Influence of altitude on cerebral and splanchnic oxygen saturation in critically ill children during air ambulance transport

Tova Hannegård Hamrin1,2*, Staffan Eksborg1,3, Jonas Berner1,2, Urban Fläring1,2, Peter J. Radell1,2

1 Pediatric Perioperative Medicine and Intensive Care, Astrid Lindgren Children’s Hospital, Karolinska University Hospital Solna, Stockholm, Sweden, 2 Department of Physiology and Pharmacology, Section of Anesthesiology and Intensive Care, Karolinska Institutet, Astrid Lindgren Children's Hospital, Karolinska University Hospital Solna, Stockholm, Sweden, 3 Childhood Cancer Research Unit, Department of Women’s and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Barnläkemedelsgruppen, Norrbacka S3:04, Karolinska University Hospital Solna, Stockholm, Sweden

* tova.hannegard-hamrin@sll.se

Abstract

Objective

The aim of the current study was to investigate how cerebral and splanchnic oxygen saturation (rSO2-C and rSO2-A) in critically ill children transported in air ambulance was affected by flight with cabin pressurization corresponding to \( \geq 5000 \) feet. A second aim was to investigate any differences between cyanotic and non-cyanotic children in relation to cerebral and splanchnic oxygen saturation during flight \( \geq 5000 \) feet. The variability of the cerebral and splanchnic Near Infrared Spectroscopy (NIRS) sensors was evaluated.

Design

NIRS was used to measure rSO2-C and rSO2-A during transport of critically ill children in air ambulance. rSO2 data was collected and stored by the NIRS monitor and extracted and analyzed off-line after the transport. Prior to evaluation of the NIRS signals all zero and floor-effect values were removed.

Setting

The Pediatric Intensive Care Unit (PICU) at Astrid Lindgren Children’s Hospital, Karolinska University Hospital in Stockholm, Sweden.

Patients

In total, 44 critically ill children scheduled for inter-hospital transport by a specialized pediatric transport team were included in the study between January 2014 and January 2019 (convenience sampling).
Intervention
No interventions were conducted.

Measurements
All study patients were monitored with a cerebral NIRS-sensor placed over the forehead and an abdominal NIRS-sensor placed in the infra-umbilical area for cerebral and splanchonic regional oxygen saturation monitoring, rSO$_2$-C and rSO$_2$-A, respectively.

Main results
Complete rSO$_2$-C and rSO$_2$-A data was obtained in 39 patients. Median age was 12 days. Cyanotic congenital heart malformations were present in 9 patients (23%). In 22 patients (56%) rSO$_2$-C decreased at altitude $\geq$ 5000 feet and in 24 patients (61%) rSO$_2$-A decreased at altitude $\geq$ 5000 feet compared to baseline ($p<$0.0001). In 25 patients (64%) the rSO$_2$-C/rSO$_2$-A ratio was greater at altitude $\geq$ 5000 feet than at baseline. A ratio $\geq$ 1 was seen in 77% of patients at altitude $\geq$ 5000 feet compared to in 67% of patients at baseline.

Conclusion
Both cerebral and splanchnic oxygen saturation decreased at altitude $\geq$ 5000 feet compared to baseline. In most patients, both cyanotic and non-cyanotic, cerebral oxygen saturation was preserved more than splanchnic oxygen saturation.

Introduction
Specialized pediatric transport teams operate today as mobile intensive care units. They deliver advanced intensive care outside tertiary care centers for a wide variety of disorders using advanced monitoring equipment and skilled personnel [1–4]. Depending on distance between the referring and receiving hospital, some patients must be transported by air in helicopter or air-ambulance. Monitoring of oxygenation is important to ensure patient safety and the best possible patient outcome. Near-infrared spectroscopy (NIRS) is a noninvasive, method for monitoring of regional tissue oxygen saturation (rSO$_2$) [5]. It has been shown that cerebral oxygen monitoring with NIRS detects changes in oxygenation earlier than pulse oximetry in periods of apnea during airway surgery in pediatric anesthesia [6].

NIRS-monitoring is attractive in neonatal and pediatric practice not only because it is noninvasive, but also because the penetration of the signal into the tissue corresponds well with the anatomy of neonates, infants and children [7]. Pediatric studies have demonstrated good correlation between cerebral rSO$_2$ and jugular venous bulb saturation [8]. Anterior abdominal (splanchnic) rSO$_2$ has shown strong correlation with gastric intra-mucosal pH as well as serum lactate and systemic venous oxygen saturation (SvO$_2$) in children with congenital heart disease (CHD) [9]. In this group of patients with risk for low cardiac output, splanchnic rSO$_2$ correlated better with systemic markers of oxygenation and perfusion such as serum lactate and SvO$_2$ than did measurements over the renal bed. Multisite NIRS monitoring has been advocated to provide insight into the tissue response to different types of clinical interventions [10]. Somatic NIRS measurements may also be a better and earlier indicator of low cardiac output states than cerebral measurements, since the brain has efficient autoregulation [11].
During air transport the effects of altitude on patient oxygenation are of special importance. With increasing altitude, barometric pressure decreases and as a result also the partial pressure of oxygen. The result is lower oxygen saturations. Healthy children desaturated significantly, at times below 90%, in a hypoxic challenge test simulating the conditions of a commercial aircraft where the cabin is pressurized to 8000 feet, which equates to breathing 15% oxygen at sea level [12]. The effects of high altitude on critically ill children transported in air ambulance are not known. There are few studies of NIRS utilization in an air-transport environment and only two concerning pediatric patients [13, 14]. These studies were mainly performed in helicopters, with only 5 patients transported in air ambulance. The results suggested that cerebral oxygenation monitoring with NIRS can be used in a transport environment and that NIRS might be a useful complement to existing monitoring during inter-hospital transports.

In a previous methodological study, we found that the electronically stored NIRS data could be filtered and assessed off-line after the transport to improve reliability of the signal and thereby provide valuable post-hoc information about transport events [15].

The aim of the current study was to investigate how cerebral and splanchnic oxygen saturation in critically ill children transported in air ambulance was affected by flight ≥ 5000 feet. A second aim was to investigate any differences between cyanotic and non-cyanotic children in relation to cerebral and splanchnic oxygen saturation. Finally, we evaluated the variability of both cerebral and splanchnic NIRS sensors.

Material and methods

Ethical approval

Ethical approval for this study was provided by the Regional Ethics Review Board of Stockholm, Sweden (DNr 2013/1487-31/1 and 2016/2036-32).

Study design and population

This was a prospective observational study, registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) with registration number ACTRN12619001710112. Following written parental informed consent, 44 critically ill children scheduled for inter-hospital transport by a specialized pediatric transport team at the Pediatric Intensive Care Unit (PICU) at Astrid Lindgren Children’s Hospital, Karolinska University Hospital in Stockholm, were enrolled in the study between January 2014 and January 2019 (convenience sampling). Exclusion criteria were lack of consent, participation in any other clinical research study, flights with an estimated duration less than 50 minutes and flights with a need for sea level cabin altitude. Transports were both acute and planned transfers to and from the PICU at Astrid Lindgren Children’s Hospital. The team is staffed by a PICU consultant and a specialist anesthesia or intensive care registered nurse with a minimum of 3 years experience in pediatric anesthesia or pediatric intensive care [3].

Equipment and procedures

Patients were transported in Beech Superking Air 200 and Cessna Citation II 550 air ambulances.

Standard monitoring during transport, including pulse oximetry, electrocardiographic monitoring, blood pressure measurements, body temperature, respiratory rate and evaluation with Comfort-B scale for level of sedation/comfort, was performed in all study patients and checked and noted in the study protocol before transport (base-line), during flight with cabin pressurization corresponding to ≥ 5000 feet and after transport [16]. The transport risk index
of physiological stability (TRIPS) score was recorded before, during transport at ≥ 5000 feet and after transport for neonatal patients ≤ 30 days at the time of transport [17].

All study patients were monitored with a cerebral NIRS-sensor placed over the forehead and an abdominal NIRS-sensor placed in the infra-umbilical area for cerebral and splanchnic regional oxygen saturation monitoring, $rSO_2$-C and $rSO_2$-A respectively (INVOS-5100C, Covidiem, Mansfield, MA, USA). The sensors had the following dimensions: 17.25 cm$^2$ for neonates and infants and 28.8 cm$^2$ for pediatric patients. The probes had two light paths with an emitter/diode spacing of 30–40 mm and a light penetrating depth of 20–40 mm. Monitoring began at the hospital before patient transport and was continued during transfer in ground ambulance to and from the airport as well as during air ambulance transport and was finished upon arrival at the receiving hospital. Cerebral and splanchnic $rSO_2$ data were stored by the INVOS monitor during transport and extracted and analyzed off-line after the transport. The data points had a spacing of 6 seconds.

Transport personnel were instructed not to make clinical care decisions based on values presented on the INVOS monitor. Therapeutic interventions, including adjustment of fraction of inspired oxygen ($F_iO_2$), were made according to the clinical judgement of the transport team. To reduce ambient light exposure, aluminum foil was used to cover the cerebral probe and the abdominal probe was covered under the patient’s clothes and blankets. The internal battery time of the INVOS 5100C is approximately 20 minutes, which made access to an external power supply necessary for both ground and air ambulance. The NIRS data was downloaded from the monitor using a Microsoft Excel 2010 spreadsheet (Microsoft Corp., Washington, DC, USA).

Prior to evaluation of the NIRS signals all zero and floor-effect values were removed. For visual inspection of NIRS signals the Savitzky–Golay algorithm of smoothing and differentiation of data by simplified least square procedures (least-squares fitting using 20 and 50 neighbors; 2nd order polynom) was applied to perform noise reduction in the signal [15, 18].

To further evaluate differences between cerebral and splanchnic oxygenation, the cerebral — splanchnic ratio ($rSO_2$-C/$rSO_2$-A) for each patient at baseline and at altitude ≥ 5000 feet was calculated.

**Statistics**

Data is presented as median and inter-quartile range. All statistical evaluation was performed on non-smoothed data. The variability for $rSO_2$-values were expressed by the coefficient of variation and compared with the Friedman’s test with the Dunn’s multiple comparison test. Wilcoxon signed-rank test was used for the comparison of column medians to a hypothetical value. Several independent populations were compared with Kruskal-Wallis statistics with the Dunn’s multiple comparison test.

Statistics were evaluated by MS Excel (Microsoft Corporation, Redmond, Washington, USA) and Graph Pad Prism version 5.04 (Graph Pad Software Inc. San Diego, USA). All statistical tests were two sided and p values < 0.05 were considered to be statistically significant.

**Results**

In total 44 patients were monitored. Complete cerebral regional oxygen saturation ($rSO_2$-C) and splanchnic regional oxygen saturation ($rSO_2$-A) data were obtained in 39 patients (Fig 1).

Median age was 12 days and median weight 3.55 kg. Cyanotic congenital heart malformations were present in 9 patients (23%). Mechanical ventilation was used in 12 patients (31%), 4 patients (10%) needed CPAP and 4 patients (10%) needed support with high flow nasal cannula (Table 1). Patients were categorized as cyanotic due to the presence of an intracardiac
lesion or ductus arteriosus with a significant right to left shunt/mixing affecting the systemic saturation as measured by the SpO\textsubscript{2}. Diagnoses that were grouped into cyanotic congenital heart malformations were: Transposition of the Great Arteries (TGA) \( n = 3 \); Pulmonary Atresia \( n = 2 \); Pulmonary Atresia & Tricuspid Atresia \( n = 2 \); Total Anomalous Pulmonary Venous Return (TAPVR) \( n = 1 \) and Truncus Arteriosus \( n = 1 \). Median pulse oximetry registrations at Take-Off were 89\% (IQR 83.5–93) and 99\% (IQR 96–100) for cyanotic patients and non-cyanotic patients, respectively (\( p < 0.0001 \)).

Simultaneous rSO\textsubscript{2}-C and rSO\textsubscript{2}-A values for each patient were investigated before flight (departure from hospital ward—loading into ambulance—transport in ambulance—take-off), at altitude \( \geq 5000 \) feet and after flight (landing—unloading—transport in ambulance—arrival at
| Patient No. | Age (days) | Weight (kg) | Sex | Diagnosis                                           | Cabin altitude (feet) | Barometric pressure (kPa) | Breathing support | FiO₂ start | Change FiO₂ at altitude | PiO₂ (kPa) | SpO₂% min | SpO₂% max | Hb (g/L) | Transport time (min) |
|------------|------------|-------------|-----|----------------------------------------------------|-----------------------|---------------------------|---------------------|------------|------------------------|------------|------------|------------|----------|---------------------|
| 1          | 1          | 3.7         | M   | Interrupted aortic arch, ASD + VSD                | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 87         | 94         | 175      | 70                  |
| 2          | 12         | 3.3         | M   | CoA + VSD                                          | 6000                  | 81.22                     | CPAP                | 0.21       | No                     | 15.7       | 99         | 100        | 148      | 70                  |
| 3†         | 1          | 3.8         | F   | PA with intact ventricular septum                  | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 83         | 87         | 149      | 70                  |
| 4          | 5          | 5.1         | M   | PPHN, biventricular failure                        | 5000                  | 84.33                     | sp                  | 0.21       | No                     | 16.4       | 85         | 98         | 182      | 75                  |
| 5          | 109        | 4.8         | M   | Dystrophia Myotonica type I                        | 6000                  | 81.22                     | BiPaP               | 0.21       | 1 litre O₂              | 18.0       | 85         | 100        | 50       | 10                  |
| 6†         | 9          | 4.1         | F   | PA and TA, Post op status after BT-shunt           | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 68         | 88         | 72       | 70                  |
| 7†         | 8          | 3.8         | M   | TGA, septostomy                                    | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 75         | 82         | 151      | 75                  |
| 8          | 24         | 3.7         | M   | Aortic Stenosis                                    | 7400                  | 77.00                     | sp                  | 0.21       | No                     | 14.8       | 97         | 100        | 150      | 81                  |
| 9          | 23         | 3.5         | M   | Post op status after CDH                           | 6900                  | 78.49                     | HFNC                | 0.3        | 0.5                    | 36.1       | 75         | 100        | 109      | 70                  |
| 10†        | 2          | 3.2         | M   | PA and TA                                          | 6000                  | 81.22                     | intubated           | 0.21       | No                     | 15.7       | 84         | 94         | 173      | 75                  |
| 11         | 1136       | 13.0        | F   | Hemolytic uremic syndrome, anuria                  | 5800                  | 81.84                     | sp                  | 0.21       | No                     | 15.9       | 95         | 100        | 86       | 78                  |
| 12         | 4          | 3.8         | F   | Tracheomalacia                                     | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 85         | 96         | 99       | 99                  |
| 13         | 8          | 3.2         | F   | Sepsis, status after ECMO                         | 6000                  | 81.22                     | intubated           | 0.38       | No                     | 28.5       | 98         | 100        | 199      | 60                  |
| 14         | 12         | 4.1         | M   | MAS, status after ECMO                             | 6000                  | 81.22                     | intubated           | 0.46       | No                     | 34.5       | 90         | 94         | 142      | 60                  |
| 15         | 33         | 1.4         | M   | Aortic Stenosis, Left chamber hypertrophy         | 6000                  | 81.22                     | CPAP                | 0.55       | 1                      | 74.9       | 90         | 95         | 68       | 68                  |
| 16         | 3          | 3.4         | M   | CoA                                                | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 86         | 99         | 71       | 71                  |
| 17         | 39         | 1.4         | M   | Post op status after commissurotomy of aorta + PDA ligation | 6000                  | 81.22                     | intubated           | 0.45       | No                     | 33.7       | 93         | 100        | 109      | 76                  |
| 18†        | 24         | 3.2         | M   | PA, Post op status after BT-shunt                  | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 77         | 86         | 75       | 75                  |
| 19         | 7          | 3.6         | F   | CoA + VSD                                          | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 93         | 100        | 207      | 82                  |
| 20         | 2          | 3.7         | M   | CoA + VSD                                          | 6000                  | 81.22                     | sp                  | 0.21       | 1 litre O₂              | 18.0       | 83         | 100        | 179      | 80                  |
| 21         | 10         | 3.0         | M   | MAS, status after ECMO                             | 6000                  | 81.22                     | HFNC                | 0.3        | No                     | 22.5       | 90         | 100        | 109      | 70                  |
| 22         | 14         | 3.9         | M   | CoA + VSD                                          | 5120                  | 83.96                     | sp                  | 0.21       | No                     | 16.3       | 92         | 98         | 151      | 82                  |
| 23†        | 5          | 2.2         | M   | TAPVR + ASD                                        | 6000                  | 81.22                     | intubated           | 0.5        | No                     | 37.5       | 85         | 89         | 66       | 66                  |
| 24         | 58         | 3.4         | M   | Post op status after CDH, status after ECMO       | 6000                  | 81.22                     | intubated           | 0.4        | 0.5                    | 37.5       | 86         | 100        | 124      | 207                 |
| 25         | 3          | 2.5         | M   | Interrupted aortic arch, ASD + VSD                | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 98         | 100        | 172      | 71                  |
| 26         | 12         | 4.3         | F   | MAS, status after ECMO                             | 6000                  | 81.22                     | sp                  | 0.21       | 3 litre O₂              | 24.0       | 79         | 100        | 105      | 75                  |
| 27†        | 4          | 3.9         | M   | TGA, septostomy                                    | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 85         | 94         | 170      | 72                  |
| 28         | 5          | 3.9         | F   | PPHN, asphyxia. Status after ECMO                 | 6000                  | 81.22                     | intubated           | 0.35       | No                     | 26.1       | 96         | 100        | 122      | 181                 |
| 29†        | 3          | 3.4         | M   | TGA, septostomy                                    | 6000                  | 81.22                     | intubated           | 0.21       | No                     | 15.7       | 84         | 93         | 142      | 67                  |
| 30         | 2          | 3.4         | M   | CoA                                                | 6000                  | 81.22                     | sp                  | 0.21       | No                     | 15.7       | 95         | 100        | 195      | 87                  |

(Continued)
receiving hospital) after all zero values and floor effect values had been removed. Simultaneously registered numbers of readings for $rSO_2$-C and $rSO_2$-A before flight were 708 (IQR 521–1140), median registration time 53 minutes (IQR 43–71). At altitude ≥5000 feet the number of values simultaneously registered was 255 (IQR 132–435), median registration time 15 minutes (IQR 29–43) and after flight 521 (IQR 358–607), median registration time 53 minutes (IQR 41–61).

No statistically significant difference in variability was seen within $rSO_2$-C or within $rSO_2$-A when values before flight were compared to values at altitude ≥5000 feet and after flight. Overall, there was greater variability seen in $rSO_2$-A measurements than in $rSO_2$-C ($p<0.0001$), Fig 2.

Changes in $rSO_2$-C and in $rSO_2$-A between pre-flight, flight at altitude ≥5000 feet and after flight were investigated for each patient using all recorded values. There was a statistically significant difference ($p<0.0001$) and post-hoc tests for each patient and each sensor were performed (Table 2).

The data contained in Table 2 are summarized at the bottom of the table as median (IQR) for patients with and without cyanotic heart disease.

The relationship between $rSO_2$-C, $rSO_2$-A and the TRIPS score was investigated for 28 neonatal patients. Either $rSO_2$-C or $rSO_2$-A were affected in the patients ($n=10$) where the TRIPS score increased between pre-transport and flight at ≥5000 feet ($p=0.30$ and $p=0.2$, respectively). Patients were grouped into three different categories with increasing pre-transport TRIPS scores 0–10, 11–20 and 21–30. The distribution of TRIPS score categories at different times is shown in Table 3. There was a decrease in TRIPS score after transport resulting in

| Patient No. | Age (days) | Weight (kg) | Sex | Diagnosis | Cabin altitude (feet) | Barometric pressure (kPa) | Breathing support | FiO$_2$ start | Change FiO$_2$ at altitude | PiO$_2$ (kPa) | SpO$_2$% min | SpO$_2$% max | Hb (g/L) | Transport time (min) |
|------------|------------|-------------|-----|-----------|-----------------------|--------------------------|------------------|--------------|--------------------------|----------------|---------------|---------------|-----------|-------------------|
| 31         | 59         | 3.4 F       | ASD + VSD with heart failure 5900 | 81.53 | intubated | 0.25 | No | 18.8 | 96 | 100 | 112 | 60 |
| 32         | 1148       | 15.0 F      | Neck abscess 6000 | 81.22 | sp | 0.21 | No | 15.7 | 95 | 100 | 97 | 63 |
| 33         | 9          | 4.4 M       | MAS + sepsis, status after ECMO 6000 | 81.22 | intubated | 0.45 | No | 33.7 | 95 | 100 | 113 | 211 |
| 34         | 160        | 6.6 M       | BPD, ex premature 7000 | 78.19 | intubated | 0.3 | 0.4 | 28.8 | 86 | 100 | 127 | 75 |
| 35         | 87         | 2.4 M       | Ex premature. Post op PDA ligation 6000 | 81.22 | HFNC | 0.3 | 0.35 | 26.2 | 89 | 100 | 142 |
| 36*        | 3          | 3.2 F       | Truncus arteriosus 6000 | 81.22 | CPAP | 0.21 | No | 15.7 | 86 | 95 | 196 | 84 |
| 37         | 701        | 6.9 M       | Post op status after AVSD, PPHN. 6000 | 81.22 | HFNC | 0.7 | No | 52.4 | 96 | 100 | 98 | 72 |
| 38         | 162        | 6.3 F       | Tracheal stenosis 6000 | 81.22 | sp | 0.21 | No | 15.7 | 93 | 100 | 148 |
| 39         | 19         | 3.5 M       | Post op status after CDH, status after ECMO 6000 | 81.22 | intubated | 0.3 | 0.34 | 25.5 | 89 | 100 | 127 | 156 |

FiO$_2$ = fraction of inspired oxygen, SpO$_2$ = peripheral capillary oxygen saturation, ECMO = Extracorporeal membrane oxygenation, CoA = Coarctation of the aorta, PPHN = Persistent Pulmonary Hypertension in the Newborn, MAS = Meconium Aspiration Syndrome, BPD = Bronchopulmonary dysplasia, CHD = Congenital Heart Disease, CDH = Congenital Diaphragmatic Hernia, TGA = Transposition of the Great Arteries, PDA = Patent Ductus Arteriosus, TAPVR = Total Anomalous Pulmonary Venous Return, BT-shunt = Blalock-Tausig shunt, ASD = Atrial Septal Defect, VSD = Ventricular Septal Defect, sp = Spontaneous breathing, CPAP = Continuous Positive Airway Pressure, BiPAP = Biphasic Positive Airway Pressure, HFNC = High-Flow Nasal Cannula, PA = Pulmonary Atresia, TA = Tricuspid Atresia

* = cyanotic CHD. PiO$_2$ given is with FiO$_2$ added/increased where applicable.
fewer patients in TRIPS category 21–30 compared to pre-transport. In most patients, the TRIPS score did not change during transport.

Older patients (n = 10) were monitored with Comfort-B scores for level of sedation, there was no statistically significant difference in the Comfort B levels between pre-flight, flight at altitude ≥ 5000 feet and after flight. In 22 patients (56%) rSO\textsubscript{2-C} decreased at altitude ≥ 5000 feet compared to baseline, in 9 patients there was no significant difference and in 8 patients rSO\textsubscript{2-C} increased at altitude. In 24 patients (61%) rSO\textsubscript{2-A} decreased at altitude ≥ 5000 feet compared to baseline, in 8 patients there was no statistically significant difference and in 7 patients rSO\textsubscript{2-A} increased at altitude. In patients with cyanotic heart malformations the rSO\textsubscript{2-C} value at altitude ≥ 5000 feet decreased compared to baseline in 6 of 9 patients and rSO\textsubscript{2-A} decreased in 4 patients. These findings are illustrated by plotting of the median values for rSO\textsubscript{2-C} and rSO\textsubscript{2-A} in each patient at baseline, altitude ≥ 5000 feet and after flight. Cyanotic and non-cyanotic patients are presented separately (Fig 3A–3D).

The quotients rSO\textsubscript{2-C}/rSO\textsubscript{2-A} were > 1 in 26 patients (67%) at baseline and in 30 patients (77%) at altitude ≥ 5000 feet. The ratio shifted from being < 1 at baseline to being > 1 at altitude in seven patients and in four patients the ratio shifted from being > 1 at baseline to being < 1 at altitude. In 25 patients (64%) the rSO\textsubscript{2-C}/rSO\textsubscript{2-A} ratio was greater at altitude ≥ 5000 feet than at baseline. A statistically significant difference between rSO\textsubscript{2-C}/rSO\textsubscript{2-A} at baseline and at altitude was found in 36 subjects (92.3% of patients).
Table 2. Regional oxygen saturation values for all patients.

| Patient No. | Pre flight | Post flight | Pre flight | Post flight |
|-------------|------------|-------------|------------|-------------|
|             | rSO\textsubscript{2}-C (%) | rSO\textsubscript{2}-A (%) | rSO\textsubscript{2}-C (%) | rSO\textsubscript{2}-A (%) |
| 1           | 81 (80–82) | 97 (77–80) | 85 (84–86) | 50 (45–56) |
| 2           | 71 (68–74) | 72 (68–74) | 72 (71–76) | 50 (47–53) |
| 3           | 61 (60–63) | 64 (62–65) | 62 (61–63) | 55 (49–60) |
| 4           | 79 (75–82) | 70 (67–72) | 78 (76–81) | 78 (74–83) |
| 5           | 64 (63–66) | 75 (66–78) | 70 (67–73) | 66 (60–71) |
| 6           | 63 (61–65) | 61 (58–62) | 65 (62–67) | 54 (51–59) |
| 7           | 61 (59–64) | 57 (55–59) | 62 (60–63) | 48 (46–49) |
| 8           | 80 (77–81) | 78 (75–79) | 80 (78–82) | 86 (78–91) |
| 9           | 63 (60–67) | 61 (60–62) | 75 (73–76) | 44 (36–51) |
| 10          | 76 (61–78) | 66 (62–69) | 71 (69–74) | 43 (37–49) |
| 11          | 68 (67–70) | 62 (60–63) | 67 (66–68) | 58 (51–64) |
| 12          | 71 (69–72) | 58 (57–61) | 67 (66–69) | 93 (90–94) |
| 13          | 64 (62–65) | 65 (64–66) | 69 (66–70) | 74 (72–77) |
| 14          | 86 (85–88) | 90 (89–90) | 86 (85–88) | 61 (57–64) |
| 15          | 82 (76–84) | 73 (71–76) | 80 (75–84) | 70 (65–73) |
| 16          | 80 (76–83) | 71 (69–73) | 79 (77–82) | 91 (88–93) |
| 17          | 82 (79–86) | 69 (67–70) | 72 (71–74) | 37 (28–50) |
| 18          | 51 (50–52) | 40 (38–43) | 54 (51–56) | 44 (42–46) |
| 19          | 82 (79–87) | 77 (76–78) | 80 (77–83) | 83 (79–87) |
| 20          | 86 (84–88) | 80 (77–84) | 87 (86–89) | 69 (67–70) |
| 21          | 66 (63–68) | 63 (62–65) | 66 (64–68) | 68 (59–72) |
| 22          | 71 (68–73) | 64 (62–66) | 77 (75–79) | 78 (72–83) |
| 23          | 64 (62–66) | 63 (63–63) | 67 (66–67) | 66 (62–69) |
| 24          | 64 (62–66) | 69 (68–70) | 72 (71–73) | 54 (50–57) |
| 25          | 62 (58–68) | 76 (73–80) | 70 (66–73) | 66 (64–68) |
| 26          | 64 (63–66) | 59 (57–71) | 66 (65–68) | 73 (67–78) |
| 27          | 63 (61–66) | 52 (50–53) | 63 (62–65) | 54 (51–57) |
| 28          | 78 (75–81) | 70 (50–74) | 79 (77–80) | 58 (51–64) |
| 29          | 74 (69–81) | 67 (65–69) | 72 (70–75) | 57 (49–66) |
| 30          | 76 (73–81) | 69 (64–72) | 73 (69–77) | 86 (84–88) |
| 31          | 74 (71–76) | 73 (71–74) | 70 (68–72) | 59 (55–64) |
| 32          | 66 (65–67) | 55 (53–57) | 64 (63–65) | 70 (68–72) |
| 33          | 71 (69–73) | 67 (64–69) | 67 (64–68) | 62 (45–73) |
| 34          | 80 (77–81) | 80 (76–81) | 82 (81–87) | 72 (71–74) |
| 35          | 60 (55–65) | 62 (57–65) | 55 (45–57) | 61 (57–73) |
| 36          | 67 (65–68) | 68 (67–69) | 66 (64–67) | 68 (65–72) |
| 37          | 65 (63–67) | 57 (55–58) | 55 (52–59) | 47 (42–50) |
| 38          | 89 (87–91) | 91 (87–92) | 90 (88–92) | 72 (70–74) |
| 39          | 73 (72–76) | 76 (66–79) | 75 (73–77) | 51 (48–57) |

rSO\textsubscript{2}-C = cerebral oxygen saturation. rSO\textsubscript{2}-A = splanchnic oxygen saturation. Data are expressed as median values (IQR).

* = cyanotic CHD.

https://doi.org/10.1371/journal.pone.0239272.t002
Nine patients required additional oxygen during flight. The differences and responses seen in SpO$_2$, rSO$_2$-C and rSO$_2$-A with an increase in FiO$_2$ are illustrated in Fig 4 for all nine

Table 3. TRIPS score.

| TRIPS score category | Pre-transport (n) | Take-Off (n) | Altitude ≥ 5000 feet (n) | Post flight (n) | At receiving hospital (n) |
|----------------------|------------------|--------------|--------------------------|-----------------|--------------------------|
| 0–10                 | 20               | 19           | 20                       | 20              | 20                       |
| 11–20                | 2                | 3            | 5                        | 5               | 5                        |
| 21–30                | 6                | 6            | 3                        | 3               | 3                        |

Pre-transport TRIPS and change in TRIPS scores during and after transport. TRIPS = The transport risk index of physiological stability. n = number.

https://doi.org/10.1371/journal.pone.0239272.t003

Fig 3. The median values of rSO$_2$-C and rSO$_2$-A. Data were derived from all recorded values, determined for rSO$_2$-C and rSO$_2$-A in each individual patient at baseline, at altitude ≥ 5000 feet and after flight. 3A: rSO$_2$-C in non-cyanotic patients, 3B: rSO$_2$-A in non-cyanotic patients, 3C: rSO$_2$-C in cyanotic patients and 3D: rSO$_2$-A in cyanotic patients.

https://doi.org/10.1371/journal.pone.0239272.g003
patients. In five patients: two spontaneously breathing, one on BiPaP, one on CPAP and one on HFNC, oxygen supply was changed (added or increased) during a limited time (minute to 15 minutes) of the flight (Fig 4A–4E). In the remaining four patients: three intubated patients and one patient on HFNC, oxygen was increased and continued at the higher FiO\textsubscript{2} level during the remaining part of the transport (Fig 4F–4I).

**Discussion**

To the best of our knowledge this is the first study to investigate regional tissue oxygen saturation with multisite registrations from both cerebral and splanchnic areas during inter-hospital transport of critically ill children. It is also the first study which has focused on monitoring of regional tissue oxygen saturation during inter-hospital transportation of critically ill children in air ambulances.

To evaluate the consistency in measurements within each sensor throughout the entire transport event for every patient as well as between rSO\textsubscript{2}-C and rSO\textsubscript{2}-A sensors we studied the coefficient of variability (Fig 2). We found that the transport process per se had no influence on the variability in either sensor. Our findings of a greater variability in rSO\textsubscript{2}-A when compared to rSO\textsubscript{2}-C are consistent with others \[19\]. All patients, including those mechanically ventilated, were transported without using muscle relaxants as this is our clinical routine. The greater variability seen in rSO\textsubscript{2}-A could result from the abdomen being a more mobile body...
area compared to the forehead, also in small children. Interestingly, we found that all patients excluded due to poor signal acquisition in the splanchnic sensor, had had previous abdominal surgery (Fig 1).

This study showed that in a majority of patients rSO$_2$-C and rSO$_2$-A had a statistically significant decrease at altitude ≥ 5000 feet compared to baseline. (Fig 3, Table 2). A large amount of data has been collected in this study and values should be interpreted and valued in a clinical perspective, since also small differences show statistical significance. Previous research has defined low rSO$_2$-C as a continuous decrease of > 20% from baseline [20]. When analyzing our data in this perspective we found a decrease of 20% in median values in only one patient. This patient (Patient 18), who belonged to the cyanotic group of patients, showed a simultaneous decrease in SpO$_2$. rSO$_2$-A values in healthy newborns were found to resemble rSO$_2$-C values by 48 h postnatal age [20]. We found 4 patients who had a 20% reduction from baseline in rSO$_2$-A, one without a simultaneous decrease in SpO$_2$. No clinical deterioration was observed in this patient during the transport, and therefore, no clinical interventions occurred.

By evaluating changes in rSO$_2$-C and rSO$_2$-A in relation to SpO$_2$, we found that 6 patients showed a substantial decrease in SpO$_2$, without a corresponding decrease in rSO$_2$-C and rSO$_2$-A, interestingly 3 of these patients belonged to the cyanotic group. A more profound decrease in rSO$_2$-C and/or rSO$_2$-A than in SpO$_2$ was found in 5 patients, most obvious in rSO$_2$-A.

By using the rSO$_2$-C/rSO$_2$-A ratio we wanted to compare regional oxygen saturation of cerebral and splanchnic tissue in this cohort and investigate if a relative change could be detected at ≥ 5000 feet as an effect of altitude. A ratio ≥ 1 was seen in a majority of patients at baseline and in even more patients (77%) at altitude ≥ 5000 feet (FiO$_2$ was increased in only 2 patients). Among patients with a ratio < 1 at baseline, all but 2 had an elevated ratio closer to 1 at altitude. We speculate that an increasing ratio might imply that cerebral tissue was protected by auto-regulation in this increasingly hypoxic environment. We found no association between age, breathing support or diagnosis in patients with a ratio < 1. Ideally oxygen extraction would have been a more reliable measurement which could have provided additional information, but we were not able to extract continuous data from the pulse oximetry device, which limited this possibility.

We were concerned about cyanotic patients and the effects of altitude on rSO$_2$, but we found no specific patterns in rSO$_2$-C or rSO$_2$-A in relation to altitude in this group of patients, regardless of breathing support. We did note however that 7 of 9 (78%) cyanotic patients had a rSO$_2$-A value < 60% at baseline but only 10 of 30 (30%) non-cyanotic patients, and that all but one patient in the cyanotic group (Total Anomalous Pulmonary Venous Return) showed a decrease in SpO$_2$ at altitude ≥ 5000 feet.

We found no clear relationship between certain diagnosis and the effect of altitude. Our cohort had several patients with congenital heart disease, which could possible complicate assessment, but different reactions were also seen among other patients. This is illustrated in Fig 4 where 4A shows a spontaneously breathing patient with TGA on Prostaglandin E1 infusion and after balloon atrial septostomy, 4B a patient with high flow nasal cannula after ECMO treatment for meconium aspiration and 4C a spontaneously breathing patient with coarctation of the aorta without a patent ductus arteriosus.

Caution should be paid to meticulous application and protection of sensors in order to reduce the number of artefacts, and values should be interpreted in relation to clinical...
assessments. We found that measurements of rSO\(_2\)-A involved more difficulties than rSO\(_2\)-C, such as greater variability and a higher number of artefacts, but also gave more information in addition to measurements from pulse oximetry than did rSO\(_2\)-C.

Limits of this study were that SpO\(_2\) values from pulse oximetry were single values and not from continuous measurements which made calculations of fractional tissue oxygen extraction unreliable. The difficulties in obtaining reliable measurements on oxygen extraction is explained in more detail in supplementary materials. Infants with cyanotic congenital heart disease may have significant preductal/post-ductal SpO\(_2\) differences and the lack of both pre- and post-ductal registrations with SpO\(_2\) during the flight protocol is a weakness. Therefore, the potential for differences in arterial saturation across the aortic arch confounds interpretation of regional rSO\(_2\) changes in these patients. Changes to NIRS readings not solely based on changes in altitude is a possible source of confounding. These changes could be due to clinical severity. A transport risk index of physiologic stability (TRIPS) score was therefore used to further group neonatal patients based on their clinical severity and the effect on rSO\(_2\) during the transport. In most patients, the TRIPS score did not change during transport. Furthermore, we found no evidence that changes in rSO\(_2\)-readings were due to other clinical severity, as rSO\(_2\)-readings were not affected in patients who had a higher TRIPS score at altitude ≥ 5000 feet than pre-transport.

In contrast the strengths of the current study were the large number of NIRS measurements collected both at baseline and during transport at altitude and our ability to remove nonsense values such as zero values and floor effect values prior to evaluation to limit the impact of artefacts on the results.

An important question on transport, where equipment needs to be limited due to space and weight, is what NIRS would add to the existing monitoring system and clinical management, and ultimately if patients’ outcome would be better if NIRS is added compared to simply monitoring with pulse oximetry. Our opinion is that NIRS should be added, during transport, to those patients where the clinical management during anesthesia and intensive care would have included monitoring with NIRS in a hospital setting. Namely situations where measurements of venous saturations provide a means of titrating medications such as inotropes, vasoactive medicines and volume, or other situations with very low perfusion and oxygenation conditions in which traditional pulse oximetry could fail. To other patients, NIRS monitoring during transport is probably superfluous and would not add any clinical utility.

Conclusions

Both cerebral and splanchnic oxygen saturation decreased at altitude ≥ 5000 feet compared to baseline in a majority of patients. In most patients cerebral oxygen saturation was preserved more than splanchnic oxygen saturation. This was also the case for cyanotic patients even though low baseline splanchnic oxygen saturation values were observed in most cyanotic patients. The transport process per se had no influence on the variability in either sensor. NIRS-monitoring may be useful in the transport environment in the same clinical situations where it would have been used in a hospital setting. To other patients, NIRS monitoring during transport is probably superfluous and would not add any clinical utility to existing monitoring. Future studies should include equivalent continuous data for pulse oximetry for calculation of oxygen extraction to further determine the usefulness of regional oxygen saturation monitoring during transport.

Supporting information

S1 File.

(DOCX)
Author Contributions

Conceptualization: Tova Hannegård Hamrin.

Formal analysis: Tova Hannegård Hamrin, Jonas Berner, Urban Flåring, Peter J. Radell.

Investigation: Tova Hannegård Hamrin, Peter J. Radell.

Methodology: Tova Hannegård Hamrin, Staffan Eksborg, Jonas Berner, Urban Flåring, Peter J. Radell.

Project administration: Tova Hannegård Hamrin.

Software: Staffan Eksborg.

Supervision: Staffan Eksborg, Jonas Berner, Urban Flåring, Peter J. Radell.

Validation: Tova Hannegård Hamrin.

Visualization: Staffan Eksborg.

Writing – original draft: Tova Hannegård Hamrin.

Writing – review & editing: Tova Hannegård Hamrin, Staffan Eksborg, Jonas Berner, Urban Flåring, Peter J. Radell.

References

1. Orr RA, Felmet KA, Han Y, McCloskey MA, Bills DM, et al. Pediatric specialized transport teams are associated with improved outcomes. Pediatrics. 2009; 124(1):40–48. https://doi.org/10.1542/peds.2008-0515 PMID: 19564281

2. Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. Lancet. 2010; 376(9742):698–704. https://doi.org/10.1016/S0140-6736(10)61113-0 PMID: 20708295

3. Hamrin TH, Berner J, Eksborg S, Radell PJ, Flåring U. Characteristics and outcomes of critically ill children following emergency transport by a specialist paediatric transport team. Acta Paediatr. 2016; 105:1329–1334. https://doi.org/10.1111/apa.13492 PMID: 27241071

4. Moynihan K, McSharry B, Reed P, Buckley D. Impact of Retrieval, Distance Traveled, and Referral Center on Outcomes in Unplanned Admissions to a National PICU. Pediatr Crit Care Med. 2016; 17:e34–e42. https://doi.org/10.1097/PCC.0000000000000586 PMID: 26673843

5. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science. 1977; 198(4323):1264–7. https://doi.org/10.1126/science.929199 PMID: 929199

6. Tobias JD. Cerebral oximetry monitoring with near infrared spectroscopy detects alterations in oxygenation before pulse oximetry. Intensive Care Med. 2008; 23:384–388. https://doi.org/10.1177/088506608324380 PMID: 18794168

7. Scott JP, Hoffman GM. Near-infrared spectroscopy: exposing the dark (venous) side of the circulation. Paediatr Anaesth. 2014; 24(1):74–88. https://doi.org/10.1111/j.12301 PMID: 24267637

8. Nagdyman N, Fleck T, Schubert S, Ewert P, Peters B, Lange PE, et al. Comparison between cerebral tissue oxygenation index measured by near-infrared spectroscopy and venous bulb saturation in children. Intensive Care Med. 2005; 31(6):846–850. https://doi.org/10.1007/s00134-005-2618-0 PMID: 15803294

9. Kaufman J, Aldomovar MC, Zuk J, Friesen RH. Correlation of abdominal site near-infrared spectroscopy with gastric tonometry in infants following surgery for congenital heart disease. Pediatr Crit Care Med. 2008; 9(1):62–68. https://doi.org/10.1097/01.PCC.0000298640.47574.DA PMID: 18477915

10. Booth EA, Dukatz C, Ausman J, Wider M. Cerebral and somatic venous oxygenometry in adults and infants. Surg Neurol Int. 2010; 1:75. https://doi.org/10.4103/2152-7806.73316 PMID: 21170366

11. Mittnacht AJ. Near infrared spectroscopy in children at high risk of low perfusion. Curr Opin Anaesthesiol. 2010; 23(3):342–347. https://doi.org/10.1097/ACO.0b013e3283393936 PMID: 20421789
12. Kobbernagel HE, Nielsen KG, Hanel B. Hypoxic challenge test applied to healthy children: influence of body positions and exertion on pulse oximetric saturation. Arch Dis Child. 2013; 98(8):602–606. https://doi.org/10.1136/archdischild-2012-302763 PMID: 23814087

13. Stroud MH, Gupta P, Prodhan P. Effect of altitude on cerebral oxygenation during pediatric interfacility transport. Pediatr Emerg Care. 2012; 28(4):329–332. https://doi.org/10.1097/PEC.0b013e31824d8b3c PMID: 22453725

14. Valente ME, Sherif JA, Azen CG, Pham PK, Lowe CG. Cerebral Oxygenation and Acceleration in Pediatric and Neonatal Interfacility Transport. Air Med J. 2016; 35(3):156–160. https://doi.org/10.1016/j.amj.2016.01.006 PMID: 27255878

15. Hamrin TH, Radell PJ, Flåring U, Berner J, Eksborg S. Performance of regional oxygen saturation monitoring by near-infrared spectroscopy (NIRS) in pediatric inter-hospital transports with special reference to air ambulance transports: a methodological study. J Clin Monit Comput. 2018; 32(5):841–847. https://doi.org/10.1007/s10877-017-0094-z PMID: 29282591

16. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med 2005; 6 (1):58–63. https://doi.org/10.1097/01.PCC.0000149318.40279.1A PMID: 15636661

17. Lee SK, Zupancic JA, Pendray M, Thiessen P, Schmidt B, Whyte R, et al; Canadian Neonatal Network. Transport risk index of physiologic stability: a practical system for assessing infant transport care. J Pediatr 2001; 139:220–226. https://doi.org/10.1067/mpd.2001.115576 PMID: 11487747

18. Savitzky A, Golay MJE. Smoothing and differentiation of data by simplified least squares procedures. Anal Chem. 1964; 36(8):1627–1639. https://doi.org/10.1021/ac60214a047.

19. Bailey SM, Hendricks-Munoz KD, Mally P. Cerebral, renal, and splanchnic tissue oxygen saturation values in healthy term newborns. Am J Perinatol. 2014; 31(4):339–344. https://doi.org/10.1055/s-0033-1349894 PMID: 23873114

20. Garvey AA, Kooi EMW, Smith A, Dempsey EM. Interpretation of Cerebral Oxygenation Changes in the Preterm Infant. Children (Basel). 2018; 5(7). pii: E94. https://doi.org/10.3390/children5070094 PMID: 29987227