

# openheart O<sub>2</sub> pulse slope correlates with stroke volume during exercise in patients with a Fontan circulation

Karina Laohachai <sup>1,2</sup>, Rachael Cordina,<sup>2,3</sup> Yves D'Udekem,<sup>4</sup> Kathryn Rice,<sup>5</sup> Robert Weintraub,<sup>6</sup> Julian Ayer<sup>2,7</sup>

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## ABSTRACT

**Background** Peak oxygen pulse (O<sub>2</sub>pulse= oxygen consumption/heart rate) is calculated by the product of stroke volume (SV) and oxygen extraction. It has been shown to be reduced in patients with a Fontan circulation. However, in the Fontan population, it may be a poor marker of SV. We propose that the slope of the O<sub>2</sub> pulse curve may be more reflective of SV during exercise.

**Methods** We analysed cardiopulmonary exercise test data in 22 subjects with a Fontan circulation (cohort A) and examined the association between peak SV during exercise (aortic flow measured on exercise cardiac MRI), and O<sub>2</sub> pulse parameters (absolute O<sub>2</sub> pulse and O<sub>2</sub> pulse slopes up to anaerobic threshold (AT) and peak exercise). In a separate Fontan cohort (cohort B, n=131), associations between clinical characteristics and O<sub>2</sub> pulse kinetics were examined.

**Results** In cohort A, peak aortic flow was moderately and significantly associated with O<sub>2</sub>pulseslope<sup>PEAK</sup> (r=0.47, p=0.02). However, neither absolute O<sub>2</sub>pulse<sup>AT</sup> nor O<sub>2</sub>pulse<sup>PEAK</sup> was significantly associated with peak aortic flow. In cohort B, O<sub>2</sub>pulseslope<sup>PEAK</sup> and O<sub>2</sub>pulseslope<sup>AT</sup> were not significantly associated with clinical parameters, apart from a weak association with forced vital capacity.

**Conclusion** The slope of the O<sub>2</sub> pulse curve to peak exercise may be more reflective of peak SV in the Fontan population than a single peak O<sub>2</sub> pulse value.

## INTRODUCTION

Cardiopulmonary exercise testing (CPET) is an important tool in assessing the haemodynamic response to exercise in patients with a Fontan circulation, and certain CPET parameters are emerging as useful in the prognostic assessment of these patients.<sup>1,2</sup> However, maximal exercise is not met in a substantial proportion of Fontan patients<sup>3</sup> and hence there is significant interest in submaximal exercise parameters, their determinants and association with clinically relevant outcomes.<sup>4,5</sup>

One maximal parameter, peak oxygen (O<sub>2</sub>) pulse, has been shown to be reduced in patients with a Fontan circulation.<sup>3,6</sup> O<sub>2</sub> pulse represents the relationship between oxygen

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with a Fontan circulation have reduced peak oxygen pulse, a marker of stroke volume (SV) in the healthy population. However, with the potential of impaired oxygen extraction by exercising muscles, peak O<sub>2</sub> pulse may be a poor marker for SV in this cohort.

## WHAT THIS STUDY ADDS

⇒ Peak O<sub>2</sub> pulse slope may be more reflective of peak SV in the Fontan population than a single peak O<sub>2</sub> pulse value.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The O<sub>2</sub> pulse slope may be a useful submaximal marker of SV in the Fontan cohort.

consumption (VO<sub>2</sub>) and heart rate (HR) (O<sub>2</sub> pulse=VO<sub>2</sub>/HR) and is determined by the product of stroke volume (SV) and oxygen extraction (arteriovenous oxygen difference (a-vO<sub>2</sub>)).<sup>7</sup>

In healthy populations, the change in a-vO<sub>2</sub> between rest and peak exercise is predictable, such that peak O<sub>2</sub> pulse has been used as a non-invasive surrogate measure of SV.<sup>8,9</sup> However, as SV plateaus from mid-range exercise onward,<sup>10</sup> O<sub>2</sub> pulse from mid-exercise is mainly determined by a-vO<sub>2</sub>. As skeletal muscle abnormalities are highly prevalent and variable in patients with a Fontan circulation,<sup>11,12</sup> with the potential of impaired oxygen extraction by exercising muscles,<sup>13</sup> peak O<sub>2</sub> pulse may be a poor marker for SV in this cohort.<sup>14</sup>

O<sub>2</sub> pulse can be evaluated across the whole of exercise and O<sub>2</sub> pulse kinetics, including the slope of the O<sub>2</sub> pulse curve, have been examined in patients with a Fontan circulation.<sup>15</sup> Fontan patients have been shown to have an altered O<sub>2</sub> pulse slope compared with healthy controls. Given that O<sub>2</sub> pulse slope takes into account both submaximal and maximal responses to exercise, we postulated

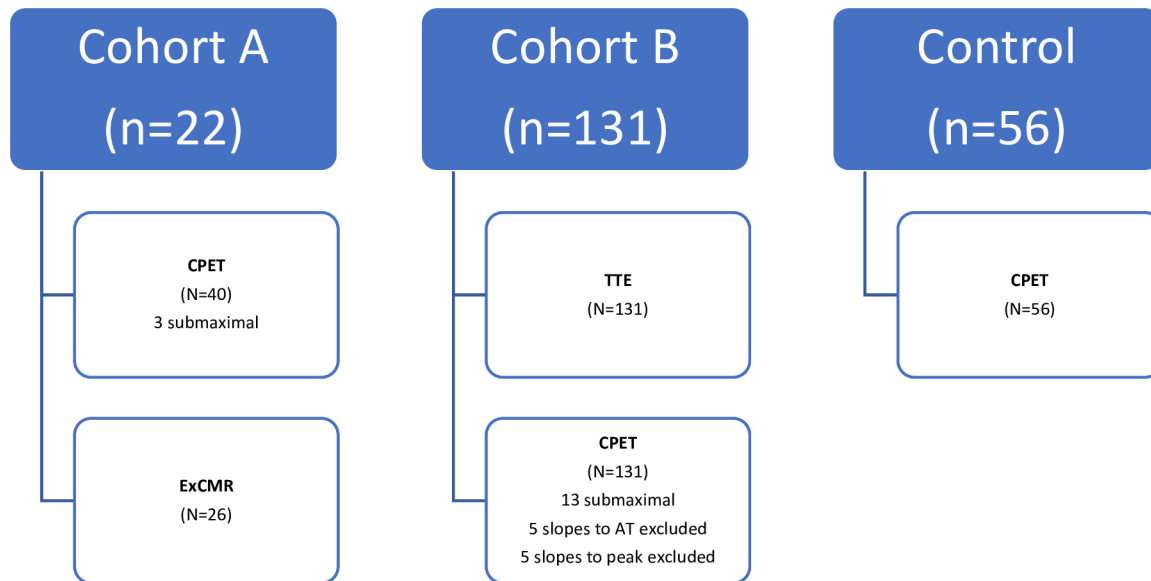


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For numbered affiliations see end of article.

## Correspondence to

Dr Karina Laohachai; karina.laohachai@sa.gov.au



**Figure 1** Study participants. AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; ExCMR, exercise cardiac magnetic resonance; n, number of subjects; N, number of tests; TTE, transthoracic echocardiogram.

that it, rather than peak  $O_2$  pulse, may be more strongly associated with SV.

The relationship between SV during exercise and  $O_2$  pulse slope in Fontan patients has not been determined. Thus, the primary aim of this study in patients with a Fontan circulation was to examine the association between SV (assessed as ascending aortic flow measured by exercise cardiac MR (exCMR)) obtained during exercise, and peak  $O_2$  pulse and  $O_2$  pulse slope during CPET. As a secondary aim, we explored associations between clinical characteristics and both peak  $O_2$  pulse and  $O_2$  pulse slope in a larger cohort of patients with a Fontan circulation.

## METHODS

### Recruitment

Two cohorts of Fontan participants were used in this study as follows (figure 1):

1. In the first cohort (cohort A—22 subjects with 40 CPETs and 26 exCMR analysed), we examined the association between absolute  $O_2$  pulse,  $O_2$  pulse slope and SV during exercise. These participants were part of a study analysing the effects of inspiratory muscle training, as previously described.<sup>16</sup> Cohort A was participants identified through the cardiology database at The Children's Hospital at Westmead (CHW) in Sydney, Australia. Only participants with a non-fenestrated extracardiac conduit aged 12–20 years were included.
2. In the second cohort (cohort B—131 subjects with 131 CPETs and transthoracic echocardiograms (TTE)), we examined the association between clinical characteristics and  $O_2$  pulse parameters. These participants with a Fontan circulation were identified through the Australian and New Zealand Fontan Registry (ANZFR) and were part of the ANZFR Functional Outcomes after

Fontan study conducted across Sydney, Melbourne and Auckland. Inclusion criteria for this study were age  $\geq 13$  years and  $\geq 5$  years since Fontan completion.

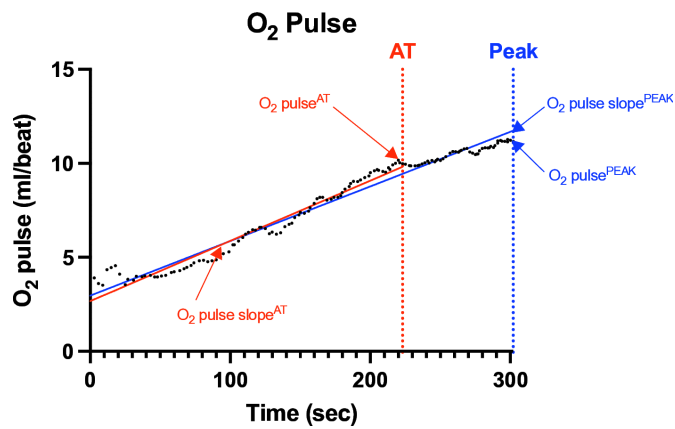
Exclusion criteria for both cohorts were those with severe heart failure, a history of significant exercise-induced arrhythmia, severe systemic outflow tract obstruction or severe systemic hypertension at rest, or significant cognitive impairment or intellectual disability. Clinical data for Fontan participants were retrospectively collected from the local cardiology database at CHW (cohort A) and the ANZFR REDCap database (cohort B, hosted by the Murdoch Children's Research Institute).

Cohort A subjects underwent CPET at CHW. A subset of these patients underwent exCMR, also performed at CHW.<sup>16</sup> Cohort B subjects underwent CPET and TTE at one of four sites—Sydney (CHW and The Royal Prince Alfred Hospital, RPAH), Melbourne (The Royal Children's Hospital) and Auckland (Starship Children's Hospital).

To compare  $O_2$  pulse parameters between Fontan subjects and healthy controls, data from healthy controls were obtained through the exercise labs at CHW, RPAH and the Women's and Children's Hospital in Adelaide, Australia (n=56). These subjects had no underlying cardiac, respiratory or neurological conditions and were undergoing exercise testing for non-specific symptoms.

### Cardiopulmonary exercise testing

CPET was performed in all participants, in a standardised fashion on an upright cycle ergometer using a progressive ramp protocol, aiming to achieve peak oxygen consumption ( $VO_2$ ) within 7–10 min. Cohort A underwent CPET at baseline and at 6 weeks after inspiratory muscle training (n=40). HR, blood pressure and oxygen saturations were recorded from rest to recovery. Breath-by-breath  $VO_2$ , carbon dioxide consumption ( $VCO_2$ )



**Figure 2** O<sub>2</sub> pulse. AT, anaerobic threshold.

and minute ventilation (VE) were measured. Anaerobic threshold (AT) was calculated using a combination of the V-slope, ventilatory equivalents and respiratory exchange ratio methods.

O<sub>2</sub> pulse was calculated throughout testing, from the start of exercise until the beginning of recovery. Absolute O<sub>2</sub> pulse was determined at AT (O<sub>2</sub>pulse<sup>AT</sup>) and at peak exercise (O<sub>2</sub>pulse<sup>PEAK</sup>). O<sub>2</sub> pulse against time curves were reviewed and the curves were determined to have an overall linear pattern, without clear inflection points at consistent time points. Due to this pattern, lines of best fit for O<sub>2</sub> pulse against exercise time up to AT (O<sub>2</sub>pulse slope<sup>AT</sup>) and peak (O<sub>2</sub>pulse slope<sup>PEAK</sup>) were determined by regression (GraphPad Prism V.9), and the slope of these regression lines were taken as the O<sub>2</sub> pulse slope (see figure 2 as representative). Lines of best fit were visually checked by two independent observers (KL and JA) and poorly fitting lines were excluded by agreement (five slopes from cohort A and five slopes from cohort B were thus excluded). No slopes from the control cohort were thus excluded. For analysis, indexing of O<sub>2</sub> pulse metrics to body surface area was not undertaken given that indexing of aortic flow was also not undertaken.

### Spirometry

Spirometry was performed in all participants using standardised techniques.<sup>17</sup> Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>) were measured, and per cent predicted FVC and FEV<sub>1</sub> were determined.<sup>18</sup>

### ExCMR imaging

ExCMR was performed (1.5T, Phillips Intera, Best, The Netherlands) at baseline (n=14) and then 6 weeks after inspiratory muscle training (n=12).<sup>16</sup> Exercise in the MRI scanner was undertaken using an MRI compatible stepper (Ergospect, Innsbruck, Austria). Testing was performed on the same day as the cardiopulmonary exercise test. The initial workload was set to 30W, and increased by 20W every 3 min until exhaustion. Flow and cine imaging was acquired from 50% of the participants' maximum workload based on the prior CPET, and at every stage thereafter until fatigue. Resting and exercise non-gated real time phase contrast flow (200 consecutive dynamics,

dynamic scan time 75 ms, corresponding to approximately 15s of flow data) was measured. Ascending aortic flow was measured at rest (Aortic flow<sup>REST</sup>) and at the final stage prior to exhaustion (Aortic flow<sup>PEAK</sup>), as a measure of SV. Typical scan parameters for balanced steady-state free-precession cine imaging have been described previously.<sup>16</sup> Ventricular volumes were determined by manual contouring of the endocardial border of each short axis slice, at end-diastole (EDV) and end-systole volume (ESV). Ejection fraction was calculated (EF=(EDV-ESV)/EDV×100%). To study the association between SV and O<sub>2</sub> pulse metrics, all ExCMR studies and their corresponding CPET (n=26) were analysed.

### Echocardiography

Participants in cohort B had TTEs performed and the following were obtained: anatomy, ventricular dominance, atrioventricular (AV)-valve regurgitation (non-trivial, or mild or more) and global systolic dysfunction as a qualitative measurement (normal or impaired).

### Statistical analyses

Statistical analyses were performed using GraphPad Prism V.9. Non-parametric and parametric data are presented as median (range) or mean±SD, respectively. Categorical and continuous data were compared between healthy and Fontan groups using  $\chi^2$  tests, t-tests or Mann-Whitney U tests, as appropriate. Correlations between clinical Fontan and O<sub>2</sub> pulse parameters were assessed using Pearson or Spearman correlation and multiple linear regression models. A p<0.05 was considered statistically significant.

### RESULTS

The baseline characteristics of cohort A and cohort B are shown in table 1. Cohort B included a wider age range, with an older mean age than cohort A (23.0 vs 15.8 years). Due to the inclusion criteria of cohort A, more subjects in cohort B were fenestrated at the time of Fontan completion and had non-extracardiac conduits. Other baseline characteristics were similar between the two Fontan groups. Characteristics of the control subjects were: 33 (59%) males, age 29.5±12.0 years, height 169.8±11.8 cm, weight 77.5±22.2 kg and body mass index 22.7±6.0. Resting and peak parameters obtained during CPET and exCMR are compared in online supplemental table 1. Results from the CPET have previously been reported.<sup>16 19</sup> Peak workload between CPET and exCMR positively correlated (r=0.64, p<0.001).

There was no significant difference in O<sub>2</sub>pulse<sup>PEAK</sup>, O<sub>2</sub>pulse<sup>AT</sup>, O<sub>2</sub>pulse slope<sup>PEAK</sup> or O<sub>2</sub>pulse slope<sup>AT</sup>, between cohort A and B (figure 3). Both Fontan cohorts had significantly lower peak VO<sub>2</sub>, O<sub>2</sub>pulse<sup>PEAK</sup>, O<sub>2</sub>pulse<sup>AT</sup> and O<sub>2</sub>pulse slope<sup>PEAK</sup> compared with healthy controls. O<sub>2</sub>pulse slope<sup>AT</sup> was significantly different between cohort A and healthy controls, but not between cohort B and healthy controls (table 2, figure 3).

**Table 1** Anthropometrics and clinical characteristics of Fontan subjects (cohorts A and B)

	Cohort A Fontan (n=22)	Cohort B Fontan (n=131)	P value
Age (years)	15.8±2.3	23.0±7.9	<0.01
Gender (male:female)	11 (50%):11 (50%)	67 (51%):64 (49%)	>0.9
Height (cm)	164.3±8.1	165±10.0	0.56
Weight (kg)	60.6±14.8	64.9±15.7	0.23
Body mass index	22.0±4.5	23.5±4.9	0.27
Dominant ventricle (right:other)	14 (64%):8 (32%)	92 (70%):39 (30%)	0.62
Age of Fontan (years)	5.2±2.0	6.0±4.3	0.40
Type of Fontan (extracardiac conduit:other)	22 (100%):0 (0%)	82 (63%):49 (37%)	<0.01
Fenestration (no:yes)	22 (100%):0 (0%)	89 (64%):41 (36%) one unknown	<0.01

In cohort A, aortic flow<sup>PEAK</sup> was moderately and significantly associated with O<sub>2</sub>pulseslope<sup>PEAK</sup> (r=0.47, p=0.02) but was not significantly associated with O<sub>2</sub>pulseslope<sup>AT</sup> (r=0.37, p=0.09). Neither O<sub>2</sub>pulse<sup>PEAK</sup> nor O<sub>2</sub>pulse<sup>AT</sup> correlated with aortic flow<sup>PEAK</sup> (r=-0.05, p=0.82; r=0.20, p=0.33, respectively). There was a weak negative association between EF measured at peak exercise on exCMR and O<sub>2</sub> pulse at peak and rest (r=-0.40, p=0.03; r=-0.53, p<0.01, respectively). There were no significant associations between EF and other O<sub>2</sub> pulse parameters.

In cohort B, neither resting nor peak oxygen saturation were correlated with any of the O<sub>2</sub> pulse parameters (data not shown). O<sub>2</sub>pulseslope<sup>PEAK</sup> correlated with O<sub>2</sub>pulse<sup>PEAK</sup> (r=0.56, p<0.01) and O<sub>2</sub>pulseslope<sup>AT</sup> with O<sub>2</sub>pulse<sup>AT</sup> (p<0.01, r=0.44). O<sub>2</sub>pulse<sup>PEAK</sup> and O<sub>2</sub>pulse<sup>AT</sup> were negatively associated with age of Fontan completion (r=-0.19, p=0.03; r=-0.20, p=0.03, respectively). O<sub>2</sub>pulseslope<sup>AT</sup> was associated with severity of AV-valve regurgitation (U=847, p=0.03) with a lower slope in those with at least mild regurgitation. However, AV-valve regurgitation was not associated with O<sub>2</sub>pulseslope<sup>PEAK</sup>. O<sub>2</sub>pulseslope<sup>PEAK</sup> and O<sub>2</sub>pulseslope<sup>AT</sup> were not significantly associated with other clinical variables including ventricular morphology or function, Fontan type, age of Fontan completion,

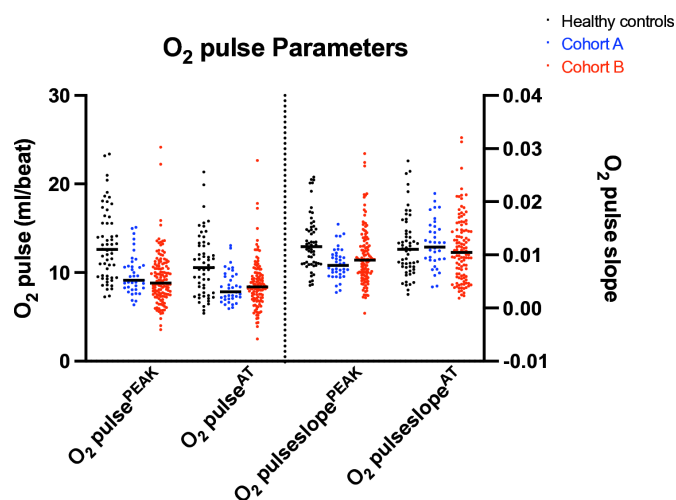
presence of fenestration or pacemaker, presence of permanent pacemaker or use of HR-limiting medications (online supplemental table 2). Baseline FVC %predicted but not FEV<sub>1</sub> was weakly associated with O<sub>2</sub>pulse<sup>PEAK</sup> (r=0.2, p=0.03) and O<sub>2</sub>pulseslope<sup>AT</sup> (r=0.21, p=0.03).

## DISCUSSION

We have demonstrated a positive association between O<sub>2</sub> pulse slope to peak exercise and SV, in patients with a Fontan circulation. We have also confirmed the lack of association between peak O<sub>2</sub> pulse and SV, as previously demonstrated by other authors.<sup>14</sup> Our data suggest that O<sub>2</sub> pulse slope, which incorporates O<sub>2</sub> pulse kinetics across exercise, may be a better surrogate marker than absolute peak O<sub>2</sub> pulse of maximal SV during exercise in Fontan patients.

### SV and the a-vO<sub>2</sub> difference

O<sub>2</sub> pulse is determined by SV and oxygen extraction (a-vO<sub>2</sub> difference). In untrained healthy subjects, SV increases during exercise but then plateaus at a submaximal load.<sup>20</sup> The a-vO<sub>2</sub> difference, however, increases as a linear function during exercise in healthy subjects, and is the main determinant of O<sub>2</sub> pulse from mid-exercise.<sup>10</sup> SV and a-vO<sub>2</sub> difference responses across exercise in

**Figure 3** O<sub>2</sub> pulse parameters. AT, anaerobic threshold.**Table 2** O<sub>2</sub> pulse parameters

Parameter	Healthy controls	Cohort A Fontan	Cohort B Fontan
Peak VO <sub>2</sub> (mL/kg/min)	36.0±10.3	25.1±7.1*	20.9±7.1*
O <sub>2</sub> pulse <sup>PEAK</sup> (mL/beat)	13.2±4.1	9.8±2.2*	9.3±2.9*
O <sub>2</sub> pulse <sup>AT</sup> (mL/beat)	10.9±3.5	8.4±1.8*	8.7±2.8*
O <sub>2</sub> pulse slope <sup>PEAK</sup>	0.01±0.005	0.008±0.003*	0.009±0.005*
O <sub>2</sub> pulse slope <sup>AT</sup>	0.01±0.006	0.01±0.004*	0.01±0.0005†

\*Compared with healthy controls, p<0.01.

†Compared with healthy controls, not statistically significant (p>0.05).

AT, anaerobic threshold.



patients with a Fontan circulation appear to be more heterogeneous.

SV has been shown to increase throughout exercise in some Fontan patients but plateau or decrease in others at maximum exertion.<sup>14 21–24</sup> This variable SV response may relate to differences in underlying patient characteristics but also to differences in the way SV is measured across different studies. Although submaximal and maximal HR is lower in Fontan patients than healthy controls,<sup>6 24 25</sup> the slope of the response of HR against workload or  $\text{VO}_2$  appears to be higher or equivalent.<sup>6 24</sup> The exercise chronotropic response of patients with a Fontan circulation may thus be adaptive to preload insufficiency in order to maintain ventricular filling and cardiac output. In keeping with these data, we did not find a difference in the  $\text{O}_2$  pulse slope up to AT between Fontan patients and controls.

In a small study of 10 Fontan subjects before and after a single dose of sildenafil, Van De Bruaene *et al* showed decreasing SV (measured by ExCMR) and increasing a- $\text{vO}_2$  difference (measured from direct arterial and venous blood sampling) from rest to peak exercise.<sup>23</sup> In a study of 15 children with a Fontan circulation, Strömwall Larsson and Eriksson showed increasing a- $\text{vO}_2$  difference across exercise but with considerable variability in the difference at peak exercise (median 16.8, range 10.5–21.5 mL/100 mL).<sup>22</sup> Rosenthal *et al* demonstrated higher a- $\text{vO}_2$  difference in 43 children with a Fontan circulation compared with healthy controls at rest and across all stages of exercise.<sup>26</sup>

The impact of chronic cyanosis on a- $\text{vO}_2$  has been poorly studied. It is possible that cyanosis, related to the either the presence of a fenestration or systemic venous collateral, results in a reduced ability to augment oxygen extraction at peak exercise or impaired microcirculatory function. We found no association between  $\text{O}_2$  pulse parameters and either the presence of a fenestration or resting or peak oxygen saturation. This is in keeping with a study by Loomba *et al* showing similar exercise arterial-venous saturation difference (utilising regional near infrared spectroscopy) in fenestrated versus non-fenestrated Fontan patients<sup>27</sup> and a study by Strieder *et al* showing similar tissue oxygenation during exercise in cyanotic versus repaired acyanotic CHD.<sup>28</sup> We speculate that a more heterogeneous a- $\text{vO}_2$  difference during exercise in patients with a Fontan circulation may explain the poor association of peak  $\text{O}_2$  pulse with SV. However, this would need to be examined in a future study where exercise SV,  $\text{O}_2$  pulse and a- $\text{vO}_2$  difference are directly measured.

#### Association between $\text{O}_2$ pulse slope and clinical variables

In our exploratory study, we found no association between clinical variables and  $\text{O}_2$  pulse slope<sup>PEAK</sup> or  $\text{O}_2$  pulse slope<sup>AT</sup>, apart from a weakly positive association with baseline FVC %predicted. There was no association with other spirometry parameters.

Fontan subjects have been shown to have abnormal spirometry, with an association between FVC and peak  $\text{VO}_2$ .<sup>19 29</sup> Its association with  $\text{O}_2$  pulse slope is beyond the scope of this study, however, may reflect a ventilation driven inability to augment pulmonary blood flow, and therefore, SV.

#### $\text{O}_2$ pulse and long-term outcomes

Neither  $\text{O}_2$  pulse nor its change over serial testing have been shown to predict long-term adverse Fontan outcomes.<sup>30</sup> We speculate that, in part, this relates to its poor correlation with SV in Fontan patients. It would be of interest to investigate the association between  $\text{O}_2$  pulse slope and its change and long-term Fontan outcomes.

#### Implications of study findings and study limitations

In a study of 411 Fontan subjects (age  $12.4 \pm 3.2$  years, 166 achieving a maximal exercise test) Paridon *et al* found, as expected, that per cent predicted peak  $\text{O}_2$  pulse was strongly associated with per cent predicted peak  $\text{VO}_2$  and moderately with per cent predicted  $\text{VO}_2$  at AT.<sup>3</sup> Based on the strength of these associations, the authors inferred that SV limitation was solely responsible for the variation in aerobic performance. However, our data suggest caution in using peak  $\text{O}_2$  pulse as a surrogate marker for SV in Fontan patients. We speculate that this may relate to a greater variability in the a- $\text{vO}_2$  difference at peak compared with submaximal exercise.

As this was a preliminary study, our study cohorts were small, and we did not have exCMR data available for cohort B. However, even based on our small cohort A, we were still able to demonstrate a moderately significant association between  $\text{O}_2$  pulse slope to peak exercise and peak SV.

Our exCMR protocol was performed using recumbent exercise, likely producing submaximal exercise testing; compared with our upright cycle ergometer CPET. The use of serial gas measurements and CMR-augmented CPET, including continuous oxygen saturation monitoring, would have allowed simultaneous assessment of gas exchange, and a- $\text{vO}_2$  during exercise.

Our healthy controls were retrospectively obtained from subjects previously undergoing CPET, and therefore, we did not have a prospectively matched cohort. However, given the older age of the control subjects, we are more likely to have underestimated the significance of the difference between our Fontan and control cohorts.

Given our relatively small sample size and short-term follow-up, we were unable to examine whether  $\text{O}_2$  pulse slope predicted adverse long-term Fontan outcomes. In our exploratory analysis of cohort B, adjustments for multiple comparisons were not performed, increasing the risk of type I error. Further larger studies would be of interest to analyse the association between  $\text{O}_2$  pulse parameters and clinical variables.

## CONCLUSION

Peak O<sub>2</sub> pulse slope may be more reflective of peak SV in the Fontan population than a single peak O<sub>2</sub> pulse value, taking into account changes in a-vO<sub>2</sub> during exercise. The O<sub>2</sub> pulse slope may be a useful submaximal marker of SV.

## Author affiliations

<sup>1</sup>Cardiology, Women's and Children's Hospital Adelaide, North Adelaide, South Australia, Australia

<sup>2</sup>Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

<sup>3</sup>Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

<sup>4</sup>Cardiac Surgery, Children's National Hospital, Washington, District of Columbia, USA

<sup>5</sup>Paediatric and Congenital Cardiac Services, Starship Children's Health, Auckland, New Zealand

<sup>6</sup>Cardiology, The Royal Children's Hospital Melbourne, Parkville, Victoria, Australia

<sup>7</sup>The Heart Centre for Children, Children's Hospital, Westmead, New South Wales, Australia

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**Contributors** KL and JA designed the study, collected the data, drafted the manuscript and were responsible for analysis and interpretation of results. All authors provided substantial contribution to reviewing the results, providing critical revisions and approving the final version of the manuscript. JA is responsible for the overall content as the guarantor.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and the study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. Reference numbers: HREC/15/SCHN/249 and HREC/14/SCHN/278. Participants gave informed consent to participate in the study before taking part.

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## ORCID iD

Karina Laohachai <http://orcid.org/0000-0003-2336-7852>

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