Feasibility of Hypoxic Challenge Testing in Children and Adolescents with Congenital Heart and Lung Disease

Mandy E. Spoorenberg; Erik H. J. Hulzebos; Tim Takken

BACKGROUND: This is a cross-sectional observational study to investigate the safety and feasibility of integrating changing body positions and physical activity in a hypoxic challenge test (HCT). The secondary objective was to compare oxygen saturation (S_pO_2) in two different locations (forehead and finger).

METHODS: Included were 12 pediatric to young adult patients with congenital heart ($N = 7$) or lung disease ($N = 5$). An HCT was performed using breathing room air (21% oxygen) while sitting and breathing a normobaric hypoxic gas mixture (15% oxygen) through a facemask while seated, lying supine, standing, walking 3 km/h, and walking 5 km/h in a nonrandomized order.

RESULTS: All patients, except one, successfully passed the HCT. Three patients reported symptoms, possibly related to hypoxia. Median S_pO_2 during the HCT decreased in all body positions compared with room air. In 9/12 (finger oximeter) vs. 6/12 (forehead oximeter) patients S_pO_2 decreased below 90% in one or more body positions at rest. In 11/12 (finger oximeter) vs. 3/12 (forehead oximeter) patients S_pO_2 decreased below 90% during mild exercise. There was no significant difference in S_pO_2 between the different body positions. However, patients desaturated significantly more during mild exercise (walking 3km/h and 5 km/h). S_pO_2% measured at the forehead gave significantly higher values compared to the index finger.

DISCUSSION: The HCT is safe and feasible in children and adolescents with congenital heart or lung disease, and gives additional information about oxygenation during physical activity in addition to resting conditions. Simulated hypoxia of 8202 ft (2500 m) induced a small but significant decrease in S_pO_2%.

Q1

KEYWORDS: congenital heart disease, congenital lung disease, air travel, hypoxemia.

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Commercial aircrafts cruising at altitude expose passengers to a low ambient cabin pressure comparable to an altitude between 5000 ft and 8000 ft (1524 m and 2438 m) above sea level.[1,2] On ascent the partial pressure of oxygen (Po_2) declines in an exponential fashion and causes hypobaric hypoxia.[1] Following the Code of Federal Regulations, pressurized cabins must be equipped to provide a cabin pressure altitude of not more than 8000 ft (2438 m) at the maximum operating altitude of the airplane under normal operating conditions.[3] At this maximum operating altitude of 8000 ft, Po_2 is equivalent to 15.1% of the ambient oxygen available at sea level.[1,4] The decline in partial pressure of oxygen is also applicable to mountain stays. The higher one gets, the lower the partial pressure of oxygen becomes.[1]

Hypobaric hypoxia at altitude can lead to significant oxygen desaturation in arterial blood in healthy children and adolescents as the partial pressure of oxygen decreases with increasing altitude.[5,6] However, healthy children and adolescents can normally compensate for altitude hypoxemia by increasing minute ventilation and cardiac output. Accordingly, mountain stays and traveling by airplane is safe and comfortable for most healthy children and adolescents. Children and adolescents with congenital heart or lung disease are likely to be more vulnerable to a low partial pressure of oxygen because the compensatory response to acute altitude hypoxemia is limited.[1,7,8] They may not have the possibility of sufficiently increasing

From the Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

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Address correspondence to: Tim Takken, M.Sc., Ph.D., Child Development & Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, KB.02.056.0, P.O. Box 85090, 3508 AB Utrecht, the Netherlands; t.takken@umcutrecht.nl.

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their minute ventilation or cardiac output. These subjects may develop signs related to hypoxia such as: breathlessness, dizziness, headache, nausea, palpitations, listlessness, fatigue, insomnia, blurred vision/tunnel vision, hot and cold flashes, tingling, numbness, hyperventilation, tachycardia, cyanosis, mental confusion, loss of muscle coordination, breathing pattern seizures, and unconsciousness.[7,8] The clinical importance of hypoxemia for a short period is unclear.

To prevent respiratory symptoms during flight, patients with congenital heart or lung disease should have a preflight evaluation. A hypoxic challenge test (HCT) is often used to determine the need for in-flight oxygen. The maximum cabin altitude (8000 ft/2438 m) is simulated with a gas mixture containing 15% oxygen in nitrogen; patients are asked to breathe this gas mixture for 20 min. Supplemental in-flight oxygen is recommended by the British Thoracic Society if $P_{a}O_2$ falls below 6.6 kPa or $S_{p}O_2$ falls below 85%.[1,9] The HCT is usually performed sitting in resting conditions. However, the possible effects of changing body position and physical activity at altitude may also be relevant. Especially during long flights children will not sit still during the entire journey. Moreover, to prevent deep vein thrombosis, it is advised to exercise regularly during air travel.[2,10,11] This is particularly important for patients with congenital heart disease because they have erythrocytosis as a response to hypoxemia, intended to increase their oxygen carrying capacity. This leads to higher blood viscosity, which increases the risk of thrombosis. [12]

Kobbernagel et al. recently performed a hypoxic challenge test (breathing 15% oxygen in nitrogen) on healthy children in seated, supine, and standing positions and during mild exercise. There was no significant difference in peripheral blood oxygen desaturation between the different body positions in healthy children, but mild exercise leads to significant further desaturation [11]. To our knowledge, such studies have not been performed in children and adolescents with congenital heart or lung disease. Only in one study was the effect of exercise at altitude in patients with cystic fibrosis examined. A significantly higher risk for hypoxemia during exercise was reported in this group.[13] To our knowledge previous studies about the effect of exercise at altitude in patients with congenital heart disease are absent.

For this reason more research about the effect of exercise on altitude hypoxia in patients with congenital heart or lung disease is required. If exercise at altitude leads to significantly more desaturation in children and adolescents with congenital heart and lung disease, the question is whether physical activity should be integrated into the HCT as preflight evaluation. Moreover, these might give more information about the cardiorespiratory reserves of the child or adolescent.

The primary aim of this current pilot study is to investigate the feasibility of integrating changing body positions and physical activity in the HCT at a simulated altitude of 8202 ft (2500 m) above sea level as preflight/mountain evaluation for children and adolescents with congenital heart or lung disease. The secondary aim is to monitor oxygen saturation ($S_{p}O_2$) at rest, during changing body positions, and during mild exercise using a pulse oximeter attached to two different locations, namely the index finger and forehead. These values will be compared to the baseline values (sea level).

METHODS

Subjects

The subjects consisted of a convenience sample of children and adolescents with congenital heart or lung disease between 8 and 18 yr of age and able to perform moderate exercise (treadmill walking). Exclusion criteria were FEV_1 below 70% predicted or $S_{p}O_2$ at rest in room air below 90%. The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht. Informed written consent was obtained from the patients and their parents. The study was performed between April and October 2015.

Procedure

An HCT was performed using the Hypoxico Everest Summit II Altitude Generator (BLM Altitude, Hoofddorp, the Netherlands) at simulated altitude of 8202 ft (2500 m). During the HCT the subjects breathed a gas mixture of 15% oxygen in 85% nitrogen, equivalent to the partial pressure of oxygen in the aircraft cabin at 2500 m. Subjects were connected to the generator through a tight-fitting facemask with a two-way nonrebreathing valve system.

The HCT consisted of six activities, performed as follows: first breathing room air (10 min), followed by breathing a gas mixture of 15% oxygen in 85% nitrogen while sitting in an airline seat (MartinAir StarClass, Schiphol-Rijk, Netherlands) and Q2 watching a DVD or Youtube movie on a wide screen (15 min), lying supine (10 min), standing (5 min), and while walking on a treadmill (Lode Valliant, Lode BV, Groningen, the Netherlands) at 3 km/h (5 min) and at 5 km/h (5 min). During the HCT the subjects were monitored: $S_{p}O_2$ and heart rate (HR) were measured continuously using a pulse oxygen saturation meter (Masimo Rad 8 clinical pulse oximeter; Masimo BV, Tilburg, the Netherlands) attached to the index finger and at the forehead of each subject. The forehead probe was secured with a head strap.

The primary main study parameter of this pilot study was the feasibility of integrating changing body positions and mild physical exercise with the HCT. Feasibility was defined as successful run through of the measurements in 75% of the subjects. The secondary main study parameters were $S_{p}O_2$ and HR during modified HCT compared with resting conditions at sea level.

Each activity in the protocol was timed and measurements during the transition to a subsequent activity were excluded. The median $S_{p}O_2$ value and HR in the last 2 min of each activity and the nadir value of $S_{p}O_2$ during an activity were identified. The last 2 min of each activity of the modified HCT was regarded as representative of a stable response to the hypoxic exposure. The percentage of the total time in each period where $S_{p}O_2$ fell below 90% was reported. Measurements during poor signal quality of the oximeter were excluded if the S_pO_2 value deviated more than 2% from the last properly measured preceding value. If more than 50% of the measurements during an activity were excluded because of poor signal quality, the total time where S_pO_2 fell below 90% was not reported for this activity.

Statistical Analysis

Results are reported as mean ± SD or median (range). Analyses were performed using statistical software (SPSS 20). Two-tailed *P*-values of < 0.05 were considered to be statistically significant. Hypothesis testing was done using paired sample testing and one way ANOVA. These data will be used for the design of a larger future study.

RESULTS

There were 12 patients (7 male), between 8 yr and 18 yr (median 14 yr), who participated in this study. Median (range) FEV_1 was 85.5 (71-106) % of predicted. Among the patients 5 were diagnosed with cystic fibrosis, 2 with Fontan circulation, 3 with tetralogy of Fallot (ToF), 1 with ventricular septum defect (VSD) and 1 with bicuspid aortic valve (BAV) and coarctation of the aorta (CoA). See **Table I** for the baseline characteristics.

All patients, except one, passed through the HCT successfully and reported that the test was feasible. One patient stopped the HCT during walking at 3 km/h because of a headache. Most patients ($N = 9$) did not report any symptoms during the HCT. However, one patient reported headache, which was already present at the start of the test, but became worse during exercise breathing 15% oxygen. A second patient did also report headache during exercise breathing 15% oxygen, after which the HCT was ended. Another patient reported dizziness during mild exercise breathing 15% oxygen. The dizziness became less after finishing the test.

Patients were monitored using a pulse oximeter attached to the index finger and at the forehead. In eight patients some data on S_pO_2 and HR during one or more periods were excluded because of a poor signal quality using the finger or forehead pulse oximeter; there was no significant difference between these two sites. In only one patient were more than 50% of the measurements of one activity excluded. Overall, the pulse oximeter attached to the forehead registered significantly higher saturations (median and minimum values) than the pulse oximeter attached to the finger ($P \leq 0.05$, df ≤ 11). Changes in S_pO_2 between sea level and simulated altitude are shown in **Fig. 1**.

The baseline S_pO_2 during resting conditions at sea level was 97% (92–99) and 99% (93–100) measured at the index finger and at the forehead, respectively. Breathing 15% oxygen, 8/12 (finger oximeter) vs. 3/12 (forehead oximeter) subjects desaturated below 90% (nadir S_pO_2) at some point in the seated position; 7/12 (finger oximeter) vs. 1/12 (forehead oximeter) in the supine position; 8/12 (finger oximeter) vs. 3/12 (forehead oximeter) in the standing position; 11/12 (finger oximeter) vs. 3/12 (forehead oximeter) while walking 3 km/h; and 9/11 (finger-oximeter) vs. 2/11 (forehead-oximeter) while walking 5 km/h (**Table II**).

In 9/12 (finger oximeter) vs. 6/12 (forehead oximeter) patients S_pO_2 decreased below 90% in one or more body positions at rest. S_pO_2 felt below 90% during a median of 0.97% (0–82.59) (finger oximeter) vs. 0% (0–70.83) (forehead oximeter) of the total time patients were monitored at rest. In 3/12 (finger oximeter) vs. 1/12 (forehead oximeter) patients S_pO_2 decreased below 85% in one or more body positions at rest.

Table I. Baseline Characteristics.

CHARACTERISTICS	STUDY SUBJECTS ($N = 12$)
Age, yr (range)	14 (8-18)
Gender	
Male	$N = 7$
Female	$N = 5$
Height (cm)	165.6 ± 17.3
Weight (kg)	56.4 ± 17.3
BMI (kg/m^2)	20.0 ± 0.9
Diagnosis	
Cystic Fibrosis	$N = 5$
Fontan	$N = 2$
Tetralogy of Fallot	$N = 3$
VSD (closed)	$N = 1$
BAV + Coarctation of the Aorta	$N = 1$
FEV_1 (% of predicted)	85.5 (71-106)

Data presented as number, median (range), or mean ± SD.

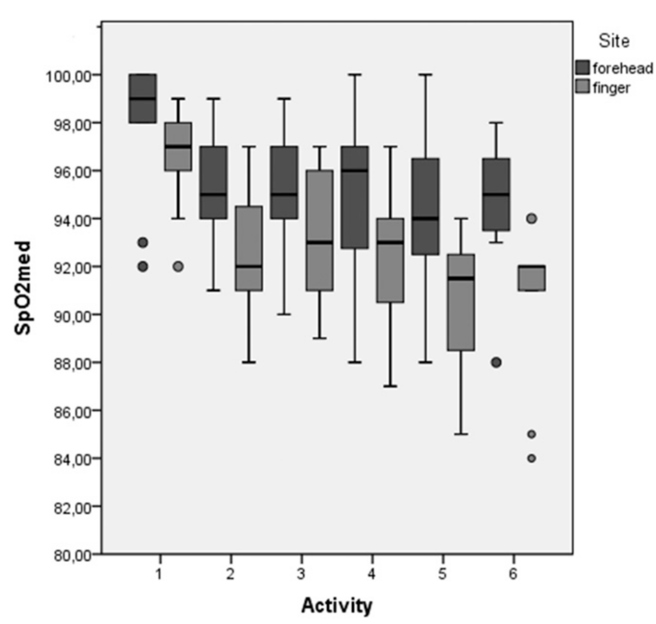

Fig. 1. Boxplot showing median S_pO_2 values in patients with congenital heart or lung disease during HCT at different periods: 1) sitting breathing room air; 2) sitting breathing 15% oxygen; 3) lying supine breathing 15% oxygen; 4) standing breathing 15% oxygen; 5) walking 3km/h breathing 15% oxygen; and 6) walking 5 km/h breathing 15% oxygen. The box represents the range of scores from lower to upper quartile, with the median shown by the black line in the box. The upper and lower whiskers represent the scores outside the interquartile range. The dots represent outliers.

Table II. Results of the HCT in Various Body Positions and While Walking; S_pO_2 and HR Were Measured Using a Pulse Oximeter Attached to the Index Finger.

	S_pO_2 MEDIAN (RANGE)	S_pO_2 (NADIR)	% OF TIME S_pO_2 BELOW < 90%	HR MEDIAN (RANGE)
Sea level, resting conditions (*N* = 12)	97 (92–99)	94 (91–97)	0 (0–0)	85 (65–103)
15% O_2, sitting (*N* = 12)	92 (88–97)	88 (83–95)	1.19 (0–76)	82 (65–101)
15% O_2, supine (*N* = 12)	93 (89–97)	89 (82–91)	1.67 (0–83)	79 (67–117)
15% O_2, standing (*N* = 12)	93 (87–97)	88 (80–95)	7.42 (0–75)	99 (70–119)
15% O_2, walking 3km/h (*N* = 12)	91 (85–93)	87 (82–90)	28.89 (0–100)	103 (77–134)
15% O_2, walking 5 km/h (*N* = 11)	92 (84–94)	88 (82–92)	10.67 (0–100)	113 (86–149)

Data presented as median (range). The median S_pO_2 value and HR in the last 2 min of each period in the HCT and the nadir value of S_pO_2 in the whole period were identified.

In 11/12 (finger oximeter) vs. 3/12 (forehead oximeter) patients S_pO_2 decreased below 90% during mild exercise. S_pO_2 felt below 90% during a median of 20.83% (0–100) (finger oximeter) vs. 0% (0–78.43) (forehead oximeter) of the total time patients were monitored during mild exercise. In 4/12 (finger oximeter) vs. 1/12 (forehead oximeter) patients S_pO_2 decreased below 85% during mild exercise.

Median pulse oximeter saturation breathing 15% oxygen decreased in all body positions (seated, supine, standing) compared with room air ($P = 0.0001$). However, there was no significant difference in pulse oximeter saturations between the different body positions. During mild exercise breathing 15% oxygen the pulse oximeter saturations decreased significantly ($P = 0.001$, $F = 14.537$, df = 1) compared to breathing 15% oxygen at rest. There was no significant difference between median S_pO_2 walking 3 km/h and walking 5 km/h ($P = 0.838$, $F = 0.42$, df = 1; **Table III**).

DISCUSSION

This present pilot study examined the feasibility of the HCT integrated with changing body positions and mild physical exercise for patients with congenital heart or lung disease. A total of 12 subjects were included: 7 patients with congenital heart disease and 5 patients with cystic fibrosis.

All study subjects, except one, successfully passed through the measurements and reported that the modified HCT was feasible. One patient stopped the HCT protocol during walking 3 km/h because of a headache. Since 11/12 patients completely passed the test, it can be concluded that the HCT integrated with changing body positions and mild physical exercise is feasible (defined as a successful run through the measurements in 75% of the subjects) in children and adolescents with congenital heart and lung disease.

We hypothesized that patients with congenital heart or lung disease were more vulnerable to hypoxemia at simulated altitude because their compensatory response to acute altitude is limited. These patients may be not able to sufficiently increase their minute ventilation or cardiac output. Cystic fibrosis patients are at risk for hypoxia due to a V/Q mismatch in the lungs. Patients with cyanotic congenital heart disease may have a reduced blood flow and poor oxygenation in peripheral tissue due to their reduced cardiac function, which can lead to stagnant hypoxia. Moreover, patients with congenital heart and lung disease may have a lower baseline P_aO_2 because of their reduced lung function or due to a right-left shunt. Further decrease of P_aO_2 at altitude can cause a dramatic fall in oxygen saturation (S_aO_2) as the P_aO_2 is on the steep part of the oxyhemoglobin dissociation curve.[8] On the other hand, most of these patients, because of their congenital condition, are adapted to chronic hypoxia and have developed other defense mechanisms such as erytrocytosis (more oxygen transport capacity),[12] pulmonary vasoconstriction (to redistribute pulmonary blood flow from regions of low PO_2 to high oxygen availability), increased levels of 2,3-diphosphoglycerate (shifting the oxyhemoglobin dissociation curve to the right), and a blunted hypoxic ventilatory response (decreased ventilatory effort through improved oxygen usage in peripheral tissues).[14] Furthermore, we hypothesized that mild exercise at altitude would led to further desaturation in patients with congenital heart or lung disease. Patients with congenital heart and lung disease often have a reduced exercise tolerance compared to healthy subjects of the same age, possibly because of an altered hemodynamic and pulmonary response to exercise due to their underlying disease and, most importantly, because of their lower training status and condition due to their insecurity about which sport they can perform safely [15].

During modified HCT S_pO_2 and HR were monitored continuously and compared with the baseline values in resting conditions at sea level. During breathing 15% oxygen, S_pO_2 decreased significantly in comparison with breathing room air. Nadir S_pO_2 below 90% appeared in several patients with congenital heart or lung disease at simulated altitude in resting conditions and during mild exercise. S_pO_2 did not significantly differ while seated, lying supine, or standing, all at rest. However, patients desaturated significantly more during mild exercise (walking

Table III. Results of the HCT in Various Body Positions and While Walking; S_pO_2 and HR Were Measured Using a Pulse Oximeter Attached to the Forehead.

	S_pO_2 MEDIAN (RANGE)	S_pO_2 (NADIR)	% OF TIME S_pO_2 BELOW < 90%	HR MEDIAN (RANGE)
Sea level, resting conditions (*N* = 12)	99 (93–100)	97 (90–100)	0 (0–0)	85 (65–104)
15% O_2, sitting (*N* = 12)	95 (93–99)	92 (88–98)	0 (0–0)	83 (65–105)
15% O_2, supine (*N* = 12)	95 (93–99)	92 (86–96)	0 (0–1)	78 (67–118)
15% O_2, standing (*N* = 12)	96 (89–100)	93 (80–99)	0 (0–68)	99 (69–117)
15% O_2, walking 3km/h (*N* = 12)	94 (91–100)	92 (83–99)	0 (0–35)	102(76–135)
15% O_2, walking 5 km/h (*N* = 11)	95 (88–98)	93 (84–96)	0 (0–76)	114 (87–149)

Data presented as median (range). Median S_pO_2 value and HR in the last 2 min of each period in the HCT and the nadir value of S_pO_2 in the whole period were identified.

3km/h and 5 km/h). Three patients reported symptoms; two patients reported a headache; another patient reported dizziness. However, the observed values in the current study are even somewhat higher compared to those reported by Kobbernagel et al. in healthy children.[11] They reported a median S_pO_2 during walking at 3 and 5 km/h of 88%.

Only S_pO_2 was measured in this pilot study. To fully evaluate the oxygenation status of these patients, blood gasses and hemoglobin levels should be determined. Pulse oximetry provides an estimate of arterial oxyhemoglobin saturation. In resting conditions pulse oximetry estimates S_aO_2, which is accurate during most of the measurements, with a difference of $\pm$3–5% [16]. Most importantly, S_pO_2 values can be interpreted as a trend which registers desaturation. In a follow-up study it is recommended to perform blood gas measurements and hemoblobin concentrations at rest and during simulated altitude.

The patients included in our study had relatively good baseline saturations at sea level: S_pO_2 in resting conditions of 97% (92–99) and 99% (93–100) measured at the index finger and at the forehead, respectively. According to our results, previous studies examining cystic fibrosis patients at (simulated) altitude of 5000–8000 ft (1524–2438 m) reported that patients with cystic fibrosis desaturated significantly and may become hypoxemic.[13,17-21] Patients with more severe disease, and with FEV_1 values $<$50% of predicted, were most at risk of hypoxemia.[13,17,19] Our current study included a patient with an FEV_1 $\geq$70% of predicted and a relatively high baseline S_pO_2 at sea level. Patients with more severe lung disease may tolerate the modified HCT differently than our current study subjects. Moreover, discomfort or symptoms at (simulated) altitude were rarely reported in previous studies,[17,18,20,21] implying that hypoxemia is well tolerated by patients with cystic fibrosis.[17,18,20,21]

Likewise, the included patients with congenital heart disease were patients with relatively high baseline saturations at sea level. Harinck et al.[11] examined patients with more severe cyanotic congenital heart disease (baseline saturations of 77–99%) and most with irreversible pulmonary vascular disease. The patients were tested in a hypobaric chamber and during actual flight. They reported a significant decrease in S_aO_2, which was well tolerated; no symptoms were reported. It was concluded that air travel is safe for patients with cyanotic congenital heart disease, possibly because patients with congenital heart disease are well adapted to chronic hypoxia.[22]

Despite most patients with congenital heart and lung disease tolerating altitude hypoxia, it is important to evaluate patients carefully. Some patients can benefit from supplemental oxygen to avoid discomfort, symptoms, and unhealthy situations due to hypoxemia.[23]

The previous studies mentioned above examined patients at (simulated) altitude in resting conditions. However, the possible effects of mild physical activity are also of interest. During long flight mild exercise, such as walking, is not uncommon and even advised to prevent deep vein thrombosis.[2,10,11] The present results suggest that mild exercise leads to further desaturations and an increased risk for hypoxemia at altitude. This was confirmed by Fisher et al.[13] They reported exercise induced hypoxemia at 8694 ft (2650 m; $Po_2 < 6.6$ kPa) in 67.5% of the patients during mild exercise (30 W) compared to 33.3% of the patients in resting conditions.[13] For this reason it is important to integrate mild exercise in fitness to fly testing of patients with congenital heart or lung disease.

Further research is necessarily to identify an appropriate cutoff value for HCT integrated with exercise in children and adolescents with congenital heart or lung disease below which supplemental in-flight oxygen is recommended. The current guidelines and cutoff values for in-flight oxygen are based on HCT in resting conditions. Re-evaluating the cutoff values is important because healthy children also desaturate during exercise at altitude. This was reported by Kobbernagel et al.[11] HCT integrated with exercise led to moments of desaturation below 90% at rest and during mild exercise. The cutoff value should discriminate between healthy children and children with congenital heart or lung disease, who may benefit from in-flight supplemental oxygen. For this reason it is questionable whether the recommended cutoff value of 90% is appropriate.

The present pilot study used two pulse oximeters; one attached to the index finger and one at the forehead to register S_pO_2. Overall, the pulse oximeter attached to the forehead registered significantly higher saturations (median and minimum values) than the pulse oximeter attached to the finger ($P \leq 0.05$). Based on the current literature, a pulse oximeter attached to the forehead might be the most reliable measurement site for HCTs. Studies comparing the finger sensor with the forehead sensor reported that forehead sensors yield measurements more concordant with arterial blood, especially during movement and in cold due to vasoconstriction in the fingers [24-26].

Further research could add more factors to pre-altitude testing. The current pilot study used the Hypoxico Everest Summit II Altitude Generator (BLM Altitude), which simulated an altitude of 8202 ft (2500 m) using a normobaric gas mixture of 15% oxygen in 85% nitrogen at rest and during mild exercise. However, the physiological response to normobaric hypoxia might be different from hypobaric hypoxia and genuine high altitude. According to Boos et al., the physiological and cardiac response to exercise in hypobaric hypoxia, normobaric hypoxia, and genuine high altitude is notablely different. They reported that the degree of hypoxemia was greater in hypobaric hypoxia and at genuine high altitude in comparison with normobaric hypoxia [27]. Future studies should evaluate the results of hypoxic challenge tests in hypobaric environments.

Also, other factors can be important. For example, hypobaric hypoxia or low air humidity as is found in aircraft cabins or altitude environments, which can lead to mucosal irritation, or cold air in case of high mountain stays, or strenuous exercise in prealtitude testing for winter sports in the mountains.

The modified HCT is safe and feasible in children and adolescents with congenital heart or lung disease and gives additional information about oxygenation during light to moderate physical activity in addition to resting conditions. Simulated hypoxia of 8202 ft (2500 m) induced a small but significant decrease in S_pO_2% in children and adolescents with congenital heart or lung disease. These values were not further lowered during mild to moderate exercise. Further research is necessary to improve pre-altitude testing and to specify the guidelines and cutoff values which determine when supplemental oxygen is needed.

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Authors and affiliation: Mandy E. Spoorenberg, M.Sc., Erik H. Hulzebos, PT, Ph.D., and Tim Takken, M.Sc., Ph.D., Child Development & Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands.

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