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Sildenafil improves the alveolar–capillary function in heart failure patients ☆

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Abstract

Background: Sildenafil is used for pulmonary hypertension treatment and its use is safe in chronic heart failure (HF) patients.
Aims: To analyze the effects of sildenafil on lung mechanics, gas diffusion, exhaled nitric oxide (eNO) at rest and during exercise in chronic HF. We did so to evaluate if sildenafil prevents exercise-induced pulmonary edema formation.
Methods: We studied 22 chronic HF males. We measured after a single dose of placebo, sildenafil (25 mg) and sildenafil (100 mg), lung diffusion (DLCO), molecular diffusion (DM), pulmonary capillary volume (VC), eNO, all at rest and during exercise, standard pulmonary function, and maximal cardiopulmonary exercise.
Results: At rest sildenafil improved pulmonary mechanics and DLCO from 23.1±6.3 ml/mmHg/min to 23.9±6.4 (25 mg, $p<0.05$) and to 25.3±6.7 100 mg, $p<0.02$). Sildenafil (100 mg) prevents edema formation (highest DM/VC during exercise). At rest eNO was low and not affected by tested drugs. With light exercise eNO was higher with sildenafil 100 mg. Peak VO_2 increased with sildenafil from 1376±331 ml/min to 1471±375 (25 mg, $p<0.01$) and 1524±461 (100 mg, $p<0.02$). Peak VO_2 increase was related to DLCO improvement.
Conclusion: In chronic HF sildenafil increases exercise performance, improves lung mechanics and gas diffusion and prevents exercise-induced pulmonary edema formation probably by restoring NO pathways.

Keywords: Exercise; Lung diffusion; Heart failure; Erectile dysfunction

1. Introduction

Sildenafil is an arteriolar vasodilating drug acting on both systemic and pulmonary vascular beds. Indeed, sildenafil is among the drugs of choice for pulmonary hypertension [1], is used safely for erectile dysfunction treatment in patients with chronic heart failure [2,3], and, sildenafil has been suggested as curative of heart failure [3–5]. Indeed, there is evidence that sildenafil improves exercise capacity, lung diffusion and vascular tone in chronic heart failure [3–5] and helps to prevent high altitude pulmonary edema [6,7]. In the present study we tested the hypothesis that sildenafil, which acts by increasing NO, improves the alveolar–capillary function and prevents pulmonary edema formation during exercise in chronic heart failure patients. To do so we analyzed the effects of acute sildenafil administration on exercise capacity, lung diffusion, exhaled NO and their changes during exercise.

2. Materials and methods

2.1. Patients population

Twenty-two male patients with long lasting (>2 years) heart failure participated in the study. All patients (age 58±8 years)

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had been in stable clinical condition for at least 3 months, and belong to a cohort of heart failure patients regularly followed at our heart failure clinic. Patients were in NYHA functional class II ($n=19$) or III ($n=3$). Heart failure ethiology was ischemic cardiomyopathy in 10 cases, and idiopathic in 12. Exclusion criteria included: left ventricular ejection fraction >50% by echocardiography, presence of primary pulmonary disease, unstable angina, recent myocardial infarction, artificial pace-makers, and use of nitrates or systemic severe hypotension (systolic blood pressure <90 mmHg). Heart failure therapy was stable, remained unchanged during the study in terms of substance doses and administration times. Therapy included: digitalis ($n=2$), diuretics ($n=18$), ACE-inhibitors ($n=17$), AT1 blockers ($n=7$), beta-blockers ($n=15$), and amiodarone ($n=6$). Cardiac dimensions and systolic function were evaluated by echocardiography; left ventricle end-diastolic and systolic volumes were 209±72 and 138±57 ml, respectively; left ventricle ejection fraction was 35±8%. The local Ethical Committee approved the study and all subjects provided written informed consent for the study.

2.2. Pulmonary function evaluation

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) was measured in triplicate and calculated, according to the American Thoracic Society criteria, through a mass flow sensor (2200 Sensor Medics, Yorba Linda, Ca) [8]. Maximal voluntary ventilation (MVV) was assumed as the greatest between MVV, measured in 12 s, and $FEV_1 \times 40$ [9]. Predicted values are from Quanjer et al. [10] and Jones [11]. Lung diffusion for carbon monoxide (DLCO) was measured with the single breath constant expiratory flow technique [12]. DLCO data are reported as absolute values or as percentage of predicted [12]. Molecular diffusion for carbon monoxide across the alveolar–capillary membrane (DM), and the pulmonary capillary blood volume (VC) were measured according to the Roughton and Forster method [13]. For this purpose, subjects inspired a gas mixture with 0.3% CH_4, 0.3% CO and 0.3% C_2H_2 containing 3 different oxygen fractions equal to 20, 40 and 60%, balanced with nitrogen. DLCO, DM and VC were measured, with patients sitting on the cyclo-ergometer, while at rest, and during constant workload light exercise (25 W, between the 3rd and 6th minute of exercise).

Table 1
Standard pulmonary function

	Placebo $n=22$	Sildenafil 25 mg $n=22$	Sildenafil 100 mg $n=18$
FEV_1 (L/min)	2.72±0.57	2.80±0.63*	2.80±0.60*
FEV_1 (%)	85±19	88±20*	90±20*
FVC (L/min)	3.70±0.45	3.81±0.61†	3.87±0.56†
FVC (%)	92±14	95±17†	97±19†
FEV_1/FVC	73±9	73±9	74±10
MVV (L/min)	102±28	113±29†	120±27*

FEV_1 = forced expiratory volume in 1 s. FVC = forced vital capacity. MVV = maximal voluntary ventilation.
*=$p<0.05$ vs. placebo, †=$p<0.02$ vs placebo.

Table 2
Alveolar–capillary diffusion data at rest

	Placebo $n=22$	Sildenafil 25 mg $n=22$	Sildenafil 100 mg $n=18$
DL_{CO} rest (ml/mmHg/min)	23.1±6.3	23.9±6.4*	25.3±6.7†
D_M rest (ml/mmHg/min)	36.7±12.2	39.0±9.1	43.0±11.6
V_C rest (ml)	105.2±42.7	96.0±36.7	92.3±50.5
D_M/V_C rest (min/mmHg)	0.41±0.22	0.47±0.24	0.57±0.24

DL_{CO} = lung diffusion for carbon monoxide. D_M = molecular diffusion for carbon monoxide across the alveolar–capillary membrane. V_C = capillary volume. *=$p<0.05$ vs placebo. †=$p<0.02$ vs placebo.

2.3. Exhaled nitric oxide measurements

Exhaled nitric oxide (eNO) was measured following the ATS recommendations by chemiluminuscence analyzer (NOATM 280, Sievers Instruments, Colorado, USA) [14]. Accordingly, exclusion of nasal NO was obtained by closure of the velopharyngeal aperture by requiring subjects to exhale against a respiratory resistor with a positive mouthpiece pressure (20 cm H_2O); furthermore, expiratory flow was kept constant, and ambient NO contamination was prevented by the use of a specific filter. To reduce oral bacterial production of NO, we asked the subjects to wash the oral cavity with HCO_3Na 3% solution [15]. Exhaled NO was analyzed on line vs. time [14]. This technique consists of a washout phase, followed by a plateau phase. We measured eNO concentration as the value of the plateau phase if exhalation was >6 s with a plateau of >3 s, and if differences between three consecutive measurements were <10%. Data reported are the mean of these three measurements. Exhaled NO was measured twice with the patient sitting on the cyclo-ergometer, and again after 3 min of constant workload exercise at 25 W.

2.4. Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed on a cyclo-ergometer utilizing a personalized ramp protocol aimed at achieving peak exercise in ~10 min [16]. Peak exercise VO_2 data are reported as absolute values or as percentages of VO_2 max predicted. Ventilation and inspiratory and expiratory gas partial pressures were measured on a breath-by-breath basis and reported as means over 30 s. Anaerobic threshold and ventilation over carbon dioxide production were measured using standard techniques [17].

2.5. Study design

All patients who met the inclusion/exclusion criteria participated in a study introduction day, during which the

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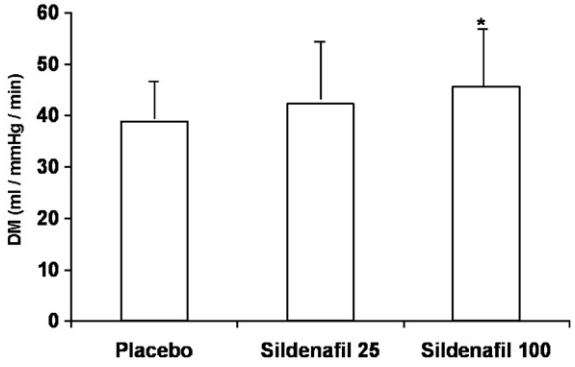

Fig. 1. Alveolar–capillary membrane diffusion (DM) during sub maximal exercise after placebo, sildenafil 25 mg and sildenafil 100 mg administration. *=$p<0.02$ vs placebo.

study was presented and patients underwent a cardiopulmonary exercise test, DLCO and eNO measurements for familiarization purposes. The study consisted in pulmonary function evaluation, eNO measurements and cardiopulmonary exercise tests done, in the morning, on three separate study days, 1 h after drug administration, placebo or 25 and 100 mg sildenafil. Specifically, patients underwent: standard pulmonary function test, DLCO measurement with its subcomponent, DM and VC, and eNO measurement, in that order. DLCO, DM and VC were measured with patients on a cycloergometer, at rest, and after 3 min of light constant exercise (25 W); the same was done for eNO measurements, but on a separate constant workload exercise test allowing at least 15 min for recovery. After complete recovery from both previous exercises, a maximal cardiopulmonary exercise test was carried out. All tests were usually completed in 120 min. The order of the study days was random.

2.6. Statistical analysis

Data are presented as means±standard deviation. Differences were evaluated by analysis of variance (ANOVA) and paired *t* test, applying the Bonferroni correction for multiple comparisons as appropriate. All analyses were implemented using the SAS system for Windows (version 6; SAS Institute) [18].

Table 3
Exhaled nitric oxide data at rest and after 3 min of constant workload exercise (25 W)

	Placebo $n=22$	Sildenafil 25 mg $n=22$	Sildenafil 100 mg $n=18$
eNO rest (ppb)	8.3±4.8	8.4±4.9	10.2±4.0
eNO 25 W (ppb)	7.7±3.9	8.3±4.9	10.0±4.0†

eNO = exhaled nitric oxide. ppb = part per billion, †=$p<0.02$ vs placebo.

3. Results

All patients completed the measurements with placebo and sildenafil 25 mg; 4 patients referred "light head sensation" with 100 mg sildenafil and did not complete the 100 mg research trial. At rest, systolic blood pressure was 115±17, 106±15* and 103±17* mmHg with placebo, 25 and 100 mg of sildenafil, respectively (where *=$p<0.02$ vs placebo); diastolic blood pressure was 78±9, 73±9* and 73±10* mmHg with placebo, 25 and 100 sildenafil, respectively (where *=$p<0.02$ vs placebo).

3.1. Pulmonary function (Tables 1 and 2, Figs. 1 and 2)

With placebo, FEV_1, FVC and MVV were low, but all improved with sildenafil both 25 and 100 mg (Table 1). DLCO with placebo was 86±20% pred. DLCO, DM, VC and DM/VC, at rest in placebo and sildenafil, are reported in Table 2. Sildenafil improved DLCO at rest. DLCO increased with exercise by 11.4±10.5%, 10.5±7.7% and 5.7±5.6% in placebo and sildenafil 25 and 100 mg. During sub maximal exercise, DM (Fig. 1) and DM/VC (Fig. 2) were greater in sildenafil (100 mg), when compared to the same data recorded during placebo. Exercise-induced changes in DM/VC are a marker of alveolar edema formation during exercise [19]. Some edema is formed during constant workload exercise with

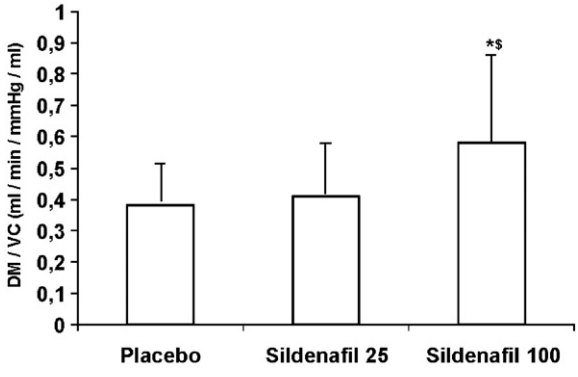

Fig. 2. DM/VC during sub maximal exercise after placebo, sildenafil 25 mg and sildenafil 100 mg administration. *=$p<0.02$ vs placebo, $=$p<0.05$ vs 25 mg.

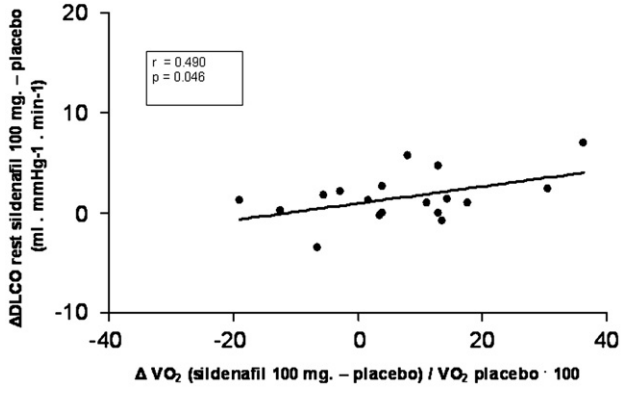

Fig. 3. Correlation between relative increment of peak VO_2 (ΔVO_2 sildenafil 100 mg−placebo/VO_2 placebo×100) vs. DLCO absolute increment, both after 100 mg of sildenafil.

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Table 4
Cardiopulmonary exercise test data

	Placebo $n=22$	Sildenafil 25 mg $n=22$	Sildenafil 100 mg $n=18$
VO_2 AT (ml/min)	916±231	933±220	943±280
Peak VO_2 (ml/min)	1376±331	1471±375[II]	1524±461†
Peak VO_2 (ml/kg/min)	17.1±3.3	18.3±4.0*	18.8±4.4*
Peak VO_2% of predicted	60±14	65±16[II]	66±19*
Workload (watt)	113±31	116±35	124±38
Vt peak (l)	1.67±0.33	1.76±0.43	1.64±0.52
Respiratory rate (bpm)	30.7±5.3	33.9±6.0[II]	35.1±4.8[II]
VE peak (l)	50.8±11.8	59.7±17.6[II]	61.9±16.7[II]
HR peak (bpm)	119±25	125±25	125±25
$\Delta VO_2/\Delta WR$ (ml/watt/min)	8.9±1.2	9.3±1.5	9.5±2.6[II]
VE/VCO_2	34.1±6.7	35.1±6.3	35.6±5.5

VO_2 = oxygen consumption, AT = anaerobic threshold, Vt = tidal volume, VE = ventilation, HR = heart rate, WR = work rate, VCO_2 = carbon dioxide production. *=$p<0.05$ vs placebo. †=$p<0.02$ vs placebo, [II]=$p<0.01$ vs. placebo.

placebo and sildenafil 25 mg (DM/VC during exercise compared to rest=−7.3% and −12.8%, respectively); Sildenafil 100 mg totally prevents it (+1.8%; $p<0.05$ vs both placebo and sildenafil 25 mg).

3.2. Exhaled nitric oxide

Exhaled NO at rest was lower when compared to normal values, but in the same range of what reported for patients with similar cardiac dysfunction. Exhaled NO values were not affected by sildenafil neither in 25 nor 100 mg therapies. In contrast to normal subjects, during exercise, eNO remained unchanged. During constant workload exercise eNO levels were higher in sildenafil 100 mg when compared to placebo (Table 3).

3.3. Cardiopulmonary exercise test results

Peak VO_2 increases with sildenafil, with a significant increase of the VO_2/work relationship. Ventilation at peak exercise increase was due to respiratory rate increase. The increment of exercise capacity by sildenafil was related to DLCO improvement (Fig. 3) (Table 4).

4. Discussion

The major finding of the present study is that sildenafil protects the alveolar–capillary membrane in chronic HF patients both at rest and during sub maximal exercise. This protection is paralleled by an increase of eNO.

It is known that, in heart failure patients, sildenafil use is safe and associated to an improvement of quality of life [2,20]. Furthermore, it is known that sildenafil enhances the exercise capacity of heart failure patients [3,5]. This improvement can be related to systemic vasodilatation [5,21], pulmonary vasodilatation [4,22] or both, with restoration of NO pathway as the therapeutic mechanism [23]. Our observations are in accord with the previous reports since sildenafil improved exercise capacity, in a dose related fashion, and that this action was associated with an improvement in lung function, both mechanics and gas diffusion, and an improvement of tissue perfusion during exercise. Indeed, we observed with sildenafil 100 mg an increase of the ΔVO_2/Watt relationship, which implies a more efficient oxygen utilization in the peripheral muscle, likely due to a more appropriate distribution of blood flow during exercise [24].

Our patients showed a mild lung impairment at rest [25]. Also, DLCO was low, as frequently observed in heart failure [2,6,26]. The correlation between exercise capacity and resting DLCO has been frequently reported in heart failure patients. Sildenafil improves mechanical lung impairment and DLCO at rest. Most importantly, sildenafil improved DLCO without affecting the capacity of heart failure patients to increase DLCO, during light exercise. This is important because exercise-induced increase in DLCO is, in heart failure, one of the compensatory mechanisms to several physical stresses such as exercise and hypoxia [27]. Our observation, that sildenafil generates a positive correlation between exercise capacity vs. DLCO changes with a preserved DLCO-increase during light exercise, reinforces the hypothesis that sildenafil acts at the alveolar–capillary level [28]. Furthermore, the analysis of the DM/VC ratio provides further information on this topic. Indeed, acute DM/VC changes are a physiological marker of alveolar edema formation [19]. DM/VC was low at rest in placebo and further reduced during light exercise, showing the physiological equivalent of edema formation. Sildenafil increases DM/VC at rest and totally prevents, with the 100 mg dose, edema formation during light exercise since DM/VC was unchanged. This is further evidence that sildenafil improves the efficiency of the alveolar–capillary membrane [26], both at rest and during light exercise, and provides a possible rationale for the preventive and curative action of sildenafil on high altitude pulmonary edema.

Expired NO is reduced in heart failure patients and, differently from normal subjects, shows either minor reduction or none at all during light exercise [29]. Expired NO is NO arriving from the airways, as well as from the alveoli. We observed, with sildenafil 100 mg, a 16% increase in eNO at rest (which was not statistical relevant, $p=0.095$), and 30% increase during light exercise ($p<0.02$). This observation is in line with the concept that sildenafil acts at the alveolar capillary membrane, inducing arteriolar vasodilatation and improving gas diffusion; indeed sildenafil increases cGMP-mediated vasodilatation and intracellular NO content as shown by Kukreja et al. [30], who demonstrated that sildenafil administration increases intracellular NO levels through stimulation of synthesis and transcription of endothelial and inducible NO synthetases. During exercise, alveolar ventilation is increased, and, albeit expiratory flow during NO measurements is fixed, alveolar air NO content is higher, likely due to a greater number of alveolar capillary units participating in gas exchange, and/or a greater amount of NO molecules diffusing from the alveolar capillary and

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epithelial cells to the alveolar air space. Moreover, because exercise may induce worsening of NO diffusion due to alveolar edema, sildenafil, by preventing exercise-induced edema formation, influences NO alveolar diffusion and this is another possibility to explain the higher eNO observed. The similar behaviour of exercise-induced changes DM/VC and eNO is strongly supportive of this hypothesis.

In conclusion, this study shows that sildenafil increases exercise performance, improves tissue oxygenation during exercise, gas diffusion at the lung level, and most importantly, sildenafil protects the alveoli from exercise-induced edema formation.

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