DETERMINANTS OF CEREBRAL OXYGENATION AND RESPONSE TO HYPOTENSION TREATMENT IN VERY LOW BIRTH WEIGHT NEONATES

By

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To my family–Mom, Dad and Jonnie–for all their love and support and to Grandma Gardner, who I wish could have lived to see my dreams fulfilled

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The normal physiologic range for blood pressure to assure adequate cerebral blood flow and oxygen delivery is unknown in very preterm infants. Some studies suggest that under a mean arterial blood pressure of 30 mmHg, cerebral blood flow is pressure-passive, but above that measure, cerebral blood flow is maintained. Ideally, one would want to monitor cerebral blood flow and target therapy at cerebral blood flow improvement. Near infrared spectroscopy (NIRS) can be used to continuously estimate regional tissue oxygenation, the primary function of cerebral blood flow, thus by-passing the intermediate step of measuring the blood flow directly. We used NIRS to continuously monitor cerebral oxygenation in 50 very low birth weight (VLBW, less than 1500 grams) neonates during the first three days of life, a time at which they are most likely to receive treatment for hypotension.

Using regression analysis, we created a model for cerebral oxygenation (rSO2) including several variables; however, our analysis found that blood pressure did not fit the model. Instead, our cerebral oxygenation model included: hematocrit (Hct), systemic oxygen saturations (SpO2) and the partial pressure of carbon dioxide (pCO2).

After generating the rSO2 model for all 50 patients, we generated a model specifically for the hypotensive study patients. Significant determinants of rSO2 using only hypotensive subjects in the model were Hct, birth weight and race. Based on the results from these models, we found blood pressure to be a poor surrogate for cerebral oxygenation.

Additionally, we evaluated the impact of two conventional treatments, normal saline and dopamine, for neonatal hypotension on blood pressure and cerebral oxygenation. We found that while normal saline and dopamine increased blood pressure, they did not change cerebral oxygenation. Our hypotension treatment data suggest that further work should explore different therapies, targeting rSO2 improvement rather than blood pressure improvement.

Based on this study, we recommend that future experiments be conducted to understand the role of factors that we identified as important to rSO2. Considering that hematocrit was the one consistent variable of significance in both rSO2 models, it may be worthwhile exploring the effects of blood transfusions on cerebral oxygenation in neonates with low hematocrit and low rSO2. Furthermore, a randomized trial evaluating the effects of red blood cell transfusions along with other therapies on rSO2 is warranted. Finally, our study was limited to the neonates' stay in the neonatal intensive care unit. Additional investigation of long term neurodevelopmental outcomes is necessary in future studies.

CHAPTER 1
INTRODUCTION

Clinical Relevance

Although neonatology has flourished as a pediatric specialty since the 1960s, the fundamental question of "what is an adequate blood pressure in very low birth weight neonates" has not been answered. Several investigators have described the normal distribution of blood pressures over the first several days of life in low birth weight infants.[1-5]

However, delivery of adequate oxygen many be more important than having blood pressure within a statistical distribution of normal, which may not be adequate in the sick, very low birth weight (VLBW, <1500 grams) baby. The circulatory system maintains oxygen delivery to the organs of the body. Oxygen delivery, in turn, depends upon the oxygen carrying capacity of the blood, the oxygen content in the blood, and the volume of blood delivered to the tissues.[6] Oxygen content is easy to measure but measurement of blood flow in VLBW neonates is much more challenging, so clinicians often use blood pressure as a surrogate. For many years, neonatal circulatory support has been based on an assumed proportionality between blood pressure and systemic blood flow, particularly within the cerebral circulation. However, having a blood pressure within a statistical distribution of normal, especially in the sick, very low birth weight (VLBW, <1500 grams) baby, may not be adequate to assure oxygen delivery to the tissues.

Limited evidence in human neonates suggests that the neonatal cerebral circulation is not pressure-passive, but rather autoregulated.[7,8] Autoregulation implies that within a certain range of blood pressures, cerebral circulation is relatively constant,

so that cerebral blood flow rises or falls only when the blood pressure is outside that range. Moreover, some evidence also exists that during illness, autoregulation fails[9,10] and this failure has been associated with neurological injuries in VLBW neonates.[11]

The normal physiologic range for blood pressure to assure adequate cerebral blood flow and oxygen delivery is unknown in very preterm infants. Despite this, up to 40% of VLBW neonates are treated for hypotension in the first 3 days of life.[12] Definitions and management of hypotension among VLBW neonates vary across neonatal intensive care units around the country. The lack of standardization may be due to a combination of reasons including the fact that blood pressure tends to increase hourly over the first day of life.[1-5]

The clinical relevance of hypotension in the VLBW preterm neonate is controversial. Concern for hypotension is raised because it has been recognized as a risk for poor neurodevelopmental outcomes.[13-15] Several studies document central nervous system morbidities associated with low blood pressure.[1, 7] One particular study published in 1987 found that in preterm neonates, a mean blood pressure remaining below 30 mmHg for an hour was associated with severe hemorrhage, ischemic cerebral lesions, or death within 48 hours, while no severe lesions developed in patients with a mean blood pressure ≥ 30 mm Hg.[16] Similarly, Munro et al.[7], using near infrared spectroscopy (NIRS) to measure cerebral blood flow in 17 extremely low birth weight infants, showed a breakpoint at approximately 30 mmHg in the cerebral blood flow-mean arterial pressure autoregulation curve. These studies would suggest that under a mean blood pressure of 30 mmHg, cerebral blood flow is pressure-passive, but above that measure, cerebral blood flow is maintained. Pressure-passivity occurs when the

vascular bed is maximally dilated and blood flow decreases passively in response to further reductions in blood pressure. Additional implications from these studies[1,7,16] suggest that maintaining mean arterial blood pressure above 30 mmHg would be important for optimal neurodevelopmental outcome in VLBW infants, and this level has been incorporated as a practice standard in a major neonatal textbook.[17]

Contrasting this notion that blood pressure below a certain level leads to CNS morbidities, others have suggested that blood pressure alone is unreliable in predicting cerebral perfusion.[18,19] Furthermore, other reports show no relationship between blood pressure and short-term neurological injury.[8]

Currently, treatment of hypotension in VLBW neonates includes volume expansion, inotropic agents (dopamine and dobutamine) and steroids, using the patient's mean arterial pressure as a marker for improvement. However, the goal of treating hypotension should be restoration of organ perfusion, particularly cerebral perfusion, and in that light, effects of various treatments differ. Using 133Xe clearance to measure cerebral blood flow, Lundstrom et al.[20] found that although dopamine led to a higher blood pressure response compared to albumin infusion, albumin led to higher cerebral blood flow. Likewise, Osborn et al.[21] demonstrated that treatment of hypotensive neonates with dopamine led to an increase in systemic blood pressure without an increase in cerebral blood flow, as estimated by superior vena cava flow. Yet, dobutamine improved cerebral blood flow by approximately 25% with no appreciable change in blood pressure.[20] Treatments for hypotension clearly need to be studied more rigorously, with improvement in cerebral perfusion and cerebral oxygenation as new end-points.

Near Infrared Spectroscopy

Non-invasive methods for determining cerebral blood flow have been developed but are not clinically practical. Such techniques such as superior vena cava blood flow[22] and Doppler[23] are cumbersome, technically challenging and cannot be performed continuously. Likewise, functional echocardiography has been used to measure cardiac output, but its use is limited by the requirement of a trained operator and an inability to record information continuously. In contrast, NIRS utilizes the near infrared region of the electromagnetic spectrum and can be used to continuously estimate regional tissue oxygenation[24-26], the primary function of cerebral blood flow, thus by-passing the need to invasively measure the blood flow directly.

When using NIRS, light photons are aimed into the skin over the forehead. After being scattered about inside the scalp, skull, and brain, some fraction of the entering photons return and exit the skin ("reflectance"). By measuring the quantity of returning photons as a function of wavelength, one can infer the spectral absorption of the underlying tissue. Human tissues (skin, fat, bone) are translucent to NIR photons of wavelengths between 650 and 1100 nm. However, at 730 nm and 810 nm wavelengths, red-colored hemoglobin molecules within red blood cells have the highest light absorption. The oxygenated state of the hemoglobin will absorb more light at 810 nm than hemoglobin does at 730 nm, and using this principle, one can measure oxygenated to total hemoglobin ratios, or the percentage of hemoglobin that is carrying oxygen. Since tissue oxygen delivery is the ultimate goal of circulatory support, measurement of tissue oxygenation should be useful in assessment of adequacy of blood pressure and obviate the need for measuring flow. This principle was proven in a study using newborn lambs which found a correlation between cerebral tissue

oxygenation and changes in cerebral blood flow.[27] Somanetics (Troy, MI) has developed the INVOS® Cerebral Oximeter, a NIRS tool which measures cerebral oxygen saturation, thus providing a non-invasive means of continuously monitoring cerebral oxygenation and ultimately, cerebral perfusion.

Data regarding the impact of low cerebral oxygenation on brain injury has been limited to date, with most studies performed in animal models or adults. In animals, histological evidence for cerebral injury occurs with cerebral saturations of <40% for 30 minutes.[28] Similar findings have been reported in adult patients. Edmonds et al.[29] reported that cerebral saturations below 40% and declines of more than 25% from baseline are associated with neurologic dysfunction and other adverse outcomes and that declines in cerebral rSO2 below 50%, or more than 20% from baseline, have shown cause for concern and intervention. Currently, minimal data link low regional cerebral oxygenation in premature, VLBW infants to brain injury. A recent case-control study in preterm neonates found that in the first two weeks of life, those with germinal matrix hemorrhages or intraventricular hemorrhages had lower cerebral oxygen saturations than those who did not develop a hemorrhage.[30]

Contemporary monitoring in neonatal intensive care units utilizes continuous blood pressure and non-invasive arterial pulse oximetry, not the more costly NIRS technology, and infers adequacy of tissue perfusion and oxygenation based on blood pressure and arterial oxygenation alone. Therefore, it would be clinically important to determine if the use of blood pressure and arterial oxygen saturation can predict adequacy of cerebral oxygenation.

Summary

By continuously monitoring very preterm neonates during the first 3 days of life, a time at which they are likely to receive hypotension treatment[12], we can determine whether there is a relationship between systemic blood pressure, systemic oxygen saturation and cerebral oxygenation (using NIRS). We can also determine if there is a critical blood pressure required to maintain adequate cerebral perfusion. Finally, we can analyze the data surrounding any treatment periods for hypotension to determine both blood pressure's and cerebral saturation's response to that particular treatment.

CHAPTER 2
MATERIALS AND METHODS

Overall Study Design

Overview

We performed an observational study of blood pressure and cerebral oxygenation in fifty very low birth weight (VLBW) neonates. This study was approved by the University of Florida Institutional Review Board. Enrollment began in November 2008 and concluded in April 2010 after accrual of the fiftieth study subject. Informed consent was obtained from a parent prior to enrollment.

Patient Selection

Infants less than 30 weeks gestational age (GA) and less than 1500 grams requiring arterial access were enrolled in the study. Infants were excluded from the study if they had cyanotic congenital heart disease, limited viability or major congenital malformations.

Clinical Protocol

As part of routine care, systemic oxygen saturation (SpO2) and arterial blood pressure (blood pressure) were monitored using either a Agilent (Santa Clara, CA) monitor or a Philips MP30 (Amsterdam, The Netherlands) monitor. As part of the study, cerebral oxygenation (rSO2) was monitored using Near Infrared Spectroscopy (NIRS) using a Somanetics (Troy, MI) INVOS® Cerebral Oximeter. A neonatal NIRS sensor was placed centrally across the neonate's forehead. Both the vital sign monitor and the INVOS® were attached to a Vital Sync™ (Somanetics, Troy, MI) computer which received transmitted data points every 30-60 seconds. Data collection began after

arterial access was established and continued for 72 hours. The data points were downloaded into a spreadsheet at the completion of the 72 hour monitoring period.

In addition to vital signs, demographic information including gestational age, birth weight, race, and gender were recorded. Laboratory values including hematocrit (Hct) and partial pressure of carbon dioxide in arterial blood samples (pCO2) were also recorded.

During the study period, if the primary clinical care team determined that a study patient required treatment for hypotension, they determined the method, all dosages and duration of treatment. While our NICU has no standard protocol in place which dictates hypotension treatment in VLBW neonates, the clinical staff typically employs an approach that begins with volume expansion with a 10-20 ml/kg normal saline bolus. If the neonate remains hypotensive, they initiate a dopamine infusion at 5 mcg/kg/min, which is then titrated until either the desired blood pressure is achieved or it is maximized at 20 mcg/kg/min. If the neonate remains hypotensive once he/she has received the maximal dopamine infusion, the clinical staff typically begins supra-physiologic steroid replacement with hydrocortisone at 20 to 30 mg/m^2 per day IV in 2 or 3 doses.

Statistical Considerations

To generate a model for determinants of cerebral oxygenation, we performed a regression analysis of GA, birth weight (BW), race, gender, Hct, pCO2, mean arterial blood pressure (MAP), and systemic arterial oxygen saturation (SpO2). The pCO2 was obtained from the study subjects' arterial blood gas and hematocrit from the subjects' complete blood cell count (CBC), obtained as part of routine care in the NICU. The other variables in the model were obtained from data collected at the same time. All

independent variables were included in the original model and the least significant excluded until only significant variables at $p \leq 0.05$ remained in the model. The regression analysis was performed on all 50 study subjects. An additional analysis was performed on 20 subjects who were hypotensive (defined as a MAP less than 30 mmHg) at the time of pCO2 attainment.

To determine the blood pressure and cerebral oxygenation changes in response to treatment of hypotension, in the 20 patients treated for hypotension, we determined the average cerebral oxygenation and mean arterial blood pressure (MAP) during the 30 minutes prior to treatment and during the 30 minutes following completion of normal saline (NS) boluses. When patients were treated with dopamine, we determined their average cerebral oxygenation and MAP after 30 minutes of dopamine infusion. We used a paired t-test to assess changes in cerebral oxygenation and MAP after treatment.

To determine if there were associations between the variables analyzed in the cerebral oxygenation model and time to discharge, corrected gestational age at discharge, and death, we performed a bivariate correlation analysis to generate a Pearson's correlation coefficient. SPSS version 18.0 (IBM, Somers, NY) was used for all statistical analysis. We considered a p value < 0.05 as statistically significant.

Assuming a standard deviation of 10 or 20% of the measure, we anticipated detecting a 20% change in blood pressure, assuming alpha of 0.05 and 2-tailed design (Table 2-1). Given that hypotensive patients all had starting blood pressures <30 mmHg, this narrowed the standard deviation of measurement considerably from non-hypotensive patients. In order to achieve a power of 0.8, we would require 15-20

hypotensive patients. Previous studies have demonstrated that up to 40% of VLBW neonates are treated for hypotension[12]. Thus, we required an overall sample size of 50 patients in order to accrue 15-20 hypotensive patients.

Table 2-1. Sample size and power calculation

N	α	Percent change BP	Std Dev	β
15	0.05	20%	3	1.0
15	0.05	20%	6	0.76
20	0.05	20%	3	1.0
20	0.05	20%	6	0.89

CHAPTER 3
RESULTS

Patient Demographics

The average GA of patients enrolled was 26.5 weeks with a standard deviation of 1.8 weeks. Enrolled patients had an average BW of 929 grams with a standard deviation of 229 grams. Racial breakdown of study subjects included 46% African American, 38% Caucasian and 16% other (including Hispanic, Asian and multiracial). Among the study subjects, 54% were female and 46% were male.

rSO2 Model

We created a model for rSO2 incorporating variables which potentially impact cerebral oxygenation and cerebral perfusion (Table 3-1). The initial regression model we generated (Table 3-2), accounting for all variables, indicated that several variables were not statistically significant. After eliminating the least significant variables in a step-wise fashion until only statistically significant variables remained, we generated a model that included SpO2, pCO2 and Hct (Table 3-3). Our final regression model after evaluating all variables (Table 3-4), -93.516 + 1.208 SpO2 + 0.836 Hct + 0.359 pCO2, yielded an R^2 of 0.296 for goodness of fit.

rSO2 Model in Hypotensive Patients

We additionally created a model for rSO2 during times of hypotension (see Table 3-5 for descriptive statistics of variables). The initial regression model we generated (Table 3-6), accounting for all variables, indicated that several variables were not statistically significant. After eliminating the least significant variable in a step-wise fashion until only statistically significant variables remained, we generated a model that included Hct, BW and Race (Table 3-7). Our final regression model after evaluating all

variables (Table 3-8), 9.74 + 1.085 Hct + 0.033 BW – 6.446 Race, yielded an R^2 of 0.562 for goodness of fit.

Hypotension Treatment

We evaluated the effects of normal saline boluses and dopamine infusions on the blood pressure and cerebral oxygenation in very low birth weight neonates. While NS and dopamine increased study subjects' blood pressures (Figure 3-1), they did not increase cerebral oxygenation (Figure 3-2).

Discharge and Death Outcomes

The average time to discharge was 86 days, with an average corrected gestational age at discharge of 39 weeks with a standard deviation of 3 weeks. Discharge data were unavailable for two patients who were transferred to community hospitals for continued care. Several variables were associated with longer time to discharge including: lower birth weight, lower gestational age, lower rSO2, lower MAP and lower SpO2 (Table 3-9). The only two variables associated with an older corrected gestational age at discharge included lower birth weight and lower SpO2 (Table 3-10, Figures 3-3 and 3-4).

There were eight deaths among the study subjects which were due to respiratory, infectious and gastrointestinal complications (see Table 3-11 for etiologies). Upon analysis, the only variables associated with death included lower birth weight and lower MAP (Table 3-12).

Table 3-1. Descriptive statistics of variables in rSO2 model

	Mean	Std. deviation	N
rSO2 (%)	73.02000	11.431232	50
MAP (mmHg)	31.70000	6.178468	50
SpO2 (%)	95.40000	4.035556	50
Hct (%)	43.01400	5.526597	50
pCO2 (mmHg)	42.76000	10.860075	50
GA (weeks)	26.52000	1.787028	50
BW (grams)	929.08000	228.917046	50

Table 3-2. Preliminary regression output for rSO2 model

Coefficients[a]					
	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	t	Sig.
(Constant)	-106.091	52.211		-2.032	.049
MAP	-.432	.318	-.233	-1.356	.182
SpO2	1.056	.475	.373	2.223	.032
Hct	.895	.279	.433	3.211	.003
pCO2	.260	.173	.247	1.503	.140
GA	1.724	1.240	.269	1.390	.172
BW	-.001	.009	-.015	-.087	.931
Gender	.756	3.013	.033	.251	.803
Race	-1.609	2.254	-.100	-.714	.479

[a] Dependent variable: rSO2.

Table 3-3. Final regression output for rSO2 model

Coefficients[a]					
	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	t	Sig.
(Constant)	-93.516	45.194		-2.069	.044
SpO2	1.208	.413	.426	2.924	.005
Hct	.836	.257	.404	3.253	.002
pCO2	.359	.153	.341	2.343	.024

[a] Dependent variable: rSO2

Table 3-4. Complete patient data for all variables used in rSO2 regression model

Subject	MAP (mmHg)	SpO2 (%)	rSO2 (%)	Hct (%)	pCO2 (mmHg)	GA (weeks)	BW (grams)	Gender	Race
1	30	94	72	41	45	27	940	1	2
2	45	97	66	37.5	30	28	1180	0	1
3	29	100	76	39.7	23	29	1166	0	3
4	25	94	46	42.3	40	23	597	0	2
5	43	94	78	58.6	45	28	762	0	1
6	25	94	90	43.8	42	25	705	0	1
7	27	84	78	50.8	59	28	1175	1	3
8	41	100	57	38.4	20	28	970	0	2
9	29	98	76	50.1	37	24	810	1	3
10	32	93	55	41.9	41	28	1040	0	1
11	32	100	72	43.6	37	28	975	1	3
12	38	96	80	50.2	40	28	975	0	1
13	28	100	81	39.4	46	27	1074	0	1
14	37	92	68	44.7	78	28	1102	1	1
15	40	95	64	29.4	54	28	1045	1	1
16	35	95	80	49.2	46	29	786	0	1
17	34	100	83	42.8	38	27	875	0	2
18	31	100	74	48.5	39	28	1333	0	2
19	30	99	62	42.7	44	26	1045	0	2
20	32	91	79	46.3	51	27	982	0	1
21	23	90	55	33.6	33	23	607	0	2
22	28	89	75	38.7	62	28	1207	0	3
23	27	89	71	44	57	27	761	1	3
24	27	98	81	41.5	40	25	811	1	2
25	22	95	72	44.1	41	25	840	1	2
26	35	93	73	45.1	50	25	762	0	2
27	31	100	88	41.9	38	26	815	1	1
28	31	98	95	44.7	42	27	949	0	2
29	26	100	91	34.6	60	28	1441	1	1
30	16	93	53	38.3	51	26	865	1	2
31	28	94	51	37.2	41	25	690	0	2
32	32	95	77	44.6	40	24	595	0	2
33	32	100	94	42.8	32	29	749	1	3
34	30	93	66	37	57	25	691	0	2
35	29	95	59	30.6	43	24	855	1	2
36	43	100	61	41.1	23	29	1437	1	2
37	40	96	77	41.9	36	28	719	1	2
38	42	100	94	50.3	53	29	1270	0	1
39	37	94	68	50.9	35	25	700	1	2
40	33	97	73	42.7	34	26	880	1	1

Table 3-4. Continued.

Subject	MAP (mmHg)	SpO2 (%)	rSO2 (%)	Hct (%)	pCO2 (mmHg)	GA (weeks)	BW (grams)	Gender	Race
41	24	92	77	41.3	42	26	962	0	1
42	33	95	88	47.9	51	28	1313	1	3
43	39	100	82	48.1	37	25	1050	1	1
44	31	93	72	51.1	41	26	1109	1	2
45	35	96	68	44.2	40	26	1082	0	2
46	38	98	63	44.1	32	28	642	0	2
47	23	93	70	38.4	40	23	590	0	2
48	28	83	79	46.9	53	24	704	0	1
49	25	96	68	44	53	24	630	1	1
50	34	99	73	38.2	26	28	1191	1	1

Gender variable: females coded as 0 and males coded as 1. Race variable: Caucasians coded as 1, African Americans as 2 and Other as 3.

Table 3-5. Descriptive statistics of variables in rSO2 model of hypotensive patients

	Mean	Std. Deviation	N
rSO2 (%)	70.75000	12.481038	20
MAP (mmHg)	25.80000	3.138890	20
SpO2 (%)	93.45000	4.795557	20
Hct (%)	41.22000	5.175306	20
pCO2 (mmHg)	45.45000	9.832679	20
GA (weeks)	25.45000	1.848897	20
BW (grams)	862.60000	237.075471	20

Table 3-6. Initial regression output for rSO2 model in hypotensive patients

	Coefficients[a]				
	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	t	Sig.
(Constant)	-21.339	95.312		-.224	.827
Hct	1.000	.522	.415	1.915	.082
BW	.024	.023	.460	1.036	.322
Race	-8.158	4.069	-.496	-2.005	.070
MAP	.900	.838	.226	1.074	.306
SpO2	-.025	.758	-.009	-.032	.975
pCO2	-.164	.387	-.130	-.425	.679
GA	1.225	2.957	.182	.414	.687
Gender	2.746	6.255	.112	.439	.669

[a] Dependent variable: rSO2.

Table 3-7. Final regression output for rSO2 model in hypotensive patients

Coefficients[a]					
	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	t	Sig.
(Constant)	9.740	19.040		.512	.616
Hct	1.085	.411	.450	2.640	.018
BW	.033	.009	.636	3.768	.002
Race	-6.446	2.811	-.392	-2.293	.036

[a] Dependent variable: rSO2

Table 3-8. Complete patient data for all variables used in rSO2 regression model of hypotensive patients

Subject	MAP (mmHg)	SpO2 (%)	rSO2 (%)	Hct (%)	pCO2 (mmHg)	GA (weeks)	BW (grams)	Gender	Race
3	29	100	76	39.7	23	29	1166	0	3
4	25	94	46	42.3	40	23	597	0	2
6	25	94	90	43.8	42	25	705	0	1
7	27	84	78	50.8	59	28	1175	1	3
9	29	98	76	50.1	37	24	810	1	3
13	28	100	81	39.4	46	27	1074	0	1
21	23	90	55	33.6	33	23	607	0	2
22	28	89	75	38.7	62	28	1207	0	3
23	27	89	71	44	57	27	761	1	3
24	27	98	81	41.5	40	25	811	1	2
25	22	95	72	44.1	41	25	840	1	2
26	27	92	66	45.1	46	25	762	0	2
29	26	100	91	34.6	60	28	1441	1	1
30	16	93	53	38.3	51	26	865	1	2
31	28	94	51	37.2	41	25	690	0	2
35	29	95	59	30.6	43	24	855	1	2
41	24	92	77	41.3	42	26	962	0	1
47	23	93	70	38.4	40	23	590	0	2
48	28	83	79	46.9	53	24	704	0	1
49	25	96	68	44	53	24	630	1	1

Gender variable: females coded as 0 and males coded as 1. Race variable: Caucasians coded as 1, African Americans as 2 and Other as 3.

Table 3-9. Correlation between time to discharge and variables

Variable	Pearson correlation	Significance
BW	-0.708	0.01
GA	-0.617	0.01
rSO2	-0.324	0.041
MAP	-0.437	0.005
SpO2	-0.36	0.023
Hct	-0.179	0.269
pCO2	0.012	0.94

Table 3-10. Correlation between corrected gestational age at discharge and variables

Variable	Pearson correlation	Significance
BW	-0.518	0.001
GA	-0.218	0.177
rSO2	-0.201	0.213
MAP	-0.269	0.094
SpO2	-0.315	0.048
Hct	-0.132	0.418
pCO2	0.07	0.67

Table 3-11. Cause of death for study subjects

Age at death (days)	Cause of death
11	Necrotizing enterocolitis
33	Necrotizing enterocolitis
36	Necrotizing enterocolitis
2	Peptostreptococcus sepsis
11	Fungal sepsis
29	Pseudomonas sepsis
1	Hypoxic respiratory failure
134	Cor pulmonale

Table 3-12. Correlation between variables and death

Variable	Pearson correlation	Significance
BW	-0.282	0.047
GA	-0.221	0.123
rSO2	-0.141	0.33
MAP	-0.335	0.017
SpO2	-0.057	0.692
Hct	-0.082	0.572
pCO2	0.066	0.651

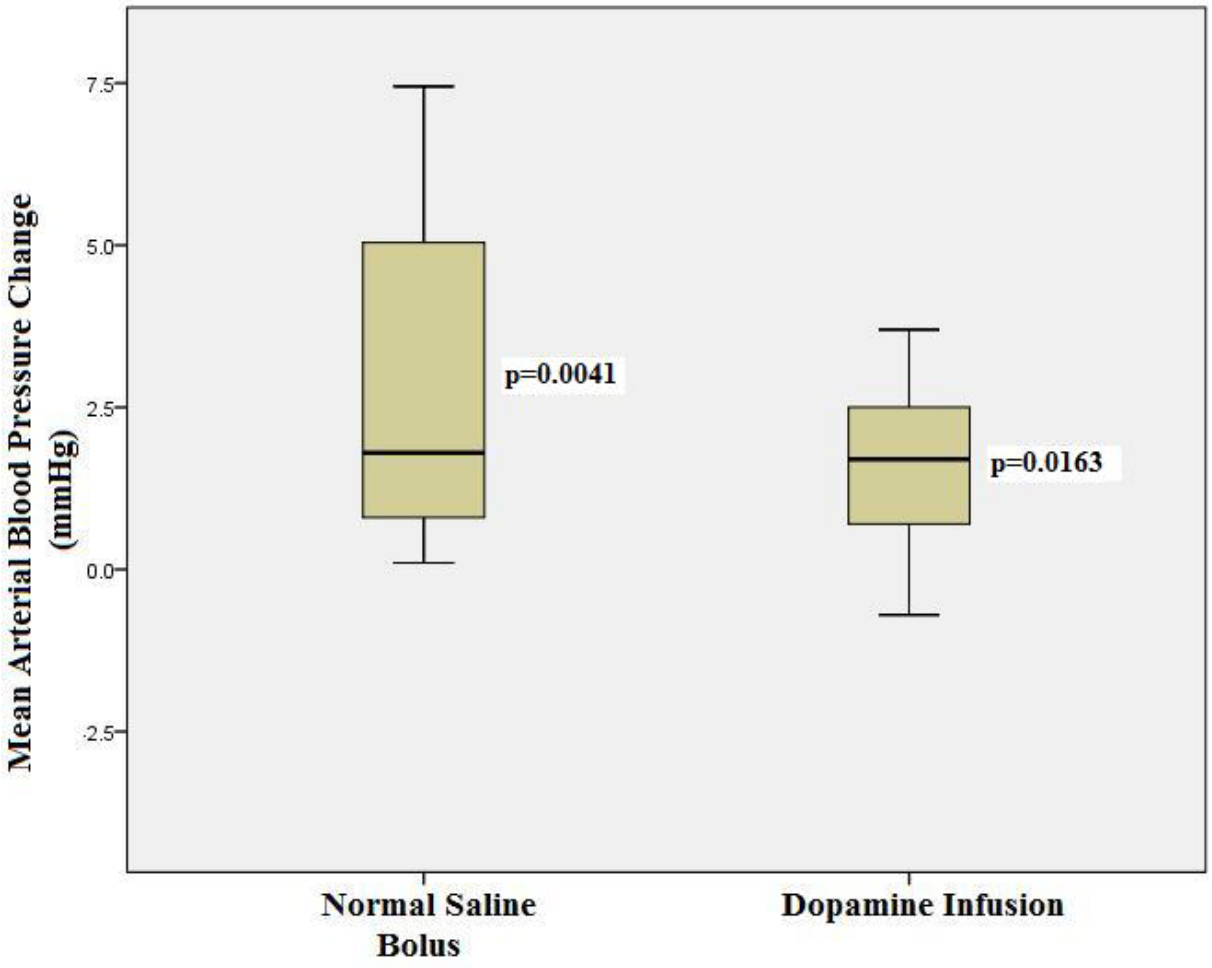

Figure 3-1. Changes in blood pressure after normal saline bolus and dopamine infusion. Box plots of the change in MAP with normal saline bolus and dopamine infusion. The horizontal line indicates median level of MAP, the box indicates 25th and 75th percentiles and the bars denote minimum and maximum values.

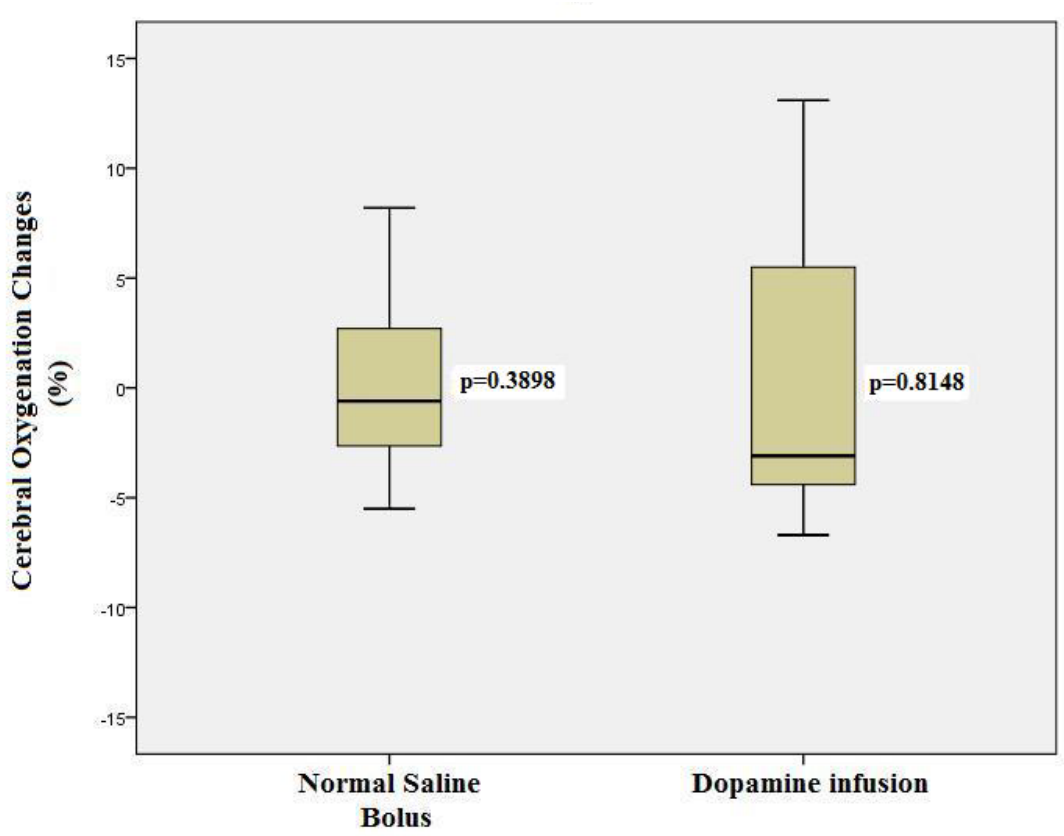

Figure 3-2. Changes in cerebral oxygenation with normal saline bolus and dopamine infusion. Box plots of the change in rSO2 with normal saline bolus and dopamine infusion. The horizontal line indicates median level of MAP, the box indicates 25th and 75th percentiles and the bars denote minimum and maximum values. Neither treatment resulted in a significant change in rSO2.

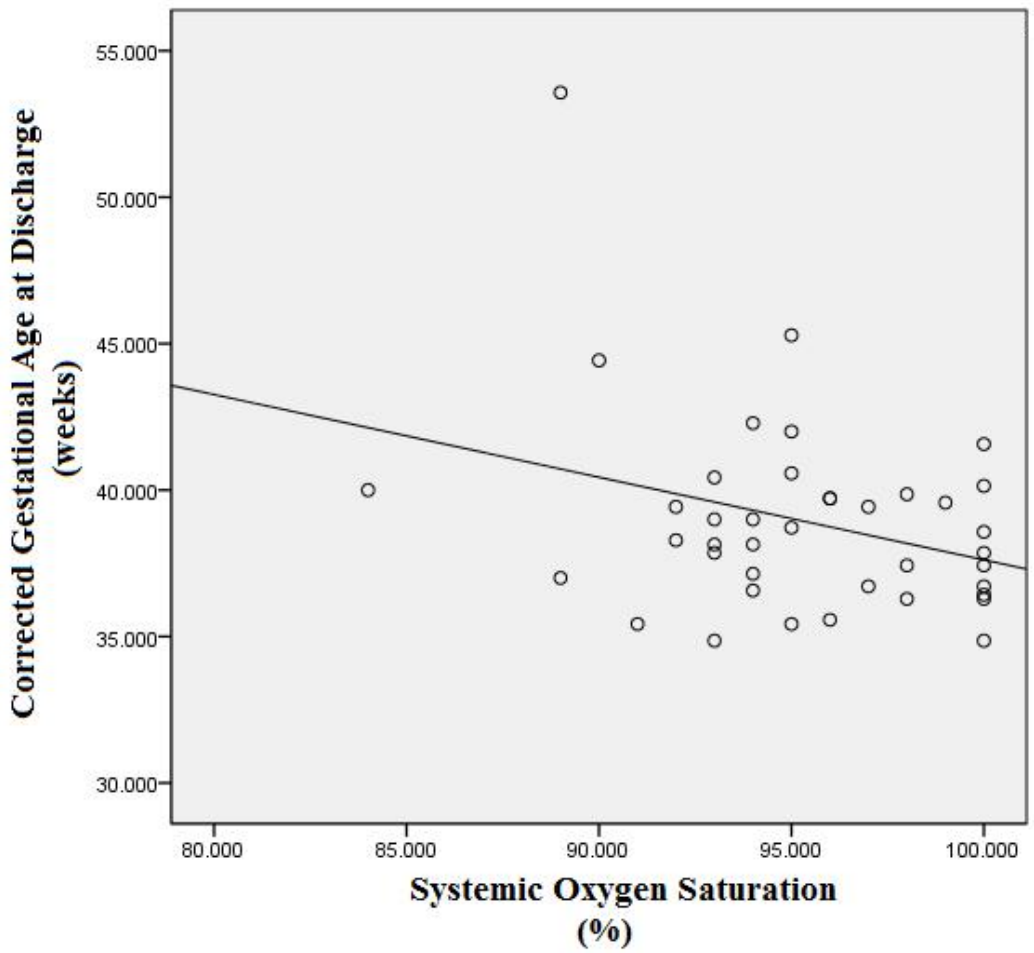

Figure 3-3. Systemic oxygen saturation and corrected gestational age at discharge correlation. Scatter plot of corrected gestational age at discharge and systemic oxygen saturation. Best fit line included (R2 linear of 0.099).

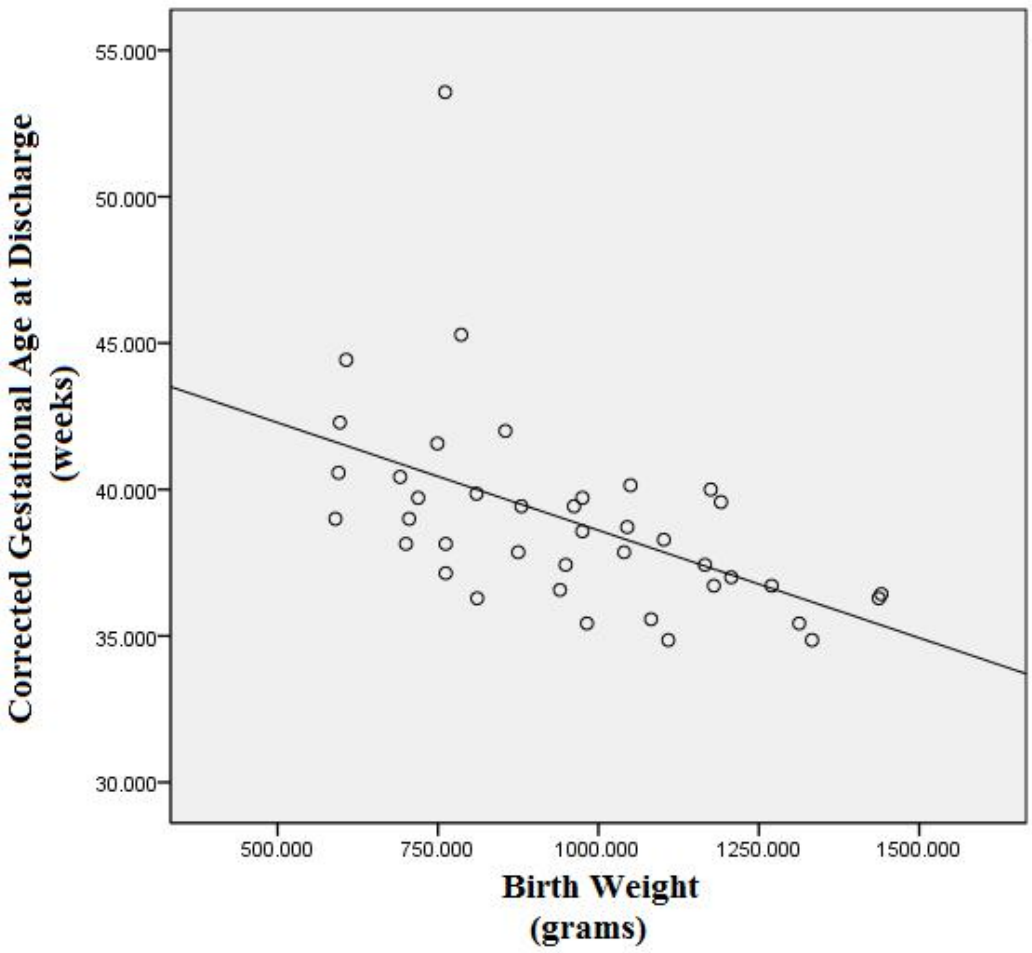

Figure 3-4. Birth weight and corrected gestational age at discharge correlation. Scatter plot of corrected gestational age at discharge and birth weight. Best fit line included (R^2 linear of 0.268).

CHAPTER 4
DISCUSSION

Summary and Significance of Results

Our study confirmed that blood pressure is a poor surrogate for cerebral perfusion in VLBW neonates. In neither of our cerebral oxygenation models did blood pressure play a significant determining role. Additionally, while treatment of hypotension improved blood pressure, it did not result in an improvement in cerebral oxygenation. Overall, these findings suggest that treatment should aim at improving cerebral oxygenation rather than hypotension.

Our regression models explored the impact of several variables on cerebral oxygenation in VLBW neonates. The cerebral oxygenation model inclusive of all 50 study subjects found only SpO2, Hct and pCO2 to be significant variables impacting cerebral oxygenation. From a physiologic standpoint, these variables should play an important role in cerebral oxygenation and perfusion as hematocrit determines oxygen carrying capacity, systemic oxygen saturations should impact regional oxygen saturations and pCO2 influences cerebral vascular resistance. While the variables within this model were statistically significant, the R^2 value was low at only 0.296. Thus, approximately 70% of cerebral oxygenation is determined by factors unaccounted for by the model.

In contrast, the cerebral oxygenation model for hypotensive patients included Hct, BW and Race as significant variables. Interestingly, hematocrit was the only consistent variable between the two models. In contrast to the model inclusive of all study subjects, the hypotensive patient model elicited race as a variable important for cerebral oxygenation, with African American and Other subjects exhibiting a lower

cerebral oxygenation than Caucasian subjects. Pigmentation cannot account for the racial differences in cerebral oxygenation as NIR photons penetrate through skin. Thus, some unknown racial difference other than skin pigmentation accounts for varying cerebral oxygenation in Caucasians and African Americans. The R^2 value for the hypotensive study subject model was 0.562, meaning that factors unaccounted for in the model account for approximately 46% of cerebral oxygenation. While this model was a better fit than the model inclusive of all study subjects, its goodness of fit was far from ideal.

The hypotension treatment data revealed that while two of our conventional therapies for neonatal hypotension increase blood pressure, they do not impact cerebral oxygenation. When used as treatment for hypotension, both normal saline and dopamine resulted in statistically significant changes in blood pressure (p-values of 0.0041 and 0.0163 respectively). Yet, neither normal saline nor dopamine resulted in any change in cerebral oxygenation (p-values of 0.3898 and 0.8148 respectively). When physicians treat hypotension, they aim to improve end organ perfusion, particularly cerebral perfusion. Based on our data, it appears that normal saline and dopamine improve the surrogate measure (blood pressure), but not cerebral oxygenation. Furthermore, while neonatologists have considered blood pressure an appropriate surrogate, using the NIRS technique we found that blood pressure is not an adequate measure of cerebral perfusion.

Our study also evaluated the impact of several variables we considered in our cerebral oxygenation model on discharge and survival outcomes. While we found several variables to be associated with longer time to discharge, we decided that time to

discharge is not an ideal outcome measure in this population. Neonates within the study were born at varying gestational ages. As a general rule, most preterm neonates reach discharge readiness close to their mother's due date. In order to be "discharge ready," a preterm neonate must have reached a sufficient weight to maintain an adequate body temperature outside the isolette, must be able to feed exclusively by mouth and gain weight and must outgrow apnea and bradycardia. Thus, we decided that corrected GA at discharge might provide a more standardized discharge measure for our study subjects of varying gestational ages. We found only two variables associated with an older corrected gestational age at discharge: lower birth weight and lower SpO2. Some neonates experience intrauterine growth restriction (IUGR) which results in a birth weight much lower than their counterparts who were a size appropriate for gestational age (AGA). IUGR neonates must reach a similar discharge weight as their AGA counterparts, which usually results in a greater corrected GA at discharge. The correlation between lower SpO2 and increased corrected GA at discharge, does not present a straightforward explanation. Perhaps the neonates with lower SpO2 at birth had worse respiratory distress syndrome and thus went on to develop chronic lung disease, increasing their corrected age at discharge.

We also examined the causes of death in the eight study subjects who died. The causes of death were common complications of prematurity and not unexpected. Lower birth weight and lower MAP were the only two variables significantly correlated with death. Neonates who are born at a lower birth weight have a lower chance of survival than those who are born at higher birth weight.[31] Three of the eight subjects died from necrotizing enterocolitis (NEC). While the etiology of NEC remains a mystery in our

field, some have hypothesized that mesenteric hypoperfusion is a major pathogenic factor.[32,33] Perhaps, these neonates suffered an early hypoperfusion insult which predisposed them to later development of NEC. Thus, the correlation between low MAP and death is not necessarily one of direct causation, and most likely multifactorial.

Study Limitations

One of the main limitations of our study was in its observational nature. The blood pressure treatment data was most affected by the observational design. Neonates were not randomized to treatment. Prior to receiving dopamine, neonates received a normal saline bolus. Had neonates been randomized to dopamine as a first line treatment of hypotension, results may have differed. Additionally, the non-randomized nature of our study limited neonates to the approach to hypotension treatment taken by clinicians in our unit. Other units employ a different treatment approach, using other vasopressors such as dobutamine and epinephrine and corticosteroids. The effects of these hypotension treatments were not investigated in our study as they were not used routinely by our treating physicians.

Our data points in the rSO2 analysis were taken from the time at which the neonate had an arterial blood gas including a pCO2. The treating team determined the timing of blood gas acquisition. While these blood gases were obtained within the first 24 hours of life, the exact timing was not consistent among the neonates. Ideally we would like to have acquired all data points for comparison at the same postnatal hour. However, the time to establish arterial access is impossible to standardize and thus some neonates had their first blood gas obtained earlier than others.

Future Directions

Our study yielded interesting results that should direct further study. Clearly, the two conventional treatments for hypotension we explored did not improve cerebral oxygenation. However, blood pressure was not a significant variable for rSO2 in our models. We suggest that blood pressure should no longer be used as a surrogate for cerebral perfusion. Rather, neonatologists can use rSO2 as a continuous, bedside marker of cerebral perfusion. Additionally, further exploration is warranted into treatments that can improve cerebral oxygenation and cerebral perfusion. Within neonatology our mindset has focused on blood pressure as a surrogate for cerebral perfusion. If we shift our mindset to cerebral oxygenation as a marker of cerebral perfusion we should investigate treatment of low cerebral oxygenation rather than hypotension. As hematocrit was the one consistent variable of significance in both rSO2 models, it may be worthwhile exploring the effects of blood transfusions on cerebral perfusion in neonates with low hematocrit and low rSO2. Additionally, past evidence has suggested that dobutamine[21] and albumin[20] may improve cerebral perfusion. A randomized trial evaluating the effects of dobutamine, albumin and red blood cell transfusions on rSO2 would be a valuable next step.

Another avenue warranting further exploration is the effect of low rSO2 on neurologic outcomes in VLBW neonates. Neurologic outcome measures should include neuroimaging in the form of cranial ultrasounds to evaluate for intraventricular hemorrhage and term equivalent brain MRIs to evaluate for PVL. Additionally, long-term follow up of VLBW neonates should include neurodevelopmental assessment in the form of a scoring system such as the Bayley psychomotor and mental test at 18-22 months, which is the typical follow-up time for this patient population.

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BIOGRAPHICAL SKETCH

Rachel S. Garner was born in Albuquerque, NM. She grew up in the San Francisco Bay area and graduated from Valley Christian High School (Dublin, CA) in 1997. She received her BS degree with a major in molecular, cell and developmental biology and minors in classical civilizations and political science from the University of California, Los Angeles in 2001. Rachel then attended Medical School at Albert Einstein College of Medicine in Bronx, NY where she received a Medical Doctorate with distinction in research in 2005. She completed her pediatrics residency at the University of Florida in 2008, where she received further training as a fellow in neonatology. Her fellowship research is supported by the American Heart Association Greater Southeast Affiliate Clinical Research Grant Program. After completing her fellowship in June 2011, she will continue her career in neonatology at the University of Arizona where she has accepted a faculty position.