmonary capillaries.[28] Their activation elicits the transmission of neural impulses via afferent vagal C-fibres to the ventilatory control centre of the medulla.[29] Thus, a reduced signalling from pulmonary J receptors by resolution of interstitial oedema may be reasonably interpreted to have played a key role in the modulation of EOB. In addition, changes in pulmonary vascular pressure were accompanied by a mild rise in CO, which may also have contributed to blunting the cardiac-related fluctuations in the pulmonary vascular bed, eliminating the phasic cycle of ventilation.[12]

However, the lack of correlation between changes in CO and in VE amplitude and the positive significant correlation of changes in PVR and PAP with variations in VE amplitude are in favour of a direct pulmonary vasoactive effect as a predominant contributor to sildenafil effectiveness.

Although the present results suggest that our original hypothesis may be correct, we cannot exclude a favourable intervention of sildenafil on the peripheral and central controllers of breathing during exercise. There is evidence that sildenafil may temper the excessive ventilatory response to ergoreflex stimulation as a result of a facilitated endothelial-mediated perfusion of working muscles.[29] Whether such an effect might also influence the EOB response remains unknown and warrants further investigation.

Another possibility that needs to be tested in pre-specified studies is whether PDE5 inhibition benefits the abnormal gain in peripheral and/or central chemoreflex activity. No previous trials have addressed the effectiveness of pulmonary vasodilator interventions on EOB resolution. except for one performed by Ribeiro *et al.*[30] in a small number of patients. In three patients with severe HF and left-sided PH, the inodilator milrinone was capable of acutely reversing EOB, suggesting that a combined inotropic and vasodilating effect may have accounted for the observed benefits. Our findings extend these initial observations to an optimally treated, advanced HF cohort and demonstrate long-term sildenafil efficacy and tolerability.

Study limitations

The study has limitations that need to be considered. We did not perform a haemodynamic assessment during exercise because the Ethical Committee did not allow it. Despite a mild increase in resting CO and the lack of correlation between CO and VE amplitude changes, a true causal relationship between CO amelioration and disappearance of the cyclic response in ventilation would have required a precise beat to beat analysis of stroke volume changes during the incremental stages of exercise. We recognize the limitation of presenting EOB sometimes as a qualitative variable.

As a prespecified endpoint we aimed to study the effects of a new therapeutic approach on the ventilatory abnormalities observed during maximal exercise. We did not assess a possible relationship between EOB and sleep-disordered breathing, even though it is recognized that sleep studies would have provided additional clinical information considering that sleep apnoea and EOB often co-exist and their combination worsens prognosis.[31]

Our population of systolic HF patients exhibited a low rate of hospitalization, possibly because they were rigorously monitored during the follow-up (every month). Thus, the present population may substantially differ from the HF population with a comparable degree of left ventricular dysfunction and left-sided PH followed-up in the community. We did not include women as all evidence so far available on the use of chronic PDE5 inhibition in HF has been obtained in male subjects.

Finally, although the amelioration of EOB was impressive, the number of statistical tests may inflate type I error and the small sample size necessitates the need to define this work as a pilot analysis requiring further investigation.

Conclusions

In conclusion, this study provides evidence that EOB can be an important therapeutic target in HF patients and that PDE5 inhibition is effective in the long term. Considering the remarkable unfavourable profile related to EOB, the present observations may have clinical implications even though the basic question of whether correction of this negative prognostic signal translates into a better survival remains unanswered at the moment.

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Conflict of interest: none declared.

Authors' contributions: M.G. was primarily involved in the trial design, data elaboration, and manuscript writing. M.V. was involved in patients' enrolment and performance of tests. R.A. participated in the haemodynamic evaluations, performed statistical analysis, and revised the manuscript

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