Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients

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Aims
We sought to assess the effects of sildenafil on exercise capacity and haemodynamic response to exercise in Fontan patients.

Methods and results
We prospectively studied 27 patients with Fontan circulation (age 22.8 ± 4.9 years). All patients underwent a baseline exercise test with non-invasive measurement of cardiac index (CI) and pulmonary blood flow (PBF) index, and peak exercise oxygen uptake (VO2). After the baseline test, patients were randomly assigned to receive either a single 0.7 mg/kg body weight oral dose of sildenafil citrate (n = 18) or no treatment (control group, n = 9). After 1 h of rest, all patients performed a second exercise test. All patients completed the study protocol. The dose of sildenafil ranged from 25 to 50 mg. The change in peak VO2, the primary endpoint, was greater in the sildenafil group (9.4 ± 5.2%) than in the control group (0.3 ± 4.1%, P < 0.05). Sildenafil increased rest and peak exercise PBF index (P < 0.01 and P < 0.05 vs. control group, respectively), as well as rest and peak exercise CI (P < 0.001 and P < 0.05 vs. control group, respectively), without altering rest or peak exercise transcutaneous arterial blood oxygen saturations (P > 0.05 vs. control group for both). No patient reported serious adverse events after sildenafil.

Conclusion
In Fontan patients, oral administration of a single dose of sildenafil improves exercise capacity and haemodynamic response to exercise.

Keywords
Fontan • Cardiac output • Oxygen uptake • Exercise

Introduction
Although the Fontan operation has contributed greatly to the improvement of mortality rate in patients with a single ventricle, recent studies have emphasized a continuing risk of late failure and poor functional outcome in some long-term survivors. Decreased exercise tolerance and abnormal haemodynamic response to stress have also been clearly recognized in patients after this procedure. These results strongly suggest fundamental limitations inherent in Fontan physiology. The limitations are related to increased afterload and reduced ventricular filling capacity with subsequent limited preload reserve, especially during conditions associated with the increased heart rate (HR), e.g. exercise.

It has been suggested that reduced preload reserve might be related to the lack of pulmonary ventricular energy propelling venous blood flow into the ‘single ventricle’. Furthermore, Fontan patients may have a pulmonary vascular dysfunction, with blunted release of endothelium-derived nitric oxide (NO). This is consequent to the loss of flow pulsatility in the Fontan pulmonary circulation. Pulmonary endothelial dysfunction might lead to increased pulmonary vascular resistance and attenuation of the physiologic lowering of pulmonary vascular resistance induced by NO release. Administration of the selective pulmonary vasodilator inhaled NO to patients with Fontan circulation reduces pulmonary vascular resistance. However, NO has a high selectivity for the pulmonary circulation, with the potential disadvantage of increasing pulmonary capillary wedge pressure in patients with systemic ventricular dysfunction. Further, in a previous study, NO failed to increase cardiac output (CO) in Fontan patients. Sildenafil is a selective phosphodiesterase-5 (PDE-5) inhibitor, the predominant

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PDE isoform responsible for hydrolysis of cyclic guanosine-5'-monophosphate (GMP) (the second messenger of NO in vascular smooth muscle cells) in the lungs. Sildenafil has been shown to be as effective a pulmonary vasodilator as inhaled NO in patients with pulmonary arterial hypertension, and in children with congenital heart disease. Sildenafil also recently showed to be able to increase exercise capacity and pulmonary haemodynamics in pulmonary hypertension patients and in patients with acquired heart failure.

The present randomized study sought to assess the short-term effects of sildenafil on cardiopulmonary function and on the haemodynamic response to exercise in Fontan patients.

**Methods**

**Study population**

All Fontan patients >16 years old and currently followed-up at the Pediatric Cardiology and Adult Congenital Unit, University of Bologna, were candidates for inclusion in the study. Eligibility criteria for the study were: stability of clinical condition over the last 3 months and consent to participate in the study after information concerning procedures, risks, and possible clinical benefits. Exclusion criteria considered were severe heart failure (New York Heart Association functional class IV), presence of liver or renal dysfunction, transcutaneous arterial blood oxygen saturation ($\text{SaO}_2$) $< 85\%$ at rest, evidence of Fontan pathway obstruction, history of exercise-induced severe arrhythmias, and known or suspected pregnancy. Thirty-five patients were assessed for eligibility for the study (Figure 1). Five patients were excluded from the study because of non-compliance with the inclusion/exclusion criteria. Three patients refused to participate in the study. Twenty-seven eligible patients agreed to participate in the study. Data compiled for each patient included clinical and surgical history, physical examination, and exercise test results. All patients gave their written informed consent before participating in the study. The local ethics committee approved the study protocol.

**Study design**

The study was planned as a prospective, randomized assessment of the acute effects of oral sildenafil on exercise capacity and haemodynamic response to exercise. The study protocol is illustrated in detail in Figure 1. Eligible patients were randomly assigned in a 2:1 fashion to sildenafil treatment or to no treatment. Allocation to the treatment or to the control group was done using minimization, considering the age ($< 22$ vs. $> 22$ years) and type of the Fontan (atrio-pulmonary vs. total cavo-pulmonary connection) as stratification variables. Patients who agreed to participate and fulfilled the inclusion criteria were progressively entered into MINIM computer software which provided information on the allocation of each patient to treatment or no treatment. Two different investigators were responsible for the randomization procedure and for the assignment to study group. All patients had performed a previous exercise test to become familiar with the procedure at an average of 11 $\pm$ 9 days before the study date (exercise test no. 1; Figure 2). On the day of the study, all patients underwent a baseline exercise test (exercise test no. 2). After having rested for 1 h, 18 patients allocated to treatment were given 0.7 mg/kg body weight sildenafil citrate orally (range 25–50 mg). These 18 patients repeated the exercise test (exercise test no. 3) 1 h after sildenafil administration, coinciding with the expected peak plasma concentration after oral loading. The remaining nine patients included in the control group received no treatment and repeated the exercise protocol after 2 h of rest. Both patients and investigators were not blinded to the results of the randomization procedure.

**Study endpoints and calculation of the sample size**

The primary endpoint of the study was the change in peak VO$_2$ from exercise test no. 2 to exercise test no. 3. For this endpoint, a non-
Exercise test procedure

Exercise tests were performed with upright cycle ergometry (Ergoline, Germany), with the patient having fasted for at least 1 h. Oxygen uptake (VO₂), carbon dioxide output (VCO₂), and minute ventilation (VE) were measured with a computerized breath-by-breath analyzer (Innocor, Odense, Denmark). Patients performed a maximal exercise test using a 2 min incremental bicycle protocol with a work rate increment of 20 W every 2 min. Initial workload was 20 W. Criteria for test ending considered were patient exhaustion with a respiratory exchange ratio ≥1.09. A 12-lead electrocardiogram and SaO₂ were also continuously monitored throughout the study and cuff blood pressure was determined manually every 2 min. The technical details of measurement of peak VO₂ and VE/VCO₂ slopes were previously published. 19 Resting HR was measured after at least 120 s in a seated position, and peak HR was defined as the maximal HR achieved during exercise. None of the patients were unable to exercise.

Haemodynamic measurements

The Innocor system was used to measure pulmonary blood flow (PBF) using a foreign gas rebreathing technique. The Innocor rebreathing system uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulphur hexafluoride) from a 4 L pre-filled anaesthesia bag. Photoacoustic analysers measure gas concentration over a 5-breath interval. During exercise, tidal volume was progressively increased in the closed circuit to match the physiologic increase. The use of sulphur hexafluoride allowed us to measure the volume of the lungs, valve, and rebreathing bag. Nitrous oxide concentration decreases during the rebreathing manoeuvre, with a rate proportional to PBF. Three to four respiratory cycles were needed to obtain nitrous oxide washout. Patients performed the exercise tests as described above, using a mouthpiece connected to the Innocor breathing system. Patients were instructed to signal approximately 1 min before peak exercise, to allow for measurement of peak exercise data. As previously reported, this technique is very reliable to measure effective PBF, both in children with the congenital heart disease and in adults with acquired heart failure. 20–22 In all patients, blood haemoglobin concentration (g/dL) was assessed just before the first exercise test and was used in further analysis as reported. Before each test, all patients were exhaustively instructed on the breathing technique and performed at least two practice measurements before each test.

At baseline, three measurements of PBF were obtained at 3 min distance one from the other. During the measurement of PBF, all patients underwent a contemporaneous measurement of systolic and diastolic cuff blood pressure, of HR and of arterial SaO₂. Further measurements of PBF were done in every patient at peak exercise. For all patients, the values of pulmonary vein saturations obtained in room air during the most recent cardiac catheterization were used in the analysis (average of 1.9 ± 1.4 years before the study). CO was measured using the formula: CO = 1/[(arterial O₂ content − venous O₂ content)/VO₂ + 1/PBF]. The values of PBF and CO obtained were indexed for body surface area to obtain PBF index and CI, respectively.

Inter-test assessment and adverse events

During the 60 min period before exercise test no. 3, patients were asked to rest in a supine position. Systolic and diastolic arterial blood pressures and SaO₂ were measured every 15 min during this period. Patients in the treatment arm were asked to report any symptom occurring up to 12 h after sildenafil administration.

Statistical analysis

Continuous normally distributed variables are expressed as mean ± SD. Comparison of the percentage change in peak VO₂, percentage change in rest and peak PBF index, CI, and SO₂ observed from exercise test no. 2 to exercise test no. 3 in the sildenafil treatment group vs. the control group was made by Kruskal–Wallis test with Dunn’s post-test to correct for multiple comparisons. The GraphPad 4.03 statistical software was used for statistical analysis. A two-tailed probability value ≤0.05 was used as the criterion for statistical significance.

Results

Twenty-seven patients (age 22.8 ± 4.9 years, range 16–32 years) were enrolled from February 2007 to August 2007. Eighteen patients received sildenafil treatment and nine patients received no treatment (Table 1). All patients completed the study protocol. No patient had additional forward flow to the pulmonary artery. Five patients in the treatment group and one patient in the control group had undergone previous pulmonary artery banding. All patients were free of complicating acute or chronic respiratory disease or other conditions that might affect exercise performance. Six patients in the sildenafil group and three patients in the control group had a SaO₂ at rest >95%.

Details on the cardiopulmonary and haemodynamic data observed in the treatment and control groups at rest and at each exercise stage are presented in Table 2.

Cardiopulmonary exercise test results

All subjects exercised to the point of exhaustion. Patients receiving sildenafil had a higher improvement in peak VO₂ (Figure 3) than control patients. SaO₂ at rest and at peak exercise appeared to be similar in patients who received sildenafil and in the control group (Table 3). VE/VCO₂ slope decreased by −6.9 ± 3.2% in patients treated with sildenafil (from 35.8 ± 6.9 to 33.2 ± 6.1), whereas it increased by 0.2 ± 3.3% in the control group (from 35.4 ± 7.3 to 35.4 ± 6.9). Exercise duration increased by 4.1 ± 3.2% and by 1.8 ± 2.9% in the sildenafil and control groups, respectively.
Haemodynamic response to exercise
Details on the changes in haemodynamic variables observed in treatment group vs. the control group from exercise test no. 2 to exercise test no. 3 are shown in Table 3. Patients receiving sildenafil showed a higher increase in rest and peak exercise CI and PBFi when compared with the control group patients. No difference in the response of HR to exercise was observed in the two groups.

Inter-test assessment and adverse events
During the 60 min observation period before exercise test no. 3, we observed a progressive reduction in systolic and diastolic arterial blood pressures and an increase in SaO2 in the sildenafil treatment group, whereas no change was observed in the control group (data not shown). All patients tolerated sildenafil well; specifically, there was no symptomatic hypotension, facial flushing, or vision
Effect of sildenafil on haemodynamic response

Table 2  Change in cardiopulmonary and haemodynamic variables observed in exercise test nos 2 vs. 3 in the sildenafil treatment and in the control group at each exercise stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Before After</td>
<td>Before After</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.9 ± 0.8 3.7 ± 1.0</td>
<td>2.9 ± 0.9 2.9 ± 0.9</td>
</tr>
<tr>
<td>PBF index (L/min/m²)</td>
<td>2.2 ± 0.6 2.8 ± 0.5</td>
<td>2.4 ± 0.5 2.4 ± 0.6</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>81 ± 10 83 ± 11</td>
<td>80 ± 12 82 ± 13</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>109 ± 17 100 ± 11</td>
<td>111 ± 21 109 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 ± 13 67 ± 13</td>
<td>72 ± 16 70 ± 11</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>90 ± 6 90 ± 5</td>
<td>91 ± 6 91 ± 5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. PBF, pulmonary blood flow; SO₂, arterial oxygen saturation.

Discussion

The present study demonstrates that, in Fontan patients, the administration of a single oral dose of the PDE-5 inhibitor sildenafil might acutely improve exercise capacity and increase PBF and CI, both at rest and during exercise conditions.

Effect of sildenafil on Fontan haemodynamics

Although the Fontan operation has contributed greatly to the improvement of mortality rate in patients with a single ventricle, recent studies have emphasized a continuing risk of late failure and poor functional outcome in some long-term survivors. Decreased exercise tolerance and abnormal haemodynamic response to stress have also been clearly recognized in patients after this procedure. These results strongly suggest fundamental limitations inherent in Fontan physiology, related to increased afterload and reduced ventricular filling capacity with subsequently limited preload reserve, especially during conditions associated with increased HR.

Fontan patients, as patients with heart failure due to different aetiologies, have an abnormal systemic vascular tone, which may contribute to diminish skeletal muscle perfusion and heightened systemic vascular tone. Fontan patients also have an abnormal endothelium-dependent flow-mediated brachial artery dilation, which contributes to a reduced CO and to reduced exercise capacity. Sildenafil has previously been shown to improve endothelium-dependent flow-mediated brachial artery dilation in patients with heart failure, and to have systemic vasodilative properties as well. Lewis et al. demonstrated that oral administration of sildenafil is associated with a decrease in resting systemic vascular resistances and improved CI at rest and at peak exercise. Such an effect on systemic vascular resistances seems to be absent in normal subjects. Theoretically, sildenafil might have decreased ventricular afterload in Fontan patients in a similar way, acting as a systemic vasodilator, thus promoting increase in CI at rest and at peak exercise.

Another mechanism that might have contributed to explain the effect of sildenafil administration on CI and PBF index is an improvement in pulmonary haemodynamics. Evidence exists that a large proportion of the improvement in rest and exercise CI observed in adults with left ventricular systolic dysfunction after sildenafil administration is related to a decrease in pulmonary vascular resistances. The reason for this response lies in the presence of pulmonary endothelial dysfunction with increased pulmonary vascular resistance. Similarly, there is increasing evidence that up to 47% of Fontan patients may have increased pulmonary vascular resistance after a Fontan operation, as a consequence of pulmonary endothelial dysfunction. The mechanisms of pulmonary endothelial dysfunction in Fontan patients are only partially known, but the role of the loss of flow pulsatility appears to be important. Indeed, pulsatile flow is important for maintaining a low resistance in the pulmonary vasculature by passive recruitment of capillaries and shear-stress-mediated release of NO. Pulsatile flow has also been shown to be a more potent stimulus for release of NO to the same volume of laminar flow.

Changes. However, one female patient reported mild headache that spontaneously resolved within 2 h from sildenafil administration.
Pulsatile shear stress acts on the endothelium via diverse mechanisms.\textsuperscript{28} Experimentally, induction of hyperpolarization of endothelial cell causes elevation of cyclic GMP via an NO-dependent mechanism, redistribution of the endothelial cytoskeletal protein (actin), and up-regulation of NO synthase gene transcription, which may be caused by pulsatile shear stress. Thus, reduced pulsatle shear stress in the Fontan pulmonary circulation may downregulate the endothelial NO synthase expression and attenuate endothelial-dependent vasodilatation. This endothelial dysfunction seems to be reverted by inhaled NO.\textsuperscript{10} Given these hypotheses, the improvement in PBF index observed both at rest and during exercise after sildenafil administration could potentially be the result of decreased pulmonary vascular resistance induced by sildenafil through augmentation of cyclic GMP. In a recent contribution focusing on adults with left ventricular dysfunction, Lewis et al.\textsuperscript{15} have shown that the improvement in peak VO\textsubscript{2} and peak CI following sildenafil administration was not uniform across the study cohort and was significantly higher in patients with pulmonary hypertension than in patients without. This finding could potentially hold true also for Fontan patients,\textsuperscript{25} as well other heart failure populations,\textsuperscript{24} to early anaerobic metabolism during exercise. Improvement in blood perfusion to exercising muscle might also have contributed by reducing the inappropriate ventilatory drive that is usually observed during exercise.

\textbf{Safety of sildenafil}

No major reactions to sildenafil occurred during the study period or during the following 12 h, supporting the good tolerability profile previously reported in arterial pulmonary hypertension.\textsuperscript{16} However, one female patient reported mild headache that spontaneously resolved within 2 h from sildenafil administration.

\textbf{Limitations}

The present study has some limitations. First, patients were aware of receiving treatment or not. Therefore, we cannot exclude that the patient expectations might have lead to a higher level of effort during test no. 3 than during test no. 2. This could potentially lead to increased peak VO\textsubscript{2} and peak exercise PBF and CI. However, we observed that individual peak respiratory quotient and peak HR values appeared to be similar in the two tests. Furthermore, increased effort would not explain the increase in PBF and CI observed at rest. Second, study subjects underwent two exercise tests on the same day. Hence, we are unable to determine whether antecedent exercise might have caused a different haemodynamic or gas exchange response to exercise during test no. 3 in the sildenafil vs. control group. Third, even though the increase in

\begin{table}[h]
\centering
\caption{Change in cardiopulmonary and haemodynamics variables observed in the sildenafil treatment and in the no treatment arm for exercise test nos 2 vs. 3}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Variable} & \textbf{\%Δ exercise test nos 2 vs. 3} & \textbf{Sildenafil (n = 18)} & \textbf{No treatment (n = 9)} & \textbf{Treatment effect} & \textbf{P} \\
\hline
\multirow{2}{*}{Peak VO\textsubscript{2}} & & 9.4 ± 5.2 & 0.3 ± 4.1 & 9.1% & <0.05 \\
& & (n = 18) & (n = 9) & & \\
\hline
PBF index & Rest & 28.8 ± 12.2 & 1.1 ± 3.4 & 27.6% & <0.01 \\
& Peak exercise & 11.2 ± 7.0 & 1.0 ± 3.4 & 10.2% & <0.05 \\
\hline
CI & Rest & 29.0 ± 13.1 & 1.6 ± 3.7 & 27.4% & <0.001 \\
& Peak exercise & 10.0 ± 7.2 & 0.9 ± 4.3 & 9.1% & <0.05 \\
\hline
SaO\textsubscript{2} & Rest & 0.5 ± 1.8 & 0.1 ± 0.8 & 0.4% & >0.05 \\
& Peak exercise & 1.3 ± 2.6 & -0.2 ± 1.1 & 1.5% & >0.05 \\
\hline
\end{tabular}
\end{table}

Cl, cardiac index; PBF, pulmonary blood flow; SaO\textsubscript{2}, arterial oxygen saturation; VO\textsubscript{2}, oxygen uptake.
peak VO₂ appeared statistically significant, the clinical relevance to patients receiving the treatment is yet to be demonstrated. Furthermore, it is currently unknown if the benefit in terms of exercise capacity observed acutely might persist during chronic treatment.

**Conflict of interest:** none declared.

**References**


