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# Association of Cerebral Oxygenation During Prehospital Anaesthesia and Functional Outcome: A Prospective, Observational Multi-Centre Cohort Study of 1014 Patients

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## ABSTRACT

**Background:** Many patients undergoing prehospital anaesthesia may be at risk of inadequate cerebral oxygenation due to underlying conditions or adverse events like hypotension or hypoxia. This study examined whether a decrease in regional cerebral oxygen saturation ($rSO_2$) measured with near-infrared spectroscopy (NIRS) during prehospital anaesthesia associates with worse outcomes.

**Methods:** We conducted a prospective, observational study including adult patients anaesthetised by six prehospital critical care teams. A relative cerebral desaturation event (rCDE) was defined as a $\geq 10\%$ decrease in $rSO_2$ for $\geq 5$ min from baseline. An absolute cerebral desaturation event (aCDE) was defined as $rSO_2 < 60\%$ during anaesthesia or lower than baseline if already $< 60\%$. The primary outcome was favourable functional outcome (modified Rankin Scale $\leq 2$) at 30 days and secondary outcomes included 30-day survival, 1-year functional outcome, and 1-year survival.

**Results:** Among 1014 patients, 199 experienced an rCDE, with 125 (63%) having supraphysiological baseline. rCDE was not associated with outcomes. Of 182 patients with aCDE, 30-day favourable outcomes were not significantly different (30% vs. 36%, $p = 0.14$, adjusted OR 0.92, 95% confidence interval 0.62–1.34). However, aCDE was associated with lower 30-day survival (46% vs. 58%, $p = 0.006$) and less favourable 1-year outcomes (31% vs. 41%, $p = 0.043$). Adjusted analyses showed no significant associations.

**Conclusion:** An rCDE was not associated with worse functional outcomes. While aCDEs were linked to unfavourable outcomes in unadjusted analyses, these associations were not significant after adjustment, highlighting the complexity of interpreting NIRS in heterogeneous populations. Condition-specific studies are needed to clarify its role.

**Editorial Comment:** Cerebral oxygen delivery may be jeopardized in critically ill patients undergoing prehospital anaesthesia. This study assessed near-infrared spectroscopy on the forehead in a large number of cases requiring general anaesthesia and subsequent transportation to hospital by helicopter. In unadjusted analysis, patients with an at least 10% decline in forehead

saturation had higher survival and better functional outcome, whereas those with a forehead saturation below 60% had lower survival and worse functional outcome. Upon multivariable regression, age, patient category, systemic oxygen saturation and Glasgow Coma Scale score were independent predictors of worse outcomes, but forehead oxygen saturation was not. NIRS-measured forehead saturation decrease appears to associate in a complex fashion with more traditional predictors of patient outcomes. Whether effects of resuscitation interventions like these can be assessed reliably by NIRS is not yet well understood.
**Trial registration:** The study protocol was published beforehand on clinicaltrials.gov (NCT04144803) on 7th October 2019

## 1 | Background

Prehospital anaesthesia and airway management are among the most common advanced interventions in prehospital critical care [1]. Critical patients are at risk of inadequate cerebral oxygenation by various mechanisms. Hemorrhagic shock or decreased cardiac function may lead to insufficient cerebral perfusion, intracranial lesions may increase intracranial pressure and prolonged epileptic seizures may significantly increase oxygen consumption [2]. Furthermore, autoregulation of cerebral blood flow may be compromised after neurotrauma or out-of-hospital cardiac arrest (OHCA) and even brief episodes of hypoxia or hypotension may propagate secondary brain injury [3–6]. Therapies to sustain sufficient brain perfusion and oxygenation are guided by vital signs, which are insufficient for adequately representing perfusion in the brain of individual patients [7].

Near-infrared spectroscopy (NIRS) utilises near-infrared light which can penetrate superficial cranial structures. The absorption of different wavelengths is analysed to measure regional oxygen saturation ($rSO_2$) in venous and arterial blood [8]. Diminished perfusion leads to increased oxygen utilisation. Hence, NIRS has been suggested to detect changes in blood flow and the oxygenation of brain tissue and has shown high specificity for identifying intraoperative ischemia during carotid endarterectomy [9–11]. Lower cerebral $rSO_2$ has been associated with elevated intracranial pressure and worse outcomes in neurotrauma [10]. Being a non-invasive, rapidly implementable and mobile technology, NIRS is the most compelling option for improving prehospital neuromonitoring.

Previous literature on the prehospital use of NIRS is minimal. In a pilot study, we previously demonstrated the feasibility of NIRS during prehospital anaesthesia [12]. If NIRS were to prove effective in detecting developing brain injury, it could be used to individualise circulation and ventilation to individual patients. It could also be used as a surrogate marker in studies to better understand mechanisms and treatment targets for neuroprotective anaesthesia. This study aimed to investigate whether a decrease in cerebral $rSO_2$ during prehospital anaesthesia is associated with unfavourable functional outcomes.

## 2 | Methods

### 2.1 | Study Design

We conducted a prospective, observational, multi-centre cohort study to investigate whether a decrease in cerebral $rSO_2$ during prehospital anaesthesia is associated with less favourable functional outcomes or lower survival rates at 30 days and 1 year.

Study permits were acquired from all hospital districts within the operational area of Finnish Helicopter Emergency Medical Service (HEMS) units (Turku University Hospital, Tampere University Hospital, Oulu University Hospital, Lapland Hospital District, Kuopio University Hospital). We have reported our findings in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13].

The study protocol was accepted by the ethical review board of Helsinki University Hospital (HUS/757/2019). According to the ethical committee decision, data collected during prehospital care was used without obtaining consent if the patient was deceased before being interviewed. Informed consent was acquired from all other subjects before the follow-up interview, in which the functional outcome was assessed.

The pilot study's protocol was registered in advance (http://clinicaltrials.gov ID:NCT03948711). Conducted at two centres, it aimed to estimate the incidence of rCDEs for sample size calculation and to assess feasibility. The pilot study took place from 20th May 2019 to 30th September 2019, with results published previously [14]. The protocol for the main study was registered after the pilot was completed (http://clinicaltrials.gov ID:NCT04144803). Since there were no changes to data collection or inclusion criteria, participants from the pilot were also included in the main trial. The main study ran from 18th November 2019 to 25th September 2022.

### 2.2 | Setting

During the study period, six HEMS units operated in Finland, all of which participated in the study. Five units are staffed with a physician, a pilot, and a HEMS crew member. Physicians are mostly anaesthesiology consultants, while HEMS crew members are paramedics or firefighters with special training in prehospital critical care and aviation. One HEMS unit operates in the sparsely populated northern region of Finland with a crew of two pilots and two HEMS paramedics. All units operate by helicopter or a rapid response vehicle according to weather conditions and logistics. Patients are often transported to hospital by ground-based Emergency Medical Services (EMS) escorted by a HEMS crew.

HEMS units are primarily dispatched directly by the national Emergency Response Centre during the initial emergency call if predetermined criteria are met. HEMS may also join ongoing EMS missions by decision of the HEMS crew or when requested by ground-based EMS. The most common dispatch criteria include OHCA, high-risk trauma and a decreased level of consciousness. We describe the national HEMS in more detail in a separate paper [15].

Anaesthesia and advanced airway management are the most frequent interventions initiated by Finnish HEMS [1]. The units are equipped with propofol, esketamine, midazolam, fentanyl, rocuronium and some also carry succinylcholine. The medicines used for the induction and maintenance of anaesthesia are chosen by the provider on scene.

## 2.3 | Participants

Patients 18 years or older were included in the study if they underwent medically facilitated tracheal intubation and were escorted to hospital by a HEMS crew. OHCA patients were included only when medically facilitated intubation was performed during post-resuscitation care.

Patients were excluded if $rSO_2$ could not be measured from the forehead due to physical barriers, such as facial trauma. If the workload was deemed excessively high to the point that the protocol for this study could have compromised the quality of care, the patient was excluded. Patients unable to communicate in Finnish, Swedish or English for follow-up interviews were excluded. Vulnerable patient groups were excluded according to the Declaration of Helsinki.

## 2.4 | Measurements

A CO-Pilot H500 oximeter (Nonin Medical Inc., Plymouth, MN, USA) was used together with single-use regional oximetry sensors SenSmart 8204CA with EQUANOX Technology (Nonin Medical Inc.). The H500 system uses a signal processor that is connected to the sensor using the INT-100 interface cable (Nonin Medical Inc.). The signal processor transmits the data wirelessly using Bluetooth to the monitor of the oximeter. The sensor uses four wavelengths of near-infrared light (730, 760, 810, and 880 nm) to minimize artefacts from superficial tissues. The adhesive sensor was applied firmly to the left side of the forehead once inclusion criteria were met; if this area was unsuitable due to external lesions, the right side was used. When necessary, wet or bloody skin was cleaned and dried before placement to ensure good signal quality.

The CO-Pilot H500 oximeter displays a real-time rSO2 reading with a graphical visualisation of the temporal trend. A single value for $rSO_2$ is recorded every second on the device's internal storage, from which it was exported to an external USB drive for later analysis. Continuous monitoring was maintained until hospital handover. The study devices were rented, and the single-use sensors were purchased directly from the manufacturer. The particular device was chosen because of its compact form factor, making it a good candidate for HEMS. No financial or material support was received from the manufacturer.

The research nurse reviewed all $rSO_2$ recordings manually. Periods where the $rSO_2$ showed very rapid and large physiologically implausible fluctuations, which were highly likely to be caused by movement artefact or other error, were flagged as measurement errors. These measurements were subsequently excluded from analyses. When there was any ambiguity regarding whether measurements were erroneous, the values were included in the analyses.

Personnel were not blinded to $rSO_2$ measurements. This allowed them to adjust or reapply the sensor of the oximeter if it indicated poor signal quality or inconsistent, quickly fluctuating readings. HEMS teams were prohibited from making clinical decisions solely based on $rSO_2$ readings and were advised to reassess other parameters instead. Shortly after patient contact, the HEMS team recorded the initial vital signs present since their arrival. Blood pressure, peripheral capillary oxygen saturation ($SpO_2$) and heart rate were measured using EMS or HEMS equipment based on convenience. A variety of monitoring devices were used. Additionally, respiratory rate and Glasgow Coma Scale (GCS) were assessed by HEMS providers. Although not mandated by the study protocol, invasive arterial pressure monitoring was initiated at the discretion of a HEMS physician when feasible.

Enrolled patients were contacted via phone by the research nurse 30 and 365 days after the events. Functional outcome status was assessed using a structured phone interview and scored using a modified Rankin Scale (mRS). A favourable functional outcome was defined as a modified Rankin Scale (mRS) score of 0–2. If a patient's condition was too severe to permit a telephone interview, the mRS score was determined by interviewing next of kin. The research nurse made five attempts to contact the patient by telephone. If contact was not established, patients were contacted by mail. If the patient or their next of kin could not be reached, the mRS score was determined by reviewing electronic patient records whenever possible, as this has been shown to be in good agreement with phone interviews [16]. At one year, a further attempt was made to contact patients using the same protocol. If contact was still unsuccessful, patient records were reviewed. If the functional outcome could not be determined at this point, the patient was considered lost to follow-up. During the 1-year follow-up interview health-related quality of life was measured using the 15D-instrument. Due to the wide scope of quality-of-life measures, these results will be reported separately.

## 2.5 | Variables

Cerebral oxygen saturation was determined as the frontal lobe $rSO_2$ value. The pre-induction $rSO_2$ level was determined as the mean of $rSO_2$ values measured before the start of induction. If an $rSO_2$ level equal to or exceeding 10 percentage points (p.p.) lower than this level was sustained for five consecutive minutes, it was considered a relative cerebral desaturation event (rCDE). These thresholds were predefined in a pilot study [14]. Analysis revealed that this predetermined definition was heavily influenced by the large proportion of patients with abnormally high pre-induction $rSO_2$ levels. Therefore, a revised definition was created post hoc to address the shortcomings of the a priori definition. Some studies suggest cerebral $rSO_2$ values below 50%–60% to be considered concerning [17–19]. The pilot study used an absolute cut-off of 50%, but this yielded a low incidence [14]. Therefore, we defined an absolute Cerebral Desaturation Event (aCDE) as any $rSO_2$ value below 60% after induction or under the pre-induction level when it was less than 60%. All per-protocol analyses were repeated with this definition and are presented beside the a priori definition. A separate sensitivity analysis using 50% as the cut-off for aCDE is shown in a separate online supplement (Data S2).

The exact time the anaesthetic agent was administered was manually recorded on the $rSO_2$ monitor. This timestamp was used to determine the $rSO_2$ baseline. Any ongoing treatment continued while $rSO_2$ monitoring was being set up and the pre-induction $rSO_2$ level was being determined.

The rare cases where patients had been medically sedated before HEMS arrival were recorded as "sedated" instead of a numeric GCS. In our descriptive analyses, we assumed the GCS of these patients to be three. Based on information available during care, the HEMS provider assigned the patient to a category according to medical condition as defined by the guidelines [20].

### 2.6 | Outcome

The primary outcome variable was favourable functional outcome, defined as mRS $\leq 2$ at 30 days. Our secondary outcomes were 30-day survival, 1-year favourable functional outcome and 1-year survival.

### 2.7 | Data Sources

Finnish HEMS routinely records details on all missions to a shared database, the FinnHEMS Database (FHDB). Data is recorded by the personnel on each mission shortly after the mission has ended. This database includes, among other variables, timestamps regarding logistics, clinical measurements, medication administered and other interventions. According to international guidelines for data collection in physician-staffed prehospital services, when entering mission details, the staff assigns the patient one of the following categories based on the information available at the time: cardiac arrest, trauma, chest pain, stroke, neurologic non-stroke, psychiatric, gynaecological or obstetric, infection, intoxication, or other [20, 21]. Patients are encoded with unique identifiers that enable appending data from other sources for study purposes. The database has been described previously [15, 22].

### 2.8 | Study Size

Before the main study, a power calculation was performed. Based on the pilot study, we assumed a 25% incidence of rCDE and a 50% survival rate with a favourable functional outcome among patients without an rCDE [14]. To show a 10% difference in favourable functional outcomes with a two-sided significance of 0.05 and a power of 0.8, we calculated that 1040 patients would be necessary. To account for a 20% loss in follow-ups, the initial target was 1300 patients.

### 2.9 | Statistical Methods

Continuous variables are reported as median (25th–75th percentile). Categorical data is presented as *n* (%). Previous studies in Finnish HEMS have shown that the following patient categories are present only in small numbers in our data and rarely require advanced airway management: chest pain, psychiatric, gynaecological or obstetric, and infection. We combined these categories with the category 'other' [23]. This was done to improve readability and to avoid very small categories that may lead to erroneous results in statistical analyses. According to previous literature, $rSO_2$ is described as high (> 80%), normal (60%–80%) and low (< 60%) [17, 24]. Patients were grouped according to whether they experienced an rCDE or aCDE. Proportions between groups were compared for favourable functional outcomes and overall survival at 30-day and 1-year horizons. The significance level was determined using a two-tailed chi-squared test and $p < 0.05$ was considered statistically significant.

We investigated the association between an rCDE and favourable functional outcomes at 30 days. For this, we used multivariable logistic regression. Whether the patient experienced an rCDE or not was included as a covariate. Patient category, sex and age were controlled for by including them as covariates. These variables were chosen to control for the heterogeneous case mix. Other potential confounders, such as vital signs, were not adjusted for, as extreme values are likely to affect outcomes differently across conditions (e.g., stroke vs. OHCA). Therefore, a linear relationship with the logit of the outcome could not be assumed. Further, many of these variables were likely to be highly correlated with $rSO_2$. Patients with missing data for any covariates or outcome variables were excluded from the analysis. The same method was used for 30-day survival, 1-year favourable functional outcome and 1-year survival as secondary outcomes. All analyses were repeated using aCDE in place of rCDE.

In a sensitivity analysis, additional covariates were examined. Vital signs at the HEMS encounter and the delay from alarm to patient contact were tested in univariable logistic regression with 30-day functional outcome as the dependent variable. Predictors with $p < 0.05$ were entered into a multivariable logistic regression model for the primary and secondary outcomes.

Data preprocessing was performed using Python version 3.12 (Python Software Foundation. Python Language Reference, version 3.12. Available at https://www.python.org) and pandas version 2.2.1 (The pandas development team 2024. Zenodo. https://doi.org/10.5281/zenodo.10697587) [25].

All statistical analyses were conducted using R version 4.3.0 (R Core Team 2023. R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Figures were created using ggplot2 (H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016). Tables were drafted using the gtsummary package for R [26].

## 3 | Results

### 3.1 | Participants

After exclusions, 1295 patients were enrolled. NIRS recording was successful in 1183 cases of which 1014 had outcome data available at either 30 days or 1 year and were subsequently analysed (Figure 1).

Patients' median age was 65 years (50–74), and the majority were male. OHCA was the most common patient category. Patient characteristics, including missing data, are described in Table 1.

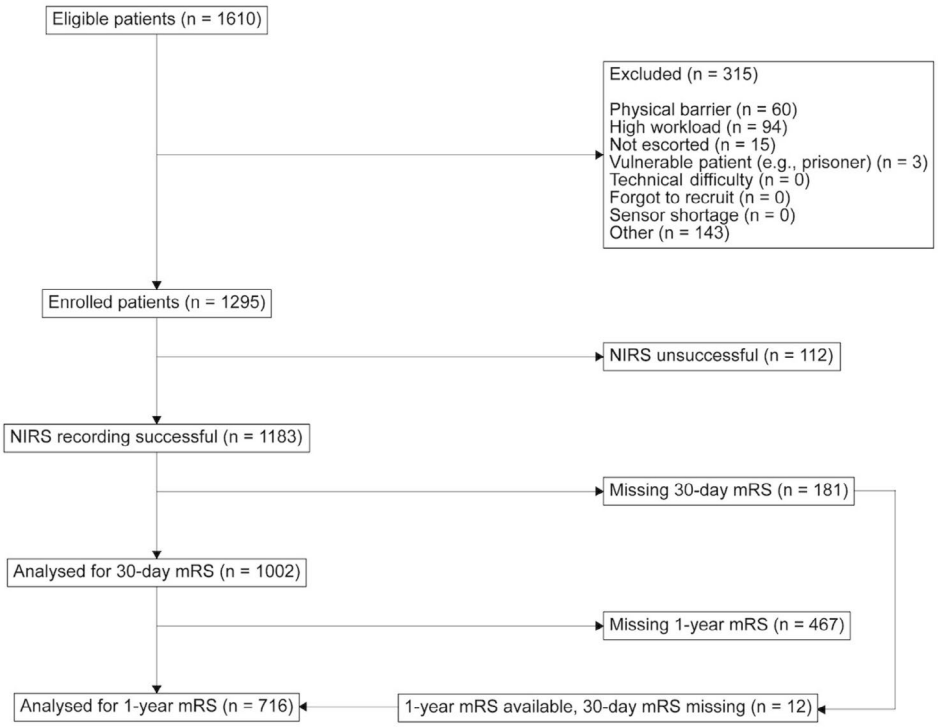


**FIGURE 1** | Patient selection flowchart. mRS: Modified Rankin Scale. NIRS: Near-infrared spectroscopy.

### 3.2 | Cerebral Oxygenation

Of all the NIRS recordings, 3.9% of $rSO_2$ values were deemed erroneous and excluded from analysis. The median of pre-induction mean $rSO_2$ level was 77% (71–84). 397 (39%) patients had a mean pre-induction mean $rSO_2$ level above 80%, whereas 66 (6.5%) were below 60% (Figure 2). The median duration of $rSO_2$ registration was 53 (39–73) minutes. In total, 199 (20%) patients experienced an rCDE. Of these, 125 (63%) occurred amongst patients with a high initial $rSO_2$. aCDE occurred in 182 (18%) patients.

### 3.3 | Outcome

The 30-day functional outcome was available for 1002 of 1183 patients (85%). The 1-year functional outcome was available for 716 patients (60%) and the 1-year survival for 858 patients (73%), respectively. For 12 patients, the outcome could not be determined at 30 days, but the 1-year functional outcome was attained. At 30 days, 346/1002 patients (35%) had a favourable functional outcome, and 557/1002 (56%) were alive. At 1 year, 279/716 patients (39%) had a favourable functional outcome, and 473/858 (55%) were alive.

At 30 days, outcome was obtained by telephone interview for 458/1002 patients (46%) and from hospital records for 542/1002 patients (54%), of whom 442/542 (82%) had died; in 2 patients, the source was not recorded. At 1 year, functional outcome was obtained by telephone interview for 320/716 patients (45%) and from hospital records for 393/716 patients (55%), of whom 382/393 (97%) had died; in 3 patients, the source of outcome was not recorded. For 142 patients, 1-year survival could be determined from patient records, but sufficient information was not available to assess functional outcome.

Unadjusted, an rCDE was associated with a statistically non-significant trend toward better functional outcomes (Figure 3) and survival at 30 days. 1-year favourable outcome and 1-year survival were higher among patients with an rCDE. An aCDE was associated with lower 30-day survival and 1-year favourable functional outcome before adjusting. It also showed a statistically non-significant trend toward less favourable functional outcomes at 30 days and lower 1-year survival (Table 2).

In a sensitivity analysis using a lower threshold of 50% for aCDE, 67 patients (7%) fulfilled the criterion. Under this definition, aCDE was not associated with a favourable functional outcome but was linked to lower survival at 30 days (528/934 [57%] for no CDE vs. 28/66 [42%] for CDE; $p = 0.026$) and 1-year (449/799 [56%] vs. 23/57 [40%]; $p = 0.020$, respectively). After adjustment for age, sex, and patient category, no statistically significant association with the primary or secondary outcomes remained. In another sensitivity analysis, univariable logistic regression identified age, patient category, oxygen saturation, systolic blood pressure, GCS, and the delay from alarm to HEMS arrival as being associated with a favourable 30-day functional outcome. These variables were included as covariates in a multivariable logistic regression model. In this analysis, neither aCDE nor rCDE was associated with worse outcomes for the primary or any of the secondary outcomes. Detailed results for all sensitivity analyses are provided in an online supplement (Data S2).

Patients with unknown outcomes at 30 days and 1 year were younger and more likely to be categorised as intoxications than those with known outcomes. A detailed comparison is shown in

**TABLE 1** | Patient characteristics. OHCA, out-of-hospital cardiac arrest; $SpO_2$, peripheral capillary oxygen saturation; HEMS, helicopter emergency medical services. Continuous variables are presented as medians [25th–75th percentile]. Categorical data is presented as *n* (%).

| | All patients ($n = 1014$) | Missing |
|---|---|---|
| Patient characteristics | | |
| Age (yr) | 65 [50–74] | 0 (0) |
| Sex; male | 666 (66) | 3 (0.3) |
| Patient category | | 0 (0) |
| OHCA | 315 (31) | |
| Stroke | 203 (20) | |
| Trauma | 195 (19) | |
| Neurologic non-stroke | 149 (15) | |
| Intoxication | 97 (9.6) | |
| Other | 55 (5.4) | |
| Vital signs when encountered by HEMS | | |
| $SpO_2$ (%) | 97 [92–99] | 143 (14) |
| Respiratory rate ($min^{-1}$) | 16 [10–21] | 176 (17) |
| Heart rate ($min^{-1}$) | 92 [73–112] | 108 (11) |
| Systolic blood pressure (mmHg) | 139 [110–169] | 121 (12) |
| Glasgow Coma scale | 3.00 [3.00–6.00] | 0 (0) |
| Operational characteristics | | |
| Time from alarm to patient (min) | 24 [18–38] | 0 (0) |
| On-scene time (min) | 33 [24–45] | 17 (1.7) |
| Duration of transport (min) | 25 [15–39] | 24 (2.4) |
| Medication used for airway management | | |
| Esketamine | 759 (75) | 0 (0) |
| Propofol | 331 (33) | 0 (0) |
| Rocuronium | 957 (94) | 0 (0) |
| Succinylcholine | 12 (1.2) | 0 (0) |
| Fentanyl | 690 (68) | 0 (0) |
| Midazolam | 115 (11) | 0 (0) |
| Vasoactive agent | 234 (23) | 0 (0) |

an online supplemental file (Data S2). Due to study permissions, we cannot share characteristics of excluded patients. In many cases where there were problems setting up NIRS monitoring, the provider considered the patient excluded from the study, and thus, we lack details on the majority of these patients. Among those with available data, patients with successful NIRS monitoring had a higher median respiratory rate of 16/min [10–21], compared with 14/min [7–18] in those with unsuccessful monitoring. Patients with successful NIRS had a slightly higher oxygen saturation of 97% (93–99) versus 94% (86–97). Other characteristics were similar between the groups (Data S2).

## 4 | Discussion

At the time of writing, this paper represents the largest prehospital study utilising NIRS. Contrary to our hypothesis, rather than being detrimental, an rCDE was associated with improved outcomes. The analysis clearly demonstrated a flaw in our protocol. During elective surgery, a baseline for $rSO_2$ can be established during a physiologic state [11]. In these situations a clinical neurological examination can be done to ensure sufficient cerebral oxygenation at the determined baseline. In our population, the indication for anaesthesia was often hypoventilation and a decreased level of consciousness. After reviewing our results, we have little confidence that measurements in this critical state can be used to establish $rSO_2$ target values for management. Hypercarbia causes cerebral vasodilation and hence higher $rSO_2$ values [27, 28]. Pre-oxygenation is often initiated before HEMS arrival when airway management is deemed necessary, further elevating $rSO_2$ [27]. Therefore, many patients are likely to have shown an inflated initial $rSO_2$ level, providing a poor baseline for comparison.

There are also other possible causes for the inflated initial $rSO_2$ values. A large proportion of patients suffered strokes or cardiac arrest. Some of these patients may have regained perfusion to the injured areas of the brain, where, due to lesions, metabolism may be low, resulting in high oxygenation.

In our study, most patients in the CDE group did not experience low $rSO_2$ levels at all but were returned to a level that could be considered physiological by controlled ventilation. For patients with a high baseline, subsequent decreases in $rSO_2$ might also represent regression to the mean. As relative changes from the inherently abnormal baseline cannot guide management, device- and age-specific absolute reference ranges are needed. Observational studies collecting data from various clinical settings could help establish ranges within normal variation. Comparisons between devices would be significantly easier if manufacturers were willing to standardise or share algorithms used in devices.

To address this, we studied the group of patients that actually experienced low $rSO_2$ values. Here, we saw an association with worse outcomes. However, this association was absent after adjustment. We acknowledge that the threshold for aCDE was determined post hoc, and therefore these analyses should be regarded as exploratory. Additionally, several studies have demonstrated that absolute $rSO_2$ values between different manufacturers are not interchangeable, and there is no consensus on which absolute $rSO_2$ values should be considered physiological [29–31]. Few studies report absolute thresholds for cerebral hypoxia, but among those that do, few cite thresholds higher than 60% or lower than 50%, regardless of the device used [17, 19, 29–32]. Since values below 50% were rare, we chose 60% as the threshold for aCDE. We include a separate sensitivity analysis (Data S2) using 50% as the threshold.

Since the pilot study cohort was included in this study, we acknowledge that a proportion of patients were recruited and their

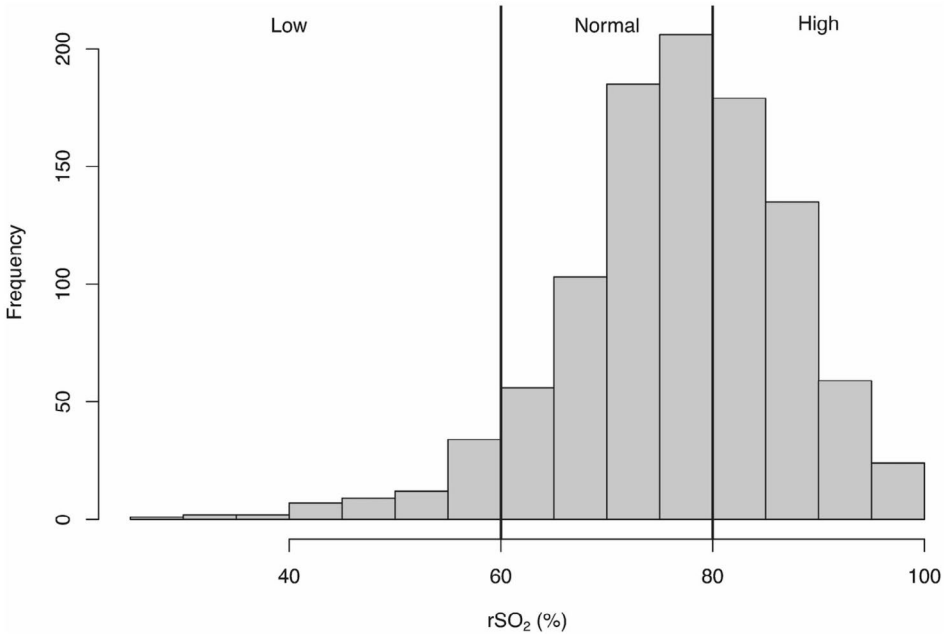


**FIGURE 2** | Distribution of pre-induction regional cerebral oxygenation level ($rSO_2$), defined as the mean of values before induction.

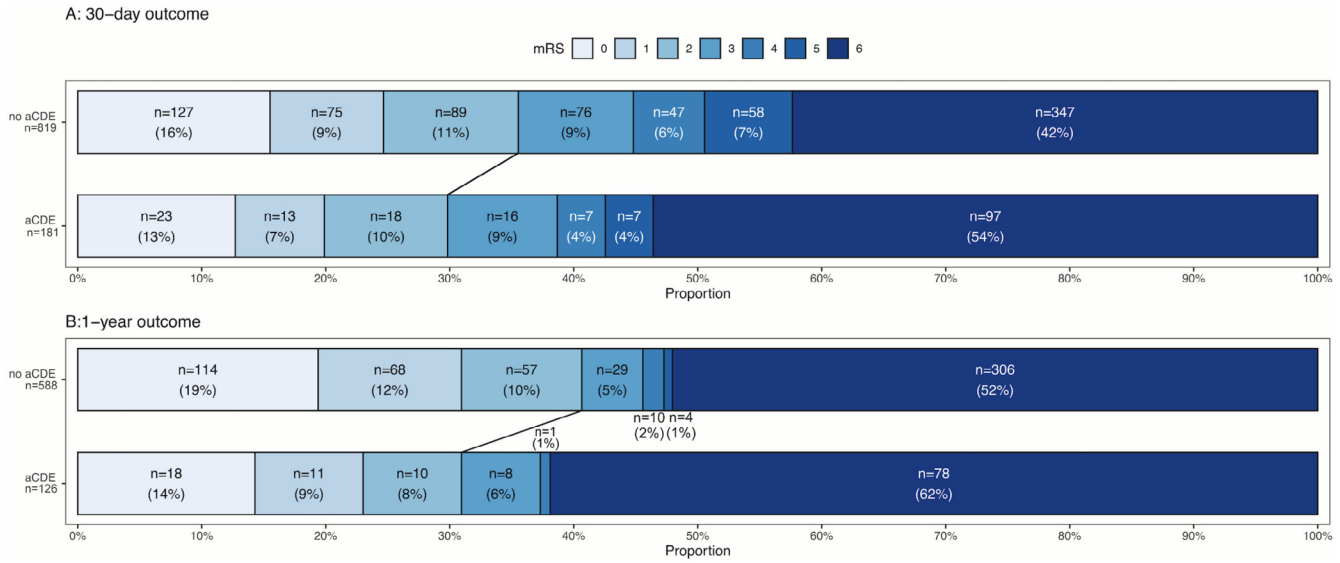


**FIGURE 3** | Patient outcomes. Absolute cerebral desaturation event (aCDE) defined as any regional cerebral oxygen saturation ($rSO_2$) < 60% at any time after induction, or lower than the pre-induction mean when that mean is < 60%. mRS: Modified Rankin Scale.

results were available prior to the registration of the main study protocol. However, because the inclusion criteria and data collection methods remained consistent, we believe this does not compromise the validity of our results.

Because HEMS teams working in prehospital settings do not have full control over the environment, it's difficult to rule out or quantify interference from external light sources or electromagnetic disturbances. Some studies have also expressed concerns that NIRS may be heavily influenced by changes in blood flow through the scalp [33, 34]. The sensor used in the study is designed to eliminate surface tissue artefacts by using four different wavelengths of light, but in the end, we cannot rule out or measure the impact caused by superficial tissues or external light sources [33].

The effects of vasoactive medications on cerebral $rSO_2$ and perfusion are not well understood. An animal model demonstrated an increase in cerebral oxygenation following an adrenaline bolus [35], whereas human studies suggest these drugs may affect peripheral and intracranial blood vessels differently, possibly misrepresenting intracranial oxygenation [33]. Patients with impaired cerebral autoregulation may respond differently than those with intact autoregulation [36].

Over a fifth of patients in this study received vasoactive medication as part of their airway management. A preplanned secondary study on how vasoactive medication affects cerebral $rSO_2$ will be carried out, but due to the complexity of the topic, it is beyond the scope of this paper.

**TABLE 2** | Outcomes. Categorical data is presented as n/N (%). Continuous data is presented as means (standard deviation). rCDE is defined as a ≥ 10 percentage point decrease for ≥ 5 min from mean regional cerebral oxygen saturation ($rSO_2$) before induction; aCDE is defined as any $rSO_2$ value below 60% after induction or under pre-induction mean if less than 60%; aOR for the outcome of patients with CDE compared to no CDE. Adjusted for age, sex and patient category using multivariable logistic regression analysis. CDE: Cerebral desaturation event, CI: Confidence interval, aOR: Adjusted odds ratio.

| | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| **rCDE** | **no rCDE *n* = 815** | **rCDE *n* = 199** | ***p*** | **aOR** | **95% CI** | ***p*** |
| Primary outcome | | | | | | |
| Favourable functional 30-day outcome (mRS ≤ 2) | 272/809 (34) | 74/193 (38) | 0.2[a] | 1.22 | 0.84–1.74 | 0.3 |
| Secondary outcomes | | | | | | |
| 30-day survival | 439/809 (54) | 118/193 (61) | 0.084[a] | 1.39 | 0.99–1.98 | 0.061 |
| Favourable functional 1-year outcome (mRS ≤ 2) | 215/582 (37) | 64/134 (48) | 0.021[a] | 1.22 | 0.84–1.74 | 0.3 |
| 1-year survival | 372/699 (53) | 101/159 (64) | 0.018[a] | 1.66 | 1.13–2.46 | 0.011 |
| | **Unadjusted** | | | **Adjusted** | | |
| **aCDE** | **No aCDE *n* = 830** | **aCDE *n* = 182** | ***p*** | **aOR** | **95% CI** | ***p*** |
| Primary outcome | | | | | | |
| Favourable functional 30-day outcome (mRS ≤ 2) | 291/819 (36) | 54/181 (30) | 0.14[a] | 0.92 | 0.62–1.34 | 0.7 |
| Secondary outcome | | | | | | |
| 30-day survival | 472/819 (58) | 84/181 (46) | 0.006[a] | 0.80 | 0.56–1.14 | 0.2 |
| Favourable functional 1-year outcome (mRS ≤ 2) | 239/588 (41) | 39/126 (31) | 0.043[a] | 0.75 | 0.48–1.16 | 0.2 |
| 1-year survival | 400/706 (57) | 72/150 (48) | 0.053[a] | 0.93 | 0.63–1.37 | 0.7 |

[a]Pearson's Chi-squared test.

Two previous studies of OHCA patients demonstrated that higher $rSO_2$ values at hospital arrival were associated with better functional outcomes [37, 38]. Neither of these studies controlled for age, raising the possibility of confounding. However, older patients may be at a higher risk of cerebral hypoperfusion and subsequent sequelae. By adjusting for age, the vulnerability of older patients to cerebral hypoxia may be lost [39].

The current study had a heterogeneous patient population, ranging from OHCA to intoxication, and merely controlling for patient category may be insufficient to account for condition-specific pathophysiology. Furthermore, a previous study showed that miscategorisation was not uncommon [21]. Tailored studies will be necessary to better establish potentially harmful $rSO_2$ patterns in different age groups and conditions.

Very low $rSO_2$ levels during prehospital care were surprisingly rare in the current study, which may reflect a high quality of care provided by both EMS and HEMS crews. The Finnish HEMS is characterised by experienced providers, mostly anaesthesiologists, with a subspeciality in prehospital critical care and, consequently, a high level of competence in prehospital anaesthesia [40]. The providers did have access to NIRS monitoring as part of this study.

Although providers were not allowed to make clinical decisions based on NIRS, it is possible that low rSO2 values led them to assess and intervene on other parameters that might otherwise have been left unchanged, potentially introducing a source of bias. Thus, a different system or blinded study might produce a wider variance of $rSO_2$ values. Additionally, most patients had been treated by paramedics before HEMS contact. Therefore, patients with the most critical $rSO_2$ levels are likely to have received pre-oxygenation and other treatment before $rSO_2$ monitoring was initiated.

The 30-day mortality rate of 44% observed in the current study was high compared to 24% during the pilot phase [14].

The median on-scene time is a few minutes longer than seen in our previous studies on Finnish HEMS patients undergoing prehospital anaesthesia [23, 41]. While the overall impact is minor, delaying urgent care for unstable patients to enable monitoring can be unacceptable. High workload was a common reason for exclusion. Sixty patients were excluded due to a physical barrier (e.g., bilateral laceration at the sensor site). Many of these may be patients with concomitant traumatic brain injury. Additionally, among cases with failed NIRS monitoring, oxygen saturation and respiratory rate were slightly lower, suggesting they might have shown a higher rate of brain oxygenation. These factors

suggest that some of the most critically ill patients, who might benefit the most from enhanced neuromonitoring, may have been excluded, potentially introducing bias.

Favourable functional outcome was also less common compared to the pilot study. This is probably, in part, due to the different case mix of the six HEMS units, as only two of them participated in the pilot study. Our study design is susceptible to some degree of survival bias. If the patient deceased within 30 days, it was most likely recorded in their patient records. Patients that cannot be contacted and are without new electronic patient records are likely to be alive but would be considered lost in the follow-up. Support for this comes from the fact that patients lost to follow-up were generally younger and more often classified as intoxication, despite vital signs and other parameters not suggesting they were at a higher risk.

Whether the use of NIRS can improve prehospital care is still unclear. During major surgery, NIRS-guided algorithms to ensure adequate cerebral oxygenation have been shown to reduce peri-operative stroke [11]. Because of the observational study design, we are unable to deduce whether a similar approach should be adopted in prehospital care. However, this large-scale observational study provides useful insights for future studies. Our main suggestions are: (1) Not to use initial $rSO_2$ levels of unstable patients as a baseline, (2) to focus on more homogenous patient groups likely to benefit from $rSO_2$ monitoring (e.g., neurotrauma), (3) combining $rSO_2$ measurements with simultaneous invasive arterial pressure if possible. However, more research is needed before the prehospital implementation of NIRS can be recommended.

## 5 | Conclusions

In this heterogeneous patient population, an rCDE was not associated with worse outcomes. The primary analysis was markedly influenced by unusually high pre-induction $rSO_2$ values, possibly due to pre-oxygenation or hypoventilation. Although low absolute $rSO_2$ values were associated with worse outcomes, this association was lost after adjustment for age, sex and patient category. Studies focused on specific conditions are necessary.

### Author Contributions

Study design: Anssi Saviluoto, Lasse Raatiniemi, Simo Mäkelä, Tuukka Toivonen, Piritta Setälä, Hetti Kirves, Miretta Tommila, Pamela Toivonen, Simo Tukia and Jouni Nurmi. Data acquisition: Tuukka Toivonen, Piritta Setälä, Hetti Kirves, Miretta Tommila, Pamela Toivonen, Jouni Nurmi, Simo Tukia and Lasse Raatiniemi. Data analysis: Anssi Saviluoto, Simo Mäkelä and Tuukka Toivonen. Data interpretation: Anssi Saviluoto, Lasse Raatiniemi, Simo Mäkelä and Jouni Nurmi. Writing and processing the draft: Anssi Saviluoto, Lasse Raatiniemi, Simo Mäkelä, Tuukka Toivonen, Piritta Setälä, Hetti Kirves, Miretta Tommila, Pamela Toivonen, Simo Tukia and Jouni Nurmi. All authors have read and accepted the final manuscript.

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Multivariate logistic regression analysis for primary and secondary outcomes. A favourable functional outcome is defined as a modified Rankin Score of $\leq 2$. A relative cerebral desaturation event defined as a $\geq 10$ percentage point decrease for $\geq 5$ min from mean regional cerebral oxygen saturation ($rSO_2$) before induction. An absolute cerebral desaturation event defined as any $rSO_2$ drop below 60% after induction or under the pre-induction mean if it was less than 60%, CI: confidence interval, OHCA: out-of-hospital cardiac arrest, OR: odds ratio. **Data S2:** Sensitivity analyses Alternative definition for Cerebral desaturation event (CDE).