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Effects of persistent Fontan fenestration patency on cardiopulmonary exercise testing variables

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Abstract

Cardiopulmonary exercise testing (CPET) aids in clinical assessment of patients with Fontan circulation. Effects of persistent fenestration on CPET variables have not been clearly defined. Associations between fenestration and CPET variables at anaerobic threshold (AT) and peak exercise were explored in the Pediatric Heart Network Fontan Cross-Sectional Study cohort. Fenestration patency was associated with a greater decrease in oxygen saturation from rest to peak exercise (fenestration -4.9 ± 3.8 v. nonfenestration -3 ± 3.5; $P < .001$). Physiological dead space at peak exercise was higher in fenestrated v. nonfenestrated (25.2 ± 16.1 v. 21.4 ± 15.2; $P = .03$). There was a weak association between fenestration patency and maximal work and heart rate. Fenestration patency was also weakly correlated with oxygen pulse, work and VE/VCO2 at AT. The effect of persistent fenestration on CPET measurements was minimal in this study, likely due to the cross-sectional design.

KEYWORDS

Exercise testing, fenestration, Fontan

1 | INTRODUCTION

Cardiopulmonary exercise testing (CPET) is a valuable tool used in the evaluation and management of patients with heart disease, providing important physiological and diagnostic information.[1] There is growing evidence that CPET has significant prognostic value in congenital heart disease and has thus led to its increased utilization.[2] Both clinical and research experience with CPET have contributed to an expanding knowledge base regarding the factors that influence CPET variables in the Fontan population.[3–7]

The Fontan operation commonly includes fenestration creation, with the aim of decreasing perioperative morbidity. Percutaneous fenestration closure can be performed postoperatively to attenuate the risks that accompany persistent fenestration patency, such as arterial hypoxemia and paradoxical emboli.[8] However, limited evidence regarding persistent fenestration patency indicates that there may be no significant advantage to closure.[9] The effects of persistent fenestration patency on CPET variables, which serve as surrogate measures of clinical performance and functionality, have not been clearly defined. The aim of this study was to describe the effects of Fontan fenestration patency on multiple CPET variables in patients with Fontan physiology, utilizing a multi-institutional cross-sectional database.

2 | METHODS

This study was approved by the Institutional Review Board of the Medical University of South Carolina. Data from the multi-institutional NIH/NHLBI Pediatric Heart Network (PHN) Fontan Cross-Sectional Study was downloaded from the PHN web site (www.pediatricheartnetwork.org). Details regarding the methods and results of the PHN Fontan study have been previously reported.[10] Briefly, medical records of children between the ages of 6 and 18 years, who had undergone Fontan operation at a participating institution, were screened for study eligibility. A total of 546 children were enrolled; of those, 411 (75%) underwent exercise testing. Core echo labs confirmed fenestration patency; those with indeterminate fenestration status were excluded. Fenestration was present in 38, absent in 325 and indeterminate in 48.

2.1 | Resting pulmonary measurements

Following familiarization with the equipment, subjects completed inspiratory and expiratory flow volume loops. Subjects performed hyperventilation for 10 seconds to measure maximal voluntary ventilation (MVV, L/min).[11] Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were also measured.

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2.2 | Exercise testing

The exercise protocols employed during the study have been previously published.[11] Patients underwent maximal exercise testing using a cycle ergometer with a ramp protocol. Peak oxygen consumption (peak VO_2) was defined as the maximal oxygen consumption obtained during exercise. Anaerobic threshold (AT) was calculated by the V-slope method, when it could be accurately determined. Ventilatory equivalents for carbon dioxide production (VE/VCO_2) and oxygen consumption (VE/VO_2) were measured at AT and peak exercise. The oxygen pulse (O_2 pulse) at peak exercise and AT was calculated by dividing VO_2 at each time point by heart rate (HR). Work, measured in Watts, was recorded at AT and peak exercise. The respiratory exchange ratio (RER) (VCO_2/VO_2) was measured continuously.

2.3 | Data analysis

Associations between CPET variables and fenestration status were analyzed with nonparametric univariate analysis and multivariate logistic regression. For analysis of peak CPET variables, only patients who reached peak exercise, defined as respiratory exchange ratio (RER) greater than 1.1 at maximal effort, were included. For analysis of AT variables, only patients who were reported to have an identifiable AT were included. All statistical analyses were performed using IBM SPSS v.21 (Armonk, NY, USA).

3 | RESULTS

Of the 546 patients who were recruited, 411 underwent exercise testing; 166 (40%) had maximal exercise tests and 317 (77%) had an adequate AT calculated. The baseline patient characteristics are listed in Table 1. There were no significant differences between fenestration groups with regard to age, gender, weight, height, or body surface area at time of exercise test. Resting HR, VO_2, FVC, FEV_1 and MVV were also similar between the two groups. As expected, the two groups differed with regard to average resting oxygen saturation (fenestrated; 89.9 ± 4.7% v. nonfenestrated; 92.8 ± 14.5%, $P < .001$). The results of the univariate analysis comparing CPET variables at both AT and peak exercise of the fenestrated vs. nonfenestrated groups are listed in Tables 2 and 3. Fenestration patency was associated with a greater decrease in oxygen saturation from rest to peak exercise (fenestrated; −4.9 ± 3.8% v. nonfenestrated; −3 ± 3.5%, $P < .001$). Physiological dead space at peak exercise was noted to be higher in the fenestrated compared to the nonfenestrated patients (25.2 ± 16.1% v. 21.4 ± 15.2% $P < .031$). The difference in VE/VCO_2 at peak exercise between the fenestrated and nonfenestrated cohorts approached, but did not ultimately reach, statistical significance (35.8 ± 23.6 v. 31.8 ± 21.6, $P = .062$).

Multivariate analysis demonstrated that oxygen pulse ($P = .04$), work ($P \leq .01$) and VE/VCO_2 ($P = .02$) at AT were weakly associated

TABLE 1 Baseline patient characteristics. All values expressed as mean ± SD

	Fenestration ($n = 38$)	No fenestration ($n = 325$)	*P*-value
Age (years)	12 ± 3.3	12.4 ± 3.2	.402
Weight (kg)	38.1 ± 11.7	43 ± 16.6	.191
Height (cm)	144.3 ± 14.5	147.1 ± 16.5	.338
BSA (m^2)	1.2 ± 0.2	0.9 ± 2.1	.182
HR (bpm)	78 ± 16.1	79.5 ± 16.1	.553
O_2 sat (%)	89.9 ± 4.7	92.8 ± 14.5	.001
FVC (L)	2 ± 0.7	2 ± 1.8	.242
FEV_1 (L)	1.7 ± 0.7	1.7 ± 1.9	.130
MVV (L/min)	53.8 ± 25.5	63 ± 32.6	.135
Physiologic dead space (%)	35.7 ± 20.7	34.3 ± 18.3	.284
VO_2 (mL/kg/min)	4.9 ± 1.6	4.6 ± 2.4	1.000

TABLE 2 CPET values at AT. All values expressed as mean ± SD

	Fenestration ($n = 29$)	No Fenestration ($n = 239$)	*P*-value
HR (bpm)	95.5 ± 56.9	93 ± 60.4	.833
O_2 pulse (mL O_2/heartbeat)	3.2 ± 4.7	4.1 ± 5.5	.187
Work (watts)	29.1 ±24.9	38.6 ± 32.7	.105
Minute ventilation (VE) (L/min)	21.9 ± 16.7	24.4 ± 20	.419
VO_2 (mL/kg/min)	12.6 ± 10	13.5 ± 11.5	.605

TABLE 3 CPET values at peak exercise. All values expressed as mean ± SD

	Fenestration ($n = 36$)	No Fenestration ($n = 127$)	*P*-value
HR (bpm)	149.1 ± 35.9	152 ± 30.1	.681
Δ HR (peak-rest, %)	75.9 ± 31.3	74.9 ± 27.6	.855
O_2 sat (%)	82.4 ± 16.7	81 ± 31.9	.001
Δ O_2 sat (peak-rest, %)	−4.9 ± 3.8	−3 ± 3.5	.001
O_2 pulse (mL O_2/heartbeat)	6.1 ± 3.5	7 ± 4.1	.210
Work (watts)	67.4 ± 30.8	78.3 ± 39.3	.160
Tidal volume (VT) (L)	0.8 ± 1.9	0.8 ± 1.6	.743
Minute ventilation (VE) (L/min)	46.8 ± 18.1	48.6 ± 23.3	.815
Physiologic dead space (%)	25.2 ± 16.1	21.4 ± 15.2	.031
VO_2 (mL/kg/min)	24.9 ± 8	25.5 ± 8.9	.558
VE/VO_2	34.9 ± 23.7	30.8 ± 21.1	.094
VE/VCO_2	35.8 ± 23.6	31.8 ± 21.6	.062

with fenestration status ($R^2 = 0.18$) and that work ($P = .04$) and heart rate ($P = .02$) at peak exercise were weakly associated with fenestration patency ($R^2 = 0.2$).

4 | DISCUSSION

Acute physiologic changes associated with Fontan fenestration closure have been previously well documented.[9] These changes include increased systemic oxygen saturation, increased Fontan (central venous) pressure and decreased cardiac index.[9] However, the long-term clinical implications of fenestration closure are less well understood. CPET provides a way to quantify the potential functional effects of persistent fenestration patency in patients with Fontan circulation.

4.1 | Cardiac response to exercise

As expected, our data demonstrate that systemic desaturation becomes more pronounced with exercise in patients with a patent Fontan fenestration, an effective right-to-left shunt. It is reasonable to deduce that increased systemic desaturation would impair oxygen delivery to active muscle tissue and result in decreased exercise capacity, quantified as peak VO_2. The results of this study are consistent with prior studies, such as the one conducted by Meadows et al., and did not find a significant difference in peak VO_2 between the two groups.[12] In order for oxygen consumption at peak exercise to remain unchanged regardless of fenestration status, it may be hypothesized that oxygen delivery must also remain the same despite increased systemic desaturation in fenestrated patients. In order for oxygen delivery to remain stable, there must be either increased oxygen extraction at the tissue level, or increased cardiac output. Our study did not address the former, however, Loomba et al. were unable to demonstrate a significant difference in regional oxygen extraction between patients with and without patent fenestrations.[13] It is known that Fontan patients are extremely preload-dependent for augmentation of cardiac output, with much less contribution from HR and ventricular contractility.[14] The results of our univariate analysis similarly failed to show a significant difference in HR response to exercise between patients with and without fenestrations, however, the multivariate analysis demonstrated a weak association at peak exercise. It may be hypothesized that, in patients with patent fenestrations, increased preload from right to left fenestration flow during exercise results in increased stroke volume and cardiac output, resulting in stable oxygen delivery. The results of our univariate analysis did not demonstrate a significant difference in O_2 pulse (surrogate for stroke volume) at maximal exercise between the two groups, but the multivariate analysis showed a weak association at AT.

4.2 | Respiratory response to exercise

Our data demonstrate an expected increase in physiologic dead space at peak exercise in patients with patent fenestrations. This is simply the result of an increase in arterial partial pressure of carbon dioxide (pCO_2) that occurs with any effective right to left shunt.[15] VE/VCO_2 is another respiratory variable that has gained recent interest and may be clinically useful. As described by Meadows et al., closure of a Fontan fenestration is expected to decrease, but not normalize, the VE/VCO_2 slope.[12] The reasoning behind this is two-fold. First, closure of a fenestration, which minimizes or eliminates right-to-left shunting, results in a decrease in pCO_2. The expected chemoreceptor response of increased minute ventilation in response to increased pCO_2 that occurs with right-to-left shunting no longer occurs, so the VE/VCO_2 slope should theoretically decrease.[12,15] Second, fenestration closure results in increased pulmonary blood flow during exercise. The result of which should be increased ventilation-perfusion matching and, therefore, increased ventilatory efficiency. Our results demonstrate a slightly higher peak VE/VCO_2 in the fenestrated group, however it did not reach statistical significance. This may be attributed to the cross-sectional nature of the data. We expect that analysis of the Fontan 3 longitudinal dataset, with comparison of CPET variables and fenestration patency for individual patients, would clearly demonstrate the trend toward normal of the ventilatory response to exercise with fenestration closure.

5 | LIMITATIONS

The primary limitation of this study is the cross-sectional design. The data analyzed are cross-sectional in nature so lack the ability to evaluate variables pre- and post-fenestration closure in individual patients. The use of a retrospective dataset also prevents our ability to verify existing information or collect missing data. Many patients, as is common among many patient populations in whom CPET is used clinically, were unable to complete maximal effort studies. This is likely secondary to the rigorous nature of the test and results in limited peak exercise data. There is a growing body of literature to suggest that analysis of CPET variables at submaximal exercise may be more clinically useful and should be explored.[16]

6 | CONCLUSIONS

This study sought to analyze exercise data with regard to fenestration status in patients with Fontan physiology, with the goal of aiding clinician interpretation of CPET results. Fenestration patency is associated with more pronounced systemic desaturation during exercise. VO_2 and O_2 pulse (surrogate for stroke volume) at peak exercise are not significantly altered by fenestration status. HR at peak exercise and O_2 pulse at AT are weakly associated with fenestration status. Patent fenestration is weakly associated with a slightly higher VE/VCO_2 at peak exercise. The findings of this study are not sufficient to guide decision making with regard to fenestration creation at the time of Fontan operation or timing of fenestration closure. The findings do suggest, however, that persistent fenestration patency alone does not result in a measureable functional limitation. Further insight and clinical utility may be gained from similar analysis of the recently completed Fontan 3 longitudinal study.

DISCLOSURES

The NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study dataset was used in preparation of this work. Accessed from

https://www.pediatricheartnetwork.org. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript and its final contents.

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