Published in final edited form as:

Pediatr Cardiol. 2016 January ; 37(1): 184–191. doi:10.1007/s00246-015-1262-x.

Effect of Sildenafil on Pressure–Volume Loop Measures of Ventricular Function in Fontan Patients

Ryan J. Butts¹, Shahryar M. Chowdhury¹, George H. Baker¹, Varsha Bandisode¹, Andrew J. Savage¹, and Andrew M. Atz¹

¹Division of Cardiology, Department of Pediatrics, Medical University of South Carolina, 165 Ashley Avenue, MSC 915, Charleston, SC 29425, USA

Abstract

Sildenafil has been reported to improve exercise capacity in Fontan patients, but the physiologic mechanisms behind these findings are not completely understood. The objective of this study was to study the acute effect of sildenafil on pressure–volume loop (PVL) measures of ventricular function in Fontan patients. Patients after Fontan operation who were presenting for a clinically indicated catheterization were enrolled. Patients were randomized in a double-blinded fashion to receive placebo ($n = 9$) or sildenafil ($n = 10$) 30–90 min prior to catheterization. PVLs were recorded using microconductance catheters at baseline and after infusion of dobutamine (10 mcg/kg/min). The primary outcome was change in ventriculoarterial (VA) coupling. For the entire cohort, VA coupling trended toward improvement with dobutamine (1.4 ± 0.4 to 1.8 ± 0.9 , $p = 0.07$). End-systolic elastance showed improvement (2.6 ± 0.9 to 3.8 ± 1.4 mmHg m²/ml, $p < 0.01$) with dobutamine infusion. The cohorts had similar VA coupling at baseline ($p = 0.32$), but the sildenafil cohort trended toward having less of an improvement in VA coupling with dobutamine stress ($p = 0.06$). There were no differences between PVL measures of systolic or diastolic function between treatment groups, both at baseline and after dobutamine infusion. Patients with Fontan circulation had improved contractility and trended toward improvement in VA coupling with dobutamine stress. Acute sildenafil administration was not associated with improved PVL measurements of ventricular function in this population. These results suggest that clinical improvements seen with administration of sildenafil in Fontan patients are not associated with an acute improvement in ventricular function.

Keywords

Single-ventricle heart disease; Pressure–volume loop; Sildenafil; Fontan

Ryan J. Butts, butts@musc.edu.

Compliance with Ethical Standards

Conflict of interest No authors have relevant conflicts of interest to report.

Clinical Trial Registration: www.clinicaltrials.gov; Clinicaltrials.gov Identifier: NCT01815502.

Introduction

Modifications to surgical procedures and medical treatment have led to a rapidly declining mortality rates in patients with single-ventricle heart disease (SV) [9, 17]. However, SV patients still suffer from lower quality of life, decreased exercise capacity, worse neurodevelopmental outcomes and many other morbidities [1, 2, 9, 13, 20, 21, 25, 35]. While patients with SV circulation only make a small portion of all congenital heart diseases, 2–4 %, they require a great deal of resource utilization [9, 12, 24, 30].

Standard medical treatments for adult heart failure have not had the same success in the SV population [32]. Phosphodiesterase 5 (PDE5) inhibitors have recently become a frequently used medication class in patients with SV heart disease to treat pulmonary hypertension, heart failure, as well as “Fontan” failure (i.e., plastic bronchitis and protein-losing enteropathy) [10, 15, 16, 22, 23, 28, 36]. While there have been findings of improved measures of exercise capacity and some reports of improved symptoms of heart failure, the physiologic mechanisms behind these findings are not completely understood [7, 15, 23, 28]. There have been reports, indicating that the phosphodiesterase five inhibitors improve ventricular function in biventricular circulation patients and animal models [5, 18,19]. The aim of our study was to investigate the effect of acute PDE5 inhibition on ventricular function in SV patients after the final palliative surgery, the Fontan procedure.

Methods

Patients

Patients presenting for clinically indicated catheterization were screened for enrollment. Inclusion criteria included a previously performed Fontan procedure, age 3–40 years and informed consent. Exclusion criteria were as follows: the use of PDE5 inhibitor within 1 month of catheterization; hemodynamically significant arrhythmia within 2 months of catheterization; venous, arterial or cardiac malformation that would preclude the proper placement of a microconductance catheter; allergy or previous significant adverse reaction to sildenafil or other PDE5 inhibitors.

Informed Consent

The protocol was approved by the Medical University of South Carolina institutional review board. Informed consent was obtained from the parent or legal guardian (age < 18 years) or from the patient (age ≥ 18). Assent was obtained for all patients between ages 12–17 years. ([Clinicaltrials.gov](https://clinicaltrials.gov) Identifier: NCT01815502).

Pressure–Volume Loop Data

Pressure–volume loops (PVLs) were obtained through direct measurement using four French microconductance catheters (CD Leycom®, Zoetermeer, Netherlands). For patients with a patent Fontan to atrial communication, microconductance catheters were placed in the ventricle via an antegrade approach. A five-French transseptal sheath was used to stabilize the catheter. For patients without a patent Fontan to atrial communication, a microconductance catheter was placed into the single ventricle using a retrograde approach.

PVLs were obtained under general anesthesia during an expiratory breath hold. Careful attention was given to place the catheter in the center of the ventricle and eliminate volume segments outside of the ventricle in the analysis.

Pressure–volume loop analysis was performed offline using specialized software (LabScribe2[®], iWorx, Dover, NH). PVLs were volume calibrated using the parallel conductance technique. In short, each patient underwent 3 injections of 5 % hypertonic saline (10 cc/injection) into the Fontan circuit. Cardiac output was measured calculated using the Fick equation using directly measured oxygen consumption (Ultima[™] metabolic cart, MGC Diagnostics, Saint Paul, MN). Volume calibration was performed both at baseline and after dobutamine stress. All PVLs were assessed by a single-blinded reviewer (RB).

Systolic PVL indices included end-systolic elastance (Ees), stroke work (SW), maximum rate of pressure change ($dP/dT_{\max}$) and ejection fraction (EF). Ees was calculated using a previously described and validated single-beat technique [33]. Stroke work was defined as the area encompassed by the PVL. Arterial elastance (EA) was defined as end-systolic pressure divided by stroke volume. Ventricular–arterial (VA) coupling was determined by the ratio of Ees to EA. Diastolic PVL indices included isovolumic relaxation time constant (Tau), rate of ventricular filling, and maximal rate of pressure decline ($dP/dT_{\min}$). Rate of ventricular filling was defined as the difference between end-systolic volume and end-diastolic volume divided by the diastolic filling time. To account for significant differences in size of patients, indices that incorporated stroke volume in their derivation (Ees, EA, SW and filling rate) were indexed to body surface area.

Dobutamine and Study Drug Administration

After baseline PVLs were recorded, each patient received an infusion of dobutamine at 10 mcg/kg/min for 10 min or until heart rate reached a steady state. At the end of the dobutamine infusion, repeat PVLs were recorded.

Patients were 1:1 randomized to a single dose of 1 mg/kg of sildenafil (max dose of 20 mg) or placebo 30–90 min prior to beginning of catheterization. Timing of the study drug dosing was based upon maximizing the hemodynamic effects of sildenafil based upon known pharmacokinetics [37]. Study drug was dispensed through our institution's research pharmacy. All investigators except the research pharmacist remained blinded to study assignment until all subjects were enrolled and PVL analyses completed.

Sample Size Estimation and Statistical Analysis

The study was designed so that the selected sample size would provide 80 % power to detect between-group differences in VA coupling, assuming 2-sided hypothesis testing and an alpha level of 0.05. Using previously reported study that assessed the effect of oral sildenafil on the noninvasively measured ventriculoarterial coupling in patients with Fontan circulation, the study was powered to detect a 25 % improvement in VA coupling with sildenafil [31]. With these assumptions, the number needed to enroll in each treatment group was nine.

Comparison between baseline PVL measurements in the treatment groups was performed using Wilcoxon rank sum test. To investigate the change in PVL measurements after administration of dobutamine, a general linear model was constructed. The dependent variable was change in the PVL measurement. The primary independent variables were study drug (placebo vs. sildenafil) and baseline PVL measurement served as a covariate in the model. Therefore, treatment group's (sildenafil vs. placebo) association with change in PVL measurement was investigated while controlling for PVL measurement at rest. All continuous variables were log transformed prior to model construction in order to obtain normally distributed residual errors. Set significance level was p value of <0.05 . All statistics were performed using IBM SPSS® v.21 (Armonk, NY).

Results

Patient Characteristics

Twenty-seven consecutive subjects meeting all eligibility requirements and scheduled for clinically indicated catheterization were approached for participation; 20 consented (74 %). Nineteen of 20 (95 %) consented subjects completed the study protocol. One patient had technical issues during baseline PVL acquisition that made study data not analyzable and therefore did not receive dobutamine. Median age for the cohort was 8 years (IQR 4, 17 years) with a median weight of 22.7 kg (IQR 16, 59 kg). Of the 19 patients, 13 (68 %) had a dominant right ventricle and 6 (32 %) were female. The entire cohort had a median EF of 59.7 % (IQR 47.4, 63 %) and median end-diastolic volume of 82 ml/m² (IQR 62, 101 ml/m²). As given in Table 1, there were no differences between treatment groups in terms of age, weight, BSA, gender, ejection fraction, end-diastolic volume or dominant ventricle morphology. The indication for catheterization was possible fenestration closure in 14, lower saturations in 2, combined hemodynamic and electrophysiological study in 2 and hemodynamic assessment only in 1.

Response to Dobutamine

Nineteen patients completed the study as designed in the protocol. None of the 19 patients that received dobutamine had an adverse event related to dobutamine. Specifically, no patients had a tachyarrhythmia or significant hypo or hypertension. All 19 patients had dobutamine infused at 10mcg/kg/min for at least 10 min or until a new baseline heart rate was obtained. The median heart rate prior to dobutamine was 89 bpm (IQR 67, 93 bpm) and increased to 120 bpm (IQR 100, 139 bpm) ($p < 0.01$), an increase of 43 % (Fig. 1). During dobutamine stress, EF increased by 13 % (95 % CI 8, 19, $p < 0.01$). However, end-diastolic volume did not change significantly with a mean decrease of 7.6 ml/m² (95 % CI -2.1, 17.3 ml/m², $p = 0.12$).

PVL indices at baseline and after dobutamine infusion can be found in Fig. 2. Measures of systolic function increased from baseline after dobutamine infusion. Ees increased from 2.6 ± 0.9 mmHg m²/ml prior to dobutamine to 3.8 ± 1.4 mmHg m²/ml at the end of dobutamine infusion ($p < 0.01$; Fig. 3). Stroke work almost doubled from 0.38 ± 0.14 to 0.67 ± 0.28 J/m² ($p < 0.01$) after dobutamine infusion, and $dP/dT_{\max}$ increased from 1022 ± 257 to 2769 ± 911 mmHg/ms ($p < 0.01$). Despite the improvement in systolic indices, EA showed a trend

toward worsening, from baseline of 2.1 ± 0.9 to 2.5 ± 1.2 mmHg m²/ml after dobutamine infusion ($p = 0.07$). There was a trend toward improved VA coupling after dobutamine infusion (1.4 ± 0.4 to 1.8 ± 0.9 , $p = 0.07$).

Indices of diastolic function showed improvement after dobutamine infusion for the entire cohort. The $dP/dT_{\min}$ improved from -1435 ± 348 to -2237 ± 641 mmHg/ms ($p < 0.01$), and Tau went from 35 ± 6.5 to 25 ± 4.8 ms with dobutamine infusion ($p < 0.01$). Filling rate of the single ventricle was faster after dobutamine compared to baseline (0.13 ± 0.05 vs. 0.20 ± 0.07 ml m²/ms, $p < 0.01$).

Comparison of Sildenafil Versus Placebo

Study drug was given within 30–90 min of starting catheterization for all 20 enrolled patients. The indication for catheterization did not differ between treatment groups, both groups had seven patients who presented for possible fenestration closure, and both had one patient for combined electrophysiological and hemodynamic catheterization. No patients had an adverse event related to study drug. Median arterial saturation for the placebo cohort was 89 % (IQR 88–95), which did not differ from the sildenafil cohort, median 91 % (IQR 85–95, $p = 1.0$). Treatment groups did not differ in end-diastolic pressure ($p = 0.86$), Fontan pressure ($p = 1.0$) or pulmonary vascular resistance indexed to body surface area ($p = 0.61$).

There were no differences in baseline PVL measures of systolic, diastolic indices or VA coupling between treatment groups (Table 2). To explore associations between treatment group and changes in PVL measurements after dobutamine infusion, a generalized linear model was employed. Table 3 summarizes the changes in each treatment arm.

When investigating changes in VA coupling with dobutamine infusion, the sildenafil arm of the study had a smaller improvement (Table 3). However, in the general linear model, an association between change in VA coupling and treatment group did not reach statistical significance ($R^2 = 0.33$, $\beta = 0.39$, $p = 0.06$). Changes in EA were similar between treatment groups (Table 3), and change in EA was not associated with treatment group in the general linear model ($R^2 = 0.32$, $\beta = -0.3$, $p = 0.14$).

Changes in Ees were negatively associated with baseline Ees ($R^2 = 0.42$, $\beta = -0.73$, $p < 0.01$), demonstrating that patients with the largest change in Ees with dobutamine were those with lower Ees at baseline. In the general linear model, treatment group was not statistically associated with change in Ees ($\beta = 0.16$, $p = 0.32$). Similarly, changes in $dP/dT_{\max}$ and SW were not associated with treatment arm ($p = 0.10$, $p = 0.57$, respectively, Table 3). There was no difference in improvements in EF between treatment groups; median change in sildenafil arm was 8 % (3–15 %) versus 14 % (6–24 %) in the placebo group, $p = 0.30$. Therefore, for systolic indices, treatment group was not associated with response to dobutamine.

For diastolic function, the median change in filling rate for the sildenafil arm was 0.04 (0.01, 0.08) versus 0.08 (0.06, 0.14) ml m²/ms for placebo. This difference did not reach statistical significance ($R^2 = 0.11$, $\beta = 0.23$, $p = 0.20$). Tau improved similarly between treatment arms (Table 3), and in the general linear model treatment group was not associated with change in tau ($R^2 = 0.21$, $\beta = -0.03$, $p = 0.73$). The placebo group trended toward having a greater

change in $dP/dT_{\min}$, median change of 953 (654, 1482) mmHg/ms versus a change of 499 (367, 899) mmHg/ms. However, this trend was not statistically significant ($R^2 = 0.19$, $\beta = 0.18$, $p = 0.08$).

Discussion

Despite a lack of physiologic mechanistic information, there has been increasing use of PDE5 inhibitors in children with single-ventricle physiology given their perceived impact on pulmonary vascular resistance and ventricular performance. This is the first study to systematically and invasively assess the effect of PDE5 inhibition, as well as the response to dobutamine stress, in Fontan patients using PVL analysis. PVLs are the gold standard method to assess ventricular mechanics as distinct phases of the cardiac cycle can be studied in great detail. Microconductance catheters allow for simultaneous high-fidelity acquisition of both pressure, through a micromanometer, and volume, through conductance technology. The PVL analyses performed in this study produced three significant findings. First, there were improvements in diastolic and systolic PVL measurements with dobutamine stress in Fontan patients. Second, afterload, measured by EA, trended toward worsening with dobutamine infusion. Finally, both treatment groups (sildenafil vs. placebo) had similar PVL measurements at baseline and change in PVL measurements during dobutamine infusion.

There have been multiple reports demonstrating improvement in exercise capacity with PDE5 inhibition in Fontan patients [14, 15]. However, our results suggest that the observed improvements in exercise with sildenafil are not from improved cardiac function. Possible explanations for improvement in exercise function after sildenafil include improved O_2 delivery to skeletal muscle or improved lung function. Sperandio et al. [34] demonstrated an improvement in oxygen delivery at the microvascular level after sildenafil administration in chronic adult heart failure patients. Fontan patients and adult heart failure patients have elevated central venous pressure, and therefore, this effect of sildenafil may occur in Fontan patients. Also, sildenafil has been demonstrated to improve pulmonary mechanics and gas diffusion in chronic heart failure; this may be particularly important in Fontan patients who have a high incidence of restrictive lung disease [6,11]. The etiology of improved exercise tolerance in the Fontan population after sildenafil administration remains unclear and warrants further investigation.

Dobutamine is a well-studied beta agonist, and its inotropic and lusitropic effects have been previously described in biventricular circulation [8]. Our study found similar results with improved Ees, $dP/dT_{\max}$, SW and EF with dobutamine stress. Diastolic function also improved with dobutamine infusion evidenced by improved diastolic filling rate, Tau and $dP/dT_{\min}$. Therefore, Fontan patients have the ability to improve systolic and diastolic function during stress. Fontan patients' improvement in ventricular function with dobutamine stress should be compared to age-matched normal controls to see whether the response to dobutamine is similar. Difference between groups will likely lead to a better understanding the ventricular mechanics that lead to heart failure in Fontans.

Dobutamine is known to improve VA coupling in normal subjects by improving Ees and decreasing EA [26]. However, our results show that possible improvements in VA coupling

from improved Ees were mitigated by an increase in EA. Only 4/19 (21 %) of patients had a decrease in EA with dobutamine stress. A recent study of adult heart failure observed the same phenomenon, where approximately 50 % of adult patients with dilated cardiomyopathy had increasing EA with dobutamine stress [26]. Dobutamine typically decreases afterload, and therefore EA, by arteriolar vasodilation and venodilation [3]. However, in studies of heart failure these vascular responses to dobutamine can be impaired and lead to venoconstriction [27, 38]. Given that Fontan patients have increased venous thickening, chronically elevated central venous pressure and altered endothelial function, it is likely that they would have abnormal venous responses to dobutamine stress [4, 29].

The study protocol was well tolerated by all patients. No patients had an adverse event with study drug (placebo vs. sildenafil) or dobutamine infusion. Only one patient had PVLs that were not able to be analyzed. PVLs are well suited for assessing ventricular function in SV patients as there are no geometric assumptions in PVL indices of ventricular function. Therefore, PVL analysis obtained by microconductance catheters with dobutamine infusion can be an appropriate and effective method of investigating ventricular mechanics in patients with SV physiology.

Limitations

The study was designed to test the effect of an acute effect of PDE5 inhibition on ventricular mechanics in Fontan patients. This study did not investigate the effects of chronic PDE5 inhibition on ventricular function. Chronic PDE5 inhibition could lead to improved ventricular mechanics. In addition, chronic PDE5 inhibition may lead to improvements in cardiac, pulmonary or skeletal muscle function that cannot be measured by PVLs and therefore may very well provide a clinical benefit in this population not evaluated in our study. We were unable to perform volume reduction when doing PVL measurements and therefore used previously validated single-beat measurements to estimate Ees.

Conclusion

Patients with Fontan circulation are able to improve systolic and diastolic function with dobutamine stress. The acute administration of sildenafil is not associated with improved ventricular function in Fontan patients.

Acknowledgments

The authors would like to acknowledge Dr. Paul Nietert for his contribution to the statistical analysis.

Funding Sources This work was supported by the American Heart Association Mentored Clinical Research Program Grant 13CRP14780092 (author: R.B. & A.A.). This work was supported in part by the National Center for Advancing Translational Sciences (UL1TR000062). This work was supported by NIH/NHLBI Grant 5T32-HL0771019 (author: S.C.)

References

1. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, Gersony WM, Gallagher D, Geva T, Margossian R, McCrindle BW, Paridon S, Schwartz M, Stylianou M, Williams RV, Clark BJ 3rd. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. *J Am Coll Cardiol*. 2008; 52:85–98. [PubMed: 18598886]

2. Bernstein D, Naftel D, Chin C, Addonizio LJ, Gamberg P, Blume ED, Hsu D, Canter CE, Kirklin JK, Morrow WR. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. *Circulation*. 2006; 114:273–280. [PubMed: 16847155]
3. Binkley PF, Murray KD, Watson KM, Myerowitz PD, Leier CV. Dobutamine increases cardiac output of the total artificial heart. Implications for vascular contribution of inotropic agents to augmented ventricular function. *Circulation*. 1991; 84:1210–1215. [PubMed: 1884450]
4. Binotto MA, Maeda NY, Lopes AA. Altered endothelial function following the Fontan procedure. *Cardiol Young*. 2008; 18:70–74. [PubMed: 18093358]
5. Borgdorff MA, Bartelds B, Dickinson MG, Boersma B, Weij M, Zandvoort A, Sillje HH, Steendijk P, de Vroomen M, Berger RM. Sildenafil enhances systolic adaptation, but does not prevent diastolic dysfunction, in the pressure-loaded right ventricle. *Eur J Heart Fail*. 2012; 14:1067–1074. [PubMed: 22730335]
6. Bussotti M, Montorsi P, Amato M, Magini A, Baldassarre D, Tantardini F, Veglia F, Agostoni P. Sildenafil improves the alveolar-capillary function in heart failure patients. *Int J Cardiol*. 2008; 126:68–72. [PubMed: 17490765]
7. Ciliberti P, Giardini A. Impact of oral chronic administration of sildenafil in children and young adults after the Fontan operation. *Future Cardiol*. 2011; 7:609–612. [PubMed: 21929341]
8. Cucchini F, Bolognesi R, Javernaro A, Zeppellini R, De Domenico R, Visioli O. Do inotropic drugs always induce a positive lusitropic effect? A comparison between k-strophanthidin and dobutamine in patients with coronary artery disease. *Eur Heart J*. 1994; 15:1666–1672. [PubMed: 7698137]
9. Dean PN, Hillman DG, McHugh KE, Gutgesell HP. Inpatient costs and charges for surgical treatment of hypoplastic left heart syndrome. *Pediatrics*. 2011; 128(5):e1181–e1186. [PubMed: 21987703]
10. Fraisse A, Butrous G, Taylor MB, Oakes M, Dilleen M, Wessel DL. Intravenous sildenafil for postoperative pulmonary hypertension in children with congenital heart disease. *Intensive Care Med*. 2011; 37:502–509. [PubMed: 21069290]
11. Fredriksen PM, Therrien J, Veldtman G, Warsi MA, Liu P, Siu S, Williams W, Granton J, Webb G. Lung function and aerobic capacity in adult patients following modified Fontan procedure. *Heart*. 2001; 85:295–299. [PubMed: 11179270]
12. Gajarski RJ, Towbin JA, Garson A Jr. Fontan palliation versus heart transplantation: a comparison of charges. *Am Heart J*. 1996; 131:1169–1174. [PubMed: 8644597]
13. Giardini A, Hager A, Pace Napoleone C, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. *Ann Thorac Surg*. 2008; 85:818–821. [PubMed: 18291148]
14. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J*. 2008; 29:1681–1687. [PubMed: 18534975]
15. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. 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; 123:1185–1193. [PubMed: 21382896]
16. Haseyama K, Satomi G, Yasukochi S, Matsui H, Harada Y, Uchita S. Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 2006; 132:1232–1233. [PubMed: 17059953]
17. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. 2010; 56:1149–1157. [PubMed: 20863956]
18. Loganathan S, Radovits T, Wirotanseng IR, Veres G, Hagl S, Szabo G. Effects of vardenafil, a selective phosphodiesterase-5-inhibitor, on cardiovascular function in a rat model. *BMC Pharmacol*. 2007; 7:1. [PubMed: 17274812]
19. Loganathan S, Radovits T, Korkmaz S, Hirschberg K, Barnucz E, Weymann A, Bomicke T, Arif R, Karck M, Szabo G. Enhancement of myocardial and vascular function after phosphodiesterase-5 inhibition in a rat model. *Thorac Cardiovasc Surg*. 2012; 60:247–254. [PubMed: 22252326]

20. Manlhiot C, Knezevich S, Radojewski E, Cullen-Dean G, Williams WG, McCrindle BW. Functional health status of adolescents after the Fontan procedure—comparison with their siblings. *Can J Cardiol*. 2009; 25:e294–e300. [PubMed: 19746247]
21. McCrindle BW, Williams RV, Mitchell PD, Hsu DT, Paridon SM, Atz AM, Li JS, Newburger JW. Relationship of patient and medical characteristics to health status in children and adolescents after the Fontan procedure. *Circulation*. 2006; 113:1123–1129. [PubMed: 16490823]
22. Mitani Y, Ohashi H, Takabayashi S, Shimpō H, Komada Y. Acute effect of sildenafil on hypoxemic patients (excluding those with Eisenmenger syndrome) with incurable congenital heart disease and disturbed pulmonary vasculature in the mid-term follow-up. *Int J Cardiol*. 2011; 146:273–274. [PubMed: 21131076]
23. Morchi GS, Ivy DD, Duster MC, Claussen L, Chan KC, Kay J. Sildenafil increases systemic saturation and reduces pulmonary artery pressure in patients with failing fontan physiology. *Congenit Heart Dis*. 2009; 4:107–111. [PubMed: 21866231]
24. Moss, AJ.; Allen, HD. Moss and Adams' heart disease in infants, children, and adolescents: including the fetus and young adult. 7th edn.. Wolters Kluwer Health/Lippincott Williams & Wilkins; Philadelphia: 2008.
25. Ovroutski S, Ewert P, Miera O, Alexi-Meskishvili V, Peters B, Hetzer R, Berger F. Long-term cardiopulmonary exercise capacity after modified Fontan operation. *Eur J Cardiothorac Surg*. 2010; 37:204–209. [PubMed: 19683458]
26. Pingitore A, Aquaro GD, Lorenzoni V, Gallotta M, De Marchi D, Molinaro S, Cospite V, Passino C, Emdin M, Lombardi M, Lionetti V, L'Abbate A. Influence of preload and afterload on stroke volume response to low-dose dobutamine stress in patients with non-ischemic heart failure: a cardiac MR study. *Int J Cardiol*. 2013; 166:475–481. [PubMed: 22169733]
27. Rabelo ER, Ruschel K, Moreno H Jr, Rubira M, Consolim-Colombo FM, Irigoyen MC, Rohde LE. Venous endothelial function in heart failure: comparison with healthy controls and effect of clinical compensation. *Eur J Heart Fail*. 2008; 10(8):758–764. [PubMed: 18619901]
28. Reinhardt Z, Uzun O, Bhole V, Ofoe V, Wilson D, Onuzo O, Wright JG, Stumper O. Sildenafil in the management of the failing Fontan circulation. *Cardiol Young*. 2010; 20:522–525. [PubMed: 20519058]
29. Sarkola T, Jaeggi E, Slorach C, Hui W, Bradley T, Redington AN. Assessment of vascular remodeling after the Fontan procedure using a novel very high resolution ultrasound method: arterial wall thinning and venous thickening in late follow-up. *Heart Vessels*. 2013; 28:66–75. [PubMed: 22331173]
30. Schwedler G, Lindinger A, Lange PE, Sax U, Olchvary J, Peters B, Bauer U, Hense HW. Frequency and spectrum of congenital heart defects among live births in Germany: a study of the competence network for congenital heart defects. *Clin Res Cardiol*. 2011; 100:1111–1117. [PubMed: 21909849]
31. Shabanian R, Shahbaznejad L, Razaghian A, Kiani A, Rahimzadeh M, Seifirad S, Kocharian A, Gilani JS, Navabi MA. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. *Pediatr Cardiol*. 2012; 34:129–134. [PubMed: 22864675]
32. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN, Burr J, LaSalle B, Holubkov R, Lukas MA, Tani LY. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007; 298:1171–1179. [PubMed: 17848651]
33. Shishido T, Hayashi K, Shigemi K, Sato T, Sugimachi M, Sunagawa K. Single-beat estimation of end-systolic elastance using bilinearly approximated time-varying elastance curve. *Circulation*. 2000; 102:1983–1989. [PubMed: 11034949]
34. Sperandio PA, Oliveira MF, Rodrigues MK, Berton DC, Treptow E, Nery LE, Almeida DR, Neder JA. Sildenafil improves microvascular O₂ delivery-to-utilization matching and accelerates exercise O₂ uptake kinetics in chronic heart failure. *Am J Physiol Heart Circ Physiol*. 2012; 303:H1474–H1480. [PubMed: 23023868]
35. Uzark K, Lincoln A, Lamberti JJ, Mainwaring RD, Spicer RL, Moore JW. Neurodevelopmental outcomes in children with Fontan repair of functional single ventricle. *Pediatrics*. 1998; 101:630–633. [PubMed: 9521946]

36. Uzun O, Wong JK, Bhole V, Stumper O. Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. *Ann Thorac Surg.* 2006; 82:e39–e40. [PubMed: 17126088]
37. Walker DK, Ackland MJ, James GC, Muirhead GJ, Rance DJ, Wastall P, Wright PA. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. *Xenobiotica.* 1999; 29:297–310. [PubMed: 10219969]
38. Zelis R, Flaim SF. Alterations in vasomotor tone in congestive heart failure. *Prog Cardiovasc Dis.* 1982; 24:437–459. [PubMed: 6805039]

Fig. 1. Change in heart rate from baseline (*left side of graph*) to post-dobutamine heart rate (*right side of graph*). Each line represents an individual patient. Median heart rate increased from 80 to 120 beats/min

Fig. 2.

Boxplot of end-systolic elastance (Ees), end-arterial elastance (EA) and VA coupling (Ees/EA). *White boxplots* represent baseline pressure–volume loop measurements; *gray boxplots* represent measurements after dobutamine stress. There was an improvement in Ees with dobutamine ($p < 0.01$), a trend toward increasing EA ($p = 0.07$) and trend toward improving VA coupling ($p = 0.07$)

Fig. 3. Representative pressure–volume loops acquired from one study patient. Pressure–volume loop with *dashed line* displays baseline recordings. *Solid line* pressure–volume loop displays recording with dobutamine stress. *Lines* represent respective calculated end-systolic elastance lines. Steeper slope of dobutamine endsystolic elastance demonstrates improved contractility

Table 1

Patient characteristics by treatment group

	Entire cohort (<i>n</i> = 19)	Sildenafil (<i>n</i> = 10)	Placebo (<i>n</i> = 9)	<i>p</i> value
Age (years)	8 (5, 17)	10 (6, 17)	8 (5, 15)	0.72
Weight (kg)	27 (19, 59)	37 (21, 90)	27 (16, 58)	0.31
BSA (m ²)	1.2 (0.78, 1.6)	1.2 (0.81, 2.1)	1.0 (0.68, 1.6)	0.32
Female (<i>n</i> , %)	6 (32 %)	3 (30 %)	3 (33 %)	1
Ejection fraction (%)	60 (47, 63)	55 (45, 62)	61 (50, 64)	0.44
End-diastolic volume (ml/m ²)	80 (62, 100)	83 (55, 101)	79 (62, 100)	0.84
RV morphology (<i>n</i> , %)	13 (68 %)	6 (60 %)	7 (78 %)	0.37

Displayed values for continuous variables are median (IQR)

BSA body surface area, *RV* right ventricle

Table 2

Comparison of baseline pressure–volume loop measurements and treatment groups

PVL measure	Sildenafil (<i>n</i> = 10)	Placebo (<i>n</i> = 9)	<i>p</i> value
VA coupling and afterload			
VA coupling	2.59 (2.12, 3.26)	2.51 (1.76, 3.22)	0.32
EA (mmHg/ml/m ²)	1.82 (1.10, 2.26)	1.83 (1.45, 2.32)	0.84
Systolic indices			
Ees (mmHg/ml/m ²)	2.6 (2.1, 3.3)	2.5 (1.8, 3.2)	0.66
dP/dT _{max} (mmHg/ms)	935 (831, 1107)	1005 (845, 1132)	0.50
SW (J/m ²)	43.4 (26.6, 58.7)	43.3 (38.8, 53.7)	0.95
Diastolic indices			
Filling rate (ml m ² /ms)	0.1 (0.09, 0.16)	0.15 (0.10, 19)	0.28
Tau (ms)	34.1 (31, 41.7)	32.5 (27.8, 42.4)	0.60
dP/dT _{min} (mmHg/ms)	1488 (996, 1561)	1368 (1161, 1779)	0.92

Displayed values are median change (IQR)

VA ventriculoarterial, EA arterial elastance, Ees end-systolic elastance, SW stroke work dP/dT_{max} = maximal rate of pressure increase, dP/dT_{min} = maximal rate of pressure decline

Table 3

Changes in PVL indices with dobutamine infusion

Change in pressure–volume loop measurement	Sildenafil (<i>n</i> = 10)	Placebo (<i>n</i> = 9)	<i>p</i> value*
Afterload and VA coupling			
VA coupling	0.01 (−0.39, 0.25)	0.86 (0.26, 1.3)	0.06
Ea (mmHg/ml/m ²)	0.26 (−0.21, 2.2)	0.06 (−0.52, 0.47)	0.14
Systolic indices			
Ees (mmHg/ml/m ²)	0.85 (0.01, 1.5)	1.8 (0.74, 2.2)	0.32
dP/dT _{max} (mmHg/ms)	1212 (881, 1955)	2231 (1357, 2774)	0.10
SW (J/m ²)	0.24 (−0.01, 0.51)	0.23 (0.15, 0.44)	0.57
Diastolic indices			
Filling rate (ml m ² /ms)	0.04 (0.01,0.08)	0.08 (0.06, 0.14)	0.20
Tau (ms)	−8.8 (−13.9, −5.6)	−9.5 (−16.2, −4.4)	0.73
dP/dT _{min} (mmHg/ms)	499 (367,899)	953 (654, 1482)	0.08

Displayed values are median change (IQR)

VA ventriculoarterial, EA arterial elastance, Ees end-systolic elastance, SW stroke work dP/dT_{max} = maximal rate of pressure increase, dP/dT_{min} = maximal rate of pressure decline

* *p* values are significance of treatment group in general linear model