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ARTICLE

Monitoring cerebral oxygenation of preterm infants using a neonatal specific sensor

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Abstract

Introduction Cerebral oxygenation ($rcSO_2$) monitoring in preterm infants may identify periods of cerebral hypoxia or hyperoxia. We hypothesised that there was a relationship between $rcSO_2$ values and short term outcome in infants of GA < 32weeks.

Methods $RcSO_2$ values were recorded for the first 48 h of life using an INVOS monitor with a neonatal sensor. The association between cranial ultrasound scan measured brain injury and $rcSO_2$ was assessed.

Results 120 infants were included. Sixty-nine percent (83) of infants had a normal outcome (no IVH, no PVL, and survival at 1 month); less than one-quarter, 22% (26), had low grade IVH 1 or 2 (moderate outcome); and 9% (11) of infants had a severe outcome (IVH ≥ 3, PVL or died before 1 month age). $rcSO_2$ values were lower for infants GA < 28weeks when compared with those GA 28–32, $p < 0.001$. There was no difference in absolute $rcSO_2$ values between the three outcome groups but a greater degree of cerebral hypoxia was associated with preterm infants who had low grade 1 or 2 IVH.

Conclusion Infants of GA < 28 weeks have lower cerebral oxygenation in the first 2 days of life. A greater degree of hypoxia was seen in infants with grade 1 or 2 haemorrhage. Normative ranges need to be gestation specific.

Introduction

Acquired brain injury in very preterm infants usually results from haemodynamic instability and cerebral dysautoregulation. Germinal matrix intra-ventricular haemorrhage (GM-IVH) and periventricular leucomalacia (PVL) account for the majority of cerebral injury in very preterm infants [1]. Neuro-monitoring strategies are limited in preterm infants. Cerebral oxygenation monitoring with near infrared spectroscopy (NIRS) provides one potential method. Cerebral NIRS is non-invasive, portable, painless and easy to apply. This device can continuously measure regional cerebral oxygen saturations ($rcSO_2$) and can indirectly estimate cerebral blood flow and cerebral tissue oxygen extraction (cTOE) [2]. $rcSO_2$ or cTOE could be used to monitor the timing of GM-IVHs and PVL development in preterm infants [3, 4]. This information could be used to develop therapeutic interventions, which may prevent some causes of cerebral brain injury.

In the recent SafeboosC trial an adult NIRS sensor was used in preterm infants less than 28 weeks gestation. Normative regional cerebral oxygenation values of 55 to 85% [5] in the first 72 h of life were utilised based on previous unpublished data [6]. The Safeboosc trial showed that if cerebral saturation values were visible to the bedside clinician it was possible to obtain stable values between 55 and 85% in the first 72 h of life. More recent data from the group at Utrecht has been published. This group have pioneered the utilisation of NIRS in newborn infants [4, 7–9]. The data from this recent publication was obtained from a very large cohort of almost 1000 newborn infants, and predominantly utilised the adult sensor. This study provided normative data for various gestational age groups and showed gestation specific cerebral NIRS values over the first days of life [10]. They also evaluated the discrepancy between the adult sensor and the neonatal sensor in a small subgroup of infants, highlighting that neonatal sensors tend to overestimate $rcSO_2$ values by 8–14% compared to the adult sensor [10]. Neonatal NIRS sensors, which are relatively

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smaller than standard adult sensors, are now available, are easy to apply and are used in preterm infants.

The aim of this study was to evaluate the temporal evolution of the $rcSO_2$ over the first 48 h of life using a neonatal NIRS sensor. We also explored the relationship between $rcSO_2$ and short-term neurologic outcome (STNO) in a cohort of preterm infants <32 weeks' gestation. We hypothesised that there was a relationship between changes in postnatal transition $rcSO_2$ values obtained in the first 48 h of life and STNO in preterm infants <32 weeks when using the NIRS device with the neonatal sensor.

Methods

This was a prospective observational study performed in a level three neonatal intensive care unit in Cork, Ireland. Data for this study was collected from two separate infant cohorts enroled between December 2009 and April 2015. All infants born <32 weeks of gestation were eligible for recruitment. Written informed parental consent was obtained prior to recruitment. Infants with known major chromosomal abnormalities or congenital abnormalities were excluded. The study was approved by the local Cork Research Ethics committee.

Materials

Cerebral oxygenation data was collected using the INVOS 5100 NIRS (Covidien, Mansfield, MA, USA) with a neonatal sensor, the OxyAlert™ NIRSensor (Covidien IIc, Mansfield, MA, USA). Recording began as soon after birth as feasible and continued for up to 48 h. $rcSO_2$ data was stored on the INVOS device with a sampling period between 5 and 6 s and later exported for off-line analysis. Recordings of duration <6 h were excluded from further analysis.

Cranial ultrasound scans (CRUS)

CRUS were performed routinely as per unit protocol for all infants born <32 weeks of gestation. Scans were usually performed on day 1 to day 3, between day 10 and 14 and at ~1 month of age. All cranial ultrasound scans were formal clinical scans performed and reported by a Paediatric Radiologist who was not involved in the study and was blinded to NIRS data. The reports of the scans were used to define STNO. This was defined as the presence of GM-IVH, PVL, or death within 1 month of birth. Outcome was divided into three groups: severe, GM-IVH grade three or four, PVL, or death within 1 month after birth; moderate, GM-IVH grade one or two, absence of PVL, and survival by 1 month; and normal, absence of GM-IVH,PVL and survival to 1 month.

Analysis of $rcSO_2$

A mixed-effects model was fitted to the $rcSO_2$ data to describe the evolution of $rcSO_2$ over time and to explore the effect of variables such as outcome and gestational age on $rcSO_2$. The INVOS NIRS device measures $rcSO_2$ within the range 15–95% where a value of 15% represents periods when skin-contact was lost with the sensor; accordingly, $rcSO_2$ values of 15% were removed from further analysis. For the mixed model, the $rcSO_2$ was low-pass filtered using a 1-h moving-average filter with 50% overlap to enable the model to capture the trend of rcSO2 over time.

A linear, quadratic, and cubic-time model was fitted to the data, with each infant's $rcSO_2$ recording representing a random effect. Gender, outcome, and gestational age (GA) groups were included as fixed effects. Outcome was defined in three groups, as previously described, and GA was dichotomised as either extremely premature, with GA < 28 weeks, or very premature, with GA ≥ 28 and <32 weeks. Model selection was achieved by a backwards elimination procedure, starting with all terms in the model. Terms were removed only when the model fit did not significantly improve, as tested by the log-likelihood ratio test, using a χ^2 distribution, with $P < 0.05$. Where appropriate, random effects of time, time-squared, and time-cubed were removed first, followed by the fixed effects of outcome, gender, GA groups, and the relevant time interactions. Lastly, time, time-squared, and time-cubed fixed-effects were removed if model fit did not significantly improve.

Two other features of the $rcSO_2$, independent of the absolute $rcSO_2$ values, were used to test possible association with outcome. These two features represented the total area below 55% and the total area above 85% and were previously developed to quantify the level of hypoxia (area < 55%) and level of hyperoxia (area > 85%) [11]. To incorporate expected differences in $rcSO_2$ depending on GA, we increase these thresholds by 5% for the very preterm group, to 60 and 90%, while keeping the lower thresholds (55 and 85%) for the extremely preterm infants. These area measures were estimated on the raw $rcSO_2$ signal. Because these unfiltered $rcSO_2$ signals may contain artefacts, a 30 s collar was applied around the 15% $rcSO_2$ data points which were then removed from further analysis. Area was measured using the trapezoidal method, a numerical approximation of integration. The area measures were normalised to produce a value between 0 and 1 and then log-transformed to offset the skewed (towards 0) nature of the measures [11]. The Kruskal–Wallis test was used to ascertain differences in the area values between the three outcome groups. If there was a significant difference, with $P < 0.05$, Mann–Whitney tests were used to test pair-wise associations. For this comparison the Holms procedure [12] was used to correct the *P*-value for multiple comparisons; both the adjusted *P*-value and

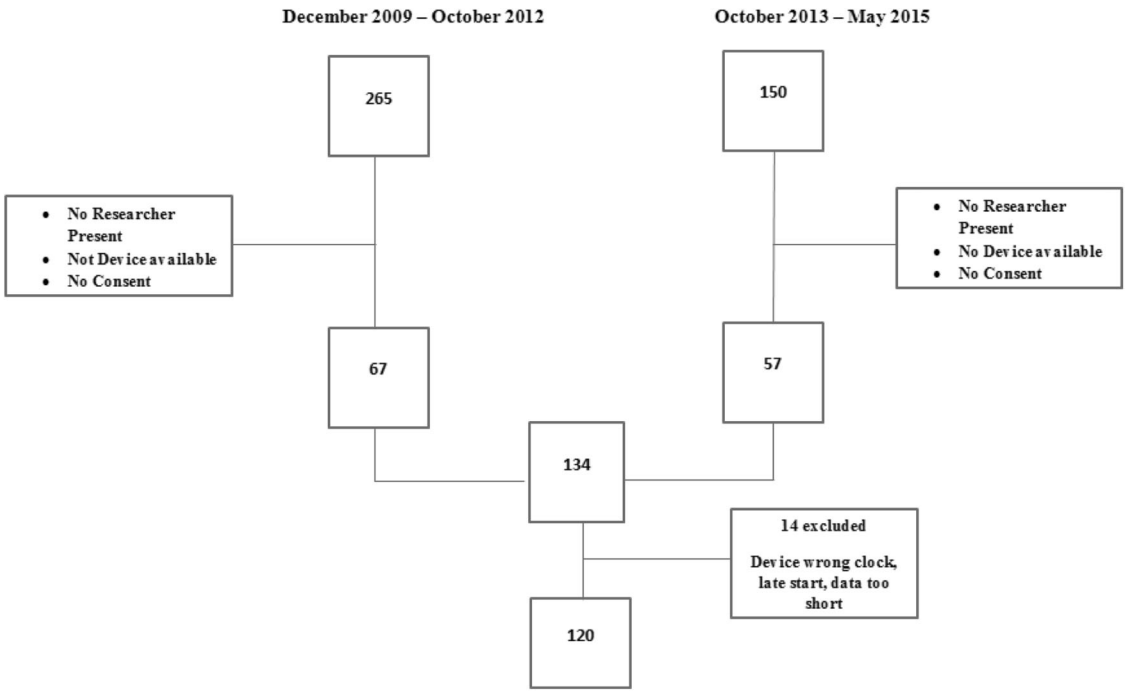

Fig. 1 This Figure provides a breakdown of the patient enrolment for the study

the un-adjusted *P*-values were reported. We did not calculate cFTOE because of concerns about variability in synchronisation of our SpO_2 data and $rcSO_2$ data which would have made the calculation of this feature thus unreliable.

The $rcSO_2$ data were processed using the Matlab software package (Release 2013a, The MathWorks, Inc., Natick, Massachusetts, US). The mixed-effect models were implemented in R (version 3.3.1, The R Foundation of Statistical Computing, http://www.r-project.org) using the *lme4* package (version 1.1-10). Patient characteristics were compared in R using the Kruskal–Wallis and Fisher's exact tests as appropriate.

Code availability: Matlab and R code used to generate the mixed-effect model and measures of hypoxia and hyperoxia is freely available (version 0.1.3, https://github.com/otoolej/rcSO2_temp_evolution). This code is distributed under a permission free software licence (BSD 3-clause licence).

Results

Patient characteristics

Figure 1 provides a breakdown of the patient enrolment. The principal reasons for non-enrolment were the unavailability of research staff and the lack of a device. A total of 134 preterm infants meeting recruitment criteria with NIRS recordings were considered for the analysis. Analysis was limited to the first 2 days of postnatal age (≤48 h). From this cohort, infants were excluded because the recording duration of NIRS was <6 h ($n = 4$), incorrect timing on NIRS machine clock ($n = 5$), and recording started after 48 h of age ($n = 5$). Thus, a total of 120 infants were included in the analysis. Median (IQR) GA was 29 (26.7–30.5) weeks, birth weight was 1.14 (0.88–1.45) kg, and there was 61 (50.8%) male infants. The majority of infants (83%) were born by C-section. Over two thirds of infants (69%) had a normal outcome, less than a quarter of infants (22%) had a moderate outcome, and 9% of infants had severe outcome. Patient characteristics are summarised in Table 1.

NIRS data analysis

The median (IQR) duration of NIRS recordings was 40.3 (24.7–46.6) hours and percentage of missing data, including removed artefacts, was 0.6% (0.1–4.3%). Figure 2, shows a plot of mean absolute $rcSO_2$ values for these 2 GA groups and indicates that there is no obvious trend in $rcSO_2$ over time, but that $rcSO_2$ values are lower for extremely preterm infants comparative to very preterm infants. The following mixed-effect model analysis confirms these observations.

Mixed effects model analysis

The mixed effects model included time, time-squared, time-cubed, and gestational age group as fixed effects and time, time-squared, and time-cubed as random effects. Coefficients of the fixed effects in Table 2 indicate that extremely

Table 1 Patient baseline characteristics represented either as median (IQR) or *n* (%)

Feature	All infants	Normal outcome ($n = 83$)	Moderate outcome ($n = 26$)	Severe outcome ($n = 11$)	*p*-value
Gestational age	29 (26.7–30.5)	29.1 (26.8–30.6)	29 (28.2–30.5)	26.3 (25.4–29.1)	0.106
GA <28 weeks	41 (34.2%)	30 (36.1%)	5 (19.2%)	6 (54.5%)	0.084
Birth weight	1.14 (0.88–1.45)	1.12 (0.89–1.40)	1.33 (1.04–1.61)	0.93 (0.75–1.28)	0.064
Gender male	61 (50.8%)	44 (53.0%)	11 (42.3%)	6 (54.5%)	0.646
Apgar score at 1 min	7 (5–8)	7 (5–8)	8 (5–8)	6 (4.5–8)	0.651
Apgar score at 5 min	9 (7–9)	9 (7–9)	9 (8–9)	8 (7–8)	0.119
Delivery by C. section	100(83.3%)	52 (62.7%)	19 (73.1%)	6 (54.5%)	0.917
IVH	**32 (28.7%)**	**0 (0%)**	**26 (100%)**	**6 (54.5%)**	**< 0.001**
PVL	**4 (3.3%)**	**0 (0%)**	**0 (0%)**	**4 (36.4%)**	**< 0.001**
Mortality	**5 (4.2%)**	**0 (0%)**	**0 (0%)**	**5 (45.5%)**	**< 0.001**
PDA	49 (40.8%)	30 (36.1%)	13 (50%)	6 (54.5%)	0.319
NEC	17 (14.2%)	9 (10.8%)	2 (7.7%)	6 (54.5%)	0.002
Sepsis<48 h	5 (4.2%)	2 (2.4%)	2 (7.7%)	1 (9.1%)	0.196
Sepsis>48 h *n* (%)	32 (28.7%)	20 (24.1%)	7 (26.9%)	5 (45.5%)	0.326

IVH: Intraventricular haemorrhage

PVL: Periventricular Leukomalacia

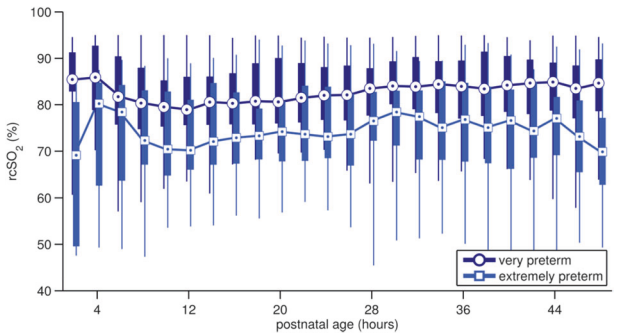

Fig. 2 $rcSO_2$ data summarised per recording (mean) over a 2-h epoch, showing that infants born extremely preterm ($n = 41$) have relatively lower ranges of $rcSO_2$ values compared to the very preterm infants ($n = 79$). Circles and squares represent median values, thick bars represent inter-quartile range, and thin lines represent 95 percentiles

preterm infants, comparative to the very preterm infants, have an $rcSO_2$ that is 7.13% lower (CI: 4.18–10.07, $P < 0.001$). We found no significant GA group by time interactions thus indicating that the difference for GA groups is independent of time. Also, outcome and gender were not found to significantly improve model fit and were therefore not included in the mixed-effect model. Figure 3 plots the temporal evolution of the mixed effects model, showing a slow oscillation with a maximum deflection of ~5%. There does not appear to be any obvious $rcSO_2$ increase or decrease in overall trend over the 48 h period.

Table 2 Estimates of fixed effects from a mixed-effects model of $rcSO_2$ within the first 48 h after birth

Coefficient	Estimates (95% CI)
Intercept ($rcSO_2$ %)	75.8* (72.1 to 79.4)
Time ($rcSO_2$ % /days)	−13.4** (−23.0 to −3.8)
Time^2 ($rcSO_2$ %/day^2)	17.5* (7.9 to 27.2)
Time^3 ($rcSO_2$ %/days^3)	−5.79* (−8.72 to −2.85)
Gestational age group[a]	7.13* (4.18 to 10.07)

[a]Reference group: <28 weeks. *P<0.001; **P<0.01

Relationship with outcome

Table 3 shows the relationship between hypoxia and hyperoxia, as defined by the $rcSO_2$ area < 55/60% and area > 85/90% measures, and the three outcome groups. Results indicate a difference in hypoxia for outcome ($P = 0.009$) but no difference in hyperoxia for outcome ($P = 0.680$). Pairwise comparison between the three different outcome groups show a greater degree of hypoxia for the moderate comparative to the normal group ($P = 0.015$) and moderate group comparative to the severe group ($P = 0.042$).

Discussion

Our study describes trends in $rcSO_2$ values in a large cohort of preterm infants born before 32 weeks of gestation

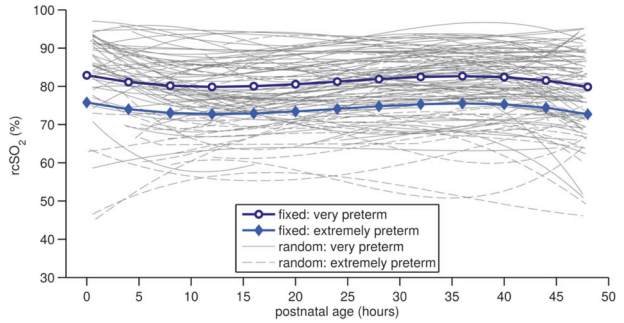

Fig. 3 Mixed-effects model with cubic-time for rcSO2. Random effects represent the fitted trend for each infant's $rcSO_2$ and fixed effects represent an average trend over the groups

monitored with the neonatal INVOS sensor over the first 48 h of life. The results show that cerebral oxygenation values are relatively stable over the 48 h period. Although the raw $rcSO_2$ changes over time for each infant, over all infants we find no clear temporal trends in $rcSO_2$ for either gestational age group (Fig. 3). Extreme preterm (<28 weeks) infants had a relatively lower $rcSO_2$ values compared to those born very preterm (28–32 weeks) throughout the 48 h (Figs. 2, 3 and Table 2). The mixed model estimates this significant difference between groups as 7.13% (95% CI: 4.18–10.07, $P < 0.001$), and $rcSO_2$ for both groups follow the same cubic trajectory over time. The intercept value, which represents the average $rcSO_2$ values at time zero at the beginning of recording in both the gestational age groups, is 75.8% for the extreme preterm and 82.9% for the very preterm. This reflects higher $rcSO_2$ average values for the neonatal sensor than existing data from the adult probe [13] and these values need to be considered when designing future trials of cerebral NIRS in preterm infants. The work of Alderstein and colleagues highlighted this difference in a 16 preterm infants with a mean gestational age of 30 weeks who had both the neonatal and the adult sensor in place simultaneously, showing a difference of about 10% between the devices [10]. Greisen and colleagues recently evaluated various devices on a phantom model and highlighted various inter-device differences [14–16].

Our results indicate that there was a statistically significant association between cerebral hypoxia and outcome ($P = 0.009$) but no difference between cerebral hyperoxia and outcome ($P = 0.680$). Though the association between cerebral hypoxia and poor neurologic outcome may not be surprising, this is important to note, as this suggests that it may be possible to use NIRS as a monitoring tool to predict and ultimately prevent brain injury in this group of preterm infants. In an exploratory analysis the Safeboosc group noted a higher incidence of brain injury for those infants in the lowest quartile for cerebral hypoxia [17].

Pairwise comparisons showed an increase in hypoxia for the group with a grade 1 or 2 haemorrhage compared to

Table 3 Features of the rcSO2 relating to grades of outcome: normal, $n = 83$; moderate: $n = 26$; severe: $n = 11$

	Median (IQR)			*P*-values			
	Normal	Moderate	Severe	All[a]	Normal vs. moderate[b]	Moderate vs. severe[b]	Normal vs. severe[b]
Hypoxia (log area <55/60%[c])	−8.24 (−11.01 to −6.48)	−6.68 (−8.35 to −5.31)	−10.11 (−36.04 to −6.37)	**0.009**	**0.015(0.01)**	**0.042(0.02)**	0.395 (0.40)
Hyperoxia (log area >85/90%[c])	−3.30 (−6.74 to 1.51)	−3.50 (−5.29 to −2.03)	−4.08 (−11.05 to −1.76)	0.680			

[a] Kruskal–Wallis test; [b] Mann–Whitney *U* test with *P*-values from Holm correction procedure and uncorrected *P*-values in parenthesis.
[c] 55 and 85% threshold for infants < 28 weeks and 60 and 90% thresholds for infants ≥28 weeks of gestational age. *IQR* inter-quartile range

both the normal ($P = 0.015$) and severe groups ($P = 0.042$). This was an interesting finding because we expected the severe groups to have a greater degree of hypoxia when compared to the normal group. They were more immature, of a lower birth weight and had more respiratory support. We suspect that these infants were more likely to receive more interventions, primarily in the form of respiratory management. The SafeboosC trial highlighted that adjustment in fractionated oxygen support was the most common intervention performed in the sickest preterm infants [5]. However we can only postulate as we did not measure the number of interventions within groups. It is important to note that our study was observational and the NIRS data was collected but not acted upon by the bedside clinician. It is conceivable that NIRS values were similar as significantly increased interventions may have occurred in the more immature group. However these questions can only be answered with appropriately designed trials utilising appropriately chosen target ranges, incorporating quantitative measures of degree of hypoxia, or investigating different signal features which may be better predictors of risk of brain injury [18].

A recent study [4] assessing neurologic outcome and NIRS-measured $rcSO_2$ showed that infants who developed GM-IVH had higher $rcSO_2$ and lower cFTOE values before the development of GM-IVH, suggesting increased perfusion [4]. These findings contrasted with another [19], which reported that patients with GM-IVH tended to have lower left ventricular output and cerebral rSO_2 and higher cFTOE during the first 12 h. In the present study, we looked at the cumulative $rcSO_2$ data over the first 48 h, but we could not determine the exact timing of brain injury, as frequent ultrasound scanning in the first days of life was not routinely performed. A recent study that assessed long term neurologic outcome following NIRS monitoring found that $rcSO_2$ values monitored during the first 2 weeks after birth had an association with longterm neurodevelopmental outcome at 2–3 years, specifically high and low $rcSO_2$ on day one of life [20]. Identifying the specific timing of brain injury could potentially allow clinicians to understand in more detail the changes that occur to the infant's cerebral haemodynamics, including $rcSO_2$ values, prior to or during the event, and could in turn help develop specific treatment or preventative measures. Future work in this area is warranted.

There are a number of limitations. Filtering $rcSO_2$ values for the mixed-effect model suppresses faster oscillations in the signal, thus there might be discriminatory information in these faster oscillations that we have not examined here. The neonatal sensor has known limitations in detecting hyperoxia in preterm infants, which we also confirmed in the present study. In our study the majority of infants who developed IVHs had mild to moderate grades (grade less than II). We categorised these infants as having poor STNO, because there is evidence suggesting that the presence of grade I–II GM-IVH, even with no documented white mater injury or late ultrasound abnormalities, may be associated with poor neurodevelopment outcome in extremely preterm infants [21]. Even though we had a larger cohort of infants monitored with the neonatal sensor compared to previous studies, the overall number of infants with a poor STNO was low.

Conclusion

Immature preterm infants have relatively lower $rcSO_2$ values compared with their more mature counterparts but $rcSO_2$ values are relatively stable over the first 48 h of life, showing no obvious increase or decrease in overall trends There was no statistical difference in the absolute values or temporal trajectories of $rcSO_2$ between the three outcome groups. It remains difficult to quantify hyperoxia for infants >28 weeks GA using the neonatal sensor. Further trials are warranted to determine if actively intervening to maintain $rcSO_2$ within certain limits results in improved outcome.

Author contribution MK conceptualised and designed the study, collected the data and drafted the initial manuscript. JMO carried out the initial data analysis and statistical analysis, and reviewed and revised the manuscript. GAH, WH, MW, and EL carried out the data collection, and reviewed and revised the manuscript. GBB critically reviewed and revised the manuscript. ACR and EMD supervised and helped design the study and data collection instrument and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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