Intravenous sildenafil acutely improves hemodynamic response to exercise in patients with connective tissue disease

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Abstract

Background

Hemodynamic assessment during exercise may unmask an impaired functional reserve of the right ventricle and the pulmonary vasculature in patients with connective tissue disease. We assessed the effect of intravenous sildenafil on the hemodynamic response to exercise in patients with connective tissue disease.

Methods

In this proof-of-concept study, patients with connective tissue disease and mean pulmonary arterial pressure (mPAP) >20 mm Hg were subjected to a supine exercise hemodynamic evaluation before and after administration of intravenous sildenafil 10 mg.

Results

Ten patients (four with moderately elevated mPAP 21–24 mm Hg; six with mPAP >25 mm Hg) underwent hemodynamic assessment. All of them showed markedly abnormal exercise hemodynamics. Intravenous sildenafil was well tolerated and had significant hemodynamic effects at rest and during exercise, although without pulmonary selectivity. Sildenafil reduced median total pulmonary resistance during exercise from 6.22 (IQR 4.61–8.54) to 5.24 (3.95–6.96) mm Hg·min·L^{-1} (p = 0.005) and increased median pulmonary arterial capacitance during exercise from 1.59 (0.93–2.28) to 1.74 (1.12–2.69) mL/mm Hg (p = 0.005).

Conclusions

In patients with connective tissue disease who have an abnormal hemodynamic response to exercise, intravenous sildenafil improved adaption of the right ventricular-pulmonary

vascular unit to exercise independent of resting mPAP. The impact of acute pharmacological interventions on exercise hemodynamics in patients with pulmonary vascular disease warrants further investigation.

Trial registration

Clinicaltrials.gov NCT01889966.

Introduction

The importance of assessing pulmonary hemodynamics during exercise, in addition to measurements made at rest, is increasingly being recognized due its diagnostic and prognostic value in different cardiopulmonary diseases [1–6]. In this context, the changes in hemodynamic parameters during exercise provide a measure of right ventricular (RV) contractile reserve and pulmonary vascular reserve [7, 8]. Hemodynamic parameters have been shown to correlate well with the results of cardiopulmonary exercise testing [6, 9].

Sildenafil, an inhibitor of phosphodiesterase 5, is frequently used to treat patients with pulmonary arterial hypertension (PAH)[10]. It leads to an elevation of cyclic guanosine monophosphate levels and thus increases signaling via the nitric oxide pathway, resulting in preferential pulmonary vasodilation[11]. An acute improvement in exercise-induced RV dysfunction by administration of sildenafil was shown in acute hypoxia [12], chronic obstructive pulmonary disease [13], chronic thromboembolic pulmonary hypertension [14], and in Fontan patients [15].

A comprehensive hemodynamic study of the acute effects of intravenous sildenafil for the assessment of the hemodynamic response to exercise in patients with connective tissue disease (CTD), who present with elevated mean pulmonary artery pressure (mPAP), has not yet been performed. We therefore conducted a proof-of-concept study to assess the RV and pulmonary vasculature responses to exercise before and after acute administration of intravenous sildenafil and to evaluate the safety of intravenous sildenafil in patients with CTD.

Materials and methods

Study design and setting

The present study was conducted as a prospective, open-label, single-center, single-group study between May 2013 and January 2015 at the Departments of Cardiology and Rheumatology and Clinical Immunology of the Kerckhoff-Klinik, Bad Nauheim, Germany (ClinicalTrials.gov identifier: NCT01889966). The first patient was recruited on 05/29/2013, whereas the registration at ClinicalTrials.gov was completed on 06/09/2013. This delay was due to technical problems; nevertheless the registration process was started before inclusion of the first patient. The authors confirm that all ongoing and related trials for this drug/intervention are registered. The last follow-up of the last patient was performed on 01/27/2015. The study complies with the Declaration of Helsinki, and the research protocol was approved by the locally appointed ethics committee on 11/02/2012 (University of Giessen, Approval No. 168/12). Written informed consent was obtained from every patient before any study-specific procedure was performed. The present analysis focuses on the effects of acute drug administration without taking follow-up data into account, because these have no influence on the interpretation of the acute results and were analyzed separately for reasons of clarity.

Participants

Twenty-one patients with CTD without a previous diagnosis of PAH were screened noninvasively. They had been referred to the Department of Rheumatology and Clinical Immunology, Kerckhoff-Klinik GmbH, Bad Nauheim, Germany for inpatient treatment. Screening for PAH was performed if there was a clinical reason, e.g. worsening dyspnea or fatigue. All tests and data collection were performed in the cardiology outpatient clinic. If cardiopulmonary exercise testing (CPET), echocardiography, or N-terminal pro-brain natriuretic peptide (NT-proBNP) levels showed abnormal results, right heart catheterization was performed. Inclusion criteria were an exercise-induced rise in mPAP >30 mmHg and an abnormal pulmonary vascular reserve defined as an increase in mPAP relative to cardiac output (total pulmonary resistance, TPR) >3 mmHg/L/min. These criteria have been suggested to define exercise pulmonary hypertension [5, 6, 16].

Exclusion criteria were an inability to perform exercise tests, contraindications to sildenafil treatment, pre-treatment with PAH drugs (e.g. bosentan for digital ulcerations), pregnancy, arterial hypotension with systolic pressure repeatedly <90 mm Hg, and advanced liver or renal disease (Fig 1).

Study treatments and assessments

The intervention was carried out in the right heart cardiac catheterization laboratory of the heart failure outpatient clinic. After baseline measurements at rest, an initial submaximal, symptom-limited exercise test using a bicycle ergometer was performed with simultaneous invasive hemodynamic measurements. After a recovery period when mPAP returned to the initially recorded value, resting patients received an intravenous injection of sildenafil 10 mg within 10 min (delivered by AJR). Comprehensive hemodynamic measurements were
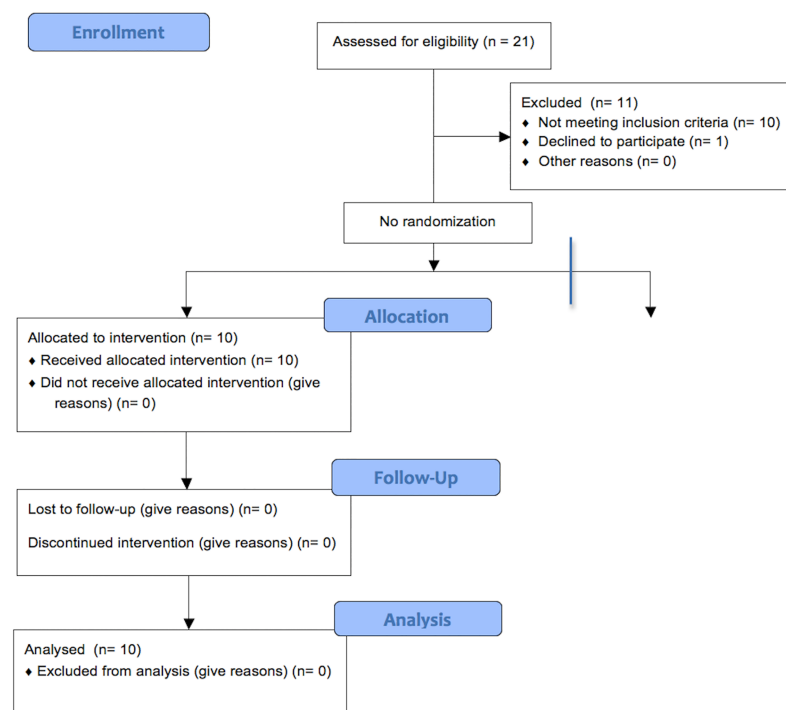

Fig 1. Study flow diagram.

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repeated (at rest) 15, 30, and 60 min after the start of the sildenafil injection. Finally, a second exercise test with simultaneous invasive hemodynamic measurements was performed to demonstrate the importance of these measurements [17] in showing the effect of the drug on the hemodynamic response to exercise. The individual first and second exercise tests during right heart catheterization were performed with comparable workloads and mixed-venous oxygen saturations at the end of exercise (S1 Table). All right heart catheterization and echocardiographic procedures were performed by one experienced examiner (AJR).

Hemodynamic measurements were performed in the supine position at end-expiration with a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore), as described previously in detail [18–20]. The pressure transducer was set at 50% of the thoracic diameter. The following parameters were measured at rest and during exercise, both before and after sildenafil injection: right atrial pressure (RAP); systolic and diastolic pulmonary arterial pressure (sPAP and dPAP, respectively); mPAP; pulmonary arterial wedge pressure (PAWP); cardiac output (CO) measured using the thermodilution method; and oxygen saturation in the pulmonary artery (SaO_2PA). In addition, mean and systolic systemic arterial blood pressures (MAP and SAP, respectively) were measured non-invasively. Derived parameters included the following: cardiac index; RV stroke work index (RVSWI); pulmonary vascular resistance (PVR); systemic vascular resistance (SVR); ratios of PVR/SVR and mPAP/MAP (changes in these ratios following drug administration purportedly reflect pulmonary selectivity of a drug); pressure–flow relationship (mPAP/CO slope = change during exercise in mPAP [ΔmPAP]/ΔCO); total pulmonary resistance (TPR = mPAP/CO); and pulmonary arterial capacitance (PAC; stroke volume/pulse pressure = [CO/heart rate]/[sPAP–dPAP]).

Statistical analysis

Calculations were performed using SPSS Statistics (IBM, Armonk, NY, USA). The Wilcoxon signed-rank test was used to assess the effect of intravenous sildenafil on resting and exercise hemodynamic parameters. A p-value <0.05 was defined as indicating a significant difference. Analyses using the Friedman test and linear mixed models were performed with standard versions implemented in SPSS V. 2.2.

Results

Baseline characteristics and hemodynamic response to exercise

Ten patients (seven with systemic sclerosis, two with mixed CTD, and one with systemic lupus erythematosus) were included in the study (Table 1 and S2 Table). The median age was 66.5 (interquartile range [IQR] 54.0–75.0) y, and nine of the patients were female. NYHA functional class was I–II, II, and III in two, three, and five of the patients, respectively. Echocardiographic parameters were (median [IQR]): tricuspid annular plain systolic excursion (TAPSE) 22 (14.5–25.5) mm; tricuspid annular systolic excursion velocity S´13.4 (10.9–15.0) cm/s; fractional area change (FAC) 46% (21–54); RV strain -13.85% (-9.88- -17.52); RA area 16.2 (11.8–22.3) cm^2; tricuspid regurgitation grade 1 (0.25–1.75); RV systolic pressure 58 (48–66) mmHg. The median VO₂ peak was 10.8 (8.9–13.1) mL/min/kg; breathing reserve at the end of CPET was 40 (30–47) %, with three patients $\leq$ 30%; V´E/VCO₂ slope 36.5 (32.0–43.5) (S3 Table). The median 6-min walking distance (6MWD) was 270.0 (IQR 258.8–411.3) m. The results of pulmonary function testing were: forced vital capacity 60.5 (47.3–82.5) %, total lung capacity 83 (65.3–89.8) %, forced expiratory volume in one second 66.5 (50.5–75.3) %, forced expiratory volume in one second/forced vital capacity 104 (95.8–109.5)% (S4 Table). Four of the patients had moderately elevated mPAP values (21–24 mm Hg) and the remaining six had higher mPAP values (>25 mm Hg) (S5 Table).

Table 1. Patient characteristics.

Characteristics	Study population (n = 10)
Age, years	66.5 (54.0–75.0)
Female sex, n	9
Height, cm	168.5 (161.3–171.8)
Weight, kg	70.0 (60.3–75.8)
Connective tissue disease type, n	
Systemic sclerosis	7
Systemic lupus erythematosus	1
Mixed connective tissue disease	2
NYHA functional class, n	
I–II	2
II	3
III	5
VÓ₂ peak, mL/min/kg	10.8 (8.9–13.1)
6MWD, m	270.0 (258.8–411.3)

Values represent median (interquartile range) unless otherwise specified. Abbreviations: NYHA, New York Heart Association; VȮ$_2$ peak, peak oxygen consumption during cardiopulmonary exercise testing; 6MWD, six-minute walking distance

In the absence of sildenafil action, median mPAP increased from 27.0 (IQR 23.3–34.5) mm Hg at rest to 51.0 (IQR 47.0–56.0) mm Hg during exercise, and the exercise-induced rise in mPAP was independent of resting values. This change was accompanied by increases in median RAP, PVR, TPR, and cardiac index and a decrease in median PAC (Table 2; data for individual patients are presented in S6 Table).

Acute effects of intravenous sildenafil on resting and exercise hemodynamics

Sildenafil injection was well tolerated during right heart catheterization. SAP dropped significantly after sildenafil injection, but none of the patients showed symptomatic hypotension. The acute hemodynamic effects of sildenafil at rest were greatest 30 min after the start of the injection. Sildenafil significantly reduced sPAP, mPAP, PAWP, and RAP as well as SAP at rest and during exercise, and it significantly increased the cardiac index at rest but not during exercise. Sildenafil also significantly reduced PVR, TPR, and PAC at rest and during exercise and SVR at rest but not during exercise. Heart rate and pulmonary-to-systemic ratios were not significantly altered by sildenafil (Fig 2 and Table 2).

The median pressure–flow relationship during exercise, expressed as the mPAP/CO slope, decreased from 8 (IQR 5.53–10.38) mm Hg/L/min without sildenafil to 5.94 (IQR 4.85–10.92) mm Hg/L/min after sildenafil injection ($p = 0.051$). Patients with mPAP <25 mmHg (N = 4) showed effects of sildenafil on PAC and TPR that were comparable to those of patients with mPAP ≥25 mmHg (N = 6), whereby exercise TPR and PAC improved more in the latter group (S7 and S8 Tables).

The results of analyses using the Friedman test and linear mixed models underline the significance of sildenafil-induced hemodynamic changes, in particular the predominant reduction of sPAP and mPAP, followed by SAP and HR. F-statistics pointed to associations between: 6MWD and HR; 6MWD and RAP; TAPSE and SVR; TAPSE and TPR; TAPSE and

Table 2. Acute hemodynamic effects of sildenafil at rest and during exercise.

Parameter	At rest			During exercise		
	Pre-sildenafil	30 min post-sildenafil	p (pre- vs. post-sildenafil)	Pre- sildenafil	Post-sildenafil	p (pre- vs. post-sildenafil)
sPAP, mm Hg	42.5 (37.8–53.0)	34.0 (30.3–47.3)	0.005	75.5 (67.5–93.0)	67.0 (58.3–84.5)	0.005
mPAP, mm Hg	27.0 (23.3–34.5)	22.0 (18.5–30.8)	0.005	51.0 (47.0–56.0)	44.0 (41.0–54.0)	0.007
PAWP, mm Hg	12.0 (11.0–12.8)	8.0 (6.3–10.5)	0.038	20.5 (15.5–24.0)	16.5 (11.3–21.8)	0.032
RAP, mm Hg	7.0 (6.0–8.0)	5.0 (3.3–7.8)	0.017	12.5 (9.8–21.0)	9.5 (6.3–11.0)	0.005
SAP, mm Hg	133.5 (127.5–149.8)	121.5 (111.3–128.5)	0.005	172.5 (154.0–182.8)	163.5 (152.0–180.5)	0.022
Heart rate, bpm	72.5 (62.5–75.0)	73.5 (69.3–76.5)	0.385	107.0 (98.0–112.0)	105.0 (97.8–113.0)	0.153
Cardiac index, L/min/m^2	2.6 (2.3–2.8)	2.8 (2.6–3.2)	0.012	4.2 (3.4–5.7)	4.3 (3.8–5.6)	0.333
mPAP/CO slope, mm Hg·min·L^{-1}				8.0 (5.53–10.38)	5.94 (4.85–10.92)	0.051
PVR, dyn·s·cm^{-5}	278.6 (182.5–348.4)	206.6 (146.1–265.8)	0.005	327.6 (207.9–407.0)	304.3 (160.1–346.1)	0.009
SVR, dyn·s·cm^{-5}	1625.9 (1119.9–1800.0)	1338.4 (912.4–1557.0)	0.007	1056.3 (804.4–1528.6)	1075.0 (812.4–1307.7)	0.575
PVR/SVR	0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.171	0.3 (0.2–0.4)	0.2 (0.2–0.4)	0.102
mPAP/MAP	0.3 (0.3–0.4)	0.3 (0.2–0.4)	0.107	0.5 (0.4–0.5)	0.4 (0.3–0.5)	0.185
PAC, mL·mm Hg^{-1}	2.3 (1.6–3.5)	2.5 (2.3–3.9)	0.013	1.6 (0.9–2.3)	1.7 (1.1–2.7)	0.005
TPR, mm Hg·min·L^{-1}	5.7 (4.7–6.9)	4.7 (3.1–5.6)	0.005	6.2 (4.6–8.5)	5.2 (4.0–7.0)	0.005
SaO$_2$PA, %	70.1 (63.5–74.4)	70.3 (61.5–76.0)	0.953	48.9 (40.3–57.0)	48.4 (40.8–61.2)	0.799
RVSWI, g·m/m^2	11.8 (7.9–16.8)	11.4 (7.9–13.9)	0.114	20.0 (12.5–26.0)	22.0 (15.9–26.4)	0.646

Values represent median (interquartile range). MAP, mean systemic arterial pressure; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SaO$_2$PA, oxygen saturation in the pulmonary artery; SAP, systolic systemic arterial pressure; sPAP, systolic pulmonary arterial pressure; SVR, systemic vascular resistance; TPR, total pulmonary resistance.

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PVR; troponin and PAC; CAMPHOR questionnaire and CI; CAMPHOR questionnaire and the mPAP-mSAP ratio (S9 Table).

Discussion

In the current study, we used a protocol involving exercise challenge in patients with CTD to demonstrate the following: (1) improvement of RV and pulmonary vascular functional reserve during exercise after acute administration of intravenous sildenafil; and (2) adequate safety of intravenous sildenafil administration in this setting.

We chose patients with CTD as a group with a high risk of developing PAH (e.g. estimated prevalence of 9% in systemic sclerosis)[21], which is a principal cause of death among these patients [22]. In comparison to subjects with idiopathic PAH, RV contractile reserve is more depressed in subjects with systemic sclerosis [8].

The exercise challenge demonstrated a reduced functional reserve of the RV and pulmonary vasculature independent of resting mPAP and RV function determined echocardiographically at rest, which was preserved in the majority of our patients. Mean PAP was >20 mmHg in all patients; several studies indicate that in patients with CTD, mPAP >20 mm Hg leads to an elevated risk of manifest PAH and a worse prognosis compared with mPAP ≤20 mm Hg [23–25]. Furthermore, patients with mPAP in the range of 21 to 24 mm Hg have a higher risk of developing progressive pulmonary vascular disease if they also have an exaggerated PAP response to exercise [1, 26].
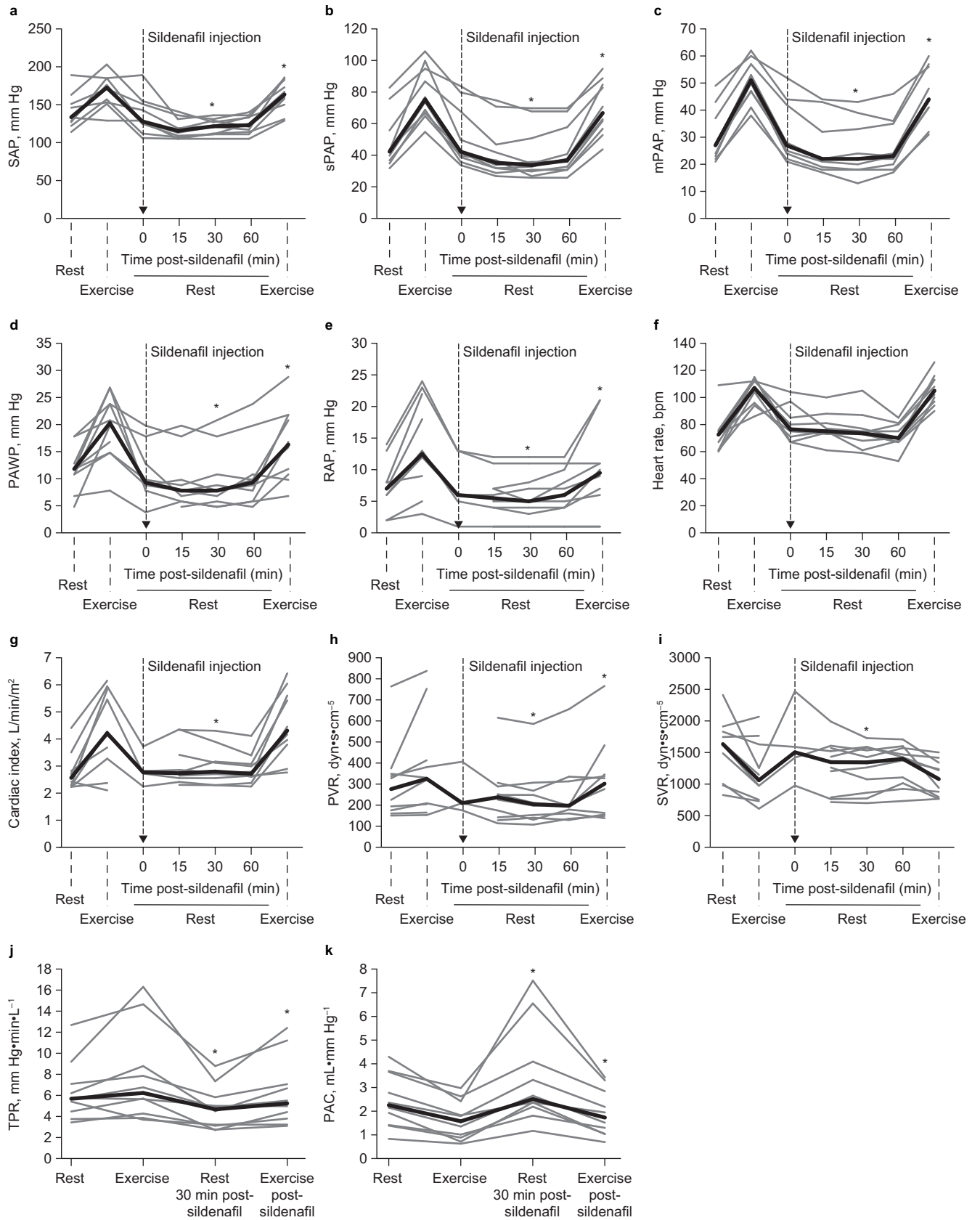
Fig 2. Acute responses of various parameters to intravenous sildenafil at rest and during exercise challenge. SAP (a), sPAP (b), mPAP (c), PAWP (d), RAP (e), heart rate (f), cardiac index (g), PVR (h), SVR (i), TPR (j) and PAC (k). Thin gray lines indicate individual patient data, and thick black lines indicate the median. *p < 0.05 (30 min post-sildenafil at rest vs pre-sildenafil at rest; post-sildenafil exercise challenge vs pre-sildenafil exercise challenge). mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SAP, systemic systolic arterial pressure; sPAP, systolic pulmonary arterial pressure; SVR, systemic vascular resistance; TPR, total pulmonary resistance.

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In addition to the PAP response, the relationship of mPAP to CO during exercise (mPAP/CO slope, maximum TPR during exercise) is being used increasingly to detect abnormal pulmonary hemodynamics [5, 6, 27]. PAC is a relatively new parameter that reflects pulmonary vasculopathy, which is known to be associated with increased mortality in patients with PAH [28–30] and which has rarely been investigated during exercise. Both resting and exercise TPR, PVR, and PAC were markedly abnormal in our cohort. Thus, hemodynamic assessment during exercise may unmask dysfunction of the RV-pulmonary vascular circuit in CTD patients with mPAP >20 mmHg and identify patients at particularly high risk of developing PAH [31–33].

Sildenafil 10 mg administered as an intravenous injection was safe and well tolerated in these patients; neither symptomatic arterial hypotension nor other adverse reactions occurred. Although sildenafil is considered to be a highly selective inhibitor of phosphodiesterase 5 localized in the pulmonary arteries and the heart [34], sildenafil injection led to a significant decline in systemic blood pressure, SVR, and PAWP but not in ratios of pulmonary/systemic pressures and vascular resistance. Similar effects have been described in patients with left heart failure [35]. The significant reduction of PAWP following sildenafil points to an acute reduction of left ventricular (LV) afterload by inhibition of phosphodiesterase 5 in the systemic vasculature [36–38] and may also indicate an improvement of LV diastolic function [39]. Due to the serial function of the two circulations, these effects on the LV-systemic vasculature unit may have contributed to the effects on pulmonary circulation described above.

After administration of intravenous sildenafil, the second exercise challenge resulted in a different pulmonary hemodynamic response with lower maximal mPAP, PVR, and TPR, a more shallow mPAP/CO slope, and increases in PAC and CO. Measures of RV steady (PVR) and pulsatile (PAC) afterload [40], pulmonary vascular reserve (TPR) [41], and RV backward failure (RAP) showed improvement due to an acute unloading. However, aside from RAP, any of these calculated parameters depend on CO and therefore cannot be interpreted in the absence of RV contractility. Pressure-volume measurements can be used to separate RV contractility from afterload within the complex RV-pulmonary circulation unit [42, 43], but these were not performed in our study.

The sildenafil effects were mostly independent of resting mPAP. In patients with chronic thromboembolic pulmonary hypertension or chronic obstructive pulmonary disease in whom a similar approach has been applied [13, 14], exercise hemodynamic parameters of RV afterload improved after sildenafil administration to a similar extent compared with results for our cohort of CTD patients. Therefore, the results of an exercise challenge before and after administration of sildenafil appear to reflect improved RV adaptation to exercise in several different forms of pulmonary vascular disease.

It is important to emphasize that sildenafil is currently not approved for patients with resting PAWP >15 mmHg and its use in these patients is discouraged by the guidelines [11]. Therefore, apart from clinical studies, it should not be used in this population.

Limitations

Limitations of the study are the lack of a control group and the small sample size. Another source of bias may be the multifactorial exercise limitation in CTD patients, which may be

caused by pulmonary vasculopathy, respiratory limitation, and LV dysfunction (LVD) [44]. Pulmonary function tests indicated moderate restrictive pulmonary disease in most patients in our cohort. CPET revealed signs of respiratory as well as pulmonary vascular and cardiac exercise limitation. The primary focus of this study, however, was the pulmonary vascular and cardiac exercise limitation, which is the specific subject of hemodynamic measurements repeated under the same conditions including respiratory exercise limitation. Therefore, a bias of the results of hemodynamic measurements by respiratory disease seems unlikely.

We included two patients with slightly elevated resting PAWP and several patients with a significant rise in PAWP during exercise, which is indicative of coincident diastolic LVD in most of our patients. Diastolic LVD may be associated with PAH in patients with CTD [1], and it is frequently found in an elderly population [45]; as the median age was 66.5 years in our sample, the likelihood of finding PAH without diastolic LVD was low. An overlap between PAH and LVD has been described as a pathophysiological continuum [46] with a significant heterogeneity, also in clinical studies [47]. In our cohort, our observation of an acute improvement of RV and pulmonary vascular functional reserve after sildenafil administration does not seem to be affected by this heterogeneity. The exercise-associated rise in PAWP was attenuated in most of our patients after sildenafil administration (Fig 2D), so the overall sildenafil effect may result in part from an improvement of LVD.

Finally, the choice of exercise protocol may also have influenced the results. The protocol used in the current study is well established [20], however, and the observed heart rate response (Fig 2F) demonstrated reproducibility.

Conclusions

The current proof-of-concept study provides the first evidence that intravenous sildenafil substantially enhances the hemodynamic response to exercise in patients with CTD and mPAP >20 mmHg. Our results suggest that acute pre-treatment with intravenous sildenafil is well tolerated and may improve the RV and pulmonary vascular reserve during exercise in patients with CTD independent of the degree to which resting mPAP surpasses 20 mmHg. The role of exercise hemodynamics combined with acute pharmacological interventions in pulmonary vascular diseases should be further examined. Furthermore, the investigation of PAH therapy in CTD patients with mPAP >20 mmHg might yield promising results.

Supporting information

S1 Table. Workloads and mixed-venous oxygen saturations at the end of exercise in individual patients.
(DOCX)

S2 Table. Characteristics of individual patients.
(DOCX)

S3 Table. Cardiopulmonary exercise testing in individual patients.
(DOCX)

S4 Table. Pulmonary function tests in individual patients.
(DOCX)

S5 Table. Baseline resting hemodynamics in individual patients.
(DOCX)

S6 Table. Baseline exercise hemodynamics in individual patients.
(DOCX)

S7 Table. Resting and exercise mPAP / TPR in patients with resting mPAP $</\geq$ 25 mmHg.
(DOCX)

S8 Table. Resting and exercise mPAP / PAC in patients with resting mPAP $</\geq$ 25 mmHg.
(DOCX)

S9 Table. Linear mixed models (H- and F-statistics).
(DOCX)

S1 Document. Study protocol.
(PDF)

S2 Document. TREND checklist.
(PDF)

S3 Document. CONSORT flow diagram.
(DOC)

Acknowledgments

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