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Impact of Oral Sildenafil on Exercise Performance in Children and Young Adults After Fontan Operation: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Abstract

Background—Children and young adults with single ventricle physiology have abnormal exercise capacity after Fontan operation. A medication capable of decreasing pulmonary vascular resistance should allow for improved cardiac filling and improved exercise capacity.

Methods and Results—This study was a double-blind, placebo-controlled, crossover trial conducted in children and young adults after Fontan. Subjects were randomized to receive placebo or sildenafil (20 mg tid) for 6 weeks. After a 6-week washout, subjects crossed over for an additional 6 weeks. Each subject underwent an exercise stress test at the start and finish of each phase. Following sildenafil subjects had a significantly decreased respiratory rate and decreased minute ventilation at peak exercise. At the anaerobic threshold subjects had significantly decreased ventilatory equivalents of carbon dioxide. There was no change in oxygen consumption during peak exercise although there was a suggestion of improved oxygen consumption at the anaerobic threshold. Improvement at the anaerobic threshold was limited to the subgroup with single left or mixed ventricular morphology and to the subgroup with baseline serum brain natriuretic peptide levels ≥ 100 pg/ml.

Conclusion—In this cohort, sildenafil significantly improved ventilatory efficiency during peak and sub-maximal exercise. There was also a suggestion of improved oxygen consumption at the anaerobic threshold in two subgroups. These findings suggest that sildenafil may be an important

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Disclosures
None.

agent to improve exercise performance in children and young adults with single ventricle physiology following Fontan operation.

Keywords

Fontan procedure; exercise; physiology; trials

The Fontan operation is the final surgery in the strategy of staged palliation for children born with single ventricle congenital heart disease[1, 2]. Fatal if not intervened upon, these lesions can be effectively managed through the application of the principles of cavopulmonary surgery allowing for survival in most cases[3–6]. However, despite dramatically improved early operative success achieved over the past two decades, late morbidity and mortality are still a challenge[7]. Staged palliation does not recreate a normal two-ventricle circulation. Instead this series of surgeries creates a unique physiology in which exercise capacity is characteristically diminished[8–11].

Multiple factors contribute to diminished exercise capacity after the Fontan operation. One of the most important is the inability of cardiac output to increase appropriately in response to increased metabolic demand. After the Fontan operation there is no pre-pulmonary ventricle to propel blood through the pulmonary vasculature. This results in diminished cardiac filling and diminished cardiac output (CO), and amplifies the role of pulmonary vascular resistance (PVR) in determining the transit of passive blood flow across the pulmonary circuit[12]. A medication capable of decreasing PVR could result in increased pulmonary blood flow, better cardiac filling, and increased stroke volume, thereby allowing for an improved CO response to exercise.

Sildenafil is a phosphodiesterase 5 (PDE5) inhibitor that increases intracellular cyclic GMP and exerts a potent selective vasodilatory effect on the pulmonary vasculature[13–17]. Sildenafil is widely used to reduce PVR in infants and children with pulmonary hypertension. Although theoretically of great potential benefit, reports of its use in children after Fontan operation are limited, with treatment efficacy demonstrated in select cases of plastic bronchitis and protein-losing enteropathy[18, 19].

In this study we report the results of a phase-II clinical trial of oral sildenafil designed to evaluate efficacy in children and young adults late after Fontan operation (Sildenafil After Fontan Operation - SAFO trial; clinicaltrials.gov identifier: NCT00507819). Our primary objective was to determine if oral sildenafil improves functional outcome as measured by maximal and sub-maximal indices of exercise capacity. We also assess variables that may modify efficacy and we characterize the safety profile of this agent when administered over a six-week period to the potentially fragile population of children and adolescents with single ventricle congenital heart disease.

Methods

Study Design

This study is a randomized, double-blind, placebo-controlled, crossover trial of oral sildenafil (20 mg three times daily) conducted in children and young adults after the Fontan operation. Following a baseline screening assessment, subjects were randomized to start with a six-week course of either placebo or sildenafil (phase 1). Next, after a six-week washout period of no drug or placebo, subjects switched treatments for an additional six weeks (phase 2); each subject in principle acting as their own control. Subjects underwent exercise testing at the beginning and end of each phase for a total of four assessments. Placebo capsules were identical in appearance to sildenafil capsules and were taken

according to the same schedule (three times daily). The study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital of Philadelphia (CHOP IRB # 5034, Food and Drug Administration IND # 77,927).

Inclusion/Exclusion Criteria

Children and young adults age 8 years or older with single ventricle congenital heart disease following the Fontan operation who met the physical requirements for exercise stress testing and were followed as outpatients at The Children's Hospital of Philadelphia were screened for participation in the study. As this was a proof of concept study, we intentionally selected subjects who we felt would have sufficient exercise capacity to complete the study protocol. In order to exclusively study the effects of sildenafil on the physiology of the Fontan circulation, recruitment was intentionally aimed at a relatively healthy cohort of outpatients without significant additional complications. Subjects with implantable pacemakers, residual cardiac lesions (coarctation of the aorta, severe ventricular dysfunction, severe atrioventricular valve regurgitation, Fontan baffle or conduit obstruction, single lung Fontan connection), severe renal or hepatic dysfunction, or a history of sildenafil use in the six months prior to study enrollment were excluded from the study. Informed consent and assent were obtained prior to enrollment.

Measurements at Rest

Resting measures of heart rate, respiratory rate, oxygen saturation, and blood pressure were obtained prior to each exercise stress test by trained personnel.

Measurements During Exercise

Subjects were exercised to maximal volition using an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA). The protocol consisted of three minutes of pedaling in an unloaded state followed by a ramp increase in work rate (Watts) to maximal exercise. The steepness of the ramp protocol was determined by subject weight in kilograms and designed to achieve predicted peak work rate in 10 to 12 minutes of cycling time[20]. The ergometer was programmed to maintain a constant external workload at a cycling cadence of 50–120 revolutions per minute.

Metabolic and ventilatory data were obtained throughout the exercise study and for the first two minutes of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics V29, Yorba Linda, CA). Outcomes measured included maximal minute oxygen consumption, minute carbon dioxide production, minute ventilation, and respiratory exchange ratio as well as minute oxygen consumption and the ventilatory equivalents of carbon dioxide (VE/VCO_2) measured at the ventilatory anaerobic threshold. Ventilatory anaerobic threshold was measured by the V-slope method[21]. Heart rate and rhythm were monitored continuously. Blood pressure was measured by auscultation at rest and every three minutes during exercise and recovery.

Adverse Events and Compliance

Adverse events were collected by subject report and by weekly telephone interview with dedicated research personnel. To ensure medication compliance a pill count was performed at the end of each study period. The minimum compliance rate for inclusion of the study period in the analysis was 80%. If non-compliance was noted subjects were given the option of repeating the study phase after an additional six-week washout. No subjects were excluded from the analysis based on non-compliance.

Sample Size Calculation

The primary efficacy outcome measure was maximal oxygen consumption (VO_2 max). We specified a clinically relevant minimum detectable difference in maximal oxygen consumption of 2.8 ml/kg/min (the difference between a mean of 30.0 ml/kg/min for placebo and 27.2 ml/kg/min for sildenafil) and assumed that the standard deviation of differences was 5.0 ml/kg/min. Therefore, we selected a sample size in each treatment sequence (placebo → sildenafil and sildenafil → placebo) of 14, for an overall sample size of 28, to have 80% power to detect the specified minimum detectable difference at a two-sided significance level of 0.05.

Statistical Analysis

Baseline and demographic characteristics were summarized using means and standard deviations for continuous variables and percentages for categorical variables. Primary and secondary exercise outcomes were summarized across treatment phases (pre- and post-placebo and sildenafil) using means and standard deviations. For each exercise outcome, a linear mixed-effects model was used to estimate the difference in the average post-phase outcome between sildenafil and placebo, adjusted for pre-phase values, study phase (phase 1 or phase 2), and treatment sequence (placebo → sildenafil, or sildenafil → placebo). All observed post-phase values were included as outcomes in the model. Subject-specific random intercepts were used to account for the correlation due to repeated measurements. Subgroup analyses were specified *a priori* by ventricular morphology (single right ventricle versus single left or mixed ventricular morphology), baseline serum brain natriuretic peptide (≥ 100 pg/ml versus < 100 mg/ml), and fenestration patency (closed versus open) as determined by echocardiography. A test of interaction was performed to assess whether the size of the treatment effect differed by patient subgroup (e.g., BNP ≥ 100 pg/ml versus < 100 mg/ml). Because this was an exploratory proof of concept study, within-subgroup statistical testing for treatment effect was conducted even in the absence of a significant interaction. The distribution of subjects who reported side effects was evaluated across the sildenafil and placebo phases using McNemar's test (exact). For the primary outcome, a value of $p < 0.05$ was considered significant; for all secondary outcomes and subgroup analyses, a value of $p < 0.05$ was considered suggestive of statistical significance. All analyses were completed using R 2.10 (R Development Core Team, Vienna, Austria).

Results

Demographics and Resting Data

Of 125 eligible subjects contacted by the study team, 28 (22%) participated in the study. At least one study period was completed by all 28 subjects; demographic characteristics are summarized in Table 1. One subject withdrew related to discomfort from exercise equipment following phase 1, leaving 27 subjects who completed both phases. Two-thirds of the cohort were male and all but three subjects were Caucasian. Fifty-four percent of the subjects had single right ventricular morphology with the remaining forty-six percent comprised of a combination of subjects with either single left or mixed ventricular morphology. The cohort was non-obese with normal systolic and diastolic blood pressure. The mean baseline serum BNP level was mildly elevated. The mean oxygen saturation for those with a fenestration noted by echocardiography was 90.2% while the mean oxygen saturation for those without a fenestration was 92.3% ($p = 0.05$).

Summary statistics of resting measurements are summarized in Table 2. Sildenafil had no effect on resting heart rate, respiratory rate, or blood pressure. A suggestion of an increased oxygen saturation following sildenafil was noted but did not reach significance.

Measurements at Peak Exercise

Summary statistics for exercise outcomes measured during peak exercise are presented in Table 2. There was no significant improvement in oxygen consumption (Figure 1) and no change in peak heart rate following sildenafil. However, there were statistically significant improvements in measures of ventilatory efficiency including minute ventilation (Figure 2) and respiratory rate (Figure 3).

Subgroup analysis divided by ventricular morphology demonstrated similar findings regardless of ventricular subtype (Table 3). Those with single right ventricular morphology and those single left or mixed ventricular morphology demonstrated significant improvement in respiratory rate and minute ventilation but no significant change in maximal oxygen consumption, heart rate, or oxygen saturation. Subgroup analyses divided by baseline serum BNP level (≥ 100 pg/ml versus < 100 pg/ml) were consistent with the cohort as a whole, though in the subgroup with a serum BNP level ≥ 100 pg/ml the improvements in respiratory rate and minute ventilation did not reach statistical significance (Table 4).

Measurements at the Anaerobic Threshold

Measurements performed at the anaerobic threshold are summarized in Table 2. Accurate assessment of the anaerobic threshold could not be made in six subjects. For the remaining subjects, though no significant differences were detected in respiratory rate or minute ventilation, a significant improvement in the VE/VCO_2 was noted (Figure 4). There was also a suggestion of improved oxygen consumption, though this did not reach statistical significance (Figure 5).

Subgroup analyses demonstrated consistent significant improvements in the ventilatory equivalent for CO_2 regardless of ventricular morphology, baseline serum BNP level, or the demonstration of a fenestration on echocardiogram (Tables 3, 4). A significant improvement in oxygen consumption was found in the subgroup with single left or mixed ventricular morphology and the subgroup with baseline serum BNP levels ≥ 100 pg/ml. A reduction in respiratory rate was found in those with baseline serum BNP levels < 100 while reductions respiratory rate and in minute ventilation were found in subjects with single right ventricular morphology.

Side Effects and Compliance

The distribution of adverse events thought to have a possible or probable relationship to study drug based on published side effects (Revatio package insert; Pfizer, New York) are listed in Table 5. There was one hospital admission for constipation-related abdominal pain during the study but this event was deemed not related to study drug. There were no reports of alterations in vision or hearing, and no reports of priapism. Headache and flushing were the most commonly reported side effects. Flushing was more common during treatment with sildenafil ($p = 0.06$). No subjects withdrew from the study as a result of an adverse event. Of the subjects who completed both phases of the study, 4/27 (15%) repeated a phase due to non-compliance; 2 subjects repeated the placebo phase and 2 subjects repeated the sildenafil phase.

Discussion

This study is the first randomized, double-blind, placebo controlled, crossover trial to evaluate the impact of sildenafil on measures of exercise performance in children and young adults with single ventricle heart disease. The crossover design allowed for each subject to serve as his/her own internal control, thereby reducing the possibility of confounding given the heterogeneity of the cohort's native anatomy. The pre-placebo mean VO_2 max of 30.5

ml/kg/min demonstrates that the cohort was relatively healthy in comparison to reported measures of exercise performance for the Fontan population[9]. In this study there was no difference in VO_2 max, the primary outcome measure, following sildenafil administration as compared to placebo. However, there was an improvement in ventilatory efficiency during peak and sub-maximal exercise, and there was a suggestion of improved oxygen consumption during sub-maximal exercise. In two subgroups (those with single left ventricular or mixed ventricular morphology (n = 13) and those with BNP levels ≥ 100 pg/ml (n = 12)), the improvement in oxygen consumption during sub-maximal exercise was statistically significant.

The benefit of sildenafil in other populations is well documented. Exercise capacity, as measured by the six-minute walk, has been shown to improve in children and adults with pulmonary hypertension following treatment with sildenafil[14]. In the adult heart failure population there is a suggestion of a benefit from treatment with sildenafil and there is emerging data to suggest that PDE5 expression is part of the maladaptive myocardial response to injury[22–24]. However, in the population with single ventricle congenital heart disease, data is scarce regarding the potential benefit of sildenafil or of any other PDE5 inhibitor although, given the underlying physiology of this circulation, it makes intuitive sense that a therapy targeted at pulmonary vascular resistance and the maladaptive ventricular response to stress would be useful.

Following Fontan completion, the pulmonary and systemic circulations are effectively separated save for the potential presence of a fenestration. However, unlike in normal physiology, there is no pre-pulmonary ventricle to help deliver blood through the lungs and back to the heart. As a result, the ability to increase cardiac output in the setting of increasing metabolic demand is highly dependent on both low PVR and low ventricular filling pressure; the two components of pulmonary afterload. In order to increase flow across the pulmonary vascular bed during exercise, pulmonary afterload must drop and central venous pressure, the driving force of flow in the absence of a pre-pulmonary ventricle, must increase. In a two-ventricle circulation pulmonary vascular resistance decreases to 40–50% of the baseline value with exercise[25], and an increase in right-heart pressure is key to reaching the increase in cardiac output of four fold or more at peak exercise. In this setting, right heart systolic pressure might approach 50 mmHg or greater[26]. In the Fontan physiology, central venous pressure cannot reach these values. Therefore, a very low PVR during exercise is essential to achieve any substantial increase in cardiac output.

Resting Data

We found no significant effect of sildenafil on cardiopulmonary measures at rest. However, in post-Fontan physiology, resting cardiac output is sufficient to meet metabolic demands. A medication that impacts pulmonary afterload is therefore not likely to have a noticeable impact on resting measures except, perhaps, in the setting of a significant right-to-left shunt. In this scenario, a change in PVR might affect the shunt fraction resulting in an increased proportion of venous return traversing the lungs. This could be measured by an increase in the systemic oxygen saturation. In our population there was a suggestion of increased oxygen saturation at rest following sildenafil; a finding which has been noted previously[27], though this did not reach statistical significance. Even in the subgroup with echocardiographic evidence of patent fenestrations, the resting oxygen saturation did not increase significantly. However, it should be noted that the baseline oxygen saturation of 90.2% for this group suggests that patency by echocardiography is not the same as a physiologically important shunt.

Peak Exercise

We found no improvement in VO_2 max after a six-week course of sildenafil; a surprising finding given the suggestion of a difference during submaximal exercise. It is not clear from a conceptual standpoint why sildenafil would improve moderate levels of activity but not peak activity. There may be a limitation inherent in Fontan physiology such that a reduction in pulmonary afterload alone is not sufficient to increase cardiac output, or it may simply be that sildenafil is of no benefit at peak levels of exercise. Alternatively, we know from a recent large cross sectional study that maximal VO_2, an effort dependent measure of exercise performance, is less reliable than effort independent submaximal indices[9]. Measurements of VO_2 max may be impacted by subject effort and are therefore inherently less reliable. Although maximal exercise capacity was unchanged in our study, both respiratory rate and minute ventilation were improved. This suggests that while sildenafil does not improve maximal oxygen consumption, its most significant effect is to increase ventilatory efficiency (as a smaller minute ventilation is required for carbon dioxide removal) and to improve ventilation – perfusion matching.

Anaerobic Threshold

The suggestion of improvement in oxygen consumption at the anaerobic threshold, and the statistically significant improvement in two subgroups (those with single left ventricular or mixed ventricular morphology (13/28) and those with BNP ≥ 100 pg/ml (12/28)) are important findings of this study. The finding of statistical significance in the subgroup with BNP ≥ 100 pg/ml suggests that the impact of sildenafil might be more profound on those with ventricular distention and mild heart failure while the finding of statistical significance in the group with either left or mixed ventricular morphology suggests that there may be a ventricle-specific effect. Similar to the findings at peak exercise, ventilatory efficiency during sub-maximal exercise was significantly improved following sildenafil, again consistent with an improvement in ventilation – perfusion matching. Alternatively, the improved ventilatory efficiency may have resulted from sildenafil-induced bronchodilation which, by reducing air-trapping during exercise, engendered the observed increase in tidal volume and a presumed decrease in the dead space/tidal volume ratio. The available baseline FVC and FEV1 data did not, however, detect evidence of sildenafil induced bronchodilation.

Significance

This study demonstrates that sildenafil improved ventilatory efficiency and exercise performance at the anaerobic threshold but did not alter VO_2 max. While the overall changes in this proof of concept study were small and were not associated with an increase in work rate, these changes would be important if they translate into an attenuated slope in the decline in exercise capacity typically seen through the adolescent years in children with this physiology[11]. Although this study did not evaluate long term efficacy, if exercise capacity can be improved or maintained, this might result in a longer period of general wellness and an increase in the duration of transplant free survival after the Fontan.

The challenge of improving physiology following the Fontan operation is daunting. There are limited trials evaluating medical therapies that have not demonstrated a significant benefit[28]. Two recent case reports of sildenafil describe improvements in protein losing enteropathy and plastic bronchitis[18, 19], complications typically associated with failing Fontan physiology. One report demonstrated an improvement in VO_2 max following a single does of sildenafil[29] and a second demonstrated a selective benefit of bosentan on six-minute walk performance[30]. This is the first randomized clinical trial to suggest an improvement over time in measures of exercise performance following a medical intervention in children with single ventricle physiology late after the Fontan operation.

Limitations

Our subgroup analyses were limited by small sample size. Thus, we did not have sufficient power to demonstrate significant differences between subgroups, which limited our ability to differentiate responders from non-responders on the basis of ventricular morphology or serum BNP level. Further, characteristics of screened but not enrolled subjects were not evaluated, so that the enrolled subjects may not be a representative sample from the group at large. Although sildenafil was well tolerated with minimal side effects in our population over a six-week period, our recruitment strategy likely led to an over-representation of subjects with above average exercise capacity as compared to a random cross-section of children and young adults with single ventricle physiology. In addition, we did not evaluate the safety of sildenafil over a prolonged (> 6 week) period of continuous usage. Similarly, although efficacious over a six-week period, long-term efficacy of sildenafil was not evaluated. Therefore, before routine adoption of sildenafil for this population, a larger randomized trial stratified by patient and physiologic risk factors designed to evaluate long-term safety and efficacy and to identify responders versus non-responders should be performed.

Conclusion

This study demonstrates that sildenafil improves ventilatory efficiency and measures of submaximal exercise performance across a heterogeneous cohort of children and young adults following Fontan operation with minimal side effects and with no serious adverse events over a six-week period. The long-term impact of sildenafil on exercise capacity as well as rate of complications after Fontan operation and the long-term side-effect profile are worthy of further investigation.

Children and young adults with functional single ventricle physiology have decreased exercise capacity due to an inability to normally increase transpulmonary blood flow during exercise. A medication capable of decreasing pulmonary vascular resistance might allow for improved transpulmonary flow and increased ventricular preload resulting in improved cardiac output and performance with exercise. In this randomized, double blind, placebo controlled, crossover trial, the impact of sildenafil on exercise capacity was examined in a cohort of 28 subjects. The mean age of participants was 14.9 years and the mean time from Fontan operation was 11.3 years. In this cohort, sildenafil significantly improved ventilatory efficiency during peak and sub-maximal exercise. In two of the subgroups, those with single left or mixed ventricular morphology, and those with a baseline serum BNP level > 100, an improvement in oxygen consumption at the anaerobic threshold was observed in subjects during the sildenafil phase. The findings of this study suggest that sildenafil may be a useful agent to improve exercise performance and activity tolerance in children and young adults with single ventricle physiology following the Fontan operation. However, the long term safety and efficacy of sildenafil in this patient population remain unknown.

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References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971; 26:240–248. [PubMed: 5089489]
2. Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg. 1973; 66:613–621. [PubMed: 4518787]
3. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, Penny DJ, Brizard CP. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation. 2007; 116:I157–I164. [PubMed: 17846297]
4. Hosein RB, Clarke AJ, McGuirk SP, Griselli M, Stumper O, De Giovanni JV, Barron DJ, Brawn WJ. Factors influencing early and late outcome following the Fontan procedure in the current era. The 'Two Commandments'? Eur J Cardiothorac Surg. 2007; 31:344–352. discussion 353. [PubMed: 17236782]
5. Kim SJ, Kim WH, Lim HG, Lee JY. Outcome of 200 patients after an extracardiac Fontan procedure. J Thorac Cardiovasc Surg. 2008; 136:108–116. [PubMed: 18603062]
6. Salvin JW, Scheurer MA, Laussen PC, Mayer JE Jr, Del Nido PJ, Pigula FA, Bacha EA, Thiagarajan RR. Factors associated with prolonged recovery after the fontan operation. Circulation. 2008; 118:S171–S176. [PubMed: 18824751]
7. Rychik J. Forty years of the Fontan operation: a failed strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2010; 13:96–100. [PubMed: 20307870]
8. Durongpisitkul K, Driscoll DJ, Mahoney DW, Wollan PC, Mottram CD, Puga FJ, Danielson GK. Cardiorespiratory response to exercise after modified Fontan operation: determinants of performance. J Am Coll Cardiol. 1997; 29:785–790. [PubMed: 9091525]
9. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J, Rhodes J. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol. 2008; 52:99–107. [PubMed: 18598887]
10. Zellers TM, Driscoll DJ, Mottram CD, Puga FJ, Schaff HV, Danielson GK. Exercise tolerance and cardiorespiratory response to exercise before and after the Fontan operation. Mayo Clin Proc. 1989; 64:1489–1497. [PubMed: 2513458]
11. 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]
12. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, Gerche AL, Gorenflo M. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg. 2010; 10:428–433. [PubMed: 19995891]
13. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics. 2006; 117:1077–1083. [PubMed: 16585301]
14. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005; 353:2148–2157. [PubMed: 16291984]
15. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation. 2005; 111:3274–3280. [PubMed: 15956137]
16. Nemoto S, Sasaki T, Ozawa H, Katsumata T, Kishi K, Okumura K, Mori Y, Umegaki O. Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children. Eur J Cardiothorac Surg. 2010; 38:71–77. [PubMed: 20206543]
17. Peiravian F, Amirghofran AA, Borzouee M, Ajami GH, Sabri MR, Kolaee S. Oral sildenafil to control pulmonary hypertension after congenital heart surgery. Asian Cardiovasc Thorac Ann. 2007; 15:113–117. [PubMed: 17387192]
18. 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]

19. 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]

20. Rowland, T. Pediatric Laboratory Exercise Testing. Champaign, IL: Human Kinetics; 1993. p. 29-31.

21. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986; 60:2020–2027. [PubMed: 3087938]

22. Nagayama T, Hsu S, Zhang M, Koitabashi N, Bedja D, Gabrielson KL, Takimoto E, Kass DA. Sildenafil stops progressive chamber, cellular, and molecular remodeling and improves calcium handling and function in hearts with pre-existing advanced hypertrophy caused by pressure overload. J Am Coll Cardiol. 2009; 53:207–215. [PubMed: 19130990]

23. Zhang M, Takimoto E, Hsu S, Lee DI, Nagayama T, Danner T, Koitabashi N, Barth AS, Bedja D, Gabrielson KL, Wang Y, Kass DA. Myocardial Remodeling Is Controlled by Myocyte-Targeted Gene Regulation of Phosphodiesterase Type-5. J Am Coll Cardiol. 2010; 56:2021–2030. [PubMed: 20970280]

24. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5-Inhibition With Sildenafil Improves Left Ventricular Diastolic Function, Cardiac Geometry and Clinical Status In Patients With Stable Systolic Heart Failure: Results of a 1-Year Prospective, Randomized, Placebo-Controlled Study. Circ Heart Fail. 2010 (epub ahead of print).

25. Stickland MK, Welsh RC, Petersen SR, Tyberg JV, Anderson WD, Jones RL, Taylor DA, Bouffard M, Haykowsky MJ. Does fitness level modulate the cardiovascular hemodynamic response to exercise? J Appl Physiol. 2006; 100:1895–1901. [PubMed: 16497838]

26. Argiento P, Chesler N, Mule M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. Eur Respir J. 2010; 35:1273–1278. [PubMed: 19926746]

27. Morchi GS, Ivy DD, Duster MC, Claussen L, Chan K-C, Kay J. Sildenafil Increases Systemic Satruation and Reduces Pulmonary Artery Pressure in Patients with Failing Fontan Physiology. Congenital Heart Disease. 2009; 4:107–111.

28. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation. 1997; 96:1507–1512. [PubMed: 9315539]

29. 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]

30. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing Fontan circulation. Cardiol Young. 2009:1–9.

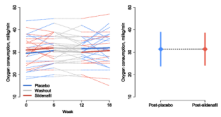

Figure 1.
Oxygen consumption at peak exercise. Left panel: observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period; right panel: Mean ± standard deviation post-placebo and post-sildenafil.

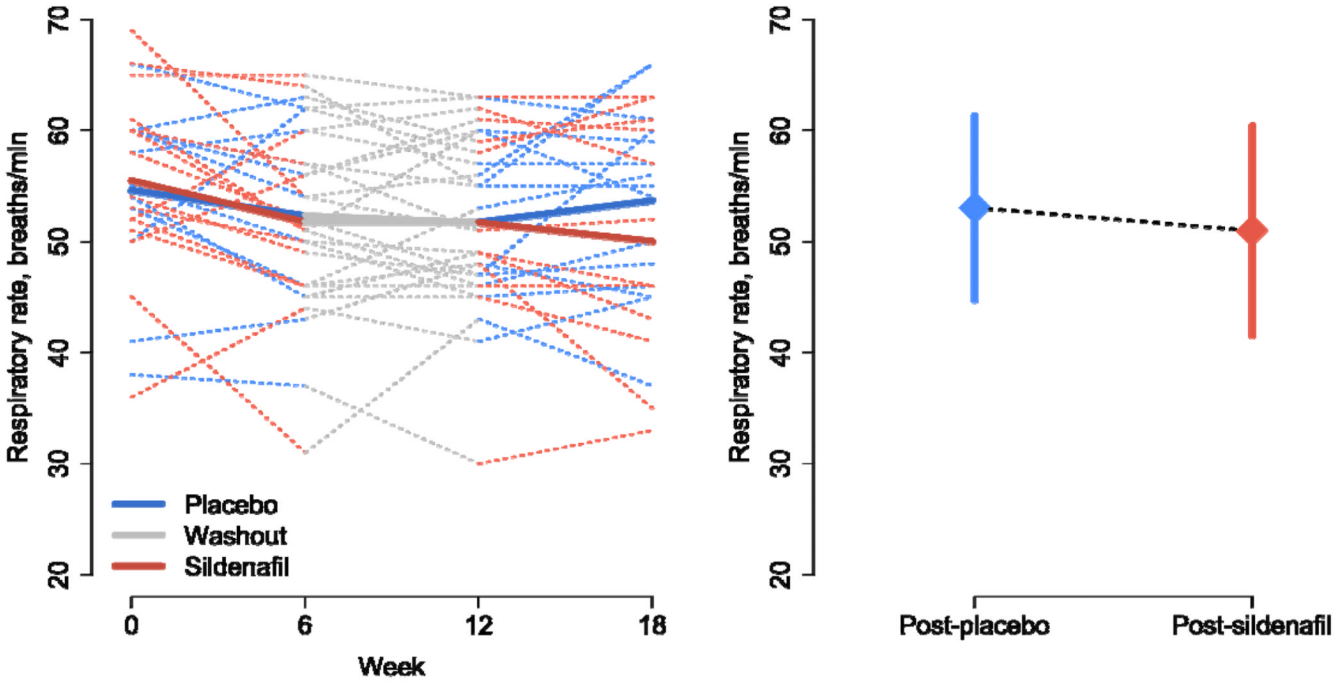

Figure 2.

Respiratory rate at peak exercise. Left panel: observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period; right panel: Mean ± standard deviation post-placebo and post-sildenafil.

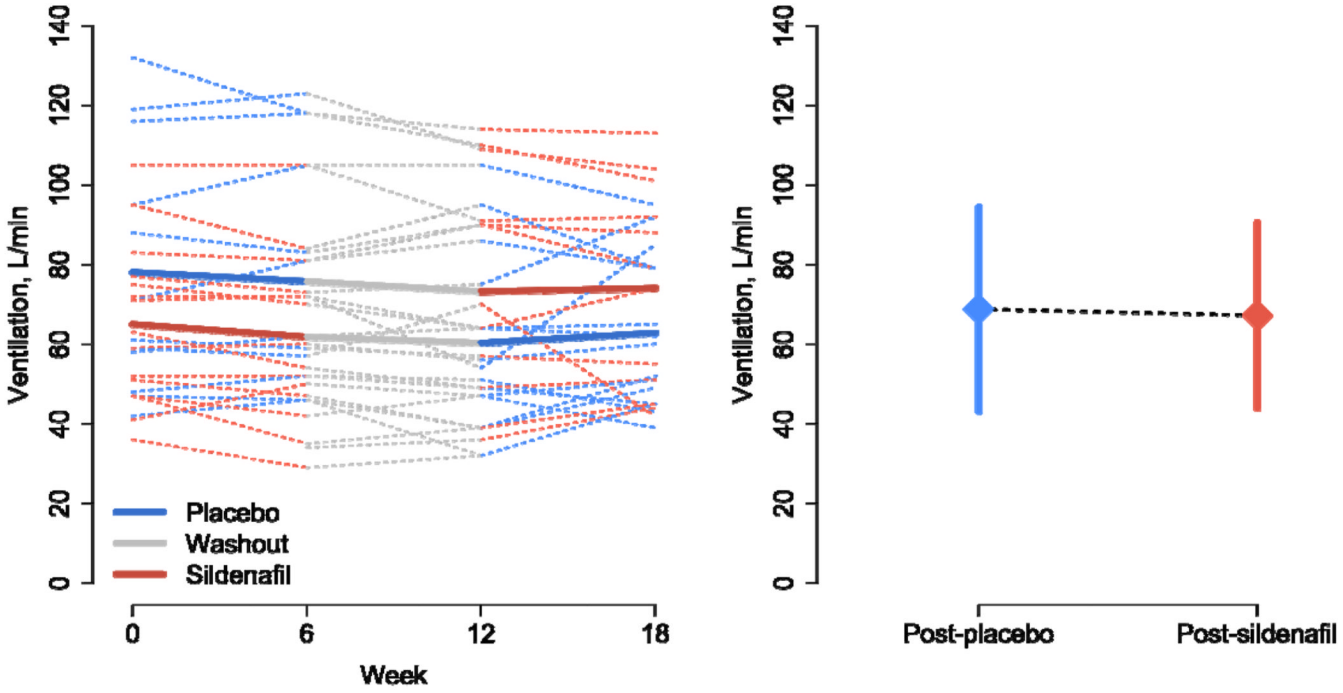

Figure 3.

Minute ventilation at peak exercise. Left panel: observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period; right panel: Mean ± standard deviation post-placebo and post-sildenafil.

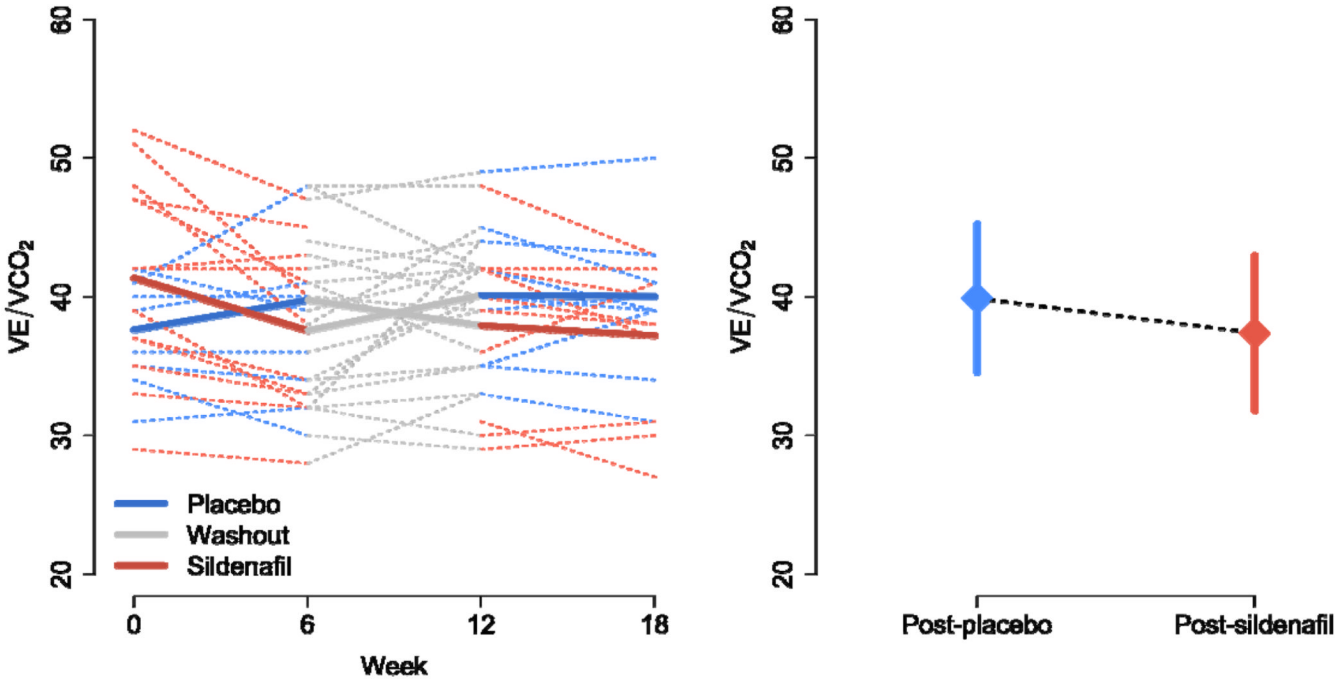

Figure 4.
VE/VCO_2 at anaerobic threshold. Left panel: observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period; right panel: Mean ± standard deviation post-placebo and post-sildenafil.

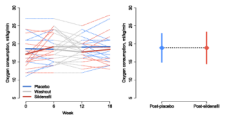

Figure 5.
Oxygen consumption at anaerobic threshold. Left panel: observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period; right panel: Mean ± standard deviation post-placebo and post-sildenafil.

Table 1

Demographic characteristics for 28 subjects at screening; summaries presented as mean (standard deviation) unless otherwise noted as *n* (%).

Age, years	14.9 (5.1)
Male, *n* (%)	18 (64%)
Race, *n* (%)	
White	25 (89%)
Black	2 (7%)
Multiracial	1 (4%)
Ventricular morphology, *n* (%)	
Single right ventricle	15 (54%)
Single left ventricle	8 (29%)
Two ventricles	5 (18%)
Time since Fontan operation, years	11.3 (3.8)
Height, cm	155 (13)
Weight, kg	48.3 (15)
Body mass index, kg/m^2	19.7 (3.9)
Oxygen saturation, %	92.3 (3.6)
Systolic blood pressure, mmHg	109 (12)
Diastolic blood pressure, mmHg	61.7 (9.0)
Serum brain natriuretic peptide, pg/ml	110 (75)

Table 2

Summary statistics for exercise measurements at each treatment phase, presented as mean (standard deviation); regression modeling results for exercise measurements, presented as coefficient, 95% confidence interval (CI), and *p* value; and number of subjects with a complete measurement series *n*.

	Summary statistics by study phase				**Regression modeling results**			
	Pre-placebo	**Post-placebo**	**Pre-sildenafil**	**Post-sildenafil**	**Coefficient**	**95% CI**	***p***	***n***
Measurements at rest								
Heart rate, beats/min	70.3 (15)	69.5 (15)	71.0 (16)	71.0 (15)	1.27	(−3.70, 6.23)	0.60	27
Respiratory rate, breaths/min	20.2 (4.1)	19.9 (4.1)	21.3 (4.9)	19.1 (3.2)	−0.46	(−1.79, 0.87)	0.48	27
Oxygen saturation, %	92.6 (3.0)	92.4 (3.3)	92.9 (2.8)	93.6 (2.4)	0.70	(−0.43, 1.83)	0.21	26
Systolic blood pressure, mmHg	113 (16)	112 (17)	112 (14)	112 (14)	−0.22	(−5.77, 5.34)	0.94	27
Diastolic blood pressure, mmHg	67.4 (8.5)	67.7 (7.3)	66.5 (10)	65.7 (7.6)	−1.55	(−5.11, 2.02)	0.38	27
Forced vital capacity, L	2.79 (1.1)	3.08 (1.1)	2.83 (1.2)	2.96 (1.1)	−0.10	(−0.27, 0.07)	0.20	12
FEV_1, L	2.43 (0.9)	2.62 (1.0)	2.41 (1.0)	2.55 (0.9)	−0.04	(−0.16, 0.08)	0.47	12
Measurements at peak exercise								
Oxygen consumption, ml/kg/min	30.5 (6.9)	31.3 (7.5)	30.5 (6.9)	31.3 (7.1)	−0.39	(−2.69, 1.92)	0.73	27
Heart rate, beats/min	163 (15)	163 (15)	163 (20)	163 (14)	−1.95	(−6.35, 2.45)	0.37	26
Respiratory rate, breaths/min	53.0 (7.5)	53.0 (8.3)	53.7 (8.9)	51.0 (9.4)	−2.69	(−5.37, −0.01)	0.05	26
Minute ventilation, L/min	68.1 (27)	68.8 (26)	68.8 (25)	67.2 (23)	−4.59	(−9.02, −0.16)	0.04	26
Oxygen saturation, %	89.4 (3.6)	89.2 (4.0)	89.3 (5.1)	89.7 (4.1)	0.56	(−0.55, 1.67)	0.30	26
Respiratory exchange ratio	1.11 (0.1)	1.12 (0.1)	1.14 (0.1)	1.17 (0.1)	0.03	(−0.02, 0.07)	0.22	26
Measurements at anaerobic threshold								
Oxygen consumption, ml/kg/min	18.9 (4.2)	18.9 (3.9)	17.4 (3.6)	18.9 (4.4)	1.38	(−0.19, 2.96)	0.08	21
Respiratory rate, breaths/min	34.4 (6.5)	34.5 (8.0)	33.7 (8.6)	32.8 (9.7)	−0.63	(−4.37, 3.11)	0.73	21
Minute ventilation, L/min	31.5 (8.5)	31.6 (6.8)	28.8 (8.4)	29.8 (7.3)	−0.22	(−2.58, 2.14)	0.85	21
Tidal volume, L	0.94 (0.3)	0.97 (0.3)	0.90 (0.3)	1.00 (0.5)	0.04	(−0.09, 0.18)	0.52	21
VE/VCO_2	39.0 (5.5)	39.9 (5.4)	40.0 (6.9)	37.4 (5.6)	−2.09	(−4.00, −0.17)	0.03	18
Work, watts	60.5 (24)	60.3 (25)	56.0 (23)	58.0 (24)	0.39	(−5.56, 6.33)	0.89	21

Each regression coefficient corresponds to difference in average post-phase outcome between sildenafil and placebo, adjusted for pre-phase values, study period, and treatment sequence. FEV_1: forced expiratory volume in one second; VE/VCO_2: ventilatory equivalents of carbon dioxide.

Table 3

Regression modeling results for exercise measurements, stratified by ventricular morphology, presented as coefficient, 95% confidence interval (CI), and *p* value.

	Single right ventricle (*n* = 15)			**Single left ventricle or mixed ventricular morphology (*n* = 13)**			
	Coefficient	**95% CI**	***p***	**Coefficient**	**95% CI**	***p***	***p****
Measurements at peak exercise							
Oxygen consumption, ml/kg/min	−0.73	(−2.45, 0.99)	0.40	0.09	(−1.75, 1.93)	0.92	0.52
Heart rate, beats/min	−0.81	(−3.91, 2.28)	0.60	−2.79	(−6.01, 0.43)	0.09	0.37
Respiratory rate, breaths/min	−1.70	(−3.03, −0.37)	0.01	−2.70	(−4.19, −1.21)	< 0.01	0.32
Minute ventilation, L/min	−3.77	(−6.96, −0.57)	0.02	−5.72	(−9.28, −2.17)	< 0.01	0.42
Oxygen saturation, %	0.36	(−0.35, 1.06)	0.32	0.57	(−0.23, 1.36)	0.16	0.69
Measurements at anaerobic threshold							
Oxygen consumption, ml/kg/min	0.63	(−0.49, 1.74)	0.26	1.77	(0.58, 2.97)	< 0.01	0.14
Respiratory rate, breaths/min	−3.00	(−4.75, −1.24)	< 0.01	−0.58	(−2.47, 1.31)	0.54	0.06
Minute ventilation, L/min	−1.63	(−3.25, −0.01)	0.05	1.17	(−0.57, 2.92)	0.18	0.02
VE/VCO_2	−2.06	(−3.35, −0.77)	< 0.01	−1.77	(−3.08, −0.46)	0.01	0.75

Each regression coefficient corresponds to difference in average post-phase outcome between sildenafil and placebo, adjusted for pre-phase values, study period, and treatment sequence. VE/VCO_2: ventilatory equivalents of carbon dioxide.

**p*-value from test of interaction evaluating whether the treatment difference is equal in the two morphology strata.

Table 4

Regression modeling results for exercise measurements, stratified by serum brain natriuretic peptide (BNP), presented as coefficient, 95% confidence interval (CI), and *p* value

	BNP ≥ 100 pg/ml (*n* = 12)			**BNP < 100 pg/ml (*n* = 16)**			
	Coefficient	**95% CI**	***p***	**Coefficient**	**95% CI**	***p***	***p****
Measurements at peak exercise							
Oxygen consumption, ml/kg/min	0.50	(−1.38, 2.38)	0.60	−0.98	(−2.60, 0.65)	0.23	0.24
Heart rate, beats/min	−2.17	(−5.62, 1.29)	0.22	−1.46	(−4.46, 1.54)	0.34	0.76
Respiratory rate, breaths/min	−1.24	(−2.76, 0.28)	0.11	−2.76	(−4.04, −1.48)	< 0.01	0.13
Minute ventilation, L/min	−3.15	(−6.77, 0.47)	0.09	−5.74	(−8.86, −2.61)	< 0.01	0.28
Oxygen saturation, %	0.51	(−0.29, 1.32)	0.21	0.41	(−0.28, 1.10)	0.25	0.84
Measurements at anaerobic threshold							
Oxygen consumption, ml/kg/min	1.85	(0.59, 3.12)	< 0.01	0.68	(−0.39, 1.75)	0.21	0.14
Respiratory rate, breaths/min	−1.26	(−3.22, 0.69)	0.20	−2.37	(−4.11, −0.62)	0.01	0.39
Minute ventilation, L/min	0.49	(−1.37, 2.34)	0.60	−0.94	(−2.57, 0.69)	0.25	0.24
VE/VCO_2	−2.40	(−3.69, −1.12)	< 0.01	−1.43	(−2.67, −0.19)	0.02	0.27

Each regression coefficient corresponds to difference in average post-phase outcome between sildenafil and placebo, adjusted for pre-phase values, study period, and treatment sequence. VE/VCO_2: ventilatory equivalents of carbon dioxide.

**p*-value from test of interaction evaluating whether the treatment difference is equal in the two BNP strata.

Table 5

Reported side effects by treatment group; number (%) of subjects who experienced at least one episode of each event.

Event	Sildenafil (*n* = 27)	Placebo (*n* = 28)
Headache	9 (33%)	5 (18%)
Flushing	5 (19%)	0 (0%)
Dizziness	2 (7%)	2 (7%)
Nausea/Vomiting	2 (7%)	0 (0%)
Abdominal Pain	1 (4%)	0 (0%)
Kidney Stone	1 (4%)	0 (0%)
Photosensitivity	1 (4%)	0 (0%)
Rash	1 (4%)	0 (0%)
Diarrhea	0 (0%)	1 (4%)
Hypotension	0 (0%)	1 (4%)
Muscle Pain	0 (0%)	1 (4%)
Tinnities	0 (0%)	1 (4%)
Tremulous	0 (0%)	1 (4%)
Any Event	11 (41%)	10 (36%)