Use of Antihypotensive Therapies in Extremely Preterm Infants

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KEY WORDS

extremely preterm infant, antihypotensive therapy, blood pressure, hypotension

ABBREVIATIONS

BP—blood pressure
GA—gestational age
IVH—intraventricular hemorrhage
MAP—mean arterial pressure
NRN—Neonatal Research Network
ROP—retinopathy of prematurity

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WHAT'S KNOWN ON THIS SUBJECT: Extremely preterm infants who receive antihypotensive therapy have worse outcomes than untreated infants. The reasons for this are not clear. High-quality randomized trials have not been performed to date because of logistical challenges, thereby necessitating alternative methods of investigation.

WHAT THIS STUDY ADDS: Antihypotensive therapy administration was not associated with improved in-hospital outcomes for any of the 15 definitions of low blood pressure investigated. Alternative methods of deciding who to treat are needed to maximize patient benefit and minimize harm.

abstract

OBJECTIVE: To investigate the relationships among blood pressure (BP) values, antihypotensive therapies, and in-hospital outcomes to identify a BP threshold below which antihypotensive therapies may be beneficial.

METHODS: Prospective observational study of infants $23^{0/7}$ to $26^{6/7}$ weeks' gestational age. Hourly BP values and antihypotensive therapy use in the first 24 hours were recorded. Low BP was investigated by using 15 definitions. Outcomes were examined by using regression analysis controlling for gestational age, the number of low BP values, and illness severity.

RESULTS: Of 367 infants enrolled, 203 (55%) received at least 1 antihypotensive therapy. Treated infants were more likely to have low BP by any definition ($P < .001$), but for the 15 definitions of low BP investigated, therapy was not prescribed to 3% to 49% of infants with low BP and, paradoxically, was administered to 28% to 41% of infants without low BP. Treated infants were more likely than untreated infants to develop severe retinopathy of prematurity (15% vs 8%, $P = .03$) or severe intraventricular hemorrhage (22% vs 11%, $P < .01$) and less likely to survive (67% vs 78%, $P = .02$). However, with regression analysis, there were no significant differences between groups in survival or in-hospital morbidity rates.

CONCLUSIONS: Factors other than BP contributed to the decision to use antihypotensive therapies. Infant outcomes were not improved with antihypotensive therapy for any of the 15 definitions of low BP investigated. *Pediatrics* 2013;131:e1865–e1873

The intrinsically abnormal condition of extremely preterm infants and their evolving complex physiology make it difficult to identify an acceptable range of blood pressure (BP) values in the immediate postnatal period. Currently, there is not a validated or widely accepted definition of hypotension in this population.[1] Difficulty with assessing organ perfusion, multiple disease processes, and unpredictable adaptation to extrauterine life also make deciding when to institute antihypotensive therapy challenging. Consequently, BP management is highly variable.[2,3] The frequency of antihypotensive therapy use during the transition from intrauterine to postnatal life ranges from 29% to 82% across NICUs.[3,4] Extremely preterm infants who receive these therapies have higher mortality and morbidity rates versus untreated gestational age (GA) matched infants,[4–12] but it is unclear whether these worse outcomes are due to the cause of low BP, associated organ hypoperfusion, therapy for low BP, or a combination of these and other factors. Interpretation of BP management data is also complicated by methodologic limitations and confounding factors, both known and unknown.[1]

Randomized placebo controlled trials investigating BP management in this population are lacking.[1] This is at least partly due to the many challenges of studying critical therapeutic interventions shortly after birth in such a vulnerable patient population. These include the inability to obtain timely and ethically valid informed consent, insufficient physician equipoise, identification of appropriate inclusion and exclusion criteria, and enrollment or selection biases.[13–16]

Difficulties with randomized placebo controlled trials have led to alternative methods of investigating BP management in preterm infants.[1,7–9,17] However, these studies are limited by their retrospective design, small sample sizes, and inconsistent definition of low BP. Currently, there is no known BP threshold below which extremely preterm infants are at an increased risk for a poor outcome and little evidence that antihypotensive therapy improves outcomes for infants with low BP, however defined. The objectives of this study were to prospectively examine BP management in the first 24 hours for extremely preterm infants and to investigate the relationship between recorded BP values, antihypotensive therapy use, and in-hospital infant outcomes in an effort to identify a BP threshold below which therapy may be beneficial.

METHODS

This was a prospective observational study of inborn extremely preterm infants $23^{0/7}$ to $26^{6/7}$ weeks' GA born at 1 of 16 academic centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN). Infants were excluded if they died in the delivery room, had a major birth defect, or had intensive care withheld or withdrawn shortly after birth because the clinical care team felt the situation was hopeless. Research personnel used study-specific data forms to record hourly BP values and the administration of all antihypotensive therapies in the first 24 hours. BP values were obtained from an arterial catheter when available or by oscillography. Antihypotensive therapy was defined as receipt of a fluid bolus (at least 10 mL/kg of crystalloid), dopamine, dobutamine, epinephrine, hydrocortisone, vasopressin, or any blood product. Therapies were administered at the discretion of the clinical care team. Data were recorded on maternal demographics, the infant's initial condition, and in-hospital outcomes. Standard definitions were applied for intraventricular hemorrhage (IVH),[18] necrotizing enterocolitis,[19] retinopathy of prematurity (ROP),[20] and bronchopulmonary dysplasia.[21] This study was approved by the institutional review board at each participating center and was conducted either with informed parent consent for each infant before enrollment or with a waiver of consent from the center's institutional review board.

For all analyses, 15 definitions of low BP were investigated: 1, 2, or ≥3 systolic, diastolic, or mean BP values less than or equal to the fifth percentile; 1, 2, or ≥3 mean arterial pressure (MAP; in mm Hg) values less than or equal to the infant's GA equivalent (in weeks); and 1, 2, or ≥3 MAP values ≤25 mm Hg. Low BP values were not necessarily consecutive. At each postnatal hour, BP percentiles were constructed for different populations (all infants, only infants who did not receive therapy, and at each specific GA) by using 2 sets of BP values (all BP values versus only invasive BP values). The fifth percentile was numerically similar (within 2 mm Hg) for all populations analyzed, and results were statistically similar irrespective of which construct was used to define the fifth percentile. Only results from the entire study population are reported. Data analyses were performed at the NRN Data Coordinating Center (RTI International, Research Triangle Park, NC). Data were entered remotely by electronic submission and periodically reviewed for quality control. Statistical analysis was performed by using SAS 9.2 software (SAS Institute, Inc, Cary, NC). The *t* test was used for continuous variables, and the χ^2 test was used for categorical variables to compare differences between infants who did versus did not receive antihypotensive therapy. Associations between antihypotensive

therapy and in-hospital outcomes were examined by using logistic models with a random intercept for NRN center while controlling for GA, illness severity, and the number of low BP values. Illness severity was defined a priori as the cumulative number of the following: a positive initial blood culture, an initial hematocrit ≤30%, a 1-minute Apgar score of ≤3, a pH <7.10 in the first 24 hours, or need for delivery room chest compressions. Regression analysis was used to investigate the relationship between NRN center variability in the frequency of low BP values and the rate of antihypotensive therapy administration and to investigate the impact of NRN center variability in the rate of antihypotensive therapy administration on patient outcomes.

RESULTS

From July 21, 2010, to January 21, 2011, there were 367 infants enrolled, including 203 (55%) infants who received ≥1 antihypotensive therapy and 104 (28%) who received a vasoactive drug (Fig 1). Fifteen enrolled infants (8 untreated, 7 treated) died in the first 24 hours. Of the 203 treated infants, 135 (67%) received a fluid bolus, 102 (50%) received a blood product, and 92 (45%), 25 (12%), and 18 (9%) received dopamine, hydrocortisone, and dobutamine, respectively. One patient received vasopressin. Many infants given a vasoactive drug also received a fluid bolus or blood product. The frequency of antihypotensive therapy use was inversely related to birth weight ($P < .001$) and GA ($P < .001$); 130 (64%) infants with a birth weight ≤750 g received therapy versus 73 (45%) infants with a birth weight of 750 to 1000 g and 88 (66%) infants born at 23 to 24 weeks' GA received therapy versus 115 (49%) infants born at 25 to 26 weeks' GA.

There were 18 709 BP values recorded (6236 systolic, 6227 diastolic, and 6246 MAP). An umbilical arterial catheter was placed for 298 (81.2%) infants, invasive BP values were obtained from 306 (83.4%) infants, and 14 593 (78%) BP values were obtained from an arterial catheter. Antihypotensive therapies were administered at similar rates for infants with low BP based on invasive versus noninvasive BP values. For the definitions of low BP investigated, the likelihood of treatment increased with the number of low BP values (Fig 2; $P < .001$); antihypotensive therapy was administered to 28% to 41% of infants without any low BP values, 51% to 77% of infants with 1 or 2 low BP values, and 71% to 97% of infants with ≥3 low BP values. Antihypotensive therapy use was lowest in infants who never had an MAP ≤25 mm Hg or the infant's GA equivalent (28% for both definitions of low BP). Three or more low BP values less than or equal to the fifth percentile of the systolic (83%), diastolic (93%), or MAP (97%) BP was associated with the highest antihypotensive therapy rates. Most treated infants had multiple low BP values. For example, 110 (54%) treated infants had ≥3 MAP values less than or equal to the infant's GA equivalent, including 81 (78%) infants who received a vasoactive drug.

Some, but not all, baseline characteristics differed between the 164 untreated infants and the 203 infants who received therapy (Table 1). In-hospital outcomes for these groups are presented in Table 2. The significant difference in the rate of survival to hospital discharge between the 2 groups was primarily due to a higher mortality rate after the first postnatal week for infants who received therapy (19% vs 11%) as the rate of survival to 1 week was not significantly different between groups. Logistic regression analysis with a random intercept for center controlling for GA, severity of illness, and the number of low BP values did not show any significant effects of antihypotensive therapy on rates of IVH or grade III/IV IVH, ROP, morbidity-free survival to hospital discharge (morbidity: necrotizing enterocolitis, ROP, bronchopulmonary dysplasia, grade III/IV IVH, or cystic periventricular

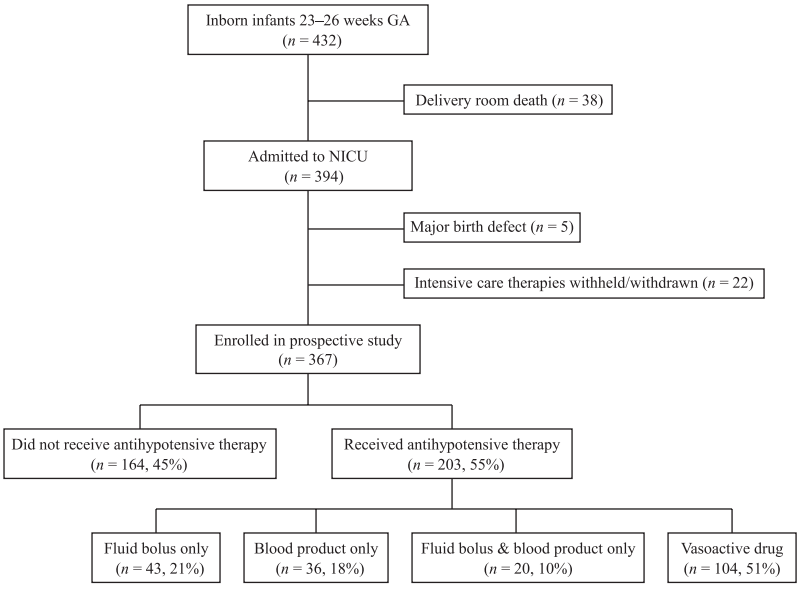

FIGURE 1
Extremely preterm infant study enrollment including classification by study group.

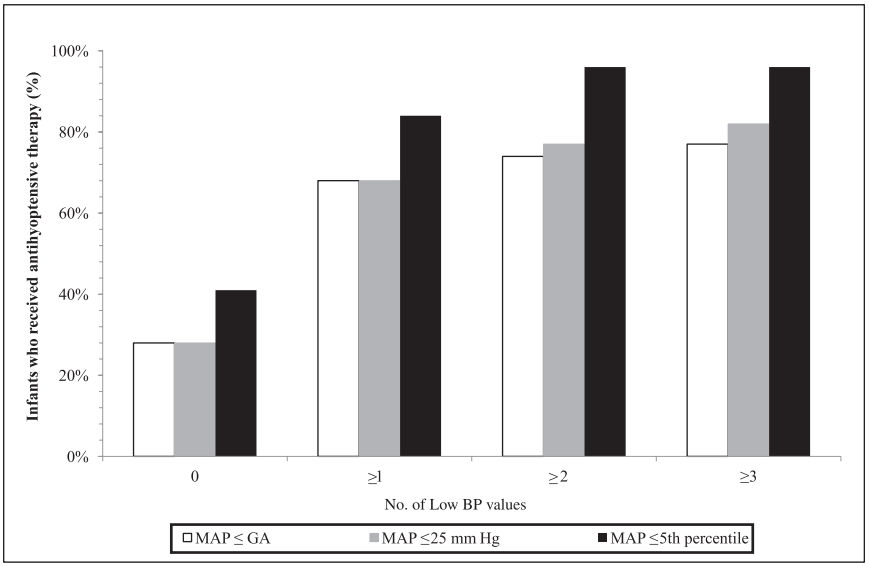

FIGURE 2
Percentage of infants with stated definition of low BP who received at ≥1 antihypotensive therapy.

leukomalacia), or survival through postnatal day 7 or until hospital discharge ($P > .05$ for all analyses, data not shown). Results were unchanged for each of the 15 definitions of low BP, when analysis was restricted to only infants with ≥1 low BP value, and when only invasive BP values were used (data not shown). There was not a definition of low BP identified for which infants who received therapy had improved rates of IVH, ROP, survival, or morbidity-free survival.

There was significant variation across NRN centers in the rate of antihypotensive therapy administration ($P < .01$), incidence of low BP ($P < .01$ for all definitions of low BP), and rate of survival to hospital discharge ($P < .01$; Fig 3). With regression analysis, the center frequency of antihypotensive therapy administration was not significantly associated with the center incidence of low BP for any of the definitions of low BP investigated ($P > .05$ for each of the 15 definitions of low BP [range in P values: .29–.89]). In addition, for each definition of low BP investigated, the center frequency of antihypotensive therapy administration was not significantly associated with the center incidences of IVH, grade III/IV IVH, other morbidities, or survival to hospital discharge ($P > .05$ for each of the 15 definitions of low BP [range in P values: .30–.84], data not shown).

TABLE 1 Baseline Characteristics for Infants Who Did or Did Not Receive Antihypotensive Therapy in the First 24 Hours

Initial Characteristic	No Therapy (n = 164)	Administered Therapy (n = 203)	P Value
Received maternal antibiotics, n (%)	126 (77)	160 (79)	.58
Received (any) prenatal steroids, n (%)	147 (90)	188 (93)	.31
Vaginal delivery, n (%)	53 (32)	68 (33)	.84
Multiple gestation, n (%)	39 (24)	63 (31)	.12
Male gender, n (%)	73 (45)	100 (49)	.36
Birth wt, g, mean ± SD	764 ± 161	698 ± 156	<.01
GA, weeks, mean ± SD	25.5 ± 0.9	25.1 ± 1.1	<.01
1-min Apgar ≤3, n (%)	70 (43)	122 (60)	<.01
5-min Apgar ≤5, n (%)	47 (29)	80 (39)	.03
DR chest compressions, n (%)	13 (8)	25 (12)	.17
First hematocrit <30%, n (%)	8 (5)	38 (19)	<.01
Positive initial blood culture, n (%)	—	8 (4)	.01
(Any) pH <7.10, n (%)	5 (3)	27 (13)	<.01

DR, delivery room.

DISCUSSION

In this prospective study of 367 extremely preterm infants, 55% received an antihypotensive therapy and 28% received a vasoactive drug. For each definition of low BP investigated, the likelihood of receiving therapy increased with the number of low BP values recorded. Antihypotensive therapy was often provided to infants without low BP and, paradoxically, not prescribed to infants with low BP. The observation that the NRN center rate of therapy was not significantly related to the center incidence of low BP is additional evidence that factors other than BP values contributed to the decision to provide antihypotensive therapy. Degree of prematurity and infant size appeared to influence this decision as the likelihood of receiving treatment was inversely related to GA and birth weight. In-hospital outcomes were not improved with therapy for any of the 15 definitions of low BP investigated, including those with ≥3 low BP values.

Results from the current study are consistent with previous investigations.[3–5,10,17,22] In a study by Laughon et al, 82% of infants 23 to 27 weeks' GA received an antihypotensive therapy, including 34% who received a vasopressor.[3] Although that study had some limitations that do not apply to the current one, the findings for each were similar in that the rate of therapy use varied across NICUs; smaller, less mature infants were more likely to receive treatment; and the decision to provide treatment was strongly influenced by which center provided care. Other studies compared outcomes

TABLE 2 In-hospital Outcomes for Infants Who Did or Did Not Receive Antihypotensive Therapy in the First 24 Hours

In-hospital Outcomes	No Therapy (n = 164)	Administered Therapy (n = 203)	P Value
Necrotizing enterocolitis requiring surgery, n (%)	11 (7)	16 (8)	.92
Bronchopulmonary dysplasia, n (%)	75 (46)	92 (45)	.26
Cystic periventricular leukomalacia, n (%)	7 (4)	11 (5)	.60
Intervention for ROP, n (%)	13 (8)	31 (15)	.03
(Any) IVH, n (%)	43 (26)	83 (41)	<.01
Grade 3/4 IVH, n (%)	18 (11)	44 (22)	<.01
Survived 24 h, n (%)	156 (95)	186 (92)	.19
Survived ≥1 week, n (%)	146 (89)	174 (86)	.20
Survived to hospital discharge, n (%)	128 (78)	137 (67)	.02
Morbidity-free survival,[a] n (%)	24 (15)	11 (5)	<.01

[a] Morbidities: necrotizing enterocolitis, ROP, bronchopulmonary dysplasia, grade 3 or 4 IVH, or periventricular leukomalacia.

between infants with low BP who received an antihypotensive therapy and those who did not.[4,17,22,23] In those studies, treatment was associated with similar or worse infant outcomes when compared with untreated infants, but no study identified a definition of low BP for which treatment improved outcomes. Neither the current study nor others support the routine use of any antihypotensive therapy for any of the current definitions of low BP in extremely preterm infants.[1,3–5,11,17,22–25]

BP values were recorded hourly for all infants because the relationship between low BP and antihypotensive therapy in previous studies has been influenced by a disproportionally higher number of BP values obtained from treated infants. Infants for whom intensive care was withheld or withdrawn in the first 24 hours (n = 22) were excluded so that analyses were not influenced by infants whose death was imminent irrespective of which therapies were administered or withheld. Analysis was limited to the first 24 hours because this is when the majority of infants who receive therapy are treated,[3,4] and the evaluation, etiology, and management of low BP that occurs later may be different. Severity of illness based on factors considered a priori as likely to affect the decision to administer therapy for low BP was controlled for with regression analysis because previous studies have suggested infants who receive antihypotensive therapy have worse outcomes because they are initially more ill.[1,23,24,26] Multiple definitions of low BP were investigated because there is not an accepted definition of hypotension in this population. Although an MAP less than or equal to the infant's GA is the most common definition used,[24] it is not evidence based and was first suggested in a policy statement on the management of respiratory distress syndrome.[27] Additional strengths of this study are the prospective data collection by experienced research personnel using a uniform approach and analysis conducted by well-trained experts. Study limitations include the lack of information regarding some variables that may have contributed to the decision to administer antihypotensive therapies, variability in infant enrollment across NRN centers, and inconsistency in how noninvasive BP values were obtained.

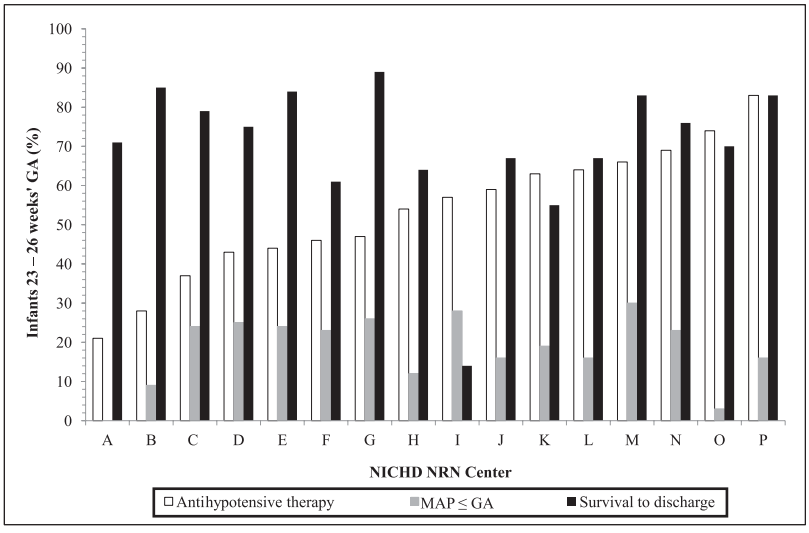

FIGURE 3
Center variation in the rate of antihypotensive therapy administration, frequency of low BP, and incidence of hospital survival.

This study was conducted because there is a lack of information to guide BP management in extremely preterm infants.[1,2,26,28] Large placebo-controlled trials have not been completed to date, and the limitations of previous studies make interpretation of their results difficult.[1–5,10,13,15,17,22,23] Two prospective interventional studies are in their early phases (Clinicaltrials.gov NCT01482559 and NCT01434251), but results are not expected from either before 2016. The prospective data collection, number of infants enrolled, and detailed data analysis plan of this study provide some of the strongest data to date regarding BP management in extremely preterm infants.

Despite the lack of evidence supporting the routine use of any antihypotensive

therapy, there may be some benefit from such therapies for some extremely preterm infants. In the current study, 12% of infants were anemic at birth, and increasing the blood volume may be appropriate in such situations. In addition, 2% of infants had early-onset sepsis, and the high risk of death or neurodevelopmental impairment in such cases[29,30] may outweigh the risks associated with antihypotensive therapy. Some extremely preterm infants with perceived low BP also have strong clinical or biochemical evidence of poor perfusion. These infants appear to be at greater risk of a poor outcome,[4,24,25,31,32] and in this scenario, the benefits of therapy may outweigh the risks even though neither can be accurately predicted.[1,2,22,33] However, infants with perceived low BP usually have adequate perfusion,[23,25,34,35] and the benefit of treatment has not been established for these infants. In this situation, therapies to increase BP appear also to be used to try to prevent or improve undocumented organ hypoperfusion, primarily cerebral blood flow.[34,35] This approach is challenging because BP may not correlate with perfusion[34–37]; infants with low BP may have adequate cerebral blood flow,[25,35,38,39] vasoactive drugs do not always increase cerebral perfusion[25,34] and have not improved outcomes,[40] and treatment of low BP has been associated with similar or worse rates of intracranial abnormalities and impaired neurodevelopment versus matched untreated infants.[3–5,17,22,23] These factors make it difficult to determine if an extremely preterm infant with perceived low BP but clinically adequate perfusion would benefit from or be harmed by therapy.

CONCLUSIONS

This prospective multicenter study of extremely preterm infants examined the relationship among 15 definitions of low BP, antihypotensive therapy, and in-hospital outcomes. Therapy was not associated with better in-hospital outcomes for any definition of low BP investigated. A numeric cutoff for deciding when to administer antihypotensive therapies, such as an MAP less than or equal to the infant's GA, is not evidence based and cannot be recommended. Until there are data to suggest otherwise, antihypotensive therapy should be used cautiously for these infants because treatment of low BP is associated with similar or worse infant outcomes without evidence of benefit.[4,17,22,23] Large, high-quality studies are needed to support evidence based recommendations for BP management in this population.

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Dr Batton is the lead study investigator for the Eunice Kennedy Shriver National Institute of Child Health & Human Development Neonatal Research Network (NRN) Early Blood Pressure study and the chair of the Early Blood Pressure Protocol Subcommittee. He developed the protocol with the assistance of the subcommittee, trained the study coordinators and principal investigators (PIs), and managed study implementation. As the Study PI at Case Western Reserve University, he oversaw study implementation at that site, which enrolled 25 infants in this study. Dr Batton drafted the manuscript and received input from the other authors as part of manuscript revision. Dr Walsh is the PI at Case Western Reserve University and the vice chair of the Early Blood Pressure Protocol Subcommittee. She mentored Dr Batton through protocol development and implementation, and, as the PI, oversaw subject recruitment and study implementation at her site, which enrolled 25 infants. She provided critical revisions to the manuscript and approved the final version of the manuscript. Dr Li served as the primary statistician for the study, providing statistical input for protocol development and completing the statistical analyses for the manuscript. He developed the tables and figures for the manuscript, provided critical revision to the manuscript, and approved the final version of the manuscript. Ms Newman is the NRN coordinator at Case Western Reserve University and a member of the Early Blood Pressure Protocol Subcommittee. She provided day-to-day assistance with protocol and procedural questions both at her site and for PIs and coordinators at other NRN sites. Ms Newman provided critical revision of the manuscript as well as approval of the final manuscript. Dr Das is the PI for the NRN Data Coordinating Center and a member of the Early Blood Pressure Protocol Subcommittee. Dr Das oversaw all aspects of the statistical analysis, provided critical revisions to the manuscript, and approved the final version of the manuscript. Dr Watterberg is the PI at the University of New Mexico and a member of the Early Blood Pressure Protocol Subcommittee. As the PI, she oversaw subject recruitment and study implementation at her site, which enrolled 13 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission. Dr Yoder is the

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