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# Effect of Fontan Fenestration on Regional Venous Oxygen Saturation During Exercise: Further Insights into Fontan Fenestration Closure

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## Abstract

Fontan fenestration closure is a topic of great debate. The body of data regarding the risks and benefits of fenestration closure is limited yet growing. Previous studies have demonstrated that Fontan patients have less exercise capacity than those with normal cardiovascular anatomy. Differences also have been noted within various subgroups of Fontan patients such as whether Fontan is fenestrated or not. This study aimed to compare trends in regional oxygen saturations using near-infrared spectroscopy (NIRS) in patients with Fontan circulations during ramping exercise to further delineate differences between patients with and without a fenestration. It was hypothesized that Fontan patients with fenestrations have better exercise times, higher absolute regional oxygen venous saturations, and smaller arteriovenous differences than Fontan patients without fenestrations. For this study, 50 consecutive Fontan patients and 51 consecutive patients with normal cardiovascular anatomy were recruited. Placement of NIRS probes was performed to obtain regional oxygen saturations from the brain and the kidney. Readings were obtained at 1-min intervals during rest, exercise, and recovery. A standard Bruce protocol was used with a 5-min recovery period. Absolute regional tissue oxygenation values ( $rSO_2$ ) and arterial-venous oxygen saturation differences ( $AVDO_2$ ) calculated as arterial oxygen saturation ( $SPO_2$ )— $rSO_2$  for normal versus Fontan patients and for fenestrated versus unfenestrated Fontan patients were compared using independent *t* tests. When normal and Fontan patients were compared, the Fontan patients had a significantly shorter duration of exercise (9.3 vs 13.2 min;  $p < 0.001$ ). No statistically significant difference in  $rSO_2$  change or  $AVDO_2$  was evident at the time of peak exercise, at 2 min into the recovery, or at 5 min into the recovery. A small oxygen debt also was paid back to the brain in the Fontan patients after exercise, as evidenced by a narrower  $AVDO_2$  than at baseline. The comparison of Fontan patients with and without fenestration showed no statistically significant difference in exercise time,  $rSO_2$  change, or  $AVDO_2$ . The Fontan patients were noted to have shorter exercise times than the normal patients and also appeared to have an alteration in postexertional regional blood flow. However, when the various Fontan subtypes were compared by presence or absence of a fenestration, no significant differences were noted with regard to change in regional oxygen saturation or arteriovenous oxygen saturation. Thus, for patients with Fontan physiology, closure of the fenestration does not seem to have an impact on the dynamics of regional oxygen extraction during exercise or recovery.

## Introduction

Findings have well documented that the Fontan procedure used as palliation for patients with a single ventricle leads to a reduction in exercise capacity. This manifests itself through a significant reduction in exercise time, peak oxygen consumption (peak  $VO_2$ ), and exercise intensity [5, 8, 10, 11, 13, 14, 16, 18, 22, 26, 32, 35, 36, 38]. This impairment in exercise capacity results from the interaction of many different factors, which include, but are not limited to, the following: a dramatic increase in pulmonary artery systolic pressure with subsequent reduction in ventricular stroke volume, a decrease in ventricular end-diastolic pressure, inadequate ventricular preload reserve, impairment of the autoregulation of systemic vascular resistance, and the absence of a prepulmonary pump [2, 4, 12, 20, 21, 27, 33, 34]. Exercise capacity is of particular importance in Fontan patients because it affects quality of life in this physiologically unique population.

During the years since the initial reports of the Fontan operation, this palliative procedure has undergone many modifications and has seen new applications. One such modification has been the introduction of a fenestration. The short-term benefits of fenestration include a shorter postoperative hospital stay, decreased chest tube drainage, and a decreased need for mechanical ventilation [1, 6, 7]. However, the long-term effects of fenestration are unclear.

The potential benefits of fenestration beyond the early postoperative period include reduction of protein-losing enteropathy, plastic bronchitis, and dysrhythmias. The potential risks of fenestration include cyanosis and

thromboembolism. The current data on the impact of fenestration on exercise capacity is similarly conflicting, with no obvious answer as to whether a benefit exists or not [24, 25].

Previous studies have demonstrated regional tissue oxygenation ( $rSO_2$ ) trends in Fontan patients using near-infrared spectroscopy (NIRS) during cardiopulmonary exercise testing (CPET) [9, 30, 31]. The NIRS techniques use the Beer–Lambert law in measuring the concentration of a substance using its absorption of light [29]. The NIRS procedure allows for a noninvasive, continuous means of monitoring  $rSO_2$  by detecting venous-weighted oxyhemoglobin saturation in real time.

This study aimed to investigate further the effect of fenestration status on exercise capacity using  $rSO_2$  while also characterizing NIRS trends in exercising Fontan patients with varying fenestration statuses.

## Methods

This study was initiated with funding assistance from the Children’s Research Institute, a division of Children’s Hospital and Health System, and the Medical College of Wisconsin, Milwaukee, Wisconsin. It received approval from the Institutional Review Board. All patients who had undergone a previous Fontan procedure were eligible for inclusion in the study if they had been referred to undergo CPET by a cardiologist at the Herma Heart Center’s Exercise Physiology Laboratory for further evaluation of symptoms or function. Patients with no structural heart disease or acquired heart disease who had been referred for CPET also were eligible for inclusion and formed the control group.

The single-ventricle patients included in the study all had undergone a three-stage approach for palliation consisting of a Norwood procedure, Glenn anastomosis, and completion Fontan. All the patients underwent a routine clinical evaluation consisting of a thorough history and physical examination before CPET. Consent and assent from the parents were obtained before enrollment of any patients in the study. All patients were tested during an outpatient visit, and no activity restrictions were given before testing.

### Preexercise Testing

The CPET protocol began with application of 12-lead electrocardiogram leads, an automated oscillometric blood pressure cuff on the left arm, and a pulse oximeter on the right index finger to measure arterial oxygen saturation ( $SpO_2$ ) (GE-Marquette, Waukesha, WI, USA). Four NIRS probes with 4-cm source-detector spacing and shallow-field rejection (Adult Somasensor, Covidien 5100C; Somanetics Corp, Troy, MI, USA) were placed on the forehead midline ( $rSO_2$  C), below the 12th rib in the left paravertebral space ( $rSO_2$  R), on the vastus lateralis ( $rSO_2$  L), and on the deltoid muscle ( $rSO_2$  A), respectively. Resting echocardiography (Siemens; Acuson, Mountain View, CA, USA) and electrocardiography (GE Medical Systems; Milwaukee, WI, USA) were performed before CPET.

Four-site regional  $rSO_2$  and  $SpO_2$  were measured and recorded continuously at 6-s intervals during rest, exercise, and a 5-min recovery period. Baseline spirometry (Care Fusion, Yorba Linda, CA, USA) was performed using a forced expiratory maneuver according to the standards of the American Thoracic Society. Forced vital capacity (FVC), forced expiratory volume in 1 s ( $FEV_1$ ), peak expiratory flow (PEF), and maximal mid-expiratory flow were collected. Measurements of breath-by-breath oxygen consumption ( $VO_2$ ), carbon dioxide production ( $VCO_2$ ), and instantaneous respiratory quotient (RQ) also were obtained.

### Exercise Testing

Patients were oriented to the treadmill and given specific instructions about what to expect during the exercise portion of the study. After 1 min of baseline data collection, a modified Bruce protocol was initiated. The workload was progressively increased at set intervals throughout the test until the patient reached voluntary or symptom-limited exhaustion (quitting time [QT]).

Electrocardiography, blood pressure, oxygen saturation, and breath-by-breath ventilatory data were recorded at 1-min intervals throughout the exercise portion of the test. Immediately after the exercise portion of the test was a 5-min recovery period (3 min of walking followed by a 2 min of sitting). All SpO<sub>2</sub>, heart rate, blood pressure, VO<sub>2</sub>, VCO<sub>2</sub>, RQ, and NIRS data were synchronously aggregated. Patients unable to complete the CPET protocol and those who had incomplete metabolic chart data acquisition were excluded from the study.

## Data Analysis

Means and standard deviations were calculated for all baseline characteristics and then compared between the control and Fontan patients and between the fenestrated and unfenestrated Fontan patients using unpaired *t* tests. The mean percentage of change in rSO<sub>2</sub> and arterial-venous oxygen saturation differences (AVDO<sub>2</sub>) from baseline to the following time points was calculated and plotted: peak exercise, 2 min after exercise, and 5 min after exercise. The mean change at these time points for the normal and Fontan groups then was compared using the unpaired *t* test. Statistical analysis was performed using SPSS statistical software, version 20.0 (SPSS, Chicago, IL, USA). All *p* values lower than 0.05 were considered statistically significant.

## Results

### Normal Versus Fontan Patients

The study enrolled 51 normal patients and 50 Fontan patients. Comparisons of the baseline characteristics between these two groups are summarized in Table 1. As expected, the Fontan patients tended to be younger and to have lower weight (in pounds), FVC, FEV<sub>1</sub>, resting systolic blood pressure, and resting diastolic blood pressure. The Fontan patients also tended to have significantly lower resting renal oxygen saturations (65.4 ± 10.8 vs 76.8 ± 9.3 %; *p* < 0.001) and lower cerebral oxygen saturations (60.7 ± 8.8 vs 69.9 ± 10.1 %; *p* < 0.001). When this relationship was further examined in terms of Fontan fenestration status, the unfenestrated Fontan patients had a lower mean resting cerebral saturation (63.1 ± 8.6 %) than the normal patients (*p* = 0.002) as well as a lower mean resting renal saturation (66.8 ± 11.0 %; *p* < 0.001).

**Table 1 Comparison of baseline characteristics between normal and Fontan patients**

	Normal	Fontan	<i>p</i> Value
No. of patients	51	50	
No. of males: <i>n</i> (%)	26 (52)	33 (66)	
Age (years)	16.6 ± 6.7	11.6 ± 3.8	<0.001
Weight (lb)	132.8 ± 34.2	79.4 ± 28.5	<0.001
Height (in.)	65.9 ± 4.9	59.8 ± 17.1	0.012
FVC (L)	3.8 ± 1.0	1.9 ± 0.8	<0.001
FEV <sub>1</sub> (L)	3.4 ± 0.9	1.6 ± 0.6	<0.001
PEF (L/min)	6.8 ± 1.7	7.3 ± 13.5	0.895
Resting respiratory rate (rpm)	49.7 ± 11.6	51.0 ± 12.3	0.626
Resting heart rate (bpm)	74.5 ± 12.5	83.3 ± 16.8	<0.001
Resting systolic blood pressure (mmHg)	110.7 ± 8.5	100.5 ± 11.1	<0.001
Resting diastolic blood pressure (mmHg)	68.0 ± 8.3	60.2 ± 8.3	<0.001
Resting systemic saturation (%)	95.0 ± 1.0	93.1 ± 4.1	0.002
Resting renal saturation (%)	76.8 ± 9.3	65.4 ± 10.8	<0.001
Resting cerebral saturation (%)	69.9 ± 10.1	60.7 ± 8.8	<0.001
Resting deltoid saturation (%)	76.8 ± 9.0	70.4 ± 7.6	
Resting vastus lateralis saturation (%)	62.9 ± 11.1	56.6 ± 8.2	0.009
Exercise time (min)	13.2 ± 2.5	9.3 ± 1.8	<0.001
VO <sub>2</sub> at peak exercise	2.6 ± 0.9	1.4 ± 0.5	0.254

End-tidal CO <sub>2</sub> at peak exercise	37.7 ± 5.0	31.5 ± 4.9	0.283
RQ at peak exercise	1.1 ± 0.1	1.0 ± 0.9	0.675

FVC forced vital capacity, FEV<sub>1</sub> forced expiratory volume in 1 s, PEF peak expiratory flow, rpm revolutions/min, bpm beats/min, VO<sub>2</sub> oxygen consumption, CO<sub>2</sub> carbon dioxide, RQ respiratory quotient

The fenestrated Fontan patients had a lower mean resting cerebral oxygen saturation (55.7 ± 7.3 %; *p* < 0.001) than the normal patients and a lower mean resting renal oxygen saturation (58.3 ± 18.5 %; *p* < 0.001). Exercise time in minutes also was significantly shorter among the Fontan patients than among the normal patients (9.3 ± 1.8 % vs 13.2 ± 2.5 %; *p* < 0.001).

Regional renal oxygen saturations showed a greater change from baseline in the Fontan patients than in the normal patients (-4.1 vs -0.6 %) 2 min into the recovery period. Otherwise, renal rSO<sub>2</sub> did not differ significantly at peak exercise or 5 min into recovery. The change in cerebral rSO<sub>2</sub> from baseline to any time point did not differ significantly between the Fontan and normal patients (Table 2). Neither did the renal or cerebral AVDO<sub>2</sub> differ significantly at the predefined time points between the Fontan and normal patients. A morphologic right ventricle was found in 27 of the Fontan patients and a morphologic left ventricle in the remaining patients.

**Table 2 Change in regional venous oxygen saturations between normal and Fontan patients at predefined times<sup>a</sup>**

	Change from rest to peak exercise	Change from rest to 2 min into recovery	Change from rest to 5 min into recovery
Kidney: normal	-18.5 (-24.1)	-0.5 (-0.6) <sup>b</sup>	1.4 (1.8)
Kidney: Fontan	-14.9 (-22.8)	-2.7 (-4.1)	-0.3 (-0.4)
Brain: normal	-5.5 (-7.6) <sup>b</sup>	0.1 (0.1)	3.9 (5.6)
Brain: Fontan	-7.0 (-11.5)	0.7 (1.2)	4.1 (6.7)
Deltoid: normal	20.2 (-26.3)	2.8 (-3.7)	1.5 (2.0)
Deltoid: Fontan	-14.5 (-20.6)	-4.6 (-6.6)	-0.9 (-1.3)
Vastus lateralis: normal	-8.3 (-13.2)	8.7 (13.8) <sup>b</sup>	9.8 (15.6)
Vastus lateralis: Fontan	-6.0 (-10.6)	3.6 (6.3)	4.6 (8.1)

<sup>a</sup>Values are expressed as absolute change (% change)

<sup>b</sup>Significant difference in rSO<sub>2</sub> between the NL and Fontan groups at any given time interval

## Fenestrated Versus Unfenestrated Fontan

Of the 50 Fontan patients, 16 were fenestrated and 34 were unfenestrated. The baseline characteristics of these two groups demonstrated significantly lower age, weight, and height in the fenestrated Fontan group (Table 3). The baseline FVC, FEV<sub>1</sub>, resting systolic blood pressure, and resting diastolic blood pressure also were significantly lower in this group. The resting systemic oxygen saturations were significantly lower in the fenestrated Fontan patients, with an average saturation of 89.3 % compared with 94.9 % in the unfenestrated Fontan patients (*p* < 0.001). The resting cerebral venous oxygen saturations also were lower in the fenestrated Fontan patients, with an average saturation of 55.7 % compared with 63.1 % in the unfenestrated Fontan patients (*p* < 0.003). The exercise times did not differ significantly between the two groups, with the fenestrated Fontan patients averaging 8.7 min compared with 9.6 min among the unfenestrated Fontan patients.

**Table 3 Comparison of baseline characteristics between Fontan patients with and without fenestration**

	Fenestrated	Unfenestrated	<i>p</i> value
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No. of patients	16	34	
No. of males: <i>n</i> (%)	9 (56)	24 (71)	
Age (years)	8.8 ± 2.1	12.9 ± 4.3	<0.001
Weight (lb)	57.7 ± 14.3	89.0 ± 28.3	<0.001
Height (in.)	50.3 ± 5.5	64.1 ± 19.0	<0.001
FVC (L)	1.3 ± 0.2	2.3 ± 0.8	0.002
FEV <sub>1</sub> (L)	1.2 ± 0.2	1.9 ± 0.6	0.006
PEF (L/min)	3.2 ± 0.9	4.5 ± 19.1	0.110
Resting respiratory rate (rpm)	59.1 ± 9.7	48.9 ± 12.3	0.049
Resting heart rate (bpm)	86.4 ± 18.5	81.9 ± 16.1	0.422
Resting systolic blood pressure (mmHg)	93.8 ± 8.3	103.7 ± 11.1	0.001
Resting diastolic blood pressure (mmHg)	53.5 ± 6.8	63.4 ± 7.1	<0.001
Resting systemic saturation (%)	89.3 ± 4.1	94.9 ± 2.8	<0.001
Resting renal saturation (%)	62.2 ± 10.4	66.8 ± 11.0	0.172
Resting cerebral saturation (%)	55.7 ± 7.3	63.1 ± 8.6	0.003
Resting deltoid saturation (%)	65.6 ± 5.7	72.4 ± 7.9	0.075
Resting vastus lateralis saturation (%)	56.8 ± 9.6	56.5 ± 8.4	0.954
Exercise time (min)	8.7 ± 1.6	9.6 ± 1.8	0.089
VO <sub>2</sub> at peak exercise	0.9 ± 0.2	1.5 ± 0.4	0.438
End-tidal CO <sub>2</sub> at peak exercise	28.9 ± 3.9	32.2 ± 4.9	0.284
RQ at peak exercise	0.9 ± 0.1	1.0 ± 0.1	0.734

FVC forced vital capacity, FEV<sub>1</sub> forced expiratory volume in 1 s, PEF peak expiratory flow, rpm revolutions/min, bpm beats/min, VO<sub>2</sub> oxygen consumption, CO<sub>2</sub> carbon dioxide, RQ respiratory quotient

The change in renal and cerebral rSO<sub>2</sub> from baseline to predefined time points is depicted in Table 4. This change from baseline to any of the predefined time points did not differ between the Fontan patients based on fenestration status. The only exception to this was observed 5 min into the recovery, at which point the unfenestrated Fontan patients had a 1.2-point increase in renal venous oxygen saturation from resting values compared with a 5.9-point decrease in the fenestrated group. Table 3 compares the average renal and cerebral rSO<sub>2</sub> trends during CPET between the fenestrated and unfenestrated Fontan patients. The AVDO<sub>2</sub> did not differ between these two groups at any of the predefined time points.

**Table 4 Change in regional venous saturations between Fontan patients with and without fenestration at predefined times**

	Change from rest to peak	Change from rest to 2 min into recovery	Change from rest to 5 min into recovery
Kidney: fenestrated	-14.4 (-23.1)	-0.4 (-5.9)	-3.7 (-5.9) <sup>b</sup>
Kidney: unfenestrated	-14.7 (-22.0)	-2.3 (-3.5)	0.8 (1.2)
Brain: fenestrated	-5.1 (-9.1)	1.2 (2.1)	4.5 (8.1)
Brain: unfenestrated	-7.6 (-12.1)	0.4 (0.7)	3.8 (6.1)
Deltoid: fenestrated	-3.2 (-4.9) <sup>b</sup>	-3.4 (-5.2)	-3.8 (-5.8)
Deltoid: unfenestrated	-16.4 (-22.6)	-5.2 (-7.2)	0.7 (1.0)
Vastus lateralis: fenestrated	-2.0 (-3.5)	0.7 (1.2)	0.1 (0.2) <sup>b</sup>

Vastus lateralis: unfenestrated	-5.3 (-9.3)	4.4 (7.7)	6.8 (12.02)
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<sup>a</sup>Values are expressed as absolute change (% change)

<sup>b</sup>Significant difference in rSO<sub>2</sub> between the fenestrated and unfenestrated groups at any given interval

In terms of peak VO<sub>2</sub>, the Fontan patients with fenestration had a mean of 33.0 mL/kg/min compared with Fontan patients without fenestration, who had a mean of 34.6 mL/kg/min. When these are converted into percentage of predicted values, the Fontan patients with fenestration had a mean of 72.1 ± 7.5 % compared with a mean of 72.3 ± 13.3 % for the Fontan patients without fenestration. Neither of these comparisons demonstrated any statistical difference, with *p* values of 0.633 and 0.977, respectively.

## Discussion

This study is the first to report the use of NIRS during CPET in Fontan patients. The findings demonstrate no significant effect of fenestration status on regional venous oxygen saturations during exercise in Fontan patients in different visceral beds with differing flow metabolism control mechanisms. Changes in cerebral, renal, and skeletal muscle NIRS values from baseline to various points in CPET did not differ significantly between the two groups except for minor differences noted at the 5-min recovery time point in cerebral venous oxygen saturations. The AVDO<sub>2</sub> also did not differ between the two groups, demonstrating that distribution of blood flow and oxygen extraction during exercise may be unaffected by fenestration status. These trends were noted despite the lower absolute regional oxygen saturations noted in the fenestrated group, a phenomenon expected because of the right-to-left shunt provided by the fenestration.

Together with similar NIRS trends, both the Fontan patients with and without fenestration also had similar exercise times in this cohort. This, however, may simply represent the findings for a relatively younger Fontan population. Previous studies have documented that Fontan patients in late adolescence tend to have the greatest decrease in exercise capacity, so it still is possible that fenestration status has effects on exercise time that are statistically significant as Fontan patients age [15, 17]. Exercise times in Fontan patients have not been reported previously with respect to fenestration status specifically.

Regarding ventilatory capacity, this study found no difference in absolute peak VO<sub>2</sub> or percentage of predicted peak VO<sub>2</sub> between the Fontan patients with and without fenestration. This indicates that exercise capacity may not differ between Fontan patients based on fenestration status. This finding is consistent with the findings of an earlier study by Meadows et al. [24], which demonstrated no improvement in peak VO<sub>2</sub> in patients before and after fenestration closure. The study by Meadows et al. [24], however, did find improvements in the VE/VCO<sub>2</sub> slope, end-tidal CO<sub>2</sub> at the anaerobic threshold, and end-tidal O<sub>2</sub> at peak exercise.

An additional finding of note was the greater AVDO<sub>2</sub> observed in the Fontan patients than in the normal patients. Although this was not surprising in and of itself, the fact that this occurred even when fenestrated and unfenestrated Fontan patients were compared with normal patients separately is surprising. This may have been due in part to a limitation in cerebral blood flow resulting from the lack of a subpulmonary ventricle and from the subsequent low systemic venous compliance. An exaggerated hyperventilatory response in Fontan patients during exercise also may contribute to this [30].

Data on significant differences between Fontan patients with and without fenestration can help to determine whether fenestration closure is necessary or not. Currently, no guidelines on fenestration closure exist, and the decision often is based on physician preference and limited anecdotal evidence. Whether a fenestration offers a benefit in the long term or not still remains to be well delineated.

A study by Ono et al. [28] demonstrated that those with a fenestration had statistically significantly longer survival and freedom from tachyarrhythmia 10 years after the Fontan procedure than those without a fenestration. Freedom from reoperation at 10 years also was greater, although this difference did not reach statistical significance.

The benefits of a fenestration in reducing the incidence of protein-losing enteropathy also have been demonstrated. One such study evaluated patients who underwent transcatheter Fontan fenestration for protein-losing enteropathy after a median of 11.3 years, with limited success in preventing future recurrences. Many of the recurrences reported occurred years after the fenestration, a point at which the fenestration may have spontaneously closed. Thus, a patent fenestration may have provided some benefit for these patients even long after the Fontan procedure [37].

The benefits of fenestration closure also have been documented. In addition to improvement in arterial oxygen saturations, improvements in aerobic capacity also have been noted [23].

Another series followed patients for 10 years after the Fontan procedure and noted improvement in oxygenation, reduction in the need for cardiac medications, and improvement in somatic growth. It also has been hypothesized that fenestration closure may reduce the risk for thromboembolic events, although this has not been substantiated by studies [3, 19].

The limitations of this study included susceptibility to bias due to its retrospective nature. Fenestrations are more common in the more recent surgical era, and this may be reason why those with fenestration had a lower baseline age.

Another limitation of this study was that the patients with and without fenestrations represented two distinct populations and not a single population before and after fenestration closure. Small sample size and no prior similar data comparing Fontan patients with and without fenestration also were limiting factors. The difference in baseline ages between the groups also was a limitation of this study.

## Conclusion

This study demonstrated that blood flow distribution, regional oxygen extraction, and exercise time did not differ between the Fontan patients with and without fenestration during rest or exercise. A paucity of data still remains with regard to the long-term risks and benefits of fenestration, although this study has added to the data demonstrating that routine fenestration closure is necessary.

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