Effects of Arterial Carbon Dioxide Tension on Cerebral and Somatic Regional Tissue Oxygenation and Blood Flow in Neonates After the Norwood Procedure With Deep Hypothermic Cardiopulmonary Bypass

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Neonates undergoing the Norwood procedure for hypoplastic left heart syndrome are at higher risk of impaired systemic oxygen delivery with resultant brain, kidney, and intestinal ischemic injury, shock, and death. Complex developmental, anatomic, and treatment-related influences on cerebral and renal-somatic circulations make individualized treatment strategies physiologically attractive. Monitoring cerebral and renal circulations with near infrared spectroscopy can help drive rational therapeutic interventions. The primary aim of this study was to describe the differential effects of carbon dioxide tension on cerebral and renal circulations in neonates after the Norwood procedure. Using a prospectively-maintained database of postoperative physiologic and hemodynamic parameters, we analyzed the relationship between postoperative arterial carbon dioxide tension and tissue oxygen saturation and arteriovenous saturation difference in cerebral and renal regions, applying univariate and multivariate multilevel mixed regression techniques. Results were available from 7,644 h of data in 178 patients. Increases in arterial carbon dioxide tension were associated with increased cerebral and decreased renal oxygen saturation. Differential changes in arteriovenous saturation difference explained these effects. The cerebral circulation showed more carbon dioxide sensitivity in the early postoperative period, while sensitivity in the renal circulation increased over time. Multivariate models supported the univariate findings and defined complex time-dependent interactions presented graphically. The cerebral and renal circulations may compete for blood flow with critical limitations of cardiac output. The cerebral and renal-somatic beds have different circulatory control mechanisms that can be manipulated to change the distribution of cardiac output by altering the arterial carbon dioxide tension. Monitoring cerebral and renal circulations with near infrared spectroscopy can provide rational physiologic targets for individualized treatment.

Keywords: NIRS (near infrared reflectance spectroscopy), cerebral oxygenation, regional blood flow, somatic oxygenation, carbon dioxide, neonatal brain, cerebral autoregulation
INTRODUCTION

The neonate undergoes profound changes in pulmonary and systemic circulations over the first week of life, with overlying developmental influences on circulatory controls of cerebral and renal-mesenteric systemic beds (1–4). While both local autoregulatory mechanisms and sympathetic nervous system modulation of regional resistance are present throughout the systemic circulation, the differential physiologic controls over cerebral and somatic regions result from profoundly different magnitudes of these mechanisms. In addition to vulnerabilities related to the transitional circulation and the neonatal myocardium, neonates with univentricular heart disease have vulnerabilities related to decreased ventricular mass, obligate mixing with arterial desaturation, and the pulmonary-systemic tradeoff inherent in parallel circulation (5–8). Such circulatory limitations increase the risk for hypoxic-ischemic injury in both cerebral and renal/somatic circulations (3, 9).

In neonates with univentricular parallel circulatory anatomy, the various systemic regional circulations compete with each other and with the pulmonary circulation. Monitoring cerebral and renal/somatic circulations with near-infrared spectroscopy (NIRS) in neonates before, during, and after surgical palliation of hypoplastic left heart syndrome (HLHS) with the Norwood procedure, has helped uncover circulatory vulnerabilities, describe relationships between monitored parameters and outcomes, and determine targets for intervention (3, 8, 10–14). Both cerebral and renal-somatic organ beds are at risk for hypoxic injury following Norwood palliation of HLHS (9, 11, 15–21). Hypothermic cardiopulmonary bypass produces significant postoperative changes in cerebrovascular resistance (3, 22–27). Resulting early postoperative cerebral desaturation has been linked to later neurodevelopmental delays (11, 28–30). Perioperative renal/somatic desaturation has been associated with acute kidney injury as well as necrotizing enterocolitis (31–33). The combination of arterial blood pressure and renal oxygenation by NIRS can define a low cardiac output condition associated with increased mortality (13).

Modulation of systemic and pulmonary vascular resistance with induced changes in arterial carbon dioxide tension has been utilized to affect systemic-pulmonary balance, with particularly prominent effects noted on the cerebral circulation (34–37). In univentricular parallel circulation, deliberate modulation of regional resistances may be helpful to avoid end-organ injury, since total oxygen delivery may be critically limited (5, 38, 39). In this report, we describe the complex effects of carbon dioxide on systemic cerebral and renal regional circulations in neonates following surgical palliation of HLHS with a Norwood procedure.

MATERIALS AND METHODS

The patient population included neonates with HLHS undergoing a Norwood procedure for arch reconstruction and systemic to pulmonary shunt placement in the first month of life. Patients underwent preoperative stabilization with prostaglandin infusion, and treatment with sedatives, inotropic-vasoactive infusions, and mechanical ventilation as necessary. Monitoring included continuous assessment of arterial oxyhemoglobin saturation (SaO2) by pulse oximetry, mean arterial pressure (MABP) transduced from an umbilical or radial artery catheter, central venous or atrial pressure from an umbilical venous or atrial catheter, and regional tissue oxyhemoglobin saturation by NIRS with probes over the midline-right forehead and right T12 to L2 flank regions for cerebral (rSO2C) and renal-somatic (rSO2R) fields, respectively. Surgical procedures were performed with deep hypothermic cardiopulmonary bypass (CPB) at 18–20 degrees Celsius with pH stat blood gas management, alpha-adrenergic blockade (AAB), and with selective antegrade cerebral perfusion (ACP) to limit duration of deep hypothermic circulatory arrest (DHCA), under high dose opioid based volatile supplemented anesthesia (3, 13, 40–42). Infusions of milrinone, epinephrine, and norepinephrine were titrated prior to weaning from CPB to achieve a calculated systemic vascular resistance index of about 12 Wood units. Physiologic targets following cardiopulmonary bypass included SaO2 75–85%, MABP > 50 mmHg, rSO2C > 50%, rSO2R > 60%. Patients were recovered in the cardiac ICU with continuation of opioid and vasoactive infusions, red blood cell transfusion, elective mechanical ventilation, controlled normothermia, and planned delayed sternal closure to achieve these physiologic goals.

Demographic surgical physiologic and hemodynamic data were collected at hourly intervals for the first post-operative 48h following the Norwood procedure and were stored in a clinical registry with IRB approval. The primary physiologic outcome measures were cerebral (rSO2C) and renal (rSO2R) field saturations, regional venous saturations (SvO2C, SvO2R), and arterio-venous differences (ΔSavO2C, ΔSavO2R) calculated from simultaneous measures using a 25%/75% arterial/venous field saturation model. Arterial blood samples were obtained at standard intervals with linear interpolation for values synchronous with hourly recordings of physiologic monitoring data. Details of measures and derivations are shown in Table 1. Physiologic data were excluded from analysis during periods of extracorporeal circulatory support. Data were summarized as mean plus or minus standard deviation, median and interquartile range and 5–95% confidence intervals.

Univariable fixed-effects models were used to test association of the primary variables regional field saturations and arteriovenous differences with linear and non-linear components for PaCO2 and postoperative time. Multivariable mixed effect models were then used to define associations of primary variables with interactions of PaCO2 and time, using other demographic, treatment, and physiologic measures as covariates. The combined effects of PaCO2 and time on the primary physiologic outcome measures were derived from these models with defined values for covariates and displayed in graphical form. Finally, the adjusted marginal effects of changes in PaCO2 on outcome measures were calculated for each postoperative hour. All models used cross-sectional panel regression methods to allow within-patient and between-patient variance specifications robust to non-independent clustering and non-normality. Model coefficients were expressed with point estimate ± standard error, with significant effects identified at p < 0.05 (*), p < 0.01 (**), and p < 0.001 (****) levels. Analyses were performed using Stata.
TABLE 1 | Sources and formulae for measured and derived physiologic variables.

| Variable         | Definition                                                                 | Source or derivation          |
|------------------|---------------------------------------------------------------------------|-------------------------------|
| SaO2             | Arterial oxyhemoglobin saturation                                         | Masimo SET                   |
| rSO2C            | Regional tissue saturation (cerebral field)                                | Medtronic/Somanetics Invos 5100A pediatric algorithm |
| rSO2R            | Regional tissue saturation (renal-somatic field)                           |                               |
| SvO2C            | Regional venous saturation (cerebral)                                      | SvO2C = (rSO2C – 0.25*SaO2)/0.75 |
| SvO2R            | Regional venous saturation (renal)                                         | SvO2R = (rSO2R – 0.25*SaO2)/0.75 |
| ΔSavO2C          | Regional arteriovenous difference (cerebral)                              |                               |
| ΔSavO2R          | Regional arteriovenous difference (renal)                                 |                               |
| ΔSarSO2C         | Regional arterial-tissue difference (cerebral)                             |                               |
| ΔSarSO2R         | Regional arterial-tissue difference (renal)                                |                               |
| fOERvC           | Regional venous extraction ratio (cerebral)                                | fOERvC = ΔSavO2C/SaO2          |
| fOERvR           | Regional venous extraction ratio (renal)                                  | fOERvR = ΔSavO2R/SaO2          |
| fOERrC           | Regional tissue extraction ratio (cerebral)                                | fOERrC = ΔSarSO2C/SaO2         |
| fOERrR           | Regional tissue extraction ratio (renal)                                  | fOERrR = ΔSarSO2R/SaO2         |
| MABP             | Mean arterial blood pressure                                               | GE Solar                      |
| CVP              | Mean venous or atrial pressure                                             | Radiometer ABL                |
| HR               | Heart rate                                                                |                               |
| PaCO2            | Arterial carbon dioxide                                                   |                               |
| PaO2             | Arterial oxygen tension                                                   |                               |
| pH               | Negative log hydrogen ion                                                 |                               |
| Hgb              | Hemoglobin concentration                                                  |                               |

TABLE 2 | Patient population demographics, operative characteristics, and outcomes.

| Characteristic | All     | Survived | Died   | P-value |
|---------------|---------|----------|--------|---------|
| N (%)         | 178 (100%) | 168 (94%) | 10 (5.6%) | 0.368    |
| Weight at S1P (kg) | 3.20 (0.70) | 3.20 (0.71) | 3.15 (1.04) | 0.121    |
| Age at S1P (days) | 7.0 (4.0) | 7.00 (4.00) | 9.50 (6.00) | 0.001    |
| Gender: Male    | 104 (58%) | 100 (60%) | 4 (40%) | 0.224    |
| Gestational age (weeks) | 38.0 (1.0) | 38.0 (1.0) | 38.0 (1.8) | 0.001    |
| CPB time (minutes) | 188 (44) | 188 (43) | 168 (88) | 0.702    |
| DhCA time (minutes) | 12 (8) | 12 (8) | 12 (15) | 0.383    |
| Shunt type: MVTS | 95 (63%) | 91 (54%) | 4 (40%) | 0.001    |
| RVPA            | 83 (47%) | 77 (46%) | 6 (60%) | 0.383    |
| ECMO support yes | 7 (4%) | 4 (2%) | 3 (30%) | <0.001   |
| No              | 171 (96%) | 164 (98%) | 7 (70%) | 0.001    |
| Hospital LOS (days) | 38 (35) | 38 (34) | 52 (85) | 0.795    |

Data are presented as median (interquartile range) and interval or count (percent). Data were excluded from analysis during ECMO and operative support, yielding an analysis set of 178 patients, with 168 (94%) operative survival through hospital discharge. Differences between survivors and non-survivors are summarized by significance testing.

RESULTS

Population

The study population was derived from 195 neonates with postoperative cerebral and renal NIRS monitoring, with operative survival in 176 (90.3%). Data were analyzable from 178 patients after exclusion of 17 patients requiring continuous ECMO support in the first 48 h following operative intervention. This analysis population had slightly higher weight at operation, with less total CPB support time, with differences shown in Supplementary Table S1. Survival in the analysis population was 94%, with ECMO used in 2% of survivors vs. 30% of non-survivors Complete population demographic and operative characteristics are shown in Table 2.

Summary Statistics and Variation

The analysis set comprised 7,644 h of data with an average of 43 h per patient. Postoperative hemodynamic state was characterized by mean SaO2 83.0 ± 4.9%, MABP 49.8 ± 5.4 mmHg, CVP 9.6 ± 2.2 mmHg, and hemoglobin 16 ± 1.5 g/dl. Regional saturations were rSO2C 65.9 ± 9.6% and rSO2R 75.9 ± 8.7%, with arteriovenous differences ΔSavO2C 23.3 ± 11.2% and ΔSavO2R 9.4 ± 11.6%. The SaO2 had the lowest overall variability, with regional saturations rSO2C and rSO2R nearly twice as variable. The measures of regional flow (arteriovenous...
TABLE 3 | Summary of physiologic parameters.

| Variable | P50 | IQR | P5 | P95 | SK | Mean | SD | SD(W) | SD(B) | (W/B) | CV | CV(W) |
|----------|-----|-----|----|-----|----|------|----|-------|-------|-------|----|-------|
| SaO2     | 83.0| 6.0 | 75.0| 91.0| −0.43| 83.0 | 4.9| 3.8    | 3.4    | 1.11  | 0.06 | 0.07  |
| rSO2C    | 66.0| 11.0| 51.0| 79.0| −0.24| 65.9 | 8.6| 5.6    | 7.6    | 0.79  | 0.13 | 0.10  |
| rSO2R    | 77.0| 11.0| 60.0| 89.0| −0.56| 75.9 | 8.7| 5.9    | 6.7    | 0.89  | 0.11 | 0.10  |
| SvO2C    | 60.3| 14.3| 40.7| 77.0| −0.25| 59.8 | 11.0| 7.2    | 8.9    | 0.81  | 0.18 | 0.15  |
| SvO2R    | 74.7| 14.7| 53.3| 90.0| −0.62| 73.6 | 11.3| 7.8    | 8.5    | 0.91  | 0.15 | 0.14  |
| ΔSaO2C   | 22.7| 14.7| 5.3 | 42.7| 0.32 | 23.3 | 11.2| 7.9    | 8.2    | 0.96  | 0.48 | 0.46  |
| ΔSavO2R  | 8.0 | 14.7| −8.0| 30.7| 0.70 | 9.4  | 11.7| 8.5    | 8.2    | 1.03  | 1.23 | 1.27  |
| ΔSavO2C  | 17.0| 11.0| 4.0 | 32.0| 0.32 | 17.4 | 8.4 | 5.9    | 6.2    | 0.96  | 0.48 | 0.46  |
| ΔSarO2C  | 6.0 | 11.0| −6.0| 23.0| 0.70 | 7.1  | 8.8 | 6.4    | 6.2    | 1.03  | 1.23 | 1.27  |
| rOERc    | 0.3 | 0.2 | 0.1 | 0.5 | 0.24 | 0.24 | 0.10| 0.07   | 0.07   | 1.00  | 0.47 | 0.47  |
| rOERr    | 0.1 | 0.2 | −0.1| 0.4 | 0.55 | 0.11 | 0.11| 0.08   | 0.08   | 1.07  | 1.24 | 1.33  |
| rOERcc   | 0.2 | 0.1 | 0.1 | 0.4 | 0.24 | 0.21 | 0.10| 0.07   | 0.07   | 0.92  | 0.47 | 0.43  |
| rOERRc   | 0.1 | 0.1 | −0.1| 0.3 | 0.55 | 0.08 | 0.10| 0.07   | 0.07   | 1.01  | 1.24 | 1.25  |
| PaCO2    | 47.0| 10.4| 36.4| 62.9| 0.78 | 48.1 | 8.2 | 6.2    | 6.0    | 1.03  | 0.17 | 0.18  |
| PaO2     | 46.6| 6.4 | 38.6| 56.4| 0.57 | 46.9 | 5.4 | 3.5    | 4.3    | 0.83  | 0.12 | 0.10  |
| pH       | 7.4 | 0.1 | 7.2 | 7.5 | −0.50| 7.36 | 0.08| 0.06   | 0.06   | 1.02  | 0.01 | 0.01  |
| MABP     | 50.0| 7.0 | 41.0| 60.0| 0.40 | 49.8 | 5.7 | 4.3    | 4.2    | 1.02  | 0.11 | 0.11  |
| CVP      | 10.0| 3.0 | 6.0 | 13.0| 0.18 | 9.6  | 2.2 | 1.6    | 1.6    | 1.01  | 0.23 | 0.23  |
| HR       | 173.0| 18.0| 150.0| 195.0| −0.01| 173 | 13.7| 9.6    | 10.9   | 0.88  | 0.08 | 0.07  |
| Hb       | 15.9| 2.0 | 13.7| 18.6| 0.16 | 16.0 | 1.5 | 1.1    | 1.1    | 1.00  | 0.09 | 0.09  |

Data were collected for 48 postoperative hours in 172 patients for a total of 7644 hourly measures. Variables are summarized by P50, median; IQR, interquartile range; P5, 5th percentile value; P95, 95th percentile value; SK, skewness; SD, mean, standard deviation; SD-W, within-subject standard deviation; SD-B, between-subject standard deviation; W/B, ratio of within-subject vs. between-subject coefficient of variation; CV, coefficient of variation; CV(W), within-patient component of the coefficient of variation.

differences and fractional extraction) showed the greatest overall variation. Variance partitioning revealed a range of within-patient and between-patient variance components. Measures of PaCO2 and cerebral oxygenation and flow showed the most between-patient variation, while SaO2 showed the most within-patient variability, followed by renal arteriovenous difference. Details of physiologic parameters including components of deviation between and within patients are shown in Table 3.

Temporal Trends
Time-dependent changes in arterial and regional oxygenation were evident in univariable models. The SaO2 gradually increased over time (linear slope term 0.12 ± 0.01%/h, p < 0.001) in the early postoperative period. This increase was largely paralleled by the cerebral rSO2C (slope 0.55 ± 0.02%/h, p < 0.001), while the renal rSO2R did not change significantly (slope −0.01 ± 0.01%/h, p = 0.578). The time-dependent changes were opposite in direction for ΔSavO2C (−0.57 ± 0.03%/h, p < 0.001) vs. ΔSavO2R (+0.16 ± 0.03%/h, p < 0.001). These differential changes emphasize the importance of both the arterial oxygen content and regional vascular controls as determinants of regional oxygenation (see Figure 1).

Univariable Models of PaCO2 Effects
Associations of regional measures with arterial PaCO2 were tested first in univariable models. There was positive association of cerebral rSO2C with PaCO2 (linear slope term = +0.54 ± 0.07%/torr, p < 0.001), while the relationship for somatic rSO2R with PaCO2 was not significant (slope −0.02 ± 0.07%/torr, p = 0.769), and the relationship for arterial saturation with PaCO2 was inverse (linear slope −0.175, p < 0.001). The relationship between PaCO2 and rSO2C also showed significant non-linearity, with maximal rSO2C occurring with PaCO2 in the 45–55 torr range. Over the PaCO2 range of 25–60 torr, the average rSO2C change was +12% (56.2 ± 1.2 to 68.8 ± 0.6, p < 0.001), while the average renal rSO2R change was −9% (80.8 ± 1.3 to 71.4 ± 0.8, p < 0.001). The slope change with PaCO2 was significantly negative for ΔSavO2C (slope −0.77 ± 0.10, p < 0.001), but not significant for ΔSavO2R (−0.11 ± 0.10, p = 0.186). The cerebral and renal regions showed distinctly different baseline patterns of saturation and blood flow, with the cerebral region showing lower saturation and wider arteriovenous difference over the range of PaCO2 compared to the renal region, despite differential changes with PaCO2 (see Figure 2).

Time-Dependent PaCO2 Effects
Complex interactions were observed between the effects of PaCO2 and time on regional oxygenation and flow measures. Compared to hours 24–48, the first 12 postoperative hours showed the average cerebral rSO2C was 7% lower (60.2 ± 0.2 vs. 67.6 ± 0.3, p < 0.001), renal rSO2R was 3% higher (77.6 ± 0.4 vs. 74.2 ± 0.4, p < 0.001), cerebral ΔSavO2C was 7% larger (29.1 ± 0.5 vs. 21.4 ± 0.4, p < 0.001), and renal ΔSavO2R was 7% smaller (5.9 ± 0.6 vs. 12.9 ± 0.5, p < 0.001). Compared
to hours 24–48, the effect of PaCO2 over the range 25–60 torr during the first 12 postoperative hours on cerebral rSO2C was 6% greater (+15.1 ± 2.0 vs. +9.5 ± 1.5, p < 0.001), and the effect on renal rSO2 was 3% lower (−6.7 ± 2.4 vs. −10.4 ± 1.9, p < 0.036). During the first 12 postoperative hours, a PaCO2 > 55 torr was necessary to achieve a cerebral rSO2 of 60%, while this target could be met with PaCO2 of 40 torr after the first 24 h. Overall, the differences between PaCO2 effect on cerebral and renal regional measures was greater in the early postoperative period. A graphical summary is presented in Figure 3.

**Multivariable Models**

Multivariable models were used to reveal the influence of individual factors on observed changes in regional oxygenation and blood flow as observed over time. The effects of PaCO2 and postoperative time were determined with a complex interaction expression to allow for non-linearity. Multiple factors had significant individual effects, some with differential effects for cerebral and renal regional measures. The known determinants of tissue oxygen delivery (SaO2, MABP, and Hb) all showed significant effects. For all primary dependent variables, there were significant independent effects of PaCO2 (alone and interacted with time) after controlling for these other factors. Neither shunt type nor survival status had influence on regional oxygenation or flow measures in multivariable models. The simplified model results are summarized in Table 4, and the complete models are shown in Supplementary Table S2.

**Time-Dependent Multivariable Effects**

These complex time-dependent non-linear effects of PaCO2 were simplified by computing the instantaneous slope of the change in regional saturation measure per unit change in PaCO2 at each hour with other covariates held constant at realistic clinical values near their observed means (SaO2 = 83%, MABP = 51 mmHg, Hb = 15 gm/dl, weight = 3.2 kg, and age = 8 days). The average expected response to a 1-unit increase in PaCO2 on cerebral rSO2C was positive (+0.350 ± 0.017, CI: 0.316 to 0.384, p < 0.001), while the expected response on renal rSO2R was negative (−0.220 ± 0.020, CI: −0.258 to −0.182, p < 0.001). For arteriovenous difference, the expected response on cerebral

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**FIGURE 1** | Changes in regional oxygenation and arteriovenous difference with time in univariable models.

**FIGURE 2** | Changes in regional oxygenation and arteriovenous difference with arterial PaCO2 in univariable models.

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**FIGURE 3** | Graphical summary of multivariable model results.
\( \Delta \text{SavO}_2 \)C was negative \((-0.467 \pm 0.023, CI: -0.512 to -0.422, p < 0.001)\), while the response on renal \( \Delta \text{SavO}_2 \)R was positive \((+0.293 \pm 0.026, CI: 0.242 to 0.344, p < 0.001)\). These expressions clarify the differential effects of changes in PaCO2 on regional circulations, with a change in PaCO2 consistently resulting in opposite effects on cerebral vs. renal circulations. The magnitude of these responses changed significantly over time, with cerebral effects highest in the first 18 postoperative hours, and renal effects reaching a maximum at 18–32 postoperative hours, as shown in Figure 4. The differences in both baseline oxygenation and time-dependent effects of PaCO2 are evident as distinct surface representations of regional circulations in Figure 5.

**DISCUSSION**

This study used NIRS to measure cerebral and renal/somatic oxygenation and blood flow following the Norwood procedure in nearly 200 neonates. Several novel observations were evident in this study. The major finding was the differential effect of changes in PaCO2 on cerebral and renal/somatic oxygenation and blood flow. These findings are consistent with known effect of increasing PaCO2 on cerebral vasodilation \((34, 43, 44)\) and pulmonary vasoconstriction \((45, 46)\), both of which might increase cerebral blood flow \((47–50)\). However, the reduction in renal/somatic blood flow with increased PaCO2 suggests that the effects of PaCO2 on the pulmonary circulation were not predominant, and an alternative mechanism might be at work. If total systemic blood flow is relatively constant, then a reduction in cerebrovascular resistance with increased PaCO2 will divert blood flow from renal/somatic to the cerebral bed, consistent with the effects we observed. Our findings suggest that manipulation of PaCO2 is an intervention to alter the distribution of systemic blood flow by exploiting the differential sensitivity of cerebral and renal circulations to PaCO2, particularly when total systemic flow is limited.

The effects of CO2 exhibited significant time-dependence, with increased CO2 sensitivity of the cerebral circulation in the early postoperative period. This finding might be related to the pH-stat CPB management strategy that utilizes deliberate induction of extreme hypercapnia \((\text{PaCO}_2 80–100 \text{ torr})\) to counteract the leftward shift in oxyhemoglobin affinity during deep hypothermia. Regardless of duration of whole-body CPB, ACP, or DHCA, these patients were treated using pH-stat blood gas management strategies to maintain tissue oxygen tension during all phases of deep hypothermia. Hysteresis in the CO2-cerebrovascular resistance relationship \((45)\) could therefore explain the observed shift over the first postoperative day. These observations suggest that targeted modulation of PaCO2 with deliberate hypercapnia in the early postoperative period is a physiologically rational strategy to normalize cerebral hemodynamics following significant exposure to pH-stat hypothermic CPB.

The observed relationships of Hb and SaO2 on regional oxygenation and blood flow were largely consistent with known effects and each contributed significantly to oxygenation in both cerebral and renal fields. The regression coefficient for SaO2 on both rSO2C and rSO2R was very close to the theoretical 25% arterial contribution to field saturation from the NIRS device calibration supporting the generalizability of the validation model \((51–57)\). This empiric validation of the model also implies corresponding accuracy for derivation of regional venous saturation, arteriovenous difference, and fractional extraction by applying this model to synchronous SaO2 and rSO2 measures.

The differential relationship of MABP to cerebral and renal oxygenation deserves comments. Univentricular parallel circulation is characterized by an accentuated flow-resistance tradeoff in the systemic circulation, particularly in mesenteric and renal beds. Activation of the sympathetic nervous system with mesenteric/renal vasoconstriction is common following major operative intervention, contributing to systemic hypoperfusion, cellular hypoxia and shock even with preservation of blood pressure \((40, 58, 59)\). We have previously described a potential flow-pressure tradeoff \((60)\) and low cardiac output state utilizing renal NIRS \((13)\) following the Norwood procedure with a more complex relationship on renal oxygenation described herein. Pressure autoregulation...
Supplemental Table S2

Model parameters are shown in coefficients combining non-linear and linear independent factors are presented for clarity. Non-linear effects were included for PaCO2, hour, and the interaction (#). Simplified coefficients are expressed as point estimates and (standard error), with significance designated at \( p<0.05 \) (*), \( p<0.01 \) (**), and \( p<0.001 \) (***)

| Coefficient/Model | rSO2C | rSO2R | ΔSavO2C | ΔSavO2R |
|-------------------|-------|-------|---------|---------|
| SaO2              | 0.190*** | 0.203*** | 1.060*** | 1.063*** |
|                  | (0.0160) | (0.0181) | (0.0213) | (0.0241) |
| MABP              | 0.160*** | 0.165*** | −0.213*** | −0.230*** |
|                  | (0.0145) | (0.0164) | (0.0194) | (0.0219) |
| Hb                | 0.673*** | 0.904*** | −0.897*** | −1.205*** |
|                  | (0.0531) | (0.0601) | (0.0708) | (0.0802) |
| PaCO2             | 0.989*** | 0.412* | −1.318*** | −0.549*** |
|                  | (0.143) | (0.162) | (0.191) | (0.215) |
| Hour              | 0.457 (0.397) | 1.775*** | −0.610 | −2.366*** |
|                  | (0.443) | (0.530) | (0.591) |       |
| (IPaCO2) (# (PaCO2)) | −0.00650*** | −0.00464** | 0.00866*** | 0.00192** |
|                  | (0.00127) | (0.00143) | (0.00169) | (0.00190) |
| (All & PaCO2)     | 0.982*** | 0.407*** | −1.310*** | −0.543*** |
|                  | (0.142) | (0.160) | (0.189) | (0.214) |
| (All & hour)      | 0.462 (0.390) | 1.739*** | −0.616 | −2.318*** |
|                  | (0.435) | (0.520) | (0.550) |       |
| (All PaCO2 & hour)| 1.454*** | 2.085*** | −1.938*** | −2.780*** |
|                  | (0.498) | (0.557) | (0.664) | (0.743) |
| Heart rate        | −0.0396*** | −0.145*** | 0.0528*** | 0.193*** |
|                  | (0.00632) | (0.00713) | (0.00842) | (0.00960) |
| CVP               | −0.0896* | −0.685*** | 0.119* | 0.913*** |
|                  | (0.0359) | (0.0407) | (0.0479) | (0.0542) |
| Weight            | 0.0700 | 1.961*** | −0.0934 | −2.614** |
|                  | (0.0330) | (0.0692) | (1.118) | (0.923) |
| Age               | −0.627*** | −0.357*** | 0.836*** | 0.476*** |
|                  | (0.0097) | (0.0262) | (0.130) | (0.111) |
| Gender (female)   | −0.365 | 0.738 | 0.486 (1.207) | −0.984 |
|                  | (0.905) | (0.748) | (0.520) | (0.997) |
| CPB time          | −0.0102 | −0.0202** | 0.0136 | 0.0271** |
|                  | (0.00923) | (0.00766) | (0.0123) | (0.0102) |
| DHCA time         | −0.143* | −0.108* | 0.190* | 0.144* |
|                  | (0.0662) | (0.0548) | (0.0883) | (0.0731) |
| Shunt type (RVPA) | −0.00761 | −0.700 | 0.0101 | 0.933 |
|                  | (0.0890) | (0.743) | (0.118) | (0.991) |
| ACP + AAB         | −1.679 | 7.507*** | 2.239 (4.522) | −10.01*** |
|                  | (3.391) | (2.798) | (3.731) |       |
| Survival (constant) | −2.052 | −1.883 | 2.737 (2.521) | 2.510 |
|                  | (1.891) | (1.588) | (2.114) |       |
| N                 | 7644 | 7606 | 7644 | 7606 |
| R2 (overall)      | 0.211 | 0.356 | 0.203 | 0.371 |
| R2 (between)      | 0.161 | 0.459 | 0.0564 | 0.382 |
| R2 (within)       | 0.320 | 0.221 | 0.397 | 0.326 |
| Rho               | 0.593 | 0.430 | 0.593 | 0.430 |

Coefficients are expressed as point estimates and (standard error), with significance designated at \( p<0.05 \) (*), \( p<0.01 \) (**), and \( p<0.001 \) (***)

Non-linear effects were included for PaCO2, hour, and the interaction (#). Simplified coefficients combining non-linear and linear independent factors are presented for clarity (8) but the separate factors were used in regression models. The complete regression model parameters are shown in Supplemental Table S2.

for cerebral circulation undergoes important developmental changes, and can be impaired by hypothermia and hypercapnia (37, 61–64). The positive association between MABP and rSO2C could be explained by MABP below a theoretical lower limit of autoregulation or with impairment of autoregulation by the above mechanisms. Cerebral pressure autoregulation is likely more continuously variable than absolute (26, 62, 65, 66).

Postnatal age showed a small but significant negative relationship with cerebral rSO2C, even though age at operation was relatively tightly constrained. This postnatal decrease in rSO2C has been previously described in healthy neonates, ascribed to an increase in cerebral metabolic rate following birth. These findings suggest potential advantage of operation at younger age. Although CPB time had no apparent effect, this may be related to potential protective effects of antegrade cerebral perfusion and alpha-adrenergic blockade. These effects were measurable in the renal circulation with associated increased rSO2R and lower ΔSavO2.

Although the RV-PA (Sano) shunt type has been associated with better early survival (67, 68) possibly related to improved myocardial oxygen supply-demand balance, the global hemodynamic effects of the RV-PA shunt are not clearly different from the MBT shunt, with very similar mean arterial pressure and saturations (69–71). Accordingly, we found no influence of shunt type on determinants of regional saturation or blood flow in multivariable models. Similarly, we did not find a difference related to survival status, suggesting that regional circulator controls may not be important determinants of survival. However, this study cannot directly answer whether specific manipulation of PaCO2 to alter oxygenation and blood flow in regional circulations could also alter outcomes.

Like all patients with complete mixing of pulmonary and systemic venous blood, neonates with HLHS following a Norwood procedure will have significant hemoglobin desaturation in arterial blood, adding to risk of impaired systemic oxygen delivery, but limiting exposure of tissues to hypoxic conditions, especially compared to normal and preterm neonates (72–76). Although changes in both PaO2 and PaCO2 during re-oxygenation following birth and resuscitation have the potential to cause tissue injury through free radical pathways (77–80), this concern may have more relevance during cardiopulmonary bypass, ECMO support, or beyond the extremes of PaCO2 and PaO2 observed in this report (Table 3). Given the 5–95% intervals of PaCO2 (36–63 torr), PaO2 (38–56 torr), and SaO2 (75–91%), we would not expect significant effect of CO2 manipulation on tissue redox states or free radical generation. Both hypocapnia and hypercapnia have been associated with risk of cerebral injury in premature neonates, especially when rapid or extreme, with alteration in cerebral vascular resistance as a potential mechanism. This report describes the changes in both cerebral and renal-somatic blood flow and oxygenation associated with changes in PaCO2, and these regional NIRS measures would be thus rational targets for goal-directed ventilation strategies including dynamic manipulation of PaCO2.
The observational nature of this study is its major weakness. However, the population size and longitudinal data collection methods make the sample large enough for application of complex multivariable methods. Although multivariable multilevel and within-subject techniques were used to reduce bias and confounding, only limited causal association can be inferred. The population was restricted to patients with HLHS, undergoing Norwood repair utilizing deep hypothermic CPB, with known circulatory limitations. Although the findings are consistent with known physiologic mechanisms, caution should be observed when generalizing the observed effects to patients with other conditions and treatment strategies.

In summary, we found that arterial PaCO2 had differential effects on cerebral and renal circulation in neonates with HLHS following the Norwood procedure. The effects are measurable with a monitoring strategy that utilizes cerebral and somatic NIRS, thus facilitating individualized goal-directed interventions (81, 82).

**DATA AVAILABILITY STATEMENT**

The data analyzed in this study is subject to the following licenses/restrictions: a subset of the dataset will be available by contacting the corresponding author. Requests to access these datasets should be directed to George M. Hoffman, ghoffman@mcw.edu.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Children's Hospital of Wisconsin Institutional Review Board.
Review Board. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GH was responsible for conception and design of the study, database maintenance, statistical analysis, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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