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Regional Tissue Oxygen Extraction and Severity of Anemia in Very Low Birth Weight Neonates: A Pilot NIRS Analysis

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ABSTRACT

Objective: Anemia causes blood flow redistribution and altered tissue metabolic behavior to sustain homeostatic oxygen consumption. We hypothesized that anemia severity would correlate with increased regional fractional tissue oxygen extraction among premature neonates.

Study Design: Regional oxygen extraction was calculated using pulse oximetry and near-infrared spectroscopy data among neonates <1250g during their first ten postnatal days. Oxygen extraction was assessed for correlations with raw hematocrit levels and following grouping into hematocrit quartiles.

Results: Twenty-seven neonates with gestational age 27 ± 2wk and birth weight 966 ± 181g underwent 116 hematocrit determinations. Cerebral and flank oxygen extraction inversely correlated with hematocrit (cerebral $r = -0.527$, $p = 0.005$; flank $r = -0.485$, $p = 0.01$). Increased cerebral oxygen extraction was observed for the lowest three hematocrit quartiles (Q1 0.26 ± 0.08, $p=0.004$; Q2 0.24 ± 0.09, $p=0.01$; Q3 0.25 ± 0.09, $p=0.03$; all compared to Q4 0.18 ± 0.10). Increased flank oxygen extraction occurred for the lowest two quartiles (Q1 0.36 ± 0.12, $p<0.001$; Q2 0.35 ± 0.11, $p<0.001$; compared to Q4 0.22 ± 0.13). Splanchnic oxygen extraction demonstrated no similar correlations.

Conclusion: Increases in tissue oxygen extraction may indicate early pathophysiologic responses to nascent anemia in premature neonates.

Keywords: Anemia, hematocrit, neonate, NIRS, oxygen extraction, regional oxygenation

INTRODUCTION

Anemia occurs commonly in very low birth weight (VLBW) neonates.[1] In the neonatal intensive care unit (NICU), transfusion requirements are most-often defined by serial hematocrit or hemoglobin determinations.[2] Currently, hematocrit and clinical thresholds for packed red blood cell (pRBC) transfusion remain controversial.[2-4] What is agreed upon is that progressive anemia can create an oxygen delivery/consumption imbalance resulting in blood flow maldistribution with variations in local tissue oxygen extraction. In extreme situations, insufficient oxygen delivery results in tissue acidosis, previously illustrated in neonates by direct measurement using micro-pH electrodes, with associated systemic metabolic acidosis resulting from a shift to anaerobic metabolism.[5] To maintain homeostatic stability among VLBW neonates, these observations portend the need for more continuous, physiologically-based assessments of oxygenation adequacy to meet consumption demands during progressive anemia.[6]

Numerous studies utilize near-infrared spectroscopy (NIRS) for noninvasive bedside monitoring of *regional tissue oxygenation* (rSO_2). Whereas pulse oximetry-derived oxygen saturation (SpO_2) estimates anticipated tissue oxygen *delivery* from arterialized vessels, NIRS provides oxygen saturation data from predominantly post-capillary hemoglobin sources.[7,8] By simultaneously monitoring SpO_2 and tissue-specific rSO_2 via NIRS (e.g., cerebral, flank/renal, splanchnic), one can calculate a trendable estimate of fractional tissue oxygen extraction (FTOE = (SpO_2 – region-specific rSO_2) / SpO_2).[9-11] Identifying increases in tissue oxygen extraction could allow earlier identification of blood flow maldistribution or insufficient tissue oxygen delivery to meet metabolic demands before pathologic clinical sequelae develop.

Although previous reports have described effects of physiologic perturbations in oxygen delivery on tissue rSO_2 and FTOE,[9,12-14] data are lacking in VLBW neonates regarding organ-specific oxygen extraction relationships relative to the magnitude of anemia.[12,15] In this non-*a priori* pilot analysis, we sought to determine whether hematocrit values correlate with region-specific FTOE. Further, we aimed to investigate the tissue-specific oxygen extraction responses to varied degrees of anemia. We hypothesized that decreased hematocrit levels would be associated with progressively increased cerebral, flank, and splanchnic FTOE and that these changes in oxygenation behavior would demonstrate regional specificity.

METHODS

Study Design

This prospective observational cohort study was approved by the Institutional Review Board of New York Medical College and the Maria Fareri Children's Hospital as minimal risk. Data were acquired during a NIRS survey of VLBW neonates to evaluate region-specific baseline values and changes occurring with routine clinical practices over the first 10 postnatal days. Previous work related to this patient cohort and data set have evaluated booster pRBC transfusions,[10] quiescent baseline variability,[16] sodium bicarbonate corrections,[17] and effects of umbilical arterial blood drawing.[18] This hypothesis-generating pilot analysis was conducted *post hoc* to evaluate the relationship between hematocrit level and region-specific FTOE. The current objective was to determine whether FTOE is sensitive enough for use in a larger randomized study designed to examine the graded contributions of various factors affecting oxygen delivery/consumption balance in VLBW neonates.

Patient Population

Subjects were admitted to the 50-bed, Level IV Regional Perinatal Center at Maria Fareri Children's Hospital of Westchester Medical Center from a catchment area of 23,000 annual births. Following parental consent, VLBW neonates < 1250 grams birth weight were enrolled within the first 72 postnatal hours and were monitored for an additional seven days each. Newborns with birth weights less than 500 grams, major congenital/chromosomal anomalies, congenital heart disease, five minute Apgar score <3, not expected to survive for the study duration, or with extremely immature skin were excluded.

Monitoring

After delivery and initial management, continuous cerebral, flank, and splanchnic NIRS monitoring was initiated using the INVOS 5100C Cerebral/Somatic Oximeter with OxyAlert NIRSensors – Infant Model IS [Neonatal] (Somanetics, Troy, MI, now Medtronic, Boulder, CO). This device estimates the regional oxygenation status of underlying venous, arterial, and capillary hemoglobin sources using an assumed 75:20:5 respective ratio,[19] at a manufacturer-reported signal depth of 1.5cm beneath the monitoring sensor.[20] Regional tissue oxygen saturation (rSO_2) is displayed as a proportion of oxygenated to total hemoglobin [oxyhemoglobin/(oxyhemoglobin + deoxyhemoglobin)].[8] Consistent with numerous previous studies, NIRS sensor placement was as follows:[21]

Cerebral: Transverse across forehead

Flank/Renal: Longitudinally in right paraspinal region

Splanchnic: Transverse in infraumbilical position or obliquely from left lower

abdominal quadrant toward left flank if space limited

To protect fragile neonatal skin, NIRS monitoring sensors were placed atop Mepitel gel-impregnated gauze strips (Mölnlycke Health Care, Göteborg, Sweden). This technique was confirmed by Somanetics (now Medtronic) and our team as not affecting NIRS signal integrity while conferring adequate skin protection.[21] Monitoring sensors were removed daily for a 30 minute "*skin resting period*" to provide ongoing assessment of skin integrity.

NICU Care / Hematocrit Measurements

All NICU care and decisions regarding hematocrit determinations were rendered by attending neonatologists. Hematocrits were obtained as a component of complete blood counts using a Coulter Counter (Beckman Coulter, Brea, CA). Typically, subjects had a hematocrit drawn upon NICU admission; further hematocrit determinations were based on attending discretion. No prospective decisions, including additional laboratory testing, were made based on NIRS results. Given previously published work from this data set regarding the effects of booster pRBC transfusions on FTOE,[10] post-transfusion hematocrits were excluded from analysis in order to evaluate the relationship between hematocrit and FTOE to potentially determine transfusion thresholds for a future randomized trial.

Data Collection and Analysis

Antenatal, birth history, and hematocrit data were abstracted from subjects' medical records. Raw NIRS data were collected every 6 seconds; the most frequent data sampling setting offered by the INVOS 5100C device. For each hematocrit determination, corresponding time-synchronized pulse oximetry and cerebral, flank, and

splanchnic NIRS data were collected over 15 minute epochs to allow for simultaneous FTOE calculations ((SpO_2 - region-specific rSO_2) / SpO_2). Based on previous variability analysis, this epoch length was selected to minimize the signal-to-noise ratio resulting from differences in region-specific baseline variability.[16]

Statistics

Comparisons between cerebral, flank, and splanchnic rSO_2 and FTOE were performed using ANOVA following confirmation of normal distributions. Scatterplots were created comparing hematocrits with organ-specific FTOE values. Pearson (r) calculations were then performed to evaluate for correlations between hematocrits and region-specific rSO_2 and FTOE values. Given multiple non-independent measures, Pearson (r) analyses were additionally conducted on both pooled raw data and averaged individual-patient data.[22] Analyses of NIRS-derived data were also performed following organization of hematocrit data into quartiles. Comparisons across quartiles were performed via ANOVA (or ANOVA on ranks) with Dunnett (or Dunn's, if ranks used) post-hoc test using the highest hematocrit quartile (Q4) as baseline (normal/ideal hematocrit). Finally, multivariate logistic regression modeling was performed to evaluate the regional FTOE effects of hypotension requiring inotropic support; hemodynamically-significant patent ductus arteriosus; and intraventricular hemorrhage. Statistical significance was designated as a P value of < 0.05. All statistical analyses were performed using SigmaPlot v12.0 (Aspire Software International, Ashburn, VA).

RESULTS

Twenty-seven VLBW neonates underwent continuous NIRS monitoring between 6 and 221 hours of life. A total of 116 hematocrit determinations were performed and

verified as not preceded by pRBC transfusions during the prior 72 hours. Gestational age was 27 ± 2 wk (mean ± SD) and birth weight was 966 ± 181 g. Cesarean deliveries occurred in 59% (16/27) of subjects, delivery room intubation in 56% (15/27), and 15% (4/27) had 5-minute Apgar scores less than 7. During the seven days of NIRS monitoring, 11% (3/27) of subjects received short courses of dopamine for hypotension, 41% (11/27) were diagnosed with patent ductus arteriosus, and 26% (7/27) demonstrated intraventricular hemorrhage on routine head ultrasound. Hematocrit and corresponding vital sign data are presented in Table 1.

Cerebral, flank, and splanchnic individual-hematocrit raw data scatterplots with overall data regression lines and Pearson r correlations with 95% confidence intervals are displayed in Figure 1. As individual subjects contributed between 1 and 10 hematocrit values to this data set, an additional analysis was conducted using averaged individual-subject data to account for non-independent/repeated measures,[22] with no changes in correlations noted following this sub-analysis. Additional correlational analyses demonstrated direct relationships between hematocrit and raw cerebral and flank rSO_2 data (cerebral $r = 0.418$ and flank $r = 0.436$, both $p < 0.01$). No correlation was observed between hematocrit and raw splanchnic rSO_2 data ($r = 0.137$, $p = 0.15$).

Hematocrit quartiles (Figure 2) were subsequently analyzed for correlations with NIRS-derived data (Table 2 and Figure 3-4). Across all measurements, cerebral rSO_2 demonstrated the highest and least variable signal, with flank providing intermediate findings, and splanchnic oxygenation uniformly showing the lowest and most variable rSO_2 data ($p < 0.05$ for comparisons of both value and variability) as previously shown in other studies utilizing portions of this data set.[9,15,16] Calculated FTOE was smallest and

least variable for the cerebral vascular bed, intermediate for the flank site, and largest with the greatest variability for splanchnic measurements ($p < 0.05$ for comparisons of both value and variability).

Relationships between hematocrit quartiles and organ-specific rSO_2 and FTOE are shown in Table 2 and Figures 3-4. Cerebral rSO_2 was diminished, with corresponding elevated FTOE, for the three lowest hematocrit quartiles compared to the highest quartile. A more graded relationship was observed between hematocrit quartile and renal rSO_2 and FTOE. No statistically significant correlations were noted across hematocrit quartiles for splanchnic NIRS-derived data.

On multivariate logistic regression, the effect of hematocrit on cerebral and flank FTOE trends remained unaltered in the presence of single or multiple factors potentially affecting organ perfusion. Interestingly, hematocrit demonstrated a significant correlation with splanchnic FTOE only in the presence of other risk factors, and particularly patent ductus arteriosus. Multivariate logistic regression modeling controlling for hypotension requiring inotropic support; presence of hemodynamically-significant patent ductus arteriosus; and presence of intraventricular hemorrhage are displayed in Table 3.

DISCUSSION

This report demonstrates that in VLBW neonates during the first ten postnatal days, cerebral and flank FTOE are inversely correlated with hematocrit levels. No similar correlation was observed for the splanchnic monitoring site. Across all hematocrit values, oxygen extraction was lowest in the brain, followed by flank and splanchnic vascular beds, consistent with neuroprotective maintenance of cerebral oxygen delivery.[9] These findings suggest potential practical utility for NIRS-based trend monitoring as an

adjunctive, proportional measure of regional oxygen delivery/consumption balance among premature neonates. As homeostatic perturbations are most observable during later stages of oxygen privation,[23] these data may contribute to earlier appreciation of minimally symptomatic anemia prior to clinically apparent distress.

Anemia, both physiologic and iatrogenic, remains a common diagnosis in the NICU setting.[1,4] Unfortunately, in VLBW neonates, the need for frequent phlebotomy during the first several postnatal days contributes to anemia itself.[10] While strategies to reduce phlebotomy have been employed, relatively frequent phlebotomy is common among the smallest, most premature neonates with the lowest total blood volume and red cell mass.[2,4] Thus, techniques to noninvasively assess oxygen delivery/consumption balance in VLBW neonates before clinical symptoms occur represent a potential advancement.

As anemia reduces blood oxygen-carrying capacity, our data confirm the hypothesis that individual tissues demonstrate enhanced oxygen extraction at lower hematocrit levels. Other studies have also employed NIRS to investigate anemia in premature neonates. Common to these reports are increases in region-specific rSO_2 (or decreases in FTOE) following transfusion, whether provided for symptomatic anemia[9,12-14,24,25] or as a booster transfusion for phlebotomy-related blood losses.[10] However, none of these studies included correlational analyses to ascertain regional rSO_2 or FTOE values based solely on anemia severity.

On logistic regression modeling, decreased hematocrit remained correlated with elevated cerebral and flank FTOE even when other factors were associated with enhanced tissue oxygen extraction. Interestingly, a relationship between hematocrit and splanchnic

oxygen extraction was observed only when other perfusion-affecting comorbidities existed, particularly patent ductus arteriosus. Given the inherent variability of splanchnic monitoring,[16] it currently appears that this correlation only becomes "visible" during enhanced stages of oxygen privation. A larger future study encompassing a wider range of hematocrit values is required to validate this interesting result.

In this data set, while NIRS sensor placement is consistent with previous neonatal studies, concerns remain regarding actual tissue sampling, as regional monitoring can be affected by neighboring tissues' perfusion. For example, though flank monitoring is assumed to estimate renal oxygenation, one cannot be certain of actual renal monitoring without imaging for kidney position. Additionally, as previously reported, excessive splanchnic variability results in significant limitations in interpreting splanchnic FTOE data.[9,21] Moreover, some reports have indicated enhanced splanchnic variability as a risk factor for various outcomes, including transfusion-related acute gut injury.[26] While data averaging techniques may correct for baseline splanchnic variability, substantial uncertainty remains regarding the utility of splanchnic NIRS monitoring for clinical decision-making. Further studies, including innovative data smoothing methods, are needed to properly evaluate the possible clinical utility of splanchnic monitoring.

Whereas rSO_2 monitoring is currently used for trend analysis in specific care settings (i.e. during surgery), NIRS monitoring is not yet routinely employed in the NICU. Should continuous rSO_2 and FTOE monitoring become available at the bedside and a maximal FTOE "*zone of comfort*" established, this adjunctive, noninvasive measure could reduce dependence on empiric hematocrit thresholds for transfusions. Importantly, establishing rSO_2 and/or FTOE trends is likely more clinically relevant than absolute

values as individual patients may produce their own baselines to monitor for concerning trends (e.g., decreasing rSO_2 or increasing FTOE). Given the numerous factors which affect oxygen delivery/consumption balance in neonates, this noninvasive monitoring strategy may allow enhanced discretion for consideration of invasive bedside testing practices, including frequent blood sampling. Though larger, rigorous prospective studies are required, the NIRS modality shows promise toward providing a more individualized, physiologically-based approach for managing oxygen delivery/consumption balance among vulnerable neonates.

This study's primary strength is its proof of concept utilizing continuous NIRS monitoring with a reasonably large number and wide range of hematocrit determinations obtained from VLBW neonates during the first 10 postnatal days. However, several limitations affect the utility and generalizability of the results. Primarily, this hypothesis-generating analysis utilized a small patient sample size and non-*a priori* study design. Indeed, this report utilizes data that were collected during a prospective, normative NIRS survey among VLBW neonates not specifically designed to evaluate the relationship between hematocrit and regional FTOE. Moreover, given the large number of factors potentially affecting FTOE (e.g. inotropic support,[27] patent ductus arteriosus,[28] intraventricular hemorrhage,[29] enteral feeding status,[30] and others), important questions remain regarding the relative contribution of these parameters to tissue oxygen extraction. In addition, subtle yet significant differences in systolic and diastolic blood pressure and oxygen saturation between hematocrit quartile groups may have affected observed oxygen extraction behavior. Finally, hematocrits obtained based on clinical discretion may have inadvertently introduced a confounding selection bias based on clinical practice

variability. A larger prospective study, designed to account for the numerous confounding variables affecting oxygen delivery/consumption balance, is required to further develop FTOE trending in the management of anemia in VLBW neonates.[12,15]

In summary, in this pilot study of the relationship between hematocrit and cerebral, flank, and splanchnic FTOE, hematocrit level was inversely correlated with cerebral and flank oxygen extraction in VLBW neonates. A similar relationship was not observed for the splanchnic vascular bed, except in the presence of hemodynamically-significant patent ductus arteriosus. Further study is required to examine the graded effects of various factors affecting oxygen delivery/consumption balance on tissue oxygen extraction and to determine specific NIRS-derived FTOE patterns to aid in incorporating this noninvasive monitoring strategy.

STATEMENT OF FINANCIAL SUPPORT

This study was supported in part by an unrestricted equipment use grant from Somanetics (now Medtronic, Boulder, CO).

DISCLOSURE

All authors have no financial relationships or conflicts of interest to disclose related to this study.

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FIGURE CAPTIONS

Figure 1: Cerebral and flank fractional tissue oxygen extraction inversely correlated with hematocrit level; an effect not observed for the splanchnic site. Fractional tissue oxygen extraction was smallest and least variable at the cerebral site, intermediate in flank, and highest and most variable at the splanchnic monitoring site.

Figure 2: Corresponding hematocrit values for individual hematocrit quartiles. **p<0.001 for ANOVA comparisons of all hematocrit quartiles and post-hoc comparisons between Q1/Q2/Q3 and Q4 hematocrit quartiles.

Figure 3: Median and interquartile ranges for cerebral, flank, and splanchnic regional oxygen saturations corresponding to individual hematocrit quartiles. **p<0.001 for cerebral rSO2 ANOVA comparison of all hematocrit quartiles and post-hoc comparisons between Q1/Q2/Q3 and Q4 hematocrit quartiles. ++p<0.001 for flank rSO2 ANOVA comparison of all hematocrit quartiles and post-hoc comparisons between Q1/Q2 and Q4 hematocrit quartiles. No statistically significant interquartile differences were noted for splanchnic rSO2.

Figure 4: Median and interquartile ranges for cerebral, flank, and splanchnic fractional tissue oxygen extraction corresponding to individual hematocrit quartiles. **p<0.05 for cerebral FTOE ANOVA comparison of all hematocrit quartiles and post-hoc comparisons between Q1 (p=0.004), Q2 (p=0.01), and Q3 (p=0.03) and Q4 hematocrit quartiles. $^{++}$p<0.001 for flank FTOE ANOVA comparison of all hematocrit quartiles and post-hoc comparisons between Q1/Q2 and Q4 hematocrit quartiles. No statistically significant interquartile differences were noted for splanchnic FTOE.

TABLES

Table 1: Hematocrits and corresponding vital signs based on hematocrit quartile.

		P-value
Hematocrit (%)		<0.001 (ANOVA)
1st Quartile	33.3 ± 2.1 (33.8; 27.3-35.8)	<0.001
2nd Quartile	37.5 ± 1.0 (37.4; 35.9-39.0)	<0.001
3rd Quartile	40.7 ± 1.0 (40.7; 39.0-42.3)	<0.001
4th Quartile	46.8 ± 3.2 (46.5; 42.3-52.9)	--
ALL	39.7 ± 5.4 (39.0; 27.3-52.9)	
Heart Rate (beats/min)		0.30 (ANOVA)
1st Quartile	158 ± 11 (159; 137-182)	NS
2nd Quartile	158 ± 13 (157; 131-181)	NS
3rd Quartile	162 ± 10 (161; 136-181)	NS
4th Quartile	157 ± 10 (157; 138-175)	--
ALL	159 ± 11 (159; 131-182)	
Systolic Blood Pressure (mmHg)		0.005 (ANOVA)
1st Quartile	50 ± 8 (48; 38-78)	0.003
2nd Quartile	51 ± 9 (39; 37-74)	0.03
3rd Quartile	51 ± 10 (48; 37-76)	NS
4th Quartile	56 ± 8 (58; 37-71)	--
ALL	52 ± 9 (50; 37-78)	
Diastolic Blood Pressure		<0.001 (ANOVA)

(mmHg)		
1st Quartile	25 ± 7 (24; 17-42)	<0.001
2nd Quartile	27 ± 7 (27; 17-47)	<0.001
3rd Quartile	27 ± 7 (27; 13-40)	<0.001
4th Quartile	34 ± 6 (35; 19-49)	--
ALL	28 ± 7 (28; 13-49)	
Pulse Oximetry (%)		0.013 (ANOVA)
1st Quartile	93 ± 4 (93; 84-100)	0.006
2nd Quartile	92 ± 5 (93; 79-100)	0.008
3rd Quartile	93 ± 5 (94; 79-100)	NS
4th Quartile	96 ± 4 (97; 85-100)	--
ALL	93 ± 5 (95; 79-100)	

Data expressed as mean ± SD (median; range)

Comparisons via ANOVA (or ANOVA on ranks) with Dunnett (or Dunn's, if ranks used) post-hoc test comparing to 4th hematocrit quartile.

Table 2: Near-infrared spectroscopy data based on hematocrit quartile.

		P-value
Cerebral rSO_2 (%)		<0.001 (ANOVA)
1st Quartile	69 ± 7 (70; 53-81)	<0.001
2nd Quartile	71 ± 10 (70; 48-95)	<0.001
3rd Quartile	70 ± 10 (71; 46-85)	<0.001
4th Quartile	79 ± 11 (79; 46-93)	--
ALL	72 ± 10 (72; 46-95)	
Flank rSO_2 (%)		<0.001 (ANOVA)
1st Quartile	59 ± 12 (59; 41-83)	<0.001
2nd Quartile	61 ± 12 (62; 38-79)	<0.001
3rd Quartile	64 ± 18 (68; 27-90)	NS
4th Quartile	75 ± 13 (78; 38-95)	--
ALL	65 ± 15 (66; 27-95)	
Splanchnic rSO_2 (%)		0.10 (ANOVA)
1st Quartile	36 ± 18 (35; 15-87)	NS
2nd Quartile	39 ± 18 (36; 15-70)	NS
3rd Quartile	48 ± 21 (44; 18-91)	NS
4th Quartile	38 ± 19 (35; 16-77)	--
ALL	40 ± 19 (38; 15-91)	
Cerebral FTOE		0.004 (ANOVA)
1st Quartile	0.26 ± 0.08 (0.25; 0.10-0.41)	0.004
2nd Quartile	0.24 ± 0.09 (0.25; 0.04-0.45)	0.01
3rd Quartile	0.25 ± 0.09 (0.23; 0.12-0.42)	0.03

4th Quartile	0.18 ± 0.10 (0.18; 0.04-0.46)	--
ALL	0.23 ± 0.10 (0.22; 0.04-0.46)	
Flank FTOE		<0.001 (ANOVA)
1st Quartile	0.36 ± 0.12 (0.38; 0.14-0.56)	<0.001
2nd Quartile	0.35 ± 0.11 (0.35; 0.20-0.56)	<0.001
3rd Quartile	0.32 ± 0.17 (0.29; 0.09-0.68)	NS
4th Quartile	0.22 ± 0.13 (0.19; 0.03-0.59)	--
ALL	0.31 ± 0.14 (0.30; 0.03-0.68)	
Splanchnic FTOE		0.18 (ANOVA)
1st Quartile	0.61 ± 0.20 (0.64; 0.06-0.84)	NS
2nd Quartile	0.58 ± 0.21 (0.60; 0.16-0.85)	NS
3rd Quartile	0.50 ± 0.21 (0.52; 0.04-0.80)	NS
4th Quartile	0.60 ± 0.20 (0.64; 0.20-0.84)	--
ALL	0.57 ± 0.21 (0.59; 0.04-0.85)	

Data expressed as mean ± SD (median; range).

Comparisons via ANOVA (or ANOVA on ranks) with Dunnett (or Dunn's, if ranks used) post-hoc test comparing to 4th hematocrit quartile.

Table 3: Multivariate logistic regression including hypotension requiring inotropic support; hemodynamically-significant patent ductus arteriosus; and intraventricular

hemorrhage. Hct = hematocrit; Dopa = dopamine administration; PDA = hemodynamically-significant patent ductus arteriosus; IVH = intraventricular hemorrhage.

Site	Factor	R-Square Change	P-value
Cerebral FTOE	Hct	0.136	<0.0001
	Hct	0.136	<0.0001
	Dopa	0.115	<0.0001
	Hct	0.136	<0.0001
	PDA	0.006	0.39
	Hct	0.136	<0.0001
	IVH	0.013	0.21
	Hct	0.136	0.001
	Dopa	0.115	<0.0001
	PDA	0.002	0.61
	IVH	0.035	0.02
Flank FTOE	Hct	0.176	<0.0001
	Hct	0.176	<0.0001
	Dopa	0.158	<0.0001
	Hct	0.176	<0.0001
	PDA	0.122	<0.0001
	Hct	0.176	<0.0001
	IVH	0.002	0.62
	Hct	0.176	0.001
	Dopa	0.158	<0.0001
	PDA	0.045	0.007
	IVH	0.004	0.43
Splanchnic FTOE	Hct	0.011	0.28
	Hct	0.011	0.19
	Dopa	0.021	0.13
	Hct	0.011	0.02
	PDA	0.148	<0.0001

	Hct IVH Hct Dopa PDA IVH	0.011 0.038 0.011 0.021 0.127 0.023	0.48 0.04 0.04 0.84 <0.0001 0.09