Development of a Human Model for the Study of Effects of Hypoxia, Exercise, and Sildenafil on Cardiac and Vascular Function in Chronic Heart Failure

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Background: Pulmonary hypertension is associated with poor outcome in patients with chronic heart failure (CHF) and may be a therapeutic target. Our aims were to develop a noninvasive model for studying pulmonary vasoreactivity in CHF and characterize sildenafil's acute cardiovascular effects.

Methods and Results: In a crossover study, 18 patients with CHF participated 4 times [sildenafil (2 × 20 mg)/or placebo (double-blind) while breathing air or 15% oxygen] at rest and during exercise. Oxygen saturation (SaO_2) and systemic vascular resistance were recorded. Left and right ventricular (RV) function and transtricuspid systolic pressure gradient (RVTG) were measured echocardiographically. At rest, hypoxia caused SaO_2 ($P = 0.001$) to fall and RVTG to rise (5 ± 4 mm Hg; $P = 0.001$). Sildenafil reduced SaO_2 ($-1 \pm 2\%$; $P = 0.043$), systemic vascular resistance (-87 ± 156 dyn·s^{-1}·cm^{-2}; $P = 0.034$), and RVTG (-2 ± 5 mm Hg; $P = 0.05$). Exercise caused cardiac output (2.1 ± 1.8 L/min; $P < 0.001$) and RVTG (19 ± 11 mm Hg; $P < 0.0001$) to rise. The reduction in RVTG with sildenafil was not attenuated by hypoxia. The rise in RVTG with exercise was not substantially reduced by sildenafil.

Conclusions: Sildenafil reduces SaO_2 at rest while breathing air, this was not exacerbated by hypoxia, suggesting increased ventilation–perfusion mismatching due to pulmonary vasodilation in poorly ventilated lung regions. Sildenafil reduces RVTG at rest and prevents increases caused by hypoxia but not by exercise. This study shows the usefulness of this model to evaluate new therapeutics in pulmonary hypertension.

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INTRODUCTION

Chronic heart failure (CHF) is common, and treatment remains imperfect. New therapeutic targets and strategies should be sought. The Euro Heart Failure survey reported that 16% of an epidemiologically representative population of patients with CHF had pulmonary hypertension (PH).[1] Large retrospective studies suggest that the prevalence of PH in CHF is high and describe PH as a strong predictor of an adverse prognosis.[2,3]

In healthy subjects, the pulmonary circulation responds to acute hypoxia with arteriolar vasoconstriction and a rise in pulmonary artery (PA) pressure[4–8] and to moderate exercise with pulmonary vasodilatation that accommodates the rise in cardiac output (CO) that prevents a rise in PA pressure.[9] In CHF, increases in both pulmonary arteriolar tone and left atrial pressure may contribute to the development of PH. Hypertrophy of pulmonary arterioles[10] may result in persistent PH that might progress autonomously. The increase in right ventricular (RV) afterload caused by PH may be an important determinant of RV dysfunction.[11] Accordingly, PH might be an appropriate target for treatment in patients with CHF.

The aims of this study were to develop a model to assess the cardiovascular effects of drugs on PA pressure at rest, and during hypoxia and exercise, 2 interventions that are known to increase PA pressure in patients with CHF[12,13] and to use it to assess the effects of sildenafil, a possible treatment for PH in patients with CHF.[14]

METHODS

Study Population

Patients were recruited from the Heart Failure clinic at Castle Hill Hospital. Inclusion criteria were stable heart failure and either left ventricular (LV) ejection fraction (LVEF) <40% or aminoterminal probrain natriuretic peptide (NT-pro-BNP) ≥50 pmol/L (423 pg/mL) and mild-to-moderate tricuspid

regurgitation on Doppler echocardiography. Patients with arrhythmia (including atrial fibrillation), severe tricuspid regurgitation, primary valve disease, severe optic neuropathy, oxygen saturation (SaO_2) on air at rest <90%, SBP >170/110 mm Hg or unstable angina were excluded. Written informed consent and local ethical approval were obtained.

Study Design, Drugs, and Gas Administration

The study was a double-blind crossover trial conducted on 4 separate days. Patients were asked to breath air or 15% oxygen (single-blind) for 2 hours before receiving 2 oral doses, 30 minutes apart, of either placebo or sildenafil 20 mg (Pfizer, Sandwich, United Kingdom) in a double-blind fashion. This dosing regimen was designed to minimize the risk of hypotension and to enhance the chance of a steady-state drug concentration during the period of study. The hypoxic gas was a mixture of 15% oxygen balanced with nitrogen (BOC Gases, United Kingdom). Patients inhaled air or gas through a 2-way no-rebreathe valve and a tightly fitting face mask (Hans Rudolph) attached through rubber tubing to a Douglas bag (Cranlea, United Kingdom) if breathing hypoxic gas mixture or open to room air. The order of treatment was allocated using computer-generated random number blocks using a block size of 2.[15–18] The minimum wash-out duration between any 2 of the 4 test days was 48 hours.

Study Protocol

At the initial screening visit, demographic data, medical history, and treatment were recorded, and a full physical examination was performed. Patients were asked to continue their usual daily treatment without interruption. On each study day, the patient rated his or her general experience of breathlessness in the previous 24 hours on a 10-point scale to detect symptom instability between study days.[19]

On each study day (Fig. 1), patients were first studied at rest after breathing air for 30 minutes. Systemic hemodynamics, including systolic blood pressure (SBP), diastolic blood pressure, heart rate (HR), systemic vascular resistance (SVR), stroke volume, and CO were measured noninvasively and continuously using finger volume-clamp technology (Nexfin, BMEYE B.V. Netherlands). Oxygen saturation was measured continuously using a transcutaneous oximeter (Avant 4000; Nonin Medical Inc), and the mean value was calculated during 2 minutes at each preplanned time (75 minutes rest, exercise, and recovery). A brief echocardiogram was performed (Echo-1) to assess the imaging window.

Patients then received either placebo or sildenafil and started to breathe through mask either room air or the hypoxic gas mixture. The patient was blind to gas allocation. After 30 minutes, a second dose of sildenafil or placebo was given if the systolic arterial pressure did not decrease by >20 mm Hg or to <85 mm Hg. After 75 minutes of breathing air or 15% oxygen, a second, more complete, echocardiogram (Echo-2) was performed and venous blood was sampled. The patient then undertook low-level steady-state (25 W) semirecumbent bicycle exercise (GE, Norway) with continuous noninvasive monitoring of blood pressure and electrocardiogram. A further echocardiogram (Echo-3) was performed after 5 minutes during exercise. Patients were then encouraged to exercise for as long as they believed able, and the duration was recorded. The patients rested semirecumbent on the bicycle, and the mask was taken away. After 5 minutes of recovery, measurements were repeated (Echo-4). At the end of exercise, patients were asked to rate the severity of breathlessness before and after exercise using a modified Borg dyspnea scale.[19]

Echocardiographic Measurements

Echocardiograms were performed using a VIVID 9 machine (GE Healthcare, United Kingdom) and sets of images recommended by the American Society of Echocardiography stored for offline analysis.[20] Each measure was an average of 3 consecutive cardiac cycles. Echo-1 was purely performed for orientation. Echo-2 focused on LV and RV systolic and diastolic function and measurements of PA pressure. LV systolic function was assessed by tissue Doppler imaging (TDI) with measurement of septal and lateral mitral annular peak systolic acceleration and their mean (mean Sa_m). Diastolic LV function was assessed by measuring early (E_m) and late (A_m) transmitral flow using pulsed Doppler and the

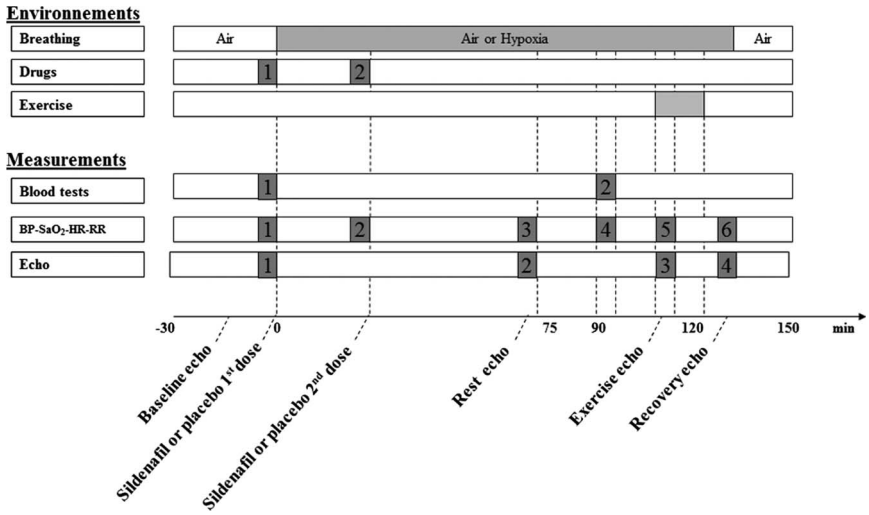

FIGURE 1. Study plan.

TABLE 1. Baseline Characteristics of the Patients With CHF

Variables	All (n = 18)	PH− (n = 11)	PH+ (n = 7)
Clinical			
Age, yr	64 ± 8	62 ± 6	69 ± 9
Men, %	16 (89)	9 (82)	7 (100)
BMI, kg/m^2	26 ± 4	26 ± 4	28 ± 4
Ischemic heart disease, n (%)	14 (78)	8 (73)	6 (86)
CABG, n (%)	9 (50)	4 (36)	5 (71)
Epworth scale, score	7.3 ± 4.0	7.1 ± 4.3	7.6 ± 3.8
SDB, n (%)	1 (6)	0	1 (14)
NYHA, class	2.2 ± 0.7	2.0 ± 0.8	2.6 ± 0.5
6-min walk test, m	405 ± 65	401 ± 59	415 ± 59
NT-pro-BNP, pg/mL	867 (548–2268)	668 (469–942)	2283 (1590–2630)
Electrocardiogram			
HR, bpm	58 ± 2	57 ± 8	60 ± 14
PR, ms	174 ± 36	162 ± 37	193 ± 27
QRS, ms	126 ± 33	129 ± 38	123 ± 27
Echocardiography			
LVEDV, mL	147 ± 67	142 ± 51	156 ± 90
LVEF, %	36 ± 9	35 ± 10	36 ± 6
RVTG, mm Hg*	24 ± 8	18 ± 3†	33 ± 5
RVEDA, cm^2	19 ± 9	15 ± 8†	25 ± 7
RVFA, %	48 ± 8	42 ± 8†	52 ± 5
Treatment, %			
β-blocker	17 (94)	11 (100)	6 (86)
ACEi	15 (83)	9 (82)	6 (86)
ARB	4 (22)	3 (27)	1 (14)
Loop diuretic	12 (67)	8 (73)	4 (57)
Spironolactone Ant	13 (72)	8 (73)	5 (71)
Statin	14 (78)	8 (73)	6 (86)
CRT	2 (11)	2 (18)	0

*RVTG value before starting the experiment the air-placebo day.

†The only variables with significant difference between PH+ and PH− were RVTG (by definition, $P = 0.0001$), RVFA ($P = 0.007$), and RVEDA ($P = 0.016$).

ACEi, angiotensin; BMI, body mass index; CABG, coronary artery bypass graft; LVEDV, left ventricular end diastolic volume; NYHA, New York Heart Association Dyspnea Scale; RVEDA, right ventricle end diastolic area; RVF, right ventricular sign of congestion; RVFA, right ventricular fractionning ar; SDB, sleep apnea disorder.

mean of the early diastolic peak velocities of the lateral and septal mitral annular using TDI; (mean Ea_m and mean Aa_m waves). Left atria pressure was estimated using E_m/mean Ea_m ratio. RV systolic function was assessed using TDI by measuring tricuspid annular peak velocities (Sa_t). RV diastolic function was estimated from the ratio of early (E_t) to late (A_t) transtricuspid diastolic flow and by the E_t/Ea_t, where Ea_t is the tricuspid annular early peak diastolic acceleration. The RV systolic tricuspid gradient (RVTG) was calculated and used as an estimate of systolic PA pressure. Patients with RVTG >25 mm Hg were defined as having pulmonary hypertension (PH+). Echo-3 was performed during exercise and included measurement of LV systolic and diastolic function, RV systolic function, and PA pressure estimation. Echo-4 was performed to ensure the return of CO and RVTG to baseline.

Statistics

To calculate the number of subjects required for the study, we defined a nominal primary outcome as the difference between PA systolic pressure measured at baseline (air rest) and at rest after breathing 15% oxygen for 75 minutes on placebo versus sildenafil. Within patient, repeated-measures of TR velocity over 1 hour have an SD of 0.3 m/s in our laboratory. Given an expected mean baseline TR velocity of 2.5 m/s (reflecting a PA pressure of approximately 30 mm Hg) and an expected change in TR velocity with hypoxia of 0.5 m/s, the study required 10 patients to show an effect of hypoxia, and assuming no placebo response, a similar number to identify a response to sildenafil. Power was set at 90% and significance at 5% (2-tailed). Conservatively, and to study possible interactions between baseline characteristics and interventions, we decided to include 18 patients. Formal adjustments for multiple comparisons were not made as the study was not designed to show therapeutic benefit but rather to explore mechanisms and assess the utility of a noninvasive model for the investigation of treatments for PH.[21]

Data are presented as mean and SD. The main comparisons of interest were the difference between rest

TABLE 2. Patient-reported Symptoms at Rest and During Exercise in Daily Life and as Reported During Direct Observation on the Day of Study

Variables	Air-Placebo	Hypoxia-Placebo	Air-Sildenafil	Hypoxia-Sildenafil
Breathlessness score during study evaluation				
At rest, 75 min after dosing (n = 18)	0.19 ± 0.49	0.18 ± 0.50	0.19 ± 0.71	0.08 ± 0.26
During exercise at 25 W after dosing (n = 16)*	2.38 ± 2.33	2.91 ± 2.76	1.38 ± 1.78†	2.09 ± 2.23
Exercise duration, s				
All patients with exercise (n = 16)	628 ± 291	533 ± 261	621 ± 258	584 ± 254
PH− (n = 11)	743 ± 273	571 ± 267‡	704 ± 261	675 ± 237
PH+ (n = 5)	436 ± 221§	463 ± 260§	483 ± 203§	434 ± 220§
Exercise stopped due to breathlessness, n (%)	9 (56)	8 (50)	6 (38)	6 (38)

Values are expressed in mean ± SD.
Breathlessness score was evaluated on each day before the study started and at rest 75 minutes after dosing and again at the end of exercise at 25 W.
*Patients were more breathless during exercise than at rest ($P < 0.0001$), but no between-group differences were observed. There was no significant difference between PH+ and PH−.
†P value for comparison between air-placebo and air-sildenafil during the exercise: $P = 0.088$.
‡$P < 0.05$ versus air placebo day in the same group (all or PH− or PH+).
§$P < 0.05$ PH + versus PH− same intervention (air-placebo, hypoxia-placebo, sildenafil-placebo, or hypoxia-placebo).

and exercise during the control period (breathing air and dosing with placebo) at 75 minutes; the difference between resting control measurements against the 3 interventions (hypoxia, sildenafil, and their combination) at 75 minutes; and a comparison of the change from rest to maximal exercise between control and the 3 interventions. In each case, paired sample t tests were used to compare each set of interventions against control. A P value ≤ 0.05 (2-tailed) was considered significant. This was an exploratory concept study, and therefore, no adjustment was made for multiple comparisons, and differences other than TR velocity should be considered nominal only.[21]

RESULTS

Noninvasive Human Model for the Study of Secondary Pulmonary Hypertension

Twenty patients were consented, but 2 had insufficient tricuspid regurgitation to allow measurement of RVTG on the first study day and were excluded from the study. All patients received 2 doses of placebo but the second dose of sildenafil was withheld in 2 patients who had an asymptomatic fall in SBP by >20 mm Hg after the first dose while breathing 15% oxygen. Two other patients declined to exercise. All patients otherwise completed the study without complications.

Baseline Characteristics

Most patients had ischemic heart disease, were in New York Heart Association class II, and were on guideline-indicated therapies (Tables 1 and 2). Baseline SaO_2 was >97% and LVEF <50% in all patients. The mean (SD) LV ejection fraction was 36 ± 9%, and the median NT-pro-BNP was 867 (interquartile range, 548–2268) pg/mL (Table 1). Mean LV filling and PA pressures were increased and RV systolic function reduced. No change in patients' day-to-day ratings of their breathlessness occurred during the course of the study.

Control Period Compared With Baseline

Compared with baseline, at rest, while breathing air 75 minutes after the first dose of placebo, there was no major change in SaO_2 (Fig. 2A), hemodynamic, or main echocardiographic variables (RVTG; Fig. 2B) (Table 3).

Hypoxia Versus Air at Rest

Compared with air, hypoxia caused a decrease in SaO_2 (−5.5 ± 0.6%, $P = 0.001$) and an increase in RVTG (4.6 mm Hg ± 4.0) (Fig. 2B and Table 4). Hemodynamic and echocardiographic variables were otherwise similar while breathing air or 15% oxygen (Table 4).

Sildenafil Versus Placebo at Rest

While breathing air, and compared with placebo, sildenafil caused a decrease in SaO_2 (Fig. 2A and Table 4), SVR, and RVTG (Fig. 2B and Table 4). Sildenafil did not exacerbate the decrease in SaO_2 induced by hypoxia (Fig. 2A). Hypoxia did not attenuate the decrease in RVTG after administering sildenafil (Fig. 2B). The effects of sildenafil in the presence and absence of hypoxia were generally similar; but in the presence of hypoxia, sildenafil may have caused more systemic vasodilation leading to a more pronounced decrement in SBP and improvement in LV systolic function as measured by Sa_m (Table 4).

Effects of Exercise

During exercise at 25 W, HR, blood pressure, CO, and RVTG increased substantially, but SVR and SaO_2 were similar to resting measurements (Table 3).

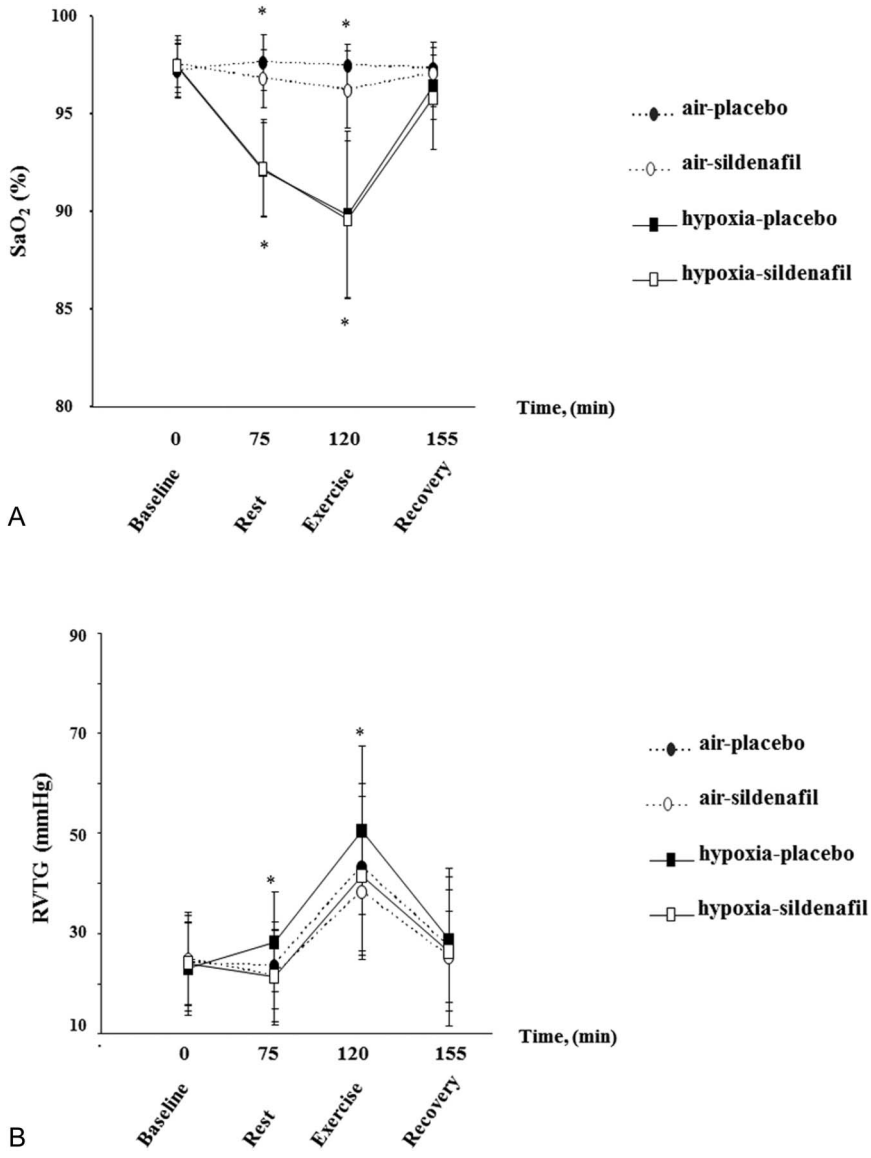

FIGURE 2. Change in SaO_2 (A) and in RVTG (B) with hypoxia and sildenafil alone and in combination in all patients. Black circle: air placebo, open circle: air sildenafil; black square: hypoxia placebo; open square: hypoxia sildenafil. *$P \leq 0.05$ versus AP.

Effects of Hypoxia During Exercise

The duration of exercise was slightly shorter when breathing 15% oxygen, an effect that was nominally significant in the subgroup that did not have PH (Table 2). SaO_2 was slightly but not significantly lower during exercise at 25 W when breathing 15% oxygen rather than room air. Few differences were observed apart from an increase in Sa_t suggesting a greater increase in RV systolic contraction (Table 5). Hypoxia had little if any effect on the rise in RVTG during exercise.

Sildenafil Compared With Placebo During Exercise

Sildenafil did not substantially reduce the rise in RVTG with exercise nor cause a decrease in SaO_2 during exercise at 25 W when breathing air. Comparing exercise after placebo while breathing air to exercise after sildenafil while breathing 15% oxygen, SaO_2 and SVR were lower and CO and RV systolic performance (Sa_t) were increased but the increase in RVTG was not attenuated (Table 5). Sildenafil prevented the decline in exercise duration associated with hypoxia in patients who did not have PH (Table 2).

Comparison of Patients With or Without PH

Patients with PH, defined as RVTG >25 mm Hg (n = 7), had a more marked decrease in SaO_2 and increase in RVTG at rest in response to hypoxia (Figs. 3A–D) and greater fall in SVR and increase in Sa_t with sildenafil (data not shown).

Breathing air, patients with PH had a markedly shorter exercise duration compared with those without PH (Table 2), which was not modified by any intervention. In contrast,

TABLE 3. Absolute Values at Rest (75 Minutes) and During Exercise at 25 W for the Air-Placebo Group

Air Placebo Variables	Rest (75 min)	Exercise	*P*
Saturation			
SaO_2, %	97.7 ± 1.4	97.4 ± 1.2	0.50
Hemodynamic			
SBP, mm Hg	114 ± 13	161 ± 21	0.0001
DBP, mm Hg	59 ± 6	88 ± 12	0.0001
SVR, $dyn \cdot s^{-1} \cdot cm^{-2}$	1357 ± 264	1503 ± 483	0.14
HR, bpm	57 ± 7	90 ± 13	0.0001
SV, mL	86 ± 13	76 ± 16	0.023
CO, L/min	4.8 ± 0.7	6.9 ± 2.0	0.001
LV			
Mean Sa_m, cm/s	5.1 ± 1.2	5.9 ± 1.4	0.019
Mean Ea_m, cm/s	5.5 ± 1.7	7.3 ± 2.8	0.013
E_m, cm/s	71 ± 30	88 ± 21	0.027
A_m, cm/s	51 ± 20	65 ± 29	0.045
E_m/A_m	1.7 ± 1.2	1.8 ± 1.2	0.79
E_m/mean Ea	15.0 ± 9.1	14.0 ± 6.9	0.79
Pulmonary pressure			
RVTG, mm Hg	23.6 ± 8.7	43.1 ± 16.7	0.0001
RV			
Sa_t, cm/s	10.1 ± 3.1	10.2 ± 3.6	0.73
Ea_t, cm/s	7.3 ± 2.3	—	—
E_t, cm/s	45 ± 11	—	—
E_t/A_t	1.3 ± 0.4	—	—
E_t/Ea_t	6.7 ± 2.7	—	—

CO, cardiac output; DBP, diastolic blood pressure; E_m and A_m, early and late diastolic peak velocities of the transmitral flow measured in pulsed Doppler; E_t, early diastolic velocities of the transtricupid flow measured in pulsed wave Doppler; Mean Ea_m, mean of the early diastolic peak velocities of the LV lateral and septal wall in tissue Doppler; Mean Sa_m, mean of the peak systolic velocities of the LV lateral and septal wall in tissue Doppler; SaO_2, oxygen saturation; S_{at} and E_{at}, peak systolic velocity and early diastolic velocity of the tricuspid annulus measured in tissue Doppler; SBP, systolic blood pressure; SV, LV stroke volume; SVR, systemic vascular resistance.

patients without PH exercised for a shorter time during hypoxia than air, an effect that was reversed by sildenafil (Table 2). The hemodynamic effects of sildenafil during hypoxia and exercise, including reductions in SVR and increases in CO and Sa_t, were more marked in those without PH (data not shown).

DISCUSSION

This study emphasizes the complex pathophysiology of pulmonary hemodynamic in patients with CHF. Four major components can be assessed in our model: left atrial pressure, fixed and variable components to pulmonary vascular resistance, and ventilation–perfusion matching. Changes in left atrial pressure can be assessed by E/Ea, the fixed component of pulmonary vascular resistance by the change in RVTG in response to an increase in exercise-induced CO, the variable component of pulmonary vascular resistance by the change in RVTG in response to hypoxia and ventilation–perfusion matching by changes in SaO_2 while breathing air that may be exacerbated by breathing 15% oxygen. The study shows that sildenafil reduces pulmonary pressure but has limited effects on left atrial pressure and on the pulmonary circulation due to what appears to be a large fixed component to pulmonary vascular resistance. Moreover, pulmonary vasodilation is relatively unselective leading to shunting of blood through poorly ventilated lung regions leading, in turn, to a decrease in SaO_2. Sildenafil did cause a decline in PA pressure at rest and completely abolished hypoxia-induced pulmonary vasoconstriction but did not substantially reduce the increase in PA pressure during exercise-induced increases in CO; although because CO was somewhat higher while exercising after taking sildenafil, pulmonary vascular resistance might have been slightly reduced. Measurements of RV function improved after sildenafil both at rest and during exercise consistent with a reduction in RV afterload or, less likely, a positive inotropic effect.[22] Overall, these data suggest a substantial relatively fixed component to PH in patients with CHF. The more favorable effects of sildenafil on hemodynamics during exercise among patients with lower PA pressure, who may have a smaller fixed component to pulmonary vascular resistance, are consistent with this concept. However, it is possible that longer term treatment with an agent such as sildenafil could cause favorable remodeling of the pulmonary vasculature leading to a reduction in this relatively fixed component.

The pulmonary circulation responds to acute hypoxia with arteriolar vasoconstriction and a rise in pulmonary artery pressure.[6–8] In normal subjects,[8,23] hypoxia causes arterial oxygen desaturation, increases in pulmonary artery pressure, HR, myocardial contractility, and CO but with no obvious effect on RV function.[23] Little is known about systemic and cardiovascular interactions induced by hypoxia in patients with CHF. Nevertheless, acute hypoxia might be frequent in patient with CHF, occurring, for example, during sleep apnea, acute heart failure, or flight travel.[24]

We have recently reported[25] that 60 minutes of 15% oxygen at rest caused an increase in systolic PA pressure to a similar level in patients with heart failure and normal subjects.[25] We found a similar increase in PA pressure after 75 minutes in this study and confirmed that short-term moderate hypoxemia had little effect on LV and RV systolic function in this population.[25]

Sildenafil blunted the hypoxia-induced increase in pulmonary artery systolic pressure at rest in patients with CHF. Similar effects have been shown in healthy volunteers in whom sildenafil inhibits the development of PH in response to acute hypoxia at high altitude.[26] Phosphodiesterase 5 inhibition is a relatively new strategy for the treatment of PH[27] and RV dysfunction,[22,28] causing both pulmonary vasodilatation and regression of pulmonary arteriolar muscular hypertrophy.[29,30] Phosphodiesterase 5 is the major enzyme responsible for degrading cyclic guanosine monophosphate in vascular smooth cells of the lung.[31] It is increased in the lung tissue of patients with PH and may contribute to decreased NO-dependent vasodilatation.[29]

Previous studies in patients with CHF due to LV systolic dysfunction suggest that sildenafil acutely reduces PA pressures, measured by catheter, both at rest and during exercise (upright bicycle), and improves peak oxygen consumption (VO_2) and right heart hemodynamics, particularly

TABLE 4. Echocardiography, Oxygen Saturations, and NonInvasive Hemodynamics at Rest 75 Minutes After Dosing

	Changes Versus Air-Placebo at Rest (Between Days)			Comparison With Air-Placebo, *P*		
Variables	**Hypoxia-Placebo**	**Air-Sildenafil**	**Hypoxia-Sildenafil**	**Hypoxia-Placebo**	**Air-Sildenafil**	**Hypoxia-Sildenafil**
Saturation						
SaO_2, %	−5.5 ± 0.6	−0.8 ± 1.6	−5.4 ± 2.4	**0.001**	**0.043**	**0.0001**
Hemodynamic						
SBP, mm Hg	+3.3 ± 11.4	−3.7 ± 9.1	−5.1 ± 10.3*	0.24	0.11	**0.05**
DBP, mm Hg	+1.1 ± 6.9	−1.7 ± 4.8	−1.8 ± 5.2	0.45	0.15	0.17
SVR, $dyn \cdot s^{-1} \cdot cm^{-2}$	−30 ± 172	−87 ± 156	−132 ± 184	0.48	**0.034**	**0.009**
HR, bpm	+1.4 ± 5.8	+1.7 ± 5.7	+2.5 ± 5.7	0.30	0.22	0.08
SV, mL	+0.75 ± 8.2	−0.35 ± 7.12	+0.35 ± 6.2	0.72	0.84	0.82
CO, L/min	+0.28 ± 0.71	+0.19 ± 0.64	+0.28 ± 0.66	0.12	0.25	0.10
LV						
Mean Sa_m, cm/s	−0.07 ± 0.65	+0.44 ± 1.33	+0.72 ± 0.86	0.69	0.19	**0.003**
Mean Ea_m, cm/s	0 ± 0.88	+0.40 ± 1.39	+0.42 ± 1.21	1.00	0.25	0.17
E_m, cm/s	−3.5 ± 16.5	+0.2 ± 17.0	−5.2 ± 4.0	0.40	0.96	0.21
A_m, cm/s	+5.4 ± 18.5	+7.2 ± 18.5	+4.8 ± 19.4	0.25	0.13	0.33
E_m/A_m	−0.14 ± 1.11	−0.13 ± 1.12	−0.17 ± 1.08	0.63	0.65	0.54
E_m/mean Ea_m	−1.7 ± 7.5	−1.7 ± 8.7	−3.6 ± 8.3	0.36	0.44	0.09
Pulmonary pressure						
RVTG, mm Hg	+4.6 ± 4.0	−2.2 ± 4.6	−2.1 ± 4.3	**0.001**	**0.05**	**0.05**
RV						
Sa_t, cm/s	+0.5 ± 1.2	+0.6 ± 1.3	+0.3 ± 1.6	0.07	0.09	0.40
Ea_t, cm/s ($cm \cdot s^{-1}$)	+1.1 ± 1.3	+0.7 ± 1.9	+0.4 ± 1.7	**0.002**	0.16	0.36
E_t, cm/s	−1.4 ± 2.7	−1.5 ± 10.8	+2.9 ± 10.6	0.62	0.58	0.30
E_t/A_t	−0.15 ± 0.28	−0.13 ± 0.27	−0.15 ± 0.40	**0.05**	0.07	0.17
E_t/Ea_t	−1.07 ± 1.8	−0.6 ± 2.7	+0.09 ± 3.00	**0.024**	0.40	0.91

*Two patients did not receive the second dosage of sildenafil due to a drop of systolic blood pressure >20 mm Hg.

CO, cardiac output; DBP, diastolic blood pressure; E_m and A_m, early and late diastolic peak velocities of the transmitral flow measured in pulsed Doppler; E_t, early diastolic velocities of the transtricupid flow measured in pulsed wave Doppler; Mean Ea_m, mean of the early diastolic peak velocities of the LV lateral and septal wall in tissue Doppler; Mean Sa_m, mean of the peak systolic velocities of the LV lateral and septal wall in tissue Doppler; SaO_2, oxygen saturation; S_{at} and E_{at}, peak systolic velocity and early diastolic velocity of the tricuspid annulus measured in tissue Doppler; SBP, systolic blood pressure; SV, LV stroke volume; SVR, systemic vascular resistance.

Bold indicates statistical difference of $P < 0.05$.

in patients with PH.[28] In this last study, the mean PA pressure was reduced by sildenafil administered open-label from 28 ± 4 mm Hg by 14 ± 5% at rest and from 36 ± 5 mm Hg by 11 ± 3% during exercise. In our study, sildenafil did not appear to reduce PA pressure during exercise substantially and did not improve breathlessness or exercise duration, except in a subgroup analysis of patients who did not have PH when breathing 15% oxygen. The reasons for these differences are not obvious but could reflect blinding, different types of exercise, posture, and protocol (6.25–12.5 W/min incremental ramp protocol) and whether exercise was conducted after an overnight fast. In contrast, long-term use of sildenafil did not improve symptoms, exercise capacity, or outcome in a recent substantial trial of patients with heart failure and preserved LVEF.[32]

In contrast to Guazzi et al,[33] we found that sildenafil reduced SaO_2 in patients with CHF. Interestingly, in an experimental model using anesthetized normal pigs, Kleinsasser et al[34] also reported that sildenafil administration reduced SaO_2 due to an increase in intrapulmonary shunt flow. In a clinical study in patients with LV dysfunction and PH, Matamis et al[35] also reported that sildenafil increased ventilation–perfusion mismatch resulting in reduction in SaO_2. These data suggest that sildenafil exacerbates ventilation–perfusion mismatch due to vasodilation of poorly ventilated lung regions. Whether ventilation–perfusion mismatch persists and, if so, its long-term consequence are unknown. Sildenafil had little effect on SaO_2 during exercise suggesting that ventilation–perfusion matching may improve during exercise. Interestingly, similar decreases in SaO_2 have been noted with endothelin antagonists in patients with CHF.[36] Although these agents may be useful for the management of PH, they have tended to have deleterious effects in patients with CHF.[36]

LIMITATIONS

This was a relatively small study but we used a double-blind crossover trial methodology, which avoids the variability created by interindividual comparison and greatly enhances the power to show differences. Most of the patients included in this study were on β-blockers, which may have inhibited the sympathetic activation induced by hypoxia, but it is more relevant to the clinical situation to study patients while they are taking

TABLE 5. Echocardiography, Oxygen Saturations, and Noninvasive Hemodynamics During 25 W Bicycle Exercise 75 Minutes After Dosing

Variables	Changes Between Rest and Exercise for Each Group (During Each Day)			
Breathing Treatment	**Air-Placebo**	**Hypoxia-Placebo**	**Air-Sildenafil**	**Hypoxia-Sildenafil**
Saturation				
SaO_2, %	−0.3 ± 1.4	−2.5 ± 3.7	−0.8 ± 1.5	−2.6 ± 3.1
Hemodynamic				
SBP, mm Hg	+48 ± 15	+48 ± 18	+46 ± 19	+50 ± 15
DBP, mm Hg	+29 ± 11	+28 ± 12	+25 ± 11	+28 ± 24
SVR, $dyn \cdot s^{-1} \cdot cm^{-2}$	+145 ± 348	+53 ± 289	+72 ± 510	−47 ± 171
HR, bpm	+33 ± 15	+31 ± 17	+28 ± 12	+31 ± 14
SV, mL	−9.7 ± 14.1	−5.6 ± 12.6	−0.7 ± 15.0	+2.0 ± 17.1
CO, L/min	+2.1 ± 1.8	+2.0 ± 1.4	+2.2 ± 1.7	+2.9 ± 1.3
LV				
Mean Sa_m, cm/s	+0.80 ± 1.16	+1.03 ± 1.00	+1.43 ± 1.09	+1.32 ± 1.34
Mean Ea_m, cm/s	+1.84 ± 2.49	+2.90 ± 3.51	+2.06 ± 2.58	+2.76 ± 2.86
E_m, cm/s	+17 ± 28	+17 ± 26	+25 ± 21	+21 ± 26
A_m, cm/s	+14.3 ± 26.0	+12.5 ± 26	+9.9 ± 24.8	+14.4 ± 26.9
E_m/A_m	+0.11 ± 1.6	+0.33 ± 1.17	+0.08 ± 0.28	+0.10 ± 0.86
E_m/mean Ea_m	−0.51 ± 7.21	−0.80 ± 4.67	−0.51 ± 6.30	−0.33 ± 3.91
Pulmonary pressure				
RVTG, mm Hg	+19.2 ± 11.3	+23.3 ± 10.4	+15.7 ± 8.5	+19.7 ± 10.1
RV				
S_{at}, cm/s	+0.11 ± 1.21	+1.29 ± 1.94	+1.36 ± 1.78	+1.62 ± 2.33

Variables	Comparison for Each Group Between Rest and Exercise (*P*)				Effect of Intervention on Exercise Response (*P*)		
Breathing Treatment	**Air-Placebo**	**Hypoxia-Placebo**	**Air-Sildenafil**	**Hypoxia-Sildenafil**	**Hypoxia-Placebo**	**Air-Sildenafil**	**Hypoxia-Sildenafil**
Saturation							
SaO_2, %	0.50	**0.014**	0.06	**0.004**	0.06	0.34	**0.02**
Hemodynamic							
SBP, mm Hg	**0.0001**	**0.0001**	**0.0001**	**0.0001**	0.54	0.83	0.61
DBP, mm Hg	**0.0001**	**0.0001**	**0.0001**	**0.0001**	0.92	0.19	0.85
SVR, $dyn \cdot s^{-1} \cdot cm^{-2}$	0.14	0.47	0.59	0.32	0.24	0.63	**0.031**
HR, bpm	**0.0001**	**0.0001**	**0.0001**	**0.0001**	0.90	0.15	0.57
SV, mL	**0.023**	0.11	0.85	0.70	0.52	**0.049**	**0.005**
CO, L/min	**0.001**	**0.0001**	**0.0001**	**0.0001**	0.59	0.60	**0.028**
LV							
Mean Sa_m, cm/s	**0.019**	**0.002**	**0.0001**	**0.003**	0.47	0.18	0.15
Mean Ea_m, cm/s	**0.013**	**0.009**	**0.011**	**0.003**	0.26	0.67	0.26
E_m, cm/s	**0.027**	**0.023**	**0.0001**	**0.007**	0.90	0.38	0.74
A_m, cm/s	**0.045**	0.085	0.15	0.066	0.82	0.36	0.91
E_m/A_m	0.79	0.43	0.47	0.71	0.66	0.45	0.67
E_m/mean Ea_m	0.78	0.53	0.77	0.76	0.80	0.84	0.95
Pulmonary pressure							
RVTG, mm Hg	**0.0001**	**0.0001**	**0.0001**	**0.0001**	0.18	0.12	0.88
RV							
S_{at}, cm/s	0.73	**0.018**	**0.008**	**0.014**	**0.023**	**0.007**	**0.011**

CO, cardiac output; DBP, diastolic blood pressure; E_m and A_m, early and late diastolic peak velocities of the transmitral flow measured in pulsed Doppler; E_t, early diastolic velocities of the transtricupid flow measured in pulsed wave Doppler; Mean Ea_m, mean of the early diastolic peak velocities of the LV lateral and septal wall in tissue Doppler; Mean Sa_m, mean of the peak systolic velocities of the LV lateral and septal wall in tissue Doppler; SaO_2, oxygen saturation; S_{at} and E_{at}, peak systolic velocity and early diastolic velocity of the tricuspid annulus measured in tissue Doppler; SBP, systolic blood pressure; SV, LV stroke volume; SVR, systemic vascular resistance.

Bold indicates statistical difference of $P < 0.05$.

guideline-indicated therapies. We did not measure metabolic gas exchange. We were not able to perform 2D strain measurement because only 14 patients had sufficiently good echocardiographic images at rest with fewer than that during exercise. Measurement of pulmonary vascular resistance to estimate change induced by hypoxia, exercise, and sildenafil

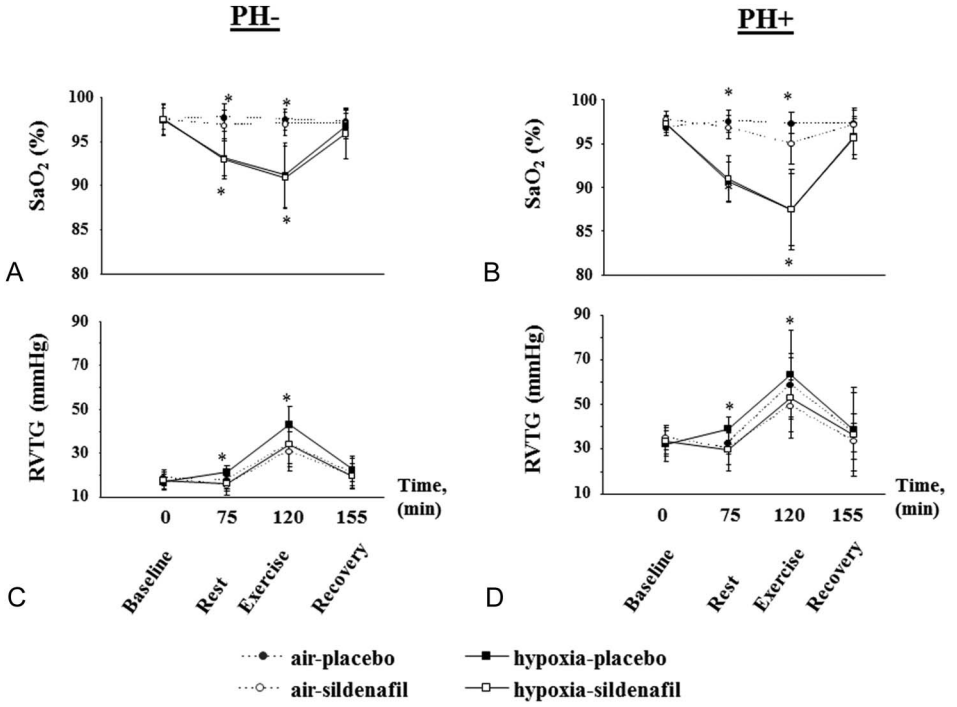

FIGURE 3. Change in SaO_2 and in RVTG with hypoxia and sildenafil, alone and in combination in subgroups of patients without (PH−; A and C) and with (PH+; B and D) PH. Black circle: air placebo, open circle: air sildenafil; black square: hypoxia placebo; open square: hypoxia sildenafil. $*P \leq 0.05$ versus AP.

would have been interesting in this model. However, noninvasive estimation of PVR by echocardiography is still challenging and with limited agreement with invasive measurement.[37,38] Because of the limited number of patients included in our study, estimation of PVR by echocardiography was not reliable.

CONCLUSIONS

A dynamic noninvasive model may prove useful for assessing the effects of intervention on pulmonary hemodynamic in patients with CHF. Exercise-induced increases in CO are associated with a marked increase in PA pressure indicating a failure of normal physiological pulmonary vasodilation. The effects of sildenafil on pulmonary hemodynamics are complex and not entirely favorable. Sildenafil increased ventilation–perfusion mismatching at rest and failed to increase pulmonary vasodilation during exercise substantially.

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