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Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension

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Summary

Pulmonary hypertension is a frequent complication of sickle cell disease that is associated with haemolysis, impaired nitric oxide bioavailability and high mortality. We sought to evaluate the safety and efficacy of selective pulmonary vasodilators and antiproliferative agents in this at-risk population. After optimising sickle cell disease therapy to stabilise haemoglobin and fetal haemoglobin levels, we evaluated the safety and efficacy of sildenafil in 12 patients with sickle cell disease and pulmonary hypertension. Sildenafil therapy (mean duration 6 ± 1 months) decreased the estimated pulmonary artery systolic pressure [50 ± 4 to 41 ± 3 mmHg; difference 9 mmHg, 95% confidence interval (CI): 0.3–17, $P = 0.043$] and increased the 6-min walk distance (384 ± 30 to 462 ± 28 m; difference 78 m, 95% CI: 40–117, $P = 0.0012$). Transient headaches occurred in two patients and transient eye-lid oedema in four patients. No episodes of priapism occurred in the three men in the study; two of them were on chronic exchange transfusions and one had erectile dysfunction. In conclusion: (1) sickle cell disease patients with anaemia and pulmonary hypertension have significant exercise limitation; (2) the 6-min walk distance may be a valid endpoint in this population; (3) therapy with sildenafil appears safe and improves pulmonary hypertension and exercise capacity. Additional phase I studies in males with sickle cell disease followed by phase II/III placebo controlled trials evaluating the safety and efficacy of sildenafil therapy in sickle cell disease patients with pulmonary hypertension are warranted.

Keywords

sickle cell disease; haemolysis; pulmonary hypertension; phosphodiesterase 5 inhibitors; nitric oxide; 6-min walk test

Pulmonary hypertension is increasingly recognised as a complication of sickle cell disease, with a prevalence of approximately 30% (Gladwin *et al*, 2004). In spite of the mild elevation

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Conflict of interest

Dr Barst is a member of the scientific advisory board and a consultant for pulmonary arterial hypertension clinical drug development for Actelion, CoTherix, Encysive, and Pfizer.

in the pulmonary artery pressure, the 2-year mortality in these patients can be as high as 50% (Castro *et al*, 2003). We recently demonstrated that in adult patients with sickle cell disease, pulmonary hypertension (defined as a tricuspid regurgitant jet velocity greater than or equal to 2.5 m/s) is a major independent risk factor for death [relative risk of death 10.1; 95% confidence interval (CI) 2.7–44] (Gladwin *et al*, 2004). It is, however, unclear whether pulmonary hypertension is a marker of disease severity or a direct cause of mortality (Hassoun & Krishnan, 2004; Klings & Farber, 2004). Nor is it known whether selective pulmonary vasodilator/antiproliferative therapies will prove efficacious in this disease because the pulmonary artery pressure is only moderately elevated, the cardiac output and pulmonary capillary wedge pressures are high, and the pulmonary vascular resistance, while increased when compared with patients without sickle cell disease is only mildly elevated (Castro *et al*, 2003; Gladwin *et al*, 2004; Hassoun & Krishnan, 2004; Klings & Farber, 2004). In this context, investigation of the response to specific therapies targeting the pulmonary hypertension could help advance our understanding of the role of pulmonary hypertension in the increased mortality seen in these patients, and potentially open the door to novel therapeutic strategies for this at-risk population.

The phosphodiesterase 5 inhibitor, sildenafil, has been shown to improve pulmonary haemodynamics and functional capacity in several forms of pulmonary arterial hypertension (Lee *et al*, 2005). Inhibition of cyclic guanosine monophosphate (GMP) degradation by phosphodiesterase 5 increases nitric oxide (NO)-mediated pulmonary vasodilation. This effect may be beneficial in patients with sickle cell disease and/or other haemolytic disorders, characterised by a state of relative NO deficiency. In sickle cell disease (and possibly in other haemolytic disorders), a haemolysis-associated endothelial dysfunction is caused by the release of erythrocyte haemoglobin, which scavenges NO (Reiter *et al*, 2002), and of erythrocyte arginase, which metabolises L-arginine, the substrate for NO synthesis (Belfiore, 1964; Azizi *et al*, 1970; Morris *et al*, 2003; Schnog *et al*, 2004; Morris *et al*, 2005) as well as a possible impairment of the pulmonary vasodilatory effects of NO (Voelkel *et al*, 1995, 1999).

In this open label uncontrolled pilot trial, we evaluated the safety and efficacy of sildenafil in patients with sickle cell disease and pulmonary hypertension. We hypothesised that patients with sickle cell disease and pulmonary hypertension, despite the mild nature of the pulmonary hypertension, have significant impairments in exercise capacity because of the combined effects of the anaemia and the increased pulmonary vascular resistance and that treatment with sildenafil may prove efficacious by improving the pulmonary hypertension and exercise capacity.

Methods

Patient characteristics

All patients were enrolled in a National Heart Lung and Blood Institute-approved human subjects protocol; all subjects provided written, informed consent. All patients had homozygous sickle cell disease, determined by high performance liquid chromatography of their haemoglobin. Sickle cell subjects with pulmonary hypertension were identified by a tricuspid regurgitant jet velocity of greater than or equal to 2.5 m/s (corresponding to an estimated pulmonary artery systolic pressure of greater than or equal to 30–35 mmHg). Consenting patients with tricuspid regurgitant jet velocity of greater than or equal to 2.9 m/s also underwent right heart catheterisation.

Validation of the 6-min walk test in patients with sickle cell disease

In order to validate the use of the 6-min walk test as a surrogate marker of functional impairment in patients with sickle cell disease and pulmonary hypertension, we evaluated the relationship

between the 6-min walk distance and pulmonary artery pressure in a previously reported cohort that included patients enrolled in this study (Gladwin *et al*, 2004).

Sildenafil study design

The study was funded by the Intramural Research Division of the National Institutes of Health and medications purchased and delivered by the Clinical Center Pharmacy Development Service. Patients with tricuspid regurgitant jet velocity of greater than or equal to 2.5 m/s (corresponding to an estimated pulmonary artery systolic pressure of greater than or equal to 30–35 mmHg) were sequentially enrolled in the study. This value was selected because tricuspid regurgitant jet velocity values of greater than or equal to 2.5 m/s were associated with a significant and independent risk of death in patients with sickle cell disease (Gladwin *et al*, 2004). Thus a unique feature of this prospective study, was the evaluation of the treatment effect of sildenafil on patients with mild-to-moderate pulmonary hypertension. To minimise the risk of priapism, male patients were allowed to participate only if they had erectile dysfunction or were on chronic transfusion therapy. All patients had comprehensive ophthalmological evaluations prior to initiating sildenafil therapy and with each dose escalation; patients with active retinopathy or a history of retinal detachment or haemorrhage were excluded. To ensure that total haemoglobin levels and fetal haemoglobin levels were stable prior to starting sildenafil therapy, as these values can significantly affect exercise capacity, patients underwent intensification of their standard sickle cell disease therapy for 3–8 months. Such therapies included hydroxyurea, erythropoietin and/or exchange transfusion therapy, based on the current standard of care. Specific therapies used for each patient are shown in Table I.

When the haemoglobin and fetal haemoglobin levels had been stable for at least 4 weeks, oral sildenafil was initiated at a dose of 25 mg three times daily. The dose was increased by 25 mg three times daily every 2–4 weeks as tolerated to a maximum dose of 100 mg three times a day (100 mg four times a day was used in one patient). Pulmonary artery systolic pressure was estimated by echocardiography at baseline and at monthly intervals thereafter. The 6-min walk distance was measured at baseline and at 3 month intervals after initiation of therapy. Echocardiographic and 6-min walk distance assessments were performed sequentially and on the same day, within 1–4 h after sildenafil dosing. Assessments of estimated pulmonary artery pressure and 6-min walk distance were only performed in patients in steady state, i.e. no measurements were made within 1 week of the end of an acute vaso-occlusive crisis. For the purposes of analysis, the presildenafil treatment 6-min walk distance and tricuspid regurgitant jet velocity measurements, after stabilisation of fetal haemoglobin (Fig 1, time zero), were compared with the last measured 6-min walk distance and tricuspid regurgitant jet velocity. Because of sequential patient enrollment, these measures were obtained after 4–12 months of sildenafil therapy (mean duration sildenafil therapy 6 ± 1 months). As an additional secondary analysis, we measured the change in the tricuspid regurgitant jet velocity values over time.

Echocardiography

Transthoracic echocardiography was performed in all patients using the Acuson Sequoia (Siemens-Acuson Inc., Mountain-view, CA, USA) and Sonos 5500 (Philips, Inc., Andover, MA, USA). Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views and a minimum of five sequential complexes were recorded. Continuous wave Doppler sampling of the peak regurgitant jet velocity was used to estimate the right ventricular to right atrial systolic pressure gradient using the modified Bernoulli equation [$4 \times (\text{tricuspid regurgitant jet velocity}) \times (\text{tricuspid regurgitant jet velocity})$]. Pulmonary-artery systolic pressure was estimated by adding the Bernoulli-derived pressure gradient to the estimated mean right atrial pressure. The mean right atrial pressure was estimated according to the degree of collapse of the inferior vena cava with

inspiration: 5 mmHg for a collapse of at least 50% and 15 mmHg for a collapse of less than 50% (Kircher *et al*, 1990). These measurements have been validated to correlate with measured pulmonary artery systolic pressure in the absence of right ventricular outflow obstruction, e.g. pulmonic stenosis (Berger *et al*, 1985). We recently validated this measurement in patients with sickle cell disease (Gladwin *et al*, 2004).

Right heart catheterisation

Right heart catheterisations were performed in nine patients in the study. Cardiac output was measured by continuous thermodilution (Sensormedics V_{\max} 229; Viasys Healthcare, Yorba Linda, CA, USA). The mean haemodynamics of a subgroup of these patients has been previously reported (Gladwin *et al*, 2004).

Acute vasodilator challenge

To evaluate vasodilator responsiveness in catheterised patients, haemodynamic measurements were performed at baseline and 10 min after inhalation of NO 40 parts per million (INO Therapeutics, Liberty Corner, NJ, USA). In a subgroup of five subjects, 50 mg of sildenafil was administered orally with hourly assessments of haemodynamic parameters.

The 6-min walk test

The 6-min walk was performed in accordance with standard practice (American Thoracic Society (ATS) Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Briefly, patients were asked to walk at an unhurried pace for 6 min along a premeasured path in the Clinical Center. A single practice walk was performed first.

N-terminal pro-brain natriuretic peptide measurement

Plasma N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured by a sandwich immunoassay using polyclonal antibodies that recognise epitopes located in the N-terminal part (1–76) of pro-BNP (1–108) (Elecys analyzer, Roche Diagnostics, Mannheim, Germany) prior to introduction of sildenafil and at the end of the study. Elevated levels of brain natriuretic peptide have been demonstrated in several forms of pulmonary hypertension and correlate with the degree of elevation in pulmonary pressures and right ventricular dysfunction in this population (Leuchte *et al*, 2004a,b, Nagaya *et al*, 1998,2000).

Statistical analysis

Differences between pre- and the most recent post-sildenafil therapy and NO responses were evaluated by Wilcoxon matched test. Comparisons of the relationship between haemoglobin, and fetal haemoglobin levels *versus* time were performed using one-way-analysis of variance (ANOVA). Repeated measures ANOVA was performed for the evaluation of the acute effects of sildenafil administration. Spearman correlations were performed where appropriate. The calculations were performed using GRAPHPAD PRISM (GraphPad Software Inc., San Diego, CA, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Validation of the 6-min walk test in patients with sickle cell disease with pulmonary hypertension

To validate the relationship between the 6-min walk distance and both the non-invasive echocardiographic estimate of pulmonary artery systolic pressure and pulmonary artery pressure measured during right heart catheterisation, we compared 11 patients without pulmonary hypertension [defined by mean pulmonary artery pressure less than 25 mmHg or tricuspid regurgitant jet velocity less than 2.4 m/s; four males, age 40 ± 3 (mean \pm SEM) years,

tricuspid regurgitant jet velocity 2.3 ± 0.1 m/s] and in 15 patients with pulmonary hypertension (defined by mean pulmonary artery pressures greater than 25 mmHg ($n = 14$) or tricuspid regurgitant jet velocity greater than or equal to 3 m/s ($n = 1$ patient); seven males, age 41 ± 2 years, tricuspid regurgitant jet velocity 3.2 ± 0.1 m/s). The control subjects were matched to the pulmonary hypertension subjects for total haemoglobin (8.5 ± 0.3 and 8.3 ± 0.2 g/dl, respectively; $P = 0.59$), fetal haemoglobin (6.9 ± 1.6 and $8.3 \pm 0.2\%$, respectively; $P = 0.9$) and age (40 ± 3 and 41 ± 2 years, respectively; $P = 0.74$). Right heart catheterisation was performed in four of the patients without pulmonary hypertension (mean pulmonary artery pressure 22 ± 1 mmHg, pulmonary vascular resistance 73 ± 8 dynes \times s \times cm⁵) and in 14 of the patients with pulmonary hypertension (mean pulmonary artery pressure 36 ± 2 mmHg, pulmonary vascular resistance 169 ± 26 dynes \times s \times cm⁵). In these patients, the 6-min walk distance correlated inversely with the tricuspid regurgitant jet velocity ($R = -0.62$, $P = 0.0001$) and with the measured mean pulmonary artery pressure ($R = -0.52$, $P = 0.01$) (Fig 2), consistent with the 6-min walk test reflecting the functional impairment in patients with sickle cell disease and pulmonary hypertension. These data supported the use of 6-min walk distance as our primary endpoint for a phase I/II open label sildenafil trial in this population.

Adverse events

No significant changes in systemic arterial blood pressure were observed with chronic therapy (data not shown). Transient headaches were reported in two patients upon initiation of the drug, however, with the exception of one patient who had migraine-like headaches at the initiation of therapy and could not complete the study, sildenafil was well tolerated. Transient eye-lid and/or periorbital subcutaneous oedema occurred in four patients, following initiation of the drug or at dose escalation. Comprehensive ophthalmological evaluation revealed no changes in visual acuity, ocular pressures or retinal appearance. No episodes of retinal haemorrhage occurred. No episodes of priapism occurred in the three male patients. It should be noted, however, that per inclusion criteria, at enrollment two male patients were on chronic exchange transfusion therapy and one male had pre-existing erectile dysfunction.

Acute haemodynamic effects of sildenafil

The acute pulmonary and systemic haemodynamic effects of sildenafil administration were evaluated in five patients with sickle cell disease (five females age 38 ± 8 years, mean pulmonary artery pressure 36.4 ± 4 mmHg, pulmonary vascular resistance 187 ± 32 dynes \times s \times cm⁵). Acute administration of sildenafil significantly decreased mean pulmonary artery pressure by 26% (95% CI: -47 to -4), pulmonary vascular resistance by 57% (95% CI: -74 to -39) and increased cardiac index by 45% (95% CI: 22 – 68). Mean arterial pressure did not statistically change (-13% change, 95% CI: 2 to -28), while both the systemic vascular resistance (-30% change, 95% CI: -41 to -18) and the ratio of pulmonary to systemic vascular resistance (-38% change, 95% CI: -64 to -12) significantly decreased, suggesting a preferential pulmonary vasodilator effect (Fig 3).

Sildenafil effects on pulmonary hypertension and exercise capacity

Thirteen patients were enrolled. One patient could not tolerate sildenafil because of persistent headaches after the initiation of the drug and was discontinued from the study. Table I illustrates the clinical characteristics of the remaining 12 patients. Table II illustrates the haemodynamic and vaso-reactivity profiles of the nine study subjects who underwent cardiac catheterisation. Haemoglobin and fetal haemoglobin levels did not change after sildenafil therapy was initiated ($P > 0.05$, Fig 1), enabling the assessment of sildenafil-dependent changes in exercise capacity. Further, lactate dehydrogenase levels did not change with after sildenafil therapy was initiated (354 ± 52 IU/l presildenafil vs. 348 ± 53 IU/l, $P = 0.5$), suggesting that the haemolytic rate did not change with sildenafil therapy.

Although the pulmonary hypertension was only mild, all patients had significant impairment in exercise capacity, as evidenced by a low 6-min walk distance (Table III). Therapy with sildenafil for a mean duration of 6 ± 1 months decreased the estimated pulmonary artery systolic pressure (50 ± 4 – 41 ± 3 mmHg; difference -9 mmHg, 95% CI: 0.3–17, $P = 0.047$), and increased the 6-min walk distance (384 ± 30 – 462 ± 28 m; difference 78 m, 95% CI: 40–117, $P = 0.003$) (Table III, Fig 4). Sildenafil produced sustained reductions in pulmonary artery pressures over time, as measured by tricuspid regurgitant jet velocities (Fig 4C). In addition, sildenafil therapy significantly decreased plasma NT-pro-BNP levels [BNP (pg/ml): 559 ± 333 – 111 ± 28 , $P = 0.002$], further suggesting that the improvement in exercise capacity was related to an improvement in pulmonary pressure and right ventricular function (Fig 4D).

Discussion

In patients with sickle cell disease and mild-to-moderate pulmonary hypertension, chronic therapy with sildenafil improved the estimated pulmonary arterial systolic pressure and exercise capacity. These effects were not related to changes in haemoglobin-oxygen carrying capacity since sickle cell disease therapy was intensified prior to initiation of sildenafil and haemoglobin and fetal haemoglobin levels remained unchanged throughout the study. This is the first therapeutic trial of chronic pulmonary vasodilator therapy in the sickle cell population in general, and in sickle cell patients with pulmonary hypertension in particular. The demonstration of an improvement in exercise capacity, as assessed by the 6-min walk test suggests that this test may be appropriate for future trials in this at-risk population.

In the present study, the acute haemodynamic effects of sildenafil and chronic effects on pulmonary artery pressures and exercise capacity were consistent with those seen in patients with other forms pulmonary arterial hypertension. Chronic sildenafil therapy increased the 6-min walk distance by 54 m in 12 patients with pulmonary hypertension secondary to inoperable chronic thromboembolic disease (Ghofrani *et al*, 2003a), by 93 m in 14 patients with severe pulmonary arterial hypertension failing inhaled iloprost therapy (Ghofrani *et al*, 2003b), and by 128 m in five other patients with severe pulmonary arterial hypertension (Michelakis *et al*, 2003). Although our patients only had mild pulmonary hypertension, these results are similar to the 78 m improvement in 6-min walk distance seen in our study, suggesting that even mild degrees of pulmonary hypertension may be poorly tolerated in chronically ill anaemic patients with sickle cell disease. Not only is the magnitude of improvement in the 6-min walk distance similar to that seen in patients with more severe pulmonary hypertension, but the baseline walk distance in our patients closely approximated that of patients enrolled in other pulmonary arterial hypertension trials (Channick *et al*, 2001; Rubin *et al*, 2002; Barst *et al*, 2004), again suggesting that even mild pulmonary hypertension is associated with significant functional impairment in patients with sickle cell disease. Even though the effects of sildenafil were similar to those observed in other patient populations, our results should be interpreted cautiously. This uncontrolled small open label study cannot conclusively rule out an effect of other confounders, such as patient selection bias or optimisation of supportive care. However, we used well-defined inclusion criteria, based on a known risk factor for mortality, and maximised all aspects of sickle cell specific care for 3–8 months prior to introduction of sildenafil. We specifically required that fetal haemoglobin levels were stable for at least 2 months prior to starting sildenafil. Finally, although the degree of pulmonary hypertension significantly improved in the majority of patients, tricuspid regurgitant jet velocities were mostly ≥ 2.5 m/s after treatment, still likely to indicate an increased risk of death.

In conclusion, pulmonary hypertension not only appears to be a marker of disease severity but also a significant cause of morbidity (i.e. poor exercise capacity) and possibly a cause of mortality in patients with sickle cell disease. Our results suggest that even mild elevations in pulmonary artery pressures are not well tolerated by patients with severe anaemia, such as

those with sickle cell disease, and that treatment of the pulmonary hypertension may improve functional outcomes in this patient population. Our study was limited by the small number of patients enrolled and the open-label design. However, the data provide 'proof of concept' for designing a larger, multicentre randomised double-blind placebo-controlled trial evaluating the safety and efficacy of sildenafil in this patient population.

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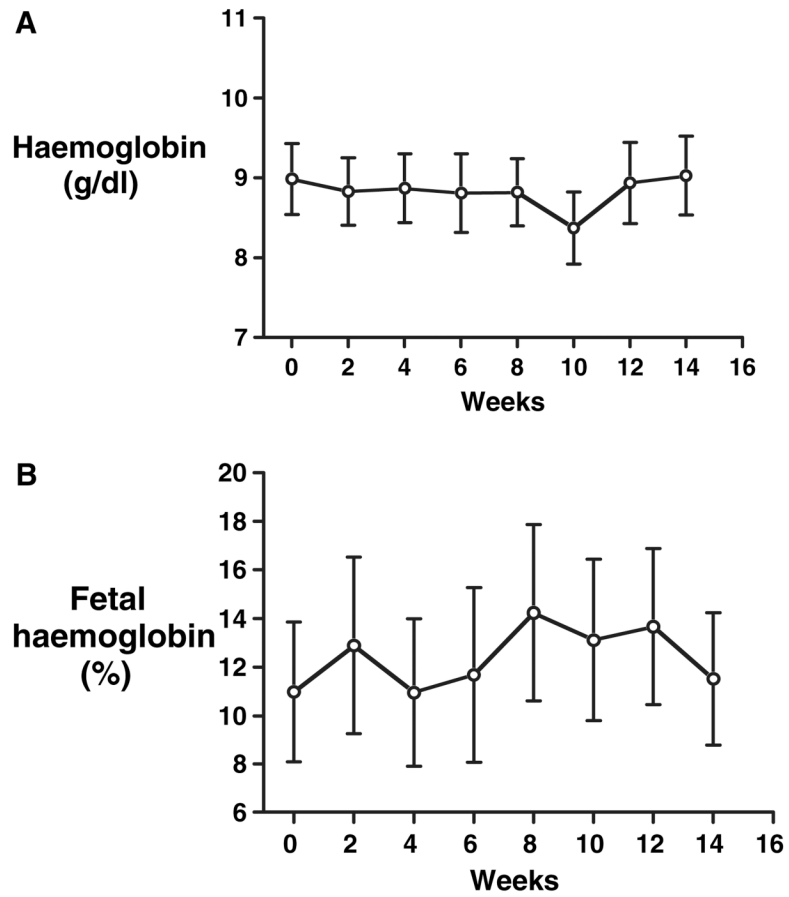


Fig 1. Haemoglobin (A) and fetal haemoglobin levels (B) remain stable with sildenafil therapy, which was started on week 0 following maximisation of sickle cell disease therapy; data mean \pm SEM.

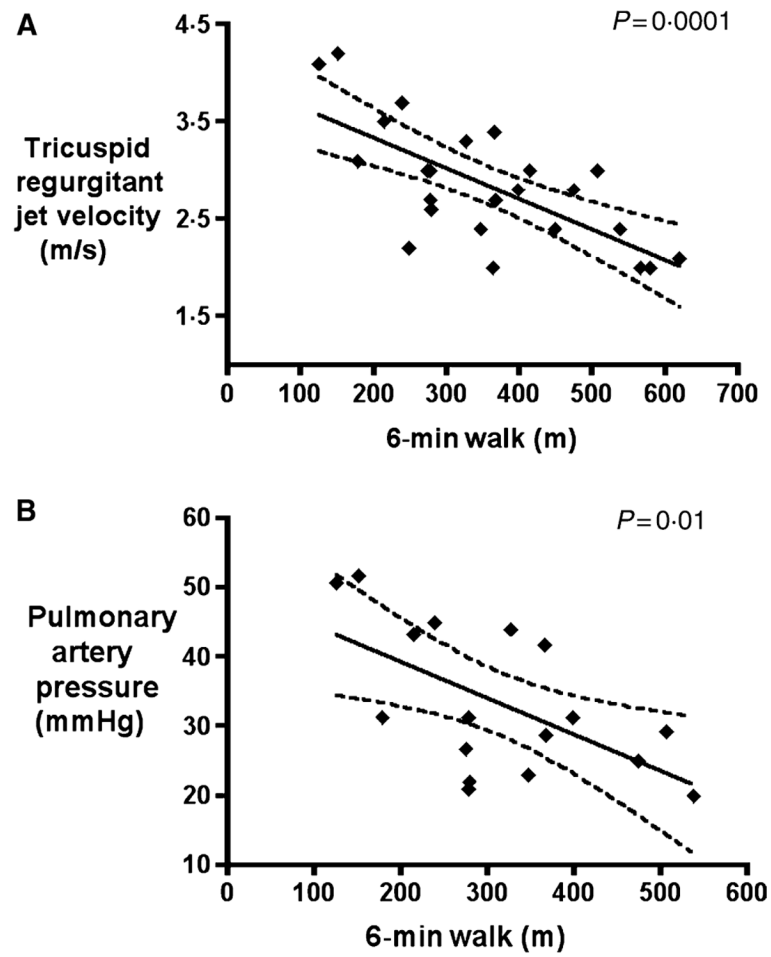
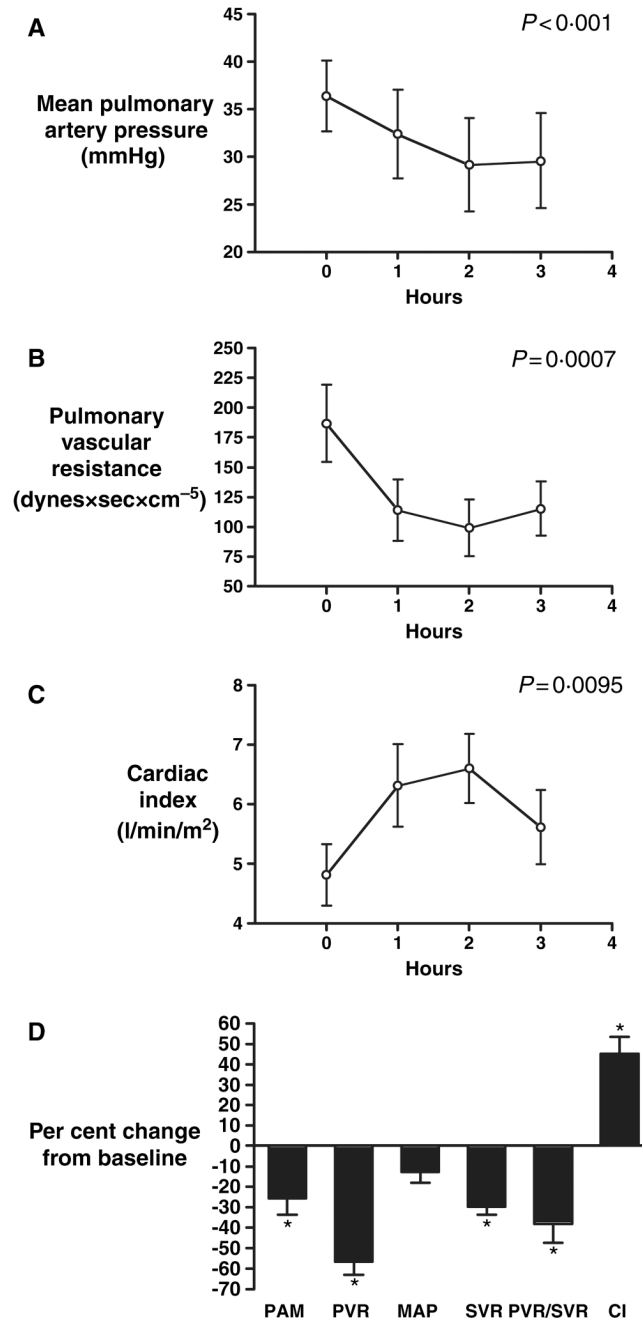


Fig 2. Six-minute walk distance correlated inversely with tricuspid regurgitant jet velocity (A) and mean pulmonary artery pressure (B).

**Fig 3.**

Acute administration of sildenafil decreased mean pulmonary artery pressure (A); pulmonary vascular resistance (B); and increased cardiac index (C). (D) Maximal effects of sildenafil on haemodynamic parameters ($n = 5$), data mean \pm SEM, * $P < 0.05$. PAM, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; MAP, mean arterial pressure; CI, cardiac index.

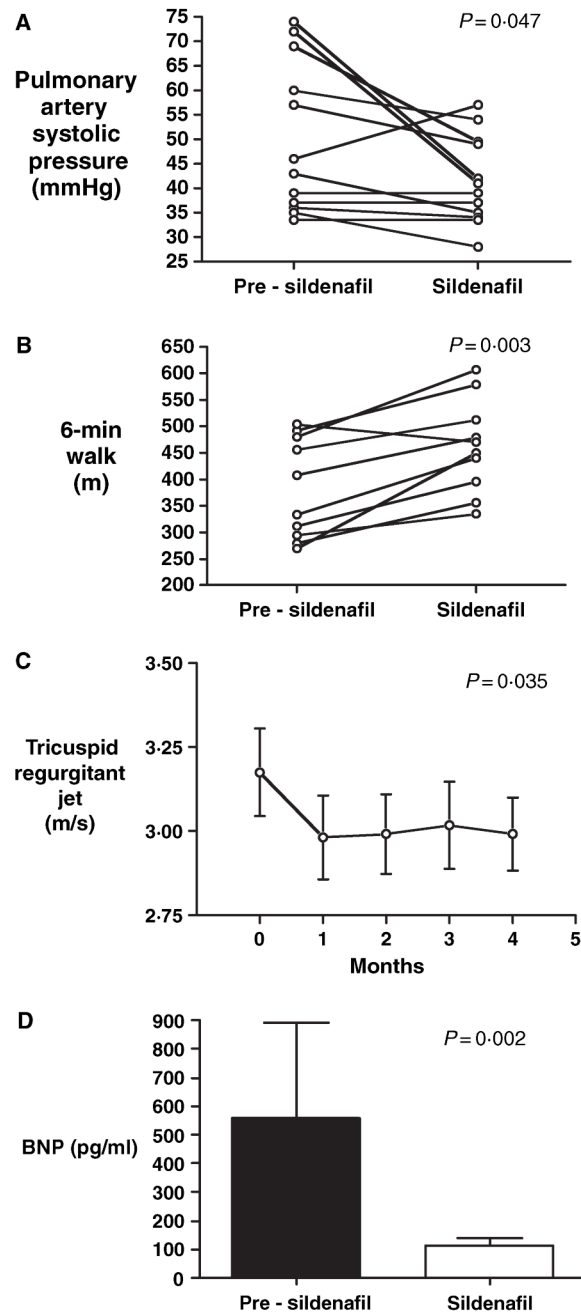


Fig 4. Effects of sildenafil on estimated pulmonary artery systolic pressure and exercise capacity in patients with sickle cell disease and pulmonary hypertension. Sildenafil therapy significantly decreased estimated pulmonary artery systolic pressure (A) and improved 6-min walk distance (B). (C) Time course of the effects of sildenafil on tricuspid regurgitant jet velocity. (D) Decrease in plasma NT-pro-BNP levels with sildenafil therapy.

Table I

Baseline clinical characteristics.

Patient	Age (years)	Gender	NYHA/ WHO functional class	Haemoglobin (g/ dl)	Fetal haemoglobin (%)	Final haemoglobin (g/ dl)	Therapy for sickle cell disease
1	41	F	II	7.5	9.8	7.8	Hydroxyurea
2	42	F	I	8.8	3.7	9.5	Hydroxyurea, erythropoietin
3	52	F	III	8.7	15.2	9.6	Hydroxyurea
4	19	F	III	9.5	4.3	9.5	Exchange transfusion
5	49	M	III	8.4	1.4	8.3	Exchange transfusion
6	45	F	III	11.6	26.1	11.4	Hydroxyurea
7	37	F	III	8.4	31.4	7.3	Hydroxyurea, erythropoietin
8	30	M	III	6.2	9.4	6.9	Hydroxyurea, erythropoietin
9	51	F	II	9.0	18.2	8.1	Hydroxyurea
10	46	F	I	10.4	1.9	10.3	Exchange transfusion
11	49	M	III	11.3	1.6	11.5	Exchange transfusion
12	39	F	II	8.0	8.7	8.0	Hydroxyurea
Mean ± SEM	43 ± 3			8.9 ± 0.5	10.9 ± 2.8	9.0 ± 0.4	

* Haemoglobin level obtained at the time of last measured 6-min walk distance and echocardiogram.

NYHA, New York Heart Association; WHO, World Health Organisation.

Table II

Baseline haemodynamic parameters and response to inhaled nitric oxide.

Patient	Baseline haemodynamic parameters*						Nitric oxide			
	mPAP (mmHg)	PVR (dynes × s × cm ⁵)	mCVP (mmHg)	CO (l/ min)	mPCWP (mmHg)	SVR (dynes × s × cm ⁵)	SVO ₂ (%)	SpO ₂ (%)	mPAP (mmHg)	CO (l/ min)
1	29	99	7	10.5	16	488	75	98	22	10.7
2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	94	n/a	n/a
3	40	238	10	8.4	15	625	n/a	100	n/a	n/a
4	39	241	16	7.3	17	760	62	98	28	11
5	47	440	9	6.0	14	1107	62	97	36	7.8
6	26	114	10	7.7	14	758	72	100	21	11
7	30	169	12	7.1	15	866	65	99	26	8.6
8	28	119	8	10.1	13	418	70	96	25	12.3
9	23	83	4	10	12	568	n/a	98	n/a	n/a
10	n/a	n/a	n/a	n/a	n/a	n/a	n/a	97	n/a	n/a
11	50	285	11	10.0	15	409	72	98	35	13
12	n/a	n/a	n/a	n/a	n/a	n/a	n/a	96	n/a	n/a
Mean ± SEM	35 ± 3	199 ± 39	10 ± 1	8.6 ± 0.5	15 ± 1	667 ± 77	68 ± 2	98 ± 0.5	28 ± 2	10.6 ± 0.7
P-value [†]									0.015	0.015

* Right heart catheterisation was performed in consenting individuals with tricuspid regurgitant jet velocity ≥2.9 m/s.

† Compared with baseline values.

mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; mCVP, mean central venous pressure; mPCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance; SVO₂, mixed-venous oxygen saturation; SpO₂, arterial oxygen saturation by pulse oximetry.

Table III
Effects of sildenafil on estimated pulmonary artery systolic pressure and exercise capacity.

Patient	Duration of sickle cell disease intensification therapy (months)	Duration of sildenafil therapy (months)	Pulmonary artery systolic pressure (mmHg)		Six-min walk distance (m) [*]	
			Presildenafil	Sildenafil	Presildenafil	Sildenafil
1	4	4	36	37	492	579
2	6	4	35	28	408	479
3	3	12	74	41	279	356
4	3	12	69	49	n/a	n/a
5	6	4	60	54	334	440
6	3	12	43	34	312	396
7	3	4	46	57	n/a	n/a
8	8	6	57	49	456	512
9	3	4	36	34	278	450
10	6	4	34	34	487	607
11	6	5	72	41	290	335
12	3	5	39	39	504	470
Mean ± SEM	4.5 ± 0.5	6 ± 1	50 ± 4	41 ± 3	384 ± 30	462 ± 28
P-value				0.047		0.003

* The 6-min walk test could not be performed in two patients because of severe chronic pain and avascular necrosis of the hip.