



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 48 h 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 (Δ SavO₂C, Δ SavO₂R) 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 \pm 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
SaO ₂	Arterial oxyhemoglobin saturation	Masimo SET
rSO ₂ C	Regional tissue saturation (cerebral field)	Medtronics/Somanetics Invos 5100A
rSO ₂ R	Regional tissue saturation (renal-somatic field)	pediatric algorithm
SvO ₂ C	Regional venous saturation (cerebral)	$SvO_2C = (rSO_2C - 0.25 \cdot SaO_2) / 0.75$
SvO ₂ R	Regional venous saturation (renal)	$SvO_2R = (rSO_2R - 0.25 \cdot SaO_2) / 0.75$
ΔSavO ₂ C	Regional arteriovenous difference (cerebral)	$\Delta SavO_2C = SaO_2 - SvO_2C$
ΔSavO ₂ R	Regional arteriovenous difference (renal)	$\Delta SavO_2R = SaO_2 - SvO_2R$
ΔSarSO ₂ C	Regional arterial-tissue difference (cerebral)	$\Delta SarSO_2C = SaO_2 - rSO_2C$
ΔSarSO ₂ R	Regional arterial-tissue difference (renal)	$\Delta SarSO_2R = SaO_2 - rSO_2R$
fOERvC	Regional venous extraction ratio (cerebral)	$fOERvC = \Delta SavO_2C / SaO_2$
fOERvR	Regional venous extraction ratio (renal)	$fOERvR = \Delta SavO_2R / SaO_2$
fOERrC	Regional tissue extraction ratio (cerebral)	$fOERrC = \Delta SarSO_2C / SaO_2$
fOERrR	Regional tissue extraction ratio (renal)	$fOERrR = \Delta SarSO_2R / SaO_2$
MABP	Mean arterial blood pressure	GE Solar
CVP	Mean venous or atrial pressure	
HR	Heart rate	
PaCO ₂	Arterial carbon dioxide	Radiometer ABL
PaO ₂	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%)	
Weight at S1P (kg)	3.20 (0.70) (2.90–3.60)	3.20 (0.71) (2.90–3.61)	3.15 (1.04) (2.52–3.56)	0.368
Age at S1P (days)	7.0 (4.0) (5.0–9.0)	7.00 (4.00) (5.0–9.0)	9.50 (6.00) (5.5–11.5)	0.121
Gender:				
Male	104 (58%)	100 (60%)	4 (40%)	0.224
Female	74 (42%)	68 (40%)	6 (60%)	
Gestational age (weeks)	38.0 (1.0) (38.0–39.0)	38.0 (1.0) (38.0–39.0)	38.0 (1.8) (37.0–38.8)	0.306
CPB time (minutes)	168 (44) (148–192)	168 (43) (148–191)	168 (88) (160–248)	0.213
DHCA time (minutes)	12 (8) (8–16)	12 (8) (8–16)	12 (15) (7–22)	0.702
Shunt type:				
MBTS	95 (53%)	91 (54%)	4 (40%)	0.383
RVPA	83 (47%)	77 (46%)	6 (60%)	
ECMO support				
yes	7 (4%)	4 (2%)	3 (30%)	<0.001
No	171 (96%)	164 (98%)	7 (70%)	
Hospital LOS (days)	38 (38) (28–66)	38 (34) (28–62)	52 (85) (25–111)	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.

Software (v17, RRID:SCR_012763) and Python Programming Language (v3.8, RRID:SCR_008394).

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 gm/dl. Regional saturations were rSO₂C 65.9 ± 8.6% 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)
SaO ₂	83.0	6.0	75.0	91.0	-0.43	83.0	4.9	3.8	3.4	1.11	0.06	0.07
rSO ₂ C	66.0	11.0	51.0	79.0	-0.24	65.9	8.6	5.6	7.6	0.79	0.13	0.10
rSO ₂ R	77.0	11.0	60.0	89.0	-0.56	75.9	8.7	5.9	6.7	0.89	0.11	0.10
SvO ₂ C	60.3	14.3	40.7	77.0	-0.25	59.8	11.0	7.2	8.9	0.81	0.18	0.15
SvO ₂ R	74.7	14.7	53.3	90.0	-0.62	73.6	11.3	7.8	8.5	0.91	0.15	0.14
ΔSavO ₂ C	22.7	14.7	5.3	42.7	0.32	23.3	11.2	7.9	8.2	0.96	0.48	0.46
ΔSavO ₂ R	8.0	14.7	-8.0	30.7	0.70	9.4	11.7	8.5	8.2	1.03	1.23	1.27
ΔSarO ₂ C	17.0	11.0	4.0	32.0	0.32	17.4	8.4	5.9	6.2	0.96	0.48	0.46
ΔSarO ₂ R	6.0	11.0	-6.0	23.0	0.70	7.1	8.8	6.4	6.2	1.03	1.23	1.27
fOERvC	0.3	0.2	0.1	0.5	0.24	0.24	0.10	0.07	0.07	1.00	0.47	0.47
fOERvR	0.1	0.2	-0.1	0.4	0.55	0.11	0.11	0.08	0.08	1.07	1.24	1.33
fOERrC	0.2	0.1	0.1	0.4	0.24	0.21	0.10	0.07	0.07	0.92	0.47	0.43
fOERrR	0.1	0.1	-0.1	0.3	0.55	0.08	0.10	0.07	0.08	1.01	1.24	1.25
PaCO ₂	47.0	10.4	36.4	62.9	0.78	48.1	8.2	6.2	6.0	1.03	0.17	0.18
PaO ₂	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, P95th percentile value; SK, skewness; SD, mean, standard deviation; SD-W, within-subject standard deviation; SD-B, between-subject standard deviation; SD, 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 $0.12 \pm 0.01\%/h$, $p < 0.001$) in the early postoperative period. This increase was largely paralleled by the cerebral rSO₂C (slope $0.55 \pm 0.02\%/h$, $p < 0.001$), while the renal rSO₂R did not change significantly (slope $-0.01 \pm 0.01\%/h$, $p = 0.578$). The time-dependent changes were opposite in direction for ΔSavO₂C ($-0.57 \pm 0.03\%/h$, $p < 0.001$) vs. ΔSavO₂R ($+0.16 \pm 0.03\%/h$, $p < 0.001$). These differential changes emphasize the importance of both the arterial oxygen content and regional vascular controls as determinants of regional oxygenation (see **Figure 1**).

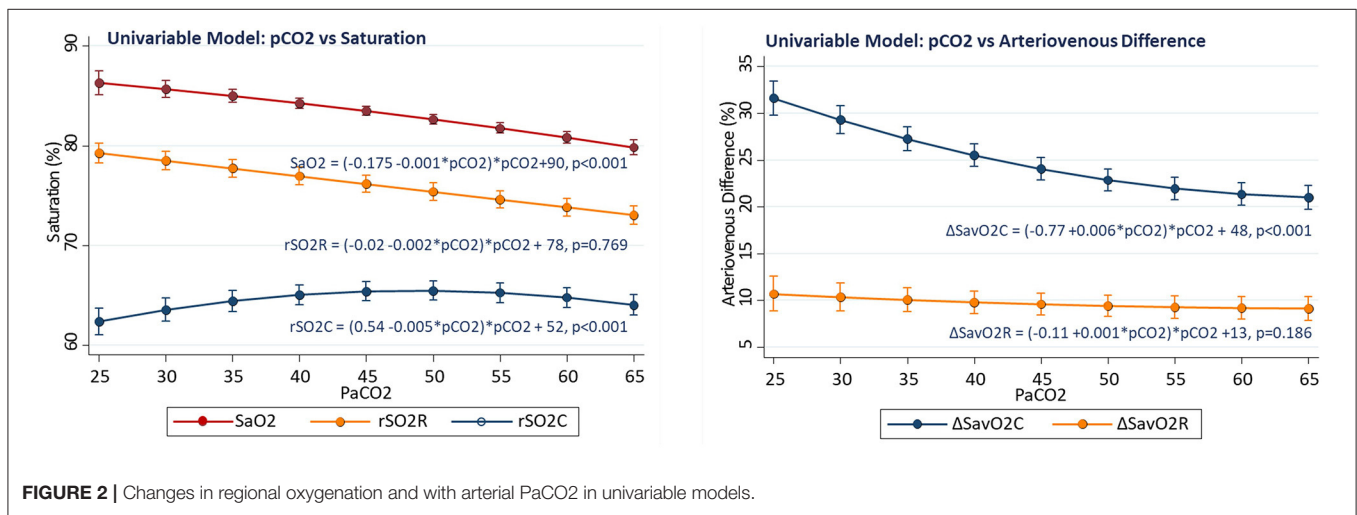
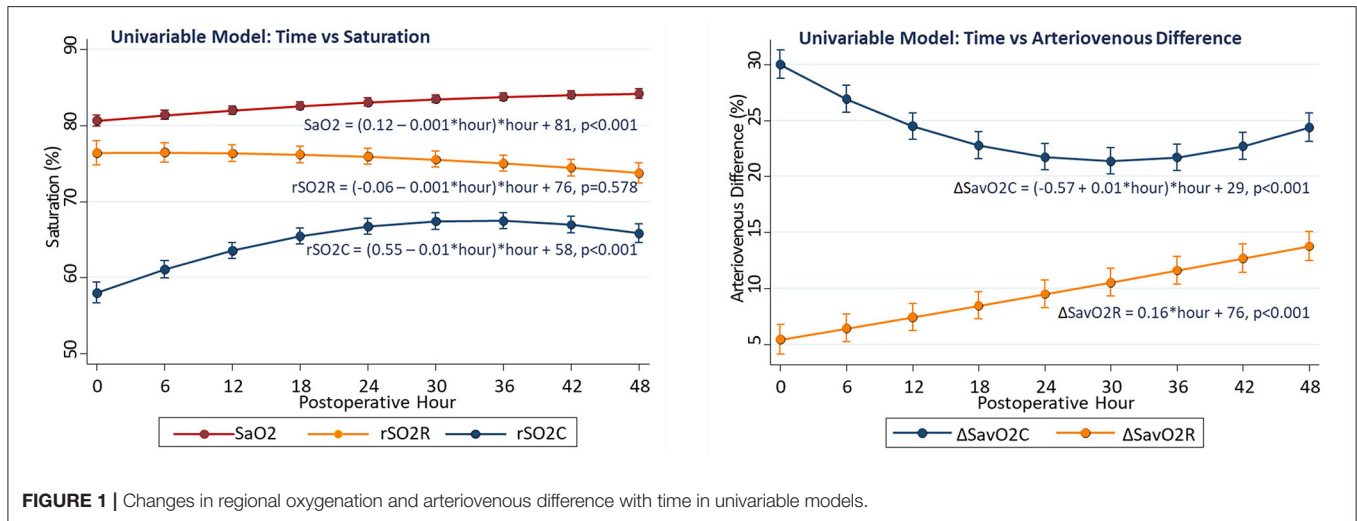
Univariable Models of PaCO₂ Effects

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 = $+0.54 \pm 0.07\%/torr$, $p < 0.001$), while the relationship for somatic

rSO₂R with PaCO₂ was not significant (slope $-0.02 \pm 0.07\%/torr$, $p = 0.769$), 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 ($+15.1 \pm 2.0$ vs. $+9.5 \pm 1.5, p < 0.001$), and the effect on renal rSO2 was 3% lower (-6.7 ± 2.4 vs. $-10.4 \pm 1.9, p < 0.036$). 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**.

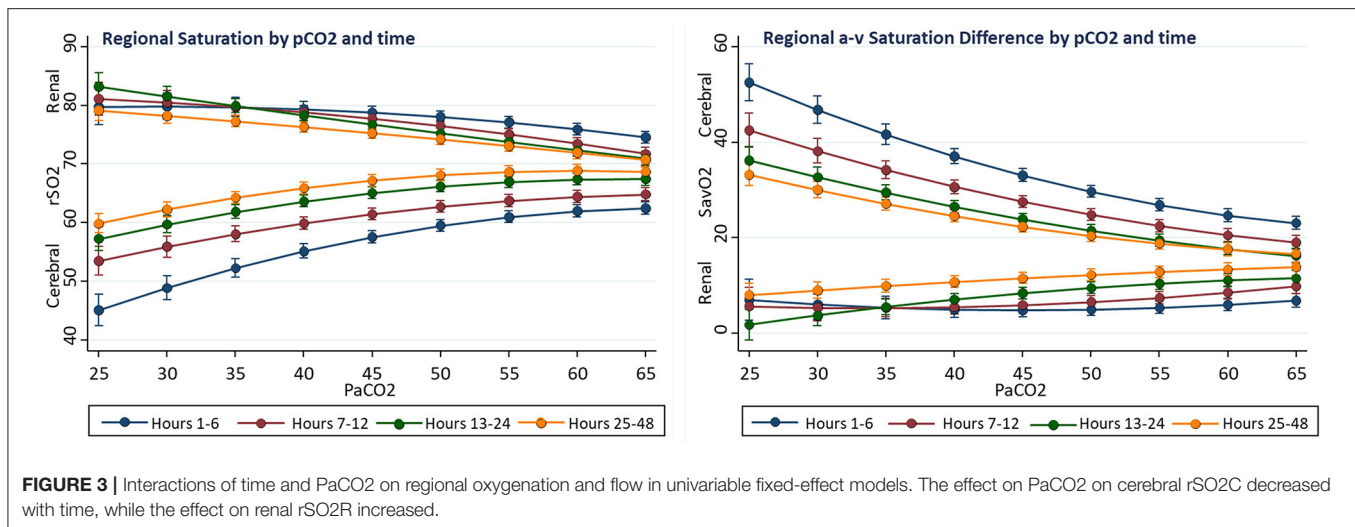
Multivariable Models

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 ($+0.350 \pm 0.017, \text{CI: } 0.316 \text{ to } 0.384, p < 0.001$), while the expected response on renal rSO2R was negative ($-0.220 \pm 0.020, \text{CI: } -0.258 \text{ to } -0.182, p < 0.001$). For arteriovenous difference, the expected response on cerebral



Δ SavO₂C was negative (-0.467 ± 0.023 , CI: -0.512 to -0.422 , $p < 0.001$), while the response on renal Δ SavO₂R 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 (PaCO₂ 80–100 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

TABLE 4 | Multivariable regression results.

Coefficient/ Model	rSO ₂ C	rSO ₂ R	ΔSavO ₂ C	ΔSavO ₂ R
SaO ₂	0.190*** (0.0160)	0.203*** (0.0181)	1.080*** (0.0213)	1.063*** (0.0241)
MABP	0.160*** (0.0145)	0.165*** (0.0164)	-0.213*** (0.0194)	-0.220*** (0.0219)
Hb	0.673*** (0.0531)	0.904*** (0.0601)	-0.897*** (0.0708)	-1.205*** (0.0802)
PaCO ₂	0.989*** (0.143)	0.412* (0.162)	-1.318*** (0.191)	-0.549* (0.215)
Hour	0.457 (0.397)	1.775*** (0.443)	-0.610 (0.530)	-2.366*** (0.591)
((PaCO ₂) # (PaCO ₂))	-0.00650*** (0.00127)	-0.00464** (0.00143)	0.00866*** (0.00169)	0.00619** (0.00190)
(All & PaCO ₂)	0.982*** (0.142)	0.407*** (0.160)	-1.310*** (0.189)	-0.543** (0.214)
(All & hour)	0.462 (0.390)	1.739*** (0.435)	-0.616 (0.520)	-2.318*** (0.580)
(All PaCO ₂ & hour)	1.454*** (0.498)	2.085*** (0.557)	-1.938*** (0.664)	-2.780*** (0.743)
Heart rate	-0.0396*** (0.00632)	-0.145*** (0.00713)	0.0528*** (0.00842)	0.193*** (0.00950)
CVP	-0.0896* (0.0359)	-0.685*** (0.0407)	0.119* (0.0479)	0.913*** (0.0542)
Weight	0.0700 (0.838)	1.961** (0.692)	-0.0934 (1.118)	-2.614** (0.923)
Age	-0.627*** (0.0997)	-0.357*** (0.0825)	0.836*** (0.133)	0.476*** (0.110)
Gender (female)	-0.365 (0.905)	0.738 (0.748)	0.486 (1.207)	-0.984 (0.997)
CPB time	-0.0102 (0.00923)	-0.0203** (0.00765)	0.0136 (0.0123)	0.0271** (0.0102)
DHCA time	-0.143* (0.0662)	-0.108* (0.0548)	0.190* (0.0883)	0.144* (0.0731)
Shunt type (RVPA)	-0.00761 (0.898)	-0.700 (0.743)	0.0101 (1.198)	0.933 (0.991)
ACP+AAB	-1.679 (3.391)	7.507** (2.798)	2.239 (4.522)	-10.01** (3.731)
Survival	-2.052 (1.891)	-1.883 (1.586)	2.737 (2.521)	2.510 (2.114)
(constant)	7.543 (6.921)	55.72*** (6.717)	-10.06 (9.228)	-74.29*** (8.956)
N	7644	7606	7644	7606
R ² (overall)	0.211	0.356	0.203	0.371
R ² (between)	0.161	0.459	0.0564	0.382
R ² (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 (&) 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 hyperoxic conditions, especially compared to normal term 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.

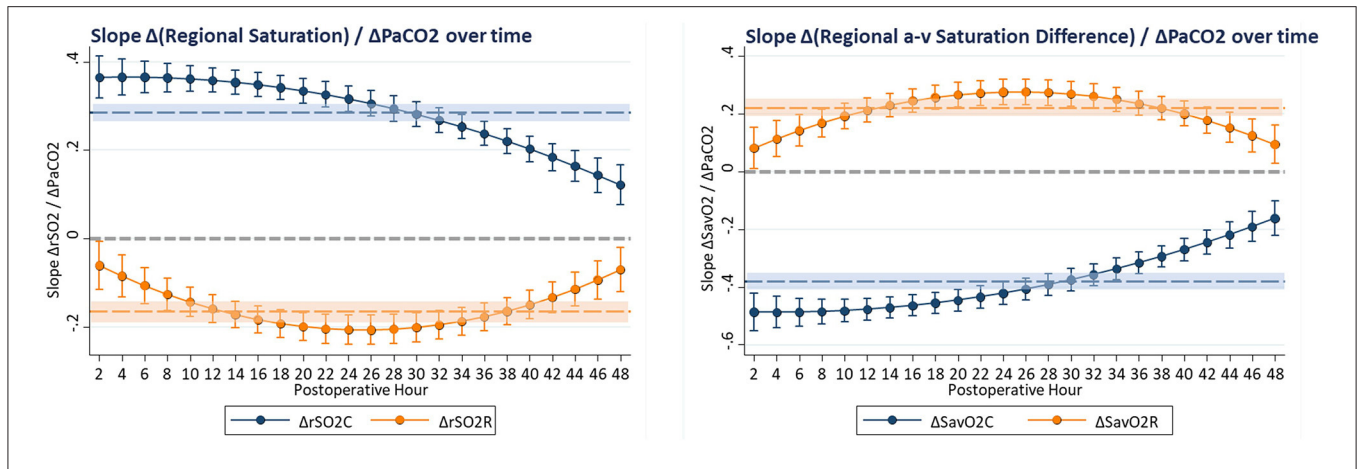


FIGURE 4 | The slope of change in regional oxygenation or arteriovenous difference vs. change in PaCO₂ was computed at hourly intervals from multivariable models. Covariates were constrained to clinically realistic values near the observed means (SaO₂ = 83%, MABP = 51 mmHg, Hb = 15 gm/dl, CVP = 10 mmHg, weight = 3.2 kg, age = 8 days, CPB time = 172 min, and DHCA time = 20 min). These hourly coefficients are displayed graphically, showing effects of PaCO₂ that change with time but have persistently differential effects on cerebral and renal circulations, with average effects shown as shaded regions.

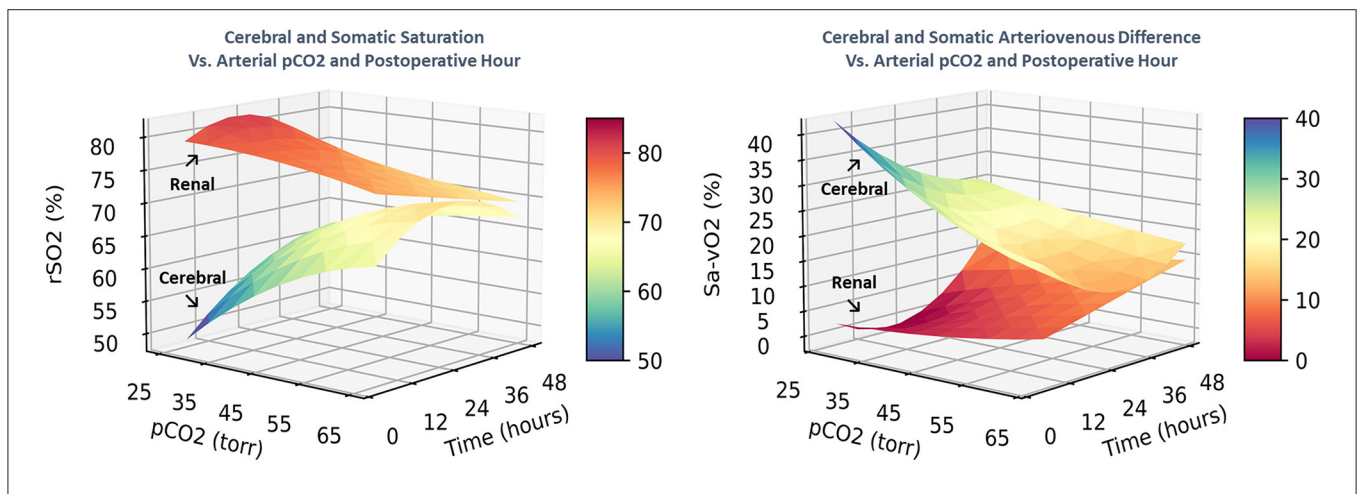


FIGURE 5 | The combined effects of postoperative time and PaCO₂ on regional saturation and arteriovenous difference are displayed as 3-dimensional surfaces. The differential circulatory controls on cerebral and renal circulatory beds are characterized by distinct spatial regions with different shapes.

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. 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

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2022.762739/full#supplementary-material>

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