ARTICLE

Cerebral Hemodynamic Changes During Intensive Care of Preterm Infants

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What's Known on This Subject

Preterm infants have immature hemodynamic regulation. Certain clinical events may be associated with major hemodynamic disturbances that predispose to brain injury.

What This Study Adds

By using a large sample, we demonstrated major systemic and cerebral circulatory disturbances across a range of event types matched to baseline quiet periods. Circulatory changes were associated with cranial ultrasound parenchymal abnormality and inversely related to maturation and illness severity.

ABSTRACT

OBJECTIVES. The objectives of this study were to examine the circulatory changes experienced by the immature systemic and cerebral circulations during routine events in the critical care of preterm infants and to identify clinical factors that are associated with greater hemodynamic-oxygenation changes during these events.

METHODS. We studied 82 infants who weighed <1500 g at birth and required intensive care management and continuous blood pressure monitoring from an umbilical arterial catheter. Continuous recording of cerebral and systemic hemodynamic and oxygenation changes was performed. We studied 6 distinct types of caregiving events during 10-minute epochs: (1) quiet baseline periods; (2) minor manipulation; (3) diaper changes; (4) endotracheal tube suctioning; (5) endotracheal tube repositioning; and (6) complex events. Each event was matched with a preceding baseline. We examined the effect of specific clinical factors and cranial ultrasound abnormalities on the systemic and cerebral hemodynamic oxygenation changes that were associated with the various event types.

RESULTS. There were highly significant differences in hemodynamics and oxygenation between events overall and baseline epochs. The magnitude of these circulatory changes was greatest during endotracheal tube repositioning and complex caregiving events. Lower gestational age, higher illness severity, chorioamnionitis, low Apgar scores, and need for pressor-inotropes all were associated with circulatory changes of significantly lower magnitude. Cerebral hemodynamic changes were associated with early parenchymal ultrasound abnormalities.

CONCLUSIONS. Routine caregiving procedures in critically ill preterm infants are associated with major circulatory fluctuations that are clinically underappreciated and underdetected by current bedside monitoring. Our data underscore the importance of continuous cerebral hemodynamic monitoring in critically ill preterm infants. *Pediatrics* 2008;122:e1006–e1013

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Key Words
prematurity, cerebral hemodynamics, systemic hemodynamics, brain injury

Abbreviations
MAP—mean arterial blood pressure
NIRS—near-infrared spectroscopy
Hbo_2—oxyhemoglobin
Hb—deoxyhemoglobin
Sao_2—oxyhemoglobin saturation
ET—endotracheal tube
HbD—hemoglobin difference signal
HbT—total hemoglobin
SNAP-II—Score for Neonatal Acute Physiology II
GM-IVH—germinal matrix–intraventricular hemorrhage

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SYSTEMIC AND CEREBRAL circulatory regulation is underdeveloped in the preterm infant.[1–7] Compared with the fetus of equivalent gestational age, the preterm infant experiences significantly greater variety and intensity of sensory stimulation. The impact of these experiences on the immature, particularly autonomic, nervous system remains poorly understood. Given the immature and inefficient cardiovascular regulation in the preterm infant and the known risk for cerebrovascular injury during this critical period of brain development, we urgently need to advance our understanding of the circulatory responses of preterm infants to potentially disturbing events during neonatal critical care, a need made more urgent as recent studies have demonstrated impaired structural and functional brain development in survivors of preterm birth.[8–18]

Our central hypothesis was that clinical events that occur during the critical care of these infants would be associated with significant hemodynamic oxygenation changes. Our goals were twofold. First, we sought to describe

changes in the immature systemic and cerebral circulations during routine events in critical care of the preterm infant. Second, we set out to identify clinical factors that are associated with greater hemodynamic oxygenation changes during these caregiving events.

METHODS

Selection Criteria

Infants who weighed <1500 g at birth and required intensive care management and continuous blood pressure monitoring from an umbilical arterial catheter were prospectively recruited for the study. We excluded infants with known congenital syndromes and those with evidence of antenatal brain injury by cranial ultrasound. The research was approved by the institutional review board at the Brigham and Women's Hospital. Informed written consent was obtained in all cases.

Study Design

Continuous Recording of Cerebral and Systemic Hemodynamic and Oxygenation Changes

Continuous recording of cerebral and systemic hemodynamic and oxygenation changes was performed in a manner previously described.[2] We recorded continuous mean arterial blood pressure (MAP) from the umbilical arterial catheter and time-locked these data with simultaneous continuous near-infrared spectroscopy (NIRS) recordings of changes in cerebral oxyhemoglobin (Hbo_2) and deoxyhemoglobin (Hb) concentration using a NIRO-500 spectrophotometer (Hamamatsu Photonics, Hamamatsu City, Japan).[2,19] In addition, we measured continuous Hbo_2 saturation (Sao_2) changes from a preductal site by using a pulse oximeter (Masimo, Irvine, CA). The MAP and Sao_2 were collected from the infant's bedside monitor through analog inputs in the NIRO-500 spectrophotometer. Recordings were continuous for up to 12 hours/day for the first 5 days after birth or until the umbilical arterial catheter was discontinued for clinical reasons. No catheter was placed or kept in place for research reasons alone. We used a sampling rate of 2 Hz, converted to digital format and stored in a laptop computer.

Identification of Event and Matched Baseline Data Sets

A study investigator was continuously present at the bedside and documented the precise timing of all events that occurred during the infant's care. We were thus able to define accurately 6 distinct types of 10-minute epochs: (1) quiet baseline periods; (2) minor manipulation; (3) diaper changes; (4) endotracheal tube (ET) suctioning; (5) endotracheal tube repositioning; and (6) complex events.

The bedside investigator identified periods during which the infants were inactive and quietly resting without spontaneous movements and without stimulation by caregivers. We selected 10-minute segments of such baseline data during the period before each event. Minor manipulation by caregivers (eg, auscultation) involved tactile stimulation with or without elicited infant movements but without significant repositioning of the infant. Diaper changes were performed by gently elevating the legs and buttocks, replacing the diaper, and then lowering the legs. The position of the thorax did not change relative to the blood pressure transducer, which was aligned at an atrial level. ET suctioning in our NICU is performed by a consistent protocol, in which brief preoxygenation is followed by in-line, closed suctioning. Closed suctioning reduces ET movement and tracheal stimulation and provides a continuous fraction of inspired oxygen and positive pressure that in part compensates for the decrease in airway pressure caused by suctioning. By using predetermined measurements, care is taken to advance the suction catheter only as far as the end of the ET to prevent direct tracheal trauma. ET repositioning is achieved by stabilizing the infant's head and neck while gently lifting the adhesive tape used to attach the ET to the infant's skin. The tube is then repositioned and retaped. When 2 or more of the events occurred during a 10-minute period, the epoch was designated a complex event.

Artifact Identification and Exclusion

Because the caregiving events studied here are not only periods of increased risk for true circulatory changes but also for artifactual signal changes, we performed a particularly rigorous series of checks to exclude artifact from our analyses. First, the bedside investigator was skilled at identifying potential sources of artifact that originated from the bedside recording devices and closely monitored recording devices during interventions. Any recordings during which the quality of the data could not be ensured were excluded from the outset. We performed a second level of artifact detection and rejection off-line, by identifying and rejecting obvious artifact by visual inspection (Fig 1) and then ran all data through a computer program with preset physiologically plausible limits for each signal.[2] Specifically, we used the following criteria for automated artifact detection and rejection. Hemoglobin difference signal (HbD) and total hemoglobin (HbT) were calculated from the raw data recordings of Hbo_2 and Hb. We rejected from the raw database any periods when Hbo_2 and/or Hb changed between 2 adjacent data points (0.5 seconds) by >10 μmol/L or >7 SD of the mean Hbo_2 (or Hb) for that data epoch. Similarly, we rejected data for which MAP changed between 2 adjacent data points by >15 mm Hg. For the Sao_2, visual inspection was used because these artifacts are easily identifiable (Fig 1).

Data Processing and Analysis

We analyzed only 10-minute event epochs with at least 80% (ie, 8 minutes) of artifact-free data points and with a matched preceding baseline epoch of data. This matching process allowed us to compare the hemodynamic changes not only across patients but also within patients and within a narrow postnatal age.

Systemic Hemodynamic and Oxygenation Variables

Systemic hemodynamic (MAP) and oxygenation (Sao_2) variables were calculated in 2 ways. Ten-minute

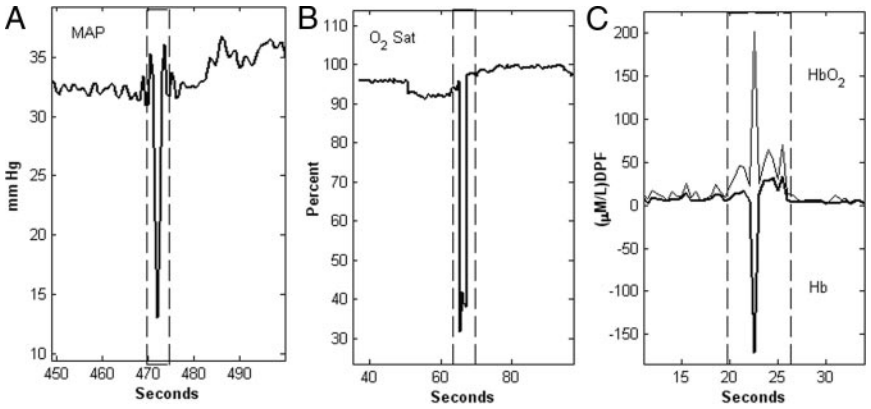

FIGURE 1
Examples of signal artifact identified by visual inspection and rejected during the initial phase of data screening. Artifacts shown are in the mean arterial pressure signal (A), the pulse oximetry signal (B), and the NIRS signals (C) for cerebral concentration changes in Hbo_2 and Hb. DPF indicates the differential pathlength factor.

mean (and SD) of Sao_2 (μSao_2) and MAP (μMAP) was calculated for each epoch. Maximum change in Sao_2 (ΔSao_2) and MAP (ΔMAP) was derived from the maximum minus minimum value of Sao_2 and MAP within the 10-minute epoch.

Cerebral Hemodynamic and Oxygenation Variables

We calculated changes in the HbD (HbD = Hbo_2 − Hb), previously shown to be highly correlated with changes in cerebral blood flow in animal models,[20,21] and changes in total hemoglobin (HbT = Hbo_2 + Hb) concentration, a reflection of changes in cerebral blood volume. The cerebral circulatory measures were expressed only as ΔHbD and ΔHbT within 10-minute epochs. Mean values of HbD and HbT were not derived; the NIRS technique used in this study does not measure the absolute cerebral concentration of Hbo_2 and Hb but rather measures absolute change in concentration from an arbitrary 0 point. We then compared the measurements between each event and its preceding baseline epoch, calculating event minus baseline measures of μMAP, ΔMAP, μSao_2, ΔSao_2, ΔHbT, and ΔHbD.

Clinical Data Collection

We examined the effect of specific clinical factors with potential hemodynamic impact on systemic and cerebral circulatory changes that were associated with various event types. We abstracted from the medical charts pertinent data regarding the maternal, pregnancy, labor/delivery, and neonatal histories (Table 1). Chorioamnionitis was recorded when documented in the clinical record by the treating obstetrician or in placental pathology records. Neonatal clinical sepsis was diagnosed by positive blood, urine, or mucosal culture or by clinical suspicion that resulted in a full course of antibiotic treatment despite negative cultures. We also calculated the Score for Neonatal Acute Physiology II (SNAP-II).[22]

Cranial Ultrasound Data

We were interested in whether the presence of brain injury might influence the circulatory measurements recorded in this study, although this factor was not a primary outcome. Stable preterm infants in our NICU undergo cranial ultrasound studies (Acuson Sequoia [Siemens, Malvern, PA]) at approximately 3, 7, and 30 days of life; however, in sick preterm infants, such as those in this study, the timing of cranial ultrasound studies was dictated primarily by clinical indications and was therefore not consistent. Because cerebral hemorrhagic and major hypoxic-ischemic injuries that were present during our circulatory studies would be detected by cranial ultrasound studies that were performed between 5 and 10 days, we included only ultrasound studies that were performed during this period. Cranial ultrasound abnormalities were categorized as germinal matrix–intraventricular hemorrhage (GM-IVH; any grade), parenchymal abnormalities (cerebral and/or cerebellar echodensities), or overall ultrasound abnormality (GM-IVH or parenchymal abnormality, or both).

TABLE 1 **Maternal, Intrapartum, Neonatal, and Postnatal Characteristics ($N = 82$)**

Characteristic	Data
Preterm labor, *n* (%)	61 (74)
Maternal steroids, *n* (%)	74 (90)
Pregnancy-induced hypertension, *n* (%)	9 (11)
Acute intrapartum hemorrhage, *n* (%)	13 (16)
Maternal temperature >100.4, *n* (%)	9 (11)
Cesarean section, *n* (%)	53 (65)
Chorioamnionitis, *n* (%)	33 (40)
Gestational age, median (range), wk	26 (23–30)
Birth weight, median (range), g	863 (460–1490)
Male gender, *n* (percent)	46 (56)
Apgar score at 5 min, median (range)	7 (0–9)
SNAP-II score, median (range)	24 (0–56)
Pressor-inotrope support, *n* (%)	64 (78)
Patent ductus arteriosus, *n* (%)	15 (18)
Clinical sepsis, *n* (%)	23 (28)
Days on mechanical ventilation, median (range)	29 (0–130)
Days on oxygen, median (range)	59 (3–134)
Death, *n* (%)	4 (5)
IVH grade I–III, *n* (%)	27 (33)
Parenchymal abnormalities, *n* (%)	14 (17)
Overall (IVH and/or parenchymal abnormalities), *n* (%)	30 (37)

Statistical Analysis

Changes in hemodynamic and oxygenation measures from baseline to event epochs were evaluated using the paired *t* test. Generalized estimating equations models were used to examine univariate associations between these measures and patient clinical factors and ultra-

TABLE 2 **Effect of Clinical Events on Systemic and Cerebral Hemodynamics and Oxygenation**

Parameter	μMAP, Mean (SD)	ΔMAP, Mean (SD)	μSao_2, Mean (SD)	ΔSao_2, Mean (SD)	ΔHbD, Mean (SD)	ΔHbT, Mean (SD)
Overall events ($n = 480$)	38.7 (5.9)	18.1 (7.2)	93.2 (3.6)	13.9 (10.1)	15.4 (8.2)	23.3 (14.7)
Overall baselines ($n = 480$)	37.6 (5.3)	10.7 (4.6)	94.5 (3.0)	7.8 (8.5)	8.4 (3.9)	13.9 (7.1)
P	<.001	<.001	<.001	<.001	<.001	<.001
Diaper change						
Event ($n = 80$)	38.6 (5.6)	17.6 (6.4)	93.6 (3.9)	13.4 (8.6)	13.9 (6.4)	22.9 (15.3)
Baseline ($n = 80$)	37.5 (5.2)	10.6 (4.0)	95.0 (3.2)	7.4 (8.9)	7.9 (3.6)	13.0 (6.9)
P	.017	<.001	.062	<.001	<.001	<.001
ET repositioning						
Event ($n = 13$)	40.5 (5.7)	23.3 (8.4)	92.0 (3.5)	15.8 (7.4)	23.9 (10.7)	44.4 (28.3)
Baseline ($n = 13$)	37.4 (3.6)	10.7 (4.4)	93.7 (4.3)	6.4 (5.9)	8.9 (5.2)	14.4 (7.5)
P	<.001	<.001	.810	.015	<.001	.002
ET suctioning						
Event ($n = 96$)	37.3 (5.4)	17.9 (7.7)	93.1 (3.0)	15.4 (9.4)	16.7 (8.6)	22.6 (12.1)
Baseline ($n = 96$)	36.4 (4.7)	9.9 (4.2)	94.5 (2.8)	6.9 (6.8)	7.7 (3.4)	13.0 (6.5)
P	.054	<.001	<.001	<.001	<.001	<.001
Minimal manipulation						
Event ($n = 138$)	38.4 (6.0)	16.1 (6.5)	93.6 (3.5)	12.2 (9.2)	13.4 (6.9)	21.9 (14.3)
Baseline ($n = 138$)	38.0 (5.6)	10.9 (4.6)	94.3 (3.1)	8.2 (7.9)	9.1 (4.2)	15.1 (8.0)
P	.003	<.001	<.001	.001	<.001	<.001
Complex Event						
Event ($n = 48$)	39.1 (6.3)	21.4 (8.0)	92.5 (4.1)	18.0 (13.7)	17.0 (9.8)	26.5 (16.5)
Baseline ($n = 48$)	36.5 (5.2)	10.5 (4.7)	95.1 (2.4)	7.3 (9.5)	7.0 (3.3)	11.7 (6.1)
P	<.001	<.001	<.001	<.001	<.001	<.001

P values indicate the statistical significance of the difference between the matched event-baseline epochs.

sound abnormalities; these models account for the correlation among multiple events within the same patient. Regression coefficients (β) and *P* values are reported. The regression coefficient estimates the change in outcome variable (hemodynamic or oxygenation measure) that is associated with the presence of a dichotomous clinical factor (eg, birth by cesarean section, pressor support) or with a specified increase in a continuous factor (eg, 1-week increase in gestational age, 100-g increase in birth weight). Generalized estimating equations models were also used for multivariate analyses of each outcome; explanatory variables in the models were birth weight, cesarean section, chorioamnionitis, SNAP-II score, pressor support, patent ductus arteriosus, and clinical sepsis.

RESULTS

Population Characteristics

We enrolled 82 infants at a median gestational age of 26 weeks (range: 23–30 weeks) and median birth weight of 863 g (range: 460–1490 g). The mean age at onset of recordings was 11.5 hours, with 50 (61%) starting within 12 hours and all but 2 starting within 24 hours of birth (Table 1).

Circulatory Changes Associated With Clinical Events and Matched Baselines

We analyzed 480 artifact-free events that could be matched with preceding 10-minute baseline epochs of quiet rest. The median number of events per subject was 6 (range 1–17). Table 2 shows circulatory measures for all event epochs and all baseline epochs, as well as for the 5 specific event categories. There were highly significant differences in hemodynamics and oxygenation between events overall and baseline epochs ($P < .001$ for all). For the large majority of event types, circulatory measures were significantly different from those in the matched baseline epochs.

Relationship Between Events and Early Cranial Ultrasound Abnormalities

Early IVH (grades I–III) was diagnosed in 27 (33%) preterm infants, whereas 14 (17%) had parenchymal abnormalities. Overall ultrasound abnormality (IVH and/or parenchymal abnormalities) was present in 30 (37%). Early IVH was significantly related to changes in mean Sao_2 ($\beta = 0.86$; $P = .01$) for events overall. Early parenchymal ultrasound abnormalities were associated with significant changes in HbD ($\beta = 16.1$; $P < .001$) and HbT ($\beta = 22.9$; $P = .05$) and with greater changes in Sao_2 ($\beta = 5.7$; $P = .01$). Similarly, overall ultrasound abnormality (IVH and/or parenchymal abnormality) on early ultrasound studies was associated with significantly greater differences in mean Sao_2 across all events ($\beta = 1.0$; $P = .002$), as well as with Sao_2 change during ET manipulation ($\beta = 5.7$; $P = .01$; Table 3).

Relationship Between Clinical Factors and the Hemodynamic Oxygenation Changes With Specific Event Types

We first performed univariate analyses to examine the association between clinical factors and the hemodynamic measure during each event type. Table 4 shows those relationships that achieved statistical significance on univariate analysis. Next we performed a multivariate analysis by entering only factors for which the uni-

TABLE 3 **Relationship (*P* Value) Between Events, Circulatory Measures, and Clinical Factors (Univariate Analysis)**

Parameter	ΔMAP	ΔSao_2	ΔHbD	ΔHbT
Overall events				
Birth weight	0.64 (.004)			0.94 (.020)
GA	0.63 (.020)	1.10 (.030)		
SNAP	−0.12 (<.001)	−0.30 (<.001)	−0.01 (.004)	
CA		−4.70 (.007)		
eIVH		0.86 (.01)		
eParen		5.70 (.010)	16.10 (<.001)	22.90 (.050)
eOverall		1.00 (.002)		
Minor events				
PDA			−2.50 (.030)	−4.60 (.010)
Diaper change				
Birth weight		1.08 (.050)		
GA		2.10 (<.001)		1.40 (.040)
SNAP		−0.27 (.010)		
PDA			2.60 (.030)	
CS				5.00 (.030)
Apg				−7.20 (.010)
ET suction				
GA	1.40 (.010)	1.50 (.040)		
SNAP		−0.29 (<.001)	−0.11 (.010)	
Apg				−6.80 (.040)
ET Reposition				
GA		4.90 (<.001)		
PRES		12.90 (<.001)		−35.80 (<.001)
eOverall		5.70 (.010)		
CA			−10.90 (.030)	
SNAP			−0.50 (.001)	
PDA			−9.60 (.002)	
Complex events				
CA		−12.80 (.006)	−2.30 (.005)	
SNAP			−0.73 (<.001)	
PRES			−8.00 (.010)	
PDA			−7.30 (.040)	
GA				3.40 (.020)

GA indicates gestational age; CA, chorioamnionitis; eIVH, intraventricular hemorrhage on early ultrasound; eParen, parenchymal abnormality on early ultrasound; eOverall, intraventricular hemorrhage and/or parenchymal abnormality on early ultrasound; PDA, patent ductus arteriosus; CS, cesarean section; Apg, Apgar score at 5 minutes; PRES, pressor-inotrope support.

variate analysis *P* value was ≤.1. Here we report only the clinical factors that remained significant at $P < .05$ in the multivariate analysis.

Multivariate Analyses

Multivariate analyses demonstrated that chorioamnionitis, birth weight, SNAP-II scores, and overall abnormality on early ultrasound (IVH and/or parenchymal abnormality) were independent predictors of systemic and cerebral hemodynamic disturbances for overall events compared with baselines. The diagnosis of chorioamnionitis was inversely related to changes in Sao_2 ($\beta = -3.3$, $P = .01$). Greater changes in Sao_2 were related to overall abnormality on early ultrasound. Higher birth weight was significantly associated with greater changes in MAP ($\beta = 0.46$, $P = .04$), HbD ($\beta = 0.41$, $P = .03$), and HbT ($\beta = 0.86$, $P = .03$). Higher SNAP-II scores were inversely related to changes in MAP ($\beta = -1.1$, $P = .002$), Sao_2 ($\beta = -2.8$, $P < .001$), and HbD ($\beta = -.79$, $P = .02$).

During minor manipulations, infants with higher SNAP-II scores had significantly smaller changes in HbD ($\beta = -1.01$, $P = .01$). Conversely, during diaper changes, higher SNAP-II scores predicted significantly greater changes in HbD ($\beta = 1.15$, $P = 002$), and higher birth weight was associated with greater HbT changes ($\beta = 1.21$, $P = .02$). During ET suctioning, infants with higher SNAP-II scores had smaller differences in MAP ($\beta = -1.60$, $P = .008$) and HbD changes ($\beta = -1.26$, $P = .009$). During complex events, chorioamnionitis ($\beta = -6.6$, $P = .04$) and higher SNAP-II scores ($\beta = -6.41$, $P = .005$) were associated with differences in Sao_2 changes; pressor support was inversely related to change in MAP ($\beta = -5.2$, $P = .003$) and SNAP-II score. ET repositioning events were excluded from this part of the analysis because of the relatively small number of such events.

DISCUSSION

We describe striking circulatory changes during routine interventions in the critical care of preterm infants. Circulatory changes to the clinical events in general were significantly greater than those that occurred during matched baseline periods of quiet rest. The magnitude of these circulatory responses was significantly lower among the most immature and sickest infants. These circulatory changes differed across the various clinical event categories but were most striking during ET repositioning and complex caregiving events. Cerebral circulatory changes were associated with early parenchymal ultrasound abnormalities.

The impact of the studied events on cerebral circulation is best appreciated when considering that total cerebral hemoglobin concentration during the first days after preterm birth is ~65 μM/L[23]; therefore, cerebral hemoglobin varies by ~20% even during baseline restful periods, and even minor manipulations cause fluctuations of >30% in total cerebral hemoglobin. The association between these changes in cerebral Hbo_2 and HbT and the presence of parenchymal ultrasound abnormalities is particularly concerning given that cranial ultrasound detects only major parenchymal lesions.[24] During ET repositioning, these fluctuations in cerebral Hbo_2 and total HbT are threefold greater than those in the matched baselines and represent an ~65% change in expected total cerebral hemoglobin.

Potential mechanisms underlying the circulatory changes in the preterm infants described in this study are multiple, complex, and poorly understood. A general protective response to stimulation may trigger systemic hemodynamic responses through activation of the sympathetic nervous system. Both global and regional coupling mechanisms between neural activation and blood flow are known to be active in preterm infants.[25–32] Repositioning of the ET was associated with the greatest perturbations in both the systemic and cerebral circulations in our study. In previous studies, ET suctioning was associated with a transient decrease in heart rate,[31–35] likely a parasympathetic reflex[32,36,37] to unloading of pulmonary pressure receptors. Sympathetic activation[32,35,38–40] by transient hypoxemia and direct tactile stimulation of tracheal sympathetic receptors triggers systemic arterial hypertension.[35,38–40] A tran-

sient increase in intracranial pressure previously described[32,35,40–42] may be related to an overwhelmed cerebral pressure autoregulation with a significant increase in cerebral blood volume, as suggested by the striking increase in total cerebral hemoglobin noted in our study.[35,43] Techniques such as preoxygenation[44] and closed suctioning may reduce the sympathetic activation; both techniques are used at our center, where we are careful to avoid direct tracheal stimulation with the suction catheter during ET suctioning; however, during repositioning of the ET, some degree of tracheal stimulation is inevitable and likely underlies the marked circulatory responses. These practices may explain the significant difference in circulatory fluctuation between ET suctioning and ET repositioning in our study.

We describe for the first time important systemic and cerebral circulatory changes during diaper changes. It is interesting that similar maneuvers are used to test autonomic cardiac reflexes in mature individuals.[45] The potential mechanisms underlying these changes include abrupt increases in venous return and cardiac preload with elevation of the lower extremities, which together with a potential Valsalva-type effect on the diaphragm may alter cerebral perfusion pressure through effects on both arterial and venous compartments.

Our data also demonstrate that maturation and illness severity were significant modifiers of event-related circulatory fluctuations. Specifically, lower gestational age, higher SNAP-II scores,[22] chorioamnionitis, low Apgar scores, and pressor-inotrope treatment all were associated with circulatory changes of significantly lower magnitude. Our findings likely reflect a critical immaturity of the autonomic nervous system in sick preterm infants.[46] Recent studies showed reduced physiologic responses to noxious stimuli in preterm infants,[47–50] including reduced autonomic (especially sympathetic) activity and central behavioral responses.[51] Recent cerebral NIRS studies demonstrated cortical responses to noxious stimuli in infants as young as 25 weeks' gestation,[28,52] which decreased significantly with lower gestational age. Gibbons et al[49,50] showed that extremely low gestational age and severity of illness were associated with a reduced response to noxious stimuli. Infection-inflammation has potentially profound effects on systemic and cerebral hemodynamics in the fetus,[53] preterm infant,[54] and adult.[55] Antenatal steroid exposure has been associated with improved postnatal BP control,[56,57] possibly mediated by increased postnatal sympathetic activity.[58–60] In our study, antenatal steroid exposure had no significant association with event-related circulatory changes in the postnatal period.

In this study, fluctuations in cerebral oxygenation and blood volume were associated with early parenchymal abnormalities. Such fluctuations might suggest failure of intrinsic cerebral vasoregulation, a known risk factor for brain injury in the high-risk infant; however, we used clinically indicated cranial ultrasound studies that were not performed at consistent, closely spaced intervals. Furthermore, preceding brain insults may disrupt cerebral autoregulation. For these reasons, we are unable to examine the cause-and-effect relationship between the circulatory changes and cranial ultrasound findings. These observations warrant additional investigation into the causal nature of the relationship.

Our study had several particular strengths, including the large number of patients and measurement epochs and the matching of each event with a preceding quiet baseline period. In addition, we used high sampling rates of invasively measured blood pressure and continuous cerebral measures using NIRS. The data were subjected to a stringent, multitiered process of artifact detection and rejection. However, there are also several limitations to this study. By confining our blood pressure measures to direct intra-arterial measurements, we could study infants only when indwelling catheters were in place. Because we rigorously identified and excluded data with suspected artifact and events without a preceding quiet baseline period, we were unable to assess the association between the cumulative effect of event-related circulatory changes during the early days of life and findings on cranial ultrasound. Furthermore, as described already, our ultrasound studies have limitations in the consistency and frequency of their timing. Finally, the acute illness severity in our population, as indicated by the need for continuous blood pressure monitoring, high SNAP-II scores, and a high prevalence of ultrasound abnormalities, may preclude direct translation of these data to less acutely ill preterm infants.

CONCLUSIONS

Our findings demonstrate that routine caregiving procedures in critically ill preterm infants are associated with major circulatory fluctuations that are clinically underappreciated. These findings emphasize the need for more advanced continuous bedside monitoring, particularly of the newborn brain. Additional studies that combine acute and intensive circulatory measurements, such as those used here, with advanced neuroimaging and comprehensive neurodevelopmental outcomes are needed to develop rational brain-oriented caregiving practices that minimize brain injury in this fragile population.

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