Exercise Oscillatory Ventilation in Patients With Fontan Physiology

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Background—Exercise oscillatory ventilation (EOV) refers to regular oscillations in minute ventilation (VE) during exercise. Its presence correlates with heart failure severity and worse prognosis in adults with acquired heart failure. We evaluated the prevalence and predictive value of EOV in patients with single ventricle Fontan physiology.

Methods and Results—We performed a cross-sectional analysis and prospective survival analysis of patients who had undergone a Fontan procedure and subsequent cardiopulmonary exercise test. Data were reviewed for baseline characteristics and incident mortality, heart transplant, or nonelective cardiovascular hospitalization. EOV was defined as regular oscillations for >60% of exercise duration with amplitude >15% of average VE. Survival analysis was performed using Cox regression. Among 253 subjects, EOV was present in 37.5%. Patients with EOV were younger (18.8±9.0 versus 21.7±10.1 years; \( P=0.02 \)). EOV was associated with higher New York Heart Association functional class \( (P=0.02) \) and \( \text{VE/VCO}_2 \) slope \( (36.8±6.9 \text{ versus } 33.7±5.7; P=0.0002) \), but not with peak \( \text{VO}_2 \) \( (59.7±14.3 \text{ versus } 61.0±16.0\% \text{ predicted}; P=0.52) \) or noninvasive measures of cardiac function. The presence of EOV was associated with slightly lower mean cardiac index but other invasive hemodynamic variables were similar. During a median follow-up of 5.5 years, 22 patients underwent transplant or died \((n=19 \text{ primary deaths, 3 transplants with 2 subsequent deaths})\). EOV was associated with increased risk of death or transplant \((\text{hazard ratio, } 3.9; 95\% \text{ confidence interval, } 1.5–10.0; P=0.002)\) and also predicted the combined outcome of death or transplant, or nonelective cardiovascular hospitalization after adjusting for New York Heart Association functional class, peak \( \text{VO}_2 \), and other covariates \((\text{multivariable hazard ratio, } 2.0; 95\% \text{ confidence interval, } 1.2–3.6; P=0.01)\).

Conclusions—EOV is common in the Fontan population and strongly predicts lower transplant-free survival. (Circ Heart Fail. 2015;8:304-311. DOI: 10.1161/CIRCHEARTFAILURE.114.001749.)

Key Words: cardiopulmonary exercise test ■ Cheyne-Stokes respiration ■ exercise ■ Fontan procedure ■ heart defects, congenital ■ ventilation

The most common surgical approach to single ventricle palliation is some variation of the Fontan procedure, which functionally separates the pulmonary and systemic circulations. Systemic cyanosis and ventricular volume overload are alleviated, but at the expense of chronically elevated systemic venous pressure and limited augmentation of stroke volume. As a consequence, the Fontan procedure is associated with almost universal, though variably, decreased functional capacity with limited cardiac output response.\(^1\)

Cardiopulmonary exercise testing (CPET) provides a reproducible assessment of aerobic capacity, in addition to detailed physiological data on ventilatory response to physical work. CPET is clinically applied in a variety of adult and pediatric cardiovascular conditions to assess functional capacity, disease severity, underlying primary cause of exercise limitation, prognosis, and treatment response. Clinical interpretation often focuses on peak oxygen uptake (peak \( \text{VO}_2 \)) and measures of ventilatory efficiency \((\text{eg, } \text{VE/VCO}_2 \text{ slope})\), which have prognostic value for patients with heart failure.\(^2\)

Abnormal ventilation (Cheyne–Stokes breathing) has long been a recognized hallmark of severe congestive heart failure.\(^3,4\) Weber, Szidon, and Janicki reported an unusual saw-toothed ventilatory response to exercise in patients with heart disease without resting Cheyne–Stokes breathing, which they hypothesized to be related to altered central or peripheral \( \text{CO}_2 \) sensitivity.\(^5\) This phenomenon of oscillatory response of minute ventilation to physical work, termed exercise oscillatory ventilation (EOV), was further described by Kremser in the late 1980s,\(^6\) and clinical investigation has since demonstrated that EOV predicts mortality and incident arrhythmia.

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independent of other known predictors in adults with heart failure.\textsuperscript{7–9} In this population, the presence of EOV may even predict adverse outcomes more robustly than either peak VO$_2$ or V$_{E}$/VCO$_2$\textsuperscript{9,10}.

The known hemodynamic consequences of the Fontan procedure suggest that EOV may be prevalent in this population, and 1 prior study reported EOV in 21 of 36 young patients with Fontan physiology.\textsuperscript{11} Our primary objective was to provide a larger perspective on the prevalence, cross-sectional demographic and clinical correlates, and longitudinal prognostic power of EOV in single ventricle Fontan patients.

Methods

Subject Identification

We identified consecutive patients who had clinically indicated ramp cycle ergometry CPET between January 1, 2000, and April 30, 2013, at Boston Children’s Hospital and had previously undergone a Fontan procedure (all types, with or without open fenestration). Data collection and analysis were limited to patients born after April 30, 1997 (ie, aged ≥16 years as of April 30, 2013). Exclusion criteria were 2-ventricle repair or transplantation between the time of initial Fontan and baseline CPET. Baseline CPET was defined as the first cycle CPET during the time period of study. We did not limit the analysis to patients with evidence of maximal effort because EOV can be assessed on submaximal tests. There was no statistically significant difference in the prevalence of EOV among the subset of patients with submaximal CPET (n=40/253 had respiratory exchange ratio, <1.05 and peak heart rate (HR), <80% predicted; 41.3% had EOV versus 36.7% in those with maximal tests; P=0.61). Results of sensitivity analysis excluding submaximal tests were equivalent to the overall sample, including for variables measured at peak exercise such as peak VO$_2$, and are not presented. The study was approved by the Boston Children’s Hospital Institutional Review Board, and the requirement for informed consent was waived.

Demographic data, including age at the time of CPET, underlying cardiac diagnosis and previous interventions, medication use, and medical comorbidities, were extracted from the medical record. Available laboratory data and cardiac imaging within 2 years of CPET, as well as invasive hemodynamic studies within 5 years of CPET, were also obtained. The primary outcome of interest was death or cardiac transplantation. A secondary combined outcome of interest included death, transplant, or incident nonelective hospitalization for cardiovascular or Fontan-related events (ie, arrhythmia, heart failure, ascites, protein-losing enteropathy, plastic bronchitis, or thromboembolism).

Data Analysis

CPET involved symptom-limited cycle ergometry using a continuous ramp protocol with electrocardiographic monitoring and breath-by-breath expiratory gas analysis (CardiO$_2$ exercise testing system; Medical Graphics, Minneapolis, MN). CPET data included rest and peak oxygen saturation (SO$_2$%), blood pressure and HR, peak VO$_2$, defined as the highest 30-s average value during the test, VO$_2$ at the anaerobic threshold (AT; assessed by V-slope method), V$_{E}$/VCO$_2$ slope before AT, peak respiratory exchange ratio, peak O$_2$ pulse, end-tidal partial pressure of CO$_2$ at AT, and spirometry variables (FEV$_1$; forced vital capacity [FVC]; FEV$_1$/FVC). To assess potential artifactual confounding of CPET data assessment because of the oscillatory nature of EOV, we repeated the analysis using (1) 2 alternative definitions of peak VO$_2$: average VO$_2$ over the final 30 and 60 s of the test and (2) various measures of V$_{E}$/VCO$_2$: V$_{E}$/VCO$_2$ slope over the entire test, V$_{E}$/VCO$_2$ at AT, and minimum V$_{E}$/VCO$_2$ during the test. Each approach yielded consistent results and only the analysis using standard definitions is presented.

EOV was assessed using custom software developed in MATLAB R2013a (MathWorks, Natick, MA) plotting time and V$_{E}$ on the x- and y-axes, respectively. EOV was defined as regular oscillations with amplitude >15% of average V$_{E}$ during the exercise test, which were present for >60% of total exercise duration (Figure 1).\textsuperscript{12} Data were analyzed through automated detection of oscillations, with user-review and manual selection as necessary. EOV was determined for each test by 2 investigators (A.S.N. and A.R.O.) blinded to subject identifying information and outcome; disagreements were adjudicated by consensus between the investigators.

Statistical Analysis

The 2-sided unpaired Student $t$ test (or Wilcoxon rank-sum test, as appropriate for distribution) and Fischer exact test were used to analyze continuous and categorical variables, respectively, between EOV and non-EOV groups. Continuous variables are presented as mean±SD. The log-rank test was used to perform univariate survival analysis, stratified by EOV status. Baseline time was defined as the date of the initial CPET, and follow-up continued until the first clinical event (either transplant-free survival or the secondary combined outcome), or was censored at the most recent clinical follow-up when outcome status was known.

The relatively low number of events for the primary combined outcome limited the ability to adjust for multiple covariates without variance inflation; therefore, we present only univariate survival analysis of the relationship between EOV and transplant-free survival. We used multivariable Cox regression with the secondary combined outcome as the dependent variable and EOV as the independent variable of interest, adjusting for the following covariates simultaneously: age, New York Heart Association functional class (NYHA FC), V$_{E}$/VCO$_2$ slope, % predicted FVC, % predicted peak HR, and peak VO$_2$.

Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) and GraphPad Prism (GraphPad Software, La Jolla, CA). A 2-sided $P$ value <0.05 was considered statistically significant.

Results

Demographic and Clinical Correlates of EOV

Among the 253 patients who met inclusion criteria, 95 demonstrated EOV (37.5%). Patients with EOV were younger (18.8±9.0 versus 21.7±10.1 years; $P=0.02$) and smaller (height

\[ \text{Figure 1. Examples of normal ventilatory response to exercise (A) and exercise oscillatory ventilation (B). V}_{E} \text{ indicates minute ventilation.} \]
156.2±14.7 versus 161.3±14.3 cm; P=0.01; weight 53.0±18.6 versus 59.1±17.2 kg; P=0.01; Table 1). There were no significant differences between patients with and without EOV in race, sex, medication use, underlying diagnosis, ventricular morphology, heterotaxy, current Fontan type, or presence of Fontan fenestration at the time of CPET. No patients were on inhaled or parenteral pulmonary vasodilators.

At the time of initial CPET, patients with EOV tended to have worse NYHA FC (P=0.02). Among patients with available testing, those with EOV had slightly lower cardiac index. There were no other statistically significant differences in laboratory measures of end-organ function, noninvasive measures of ventricular function, or hemodynamics between patients with and without EOV (Table 1).

| Table 1. Baseline Demographic and Clinical Data, by EOV Status |
|-----------------|-----------------|-----------------|-----------------|
| EOV             | Absent          | Present         | PValue          |
| Age, y          | 21.7±10.1       | 18.8±9.0        | 0.02            |
| Men, %          | 60              | 58              | 0.79            |
| Height, cm      | 161.3±14.3      | 156.2±14.7      | 0.01            |
| Weight, kg      | 59.1±14.7       | 53.0±18.6       | 0.01            |
| BMI             | 22.2±4.1        | 21.0±4.6        | 0.03            |
| BSA, m²         | 1.6±0.3         | 1.5±0.3         | 0.01            |
| Race, %         | White 93 (125/134) 94 (81/86)  | Black 1 (1) 4 (3)  | 0.32            |
| Diagnosis, %    | Tricuspid atresia 26 (41) 26 (25)  | Double-inlet LV 23 (37) 17 (16)  | 0.52            |
|                 | Left 65 (100) 60 (57)  | Other 4 (5) 1 (1)  |                |
| Ventricular morphology, % | Right 36 (55/155) 39 (37/95)  | Left 65 (100) 60 (57)  | 0.36            |
|                 | Other 0 (0) 1 (1)  |                |                |
| Heterotaxy, %   | 13 (17/134) 16 (13/84)  |                | 0.55            |
| Fontan type, at CPET, % | Atriopulmonary 27 (42/156) 27 (25/94)  | Lateral tunnel 65 (101) 67 (63)  | 0.83            |
|                 | Atriocentric or Bjork 3 (5) 1 (1) | Extracardiac 5 (8) 5 (5)  |                |
| Patient fenestration, at CPET, % | 26 (38/149) 20 (16/81)  |                | 0.41            |
| NYHA functional class, % | I 86 (136) 79 (75) | II 14 (22) 16 (15) | 0.02            |
|                 | III or IV 0 (0) 5 (5)  |                |                |
| (Continued)
Table 1. Continued

<table>
<thead>
<tr>
<th>Aortic regurgitation, %</th>
<th>Absent (n=158)</th>
<th>Present (n=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>59 (89/150)</td>
<td>62 (57/92)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mild</td>
<td>37 (55)</td>
<td>34 (31)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (5)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1)</td>
<td>1 (1)</td>
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</table>

Baseline demographic, clinical, invasive hemodynamic, and noninvasive imaging data. Continuous variables are presented as mean±SD, whereas categorical variables are presented as % (n). For categorical variables without complete data for all subjects, the number of subjects with available data is noted (n/n with available data). For laboratory and catheterization variables, the number of subjects with available data is noted next to the variable name (n=number of subjects with available data with absent, present EOV, respectively). Data for pulmonary vascular resistance are presented excluding patients with incomplete data on cardiac index, Fontan pressure or PA wedge pressure. For continuous variables, P values were calculated using an unpaired t test for most variables, but the Wilcoxon rank-sum test was used for non-normally distributed variables (cardiac index, PVR, Qp:Qs, and TPG). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ALT, alanine transaminase; AST, aspartate aminotransferase; AV, atrioventricular; AVV, atrioventricular valve; BMI, body mass index; BSA, body surface area; CPET, cardiopulmonary exercise test; EOV, exercise oscillatory ventilation; GGT, gamma-glutamyltransferase; HLHS, hypoplastic left heart syndrome; LV, left ventricle; NYHA, New York Heart Association; PA/IVS, pulmonary atresia with intact ventricular septum; PLE, protein losing enteropathy; PVR, pulmonary vascular resistance; RV, right ventricle; Qp:Qs, ratio of pulmonary flow to systemic flow; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; and TPG, transpulmonary gradient.

EOV and CPET Results

Exercise test results are given in Table 2. Baseline HR, sO2%, and systolic blood pressure were similar in patients with and without EOV. Peak HR was lower in patients with EOV (74.7±14.1% versus 79.4±13.6% predicted; P=0.01), but there was no statistically significant difference in peak sO2% or blood pressure. Although peak VO2 was similar for those with and without EOV (59.7±14.3% versus 61.0±16.0% predicted; P=0.52 and 23.5±6.9 versus 22.9±7.0 mL/kg per minute; P=0.53), EOV was associated with a lower peak work rate (96±44 versus 113±41 W; P<0.001); this difference in peak work persisted when expressed relative to normative data (61.5±16.5 versus 66.6±17.8% predicted; P=0.03) or indexed to body surface area (63±19 versus 69±19 W/m2; P=0.002). AT was also achieved earlier among those with EOV (34.3±8.8 versus 36.7±9.1% of predicted peak VO2; P=0.05).

There were no differences in baseline FEV1/VCO2, FVC, or FEV1:FVC ratio (Table 3). Exercise ventilatory response did differ between the groups, however. Patients with EOV had higher VCO2 slope (36.8±6.9 versus 33.7±5.7; P=0.0002). Peak V̇E (50.8±16.9 versus 54.6±17.3 L/min; P=0.10) was similar, but patients with EOV had higher peak respiratory rate (46.8±14.3 versus 40.8±10.4 bpm; P=0.0002) and lower tidal volume (1.2±0.5 versus 1.4±0.5 L; P=0.003).

Survival Analysis, EOV as a Predictor of Death or Transplantation

Follow-up data were available for 240 of the 253 patients (94.8%), with median follow-up duration of 5.5 years (quarters, 1–3; 2.5–9.2 years). Twenty-two patients underwent transplant or died (n=19 died without transplant, n=2 died after transplant, n=1 alive post-transplant). No patient without EOV died or underwent transplant within 2 years of CPET as compared with 7.1% of those who did demonstrate EOV. The Kaplan–Meier estimate for death or cardiac transplant at 5 years in the overall sample was 7.7% (n=15; 3 transplants, 12 deaths); this figure was 14.1% (n=11; 3 transplants, 8 deaths) among those who demonstrated EOV compared with 4.3%.

Table 2. Cardiopulmonary Exercise Test Findings, Presented by EOV Status

<table>
<thead>
<tr>
<th></th>
<th>Absent (n=158)</th>
<th>Present (n=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HR, bpm</td>
<td>84.6±15.0</td>
<td>83.4±15.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Baseline sO2%, %</td>
<td>91.8±4.7</td>
<td>92.6±4.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>113±14.6</td>
<td>110±13.7</td>
<td>0.11</td>
</tr>
<tr>
<td>V̇E at AT, mL/kg/min</td>
<td>13.7±3.9</td>
<td>13.4±4.2</td>
<td>0.54</td>
</tr>
<tr>
<td>AT/predicted peak V̇E, %</td>
<td>36.7±9.1</td>
<td>34.3±8.8</td>
<td>0.05</td>
</tr>
<tr>
<td>HR at AT, bpm</td>
<td>108.9±20.1</td>
<td>104.2±21.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>113±41</td>
<td>96±44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak work rate, % pred</td>
<td>66.6±17.8</td>
<td>61.5±16.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak V̇E, mL/kg/min</td>
<td>22.9±7.0</td>
<td>23.5±6.9</td>
<td>0.53</td>
</tr>
<tr>
<td>Peak V̇O2, % pred</td>
<td>61.0±16.0</td>
<td>59.7±14.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Peak O2 pulse, % pred</td>
<td>77.9±21.2</td>
<td>81.2±18.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Peak HR, % pred</td>
<td>79.4±13.6</td>
<td>74.7±14.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak sO2, %</td>
<td>87.9±6.4</td>
<td>88.3±6.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Peak SBP, mm Hg</td>
<td>136.6±23.6</td>
<td>131.9±23.7</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table presents data obtained at baseline cardiopulmonary exercise testing. Data are presented as mean±SD. Pvalues were calculated using the unpaired t test for normally distributed variables. The Wilcoxon rank-sum test was used for non-normally distributed variables (peak SBP, peak work rate, and peak O2 pulse % predicted), % pred indicates % predicted; AT, anaerobic threshold; bpm, beats per minute; EOV, exercise oscillatory ventilation; HR, heart rate; SBP, systolic blood pressure; and sO2, oxygen saturation.
There were 6 events among the 150 patients who did not demonstrate EOV, all primary deaths. Among those with EOV (n=90), there were 16 events: 13 primary deaths, 2 transplants followed by death, and 1 transplant without death. EOV was associated with higher risk of death or transplant over the full study period (hazard ratio, 3.9; 95% CI, 1.5–10.0; \[P = 0.002\]; Figure 2A; Table 4).

Survival Analysis, EOV as a Predictor of Death, Transplantation, or Nonelective Cardiovascular Hospitalization
NYHA FC, age, % predicted peak HR, % predicted peak VO\(_2\), and EOV (hazard ratio, 1.8; 95% CI, 1.1–3.0; \(P = 0.01\); Figure 2B) were statistically significant univariate predictors of the secondary combined outcome (n=62 events), but VO\(_2\)/V\(_{\text{CO}}\) slope was not (hazard ratio, 1.03; 95% CI, 0.99–1.08; \(P = 0.15\)). FVC tended to be inversely associated with the outcome, but this was not statistically significant (per +10% predicted; hazard ratio, 0.9; 95% CI, 0.7–1.0; \(P = 0.08\)). The only independent predictors of the combined outcome of death, transplantation, or nonelective cardiovascular hospitalization in a multivariable model inclusive of all covariates were EOV (hazard ratio, 2.0; 95% CI, 1.2–3.6; \(P = 0.01\)), NYHA FC (>I; hazard ratio, 4.0; 95% CI, 2.1–7.4; \(P < 0.001\), and % predicted peak HR (per +10%; hazard ratio, 0.77; 95% CI, 0.62–0.95; \(P = 0.01\)). Conversely, age and peak VO\(_2\) were not independent predictors in this multivariable model.

Discussion
These data demonstrate that EOV is common among patients who have had the Fontan procedure and predicts increased risk of death or heart transplant. This aligns with previous studies demonstrating the use of CPET,\(^{13–18}\) and specifically EOV,\(^{6–8,19–25}\) as a tool to predict outcomes in patients with heart failure.

EOV is thought to be due to aberrant respiratory autoregulation, which involves carotid body and medullary chemodetection of arterial PaO\(_2\), PaCO\(_2\), and pH.\(^{22}\) Feedback loop instability may generate the wide variability in ventilation characteristic of EOV. Proposed mechanisms include (1) delayed information transfer because of reduced cardiac output,\(^{8}\) (2) increased gain because of heightened chemosensitivity to PaCO\(_2\) and PaO\(_2\),\(^{26}\) and (3) reduced system damping because of baroreflex impairment.\(^{22}\) The Fontan circulation presents a prime substrate for EOV, given the intrinsically limited cardiac output augmentation, altered chemosensitivity,\(^{27}\) and dampened baroreflex responses.\(^{28}\)

There was no association between EOV and peak oxygen uptake which stands in contrast to studies of EOV in acquired heart failure where EOV has consistently been found to correspond to lower aerobic capacity.\(^{6–8,20,29}\) A previous study reporting on EOV in a group of young (average age, 12.3 years) Japanese total cavopulmonary anastomosis patients reported a sample of Fontan patients with, on average, normal

![Figure 2](http://circheartfailure.ahajournals.org/)

**Figure 2.** Kaplan–Meier survival plots, stratified by whether a patient demonstrated exercise oscillatory ventilation on cardiopulmonary exercise testing (CPET). **A.** This Kaplan–Meier plot demonstrates lower transplant-free survival for patients with exercise oscillatory ventilation (EOV). Number at risk in each group from time of CPET is listed below the graph and hatch marks designate censored observations. **B.** This Kaplan–Meier plot shows the higher risk of death, transplant, or incident nonelective hospitalization for cardiovascular (CV) or Fontan-related events for patients with EOV. Number at risk in each group from time of CPET is listed below the graph and hatch marks designate censored observations. Present and absent in both plots refer to EOV.
peak VO₂; EOV was associated with higher peak VO₂ (112% versus 103% predicted, \(P=0.02\), multivariable \(P=0.047\)).

The authors hypothesized that EOV might represent a compensatory mechanism enabling better use of the respiratory pump to augment cardiac output. That study also reported that EOV was associated with younger age and smaller body size. Interestingly, despite equivalent peak VO₂ in our study, patients with EOV achieved a significantly lower workload. This was partly because of body size and age, but an association remained even after expressing workload as a % of predicted values or indexed to body surface area. One explanation might be that a larger proportion of cardiac output (oxygen consumption divided by oxygen delivery, per the Fick principle) is used to support muscles involved in ventilation because of increased demand in the setting of EOV and ventilatory inefficiency. This is further evinced by the association between EOV and ventilatory inefficiency (\(V'_{\text{E}}/V_{\text{CO₂}}\)) because patients with EOV required higher minute ventilations to remove accumulating waste products of metabolism.

We have previously shown, in another sample of patients with Fontan physiology, further evaluation is merited to explore the use of combining biomarkers and dynamic physiological variables to increase the power of risk assessment, as has been done for adults with acquired heart failure. Investigators are actively exploring other predictors of poor outcome for Fontan patients, including creatinine, MELD-XI (Model for End-stage Liver Disease eXcluding INR), and other composite clinical scores. Because EOV represents an acute physiological response and is potentially modifiable, it may provide additive information when used in conjunction with static measures of chronic disease to help guide clinical decision making.

Recent evidence suggests that EOV may be modifiable by exercise training or medical therapy in heart failure. The development of exercise training programs for patients after the Fontan procedure, perhaps in tandem with inspiratory muscle training, could prove beneficial to the relief of morbidity and mortality. EOV may eventually be a useful outcome measure for studies of the effect of such therapies, but this will require a better physiological understanding and definition of longitudinal test characteristics.

These results must be interpreted in the context of the study design. First, our results are applicable to the Fontan population, but other types of congenital heart disease could presumably also be associated with a high prevalence of EOV and this could add to the importance of this analysis. Second, only patients who were referred for and able to perform cycle CPET testing were included. These data do not permit direct inference on the significance of EOV in Fontan patients performing staged or treadmill protocols. Third, EOV has heterogeneous definitions (which result in different prevalence estimates), and there are no data on which definition best reflects underlying physiology or predicts outcomes. Furthermore, although EOV is currently defined dichotomously (present or absent), it may represent an extreme case of a spectrum, with current definitions ignoring milder oscillations that may be clinically significant despite being less readily apparent. Assessment of EOV as a continuous variable, or with more attention to the predictive value of the duration, timing, or size of oscillations, may provide further prognostic information for these patients.

via venous collateralization, a patent fenestration or pulmonary arteriovenous malformations. More notable is the tenuous relationship between peak VO₂ and the outcomes of interest. Peak VO₂ is closely linked to functional class; in our sample, peak VO₂ was not a significant predictor of death or transplant or nonelective cardiovascular hospitalization after adjustment for NYHA FC.

Given the basis of EOV in alterations of cardiopulmonary physiology and abnormal central and peripheral chemosensitivity, it is somewhat surprising that variables suggestive of residual right-to-left shunting (hypoxemia and hemoglobin concentration) did not correspond with EOV. This may be related to the chronic, lifelong nature of congenital heart disease and alterations in chemosensitivity related to prolonged cyanosis in childhood and throughout life. An alternative explanation might be that right-to-left shunting has conflicting effects: while it lowers P\text{O}_2 and raises P\text{CO}_2, it also augments systemic stroke volume.

Although these data support a clinical role for EOV as an independent prognostic tool for patients with single ventricle Fontan physiology, further evaluation is merited to explore the use of combining biomarkers and dynamic physiological variables to increase the power of risk assessment, as has been done for adults with acquired heart failure. Investigators are actively exploring other predictors of poor outcome for Fontan patients, including creatinine, MELD-XI (Model for End-stage Liver Disease eXcluding INR), and other composite clinical scores. Because EOV represents an acute physiological response and is potentially modifiable, it may provide additive information when used in conjunction with static measures of chronic disease to help guide clinical decision making.

Recent evidence suggests that EOV may be modifiable by exercise training or medical therapy in heart failure. The development of exercise training programs for patients after the Fontan procedure, perhaps in tandem with inspiratory muscle training, could prove beneficial to the relief of morbidity and mortality. EOV may eventually be a useful outcome measure for studies of the effect of such therapies, but this will require a better physiological understanding and definition of longitudinal test characteristics.

These results must be interpreted in the context of the study design. First, our results are applicable to the Fontan population, but other types of congenital heart disease could presumably also be associated with a high prevalence of EOV and this could add to the importance of this analysis. Second, only patients who were referred for and able to perform cycle CPET testing were included. These data do not permit direct inference on the significance of EOV in Fontan patients performing staged or treadmill protocols. Third, EOV has heterogeneous definitions (which result in different prevalence estimates), and there are no data on which definition best reflects underlying physiology or predicts outcomes. Furthermore, although EOV is currently defined dichotomously (present or absent), it may represent an extreme case of a spectrum, with current definitions ignoring milder oscillations that may be clinically significant despite being less readily apparent. Assessment of EOV as a continuous variable, or with more attention to the predictive value of the duration, timing, or size of oscillations, may provide further prognostic information for these patients.

Robust
automated techniques for identifying and reporting EOV (as currently available for V̇E/V̇CO₂) would enhance the likelihood of clinical application; this has proved challenging, but efforts are ongoing to identify suitable algorithms. 45 Finally, although the results are highly statistically significant, the analysis is based on a relatively small number of events (n=22 for the primary outcome). This limits application of multivariable adjustment; furthermore, validation in an independent sample is needed to support the robustness of our findings.

In summary, EOV is common in the Fontan population and independently predicts incident death or transplant. Additional studies are needed to identify optimal definitions, physiological underpinnings, and the role of this finding in clinical management among patients with a Fontan circulation.

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Disclosures
None.

References
The presence of exercise oscillatory ventilation (EOV), defined by regular oscillations in minute ventilation with exercise, correlates with heart failure severity and worse prognosis in adults with acquired heart failure. We assessed the prevalence and predictive value of EOV in 253 patients with single ventricle Fontan physiology who underwent cardiopulmonary exercise testing. EOV was present in 37.5% of patients and those with EOV had worse New York Heart Association functional class and more severe ventilatory inefficiency; there was no difference between those with and without EOV in peak oxygen consumption. Among those with available data, resting cardiac index was marginally lower in the EOV group, but there were no other statistically significant differences in hemodynamics or noninvasive measures of ventricular function. During a median follow-up of 5.5 years, 22 patients died or underwent heart transplantation (21 deaths and 3 transplants with 2 subsequent deaths). EOV was associated with worse transplant-free survival (hazard ratio, 3.9; 95% confidence interval, 1.5–10.0; \( P=0.002 \)). EOV also predicted a combined outcome of death, transplant, or nonelective cardiovascular hospitalization after adjusting for functional class, peak oxygen consumption, and other covariates (multivariable hazard ratio, 3.9; 95% confidence interval, 1.2–3.6; \( P=0.01 \)). These results demonstrate that EOV is common in the Fontan population, and its presence is associated with adverse outcomes, including death and transplantation.
Exercise Oscillatory Ventilation in Patients With Fontan Physiology
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