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Effect of Inhaled Iloprost on the Exercise Function of Fontan Patients:

A Demonstration of Concept

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Abstract

Background—Exercise capacity following Fontan surgery is often depressed. An inability to reduce pulmonary vascular resistance appropriately during exercise may contribute to this phenomenon. The aim of this study was to determine whether administration of iloprost, a selective pulmonary vasodilator, would improve exercise function after Fontan procedure.

Methods—Double-blind, randomized, placebo controlled, crossover trial. Patients performed two cardiopulmonary exercise tests (CPX) separated by <1 month. A single nebulizer treatment (iloprost or placebo) was administered before each CPX.

Results—18 patients aged 12–49 (median 17) yrs were recruited. Mild throat discomfort developed in 10/18 patients during iloprost administration; all but 1 were able to complete treatment. No symptoms developed during placebo treatments ($p < 0.001$). Two additional patients did not complete CPX: one with atrial flutter; another with developmental issues that precluded adequate CPX. In the 15 remaining subjects oxygen pulse (a surrogate for forward stroke volume) at peak exercise was higher following iloprost (median increase 1.2 ml/beat; $p < 0.001$). Peak $\dot{V}_{O_2}$ also rose (median increase 1.3 ml/kg/min; $p < 0.04$). Nine patients had peak $\dot{V}_{O_2} < 30$ ml/kg/min; each of these patients had higher peak $\dot{V}_{O_2}$ following iloprost. Only 3/6 patients with peak $\dot{V}_{O_2} > 30$ ml/kg/min had higher peak $\dot{V}_{O_2}$ following iloprost ($p < 0.04$).

Conclusions—Iloprost improves the peak oxygen pulse and peak $\dot{V}_{O_2}$ of patients with Fontan physiology and appears to be particularly beneficial among patients with impaired exercise function. Treatment is associated with minor side effects. These findings support the concept of pulmonary vasodilator therapy in Fontan patients with limited functional capacity.

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²This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Conflict of Interest

1. Jonathan Rhodes: Recipient of investigator-initiated grant from Actelion Corporation
2. Michael J. Landzberg: Consultant/Advisory Board, Research Steering Committee, Actelion Corporation

Keywords

Fontan procedure; heart defects; congenital; exercise testing; vasodilation

Introduction

Since its introduction in 1971¹, the Fontan procedure has improved the life expectancy and quality of life of patients with single ventricle physiology.^{2,3} However, survivors of Fontan surgery almost invariably have diminished exercise capacity.⁴ Clinical deterioration with age is also common.^{3,5,6} Often, patients suffer from poor exercise tolerance despite the presence of relatively well preserved ventricular function.⁴ The term “cavopulmonary failure” has been introduced to describe these patients. It connotes the fact that these patients’ poor cardiopulmonary status arises not from “pump failure” per se, but from an inability to adequately perfuse the lungs while maintaining acceptably low systemic venous pressures.⁷

This dysfunctional physiology may be particularly apparent during exercise, a phenomenon that is likely related to the dynamic nature of the pulmonary vascular bed. In normal individuals, peak exercise is associated with up to a five-fold increase in pulmonary blood flow. This increase is accommodated by a large decline in pulmonary vascular resistance (PVR) and, consequently, only a small increase in the transpulmonary gradient.^{8–10} Although patients are typically selected for Fontan palliation only if their PVR is low at rest, their capacity to reduce PVR during exercise is rarely assessed prior to Fontan palliation. The presence of pulmonary vascular dysfunction during exercise could have profound hemodynamic and clinical implications for patients after Fontan surgery, as they lack a subpulmonary ventricle and their ability to augment their pulmonary perfusion pressure in response to an abnormally elevated PVR is therefore quite limited.¹¹

A number of studies have raised concerns regarding the health of the pulmonary vascular bed in patients with Fontan circulations. Abnormalities of endothelial function, microscopic structure, nitric oxide synthase expression and PVR have been described.^{12–16} Extrapolating from these data, the pulmonary vascular bed has been identified as a potential therapeutic target for patients with Fontan physiology, and studies on the effect of oral sildenafil (a phosphodiesterase-5 inhibitor with pulmonary vasodilator properties) on the exercise function of Fontan patients have been undertaken.^{17,18} These studies have yielded mixed results probably due, in part, to the fact that sildenafil is a relatively non-selective vasodilator that acts upon both the systemic and pulmonary vascular beds.^{17,19} Furthermore, because Fontan patients may have abnormalities of systemic as well as pulmonary vasoreactivity²⁰, it is not clear whether the effects attributed to sildenafil are due to its influence upon the pulmonary or systemic circulations.¹⁷ It is also possible that the effectiveness of sildenafil is in fact limited by its systemic side effects, and that greater benefit could be derived from a more selective pulmonary vasodilator. Finally, although advocated by some, a recent FDA warning against the use of sildenafil in pediatric patients with pulmonary hypertension has raised new concerns about its use in patients with Fontan physiology.²¹

Iloprost, (Ventavis, Actelion Inc., South San Francisco, CA) an analogue of prostacyclin, is a potent inhaled pulmonary vasodilator that (unlike sildenafil) exerts its effect primarily, or exclusively, upon the pulmonary vascular bed.^{22–24} In studies on patients with primary pulmonary hypertension iloprost's therapeutic benefits have been found to endure for approximately 2 hours.^{22–25} These properties suggest that it, or similar agents may be particularly well suited to study the influence of pulmonary vasoreactivity on the exercise function of patients with Fontan physiology. We therefore undertook this study to evaluate the effect of iloprost upon the peak $\dot{V}_{O_2}$, the oxygen pulse at peak exercise (a surrogate for the forward stroke volume at peak exercise^{26,27} that has been found to account for most of the variation in exercise function among patients with Fontan physiology⁴) and other parameters of exercise function, in patients with Fontan physiology.

Methods

We performed a prospective, randomized, double blinded, placebo-controlled, crossover study. Patients with Fontan physiology who were >12 years of age, not currently receiving pulmonary vasodilator drug therapy, and willing and able to perform a cardiopulmonary exercise (CPX) test were recruited. Patients with conditions that reviewing physicians felt had potential to place them at increased risk from iloprost therapy and/or CPX testing were excluded. These conditions included:

- History of reactive airway disease requiring hospitalization or an emergency room visit within the past year
- History of malignant ventricular arrhythmias, not palliated by an internal defibrillator
- History of syncope during exercise
- History of hypersensitivity to iloprost or to related medications.

Patients with Fontan physiology who were scheduled for clinically indicated CPX testing were identified as potential study subjects. If the patient met study criteria, approval to approach the patient was obtained from the primary referring cardiologist, and contact was made with the patient, and the patient's guardian, if appropriate, regarding study participation.

Study Protocol

All patients were scheduled to perform two CPX tests on separate days within 1 month of each other. Two and a half hours prior to the first CPX test, the patient was examined, vital signs recorded and baseline spirometric measurements obtained. A test dose of study drug (either 2.5 mcg of iloprost or an identical-appearing placebo) was then administered via the standard iloprost nebulizer system and the patient was monitored for 2 hours during which the nature and severity of any subjective symptoms or complaints were recorded and vital signs were checked at 30–40 minute intervals. At the end of the monitoring period, spirometric measurements were repeated; if they remained stable (within –20% of baseline measures), and the patient did not experience any untoward reactions or intolerable

symptoms, a full dose of iloprost (5.0 micrograms) or placebo was administered. After receiving the full dose, the patient performed the CPX test.

An identical drug administration, monitoring and testing protocol was followed on the day of the second CPX test, during which patients crossed over to placebo/iloprost inhalation in a blinded fashion. The order of the study drug administration (placebo vs. iloprost) was randomized. Study drug was not administered during the time interval between exercise tests. The patients, treating physicians and exercise physiologists were blinded to the identity of the study drug treatment. The study complied with the 1975 Declaration of Helsinki and was approved by the Boston Children's Hospital Committee on Clinical Investigation. Informed consent was obtained from the subjects (or their guardians). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.²⁸

CPX Testing

Maximal exercise testing was performed using a ramp protocol on an electronically braked cycle ergometer, as previously described.⁴ Subjects pedaled in an unloaded state for three minutes. The workload was then increased continuously with a slope chosen to achieve each subject's predicted maximal work rate after ten to twelve minutes of cycling. Expired gases were measured continuously using a Cardio2 metabolic cart (Medical Graphics Corporation, Minneapolis, MN). Only tests where subjects reached RER > 1.00 were considered for analysis. Peak $\dot{V}_{O_2}$ was defined as the highest $\dot{V}_{O_2}$ achieved by the subject during the test.

Blood Testing

Blood samples for BNP were obtained prior to the test dose of study medication. To evaluate potential chemical mediators of iloprost's physiologic effects, plasma was also collected in an EDTA tube prior to the test dose and immediately after the full dose of study medication, just prior to exercise. Plasma was spun down, aliquotted, and stored at -80°C until analysis. Levels of endothelin-1, interleukin-6, interleukin 10, tumor necrosis factor- α were assessed using two separate Milliplex® MAP kits (HCYTOMAG-60K and HAGP1MAG-12K) and run in accordance with a protocol supplied by the company (Millipore, Billerica, MA). The samples were analyzed using a Luminex 200 system (Luminex Corporation, Austin, TX) and analyzed using Milliplex Analyst software (Vigene Tech, Carlisle, MA). Levels of plasma nitrate, a stable nitric oxide metabolite proportional to levels of plasma nitric oxide, were determined using a Parameter Total Nitric Oxide and Nitrate/Nitrite Assay (R&D Systems, Minneapolis, MN). As suggested by the manufacturer, samples were filtered with 10,000 molecular weight cut-off filters (Millipore, #UFC501096). Patients were permitted to participate in the study but opt out of the blood drawing component if they desired.

Sample Size Calculation

The primary efficacy outcome measures were 1) peak $\dot{V}_{O_2}$ and 2) oxygen pulse at peak exercise. Using the Wilcoxon signed rank test conducted at the 0.05 level of significance (type 1 error <0.05) and assuming a $9.1 \pm 10.0\%$ increase in the peak $\dot{V}_{O_2}$ following iloprost

treatment compared to the placebo treatment¹⁷, we calculated that a study group of 15 patients would have a 90% chance of detecting a statistically significant difference between the treatment arms for the primary target variable (10% chance of a type 2 error). To account for patient drop-out, and to increase the power of the study with regard to secondary outcome variables, we aimed to recruit 18 subjects.

Statistical Analysis

Medians and inter-quartile ranges (IQR) were used to describe continuous variables; frequencies and percentages were used to describe categorical variables. Due to the non-normal distribution of many of the continuous variables and the small sample size, non-parametric tests were performed. A Wilcoxon signed rank test was used to compare the results of the iloprost-CPX tests to those of the placebo-CPX tests. A Fisher's exact test was used to compare subgroups of patients, where appropriate. Spearman's correlation coefficients were used to assess the relationship between changes in chemical mediators and CPX tests results.

Results

Eighteen patients were recruited for the study (Table 1). The median age was 16.7 (IQR 11.9) years; 13 (72%) were male. The most common anatomic diagnosis was hypoplastic left heart syndrome. None of the subjects had residual fenestrations, 3 had pacemakers, 5 were prescribed beta-blocker or other antiarrhythmic medications. One patient developed a severe cough while receiving the test dose of the study medication, and withdrew from the study. Another, with a history of recurrent atrial flutter, was found to be in atrial flutter when an electrocardiogram was performed prior to the initiation of the CPX test. CPX test was cancelled and the patient was withdrawn from the study. A third patient, with mild developmental delay, was determined unable to cooperate sufficiently for the CPX tests. Hence a total of 15 patients had analyzable CPX data.

CPX Results

The oxygen pulse at peak exercise was significantly higher following iloprost treatment compared to placebo (median increase 1.2; IQR 1.1 ml/beat, $p < 0.001$; Figure 1 and Table 2). The average increase in oxygen pulse at peak exercise was 13% (10.4 ± 2.1 to 11.7 ± 2.7 ml/beat). Peak $\dot{V}_{O_2}$ was also higher following iloprost administration (median increase 1.3; IQR 2.2 ml/kg/min, $p < 0.04$; Figure 2 and Table 2). The increase was less consistent and its magnitude (28.8 ± 6.7 vs. 27.5 ± 5.9 ml/kg/min; 5%) was relatively small. However, all 9 patients whose peak $\dot{V}_{O_2}$ was < 30 ml/kg/min following placebo had a higher peak $\dot{V}_{O_2}$ following iloprost; Figure 2). In contrast, only 3/6 patients with peak $\dot{V}_{O_2} > 30$ ml/kg/min on their placebo study had a higher peak $\dot{V}_{O_2}$ following iloprost ($p < 0.04$ by Fisher's exact test). Similar, albeit less pronounced trends were also observed for most of the other indices of aerobic function (Table 2).

One patient differed dramatically from the other 14 subjects, manifesting a peak $\dot{V}_{O_2}$ that was much lower on her post-iloprost CPX compared to her post-placebo study (Figure 2). This individual received placebo prior to the first CPX. Shortly after her first CPX she

developed an illness and required hospitalization for several days. During her convalescence (i.e., the one month interval between her post-placebo and post-iloprost CPX studies) she was very sedentary. When her data was excluded from the analyses, more substantial increases in the oxygen pulse, peak $\dot{V}_{O_2}$ and other indices of aerobic function (Table 3) were noted.

The heart rate at peak exercise was, on average, 7% lower on the CPX test preceded by iloprost administration (median decline 10; IQR 9 bpm, $p<0.002$). The change in peak heart rate did not correlate with the concomitant change in oxygen pulse at peak exercise (Figure 3). The subjects' respiratory rate at peak exercise also tended to be slightly higher and their tidal volumes slightly smaller during the post-iloprost CPX test (Table 2). No significant difference was detected in the systolic blood pressure, diastolic blood pressure or oxygen saturation at peak exercise, or in the baseline vital signs and oxygen saturation. Similarly, the $\dot{V}_E/\dot{V}_{CO_2}$ slope below the respiratory compensation point (an index of gas exchange efficiency during exercise) appeared unaffected by iloprost therapy.

Blood Testing

Blood samples were obtained in 12 (80%) of the subjects (Table 4). Iloprost-induced changes in peak $\dot{V}_{O_2}$ did not correlate with baseline BNP levels. Serum nitrate levels tended to increase following iloprost administration and tended to decrease following placebo. The iloprost-induced change in peak $\dot{V}_{O_2}$ did not correlate with the magnitude of the iloprost-induced increase in serum nitrate. Levels of the other potential chemical mediators were not affected by iloprost administration.

Inhalation-Related Side Effects

Mild throat/chest discomfort developed in 10/18 patients during iloprost administration; all but 1 (i.e., the patient referred to earlier) were able to complete the treatment. No symptoms were reported during placebo treatments ($p<0.001$). No other side effects or adverse events were identified. Iloprost did not have a significant impact upon baseline spirometric measurements (Table 5).

Discussion

We found that a single dose of iloprost was associated with significant acute increases in the peak $\dot{V}_{O_2}$ and oxygen pulse at peak exercise in patients with Fontan physiology. The improvement in peak $\dot{V}_{O_2}$ appeared to be particularly important among patients with depressed exercise function. Furthermore, when data from the subject who was extremely sedentary, due to an intercurrent illness and hospitalization during the interval between the post-placebo and post-iloprost CPX studies, was excluded from the analyses (on account of concern about the undue impact of deconditioning on that subject's data) more substantial improvements in indices of aerobic function were observed.

Past investigators have sought to improve the exercise function of patients with Fontan physiology by attempting to lower PVR with sildenafil. Giardini et al reported that a single dose of sildenafil administered to a group of 18 patients after Fontan surgery improved peak $\dot{V}_{O_2}$ by $9.4\pm5.2\%$, whereas peak $\dot{V}_{O_2}$ increased by only $0.3\pm4.1\%$ in nine Fontan patients

who received no treatment.¹⁷ This study was not blinded, however, and a component of the observed improvements may have been related to psychological, rather than physiologic, factors. In contrast, Goldberg et al could not detect an increase in peak $\dot{V}_{O_2}$ or oxygen pulse in a group of 28 Fontan patients who participated in a randomized, double blind, placebo-controlled, crossover trial of 6 weeks of oral sildenafil treatment.¹⁸ Hence, our current investigation is the first controlled and blinded study to demonstrate that pulmonary vasodilator treatment can have a beneficial impact upon the exercise function in subjects treated with Fontan surgery. We believe that the results of this proof of concept study constitute some of the strongest evidence supporting the use of pulmonary vasodilator therapy in patients with Fontan physiology.

Oxygen pulse, the amount of oxygen consumed per heartbeat, is the product of the forward stroke volume and the oxygen extraction (i.e., arterial oxygen content minus mixed-venous oxygen content).²⁶ Iloprost did not affect the oxygen saturation at peak exercise. In addition, because inhaled iloprost has little or no systemic effects, it is unlikely that it affected oxygen extraction or mixed venous oxygen content at peak exercise. Hence the observed increase in oxygen pulse was almost certainly due to an increase in the forward stroke volume after iloprost inhalation.

For patients with Fontan physiology, it may be more constructive to view the oxygen pulse, not as the product of forward stroke volume and oxygen extraction, but as the (mathematically equivalent but conceptually different) product of the amount of blood flowing to the lungs per heartbeat times the amount of oxygen added by the lungs to each liter of blood:²⁹

$$O_2P = SV \times [C_{aO_2} - C_{vO_2}] = (PBF/HR) \times [C_{pvO_2} - C_{paO_2}].$$

(O_2P : oxygen pulse; SV : forward stroke volume; C_{aO_2} : arterial oxygen content; C_{vO_2} : mixed venous oxygen content; PBF : pulmonary blood flow; HR : heart rate; C_{pvO_2} : pulmonary venous oxygen content; C_{paO_2} : pulmonary arterial oxygen content)

The small (7%) decline in peak heart rate following iloprost administration cannot by itself account for the more substantial (13%) increase in peak oxygen pulse that was associated with iloprost administration. Furthermore, for reasons analogous to those discussed above, it is unlikely that iloprost had an effect upon the pulmonary venous or pulmonary arterial oxygen contents. Consequently, on the basis of this line of reasoning, it appears that the increase in oxygen pulse was due largely to an increase in pulmonary blood flow. Iloprost is also unlikely to have increased the pressure in the Fontan circulation (i.e., pulmonary arterial pressure) or the transpulmonary pressure gradient. Hence, because pulmonary blood flow is equal to the transpulmonary pressure gradient divided by PVR, this equation implies that the increase in oxygen pulse was related primarily to iloprost's enhancement of the exercise-induced decline in PVR. The increased pulmonary blood flow (heart rate times stroke volume) that resulted from the iloprost-induced pulmonary vasodilation in turn led to improved ventricular preload and a higher ventricular stroke volume.¹¹

We observed that, iloprost reliably acutely improved the exercise function of subjects with Fontan palliations who had a peak $\dot{V}_{O_2} < 30$ ml/kg/min; its effect upon patients with better baseline exercise function however, was less pronounced. We believe this observation indicates that although the pulmonary vasoreactivity of some high functioning Fontan patients may be well preserved, it is almost always abnormal in patients with poor exercise function.

In the cross-sectional study of pediatric patients (age 6–18 yrs) with Fontan circulations undertaken by the Pediatric Heart Network, the mean peak $\dot{V}_{O_2}$ was 26.3 ± 6.9 ml/kg/min.⁴ In a recent cross sectional study of adult patients >16 yrs old with Fontan circulations from our institution, the mean peak $\dot{V}_{O_2}$ was somewhat lower. (21.2 ± 6.2 ml/kg/min).³⁰ Similarly, Kempny, et al reported an average peak $\dot{V}_{O_2}$ of 22.7 ± 5.8 ml/kg/min in a group of 590 patients with Fontan procedures, mean age 19.4 years.³¹ Hence, the 30 ml/kg/min threshold detected in the current study suggests that iloprost therapy may be beneficial for the majority of patients who have had Fontan palliation.

Peak heart rate tended to be lower on the CPX following iloprost administration. The cause for this phenomenon is unclear. Iloprost has not been reported to be a negative chronotropic agent or to adversely affect the sinus node. We speculate that the lower peak heart rate associated with the CPX studies following iloprost administration was related to the mild throat/chest discomfort that was frequently encountered. This symptom may have caused the patients to be somewhat apprehensive during the post-iloprost CPX. In our experience, apprehensive patients are sometimes reluctant to expend a true maximal effort during a CPX study. We believe this phenomenon probably accounts for the lower peak heart rate on the post-iloprost study compared to the post-placebo CPX. This conjecture is supported by the observation that the difference in peak heart rate between the placebo and iloprost CPX studies did not correlate with the concomitant change in peak oxygen pulse. If the observed decline in heart rate was due to a negative chronotropic effect of iloprost, the stroke volume (and oxygen pulse) at peak exercise should have increased in a manner reciprocal to the decline in peak heart, solely on the basis of the Starling mechanism (i.e., if the heart fills more secondary to the longer diastolic time associated with a slower heart rate, the stroke volume should increase).³² The lack of association between the change in peak heart rate and the change in oxygen pulse would be expected, however, if the lower heart rate was due to a less vigorous effort. Hence, if our conjecture concerning the cause of the lower peak heart rate is correct (i.e., that it was due to a slightly less vigorous effort secondary to the patients' apprehension about the mild sore throat/chest discomfort caused by the iloprost), it is likely that a greater enhancement of exercise function will be observed if/when the patients accommodate (as they usually do²⁵) to this common, minor side effect.

Although iloprost did not appear to have a significant effect upon baseline spirometric measurements, the subjects tended to have slightly smaller tidal volumes and higher respiratory rates at peak exercise during the CPX study following iloprost administration. This altered breathing pattern may be due to air trapping secondary to exercise-induced bronchospasm (iloprost therapy has, in the past been associated with an increased incidence of bronchospasm). Post-exercise spirometric measurements were not acquired for this study; it may be worthwhile to incorporate these measurements into future iloprost trials.

Study Limitations

The results of the current study demonstrate statistical acute improvement in parameters of exercise function after iloprost inhalation in patients with Fontan physiology. The improvements were relatively modest and their relevance to clinical practice, while encouraging, remains uncertain. Of note, although the dose of iloprost chosen for this study was similar to that employed in the treatment of patients with pulmonary hypertension, the dose-response curve and side effect/toxicity profile of iloprost in patients after Fontan surgery may in fact be quite different from that observed in pulmonary hypertension, and the optimal iloprost dose for these patients has not been identified. It is possible that more dramatic changes in exercise function could be achieved with different doses or a repeated scheduling of iloprost (or similar pulmonary vasoactive agents), without precipitating unacceptable side effects. Furthermore, this study only examined the acute effect of a single dose of iloprost. The effect of chronic iloprost treatment remains uncertain. The potential efficacy of chronic iloprost therapy in patients with Fontan circulations should be addressed in the context of future clinical trials. Finally, it also must be noted that invasive hemodynamic measurements were not obtained in this study, and our inferences concerning the effect of iloprost on pulmonary vascular resistance are therefore somewhat speculative.

Summary

Acute inhalation of iloprost improves the exercise function of patients with Fontan palliation, particularly those with low baseline exercise function. The acute and chronic benefits of iloprost administration, in varied doses and schedules, should be addressed in future prospective clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Effect of Iloprost on oxygen pulse at peak exercise. In 12/15 patients oxygen pulse at peak exercise was higher following iloprost administration than it was following placebo.

Figure 2. Effect of Iloprost on peak $\dot{V}_{O_2}$. The peak $\dot{V}_{O_2}$ on the exercise test preceded by iloprost administration was higher than on the test preceded by placebo for all 9 patients whose peak $\dot{V}_{O_2}$ was <30 ml/kg/min on the exercise test preceded by placebo administration.

Figure 3.

Relationship between iloprost-related change in peak heart rate and concomitant change in oxygen pulse at peak exercise. A stronger correlation would have been expected if the iloprost-related decline in peak heart rate were due to a negative chronotropic effect of iloprost. The observed poor correlation is consistent with the hypothesis that the lower peak heart rate was effort-related.

Table 1

Patient Characteristics

Patient Characteristic		n (%) or Median (IQR)
Age at First Test (years)		16.68 (11.86)
Race	White (Non-Hispanic)	14 (77.8%)
	Hispanic	4 (22.2%)
Sex	Male	13 (72.2%)
Single Ventricle Diagnosis	Tricuspid Atresia	2 (11.1%)
	Double Inlet Left Ventricle	6 (33.3%)
	HLHS	7 (38.9%)
	Other	3 (16.7%)
Type of Single Ventricle	Left	8 (44.4%)
	Right	9 (50.0%)
	Mixed	1 (5.6%)
Type of Fontan Procedure	Fenestrated Lateral Tunnel	13 (72.2%)
	Right Atrium to Pulmonary Artery	4 (22.2%)
	External Cardiac Conduit	1 (5.6%)
Time Since Surgery (years)		12.98 (13.20)
Pacemaker		3 (16.7%)
ACE Inhibitor		13 (72.2%)
Beta Blocker		2 (11.1%)
Diuretic		4 (22.2%)
Anti-Arrhythmics (Other than Beta Blocker)		8 (44.4%)
ASA or Other Anti-Platelet Therapy		11 (61.1%)
Coumadin		3 (16.7%)
Heparin		0 (0%)
No Medications		3 (16.7%)
Treatment at First Test	Placebo	9 (50.0%)
	Iloprost	9 (50.0%)
Time Between Tests (days)		20.00 (9.50)

HLHS: hypoplastic left heart syndrome; ACE: angiotensin converting enzyme; ASA: aspirin

Table 2

Cardiopulmonary Exercise Test Data

	Median (IQR)			
Exercise Parameter	Placebo	Iloprost	Iloprost-Induced Change	p-value
Baseline HR (bpm)	83 (13)	83 (11)	0.0 (9.0)	0.9866
Baseline Systolic BP (mm Hg)	116 (15)	109 (16)	-5.5 (22.0)	0.2031
Baseline Diastolic BP (mm Hg)	70.5 (12.5)	72.0 (23.0)	2.0 (30.0)	0.8081
Peak O ₂ Pulse (mL/b)	10.4 (3.3)	11.2 (4.4)	1.2 (1.1)	0.0009
Peak V _{O2} (mL/kg/min)	29.5 (10.2)	28.8 (10.4)	1.3 (2.2)	0.0353
%Predicted Peak V _{O2} (%)	70.4 (19.7)	68.7 (22.9)	3.3 (10.2)	0.1070
Peak Work Rate (W/kg)	2.1 (1.0)	2.0 (0.8)	0.0 (0.4)	0.9780
Peak RER	1.1 (0.1)	1.1 (0.1)	0.0 (0.1)	0.9912
Peak HR (bpm)	155 (31)	142 (20)	-10.0 (9.0)	0.0015
Peak Systolic BP (mm Hg)	136 (16)	130 (25)	0.0 (22.0)	0.3911
Peak Diastolic BP (mm Hg)	68 (12)	62 (14)	-6.0 (10.0)	0.1836
Peak Tidal Volume (L)	1.5 (0.6)	1.3 (0.4)	-0.2 (0.2)	0.0003
Peak RR (breaths/min)	45(10)	49 (14)	4 (12)	0.0098
V _{O2} at VAT (mL/kg/min)	14.5 (6.0)	16.6 (5.4)	0.3 (2.1)	0.3028
V _E /V _{CO2} Slope	30.0 (8.0)	30.0 (9.0)	0.0 (5.0)	0.7559
Baseline O ₂ Saturation (%)	94.0 (6.0)	93.0 (5.0)	1.0 (3.0)	0.3635
Peak O ₂ Saturation (%)	89.0 (7.0)	90.0 (6.0)	0.0 (4.0)	0.6387

V_{O2}: oxygen consumption; RER: respiratory exchange ratio; HR: heart rate; RR: respiratory rate VAT: ventilator anaerobic threshold; V_E/V_{CO2} slope; the slope of the linear portion of the minute ventilation vs. carbon dioxide production relationship, below the respiratory compensation point.

Table 3

Effect of Iloprost on Indices of Aerobic Function (outlier excluded)

Exercise Parameter	Median (IQR)			p-value
	Placebo	Iloprost	Iloprost-Induced Change	
Peak O ₂ Pulse (mL/b)	10.8 (2.9)	11.8 (3.8)	1.2 (0.9)	0.0002
Peak V _{O2} (mL/kg/min)	27.6 (10.2)	30.2 (8.8)	1.6 (2.0)	0.0040
%Predicted Peak V _{O2} (%)	68.6 (18.6)	69.5 (19.8)	3.9 (6.8)	0.0203
Peak Work Rate (W/kg)	2.1 (1.0)	2.0 (0.8)	0.0 (0.3)	0.7148
V _{O2} at VAT (mL/kg/min)	14.2 (5.9)	16.9 (5.4)	0.4 (2.0)	0.1040

Abbreviations as in Table 2

Table 4

Change in Lab Parameters Following Iloprost and Placebo Administration

Blood Test	Placebo Median (IQR)			Iloprost Median (IQR)			Iloprost-Induced Change	
	Pre	Post	Change	Pre	Post	Change	Median (IQR)	p-value
Nitrate (μmol/L)	6.90 (8.89)	5.82 (8.60)	-0.28 (3.14)	3.20 (6.90)	1.95 (9.22)	0.31 (1.47)	2.42 (5.56)	0.0830
C-Reactive Protein (n=11)	0.41 (1.22)	0.35 (1.34)	-0.02 (0.21)	0.65 (0.87)	0.56 (0.98)	0.02 (0.06)	-0.02 (0.16)	0.7490
Endothelin-1 (pg/mL)	2.23 (0.15)	2.23 (0.15)	0.00 (0.00)	2.16 (0.15)	2.16 (0.15)	0.00 (0.00)	0.00 (0.00)	1.0000
IFN-γ (pg/mL)	2.24 (1.08)	1.80 (1.70)	-0.22 (1.76)	3.01 (7.94)	2.15 (3.12)	0.00 (2.04)	0.17 (2.99)	0.5186
IL-10 (pg/mL)	3.51 (3.29)	3.52 (3.49)	-0.15 (1.29)	3.17 (8.17)	3.48 (5.26)	0.00 (2.31)	0.09 (2.02)	0.8984
IL-6 (pg/mL)	0.89 (1.81)	0.81 (3.14)	-0.08 (0.53)	1.30 (3.77)	1.36 (2.32)	0.00 (0.42)	0.00 (0.74)	0.7344
TNF-α (pg/mL)	2.64 (1.17)	3.17 (2.75)	0.00 (2.42)	3.12 (2.16)	3.18 (1.73)	0.23 (2.60)	-0.58 (4.33)	0.2334

IFN: interferon; IL: interleukin; TNF: tumor necrosing factor, BNP: brain natriuretic factor. The iloprost induced changes did not differ significantly from those observed following placebo administration, nor did iloprost induced changes correlate with concomitant changes in peak VO₂. Changes in peak VO₂ following iloprost administration were not related to baseline BNP levels.

Table 5

Spirometric Measurements

Measurement	Placebo Median (IQR)			Iloprost Median (IQR)			Iloprost-Induced Change	
	Pre	Post	Change	Pre	Post	Change	Median (IQR)	p-value
FEF 25–75 (L/s)	3.00 (1.83)	2.40 (1.60)	−0.02 (0.42)	3.27 (1.82)	2.90 (1.52)	−0.01 (0.55)	0.04 (0.42)	0.9697
FEF 25–75 % Predicted	94.00 (45.00)	76.00 (29.00)	−1.00 (10.00)	88.00 (42.00)	84.00 (34.00)	−0.50 (17.00)	1.00 (11.50)	0.9492
FEV1 (L)	2.63 (1.05)	2.46 (0.89)	−0.02 (0.09)	2.83 (1.39)	2.68 (1.20)	0.02 (0.25)	−0.01 (0.15)	0.8926
FEV1 % Predicted	93.00 (21.00)	91.00 (20.00)	0.00 (4.00)	91.00 (19.00)	92.00 (25.00)	0.00 (9.00)	−1.00 (5.00)	0.9912
FVC (L)	2.93 (1.36)	2.87 (1.33)	−0.03 (0.19)	3.06 (1.54)	3.10 (1.47)	−0.01 (0.20)	−0.03 (0.30)	0.4436
FVC % Predicted	86.00 (14.00)	91.00 (20.00)	0.00 (5.00)	88.00 (13.00)	89.00 (18.00)	0.00 (6.00)	−2.00 (8.00)	0.3140

FEF 25–75: Mean rate of expiration between 25 and 75% of forced vital capacity; FEV1: volume of air exhaled in first second of forced expiration; FVC: forced vital capacity; NS: not significant