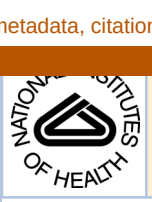

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Sildenafil exposure and hemodynamic effect after stage II single-ventricle surgery

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Abstract

Objective—To determine sildenafil exposure and hemodynamic effect in children after stage II single-ventricle surgery.

Design—Prospective, dose escalation trial.

Setting—Single-center, pediatric catheterization laboratory.

Patients—12 children post stage II single-ventricle surgical palliation and undergoing elective cardiac catheterization: median age 1.9 years (range: 0.8, 4.0), weight 11 kg (8, 13), 9 females, and 10 with a single right ventricle.

Interventions—Catheterization and echocardiography performed before and immediately after single-dose intravenous sildenafil (0.125, 0.25, 0.35, or 0.45 mg/kg over 20 minutes).

Measurements—Peak sildenafil and des-methyl sildenafil concentration, change in hemodynamic parameters measured by cardiac catheterization and echocardiography including indexed pulmonary vascular resistance, and myocardial performance.

Main Results—Maximum sildenafil concentrations ranged from 92–775 ng/ml and were above the in vitro threshold needed for 77% phosphodiesterase type-5 (PDE-5) inhibition in 80% of subjects and 90% inhibition in 80% of subjects with doses ≥0.35 mg/kg. Sildenafil lowered pulmonary vascular resistance index (PVRI) in all 12 subjects (median PVRI 2.2 [range: 1.6, 7.9]; decreased to 1.7 [1.2, 5.4] WU x m^2; $p<0.01$) with no dose-response effect. Sildenafil improved pulmonary blood flow (+8% [0, 20], p=0.04) and saturations (+2% [0, 16], p=0.04) in those with baseline PVRI ≥2 WU x m^2 (n=7). Change in saturations correlated inversely with change in PVRI ($r^2 = 0.74$ $p<0.01$). Sildenafil also lowered mean blood pressure (−12% [−20, +10]; p=0.04). There was no change in cardiac index and no effect on myocardial performance. There were no adverse events.

Conclusions—Sildenafil demonstrated non-linear exposure with high inter-individual variability but was well tolerated and effectively lowered PVRI in all subjects. Sildenafil did not acutely improve myocardial performance or increase cardiac index.

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Single ventricle; sildenafil; bidirectional Glenn anastomosis; pulmonary hypertension; pulmonary vascular resistance; pharmacokinetics

INTRODUCTION

Staged surgical palliation has markedly improved neonatal outcomes for children with single-ventricle heart defects.[1] However, operative survivors face ongoing mortality risk and significant morbidities.[2–5] These consequences are due to the physiologic constraints of the palliated single-ventricle circulation.[6] In this unique circulation, the 2 principal determinants of long-term outcome are low pulmonary vascular resistance (PVR) and adequate single-ventricle myocardial function.[2,5–7] Drugs that lower PVR and/or improve myocardial performance could optimize circulatory efficiency and potentially improve outcomes.

Sildenafil is a selective phosphodiesterase type-5 (PDE-5) inhibitor that increases cyclic guanosine monophosphate and produces vascular smooth muscle relaxation.[8] PDE-5 is highly expressed in the pulmonary vasculature, and sildenafil is approved by the U.S. Food and Drug Administration and the European Medicines Agency for treatment of pulmonary arterial hypertension in adults.[8,9] Emerging data suggest an expanded role for PDE-5 inhibitors in chronic cardiomyopathic states. Benefits including improved systolic and diastolic performance have been documented in animal models and in adults with heart failure or ventricular hypertrophy.[10,11] Clinicians have extrapolated these effects to the single-ventricle population leading to much enthusiasm within the field.[12–14] However, recent data from the Sildenafil in Treatment-naive Children, Aged 1–17 Years, with Pulmonary Arterial Hypertension (STARTS) trial have created concerns about sildenafil safety and efficacy in children. Specifically, efficacy end points were not achieved with low-dose sildenafil, while there was increased long-term mortality in those treated with high-dose vs. low-dose sildenafil.[15] These data are particularly relevant to the single-ventricle population where unique physiology may confound drug response and alter drug metabolism. No studies to date elucidate the acute hemodynamic effect of PDE-5 inhibition after single-ventricle palliation, and no studies have evaluated sildenafil pharmacokinetics (PK) in these patients.

The aim of the present study was to determine intravenous, single-dose sildenafil PK and hemodynamic effect in patients with single-ventricle heart defects. More specifically, this analysis focuses on the acute hemodynamic effect and drug exposure correlation after stage II surgery. Efficacy after stage III surgery and an expanded PK analysis are reported separately. We hypothesized that sildenafil would acutely improve cardiopulmonary hemodynamics by lowering pulmonary vascular resistance and improving global myocardial performance and that improvements in cardiopulmonary hemodynamics would be related to drug exposure.

MATERIALS AND METHODS

The study was an open-label, prospective, dose escalation trial. The institutional review board of Duke University Medical Center (Durham, North Carolina) approved the study protocol. Subjects ≥6 months and ≤10 years of age with single-ventricle heart defects post stage II surgical palliation and undergoing cardiac catheterization as a part of their routine clinical care were eligible for participation. Written informed consent was obtained for all study participants. Exclusion criteria included: 1) history of serious side effects to prior

sildenafil therapy; 2) history of sildenafil exposure 96 hours prior to the study; 3) pulmonary venous obstruction; 4) known or suspected pulmonary arterial or cavopulmonary anastomosis obstruction (catheterization gradient ≥1 mm Hg); 5) known or suspected coarctation of the aorta (catheterization gradient ≥10 mm Hg); 6) current treatment with nitrates or alpha blockade medications; and 7) significant renal failure (serum creatinine >2 times higher than the upper limit of normal), thrombocytopenia (platelet count <50,000 × 10^6/L) or leukopenia (white blood cell count <2500 grams/dL).

Study protocol

All patients were studied under general anesthesia with mechanical ventilation and a fraction of inspired oxygen of 0.21. Sedation and ventilation status were kept stable throughout the hemodynamic portion of the study. Baseline transthoracic echocardiogram and hemodynamic cardiac catheterization were performed after induction of anesthesia. Following the initial collection of hemodynamic data, patients were given a single, pre-determined dose of intravenous (IV) sildenafil (0.125 mg/kg, 0.25 mg/kg, 0.35 mg/kg, or 0.45 mg/kg) over 20 minutes. The initial patients enrolled in the study were assigned to the lowest dose category with progression to increasing dose levels after reviewing adverse events for each dose level. Immediately after sildenafil administration, the hemodynamic catheterization and transthoracic echocardiogram were repeated.

For echocardiograms, a single sonographer performed all studies using a standard cardiac ultrasound system (Vivid 7®, GE-Vingmed, Horten, Norway). Images were obtained in the parasternal long, parasternal short, apical, and suprasternal views. Measurements were performed to assess: diastolic ventricular function (atrioventricular valve inflow E : tissue Doppler E′ peak velocities), 2D systolic ventricular function (fraction of area change [FAC] for systemic right ventricles, single-plane modified Simpson's rule ejection fraction [EF] for systemic left ventricles), speckle tracking systolic function (strain, strain rate), and global myocardial performance (myocardial performance index).[16,17] Speckle tracking analysis was performed offline using Vector Velocity Imaging™ (Siemens Medical Solutions, Mountain View, CA). Two physicians associated with the study independently performed all interpretations of the echocardiographic data. Inter-rater reliability was evaluated using Spearman's correlation coefficient with r^2 values of 0.73, 0.74, 0.84, 0.76, and 0.97 ($p<0.05$ for all measures) for fractional area change, tissue Doppler E′ to atrioventricular E wave ratio, strain, strain rate, and myocardial performance index, respectively.

Catheterization assessment included measurement of saturations by co-oximetry including mixed venous, pulmonary arterial (PA), and systemic arterial oxygen saturations as well as pressure measurements in the branch pulmonary arteries, common atrium, single ventricle, and ascending and descending aorta. Pressures were obtained in the standard fashion using fluid-filled catheters. The PVR, systemic vascular resistance, pulmonary blood flow, and cardiac output were calculated by the Fick method with oxygen consumption estimated based on age and heart rate. Blood flow and resistances were indexed to the patient's body surface area. For repeat calculations, we used the same estimated oxygen consumption as was used for baseline measurements, and saturations were sampled from the same locations as those used at baseline.

PK sampling and analysis

Plasma sildenafil levels were collected immediately following completion of the infusion (t=25 minutes after initiation of drug infusion). Samples were immediately transferred into heparinized polypropylene tubes and centrifuged for 5 minutes at 3500 RPM. Samples were then stored in dry ice and transferred to a −70° C freezer. Sildenafil and des-methyl sildenafil concentrations were determined using a commercially available assay. The

quantitative analysis was performed by Covance Laboratories Inc. (Madison, WI) using high-performance liquid chromatography with tandem mass spectrometry.

Data analysis

The primary hemodynamic outcome measure was change in PVR index (PVRI). Secondary outcome measures included other hemodynamic variables as well as echocardiographic measures and exposure response. Statistical analysis included all patients receiving sildenafil. Demographic data were summarized using descriptive statistics and expressed as median (range). Change in clinical parameters was expressed as median percent change, with the exception of change in saturations, which was expressed as absolute change. Hemodynamic and echocardiographic data were calculated and presented by dosage group. Standard graphing and screening tests were used to assess for outliers and to determine data distribution. A Wilcoxon rank sum test was used to compare hemodynamics and echocardiographic measurements at baseline and after sildenafil administration. Linear regression was used to examine the correlation between response, dose levels, and hemodynamic measures expected to affect response. Statistical analysis was performed using SPSS v. 19.0 software package. A 2-tailed p value <0.05 was considered significant.

RESULTS

Between March 2011 and January 2012, 12 subjects were enrolled. Median (range) age and weight were 1.9 years (0.8–4.0) and 11.1 kg (8.0–13.2). Nine subjects (75%) were female, and 10 (83%) had a systemic right ventricle. Table 1 summarizes demographic features and baseline hemodynamic parameters.

Drug exposure data (Figure 1)

Sildenafil levels peaked immediately after infusion completion, with peak levels ranging from 92–775 ng/ml. Peak levels for the active metabolite, des-methyl sildenafil ranged from 15–43 ng/ml and were seen between 43 and 117 minutes after peak sildenafil levels. There was high inter-individual variability (coefficient of variation = 45% for peak sildenafil levels) and dose non-proportionality with non-linear increase in levels across dosing groups. Peak PK samples could not be determined for 2 subjects due to processing errors (sample hemolysis and insufficient plasma volume).

Hemodynamic effect

Sildenafil effect on hemodynamic parameters is shown in Table 2. There was no significant dose-response effect so data were pooled for assessment of hemodynamic parameters. Sildenafil lowered PA pressures (−9%, $p=0.03$), transpulmonary gradient (−23%, $p<0.01$), and PVRI (−24%, $p<0.01$). PVRI was lowered in 12/12 subjects. Linear regression demonstrated a greater change in PVRI in those with higher baseline PVRI ($p<0.01$) (Figure 1) but no difference in response based on peak sildenafil ($p=0.4$) or des-methyl sildenafil levels ($p=0.2$). Although there was no overall effect on calculated pulmonary blood flow (Qp) or saturations, a subgroup analysis of subjects with elevated baseline PVRI (≥2 WU x m^2) (n=7) demonstrated increase in Qp (median change +8%, range 0–20%, $p=0.04$) and improved saturations in 6/7 subjects (median absolute change +2%, range 0–16%, $p=0.04$). Patients with higher baseline PVRI and those with the greatest change in PVRI experienced the most meaningful improvements in saturations ($r^2=0.84$, $p<0.01$ for correlation with baseline PVRI; $r^2=0.74$, $p<0.01$ for correlation with change in PVRI) (Figure 2).

Sildenafil affected systemic hemodynamics by lowering systemic mean (−12%, $p=0.04$) and diastolic blood pressure (−11%, $p<0.01$). There was a trend towards lowered systolic blood pressure ($p=0.07$) with a noticeable decrease for all 3 subjects in the highest dosing group

(mean change: −11 ± 2 mm Hg). There was no significant change in cardiac index. Sildenafil did not affect echocardiographic measures of systolic function (FAC/EF, strain, strain rate), diastolic function (E:E′ ratio), or global myocardial performance (myocardial performance index). There was also no significant change in these echocardiographic indices when restricting the analysis to the subset of 10 patients with a systemic right ventricle. Sildenafil infusion was well tolerated by all 12 subjects with no adverse events.

DISCUSSION

This is the first prospective study evaluating single-dose sildenafil exposure and hemodynamic efficacy after stage II surgery. Peak drug levels demonstrated significant inter-individual variability and dose non-linearity. Sildenafil improved pulmonary hemodynamics, with lowered PVRI in all 12 subjects and improved oxygen saturation but with a meaningful improvement seen only in those subjects with higher baseline PVRI. Sildenafil did not acutely affect multiple measures of myocardial performance.

Despite anecdotal experience and numerous case reports suggesting increasing sildenafil use in the single-ventricle population, this is the first study to document hemodynamic efficacy in these patients. Pulmonary blood flow in the single-ventricle circulation is phasic rather than pulsatile. Phasic flow may contribute to documented endothelial dysfunction and ultimately elevated pulmonary vascular resistance.[12,18] This pathophysiology is different from shunt-related or idiopathic PA hypertension, and this difference limits extrapolation of hemodynamic efficacy from these populations. Furthermore, patients with single-ventricle physiology require substantially lower PVR than patients with a 2-ventricle circulation. It was previously unclear whether there might be a “floor effect” on the ability of therapeutic agents to lower PVRI. Our data demonstrate that sildenafil effectively lowers PVRI across a wide range of resistances, with responses ranging from 4–38% in patients with baseline PVRI ranging from 1.6–7.9 WU x m^2.

Overall, the clinical impact of sildenafil after stage II palliation is less clear. In the stage II circulation, pulmonary blood flow must first pass through the cerebral circulation. Cerebral vascular resistance is approximately 3–6 times greater than PVRI, and therefore selective pulmonary vasodilator therapy has a less significant effect on total pulmonary blood flow. Prior data on the ability of inhaled nitric oxide to improve pulmonary blood flow in the stage II circulation are conflicting.[19,20] Our data show improved pulmonary blood flow demonstrated by lowered CO2 (no ventilator changes were made during the sildenafil infusion). Using Fick calculations pulmonary blood flow was improved in the subset of subjects with baseline PVRI >2 WU x m^2. Furthermore, improvement in pulmonary blood flow was closely correlated with baseline PVRI and with change in PVRI. These data indicate that PVR manipulation can improve pulmonary blood flow after stage II palliation. However the actual clinical impact is directly related to the severity of pulmonary vascular disease. We saw clinically significant improvement in saturations in those with more markedly elevated baseline PVR. In 1 study patient with a baseline PVRI of 7.9 WU x m^2, a 32% improvement in PVRI was associated with a 16% improvement in saturations. Improvement in saturations was less clinically meaningful in the subset of patients with PVR closer to normal.

It should be noted that in the stage II circulation pulmonary blood flow is related to the interplay between total resistance to pulmonary blood flow (PVR + cerebral vascular resistance) and systemic vascular resistance. Although not statistically significant, we did see a trend towards decreased systemic vascular resistance after sildenafil administration and this may have affected pulmonary blood flow by redistributing flow to the lower extremities. This effect has been well demonstrated with infusion of enalaprilat in stage II subjects.[21]

It should also be noted that these data represent acute response. An unmeasured and theoretical longer term benefit of sildenafil may be the potential for remodeling of the pulmonary vascular bed. Remodeling has been demonstrated in animal models where sildenafil has been shown to attenuate pulmonary hypertension induced muscularization of the pulmonary arteries.[22]

Although the effect on pulmonary hemodynamics was beneficial, the present study did not demonstrate any evidence of improvement in myocardial performance. There is mounting evidence to suggest that sildenafil may be a useful therapeutic agent in patients with cardiac myopathy.[10] This novel application arises from data indicating increased PDE-5 expression in the hypertrophied or myopathic myocardium, including 1 study with autopsy evidence from a single-ventricle patient.[11] Animal data suggest that PDE-5 inhibition in the hypertrophied myocardium potentiates cyclic adenosine monophosphate activity, resulting in a direct inotropic benefit. PDE-5 inhibition has been shown to improve systolic and diastolic performance, cardiac output, and exertional tolerance. Several recent studies have demonstrated improved exercise parameters in single-ventricle patients after stage III palliation, and Goldberg et al. documented improvement in the myocardial performance index after 3-week sildenafil treatment.[23,24] The lack of response in the present study might reflect differences in myocardial pathology in younger children prior to stage III palliation. It is also possible that improved performance is time-dependent and requires myocardial remodeling.

In the present study, peak sildenafil levels were seen immediately after infusion completion (~25 minutes after start of infusion). Compared with in vitro data, peak levels were above the threshold needed for 77% PDE-5 inhibition in 8/10 subjects with measured levels and 90% inhibition for 4/5 subjects with doses ≥0.35 mg/kg.[25] For the range of doses studied (0.125–0.35 mg/kg), peak levels correspond to published levels seen in adults with doses of 10–25 mg IV administered over 5–25 minutes.[26,27] This is likely due to the linear relationship between drug volume of distribution and body weight.

Des-methyl sildenafil is the active metabolite of sildenafil and has an *in-vitro* potency for the PDE-5 receptor of approximately 50% of the parent drug. In our subjects the ratio of des-methyl sildenafil to sildenafil was similar to the approximate 15–20% ratio reported in adults after infusion. Therefore des-methyl sildenafil accounts for approximately 7–10% of overall PDE-5 inhibition.[25–27]

Our exposure analysis is based on a small sample size. Similar to prior analyses in adults and neonates, there was high inter-individual variability in peak sildenafil and des-methyl sildenafil levels. For these reasons further study is needed to more accurately define the most appropriate dosing range in this patient population. To this end, these pharmacokinetic data are being combined with data from other single ventricle patients to build an integrated population pharmacokinetic model.

Overall, sildenafil was well tolerated in this small cohort of patients with no reported adverse events. Although there was transient blood pressure lowering in the highest dosing group, no subject demonstrated clinically significant lowering or met pre-specified criteria for slowing or stopping of sildenafil infusion. All subjects demonstrated rapid recovery (<5 minutes after infusion completion) of blood pressure to pre-infusion levels. Generally, sildenafil is considered to have a wide acute safety margin. In adults, peak sildenafil concentrations up to1800 ng/mL have been well tolerated.[28] Transient blood pressure lowering has been described in neonates with rapid infusions (<5 minutes) and in children receiving higher infusion doses (0.66 mg/kg) after cardiopulmonary bypass.[29,30]

Although sildenafil is acutely well tolerated, recent data from the STARTS trial have raised concerns regarding long-term, high-dose therapy. In the STARTS trial, children with pulmonary arterial hypertension randomized to moderate- or high-dose sildenafil therapy (40 mg or 80 mg orally 3 times daily) demonstrated increased 3-year mortality when compared with lower dosing regimens.[27] The STARTS trial also did not meet its primary efficacy end point.[15] These data led to a recent U.S. Food and Drug Administration safety advisory recommending “against sildenafil treatment for pulmonary arterial hypertension in children.”[31] It should be noted that the European Medicines Agency also reviewed the STARTS data but determined that “the data support the use of sildenafil in children.”[32] The uncertainties stemming from these discrepant recommendations highlight the importance of population-specific studies such as the present study to evaluate potential efficacy and to optimize dosing for future larger-scale clinical trials.

There are several limitations to the present study. The study was an open-label study and did not use a placebo group. The open-label design was necessary to allow dose escalation in the safest manner possible, and we chose not to use a placebo group as there is inherent difficulty recruiting adequate patients for an interventional study of this nature. Although study investigators were not blinded, most of the outcome measures were relatively objective with little room for interpretability. The echocardiographic measures are the exception as these measures are subjective. While echocardiographic interpretations were performed remotely and the interpreting physicians did not specifically know the treatment, they did have access to the study time and, with effort, could have determined treatment level. However bias in interpretation would more likely result in a positive study and our echocardiographic results were negative suggesting that the readers were unbiased. There are also inherent difficulties involved in estimating pulmonary and systemic blood flow in the complex stage II circulation and these difficulties will affect calculation of resistance indices. For these reasons the absolute numbers are less important than the relative values. Saturation and pressure data were always recorded from the same location before and after sildenafil administration to ensure that changes represent true change rather than sampling error. While there is also likely error when estimating oxygen consumption, every subject served as his or her own control. Any error in calculations would be present at baseline and after therapy and therefore would not affect assessment of response. The echocardiographic measures are limited by echocardiographic windows, especially in patients with previous sternotomy, and by the limited validation data in complex single-ventricle populations. Additionally, all validated non-invasive measurements of cardiac function or myocardial performance may be affected by loading conditions. Therefore, to limit subjectivity, we relied on 2 independent physicians to perform all echocardiographic measurements. The inter-rater reliability was relatively good; however, there is some inherent subjectivity for all widely reported echocardiographic measures of myocardial performance.

CONCLUSIONS

After stage II single-ventricle palliation in this small cohort of patients, single-dose sildenafil meaningfully lowered PVR, PA pressure, and trans-pulmonary gradient. Sildenafil also lowered mean and diastolic blood pressure with a trend towards lowered systolic blood pressure. Contrary to reports in older single ventricle patients with longer term administration, sildenafil did not acutely improve myocardial performance or increase cardiac output. Although there was no overall improvement in systemic saturation, there was incremental benefit in those with higher baseline PVR with evidence of a clinically meaningful effect in those with elevated baseline PVRI. Doses ≥0.35 mg/kg corresponded to peak drug concentrations seen with standard- to high-dose ranges used in adults (10–25 mg IV). Based on these limited data we would not advocate for routine use of sildenafil after stage II palliation as there was no overall improvement in myocardial performance, cardiac

index or saturations in our population. However sildenafil may be beneficial in those with high PVRI and associated desaturation. Sildenafil may be of greater benefit after stage III palliation when the physiologic response is less confounded by the inter-relationship between relative pulmonary to systemic flow ratios and is also less influenced by cerebral vascular resistance. However, hepatic dysfunction in these patients may delay drug clearance and could affect long-term safety.

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References

1. O'Leary P. Prevalence, clinical presentation and natural history of patients with single ventricle. Prog Pediatr Cardiol. 2002; 16:31–8.
2. Gentles TL, Gauvreau K, Mayer JE Jr, et al. Functional outcome after the Fontan operation: factors influencing late morbidity. J Thorac Cardiovasc Surg. 1997; 114:392–403. discussion 4–5. [PubMed: 9305191]
3. Gersony WM. Fontan operation after 3 decades: what we have learned. Circulation. 2008; 117:13–5. [PubMed: 18172049]
4. Ohye RG, Sleeper LA, Mahony L, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med. 2010; 362:1980–92. [PubMed: 20505177]
5. Fixler DE, Nembhard WN, Salemi JL, et al. Mortality in first 5 years in infants with functional single ventricle born in Texas, 1996 to 2003. Circulation. 2010; 121:644–50. [PubMed: 20100974]
6. Khairy P, Fernandes SM, Mayer JE Jr, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008; 117:85–92. [PubMed: 18071068]
7. Hosein RB, Clarke AJ, McGuirk SP, et al. Factors influencing early and late outcome following the Fontan procedure in the current era. The 'Two Commandments'? Eur J Cardiothorac Surg. 2007; 31:344–52. discussion 53. [PubMed: 17236782]
8. Boolell M, Allen MJ, Ballard SA, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res. 1996; 8:47–52. [PubMed: 8858389]
9. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. N Engl J Med. 2009; 361:1864–71. [PubMed: 19890129]
10. Schwartz BG, Levine LA, Comstock G, et al. Cardiac uses of phosphodiesterase-5 inhibitors. J Am Coll Cardiol. 2012; 59:9–15. [PubMed: 22192662]
11. Nagendran J, Archer SL, Soliman D, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation. 2007; 116:238–48. [PubMed: 17606845]
12. Beghetti M. Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies. Heart. 2010; 96:911–6. [PubMed: 20538665]
13. Goldberg DJ, Shaddy RE, Ravishankar C, et al. The failing Fontan: etiology, diagnosis and management. Expert Rev Cardiovasc Ther. 2011; 9:785–93. [PubMed: 21714609]
14. Reinhardt Z, Uzun O, Bhole V, et al. Sildenafil in the management of the failing Fontan circulation. Cardiol Young. 2010; 20:522–5. [PubMed: 20519058]
15. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012; 125:324–34. [PubMed: 22128226]
16. Goldberg DJ, French B, Szwast AL, et al. Impact of sildenafil on echocardiographic indices of myocardial performance after the Fontan operation. Pediatr Cardiol. 2012; 33:689–96. [PubMed: 22331056]

17. Tei C, Nishimura RA, Seward JB, et al. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr. 1997; 10:169–78. [PubMed: 9083973]
18. Mahle WT, Todd K, Fyfe DA. Endothelial function following the Fontan operation. Am J Cardiol. 2003; 91:1286–8. [PubMed: 12745126]
19. Adatia I, Atz AM, Wessel DL. Inhaled nitric oxide does not improve systemic oxygenation after bidirectional superior cavopulmonary anastomosis. J Thorac Cardiovasc Surg. 2005; 129:217–9. [PubMed: 15632849]
20. Agarwal HS, Churchwell KB, Doyle TP, et al. Inhaled nitric oxide use in bidirectional Glenn anastomosis for elevated Glenn pressures. Ann Thorac Surg. 2006; 81:1429–34. [PubMed: 16564287]
21. Lee KJ, Yoo SJ, Holtby H, et al. Acute effects of the ACE inhibitor enalaprilat on the pulmonary, cerebral and systemic blood flow and resistance after the bidirectional cavopulmonary connection. Heart. 97:1343–8. [PubMed: 21646245]
22. Zhao L, Mason NA, Morrell NW, et al. Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation. 2001; 104:424–8. [PubMed: 11468204]
23. Goldberg DJ, French B, McBride MG, et al. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation. 2011; 123:1185–93. [PubMed: 21382896]
24. Goldberg DJ, French B, Szwast AL, et al. Impact of sildenafil on echocardiographic indices of myocardial performance after the fontan operation. Pediatr Cardiol. 2012; 33:689–96. [PubMed: 22331056]
25. Walker DK, Ackland MJ, James GC, et al. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. Xenobiotica. 1999; 29:297–310. [PubMed: 10219969]
26. Muirhead GJ, Rance DJ, Walker DK, et al. Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil. Br J Clin Pharmacol. 2002; 53 (Suppl 1):13S–20S. [PubMed: 11879255]
27. Vachiery JL, Huez S, Gillies H, et al. Safety, tolerability, and pharmacokinetics of an intravenous bolus of sildenafil in patients with pulmonary arterial hypertension. Br J Clin Pharmacol. 2011; 71:289–92. [PubMed: 21219411]
28. Jackson G, Benjamin N, Jackson N, et al. Effects of sildenafil citrate on human hemodynamics. Am J Cardiol. 1999; 83:13C–20C.
29. Schulze-Neick I, Hartenstein P, Li J, et al. Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. Circulation. 2003; 108(Suppl 1):II167–73. [PubMed: 12970227]
30. Steinhorn RH, Kinsella JP, Pierce C, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. J Pediatr. 2009; 155:841–7. [PubMed: 19836028]
31. U.S. Food and Drug Administration. [Accessed November 13, 2012] Medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Amendments Act of 2012 (FDASIA). Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
32. European Medicines Agency. [Accessed November 13, 2012] Science Medicines Health Assessment report for Revatio. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000638/WC500107804.pdf

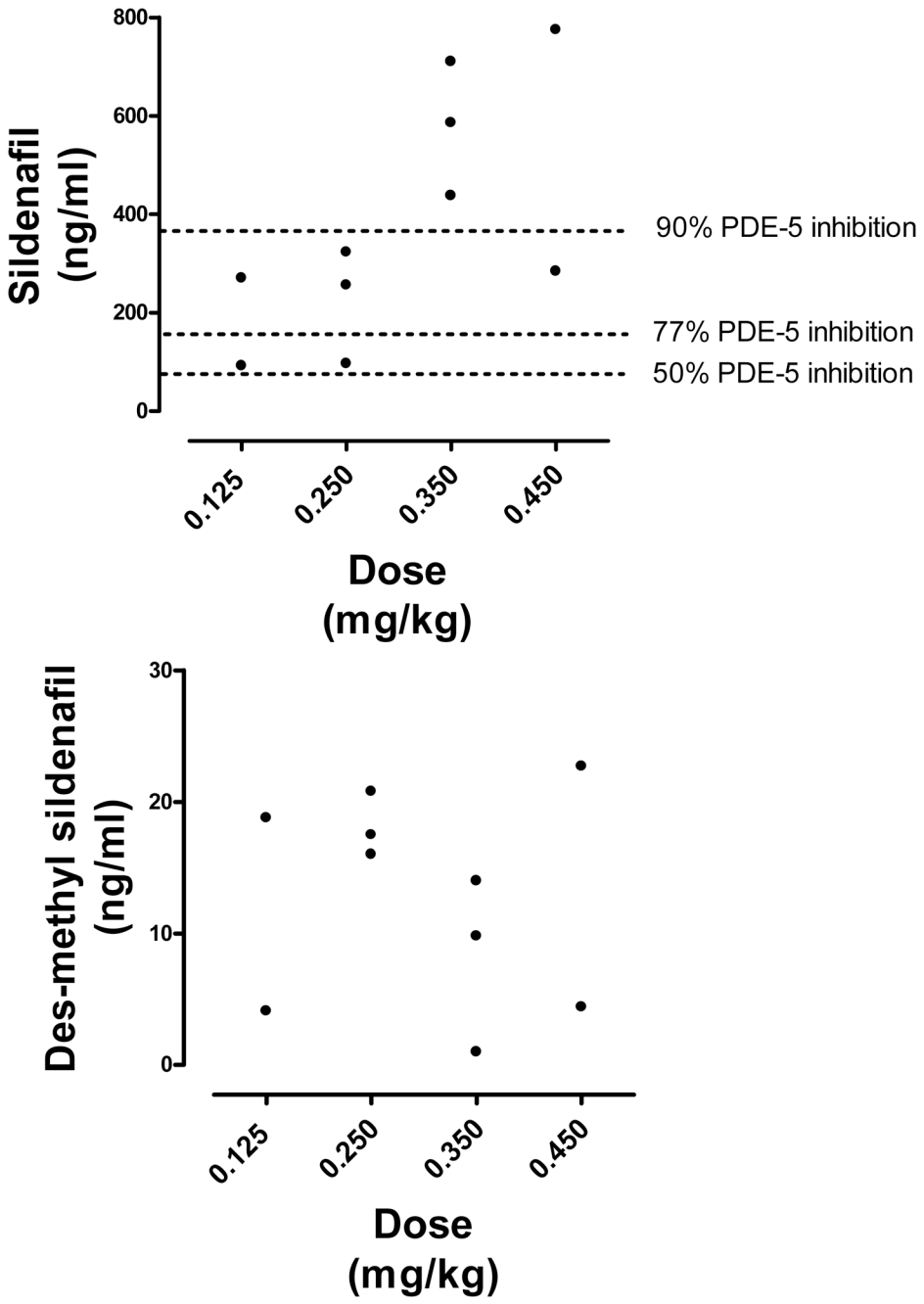

Figure 1.
Peak des-methyl sildenafil and sildenafil levels by dosing group. Two patients (dose = 0.125 mg/kg and 0.450 mg/kg) were not included due to inadequate sample for processing. Estimates of % PDE-5 inhibition are based on previously published in vitro data.[23] PDE-5, phosphodiesterase type-5.

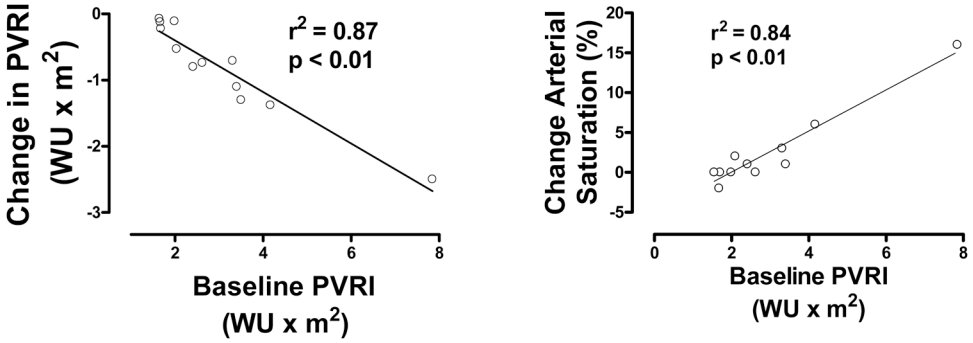

Figure 2.
Subjects with higher baseline PVRI demonstrated more significant improvement in PVRI and saturations. PVRI, pulmonary vascular resistance index; WU, Wood units.

Table 1

Demographics and baseline hemodynamics

Age (months)	Weight (kg)	Diagnosis	Mean PAp (mm Hg)	PCWP (mm Hg)	PVRI (WUxm^2)	O2 Sat (%)
8	8.0	HLHS	20	9	7.9	59
10	9.8	HLHS	15	7	3.4	81
14	9.5	HLHS	10	4	2.6	88
18	11.5	HLHS	11	5	1.9	87
20	10.4	HLHS	16	9	2.1	89
20	10.8	TA	11	6	2.4	85
26	11.4	AVSD-L	9	5	1.6	85
27	11.7	AVSD-R	19	12	4.2	72
39	12.8	HLHS	10	4	1.7	88
40	12.1	HLHS	13	7	1.7	83
41	13.2	HLHS	11	5	3.3	78
48	10.8	HLHS	11	5	1.7	80
1.9 (0.8–4.0)	11.1 (8.0–13.2)	NA	11 (9–20)	5.5 (4–12)	2.2 (1.6–7.9)	84 (59–89)

Summary statistics represent median (range).

Pap, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; O2 sat, oxygen saturation; HLHS, Hypoplastic Left Heart Syndrome; TA, Tricuspid Atresia; AVSD-L, Unbalanced Atrioventricular Septal Defect with left dominance; AVSD-R, Unbalanced Atrioventricular Septal Defect with right dominance

Table 2

Sildenafil effect on hemodynamics (n=12)

	Baseline median (range)	Sildenafil median (range)	p
Co-oximetry			
CO2 (%)	43 (38,52)	41 (35,51)	0.04
SaO2 (%)	84 (59,89)	84 (75,90)	0.08
AVO2 difference (%)	15 (7,26)	19 (11,23)	0.3
Pressures			
PA pressure (mm Hg)	12 (9,20)	11 (8,21)	0.03
Atrial pressure (mm Hg)	6 (4,12)	7 (3,12)	0.12
Trans-pulmonary gradient (mm Hg)	6 (4,11)	5 (3,9)	<0.01
End diastolic pressure (mm Hg)	8 (5,10)	7 (4,10)	0.2
Systolic BP (mm Hg)	78 (70,98)	73 (65,98)	0.07
Diastolic BP (mm Hg)	46 (38,58)	40 (39,50)	<0.01
Mean BP (mm Hg)	61 (54,82)	58 (50,70)	0.04
Calculations			
Qp (L/min/m^2)	2.4 (1.4,3.6)	2.5 (1.7,3.7)	0.3
Qs (L/min/m^2)	4.4 (2.2,7.4)	4.4 (3.4,6.9)	0.9
Qp:Qs	0.6 (0.2,0.7)	0.6 (0.4,0.7)	0.7
PVRI (WU x m^2)	2.2 (1.6,7.9)	1.7 (1.2,5.4)	<0.01
SVRI (WU x m^2)	12 (8,19)	10 (8,18)	0.09
Echocardiographic assessment			
Systolic function (FAC)	38 (23,49)	38.5 (24,55)	0.3
Diastolic function (E: E′)	11 (6,17)	9 (5,18)	0.6
Strain (%)	−14 (−20, −5)	−14 (−22,−7)	0.9
Strain rate (sec^{-1})	−0.8 (−1.3,−4.4)	−0.9 (−1.4,−0.5)	0.2
Global function (MPI)	0.4 (0.2,0.5)	0.4 (0.2,0.7)	0.4

* Percent values represent the median percent change from baseline.

SaO2, percent oxygen saturation of hemoglobin; AVO2, difference between systemic and mixed venous saturation; PA, pulmonary arterial; BP, blood pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index; FAC, fractional area change; E:E′, atrioventricular valve E wave to tissue Doppler E′ wave; MPI, myocardial performance index.