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Monitoring Gas Exchange during Hypothermia for Hypoxic-Ischemic Encephalopathy

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Abstract

Objective: Therapeutic hypothermia (TH) is standard of care in management of moderate/severe hypoxic-ischemic encephalopathy (HIE). Persistent pulmonary hypertension of the newborn (PPHN) is associated with HIE and is exacerbated by hypoxemia and hypercarbia. Gas exchange is assessed by arterial blood gas (ABG) analysis (with/without correction for body temperature), pulse oximetry (SpO_2) and end-tidal CO_2 ($ETCO_2$).

Design: A retrospective chart review

Settings: Regional perinatal center in Western NY

Patients: 58 ventilated neonates with indwelling arterial catheter on TH.

Intervention: None

Measurement and Main Results: We compared SpO_2, PaO_2, $ETCO_2$ and $PaCO_2$ during hypothermia and normothermia in neonates with HIE using 1240 ABGs with simultaneously documented SpO_2. During hypothermia, SpO_2 92–98% was associated with significantly lower temperature-corrected PaO_2 (51mmHg, IQR:43–51) compared to normothermia (71mmHg, IQR: 61–85). Throughout the range of SpO_2 values, geometric mean PaO_2 was about 23% (95% CI: 19% to 27%) lower during hypothermia compared to normothermia. In contrast, $ETCO_2$ accurately assessed temperature-corrected $PaCO_2$ during normothermia and hypothermia.

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Article tweet: Non-invasive assessment of oxygenation by pulse oximetry during whole body hypothermia is not reliable and underestimates hypoxemia. Frequent arterial blood gas analysis is warranted to accurately estimate oxygenation during hypothermia.

Conclusion: Hypothermia shifts oxygen-hemoglobin dissociation curve to the left resulting in lower PaO_2 for SpO_2. Monitoring oxygenation with ABG uncorrected for body temperature and SpO_2 may underestimate hypoxemia in HIE infants during whole body hypothermia, while $ETCO_2$ reliably corelates with temperature-corrected $PaCO_2$.

Keywords

oxygen dissociation curve; capnography; pulse oximetry; blood gas analysis; hypoxia; pulmonary hypertension; acidosis

INTRODUCTION

Moderate therapeutic hypothermia (33.5°C) is neuroprotective in infants who suffer from perinatal hypoxic-ischemic encephalopathy (HIE). The American Academy of Pediatrics (1) and Neonatal Resuscitation Program (2) support whole-body or selective head cooling for neonates with moderate to severe HIE. Neonates with HIE are at risk for neurodevelopmental impairment (NDI) and persistent pulmonary hypertension of the newborn (PPHN) (3).

A meta-analysis of 4 major cooling trials involving 614 infants demonstrated the incidence of PPHN and iNO though higher in infants with HIE, does not significantly increase with therapeutic hypothermia (4,5). In a recent trial of optimizing cooling strategies, whole body hypothermia to 32°C increased need for iNO therapy (34% vs 24%) and ECMO (9% vs 4%) compared to 33.5°C. Clinical data on the incidence of PPHN during TH are conflicting but optimizing cooling trial and animal studies suggest that pulmonary vascular resistance (PVR) may increase during hypothermia by an unknown mechanism (7)(8).

It is a common practice to monitor ventilated patients with respiratory monitors with capnography ($ETCO_2$) and pulse oximetry (SpO_2). Continuous monitoring with non-invasive parameters such as $ETCO_2$ and SpO_2 are periodically trended with $PaCO_2$ and PaO_2 measured with arterial blood gases. The optimal ranges for $PaCO_2$ and PaO_2 during whole-body hypothermia for HIE (with or without correction for bodytemperature) that minimizes the risk of NDI and PPHN are not known. Hypocapnia (9) and hyperoxia (10) are associated with an increased incidence of NDI in patients with HIE.

We studied the effect of whole-body hypothermia (33.5°C) on PaO_2, $PaCO_2$, SpO_2 and $ETCO_2$ from data in our unit. We hypothesized that the relationship between non-invasive measures of gas exchange ($ETCO_2$ and SpO_2) and $PaCO_2$ and PaO_2 is altered during whole-body hypothermia.

Methods:

This study was approved by the Children and Youth Institutional Review Board of the University at Buffalo and waived need for individual consents. Philips patient monitoring system (Phillips IntelliVue MX800, N.V. USA) was used for SpO_2 monitoring, Macquet Servo I ventilators (pressure mode of ventilation) for neonates (Rastatt, Germany) was used for ventilation. For end-tidal CO_2 monitoring we used Philips NM3 monitor (Respironics,

MA), which measures CO_2 in exhaled air/gas via infrared sensor, and Abbott i-STAT point of care (Princeton, NJ) was used for blood gas analysis.

Data on gas exchange:

For the retrospective chart review at the regional perinatal center, 74 neonates on whole-body hypothermia (33.5°C) for 72 hours for moderate to severe HIE between July 2009 and March 2016 were evaluated. Fifty-eight neonates who were intubated and had an indwelling arterial line (umbilical or peripheral) for blood draws were included in this study. The temperature for ventilator humidifier was set at 37°C throughout the study period. The data points were divided into two groups: normothermia and hypothermia (target~33.5°C) based on infant's esophageal temperature at the time of ABG collection. The following parameters: SpO_2, $ETCO_2$ were collected at the same time as blood draw. Data from 1240 ABGs (383 during normothermia and 857 during hypothermia) with simultaneous SpO_2 measurements was extracted. Sixty-six arterial blood gas samples were drawn prior to initiation of hypothermia (during 1–6 hours after birth), 857 were drawn during hypothermia and the remaining 317 after rewarming (after day 3 but prior to removal of the indwelling arterial line). Temperature-corrected PaO_2 was plotted against SpO_2 and $PaCO_2$ against $ETCO_2$.

Statistical analysis: Oxygen-Hb dissociation curves were created for hypothermia and normothermia using corresponding SpO_2 and PaO_2 values. To account for the varying number of repeated measurements by infant, methods for clustered data were used. For within-measurement comparisons of temperature-corrected and uncorrected values, we compared mean differences scores using a clustered sample paired t-test, using PROC SURVEYMEANS in SAS (SAS Institute, Cary NC). For comparing normothermic to hypothermic measurements, we fit clustered data regression models using PROC GLIMMIX in SAS with robust standard errors. For comparing clinical parameters, regression models were specified with fixed effects for infant and hypothermia status, to estimate adjusted mean within-infant differences, analogously to a paired t-test but accounting for the unbalanced number of hypothermic and normothermic measurements. For fitting dissociation curves, we specified random intercepts for infants. We modeled log-transformed PaO_2 (dependent variable) as a function of logit-transformed SpO_2 and hypothermia status, and we used untransformed values to model $PaCO_2$ (dependent variable) as a function of $ETCO_2$ and hypothermia status. SpO2 values of 100% were logit-transformed to log(99.75%/0.25%). Models were fit with and without interactions of hypothermia status and the covariate, to assess whether hypothermia modified the fitted slope, using the traditional significance threshold ($p<0.05$) for the interaction term to select the better fitting model. The regression coefficient for hypothermia status predicting log-transformed $PaCO_2$ was back-transformed (via the inverse natural logarithm, aka "exponentiation") to the original scale for $PaCO_2$, and thus represents an adjusted geometric mean ratio, expressing the relative effects of hypothermia on typical predicted values.

Results:

Retrospective chart review comparing invasive and non-invasive monitoring of gas exchange:

During the study period, 34 males and 24 female infants underwent moderate whole-body hypothermia protocol and had an indwelling arterial line. None of the infants were passively cooled prior to admission and had an esophageal temperature of ≥ 36.5°C prior to onset of therapeutic hypothermia. Median Apgar scores were 2 (IQR 1–3), 5 (4–6), and 5 (4–6) at 1, 5 and 10 minutes respectively. Cord pH was 6.9 ± 0.19. Twelve infants had severe and 46 infants had moderate HIE by modified Sarnat staging (11). Eleven infants (19.6%) had echocardiographic findings of PPHN, seven infants (12.5%) required iNO, and none were placed on ECMO. Six infants (10.7%) died prior to discharge. The cause of death was withdrawal of support due to severe HIE in 5 infants. One infant had hypoxemia due to PPHN and severe HIE and was not placed on ECMO following a discussion with parents.

Oxygen monitoring: Correction of blood gases to patient's temperature during whole body hypothermia (33.5°C) significantly reduced median (IQR) PaO_2 values from 75 (59–101) to 61 (48–82) mmHg [10(7.86–13.46) to 8.13(6.4–10.93) kPa] ($p<0.0001$, table 1). Within the most preferred range of SpO_2 from the survey (see attached supplement-92–98%), PaO_2 corrected for body temperature during hypothermia (51 mmHg, IQR:43–63) was significantly lower compared to normothermia (70 mmHg, IQR:60–85) (table 1 and figure 1A). SpO_2 values by pulse oximeter were significantly higher than SaO_2 values by co-oximetry by a median of 2% (IQR: 0–5) during normothermia and 5% (IQR: 2–10) during hypothermia ($p<0.0001$). Blood gas (PaO_2) uncorrected for temperature and SpO_2 values markedly overestimated oxygenation (corrected for temperature) during hypothermia. During cooling, maintaining $SpO_2 \leq 95\%$ resulted in 88 of 135 (65%) of PaO_2 values below 50 mmHg[6.67kPa] (a threshold point for increasing PVR in neonatal animal models, lower dashed line in figure 1A) (12). Interestingly, there were 440 ABGs corresponding to SpO_2 of 100% with FIO_2 ranging from 0.21 to 1.0 and PaO_2 ranging from 30 to 425 mmHg [4.00 to 56.66 kPa] (figure 1A). Maintaining SpO_2 between 95–99% during hypothermia corresponded to PaO_2 values were between 60 – 90 mmHg(figure 2).

Carbon dioxide monitoring: Correction of blood gases to patient's temperature during whole body hypothermia (33.5°C) significantly reduced median (IQR) $PaCO_2$ values from 49 (43–56) to 42 (37–48) mmHg [6.5(5.7–7.5) to 5.6(4.93–6.40) kPa] ($p<0.001$, table 1). End-tidal CO_2 was marginally lower than $PaCO_2$ (corrected for body temperature) during hypothermia and normothermia (figure 1B) and the gradient between arterial and end-tidal $PaCO_2$ (Pa-$ETCO_2$) was low during both normothermia (median 1 torr[0.13kPa], IQR: −2 to 4)and hypothermia (median 3 mmHg, IQR: 0 to 7). Although $PaCO_2$ uncorrected for body temperature was significantly higher, capnography accurately estimated $PaCO_2$ levels (corrected for temperature) during hypothermia (figure 1B). In mixed-effects modeling, the adjusted hypothermia vs. normothermia mean difference in $PaCO_2$ levels was not significant −0.10 (95% CI: −4.47, 4.27), p=0.96.

Oxygen-Hb Dissociation: The best fitting model included fixed effects for logit-transformed SpO_2 and hypothermia status. Hypothermia significantly shifted the fitted dissociation curve to the left, corresponding to a relative underestimation of geometric mean PaO_2 by 23% (adjusted hypothermia vs. normothermia geometric mean ratio PaO_2 = 0.77 (95% CI: 0.73, 0.81)).

Discussion:

The benefits of hypothermia in reducing mortality and NDI are well established in infants with HIE. Optimizing cerebral and pulmonary hemodynamics during hypothermia may be important to optimize outcomes in HIE. Two acid-base management approaches during hypothermia are described in the literature in reference to pediatric cardiac anesthesia management and profound hypothermia (usually 18–20°C) (7,13). However, there are no studies evaluating the optimal approach to acid-base management during mild hypothermia (33–34°C) for HIE. Management by the *α-stat technique* focuses on maintaining a normal pH and $PaCO_2$ at 37°C and not at the current body temperature (7). In the *pH-stat technique*, $PaCO_2$ in the blood gas drawn from a hypothermic patient is measured after warming the blood to 37°C but is mathematically corrected to the patient's temperature (7). Ventilation is then adjusted to achieve a normal pH and $PaCO_2$ at patient's temperature. This results in higher CO_2 (as compared to the α-stat method), and leads to concurrent cerebral vasodilation and pulmonary vasoconstriction, resulting in higher cerebral blood flow and more effective and homogenous brain cooling. In addition, animal studies demonstrate better suppression of cerebral metabolic rate with pH stat method (7). Thus, based on literature review almost all studies evaluating whole body hypothermia for HIE have adapted pH-stat method for acid-base management (6, 11, 14, 15). Data on neurodevelopmental outcome and incidence of PPHN from these trials are based on blood gases corrected for body temperature. However, our survey conducted among Neonatology Division chiefs from US institutions suggests that, only 64% of academic divisions exclusively report corrected blood gases during hypothermia (table 1). As expected, we found that that correction for actual body temperature during hypothermia decreased PaO_2 and the $PaCO_2$ (Table 1). According to Henry's law, the solubility of gas within liquid increases with a decrease in temperature of the liquid. This means that as it cools, plasma can have more dissolved gases but at a lower partial pressure of CO_2 and O_2 (7). Maintenance of the same $PaCO_2$ or PaO_2 under hypothermic conditions will require greater CO_2 or O_2 content.

No trial to date has prospectively examined the association between hypocarbia and hypercarbia with PPHN and neurodevelopmental outcome following therapeutic hypothermia for HIE. In a post-hoc analysis of the NICHD cooling trial, hypocarbia ($PaCO_2$ <35 mmHg[4.67kPa]) corrected for body temperature) was associated with higher rates of death and poor neurodevelopmental outcome (9). Similar results were reported from a retrospective analysis of CoolCap trial using corrected blood gases (16). Fluctuations in $PaCO_2$ levels during 72 hours of whole body hypothermia is also associated with poor neurodevelopmental outcome (16). When blood gases are reported at 37°C during therapeutic hypothermia, the reported $PaCO_2$ values are higher by a median of 7 mmHg [0.93kPa] as compared to $PaCO_2$ values at corrected body temperature (table 1), increasing the potential for unrecognized hypocapnia.

Similarly, hyperoxemia (PaO_2 corrected for body temperature > 100 mmHg [13.33kPa]) during initial NICU course (10) and use of high FIO_2 (17) are associated with poor neurodevelopmental outcome in infants with moderate to severe HIE. Studies in control and PPHN lambs, demonstrate that hypoxic pulmonary vasoconstriction is exacerbated with PaO_2 values less than 52.5 ± 1.7 mmHg [6.99± 0.23kPa] and 59.6 ± 15.3 mmHg[7.95 ±2.04kPa] respectively (18). However, maintaining PaO_2 > 80 mmHg (10.66kPa) does not further decrease pulmonary vascular resistance (12, 19). Hyperoxemia during the initial NICU course increased the incidence of NDI but did not reduce PPHN among patients with HIE. (10) Hence, to maintain low PVR and avoid adverse neurodevelopmental outcome, from an arterial oxygenation standpoint it may be prudent to maintain PaO_2 (corrected for body temperature) between 60 and 80 mmHg (18).

Fetal hemoglobin is adapted to operate at a lower PaO_2 than adult hemoglobin, and its fetal oxyhemoglobin dissociation curve is shifted to the left. The further leftward shift in fetal oxyhemoglobin dissociation curve induced by hypothermia has a profound influence on PaO_2 levels at lower saturations, as shown in figure 2. For a given SpO_2, PaO_2 was significantly decreased during hypothermia in our patients (figure 1A). Thus, the use of uncorrected blood gases at 37°C and pulse oximetry monitoring can underestimate hypoxemia during hypothermia.

What is the significance of these findings in clinical practice? Hypocapnia is common in HIE; 40% of moderate and 67% of severe HIE patients presented with $PaCO_2$ < 30 mmHg(4kPa) at randomization in the CoolCap trial (16). Minimizing the severity and duration of hypocapnia and reducing fluctuations in $PaCO_2$ is of paramount importance to improve outcomes in HIE. We recommend frequent blood gas monitoring and maintaining temperature-corrected $PaCO_2$ between 40 to 50 mmHg (5.3–6.67 kPa) during hypothermia. (9, 10, 16) We conducted a survey among chiefs of Neonatal Perinatal Medicine evaluating invasive and non-invasive assessment of gas exchange during hypothermia. Our survey suggests that this target range for $PaCO_2$ is preferred by academic institutions in the US (see supplemental file 1). $ETCO_2$ provides a reliable measure of temperature corrected $PaCO_2$ and the recommended range based on our study is 41–45 mmHg[5.47–6kPa] (figure 1B).

Hypoxemia and hyperoxemia are common in patients with HIE and are associated with an increased risk of PPHN (19). Based on our findings, uncorrected PaO_2 and pulse oximetry are unreliable during hypothermia (figure 1A and2). We recommend close monitoring and maintaining temperature-corrected PaO_2 between 60 and 80 mmHg (8 and 10.66 kPa) during therapeutic hypothermia for HIE.

The limitations of our study include its retrospective nature and some of the arterial gases may have been post-ductal. These differences may have influenced our results. Multiple samples were obtained from the same patient and to offset the difference we have used robust regression model. The number of blood gases before and after the onset of hypothermia are lower than that during hypothermia. We did not measure the percentage of fetal hemoglobin in these samples. Variations in the level of 2,3 diphosphoglycerate (2,3 DPG) may have contributed to changes in oxygen-hemoglobin dissociation curve. As noted above, the ventilator humidifier was set at 37°C as a standard practice throughout the

cooling and rewarming process, so the measured $ETCO_2$ may have been at a somewhat higher temperature than neonatal core temperature during hypothermia. Regardless, these findings have never been studied in neonates and is important in managing neonates with HIE undergoing whole body hypothermia.

With the current evidence from translational and clinical studies, we conclude that correcting blood gases to patient's temperature may aid in unnecessary fluctuations in $PaCO_2$ and PaO_2 which may influence cerebral blood flow and maintain oxygen delivery to the brain. We recommend frequent blood gas monitoring with less reliance on pulse oximetry during whole body hypothermia, especially in patients at risk for PPHN. Further prospective studies evaluating the optimal approach to acid-base management and target SpO_2 and $ETCO_2$ during hypothermia for HIE are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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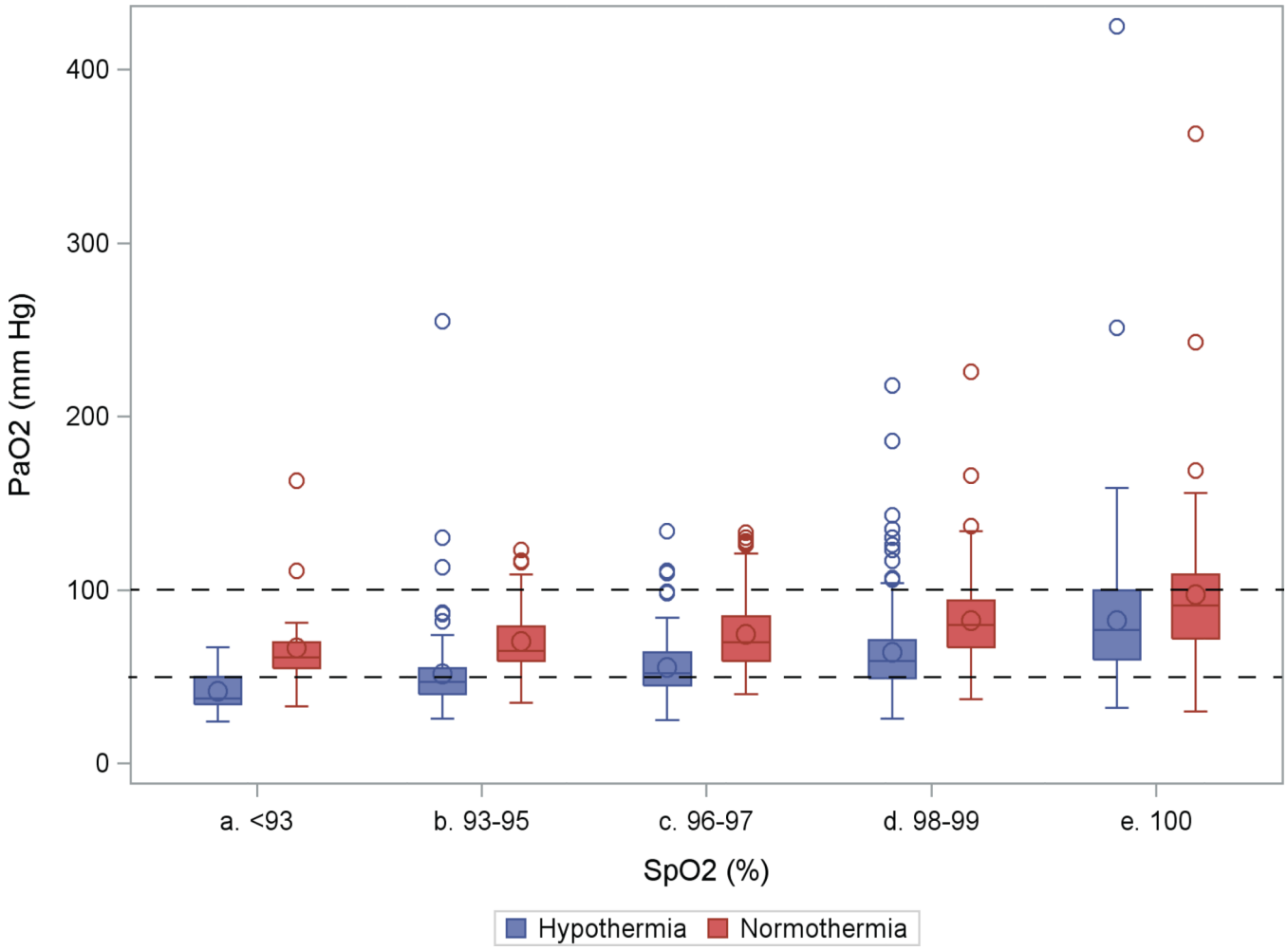

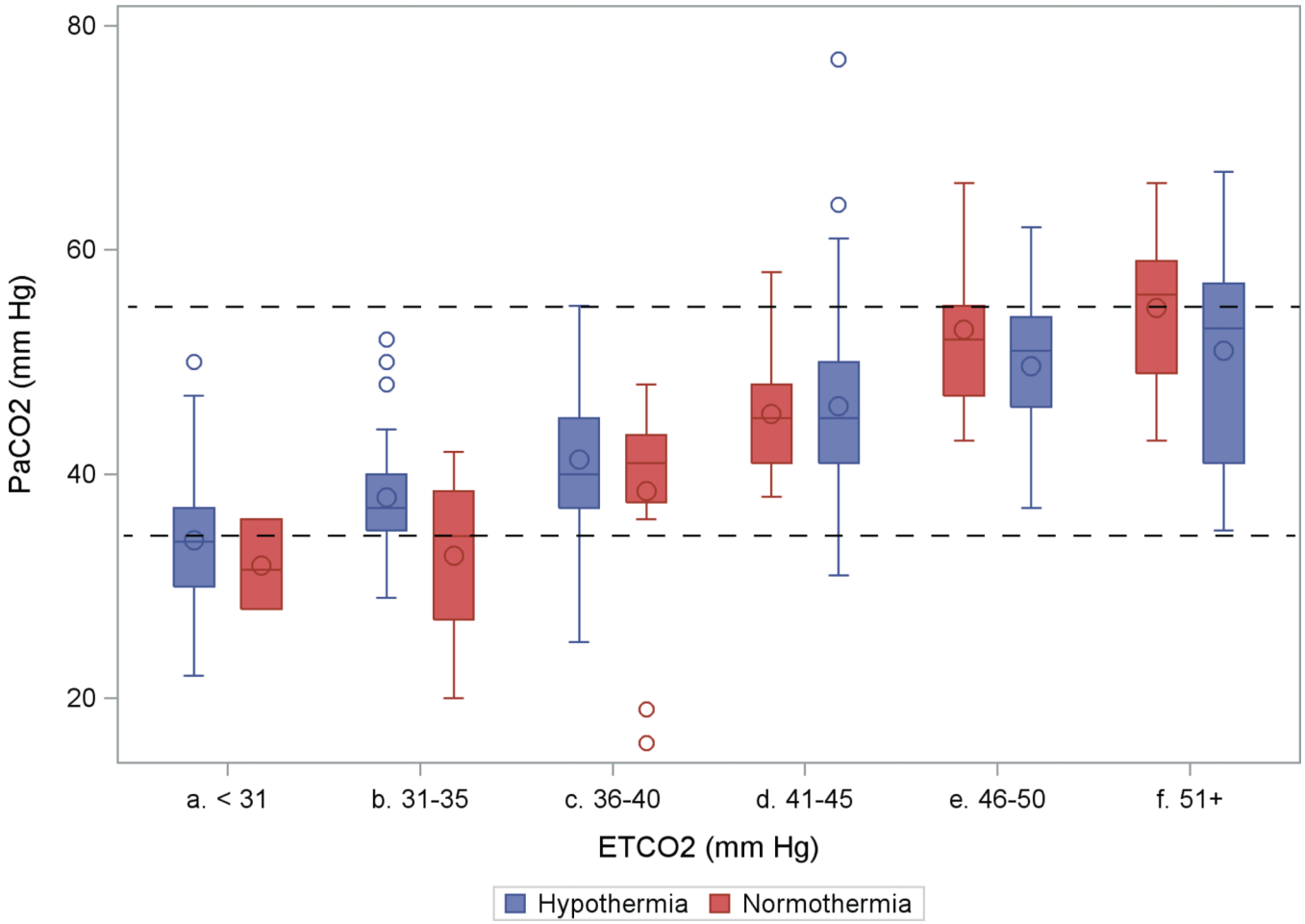

Figure 1.

A. Box and whisker plot (IQR and range) of PaO_2 (in mmHg) compared to SpO_2 (%) from pulse oximetry of 1240 arterial blood gases. * $p < 0.05$ compared to normothermia. The horizontal hyphenated lines represents the cut-off PaO_2 (50 mmHg [6.67kPa)) below which PVR increases in animal models and the PaO_2 (>100 mmHg[13.3kPa]) associated with NDI in the NICHD trial (10). B. Box and whiskers plot of $ETCO_2$ (mmHg) from capnography and $PaCO_2$ (mmHg) from 381 measurements. The bottom horizontal hyphenated line in figure B represents the hypocarbia threshold ($PaCO_2$ < 35 mmHg[4.67kPa]) associated with poor outcomes. The upper hyphenated line represents $PaCO_2$ level (56 mmHg [7.5kPa]) associated with acidosis (pH<7.25) and increased PVR in newborn calves (12). The range between the hyphenated lines represents the physiological range of PaO_2 and $PaCO_2$ that offers an optimal balance between neurodevelopmental outcome and pulmonary vasoconstriction.

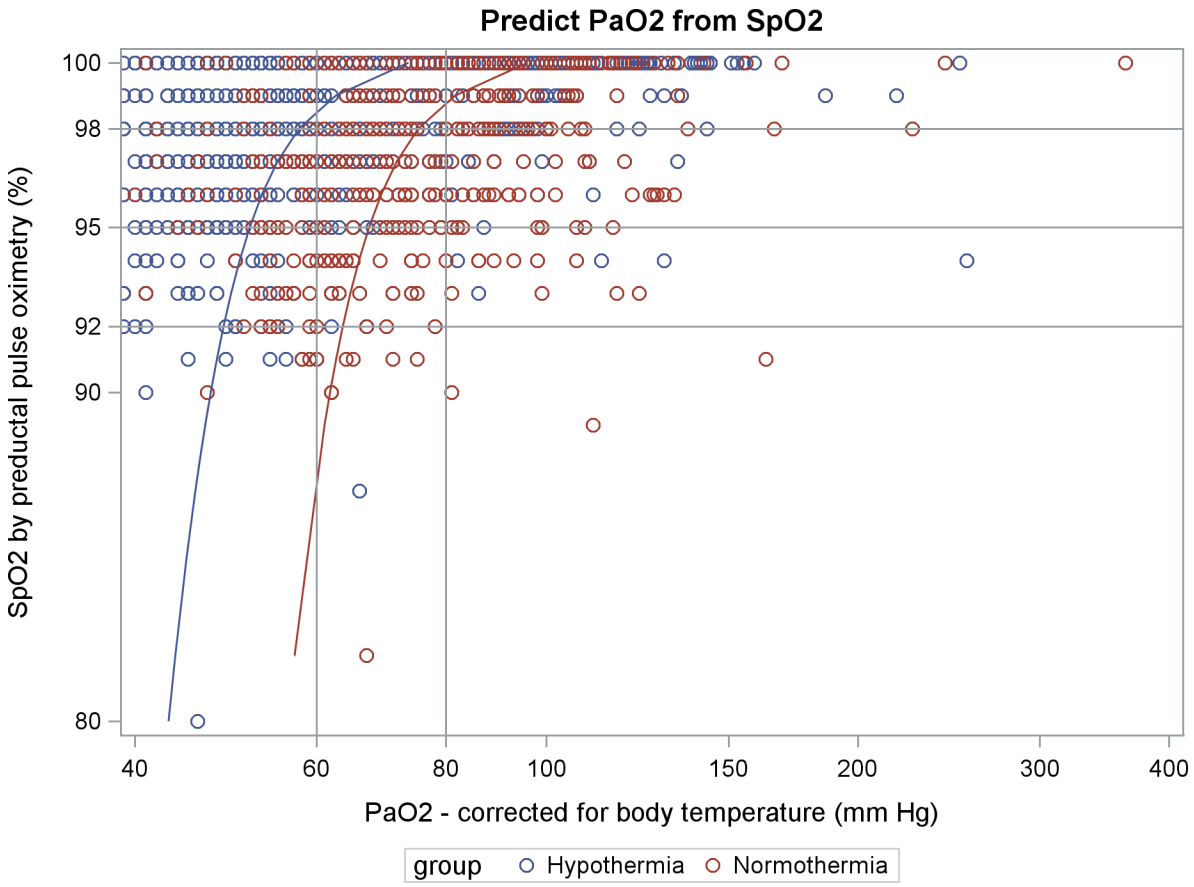

Figure 2.

Effect of temperature on oxygen-Hb dissociation curve. Scatter-plot of oxygen saturation and simultaneous arterial PO_2 values in mm Hg in 58 term human neonates undergoing whole body therapeutic hypothermia. Fitted lines from mixed-effects linear regression model of log-transformed PaO_2 (dependent variable) as a function of logit-transformed PaO_2 and hypothermia status. Blood pH for all these gases was between 6.8 and 7.62. For a clinically acceptable PaO_2 of 60–80 mmHg [7.9–10.66kPa] (vertical lines), median [IQR] pulse oximeter values were 96 [95 to 98]% during normothermia and were 99 [98 to 100]% during whole body hypothermia.

Table 1.

Blood gas comparison during hypothermia and normothermia (median, IQR)

	Normothermia (n=383)	**Hypothermia (n=857)**	**P value***
Esophageal temperature °C	37.0 (36.5–37)	33.5 (33.4–33.5)	< 0.0001
pH	7.40 (7.35–7.43)	7.37 (7.33–7.41)	0.11
$PaCO_2$ (corrected for body temperature) torr[kPa]	45 (40–52) † [6(5.3–6.93]	42 (37–48) † [5.6(4.93–6.40)]	0.046
$PaCO_2$ (at 37°C) mmHg [kPa]	46 (40–53) [6.1(5.3–7.1)]	49 (43–56) † [6.5(5.7–7.5)]	0.0007
$PETCO_2$ mmHg [kPa]	43 (39–48) n=77 [5.73(5.2–6.4)]	39 (34–44) n=287 [5.2(4.5–5.87)]	0.04
Corrected Pa-$PETCO_2$ gradient mmHg [kPa]	1 (−2 to 4) [0.13(−0.27–0.53)]	3 (0 to 7) [0.4(0–0.93)]	0.78
Uncorrected Pa-$PETCO_2$ gradient mmHg [kPa]	2 (−1 to 5) [0.27(−0.13 – 0.67)]	10 (5 to 14) [1.33(0.67–1.87)]	0.003
Calculated Alveolar PAO_2 mmHg [kPa]	130 (105–194) [17.3(14.0–25.9)]	111 (103–162) [14.8(13.7– 21.6)]	0.27
PaO_2 mmHg [kPa] (corrected for body temperature)	73 (62–91) † [9.7(8.3–12.1)]	61 (48–82) † [8.13(6.4–10.9)]	< 0.0001
PaO_2 mmHg [kPa] (at 37°C)	74 (62–92) [9.9(8.3–12.3)]	75 (59–101) [10.0(7.86–13.46)]	0.74
A-a gradient mmHg [kPa]	57 (27–128) † [7.6(3.60–17.1)]	51 (29–99) † [6.80(3.87–13.2)]	0.07
A-a gradient mmHg (at 37°C) [kPa]	54 (25–127) [7.20 (3.33 – 16.9)]	31 (5 – 81) [4.1 (0.7 – 10.8)]	0.35
SaO_2 (by co-oximetry)%	94 (91–97)	93 (88–97)	0.003
SpO_2 (from pulse oximetry)%	97 (95–99)	99 (97–100)	< 0.0001
$SpO_2 – SaO_2$	2 (0–5)	5 (2–10)	< 0.0001
FIO_2	0.25 (0.21–0.35)	0.21 (0.21–0.30)	0.32

† significantly different from corresponding measurement at 37°C, by one-sample t-test for mean difference score, adjusted for clustering by ID, a method that generalizes the paired t-test to account for clustering by ID (these tests were conducted separately in normothermic and in hypothermic measurements)

* p value for hypothermia vs. normothermia adjusted mean difference, estimated using a clustered data regression model with fixed-effects for ID (58 infants) and hypothermia, a method that generalizes the paired t-test to account for the varying and unbalanced numbers of normothermic and hypothermic repeated measures by infant. Robust standard errors were used to protect against departures from modeling assumptions.