Impact of Oral Sildenafil on Exercise Performance in Children and Young Adults After the Fontan Operation
A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial
David J. Goldberg, MD; Benjamin French, PhD; Michael G. McBride, PhD; Bradley S. Marino, MD, MPP, MSCE; Nicole Mirarchi, MA; Brian D. Hanna, MD, PhD; Gil Wernovsky, MD; Stephen M. Paridon, MD; Jack Rychik, MD

Background—Children and young adults with single-ventricle physiology have abnormal exercise capacity after the Fontan operation. A medication capable of decreasing pulmonary vascular resistance should allow 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 three times daily) 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. After taking 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.

Conclusions—In this cohort, sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise. There was also a suggestion of improved oxygen consumption at the anaerobic threshold in 2 subgroups. These findings suggest that sildenafil may be an important agent for improving exercise performance in children and young adults with single-ventricle physiology after the Fontan operation.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00507819. (Circulation. 2011;123:1185-1193.)

Key Words: exercise ■ Fontan procedure ■ physiology ■ trials
hypertension. Although theoretically of great potential benefit, reports of its use in children after the Fontan operation are limited, with treatment efficacy demonstrated in select cases of plastic bronchitis and protein-losing enteropathy.21,22

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 the Fontan operation (Sildenafil After Fontan Operation [SAFO] trial). Our primary objective was to determine whether oral sildenafil improves functional outcome as measured by maximal and submaximal indexes of exercise capacity. We also assess variables that may modify efficacy, and we characterize the safety profile of this agent when administered over a 6-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. After a baseline screening assessment, subjects were randomized to start with a 6-week course of either placebo or sildenafil (phase 1). Next, after a 6-week washout period of no drug or placebo, subjects switched treatments for an additional 6 weeks (phase 2), with each subject in principle acting as his or her own control. Subjects underwent exercise testing at the beginning and end of each phase for a total of 4 assessments. Placebo capsules were identical in appearance to sildenafil capsules and were taken according to the same schedule (3 times daily). The study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children’s Hospital of Philadelphia (No. 5034; Food and Drug Administration Investigational New Drug 77,927).

Inclusion/Exclusion Criteria

Children and young adults ≥8 years of age with single-ventricle congenital heart disease after the Fontan operation who met the physical requirements for exercise stress testing and were followed up as outpatients at The Children’s Hospital of Philadelphia were screened for participation in the study. Because this was a proof-of-concept study, we intentionally selected subjects who we felt would have sufficient exercise capacity to complete the study protocol. 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 6 months before study enrollment were excluded from the study. Informed consent and assent were obtained before enrollment.

Measurements at Rest

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

Measurements During Exercise

Subjects were exercised to maximal volition with an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA). The protocol consisted of 3 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 to 120 rpm.

Metabolic and ventilatory data were obtained throughout the exercise study and for the first 2 minutes of recovery on a breath-by-breath basis with a metabolic cart (SensorMedics V29). 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/\(\text{VCO}_2\)) 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 3 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 in the analysis was 80%. If noncompliance was noted, subjects were given the option of repeating the study phase after an additional 6-week washout. No subjects were excluded from the analysis because of noncompliance.

Sample Size Calculation

The primary efficacy outcome measure was maximal oxygen consumption (\(\text{VO}_{2\text{max}}\)). We specified a clinically relevant minimum detectable difference in maximal oxygen consumption of 2.8 mL·kg\(^{-1}\)·min\(^{-1}\) (the difference between a mean of 30.0 mL·kg\(^{-1}\)·min\(^{-1}\) for placebo and 27.2 mL·kg\(^{-1}\)·min\(^{-1}\) for sildenafil) and assumed that the SD of differences was 5.0 mL·kg\(^{-1}\)·min\(^{-1}\). 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 2-sided significance level of 0.05.

Statistical Analysis

Baseline and demographic characteristics were summarized by use of means and SDs for continuous variables and percentages for categorical variables. Primary and secondary exercise outcomes
Measurements at peak exercise

<table>
<thead>
<tr>
<th>Summary Statistics by Study Phase</th>
<th>Regression Modeling Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Placebo</td>
<td>After Placebo</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>163 (15)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>35.3 (7.5)</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>68.1 (27)</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>89.4 (3.6)</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>1.11 (0.1)</td>
</tr>
</tbody>
</table>

Measurements at anaerobic threshold

<table>
<thead>
<tr>
<th>Summary Statistics by Study Phase</th>
<th>Regression Modeling Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Placebo</td>
<td>After Placebo</td>
</tr>
<tr>
<td>Oxygen consumption, mL·kg⁻¹·min⁻¹</td>
<td>18.9 (4.2)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>34.4 (6.5)</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>31.5 (8.5)</td>
</tr>
<tr>
<td>Tidal volume, L</td>
<td>0.94 (0.3)</td>
</tr>
<tr>
<td>Ve/VCO₂</td>
<td>39.0 (5.5)</td>
</tr>
<tr>
<td>Work, W</td>
<td>60.5 (24)</td>
</tr>
</tbody>
</table>

FEV₁ indicates forced expiratory volume in 1 second; VE/VCO₂, ventilatory equivalents of carbon dioxide. Each regression coefficient corresponds to difference in average postphase outcome between sildenafil and placebo adjusted for prephase values, study period, and treatment sequence. Values are presented as mean (SD). Regression modeling results for exercise measurements are presented as coefficient, 95% confidence interval (CI), and P (n is the number of subjects with a complete measurement series).

were summarized across treatment phases (before and after placebo and sildenafil) using means and SDs. For each exercise outcome, a linear mixed-effects model was used to estimate the difference in the average postphase outcome between sildenafil and placebo, adjusted for prephase values, study phase (phase 1 or 2), and treatment sequence (placebo—sildenafil or sildenafil—placebo). All observed postphase values were included as outcomes in the model. Subject-specific random intercepts were used to account for the correlation as a result of 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 (BNP; ≥100 versus <100 pg/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 (eg, BNP ≥100 versus <100 pg/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 with the McNemar test (exact). For the primary outcome, a value of P < 0.05 was considered significant; for all

![Figure 1. Oxygen consumption at peak exercise. Left, Observed subject-specific profiles (dotted lines) and average trend for each treatment group (solid lines) over the study period. Right, Mean ± SD after placebo and after sildenafil.](image-url)
secondary outcomes and subgroup analyses, a value of $P<0.05$ was considered suggestive of statistical significance. All analyses were completed with 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 1 study period was completed by all 28 subjects; demographic characteristics are summarized in Table 1. One subject withdrew as a result of discomfort from using exercise equipment after phase 1, leaving 27 subjects who completed both phases. Two thirds of the cohort were male, and all but 3 subjects were white. Fifty-four percent of the subjects had single right ventricular morphology; the remaining 46% had either single-left or mixed ventricular morphology. The cohort was nonobese with normal systolic and diastolic blood pressures. The mean baseline serum BNP level was mildly elevated. The mean oxygen saturation for those with a fenestration noted by echocardiography was 90.2%, and the mean oxygen saturation for those without a fenestration was 92.3% ($P<0.05$).

Summary statistics of resting measurements are given in Table 2. Sildenafil had no effect on resting heart rate, respiratory rate, or blood pressure. A suggestion of an increased oxygen saturation after 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 after 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 with 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 ($<100$ versus $>100$ pg/mL) were consistent with the cohort as a whole, although 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 6 subjects. For the remaining subjects, although no significant differences were detected in
Table 3. Regression Modeling Results for Exercise Measurements, Stratified by Ventricular Morphology, Presented as Coefficient, 95% Confidence Interval, and P

<table>
<thead>
<tr>
<th>Measurements at peak exercise</th>
<th>Single Right Ventricle (n=15)</th>
<th>Single Left Ventricle or Mixed Ventricular Morphology (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Oxygen consumption, mL·kg⁻¹·min⁻¹</td>
<td>-0.73</td>
<td>-2.45 to 0.99</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>-0.81</td>
<td>-3.91 to 2.28</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>-1.70</td>
<td>-3.03 to -0.37</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>-3.77</td>
<td>-6.96 to -0.57</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>0.36</td>
<td>-0.35 to 1.06</td>
</tr>
</tbody>
</table>

Table 4. Regression Modeling Results for Exercise Measurements, Stratified by Serum Brain Natriuretic Peptide, Presented as Coefficient, 95% Confidence Interval, and P

<table>
<thead>
<tr>
<th>Measurements at peak exercise</th>
<th>BNP &gt;100 pg/mL (n=12)</th>
<th>BNP &lt;100 pg/mL (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Oxygen consumption, mL·kg⁻¹·min⁻¹</td>
<td>0.50</td>
<td>-1.38 to 2.38</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>-2.17</td>
<td>-5.62 to 1.29</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>-1.24</td>
<td>-2.76 to 0.28</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>-6.77</td>
<td>-7.47 to 0.47</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>-0.29</td>
<td>-0.93 to 0.32</td>
</tr>
</tbody>
</table>

Table 5. Regression Modeling Results for Exercise Measurements, Stratified by Serum Brain Natriuretic Peptide, Presented as Coefficient, 95% Confidence Interval, and P

<table>
<thead>
<tr>
<th>Measurements at anaerobic threshold</th>
<th>BNP &gt;100 pg/mL (n=12)</th>
<th>BNP &lt;100 pg/mL (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen consumption, mL·kg⁻¹·min⁻¹</td>
<td>1.85</td>
<td>0.59 to 3.12</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>-1.26</td>
<td>-3.22 to 0.69</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>0.49</td>
<td>-1.37 to 2.34</td>
</tr>
<tr>
<td>VO₂/VO₂C</td>
<td>-2.40</td>
<td>-3.69 to -1.12</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide; CI, confidence interval; and VO₂/VO₂C, ventilatory equivalents of carbon dioxide. Each regression coefficient corresponds to the difference in average postphase outcome between sildenafil and placebo adjusted for prephase values, study period, and treatment sequence. P from test of interaction evaluating whether the treatment difference is equal in the 2 BNP strata.
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 of 27 (15%) repeated a phase owing to noncompliance: 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 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 preplacebo mean $\text{VO}_2\text{max}$ of 30.5 mL·kg$^{-1}$·min$^{-1}$ demonstrates that the cohort was relatively healthy compared with reported measures of exercise performance for the Fontan population.9 In this study, there was no difference in $\text{VO}_2\text{max}$, the primary outcome measure, after sildenafil administration compared with placebo. However, there was an improvement in ventilatory efficiency during peak and submaximal exercise, and there was a suggestion of improved oxygen consumption during submaximal exercise. In 2 subgroups (those with single left ventricular or mixed ventricular morphology [n=13] and those with BNP levels $\equiv 100$ pg/mL [n=12]), the improvement in oxygen consumption during submaximal exercise was statistically significant.

The benefit of sildenafil in other populations is well documented. Exercise capacity, as measured by the 6-minute walk, has been shown to improve in children and adults with pulmonary hypertension after treatment with sildenafil.14 In the adult heart failure population, there is a suggestion of a benefit from treatment with sildenafil, and emerging data suggest that phosphodiesterase 5 expression is part of the maladaptive myocardial response to injury.22–24 However, in the population with single-ventricle congenital heart disease, data are scarce regarding the potential benefit of sildenafil or any other phosphodiesterase 5 inhibitor, although, given the underlying physiology of this circulation, it makes intuitive sense that a therapy targeted at PVR and the maladaptive ventricular response to stress would be useful.

After Fontan completion, the pulmonary and systemic circulations are effectively separated except for the potential presence of a fenestration. However, unlike in normal physiology, there is no prepulmonary 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 2 components of pulmonary afterload. 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
pressure might approach 50 mm Hg or greater. In the setting of a significant shunt, the right heart systolic pressure is key to reaching the increase in cardiac output of 4-fold at peak exercise. In this setting, right heart systolic pressure is essential to achieve any substantial increase in cardiac output. In post-Fontan physiology, central venous pressure cannot reach baseline value with exercise, and an increase in right-heart pressure is key to reaching the increase in cardiac output of ≥4-fold at peak exercise. In this setting, right heart systolic pressure might approach 50 mm Hg or greater. 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 affects 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 after sildenafil, a finding that has been noted previously, but it 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 patience by echocardiography is not the same as a physiologically important shunt.

### Peak Exercise

We found no improvement in VO$_2$ max after a 6-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 indexes. Measurements of VO$_2$max may be affected 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 although sildenafil does not improve maximal oxygen consumption, its most significant effects are to increase ventilatory efficiency (because a smaller minute ventilation is required for CO$_2$ 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 2 subgroups (those with single left ventricular or mixed ventricular morphology [13 of 28] and those with BNP ≥100 pg/mL [12 of 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, whereas 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 submaximal exercise was significantly improved after 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 ratio of dead space to tidal volume. The available baseline forced vital capacity and forced expiratory volume in the first second of expiration 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. Although 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. Although this study did not evaluate long-term efficacy, if exercise capacity can be improved or maintained, it 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 after the Fontan operation is daunting. Limited trials evaluating medical therapies have not demonstrated a significant benefit. Two recent case reports of sildenafil describe improvements in protein-losing enteropathy and plastic bronchitis, compli-
cations typically associated with failing Fontan physiology. One report demonstrated an improvement in VO₂max after a single dose of sildenafil, and a second demonstrated a selective benefit of bosentan on 6-minute walk performance. This is the first randomized clinical trial to suggest an improvement over time in measures of exercise performance after 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 nonresponders on the basis of ventricular morphology or serum BNP level. Furthermore, characteristics of screened but not enrolled subjects were not evaluated, so 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 6-week period, our recruitment strategy likely led to an overrepresentation of subjects with above-average exercise capacity compared with 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 use. Similarly, although efficacious over a 6-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 physiological risk factors designed to evaluate long-term safety and efficacy and to identify responders versus nonresponders should be performed.

Conclusions

This study demonstrates that sildenafil improves ventilatory efficiency and measures of submaximal exercise performance across a heterogeneous cohort of children and young adults after the Fontan operation with minimal side effects and with no serious adverse events over a 6-week period. The long-term impact of sildenafil on exercise capacity and rate of complications after the Fontan operation and the long-term side-effect profile are worthy of further investigation.

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Sources of Funding

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Disclosures

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References

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References


**CLINICAL PERSPECTIVE**

Children and young adults with functional single-ventricle physiology have decreased exercise capacity as a result of an inability to normally increase transpulmonary blood flow during exercise. A medication capable of decreasing pulmonary vascular resistance might allow 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 the Fontan operation was 11.3 years. In this cohort, sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise. In 2 subgroups, those with single left or mixed ventricular morphology and those with a baseline serum brain natriuretic peptide 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 after the Fontan operation. However, the long-term safety and efficacy of sildenafil in this patient population remain unknown.

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*Circulation*. published online March 7, 2011;
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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