Contributions of residual hypoxemia to exercise hyperventilation in Fontan patients

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ABSTRACT

It is unsettled whether increased exercise ventilation in Fontan subjects is due to increased pulmonary dead space or augmented ventilatory drive. Twenty-six Fontan patients underwent symptom-limited treadmill cardiopulmonary exercise testing. Two groups of age- and sex- matched subjects served as controls: the biventricularly repaired (Bi, n = 18), and the “true” control (C, n = 29) groups. Peak oxygen uptake (VO₂peak) was not different among groups (41.0 ± 8.4 ml/min/kg, 43.5 ± -6.6 ml/min/kg, and 45.9 ± -11.6 ml/min/kg for Fontan, Bi, and C groups, respectively, p = 0.16). Fontan subjects, however, showed steeper alveolar ventilation/carbon-dioxide (VA/V̇CO₂) regression slope (35.5 ± 5.3, 28.7 ± 3.8, and 29.5 ± 3.0 l/ml, for Fontan, Bi, and C groups, respectively, p<0.0001), and lower end-expiratory carbon-dioxide fraction (FetCO₂V̇AT) at ventilatory threshold (V̇AT) (4.4 ± 0.5%, 5.5 ± 0.5%, and 5.5 ± 0.4%, for Fontan, Bi, and C groups, respectively, p<0.001). The dead-space ventilation fraction at VAT was similar among groups (0.33 ± 0.06, 0.33 ± 0.04, 0.35 ± 0.05 for Fontan, Bi, and C groups, respectively, p = 0.54). In Fontan subjects, arterial oxygen saturation at rest (SaO₂rest) was correlated with VA/V̇CO₂ regression slope (r = –0.41, p = 0.04) and with FetCO₂V̇AT (p = –0.53, p<0.01). We conclude that Fontan patients show exercise hyperventilation due to augmented central and/or peripheral ventilatory drive, which is further augmented by residual hypoxemia.

Keywords: Fontan, exercise tolerance, oxygen uptake efficiency slope, maximal oxygen uptake, ventilatory response

Abbreviations:
CPX: cardiopulmonary exercise testing
FetO₂: the mixed end-expiratory oxygen concentration
HRpeak: peak heart rate
OUES: oxygen uptake efficiency slope
PetCO₂: end-expiratory partial pressure of carbon dioxide
RERpeak: respiratory exchange ratio
SaO₂rest: arterial oxygen saturation at rest
TCPC: the total cavo-pulmonary connection
VA: Alveolar minute ventilation
V̇A/H: ventilatory acclimatization to hypoxia
V̇CO₂: Carbon dioxide production
V̇D/V̇T: the ratio of the pulmonary dead space to tidal volume

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INTRODUCTION

Nearly half a century has passed since the introduction of Fontan operation.\(^1\) It was initially developed as the surgery for tricuspid atresia but today generally for complex congenital heart diseases to which biventricular repair is impossible. The procedure has contributed greatly to the improvement of mortality rate in these patients. However, as it is a palliative procedure, the majority of patients with Fontan circulation have been reported to suffer from impaired functional capacity and various complications including augmented exercise ventilation.\(^2\)-\(^4\)

However, it is still unsettled if it is due to increased pulmonary dead space or augmented central or peripheral ventilatory drive during exercise.\(^4\)-\(^7\) The majority of previous studies report that the lack of pulmonary pump in Fontan circulation causes maldistribution of pulmonary blood flow and ventilation/perfusion (V/Q) mismatch, leading to increased dead space ventilation.\(^5\),\(^8\) On the other hand, Ohuchi and coauthors have reported that a steeper minute ventilation-carbon dioxide production slope (the VE/VCO\(_2\) regression slope) was related with lower resting carbon dioxide tension (PaCO\(_2\)) as well as with lower resting arterial saturation, suggesting augmented peripheral and/or central ventilatory drive during exercise in Fontan patients.\(^4\),\(^9\)

The primary objective of the present study was, therefore, to test whether the augmented exercise ventilation in Fontan patients is due to increased pulmonary dead space or accentuated central and/or peripheral ventilatory drive during exercise. Also, if the latter is the case, we would try to seek for the underlying conditions related with exercise hyperventilation in Fontan patients.

METHODS

Study subjects

The present study is a single-center retrospective study. The inclusion criteria were: 1) subjects who had undergone cardiopulmonary exercise testing (CPX) for the evaluation of exercise tolerance during the period between January 2015 and August 2018, and 2) those who had been operated on for single ventricle with the Fontan operation (the total cavo-pulmonary connection method: TCPC) in Aichi Children’s Health and Medical Center. A total of 26 consecutive patients served as the study subjects (the Fontan group). It accounted for 74% of the total subjects who had undergone TCPC in our institute. The average period between Fontan operation and the CPX was 83 (s.d. = 45) months. Two groups of subjects served as controls: the biventricularly repaired (Bi) group, and the “true” control (C) group. The Bi group consisted of 18 patients with various congenital heart defects who had undergone biventricular cardiac repair. The C group consisted of 29 subjects with various mild medical conditions (i.e. mild arrhythmias that disappeared during exercise testing, or chest pain that later proved to be normal, or subjects with a history of Kawasaki disease without cardiac involvements) (Table 1). The characteristics of the subjects are listed in Table 2. A physician’s interviews and physical examinations revealed that they were

\[\dot{V}O_2: \text{oxygen uptake}\]
\[\dot{V}O_{2\text{peak}}: \text{peak oxygen uptake}\]
\[\dot{V}O_{2\text{VAT}}: \text{ventilator threshold}\]
\[\dot{V}/\dot{Q} \text{ mismatch: ventilation/perfusion mismatch}\]
\[V_t: \text{tidai volume}\]
in good conditions and judged to be tolerable for the symptom-limited treadmill exercise testing. None of the subjects was a habitual smoker. Written informed consent was obtained from each participant and/or their parents after explanation of the objective of the exercise testing. This study has been approved by the ethics committee of Chubu University and Aichi Children’s Health and Medical Center.

**Exercise tests**

Exercise tests were performed on a treadmill (MAT-2500, Fukuda Denshi Co. Ltd., Tokyo, Japan) with a standard symptom-limited Bruce protocol. An ECG and the heart rate were monitored throughout the test with the stress test system (ML-5000, Fukuda Denshi Co. Ltd., Tokyo, Japan). The cuff blood pressure was also measured every minute with an automatic indirect manometer (STBP-680F, Collin Denshi, Nagoya, Japan).

**Analysis of expired gas**

Carbon dioxide production [\(\dot{\text{V}}\text{CO}_2\) (mL/min, STPD)], oxygen uptake [\(\dot{\text{V}}\text{O}_2\) (mL/min, STPD)], minute ventilation [\(\dot{\text{V}}\text{E}\) (L/min, BTPS)], tidal volume (mL), the respiratory rate (breaths/min), the mixed end-expiratory carbon dioxide concentration [Fet\(\text{CO}_2\): (%)], and the mixed end-expiratory oxygen concentration [Fet\(\text{O}_2\): (%)] were continuously measured on a breath-by-breath basis with the Minato AE-310S metabolic measurement cart (Minato Medical Science, Osaka, Japan). To reduce breath-by-breath “noise,” data were processed with a five-breath moving average filter.

Alveolar minute ventilation [\(\dot{\text{V}}\text{A}\) (L/min, BTPS)] was derived from the following equation: where \(V_d/V_t\) is the ratio of the pulmonary dead space to tidal volume derived from the following alveolar gas equation:\(^{10,11}\)

\[
\dot{\text{V}}\text{A} = 863 \cdot \frac{\dot{\text{V}}\text{CO}_2}{\text{PaCO}_2} \\
V_d/V_t = 1 - \frac{\dot{\text{V}}\text{A}}{\dot{\text{V}}\text{E}}
\]

The \(\text{PaCO}_2\) was estimated noninvasively by the following equation derived from regression analysis of the relationships among \(\text{PaCO}_2\), \(\text{PetCO}_2\), and \(V_t\) during exercise.\(^{10}\)

\[
\dot{\text{V}}\text{CO}_2 = 5.5 + 0.9 \cdot \text{PetCO}_2 - 0.0021 \cdot V_t
\]

| Table 1 Diagnosis of the study subjects of the 3 groups |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Fontan (n = 26) | Biventricularly repaired (n = 18) | Control (n = 29) |
| DORV+PS | 8 | AS | 4 | arrhythmias | 10 |
| PAIVS | 5 | VSD | 3 | Suspected LQTS | 6 |
| TA | 3 | CoA | 2 | Chest pain without underlying heart disease | 4 |
| d-TGA | 3 | DORV | 2 | History of KD without CAL | 4 |
| AVSD+PS | 2 | c-TGA | 2 | Pre-syncpe | 3 |
| HLHS | 2 | TOF | 2 | WPW syndrome without PSVT | 2 |
| other | 3 | other | 3 | |

Abbreviations: AS: aortic stenosis, AVSD: atrioventricular septal defect, CAL: coronary arterial lesion, CoA: coarctation of the aorta, c-TGA: congenitally corrected transposition of the great arteries, DORV: double outlet right ventricle, d-TGA: d-transposition of the great arteries, HLHS: hypoplastic left heart syndrome, KD: Kawasaki disease, LQTS: long-QT syndrome, PAIVS: pulmonary atresia with intact ventricular septum, PS: pulmonary stenosis, PSVT: paroxysmal supraventricular tachycardia, TA: tricuspid atresia, TOF: tetralogy of Fallot, VSD: ventricular septal defect, WPW: Wolf-Parkinson-White syndrome
Ventilatory response to exercise was assessed by the slope of the relationship between VE and VCO₂ (the VE/VCO₂ regression slope). We also calculated the slope of the relationship between VA and VCO₂ during incremental exercise (VA/VCO₂ regression slope) for the evaluation of carbon dioxide mediated peripheral/central ventilatory drive during exercise.¹¹ The slopes were determined by linear regression analysis of the relationship between VE and VCO₂ or between VA and VCO₂ during exercise using data obtained before the occurrence of respiratory compensation.

The ventilatory anaerobic threshold (VAT) was defined as the level of VO₂ at which an increase in the VE/VO₂ without a simultaneous increase in VE/VCO₂, or the disappearance of the linear relationship between VCO₂ and VO₂ (the V-slope method).¹² The oxygen uptake efficiency slope was calculated by the logarithmic relation between VO₂ and the VE during incremental exercise.¹³ The PaCO₂ and Vd/Vt during exercise were determined from data obtained during 30 s at the VAT and during the final 30 s of peak exercise. We used the average of the 30 s data for analysis.

Table 2 Characteristics of the subjects and the results of cardiopulmonary exercise testing in the three study groups

|                     | Fontan (n = 26) | Biventricularly repaired (n = 18) | Control (n = 29) | p value |
|---------------------|----------------|----------------------------------|-----------------|---------|
| female/male         | 12/14          | 8/10                             | 14/15           |         |
| age (y.o.)          | 8.5 (3.0)      | 9.8 (3.5)                        | 9.3 (1.6)       | 0.28    |
| height (cm)         | 125 (17)       | 137 (23)                         | 137 (11)        | 0.02    |
| weight (kg)         | 26 (10)        | 37 (20)                          | 33 (10)         | 0.02    |
| HRpeak (bets/min)   | 175 (18)       | 171 (21)                         | 183 (20)        | 0.07    |
| RERpeak             | 1.03 (0.06)    | 1.03 (0.06)                      | 1.03 (0.07)     | 0.99    |
| VO₂peak (ml/min)    | 1066 (489)     | 1525 (692)                       | 1468 (354)      | 0.004   |
| VO₂peak(ml/min/kg)  | 41.0 (8.4)     | 43.5 (6.6)                       | 45.9 (11.6)     | 0.16    |
| VO₂VAT (ml/min)     | 656 (232)      | 946 (373)                        | 939 (248)       | <0.001  |
| VO₂VAT (ml/min/kg)  | 26.0 (5.3)     | 28.0 (6.6)                       | 29.2 (8.3)      | 0.24    |
| OUES (ml/min)       | 1313 (443)     | 1579 (660)                       | 1618 (333)      | 0.046   |
| OUES (ml/min/kg)    | 52.6 (11.6)    | 45.9 (8.9)                       | 50.3 (10.5)     | 0.12    |
| VE/VCO₂ regression slope | 35.5 (5.3) ab | 28.7 (3.8)                      | 29.5 (3.0)      | <0.001  |
| VA/VCO₂ regression slope | 26.9 (3.4) ab | 21.0 (2.0)                      | 21.6 (2.1)      | <0.001  |
| FetCO₂VAT (%)       | 4.4 (0.5)  ab  | 5.5 (0.5)                       | 5.5 (0.4)       | <0.001  |
| PaCO₂VAT (torr)     | 33.7 (3.2)     | 40.7 (3.1)                       | 40.7 (2.8)      | <0.001  |
| Vd/V₁VAT            | 0.33 (0.06)    | 0.33 (0.04)                      | 0.35 (0.05)     | 0.54    |
| OPVAT (ml/beat)     | 5.2 (1.8)  ab  | 7.5 (3.6)                        | 6.5 (1.7)       | 0.006   |
| OPVAT/body mass (ml/beat/kg) | 0.21 (0.04) | 0.21 (0.03)                      | 0.20 (0.05)     | 0.69    |

The mean values are tested by the analysis of variance (ANOVA). The post hoc tests are calculated with the Bonferroni’s method. a: p<0.05 between the Fontan group and the biventricularly repaired group; b: p<0.05 between the Fontan group and the control group.

Abbreviations: FetCO₂VAT: mixed end-expiratory carbon dioxide concentration, HRpeak: heart rate at peak exercise, OPVAT: oxygen pulse at the ventilatory anaerobic threshold, OUES: oxygen uptake efficiency slope, PaCO₂VAT: arterial carbon-dioxide partial pressure at the ventilatory anaerobic threshold, RERPpeak: respiratory exchange ratio at peak exercise, VA: alveolar minute ventilation, VAT: ventilatory anaerobic threshold, VCO₂: carbon-dioxide production, Vd/V₁VAT: the dead-space fraction at the ventilatory anaerobic threshold, VE: minute ventilation. VO₂peak: oxygen uptake at peak exercise, VO₂VAT: oxygen uptake at the ventilatory threshold.

Ventilatory response to exercise was assessed by the slope of the relationship between VE and VCO₂ (the VE/VCO₂ regression slope). We also calculated the slope of the relationship between VA and VCO₂ during incremental exercise (VA/VCO₂ regression slope) for the evaluation of carbon dioxide mediated peripheral/central ventilatory drive during exercise.¹¹ The slopes were determined by linear regression analysis of the relationship between VE and VCO₂ or between VA and VCO₂ during exercise using data obtained before the occurrence of respiratory compensation.

The ventilatory anaerobic threshold (VAT) was defined as the level of VO₂ at which an increase in the VE/VO₂ without a simultaneous increase in VE/VCO₂, or the disappearance of the linear relationship between VCO₂ and VO₂ (the V-slope method).¹² The oxygen uptake efficiency slope was calculated by the logarithmic relation between VO₂ and the VE during incremental exercise.¹³
Statistical analysis

Data are expressed as average +/− s.d. Relationships between two measurements were analyzed with regression analysis. Measurements obtained from the three groups were compared with the analysis of variance. Post hoc tests were further analyzed by Bonferroni test. A level of $p < 0.05$ was accepted as statistically significant.

RESULTS

Characteristics of the subjects, as well as the results of cardiopulmonary exercise testing in the three study groups are listed in Table 2. It shows that the Fontan subjects have statistically lower values of $\text{VO}_{2}\text{peak}$, $\text{VO}_{2}\text{VAT}$ and OUES. These differences, however, disappear after corrections by body mass. On the other hand, Fontan subjects show augmented exercise ventilation characterized by the steeper VE/VO$_2$ regression slope (Table 1). This is caused by exercise hyper-
ventilation, or augmented central/peripheral ventilatory drive in Fontan subjects: they show steeper $\text{VA/\overline{VCO}_2}$ regression slope, as well as lower $\text{PaCO}_{2\text{VAT}}$ and $\text{FetCO}_{2\text{VAT}}$ than the two control groups. On the other hand, the dead-space ventilation fraction ($\text{V_d/Vt\overline{VAT}}$), another possible determinant of exercise ventilation, was not different among the three groups. Also in the Fontan subjects, $\text{SaO}_2\text{rest}$, which is considered to be caused by ventilation/perfusion ($\text{V/\overline{Q}}$) mismatch$^{8,14}$ or the intrapulmonary, coronary sinus to pulmonary venous, or intra-cardiac right to left shunts,$^{3}$ was correlated with $\text{PaCO}_{2\text{VAT}}$ and $\text{FetCO}_{2\text{VAT}}$ (Figure 1).

**DISCUSSION**

The main results of the present study are:

1) Patients with Fontan circulation have almost normal exercise tolerance, at least after corrections by body mass, but have impaired ventilatory response to exercise.

2) Augmented central and/or peripheral ventilatory drive, not increased dead space ventilation, is proven to be the main cause of exercise hyperventilation.

3) Residual hypoxemia after Fontan procedure further drives exercise ventilation.

Numerous past studies have reported reduced $\bar{\text{VO}}_{2\text{peak}}$ in Fontan subjects.$^{15-20}$ For example, Müller and coauthors have reported that Fontan (TCPC) subjects showed the average $\bar{\text{VO}}_{2\text{peak}}$ of 25.0ml/min/kg, corresponding to only 59.7% of age-and sex-related reference value.$^{18}$ These results are in contrast to those of the present study showing the average $\bar{\text{VO}}_{2\text{peak}}$ of 41.0 ml/min/kg, almost normal value corresponding to 90% of the average value of the control subjects. Exercise intensity reached in the CPX sessions, indicated by the $\text{RER}_{\text{peak}}$ and $\text{HR}_{\text{peak}}$, was not different among the three study groups. The reason for the excellent exercise tolerance in our Fontan subjects is uncertain. This might be resulted from the excellence of our cardiac surgeons. Or it might be the results of selection bias: only those subjects with excellent post-surgical clinical course might have been selected for CPX. This, however, would be impossible, as the study participants accounted for most subjects (74%) who had undergone TCPC surgery in our institute.

In contrast to their almost normal exercise tolerance, our study subjects with Fontan circulation are shown to have augmented exercise ventilation, which is in accordance with previous studies.$^{2,21-23}$ This phenomenon can be explained by two different mechanisms: increased dead space fraction caused by $\text{V/\overline{Q}}$ mismatch$^{7,8,14}$ and/or exercise hyperventilation.$^{5,7,9,25}$ Matsushita et al have shown, with the xenon-133 lung scanning, abnormal distribution of pulmonary blood flow to the upper lobes compared to normal subjects, causing $\text{V/\overline{Q}}$ mismatch in Fontan subjects.$^{8}$ Another possible mechanism is exercise hyperventilation. Mertens et al are perhaps the first authors who have reported exercise hyperventilation in Fontan subjects.$^{7}$ They suggested hyperventilation in these subjects was caused by early occurrence of VAT. However, this speculation would only partially explain the phenomenon. Results of the present study that Fontan subjects had lower $\text{PaCO}_{2\text{VAT}}$ and $\text{FetCO}_{2\text{VAT}}$ as well as steeper $\text{VA/\overline{VCO}_2}$ regression slope showed hyperventilation was observed before the occurrence of VAT. Perhaps, explanations by Ohuchi et al would be more reasonable. They considered that enhanced central chemo-sensitivity,$^{9}$ often observed in patients with heart failure, as well as greater $V_i/V_t$ was the main reason for their exercise hyperventilation.$^{9}$ However, this also would explain the phenomenon only partially, as hyperventilation was observed in our Fontan subjects without heart failure who had normal $\bar{\text{VO}}_{2\text{peak}}$ and OUES in the present study. Perhaps, explanations in the Ohuchi’s older study that reduction in vital capacity and high pulmonary wedge pressure in Fontan subjects lead to arterial desaturation and subsequent hyperventilation during exercise.$^{4}$
Exercise ventilation in Fontan subjects

The present study also shows that some of our Fontan patients have mildly reduced SaO2rest, the degree of which is correlated with VA/VCO₂ regression slope, PaCO₂VAT and FetCO₂VAT. Several past studies also deal with the relation. 3, 4, 24, 25 Meadows et al 3 and Rhodes et al 24 speculated that elevated VE/VCO₂ regression slope and low FetCO₂ during exercise is due to the right-to-left shunt of CO₂-rich systemic venous blood. The consequent increase in PaCO₂ is sensed by chemoreceptors, inducing central nervous system respiratory centers to increase the patient’s respiratory drive and causing the VE/VCO₂ regression slope to rise. 23, 24 However, they failed to explain why “hyperventilation”, i.e. reduction in PetCO₂ occurs. Entering CO₂-rich blood into the systemic circulation surely drives ventilation to eliminate the carbon dioxide from the arterial blood to “normalize” the carbon-dioxide level, but never to the level to cause hyperventilation.

Instead, we consider the exercise hyperventilation in Fontan patients can be explained by “the ventilatory acclimatization to hypoxia (VAH)”. The VAH is an adaptation mechanism to chronic hypoxemia to increase ventilation that involves neural plasticity in both carotid body chemoreceptors and brainstem respiratory centers, often observed in subjects who have moved to the high altitude environments. 26, 27 Basaran and coauthors have suggested that, as VAH is generally thought to be advantageous to increase arterial O₂ levels over time in subjects with hypoxemia, this could also be beneficial for patients with chronic hypoxemia from lung diseases. 28 If it is the case, it would be no wonder that VAH is also observed in patients with chronic hypoxemia associated with cyanotic congenital heart diseases. Of course this explanation is only a hypothesis without any direct evidence to support it. However, results of the present study that SaO₂ is correlated with VA/VCO₂ regression slope, PaCO₂VAT and FetCO₂VAT would support this hypothesis.

In conclusion, the messages of the present study are, 1) patients with Fontan circulation have, in spite of almost normal exercise tolerance, increased ventilatory response to exercise, 2) augmented central and/or peripheral ventilatory drive, not increased dead space ventilation, is the main cause of exercise hyperventilation, which is further augmented by residual hypoxemia, perhaps by the mechanisms of VAH.

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CONFLICT OF INTEREST
None.

REFERENCES
1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971;26(3):240–248. doi: 10.1136/thx.26.3.240.
2. Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117(1):85–92. doi: 10.1161/CIRCULATIONAHA.107.738559.
3. Meadows J, Lang P, Marx G, Rhodes J. Fontan fenestration closure has no acute effect on exercise capacity but improves ventilatory response to exercise. J Am Coll Cardiol. 2008;52(2):108–113. doi: 10.1016/j.jacc.2007.12.063.
4. Ohuchi H, Ohashi H, Takasugi H, et al. Restrictive ventilatory impairment and arterial oxygenation characterize rest and exercise ventilation in patients after Fontan operation. Pediatr Cardiol. 2004;25(5):513–521.
5. Driscoll DJ, Durongpisitkul K. Exercise testing after the Fontan operation. *Pediatr Cardiol*. 1999;20(1):57–59. doi: 10.1007/s00246-000-1844-x.

6. Rosenthal M, Bush A, Deanfield J, Redington A. Comparison of cardiopulmonary adaptation during exercise in children after the atroventricular and total cavopulmonary connection Fontan procedures. *Circulation*. 1995;91(2):372–378. doi: 10.1161/01.cir.91.2.372.

7. Mertens L, Rogers R, Reybrouck T, et al. Cardiopulmonary response to exercise after the Fontan operation. A cross-sectional and longitudinal evaluation. *Cardiol Young*. 1996;6(2):136–142. doi: 10.1017/S1047951100003486.

8. Matsumoto T, Matsuda H, Ogawa M, et al. Assessment of the intrapulmonary ventilation-perfusion distribution after the Fontan procedure for complex cardiac anomalies: relation to pulmonary hemodynamics. *J Am Coll Cardiol*. 1990;15(4):842–848. doi: 10.1016/0735-1097(90)90284-V.

9. Ohuchi H, Miyazaki A, Watanabe T, et al. Hemodynamic deterioration during simulated supraventricular tachycardia in patients after the Fontan operation. *Int J Cardiol*. 2007;117(2):381–387. doi: 10.1016/j.ijcard.2006.05.024.

10. Jones NL, Robertson DG, Kane JW. Difference between end-tidal and arterial PCO2 in exercise. *J Appl Physiol*. 1979;47(5):954–960. doi: 10.1152/jappl.1979.47.5.954.

11. Nagano Y, Baba R, Kuraishi K, et al. Ventilatory control during exercise in normal children. *Pediatr Res*. 1998;43(5):704–707. doi: 10.1203/00006450-199805000-00021.

12. Beaver WL, Wasserman K. Muscle RQ and lactate accumulation from analysis of the VCO2-VO2 relationship during exercise. *Clin J Sport Med*. 1991;1(1):7–34.

13. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol*. 1996;28(6):1567–1572. doi: 10.1016/S0735-1097(96)00412-3.

14. Grant GP, Mansell AL, Garofano RP, et al. Cardiorespiratory response to exercise after the Fontan procedure for tricuspid atresia. *Pediatr Res*. 1988;24(1):1–5. doi: 10.1203/00006450-198807000-00001.

15. Driscoll DJ, Danielson GK, Puga FJ, et al. Exercise tolerance and cardiorespiratory response to exercise after the Fontan operation for tricuspid atresia or functional single ventricle. *J Am Coll Cardiol*. 1986;7(5):1087–1094. doi: 10.1016/S0735-1097(86)80427-7.

16. Harrison DA, Liu P, Walters JE, et al. Cardiopulmonary function in adult patients late after Fontan repair. *J Am Coll Cardiol*. 1995;26(4):1016–1021. doi: 10.1016/0735-1097(95)00242-7.

17. Paridon SM, Mitchell PD, Colan SD, et al. Pediatric Heart Network Investigators: a cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. *J Am Coll Cardiol*. 2008;52(2):99–105. doi: 10.1016/j.jacc.2008.02.081.

18. Müller J, Christov F, Schreiber C, et al. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. *Eur Heart J*. 2009;30(23):2915–2920. doi: 10.1093/eurheartj/ehp305.

19. Diller GP, Giardini A., Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. *Eur Heart J*. 2010;31(24):3073–3083. doi: 10.1093/eurheartj/ehq356.

20. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life-single centre experience and review of published data. *Eur Heart J*. 2011;32(4):1386–1396. doi: 10.1093/eurheartj/ehr461.

21. Fernandes SM, McElhinney DB, Khairy P, et al. Serial cardiopulmonary exercise testing in patients with previous Fontan surgery. *Pediatr Cardiol*. 2010;31(2):175–180. doi: 10.1007/s00246-009-9580-5.

22. Fernandes SM, Alexander ME, Graham DA, et al. Exercise testing identifies patients at increased risk for morbidity and mortality following Fontan surgery. *Congenit Heart Dis*. 2011;6(4):294–303. doi: 10.1111/j.1747-0803.2011.00500.x.

23. Egbe AC, Driscoll DJ, Khan AR, et al. Cardiopulmonary exercise test in adults with prior Fontan operation: the prognostic value of serial testing. *Int J Cardiol*. 2017;235(1):6–10. doi: 10.1016/j.ijcard.2017.02.140.

24. Rhodes I, Pollack P, Lang P. Effect of transcatheter occlusion of a pulmonary arteriovenous fistula on the cardiopulmonary response to exercise. *Pediatr Cardiol*. 2010;31(1):142–143. doi: 10.1007/s00246-009-9556-5.

25. Chua TP, Ponikowski P, Webb-Peploe K, et al. Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex. *Eur Heart J*. 1997;18(3):480–486. doi: 10.1093/oxfordjournals.eurheartj.a015269.

26. Teppema LJ, Dahan A. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiol Rev*. 2010;90(2):675–754. doi: 10.1152/physrev.00012.2009.
27. Powell FL, Milsom WK, Mitchell GS. Time domains of the hypoxic ventilatory response. *Respir Physiol.* 1998;112(2):123–134. doi.org/10.1016/S0034-5687(98)00026-7.

28. Basaran KE, Villonco M, Ho B, et al. Ibuprofen blunts ventilatory acclimatization to sustained hypoxia in humans. *PloS One.* 2016;11(1):e0146087. doi: 10.1371/journal.pone.0146087.