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MINI-FOCUS ISSUE: THE FONTAN PROCEDURE

Fontan Fenestration Closure Has No Acute Effect on Exercise Capacity but Improves Ventilatory Response to Exercise

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Objectives The aim of this study was to prospectively examine the effects of elective Fontan fenestration closure upon exercise capacity and ventilatory abnormalities.

Background For patients undergoing Fontan procedures as palliation of single ventricle physiology, the addition of a fenestration to the procedure mitigates perioperative morbidity. Although some fenestrations may close spontaneously, many remain patent and subject patients to arterial hypoxemia and risk for paradoxical emboli. For these reasons fenestration closure is routinely performed post-operatively in the cardiac catheterization laboratory. Although closure of Fontan fenestrations typically results in an immediate improvement in systemic arterial oxygen saturation, it is also associated with an acute decrease in cardiac index and systemic O_2 delivery. The sum result of these physiologic changes upon exercise capacity has not been examined.

Methods Twenty consecutive patients, age 5 to 46 (median 10) years, underwent pre- and post-fenestration closure exercise testing with expiratory gas analysis.

Results Before fenestration closure, peak oxygen consumption (VO_2) was depressed and there was systemic desaturation at rest that worsened with exercise. The ventilatory response to exercise was also abnormal, characterized by elevation of the minute ventilation (VE)/CO_2 elimination slope (VE/VCO_2), a low end-tidal CO_2, and high end-tidal O_2 at the ventilatory anaerobic threshold. Although arterial saturation improved significantly after fenestration closure, there was no change in peak VO_2 (70.9 ± 18.6% to 74.0 ± 18.6%, p = NS), heart rate, or O_2 pulse at peak exercise. In contrast, ventilatory abnormalities (VE/VCO_2) improved considerably (44.4 ± 10.9 to 33.3 ± 5.5, $p \leq 0.001$).

Conclusions Fontan fenestration closure does not significantly improve peak VO_2. However, ventilatory abnormalities improve considerably. (J Am Coll Cardiol 2008;52:108–13) © 2008 by the American College of Cardiology Foundation

Since its initial description (1) implementation of the Fontan procedure and its modifications have resulted in improved survival for a diverse group of patients with complex congenital heart disease and single ventricle physiology. Separation of the systemic and pulmonary circulations in these patients reduces systemic ventricular volume loading and provides normal or near-normal systemic arterial O_2 saturation. Fenestration of the Fontan pathway was introduced in 1990 as a means to ameliorate the perioperative course for high-risk patients (2). Although there remains debate about the indications for this modification (3–5), it is now routine in many centers for both high- and standard-risk patient populations. Although some fenestrations may close spontaneously, many remain patent and subject patients to systemic arterial hypoxemia and risk for systemic arterial emboli. For this reason fenestration closure is routinely performed in the cardiac catheterization laboratory. Although closure of Fontan fenestrations typically results in an immediate improvement in systemic arterial oxygen saturation, it is also associated with an acute decrease in cardiac index and systemic O_2 delivery (2,6–10). Given these somewhat dispiriting physiologic sequelae, it is surprising that most prior studies of the consequences of fenestration closure have remained limited to technical or acute hemodynamic examinations. Observation suggests that these patients seem to be clinically well at midterm follow-up (9); however, there exists virtually no quantitative information regarding the effects of this important inter-

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vention upon patients beyond the unique environment of the catheterization laboratory. For this reason we sought to determine, through formal exercise testing, the effect of Fontan fenestration closure upon the ability of these patients to tolerate sustained physiologic stress.

Methods

This study was designed and the data were collected prospectively. Study design and participant recruitment were reviewed and approved by departmental and institutional review boards. We prospectively recruited all patients age 5 to 46 years who were referred for elective device closure of a Fontan fenestration or significant baffle leak at Children's Hospital Boston's Cardiac Catheterization Laboratory between January 2005 and March 2007. Exclusion criteria included: patients of insufficient age to complete exercise testing with expiratory gas analysis; patients with other physical or cognitive limitations rendering them unable to undergo exercise testing; patients with history of significant exercise-induced arrhythmias; and patients with severe ventricular dysfunction, severe atrioventricular valve regurgitation, or severe systemic ventricular outflow obstruction (peak gradient >50 mm Hg) on their most recent echocardiogram. Each patient acted as his/her own control for pre- and post-exercise analysis. Participants underwent an exercise tolerance test with expiratory gas analysis before the day of the catheterization and again 1 to 12 months after closure.

Exercise protocol. All patients performed a progressive exercise test with expiratory gas analysis before and after fenestration closure. A standard Bruce treadmill protocol was used for patients who were too small for a cycle ergometer (n = 6). A ramped, cycle ergometry protocol was used for all other patients. The exercise testing protocol that was used after fenestration closure was identical to that employed for the pre-catheterization study. Expiratory gas analysis was performed with a Medical Graphics metabolic cart (Medical Graphics Corp., St. Paul, Minnesota). The highest oxygen consumption (VO_2) achieved by the subject during the test was recorded as peak VO_2. Peak exercise O_2 pulse was calculated by dividing peak VO_2 by peak heart rate. The slope of the minute ventilation (VE) versus carbon dioxide (CO_2) production relationship below the respiratory compensation point (VE/VCO_2 slope; an index of the efficiency of gas exchange during exercise) was calculated as previously described (11). The ventilatory anaerobic threshold (VAT) was determined by the V-slope method (12). To further characterize the physiology of the patients' gas exchange during exercise, we also analyzed measurements of the patients' partial pressure of end-tidal carbon dioxide ($pETCO_2$) and end-tidal pO_2 ($pETO_2$) at the VAT. This point in the exercise test was selected because the alveolar gas composition at the VAT is affected neither by the anticipatory hyperventilation commonly encountered near the start of exercise nor the compensatory respiratory alkalosis that normally develops above the anaerobic threshold. Predicted values were calculated on the basis of regression equations that take into account age, gender, and size (13).

Cardiac catheterization. All catheterizations were performed at a single institution with standard percutaneous techniques. Systemic heparinization was administered in all procedures as 100 U/kg intravenously with additional doses administered to maintain an activated clotting time >220 s. Post-procedural aspirin was recommended for all patients for a minimum of 3 to 6 months. Decisions regarding choice, timing, and technique of procedural interventions were left to the performing physician, including choice of fenestration occlusion device. Calculations of systemic and pulmonary flows and their ratio (QpQs) were made with the principles described by Fick (14), with assumed values for O_2 consumption according to data published by LeFarge and Miettinen (15). The superior vena cava saturation was taken as the mixed venous saturation and systemic arterial saturations were taken from the descending thoracic aorta. Pulmonary venous saturations were obtained directly. Total pulmonary vascular resistance was expressed in indexed Woods Units (mm Hg/l/min/m^2). The O_2 delivery was calculated as the product of cardiac index and arterial O_2 content. Because all initial hemodynamic evaluations were performed with the patients breathing room air, the contribution of dissolved O_2 was neglected from these calculations.

Statistical analysis. Continuous variables are summarized as mean ± SD or median (range). Pearson correlation coefficients were used to assess relationships between continuous variables, including hemodynamic findings at catheterization and indexes of exercise function. Because of the wide variation in patient age and size and to take into account growth-related changes between the pre- and post-fenestration closure exercise tests, analyses of exercise capacity focused upon percent predicted (rather than absolute) values. Comparison of means for pre- and post-fenestration closure data was performed with the paired *t* test.

Abbreviations and Acronyms

- pCO_2 = partial pressure of carbon dioxide
- $pETCO_2$ = partial pressure of end-tidal carbon dioxide
- $pETO_2$ = partial pressure of end-tidal oxygen
- pO_2 = partial pressure of oxygen
- QpQs = ratio of pulmonary to systemic blood flow
- RER = respiratory exchange ratio
- VAT = ventilatory anaerobic threshold
- VE = minute ventilation
- VE/VCO_2 = minute ventilation/carbon dioxide elimination
- VO_2 = oxygen consumption.

Results

The average age at catheterization was 13.8 ± 10.4 years. All patients were in sinus rhythm during exercise testing and catheterization. The systemic ventricle was left in 11 (55%) and right in the remainder. All patients had undergone a

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Table 1 Hemodynamic Result of Acute Fontan Fenestration Occlusion (n = 16)

	Before Fenestration Occlusion	After Fenestration Occlusion	Absolute Change	Percent Change	p Value
Systemic arterial saturation, %	90.7	94.4	3.7	4.1%	<0.001
Systemic venous pressure, mm Hg	13.6	15.1	1.5	11%	0.002
Mixed venous saturation, %	70.9	70.8	−0.1	0%	NS
Cardiac index, l/min/m^2	3.2	2.8	−0.4	−12.5%	0.004
Systemic oxygen delivery, ml/min/m^2	604.9	543.0	−61.9	−10.2%	0.044

lateral tunnel fenestrated Fontan performed with a 4-mm punched fenestration that was angiographically patent at the time of catheterization. Additional baffle leaks were identified in 5 (25%) and were coil occluded in 3. Fenestration closure was performed with a 17-mm CardioSEAL (NMT Medical, Boston, Massachusetts) in 17 patients and with a 4-mm Amplatzer (AGA Medical Corp., Golden Valley, Minnesota) septal occluder in the remainder. Additional interventions were performed in 11 patients, including baffle dilation in 7 patients and baffle stenting in 3 patients. Five patients underwent pulmonary arterial angioplasty. Veno-venous collaterals resulting in right-to-left shunting were coil occluded in 4 patients. Post-intervention angiography demonstrated no greater than trivial residual right-to-left shunting in all patients.

Exercise correlations of cardiac catheterization variables. There was no correlation between pre-catheterization exercise capacity as assessed by percent predicted peak VO_2 or VAT and any baseline hemodynamic variable obtained in the catheterization laboratory, including cardiac index, mixed venous saturation, systemic arterial saturation, systemic venous pressure, ventricular end-diastolic pressure, or QpQs.

Acute effects of fenestration closure. All patients underwent routine hemodynamic evaluation before fenestration closure. For those in whom data were available, comparison of pre- and post-fenestration occlusion hemodynamic findings demonstrated a significant increase in systemic arterial O_2 saturation and a small but significant increase in systemic venous pressures (Table 1). There was no change in mixed venous O_2 saturation but an average 12.5% decrease in calculated cardiac index and 10.2% decrease in systemic O_2 delivery.

Effect of fenestration closure on exercise capacity. The median time from fenestration closure to second exercise study was 5.5 months. Adequate patient effort with exercise testing was suggested by an average respiratory exchange ratio of 1.1. Before fenestration closure, peak O_2 consumption was depressed and there was systemic desaturation at rest that worsened with exercise (Table 2). The ventilatory response to exercise was also abnormal, characterized by elevation of the VE/VCO_2 slope (indicating inefficient gas exchange during exercise), a low $pETCO_2$ and high $pETO_2$ at the VAT. As expected, fenestration occlusion resulted in a marked improvement in O_2 saturation, both at rest (88.7 ± 3.6% to 95.3 ± 1.8%, $p < 0.001$) and at peak exercise (82.0 ± 4.6% to 91.7 ± 2.7%, $p < 0.001$). However, there was no significant change in the percent predicted VO_2 (70.9 ± 18.6% to 74.0 ± 18.6%, p = NS), heart rate, or O_2 pulse, at peak exercise (Table 2). In contrast, ventilatory abnormalities improved considerably after fenestration closure. In every patient, the VE/VCO_2 slope fell, and in 19 of the 20 patients the $pETO_2$ at the VAT fell and the $pETCO_2$ at the VAT rose (Fig. 1).

Discussion

Changes in exercise capacity. The acute physiologic changes that accompany Fontan fenestration closure have been documented in numerous previous investigations. The results are remarkably consistent regardless of the time interval between surgery and fenestration closure. There is a 6% to 12% increase in systemic arterial O_2 saturation, accompanied by a minor, 0.5 to 1.6 mm Hg, increase in systemic venous (Fontan) pressures and a more substantial,

Table 2 Exercise Performance Before and After Fontan Fenestration Closure (n = 20)

	Before Fenestration Occlusion	After Fenestration Occlusion	Absolute Change	Percent Change	p Value
Percent predicted peak VO_2, %	70.9 ± 18.6	74.0 ± 18.6	3.1	4.4%	NS
Percent predicted peak O_2 pulse, %	92.2 ± 26.8	93.3 ± 24.2	1.1	1.2%	NS
Peak heart rate, beats/min	153 ± 23	156 ± 23	3	2.0%	NS
Oxygen saturation at rest, %	88.7 ± 3.6	95.3 ± 1.8	6.6	7.4%	<0.001
Oxygen saturation peak exercise, %	82.0 ± 4.6	91.7 ± 2.7	9.7	11.8%	<0.001
VE/VCO_2 slope	44.4 ± 10.9	33.3 ± 5.5	−11.1	−25.0%	<0.001
End-tidal CO_2 at VAT, mm Hg	28.3 ± 4.1	34.4 ± 3.0	6.1	21%	<0.001
End-tidal O_2 at peak exercise, mm Hg	117.3 ± 4.6	109.2 ± 4.8	−7.9	−6.7%	<0.001

CO_2 = carbon dioxide; O_2 = oxygen; VAT = ventilatory anaerobic threshold; VE/VCO_2 = minute ventilation/carbon dioxide elimination; VO_2 = oxygen consumption.

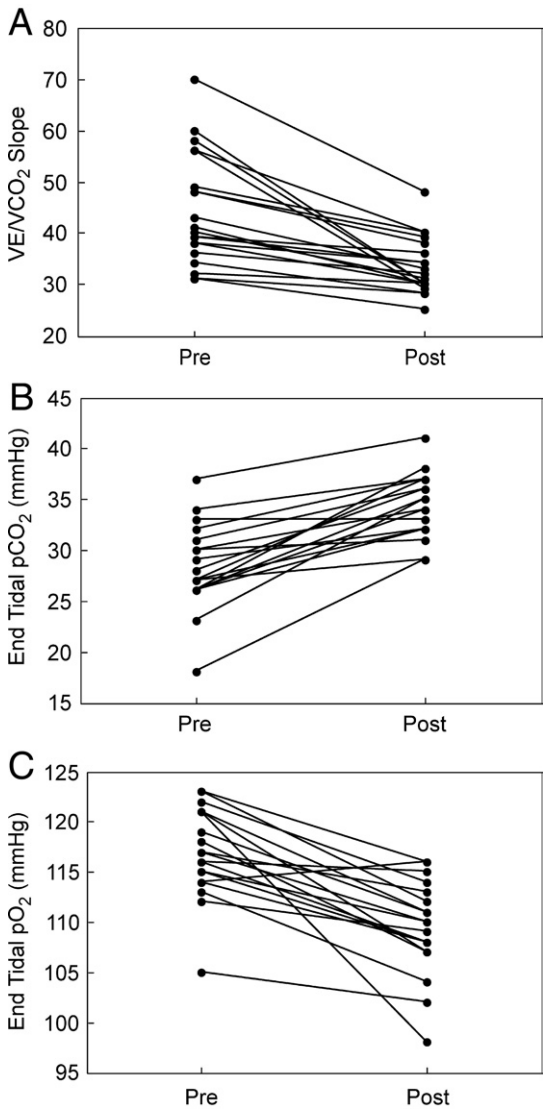

Figure 1 **Changes in Ventilatory Function During Exercise After Fenestration Closure**

Fenestration closure-associated changes in each individual patient's minute ventilation/carbon dioxide elimination (VE/VCO_2) slope **(A)**, end-tidal partial pressure of carbon dioxide (pCO_2) at the ventilatory anaerobic threshold **(B)**, and end-tidal partial pressure of oxygen (pO_2) at the anaerobic threshold **(C)**. The VE/VCO_2 slope fell in every patient. The end-tidal pCO_2 rose and the end-tidal pO_2 fell in 19 of 20 patients. Post = post-fenestration closure; Pre = pre-fenestration closure.

16% to 26%, decrease in cardiac index (2,6–10). On balance, despite an increase in systemic arterial O_2 saturation, there is a 10% to 13% decrease in systemic O_2 delivery (6–8). Our findings are consistent with these previous reports. However, in this study population, despite the diverse and sometimes adverse physiologic changes that are observed acutely after Fontan fenestration closure, we found no change in exercise capacity as assessed by percent predicted VO_2, percent predicted VAT, or O_2 pulse at peak exercise. In contrast, ventilatory pattern abnormalities improved considerably.

That exercise capacity in these patients remains unchanged seems to be at odds with the commonly held belief that improving arterial O_2 saturation will improve exercise tolerance. It also seems incompatible with the observations at catheterization that cardiac output and O_2 delivery decline acutely after fenestration closure. Although it is tempting to view this finding as the simple net result of competing variables, for numerous reasons the situation is more complex than limited consideration may imply. First, the reliability of observations obtained at catheterization during fenestration occlusion may be questioned, because they reflect not only direct cardiovascular effects of this intervention but also the combined intended and unintended affects of the medications, contrast media, and intravenous fluids routinely administered during these procedures. Consequently, data derived acutely in the catheterization laboratory provide, at best, an incomplete understanding of the lasting effects of fenestration closure upon these patients. Second, there are many additional factors (e.g., the health and function of the pulmonary vascular bed, chronotropic competency, the ability to augment stroke volume during exercise, systemic venous flow dynamics, and ventilatory dynamics) that influence the exercise function of the patient with a Fontan circulation (16–25), and the influence of fenestration closure on these variables is difficult to assess by routine methods. Finally, patients with residual right-to-left shunts also are subject to increased systemic arterial O_2 desaturation with physical exertion as well as an abnormal ventilatory response to exertion, factors that might exacerbate their perception of dyspnea during exercise, independent of peak VO_2. Hence, the numerous factors that may influence exercise capacity render difficult any a priori prediction regarding the effect of fenestration closure on an individual's exercise capacity. These considerations highlight the importance of a careful physiologic assessment of the effects of fenestration closure on the Fontan patient's exercise function.

Changes in O_2 pulse. It is interesting to note that the O_2 pulse at peak exercise did not change after fenestration closure. The O_2 pulse (VO_2/[heart rate]) is the amount of O_2 extracted from the blood with each heartbeat. The O_2 pulse is, on the basis of the Fick equation, equivalent to the product of stroke volume and O_2 extraction:

$$\begin{aligned} O_2 \text{ pulse} &= VO_2/(\text{heart rate}) \\ &= (\text{cardiac output})/(\text{heart rate}) \times (C_aO_2 - C_{mv}O_2) \\ &= (\text{stroke volume}) \times (C_aO_2 - C_{mv}O_2) \end{aligned}$$

where C_aO_2 is the arterial O_2 content and $C_{mv}O_2$ is the mixed venous O_2 content. At peak exercise, O_2 extraction is maximized and mixed venous O_2 content is reduced to approximately the same low value across a wide spectrum of cardiovascular conditions (11,13). Hence, in individuals with normal systemic arterial saturation (and normal hemo-

globin levels) the O_2 extraction at peak exercise varies little between subjects, and O_2 pulse at peak exercise is proportional to stroke volume at peak exercise. In patients with arterial desaturation, however, the physiology is less straightforward, because the reduced arterial O_2 saturation (and the associated polycythemia, if present) complicates the relationship between O_2 pulse and stroke volume. Therefore, in the case of the fenestrated Fontan patient, it is more instructive to think of the O_2 pulse as the amount of O_2 added to the blood with each heartbeat (a quantity that is conceptually different but mathematically equivalent to the amount of O_2 extracted from the blood with each heartbeat). This quantity is equal to:

$$(\text{pulmonary blood flow})/(\text{heart rate}) \times (C_{pv}O_2 - C_{mv}O_2)$$

where $C_{pv}O_2$ is the pulmonary venous O_2 content. Consequently, because fenestration closure does not change $C_{pv}O_2$, $C_{mv}O_2$, or heart rate significantly, the stability of the O_2 pulse at peak exercise before and after fenestration closure implies that the Fontan patient's exercise capacity is limited by the amount of blood that the pulmonary vascular bed can accommodate at peak exercise when it is passively perfused by systemic venous pressure. It should be noted, however, that by decreasing the right to left shunt, fenestration closure probably does increase pulmonary blood flow during submaximal exercise. We believe that this effect is linked to the improvements in gas exchange that we observed after fenestration closure.

Changes in ventilatory abnormalities. The effect of fenestration closure on the Fontan patient's ventilatory abnormalities also deserves further consideration. It has been recognized previously that patients with right-to-left shunts exhibit an abnormal ventilatory response to exercise (26,27). The physiologic mechanisms underlying this response have been illuminated by simultaneous expiratory gas and arterial blood gas analysis (28), which again emphasizes the importance of and distinction between relative pulmonary and systemic blood flow and the central mechanisms that underlie respiratory control and gas exchange in this patient population. We hypothesize on the basis of these data and our own observations that, before fenestration closure, right-to-left shunting causes CO_2-rich systemic venous blood to enter the systemic arterial circulation during exercise. The consequent increase in arterial partial pressure of carbon dioxide (pCO_2) is sensed by chemoreceptors, inducing central nervous system respiratory centers to increase the patient's respiratory drive (and VE) and causing the VE/VCO_2 slope to rise. The resulting alveolar hyperventilation (reflected by the low $pETCO_2$ and high $pETO_2$ observed in this study) reduces the pCO_2 of the pulmonary venous blood returning from the lungs and helps to normalize the patient's arterial pCO_2. The reduction in right-to-left shunting after fenestration closure reduces the entry of CO_2-rich blood into the systemic circulation (and hence the impetus for alveolar hyperventilation) and thereby decreases the patient's VE and VE/VCO_2 slope, permitting the patient to breathe less at any given level of exercise. Furthermore, by increasing pulmonary blood flow during submaximal exercise, fenestration closure might improve ventilation/perfusion matching and render gas exchange more efficient. This phenomenon might also contribute to the observed reduction in VE/VCO_2 slope.

Finally, it is also notable that although the elimination or drastic reduction of right-to-left shunting in our study population after fenestration closure resulted in a marked reduction of the VE/VCO_2 slope, it did not do so to normal levels. The inability to normalize the VE/VCO_2 relationship might represent residual right-to-left shunting and/or the ventilation/perfusion mismatch typically seen in patients with Fontan circulations (18,29) or might suggest more ominous mechanisms. An abnormal VE/VCO_2 slope has been well recognized in adults without structural heart disease but with severe congestive heart failure; and in that population this finding carries a very unfavorable prognosis (30–33). Moreover, an abnormal VE/VCO_2 relationship has also been found across a broad spectrum of adults with congenital heart disease and is inversely related to functional class and survival in those without residual cyanosis (34). It remains to be determined whether the improvements in VE/VCO_2 slope observed with fenestration closure or the degree of residual ventilatory abnormality observed in these patients carries important prognostic information.

Study limitations. There is heterogeneity to the patient population, which might be seen as a potential limitation to this study. Similarly, it might be argued that analysis of a larger patient sample might uncover significant changes in exercise capacity after fenestration closure. However, a power calculation reveals that, in this series of 20 patients, this study had a 99% chance of detecting a 10-percentage-point change in peak VO_2. Hence, it seems that fenestration closure is unlikely to have a clinically important impact upon a Fontan patient's exercise capacity. It also must be noted that some of the patients in this series underwent additional interventions during their catheterizations, which may have influenced their exercise function. However, a comparison of pre- and post-fenestration closure exercise capacity demonstrated no significant difference between patients who underwent additional intervention and those who did not. Finally, consideration of these findings should include acknowledgment that the presence of minimal angiographic right-to-left shunting at rest after fenestration closure does not preclude more significant degrees of residual shunt during exercise.

Conclusions

In this patient population, despite the diverse (and potentially adverse) cardiovascular effects of Fontan fenestration closure, exercise capacity remains unchanged. In contrast, ventilatory abnormalities during exercise improve dramati-

cally (but do not normalize). Further study is warranted on the long-term effects of fenestration closure.

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