Exercise responses in children and adults with a Fontan circulation at simulated altitude

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INTRODUCTION
The last decades, exposure to high altitude through air travel or recreational activities, such as skiing, hiking, and mountaineering have become more popular by all generations.1 On ascent from sea level to high altitude the barometric environmental pressure is reduced almost linearly with altitude. At heights of ±2500 m above sea level, the partial pressure of oxygen (PO2) drops to 15% oxygen of the ambient pressure at sea level.2 Also, through air travel passengers are exposed to a low ambient cabin pressure comparable to an altitude between 1524 and 2438 m.
As a consequence of a lower ambient pressure, the PO$_2$ declines exponentially, which is commonly assumed to be the major physiological stimulus to adaptation at high altitude and might result in hypobaric hypoxia, a state of reduced oxygen concentration in the body. Due to this hypoxia, the heart rate increases along with myocardial contractility and cardiac output. Consequently, cardiac output increases in rest and during exercise at high altitude compared to sea level. The increase of cardiac output can almost entirely be explained by the rise in heart rate, because initially stroke volume does not change after exposure to acute hypoxia. Normally, healthy persons are able to compensate for hypoxia by increasing their minute ventilation and cardiac output.

Mountain stays and traveling by airplane are safe and comfortable for most healthy individuals. However, research shows that even healthy persons can desaturate at high altitude at rest and during exercise, with extreme values below 90%. Patients with congenital heart disease are likely to be even more vulnerable to acute high-altitude exposure, since their compensatory response may be limited.

Their compensatory minute ventilation and/or cardiac output increase may be insufficient and they are therefore at risk of developing symptoms or complications related to hypobaric hypoxia.

Hypobaric hypoxia induces pulmonary vasoconstriction within minutes of exposure, and therefore may amplify risks for patients with congenital heart disease. Concerns have been expressed in particular for patients with a Fontan circulation. During palliative surgery, a Fontan circulation is being created for patients with a congenital univentricular cardiac heart disease. The surgical procedure separates the systematic and pulmonary circulations by diverting the venous return directly to the pulmonary artery and therefore reduces the mixture of venous and arterial blood within the only one functional ventricle. The cardiac output mainly depends on the left partial pressure and the transpulmonary gradient. The main cause of a reduced exercise tolerance in Fontan patients is the altered hemodynamic response to exercise. Gewillig et al reported, as expected, a reduced cardiac output about 70% of normal individuals at rest in Fontan patients. Fontan patients are limited in increasing their heart rate due to the often present chronotropic incompetence.

Furthermore, besides the limited hemodynamic capacity, the impaired pulmonary function also contributes to the reduced exercise tolerance in Fontan patients. Matthews et al reported, as lung function abnormalities, a reduced diffusing capacity and an increased residual volume in Fontan patients. This may be related to the abnormal circulation through the lungs. In addition, Larsson et al hypothesized that the nonpulsatile pulmonary blood flow leads to worsening in gas exchange in the lung. Due to a limited hemodynamic capacity and pulmonary function, altitude exposure and exercise at altitude may therefore pose a risk to Fontan patients. Furthermore, investigators have recently examined the direct effects of short-term altitude exposure on pulmonary blood flow (PBF) and exercise capacity in adult Fontan patients. Staempfli et al reported that the PBF at rest and submaximal exercise was lower in Fontan patients compared to healthy controls at sea level and high altitude. However, the relative change due to high altitude did not differ between the Fontan patients and healthy controls. Even, when compared to healthy controls, high altitude had less impact on exercise capacity in Fontan patients. So, they concluded that exposure to high altitude was well tolerated. However, Staempfli et al only included adult patients. Many congenital heart diseases are repaired in early childhood. Questions regarding the safety of altitude exposure are also applicable for children with congenital heart diseases.

Much remains uncertain about short-term altitude adaptation and tolerance in patients with Fontan circulation at rest and during exercise. So far, counseling has been based mainly on theoretical arguments. Physicians cannot provide evidence-based advice about recreational activities and traveling by airplane to their Fontan patients, because the evidence base is small. Accordingly, investigating Fontan patients at rest and during exercise at high altitude is necessary to improve clinical counseling of Fontan patients for acute high-altitude exposure for air travel (rest) and for sport activities (exercise). Therefore, the aim of this study was to investigate the effects of acute high-altitude exposure (±2500 m) on resting and exercise parameters in patients with a Fontan circulation compared to healthy controls.

## METHODS

### 2.1 Study population

The participants in this study were 21 patients with a Fontan circulation aged between 8 and 40 years and able to perform moderate exercise. Participants were recruited at Wilhelmina Children's Hospital, University Medical Centre Utrecht (UMCU) and several patient associations. Additionally, 21 age-matched healthy controls without history of cardiovascular disorders were included.

Approval was obtained from the Medical Ethics Committee of the UMCU and complied with the Declaration of Helsinki. All participants and parents of participants below 18 years, provided informed written consent before participating the study. All data were collected from September 2016 to February 2018.

### 2.2 Design and protocol

To determine the hemodynamic and pulmonary effects of acute high-altitude exposure at rest and during maximal exercise, participants performed two Cardio Pulmonary Exercise Tests (CPETs). The CPETs were performed, in random sequence, at sea level (±6 m) and at simulated high altitude (±2500 m). To simulate the partial pressure of oxygen at 2500 m a hypoxic tent of 229 × 290 × 183 cm (CAT-430 Walk-In Tent, Boulder, USA) was filled with a gas mixture of 15% oxygen and 85% nitrogen using two generators (Hypoxic Everest Summit II Generator, BLM Altitude BV, Hoofddorp, The Netherlands). Oxygen levels were monitored using an oxygen analyzer (Geisenger GOX100). Furthermore, a fan was used to ensure that the gas mixture was evenly distributed in the tent. Both tests were performed at the Wilhelmina Children's Hospital (Utrecht, The Netherlands) within a time period of three months.

Before testing, using a case report form, the amount of exercise per week (in hours), the New York Heart Association (NYHA) functional classification and medication use were noted. Furthermore, anthropometry
(height, body mass) and lung function were performed in all participants. Blood pressure at rest was obtained in a lying position using arteriography (Arteriograph.nl, Amsterdam, The Netherlands). Furthermore, body composition (eg fat percentage) of the participants was measured using the Bodystat Quadscan 400 system (Bodystat Quadscan 400, EuroMedix, Leuven, Belgium). Body composition was not measured in patients with a pacemaker, due to safety guidelines of the system.

The CPET was performed on an electronically braked upright cycle ergometer (Lode Corrival, Groningen, The Netherlands). A ramp incremental exercise protocol was used, starting with 3 minutes of warm-up cycling, without resistance, after which a ramp incremental exercise protocol with increasing workload was performed until exhaustion. Participants were encouraged to continue exercise until fatigue forced them to stop. Furthermore, participants were asked to rate perceived exertion (RPE) according to the Borg CR-10 scale.

During the CPET, participants breathed through a face mask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). Volume measurements and breath-by-breath respiratory gas analyses were performed using a flow meter, which measured the ventilation (VE), and gas analyzer for oxygen and carbon dioxide. The following pulmonary functions were continuously measured: oxygen uptake (VO₂), carbon dioxide production (VCO₂), and respiratory exchange ratio (RER = VCO₂/VO₂) were automatically calculated. The hemodynamic parameters such as stroke volume (SV) and cardiac output (CO) were measured continuously using a noninvasive thoracic impedance system (Physioflow, Accuramed bvba, Lummen, Belgium), which has been found reliable in evaluating patients with congenital heart disorders. During the cardiopulmonary exercise test a 10-lead electrocardiographic (ECG) recording system was used to monitor the heart rate (HR) continuously (AMEDTEC, AMEDTEC Medizintechnik Aue, GmbH, Germany). Additionally, blood pressure was monitored every 2 minutes using an automated cuff (Suntech Tango, Suntech Inc, USA). Oxygen saturation was continuously measured using a pulse oximeter with forehead probe (Masimo Rad 8, Masimo bv, Tilburg, The Netherlands).

2.3 Statistical analysis

Data were checked for normal distribution, using the Kolmogorov-Smirnov test. First, descriptive analyses were performed to describe the patients and healthy controls. Second, the hemodynamic and pulmonary responses due to high altitude exposure in Fontan patients and healthy controls was examined with a repeated measures analysis of variance (ANOVA). One-way within- and between participants. A P value <.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical software (IBM SPSS 21.0).

3 RESULTS

3.1 Descriptive characteristics

There were 21 patients with Fontan circulation and 21 healthy controls, between 8 and 40 years included in the analyses (22 children, 20 adults). Characteristics of the participants are presented in Table 1. Thirteen Fontan patients had NYHA class I (no limitation of physical activity) and 8 had NYHA class II (slight limitation of physical activity). A total of eight Fontan patients had a pacemaker.

All patients completed the CPET at sea level and at simulated altitude. Due to technical problems, the hemodynamic values were unsuccessfully measured in two Fontan patients, one at sea level and one at simulated altitude. Furthermore, also due to technical problems the pulmonary variables were unsuccessfully measured in one healthy control at simulated altitude.

3.2 Clinical outcome

All participants were able to perform CPET till exhaustion both at sea level and at simulated high altitude. No severe arrhythmias were detected on ECG in Fontan patients and healthy controls as well. One Fontan patient collapsed because of a vasovagal reaction after both exercise tests. Fontan patients nor healthy controls reported other severe symptoms or complications of altitude exposure.

3.3 Exercise testing

The results of the CPET test at sea level and simulated altitude in rest and at peak exercise are presented in Table 2.

3.3.1 Main effects of Fontan circulation

In rest, saturationrest, SVrest, and CTIrest were significantly lower in Fontan patients compared to healthy controls. However, arteriovenous oxygen difference (AvO₂-diff) did not differ between Fontan patients and healthy controls.

| TABLE 1 | General characteristics of the participants |
|---|---|---|
| Gender | Fontan patients | Healthy controls |
| Male | 13 | 15 |
| Female | 8 | 6 |
| Age (years) | 19.8 [8:37] | 20.8 [9:40] |
| Height (cm) | 161.1 ± 15.4 | 172.2 ± 17.0 |
| Body mass (kg) | 54.0 ± 19.6 | 61.2 ± 21.5 |
| BMI (kg/m²) | 20.3 ± 5.4 | 19.9 ± 4.0 |
| Activities (h/wk) | 3.9 ± 2.4 [1:10] | 6.2 ± 3.4 [2:13] |
| Fat percentage (%) | 21.9 ± 8.4 | 18.4 ± 6.4 |
| Resting blood pressure | | |
| Systolic (mm Hg) | 129.9 ± 15.8 | 131.2 ± 14.4 |
| Diastolic (mm Hg) | 73.3 ± 11.1 | 70.0 ± 13.1 |
| NYHA class | | |
| I | 13 | NA |
| II | 7 | NA |
| Pacemaker | 7 | NA |

Note: Data presented as number or mean ± SD or range. Abbreviation: NA, not applicable; NYHA, New York Heart Association.
# Table 2

Hemodynamic and pulmonary response in rest and during maximal exercise at sea level and high altitude of Fontan patients and healthy controls

|                | Fontan patients | Healthy controls | P valuea | P valueb | P valuec |
|----------------|----------------|-----------------|----------|----------|----------|
|                | Sea level      | High altitude   | Δ REL (%)| Sea level | High altitude | Δ REL (%)|        |          |
| Rest           |                |                 |          |          |          |
| HRrest (bpm)   | 85.0 ± 12.3    | 86.5 ± 14.3     | 1.8%     | 83.0 ± 9.8| 85.6 ± 11.7  | 3.1%     | .679   | .204    | .752    |
| Saturationrest (%) | 94.6 ± 2.9    | 92.3 ± 3.5     | −2.3%    | 99.1 ± 2.1| 95.0 ± 3.5  | −4.1%    | <.001* | <.001*  | .034*   |
| Vrest (L)      | 9.6 ± 2.2      | 10.8 ± 2.9     | 12.5%    | 10.5 ± 3.2| 10.1 ± 2.5  | −3.8%    | .921   | .312    | .088    |
| SVrest (mL)    | 59.8 ± 14.1    | 58.7 ± 17.1    | −1.8%    | 80.1 ± 16.5| 80.7 ± 17.2 | 0.8%     | <.001* | .880    | .623    |
| CTIrest        | 203.7 ± 92.5   | 210.7 ± 102.7  | 3.4%     | 379.4 ± 130.1| 371.7 ± 150.2| −2.0%    | <.001* | .983    | .547    |
| Peak exercise  |                |                 |          |          |          |
| Wpeak (Watts)  | 129.7 ± 44.5   | 119.6 ± 41.3   | −7.8%    | 255.6 ± 102.5| 237.5 ± 93.9 | −7.1%    | <.001* | <.001*  | .069    |
| VO2peak (L/min)| 1.4 ± 0.5      | 1.3 ± 0.4      | −7.1%    | 2.8 ± 1.2 | 2.4 ± 0.9   | −14.3%   | <.001* | <.001*  | .011*   |
| HRpeak (bpm)   | 146.9 ± 27.3   | 146.0 ± 29.3   | −0.6%    | 184.9 ± 10.1| 185.6 ± 8.5 | 0.4%     | <.001* | .964    | .718    |
| Saturationpeak (%) | 93.7 ± 2.9    | 87.2 ± 4.2    | −6.9%    | 98.4 ± 1.5| 90.3 ± 4.2  | −8.2%    | <.001* | <.001*  | .162    |
| Vpeak (L)      | 64.7 ± 22.0    | 67.3 ± 26.0    | 4.0%     | 112.5 ± 48.0| 108.8 ± 39.3| −3.3%    | <.001* | .862    | .294    |
| VE/VC02-slope  | 33.6 ± 5.4     | 38.0 ± 9.0     | 13.1%    | 25.6 ± 3.7 | 28.9 ± 7.1  | 12.9%    | <.001* | <.001*  | .611    |
| SVpeak (mL)    | 80.7 ± 24.6    | 81.7 ± 31.9    | 1.2%     | 100.8 ± 23.1| 107.7 ± 29.8| 6.9%     | .007*  | .225    | .360    |
| COpeak (L/min) | 11.6 ± 2.9     | 11.0 ± 2.86    | −5.2%    | 18.9 ± 4.4 | 19.7 ± 5.2  | 4.2%     | <.001* | .239    | .824    |
| AvO2-diff peak (mL/100 mL) | 12.6 ± 4.1     | 12.4 ± 4.6    | −1.6%    | 14.7 ± 4.7 | 12.0 ± 2.7  | −18.4%   | .483   | .016*   | .034*   |
| CTIpeak        | 357.2 ± 182.9  | 403.8 ± 332.8  | 13.1%    | 527.8 ± 187.6| 578.7 ± 161.8| 9.6%     | .005*  | .244    | .959    |

Note: Data presented as mean ± SD.

*P value main effect patients.

bP value main effect high altitude.

cP value interaction effect (patients*high altitude).

*P values below .05 are considered to be statistically significant.
and healthy controls in rest and during peak exercise. Furthermore, during peak exercise, $W_{peak}$, $VO_{2peak}$, $HR_{peak}$, saturation peak, $VE_{peak}$, $SV_{peak}$, $CO_{peak}$, and contractility index (CTI) peak were significantly lower in Fontan patients compared to healthy controls, and the efficiency of gas exchange during exercise ($VE/VCO_2$ slope) was significantly higher in Fontan patients compared to healthy controls.

### 3.3.2 Main effects of high altitude exposure

During peak exercise, $W_{peak}$, $VO_{2peak}$, saturation peak, and AvO$_2$-diff peak were significantly lower at high altitude compared to sea level, and VE/VCO$_2$ slope was significantly higher at high altitude compared to sea level. However, in rest only saturation was significantly lower at high altitude compared to sea level. Moreover, there was no significant main effect of high-altitude exposure on $SV_{peak}$, $SV_{rest}$, CTI$_{rest}$, and CTI$_{peak}$ ($P > .01$).

### 3.3.3 Interaction effects of high-altitude exposure between Fontan patients and healthy controls

The effect of altitude exposure was significantly different on $VO_{2peak}$ between Fontan patients and healthy controls. In Fontan patients, the $VO_{2peak}$ during maximal exercise was 7.1% lower at high altitude compared to sea level, whereas in healthy controls the $VO_{2peak}$ decreased 14.3% from sea level to high altitude. In addition, the effect of altitude exposure was significantly different between Fontan patients and healthy controls on AvO$_2$-diff peak. In Fontan patients, the AvO$_2$-diff peak during peak exercise decreased 1.6% from sea level to high altitude, whereas in healthy controls the AvO$_2$-diff peak decreased 18.4% from sea level to high altitude. There was a significantly lower decrease in resting saturation during altitude in Fontan patients (~2.3%) compared to healthy controls (~4.1%), but not at peak exercise ($P = .16$).

### 3.4 Individual results

To get a better insight into differences between low and high altitudes and the performance of both groups, individual values of the primary outcomes, saturation $rest$, $W_{peak}$, $VO_{2peak}$, and AvO$_2$-diff $peak$ are visually shown in Figure 1. Despite the significant differences in mean $W_{peak}$, the effect of altitude exposure was not significantly different between Fontan patients and healthy controls. The same pattern of decline was present in both groups. Healthy controls were more affected in saturation $rest$, $VO_{2peak}$ and AvO$_2$-diff $peak$ due to acute altitude exposure. Comparison of the patterns showed a bigger decline in the healthy controls compared to the Fontan patients.

### 4 DISCUSSION

We found a significant reduction in peak exercise capacity in both Fontan patients (7.8%) and healthy controls (7.1%) at simulated high altitude compared to sea level. The effect of high altitude was not significantly different between both groups. Garcia et al. performed a maximal exercise test in Fontan patients at simulated altitude of 3048 m and they reported a reduction of 22% in peak exercise capacity. Staempfli et al. determined the effect of high altitude exposure at high altitude (3454 m) in Fontan patients compared to healthy controls and also reported a significant lower peak exercise capacity due to altitude exposure, 16% and 12.9%, respectively. These higher proportions of reduced exercise capacity could be attributed to the higher testing altitude (3048 m vs 3454 m vs 2438 m) and/or differences between hypobaric hypoxia and normobaric hypoxia (this study). Taking into account the higher altitude of Garcia et al. and Staempfli et al., the reduction in peak exercise capacity in the current study is somewhat smaller compared to Garcia et al. and Staempfli et al.

In healthy participants, a decrease of ±10% in oxygen uptake for every additional 1000 m ascended above 1500-m altitude is expected in maximal exercise. In our study, healthy controls and Fontan patients had as expected, both a significant reduction of 14.3% and 7.1% in peak oxygen uptake from sea level to simulated high altitude which is in line with Buskirk et al. Surprisingly, high altitude had a significantly lower impact on peak oxygen uptake in Fontan patients compared to healthy controls.

At high altitude, the partial pressure of oxygen declines, which leads to a fall in arterial oxygen pressure, regardless of having congenital heart diseases. At rest, Fontan patients and healthy controls desaturated significantly from sea level to simulated high altitude. Moreover, further desaturation was observed during peak exercise in Fontan patients (6.9%) and healthy controls (8.2%). Remarkably, this indicates that high altitude had less impact on saturation during resting conditions in Fontan patients compared to healthy controls. During peak exercise at high altitude, the saturation was comparable between Fontan patients and healthy controls. The study by Staempfli et al. supports our findings; they reported significant lower saturations in Fontan patients (~11%) and healthy controls (~14%) at high altitude, without any symptoms. This might be explained by Fontan patients being accustomed to lower oxygen saturation. Garcia et al. reported that Fontan patients have increased hemoglobin, hematocrit, and red blood cells, and therefore they may have become more efficient in oxygen transportation and delivery. Overall, acute normobaric hypoxia exposure seem to be quite well tolerated, and seems to have less effect in Fontan patients compared to healthy controls.

In this study, we found a higher trend in cardiac output in Fontan patients at high altitude compared to healthy controls, but this did not reach statistical significance. In addition, stroke volume and contractility index did not change significantly during acute high-altitude exposure. However, the peak oxygen uptake and exercise capacity was significantly lower at high altitude in Fontan patients and healthy controls. Therefore, peak oxygen uptake might be affected by a change in arteriovenous oxygen difference.
During physical exercise there is an increase in the arteriovenous oxygen difference. At sea level, the arteriovenous oxygen difference was lower in Fontan patients (12.6 ± 4.1 mL/100 mL) compared to healthy controls (14.7 ± 4.7 mL/100 mL), due to the significantly lower saturation in Fontan patients. Moreover, Fontan patients already reached their maximal arteriovenous oxygen difference during exercise at sea level. They might have reached their limit of the arteriovenous oxygen difference at sea level. At high altitude, the arteriovenous oxygen difference decreased in both groups to approximately equal values. Despite of the low saturation and low arteriovenous oxygen difference in rest, the arteriovenous oxygen difference decreased less in Fontan patients during exercise at high altitude. Therefore, in hypoxic circumstances like altitude, Fontan patients seem to be well adapted.

When Fontan patients ascend to high altitude, a decrease in cardiac output due to hypoxia-related pulmonary vasoconstriction was expected, since cardiac output in Fontan patients mainly depend on the transpulmonary gradient. Moreover, hypoxia-related pulmonary vasoconstriction occurs within minutes of exposure and a significant rise in the pulmonary artery pressure is reported at altitudes between 2000 and 3000 m. However, in this study, there were no significant differences between sea level and simulated high altitude. This is in agreement with Staempfli et al who concluded the same, since they found no significant decrease in pulmonary blood flow at high altitude among Fontan patients. Therefore, we can presume that the pulmonary vasculature of Fontan patients did not react to hypoxia with vasoconstriction. It is hypothesized that the unexpected response to alveolar hypoxia could be the consequence...
of remodeling of the pulmonary vasculature as seen in adults with long-standing Fontan circulation. 26, 29

4.1 Limitations

Some limitations should be taken into account while interpreting the results of our study. First, the included Fontan patients had a maximum of NYHA class II. The included Fontan patients with NYHA class I and II experienced no limitations or slight limitations during physical activity, respectively. Therefore, the results of this study are difficult to be generalized to, for instance, Fontan patients with more severe symptoms and older Fontan patients. Clinicians should take individual differences between patients into account and evaluate Fontan patients carefully, where possible, measure patients individually at high and low altitude. For instance, in one patient a saturation of 84% in rest and 76% was observed at altitude in rest and during maximal exercise. In addition, in both study groups no symptoms or complications were reported during and after high-altitude exposure, regardless of these low levels of saturation.

Moreover, CPETs were performed at minimally allowed oxygen levels in commercial air travel. Thereby, the amount of exercise executed by the participants was without doubt far more intense than they will perform during traveling to and during exercise at high altitude. There are two types of hypoxia known in altitude studies, hypobaric hypoxia (caused by reducing the barometric pressure while maintaining a constant level of the inspired fraction of oxygen) and normobaric hypoxia (caused by reducing the inspired fraction of oxygen while maintaining a constant level of the barometric pressure). Even though, Woods et al 30 concluded that hypobaric hypoxia and normobaric hypoxia responses are broadly similar, it should be taken into account that in this study we only used simulated normobaric hypoxia. Last, this study design only measured acute high-altitude exposure effects. Therefore, this study cannot conclude whether Fontan patients do also tolerate chronic long-term altitude exposure. Johnson et al 31 identified the risk factors for adverse outcome in Fontan patients living at altitude and advised patients to consider of living at sea level.

Fontan patients should be carefully evaluated with respect to high-altitude exposure. For instance, all participants desaturated and may develop symptoms of hypoxemia. This proceeds differently in individual patients. Therefore, it is advised that patients with a Fontan circulation should undergo a hypoxic challenge test before going to high altitude. The current study investigated only acute high-altitude exposure, future research should focus on chronic exposure to high altitude, whether or not Fontan patients can also tolerate high-altitude exposure for days to weeks. Previously, Darst et al 32 showed that exercise capacity of Fontan patients decreased with increasing residential altitude. Also a lower transplant-free survival was observed in Fontan patient living at high altitude. 31 An increased pulmonary resistance might be detrimental for the cardiac function of these patients because it might predispose patients to both myocardial dysfunction and Fontan failure. A recent ESC statement recommends patients with cyanotic congenital heart disease associated with right to left shunt not to live at altitude, and recommends that patients with left to right shunt to stay at low altitude (<1500 m) to avoid the risk of pulmonary hypertension. 33

5 Conclusion

Although, acute high-altitude exposure has a detrimental effect on exercise capacity, the impact on pulmonary and hemodynamic responses of high-altitude exposure is comparable between Fontan patients and healthy controls. However, it is advised that patients with a Fontan circulation should undergo a hypoxic challenge test before going to high altitude.

6 Informed Consent

All the included participants of the study gave informed consent. When participants were under 18 years of age, their parents or caregivers gave informed consent.

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Conflict of interest

The authors of this study declare that there are no conflicts of interest.

Author Contributions

Tim Takken designed the study, and along with Alyanne Evertse and Fleur de Waard, collected data, analyzed data, and prepared manuscript. Mandy Spoorenburg, Martijn Kuipers, and Erik H. Hulzebos assisted in study design, collected and analyzed data, and prepared manuscript. Christian Schroer analyzed data and prepared manuscript.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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