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ORIGINAL ARTICLE

Evolving blood pressure dynamics for extremely preterm infants

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OBJECTIVE: To examine changes in arterial blood pressure (ABP) after birth in extremely preterm infants.
STUDY DESIGN: Prospective observational study of infants $23^{0/7}$ to $26^{6/7}$ weeks gestational age (GA). Antihypotensive therapy use and ABP measurements were recorded for the first 24 h.
RESULT: A cohort of 367 infants had 18 709 ABP measurements recorded. ABP decreased for the first 3 h, reached a nadir at 4 to 5 h and then increased at an average rate of 0.2 mm Hg h^{-1}. The rise in ABP from hour 4 to 24 was similar for untreated infants ($n = 164$) and infants given any antihypotensive therapy ($n = 203$), a fluid bolus ($n = 135$) or dopamine ($n = 92$). GA-specific trends were similar. ABP tended to be lower as GA decreased, but varied widely at each GA.
CONCLUSION: ABP increased spontaneously over the first 24 postnatal hours for extremely preterm infants. The rate of rise in ABP did not change with antihypotensive therapy.

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INTRODUCTION

The immature cardiovascular system is complex and particularly dynamic immediately after birth and this evolving physiology of extremely preterm infants contributes to a wide range in observed arterial blood pressure (ABP) values during this time.[1,2] This variability makes it difficult to define normal ABP values and to identify expected physiological changes in ABP over the first few days for this population. In more mature infants, ABP increases with increasing birth weight, higher gestational age (GA) at birth and advancing postnatal age,[3–6] but these relationships are unclear for extremely preterm infants.

Data are also limited regarding the effect of commonly prescribed antihypotensive therapies on ABP in this population.[7,8] Although ABP rises after these therapies are administered,[9–12] it is not clear whether ABP rises at a different rate with these therapies as compared with the spontaneous rise in ABP, which has been observed previously.[2,13] These uncertainties have contributed to wide variability in ABP management for extremely preterm infants.[1,14]

A better understanding of changes in ABP occurring in early postnatal life and the effect of antihypotensive therapies on ABP during this time may help to decrease clinical variability in ABP management for this population and improve infant outcomes. The goals of this investigation were to evaluate changes in ABP over the first 24 postnatal hours in infants born at 23 to 26 weeks GA and to investigate the relationship between antihypotensive therapies and ABP values.

METHODS

This is a secondary analysis of a prospective observational study of inborn extremely preterm infants of $23^{0/7}$ to $26^{6/7}$ weeks GA born at 16 academic centers of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN).[14] Infants were excluded if they died in the delivery room, had a major birth defect or had intensive care withheld or withdrawn in the first 24 h. Research personnel used study-specific data forms to record hourly ABP measurements and the administration of all antihypotensive therapies in the first 24 h. Antihypotensive therapy included a fluid bolus ($\geqslant 10$ ml kg^{-1} of crystalloid), dopamine, dobutamine, hydrocortisone, epinephrine or any blood product. Blood pressure values were obtained from a non-invasive ABP cuff, umbilical arterial catheter (UAC) or peripheral arterial line. All treatment decisions were made by the clinical care team.

This study was approved by the institutional review board of each participating center. At two centers, infants were enrolled after parents signed a study-specific informed consent form. At the remaining 14 centers, this study was incorporated into the ongoing Generic Database study of the NRN because all infants in this study qualified for Generic Database enrollment (on the basis of their GA at birth) and both studies collected de-identified patient information. The Institutional Review Board of some NRN centers allowed for Generic Database data collection with a waiver of consent.

Data analysis was performed at the NRN Data Coordinating Center (RTI International, Research Triangle Park, NC, USA). Data were entered remotely by electronic submission and were periodically reviewed for quality control. SAS 9.3 software (SAS Institute, Cary, NC) was used for statistical analysis. At each postnatal hour, ABP percentiles were constructed for different populations (all infants, infants who did not receive therapy, treated infants and infants of each specific GA) using two sets of data: all ABP values and only ABP values obtained from a UAC. After visual inspection of the data, the mixed-effects linear growth models were used to estimate the mean ABP rate of rise from hour 4 to 24 and its standard deviation (s.d.).[15] Infant demographic characteristics and in-hospital outcomes were compared across subgroups defined by the administration of antihypotensive therapy and the rate of rise in ABP.

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RESULTS

The study cohort included 367 infants born at $23^{0/7}$ to $26^{0/7}$ weeks GA from 21 July 2010 to 21 January 2011. There were 203 (55%) infants who received at least one antihypotensive therapy: 135 were given a fluid bolus, 92 received dopamine, 25 received hydrocortisone, 18 were given dobutamine and 1 patient received vasopressin. A total of 18 709 ABP values was recorded from these infants. Blood pressure values were obtained from an arterial line for most infants—298 (81.2%) infants had a UAC placed and 8 (2%) infants had a peripheral arterial line inserted—with 14 593 (78%) invasive ABP values recorded.

The systolic, diastolic and mean ABP values decreased for the first 4 h after birth, reached a nadir at 4 to 5 h and then increased until 24 h of age (Figure 1). Blood pressure percentiles were similar (within 2 mm Hg) for each population independent of whether non-invasive ABP values were included in the analysis. The estimated mean ± s.d. rate of rise in the systolic, diastolic and mean ABP from hour 4 to 24 was 0.3 ± 0.6 (range: −2.15 to 1.66), 0.2 ± 0.4 (range: −1.10 to 1.32) and 0.2 ± 0.4 (range: −1.17 to 1.37) mm Hg h^{-1}, respectively. These rates of rise were similar for the entire cohort ($n = 367$), untreated infants ($n = 164$) and infants treated with any antihypotensive therapy ($n = 203$; Table 1). Demographic data and in-hospital outcomes for treated and untreated infants in whom the mean ABP did or did not rise at the expected rate of $\geqslant 0.2$ mm Hg h^{-1} are presented in Table 2. Similarly, the percentages of infants in whom the mean ABP decreased, remained the same, increased at a rate $\leqslant 1$ mm Hg h^{-1} or increased at a rate > 1 mm Hg h^{-1} from hour 4 to 24 were similar across study cohorts (Table 3).

For 21 (89%) of the 24 h investigated, the 95th, 50th and 5th percentiles for the systolic, diastolic and mean ABP were higher for treated infants as compared with untreated infants, although these differences were generally $\leqslant 2$ mm Hg. For untreated infants ($n = 164$), systolic, diastolic and mean ABP increased significantly ($P < 0.001$) at an estimated mean ± s.d. rate of 0.3 ± 0.5 (range: −2.15 to 1.50), 0.2 ± 0.4 (range: −1.10 to 1.10) and 0.2 ± 0.4 (range: −0.90 to 1.25) mm Hg h^{-1}, respectively.

Of the 135 infants given a fluid bolus, 72 (53%) also received dopamine, dobutamine or hydrocortisone. The first bolus was given at a median age of 4 h (range: 1 to 21). Of the 92 infants administered dopamine, 14 (15%) also received dobutamine, 20 (22%) received hydrocortisone and 7 (8%) received both dobutamine and hydrocortisone. Dopamine infusion was initiated at a median of 6 h after birth (range: 1 to 23). Arterial BP values at the initiation of therapy for infants given a fluid bolus or dopamine as well as changes in ABP with each therapy are presented in Table 1.

GA-specific trends in ABP were similar to those of the entire cohort. At each GA, ABP initially decreased, reached a nadir at postnatal hour 4 to 5 and then increased at a similar rate of rise until 24 h. Arterial BP values usually increased as GA increased (Figure 2), but for each GA there was a wide range in each ABP parameter at each postnatal hour with significant overlap in ABP values across the GA range investigated.

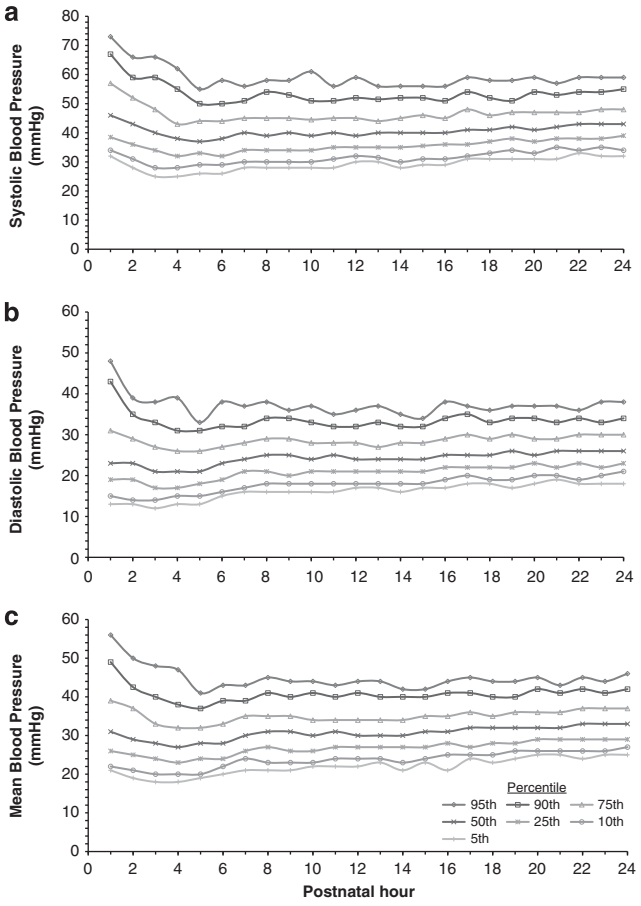

Figure 1. Systolic (**a**), diastolic (**b**) and mean (**c**) arterial blood pressure curves over the first 24 h for extremely preterm infants ($n = 367$).

DISCUSSION

The goals of this study were to examine changes in ABP during the first 24 h for extremely preterm infants and to investigate the impact of antihypotensive therapies on ABP values during this time. Similar to studies of more mature infants, ABP increased spontaneously with advancing postnatal age, and a wide range of systolic, diastolic and mean ABP values was observed at each postnatal hour.[3–6] In this population, ABP response to a normal saline bolus or initiation of dopamine was inconsistent—in some infants, ABP rose quickly with therapy, whereas in others, little or no change in ABP was observed.

Our results are consistent with several small retrospective single center studies that also examined ABP values in extremely preterm infants.[13,16,17] In two of these, the reported rate of rise in the mean ABP (0.2[13] and 0.196 mm Hg h^{-1})[17] was quite similar to our study (0.2 mm Hg h^{-1}). However, absolute ABP values in our study were generally higher. This may be due to differences in the preterm infant population investigated, methods used to measure ABP or the frequency of antenatal corticosteroid administration, which was substantially higher in our study and has been associated with higher postnatal ABP values in preterm infants.[18] Similar to more mature infants, a wide range of ABP values was observed for infants 23 to 26 weeks GA, with ABP values generally increasing with increasing GA.[2–6] However, as seen in Figure 2, this too was highly variable. There were numerous postnatal hours for which ABP percentiles were higher for infants at 23 or 24 weeks GA than for those at 25 or 26 weeks GA (data not shown) and there was significant overlap in observed ABP values across the entire GA range. It is also worth noting that although ABP values were generally higher in this study than previously reported for extremely preterm infants, infants commonly had at least one low ABP value. Two-thirds of the infants had at least one mean ABP less than or equal to their GA equivalent (in weeks). The wide range in ABP for extremely preterm infants is related to many dynamic changes in physiology during the transition to postnatal life as well as varying disease processes. Such ABP variability makes it difficult to determine whether a specific ABP value at a specific time for a specific

Table 1. Arterial blood pressure changes from postnatal hour 4–24 for infants 23–26 weeks gestation

	Systolic ABP	*Diastolic ABP*	*Mean ABP*
Data for all infants (n = 367)			
ABP at hour 4, mean ± s.d. (mm Hg)	40 ± 10	24 ± 7	30 ± 8
Rate of rise in ABP from hour 4–24, mean ± s.d. (mm Hg h^{-1})	0.25 ± 0.6	0.19 ± 0.4	0.23 ± 0.4
Data for untreated infants (n = 164)			
ABP at hour 4, mean ± s.d. (mm Hg)	42 ± 10	26 ± 7	32 ± 8
Rate of rise in ABP from hour 4–24, mean ± s.d. (mm Hg h^{-1})	0.28 ± 0.5	0.17 ± 0.4	0.21 ± 0.4
Data for infants given any antihypotensive therapy (n = 203)			
ABP at hour 4, mean ± s.d. (mm Hg)	38 ± 10	22 ± 7	28 ± 7
Rate of rise in ABP from hour 4–24, mean ± s.d. (mm Hg h^{-1})	0.24 ± 0.6	0.21 ± 0.5	0.24 ± 0.5
Data for infants given a fluid bolus (n = 135)			
ABP at initiation of therapy, mean ± s.d. (mm Hg)	36 ± 9	20 ± 6	26 ± 7
Rise in ABP over the first 6 h after initiation of therapy, mean ± s.d. (mm Hg h^{-1})	0.8 ± 1.8	0.8 ± 1.4	0.8 ± 1.5
Rise in ABP from hour 4–24, mean ± s.d. (mm Hg h^{-1})	0.2 ± 0.7	0.3 ± 0.4	0.3 ± 0.5
Data for infants given dopamine (n = 92)			
ABP at initiation of therapy, mean ± s.d. (mm Hg)	33 ± 7	18 ± 5	24 ± 5
Rise in ABP over the first 6 h after initiation of therapy, mean ± s.d. (mm Hg h^{-1})	0.9 ± 1.6	0.9 ± 1.2	0.9 ± 1.2
Rise in ABP from hour 4–24, mean ± s.d. (mm Hg h^{-1})	0.3 ± 0.6	0.2 ± 0.4	0.2 ± 0.5

Abbreviation: ABP, arterial blood pressure.

Table 2. Demographic data and in-hospital outcomes for treated and untreated infants

	Untreated expected ABP rise[a] (n = 91)	*Untreated less than expected ABP rise* (n = 67)	*Treated expected ABP rise* (n = 128)	*Treated less than expected ABP rise* (n = 70)	*ANOVA*[b] P-value
Birth weight (g), mean ± s.d.	784 ± 165	750 ± 144	692 ± 150	713 ± 168	0.0002
Gestational age at birth (weeks), mean ± s.d.	25.5 ± 0.9	25.6 ± 1.0	25.1 ± 1.1	25.3 ± 1.0	0.001
Received antenatal corticosteroids, # (%)	81 (89)	61 (91)	118 (92)	65 (93)	0.814
1 min Apgar score ⩽3, # (%)	33 (36)	33 (49)	79 (62)	49 (70)	<0.0001
DR chest compressions, # (%)	5 (5)	7 (10)	14 (11)	8 (11)	0.5
Positive initial blood culture, # (%)	0	0	3 (2)	5 (7)	0.01[c]
Any pH <7.10 in the first 24 h, # (%)	1 (1)	3 (4)	13 (10)	11 (16)	0.003
First hematocrit <30%, # (%)	4 (4)	3 (4)	25 (20)	12 (17)	0.001
Any severity of illness marker, # (%)[d]	37 (41)	37 (55)	93 (73)	56 (80)	<0.0001
Severe IVH or PVL, # (%)	11 (12)	8 (13)	28 (23)	21 (31)	0.008
NEC requiring surgery, # (%)	7 (8)	5 (8)	11 (9)	5 (7)	1.0[c]
Intervention for ROP, # (%)[e]	10 (13)	7 (13)	20 (22)	16 (25)	0.250
BPD, # (%)[e]	40 (52)	36 (67)	58 (65)	34 (65)	0.402
Survived to hospital discharge, # (%)	77 (85)	54 (81)	89 (70)	52 (74)	0.055

Abbreviations: ABP, arterial blood pressure; ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; DR, delivery room; severe IVH, grade III/IV intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
[a]The expected rise was an increase in the mean arterial blood pressure by ⩾0.2 mm Hg h^{-1}.
[b]χ^2 test, unless otherwise noted.
[c]Fisher's exact test.
[d]Includes a positive initial blood culture, pH <7.10, initial hematocrit <30%, 1 min Apgar ⩽3 or delivery room chest compressions.
[e]Percentage based on infants who survived to hospital discharge.

patient is appropriate, too high, too low, rising too quickly or remaining unchanged for too long.

The average rate of rise in each ABP parameter was similar for untreated infants, treated infants, infants who only received a fluid bolus and infants given dopamine. Each of these groups also had a similar percentage of infants for whom the ABP value at hour 24 was below the ABP value at hour 4. However, for both treated and untreated infants there was substantial variability in the range of observed ABP values at each postnatal hour. The rate of change in ABP after the initiation of antihypotensive therapies also varied considerably for treated infants. Table 2 suggests variability in the rate of change in ABP between treated and untreated infants may be partly related to variability in circumstances at the time of delivery and the presence of different morbidities for infants who receive therapy. Additional explanations for the observed variability in ABP values include the possibility infants who receive an antihypotensive therapy were sicker,[14] varying rates of antihypotensive therapy use across neonatal intensive care units,[1,14]

Table 3. Changes in mean arterial blood pressure values from postnatal hour 4–24

Cohort	*Decrease (value at hour 4 > hour 24), %*	*Same value (value at hour 4 = hour 24), %*	*Increase (value at hour 4 < hour 24) rate ⩽1 mm Hg h^{-1}, %*	*Increase (value at hour 4 < hour 24) rate >1 mm Hg h^{-1}, %*
All infants	18	5	74	3
Untreated infants	20	1	75	3
Infants given any antihypotensive therapy	16	8	73	3
Infants given a fluid bolus	16	11	71	2
Infants given only a fluid bolus	28	10	62	None
Infants given only a blood product	11	5	79	5
Infants given dopamine	16	8	74	1

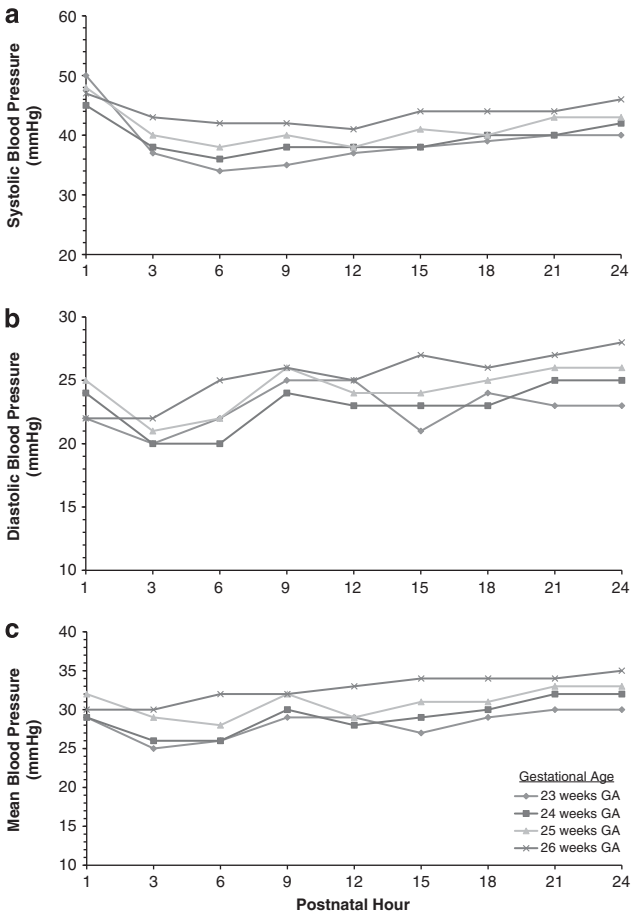

Figure 2. Gestational age-specific changes in the systolic (**a**), diastolic (**b**) and mean (**c**) arterial blood pressure 50th percentile curves over the first 24 h.

different etiologies for low ABP,[7,8,19] varying impact of antihypotensive therapies on ABP values[9–12,19] and patient to patient differences in the pharmacokinetics and pharmacodynamics of some antihypotensive therapies.[9,20] The substantial variability in observed ABP values and unpredictable response to antihypotensive therapies increases the difficulty of developing effective therapeutic algorithms for administering antihypotensive therapies and evaluating their impact on preterm infant outcomes.[7,8,19]

Study strengths include the large number of ABP measurements obtained, the narrow GA range of the study population and uniform data collection by experienced research personnel. A potential limitation is the lack of a uniform approach to ABP management across study sites. Administration of antihypotensive therapy was at the discretion of the clinical care team, and only one participating center had a written protocol for ABP management. Additional factors that were not recorded, such as clinical assessment of perfusion or the presence of a metabolic acidosis, may have been incorporated into the decision to initiate antihypotensive therapy. The hourly ABP measurement recorded may not have been representative of most ABP values observed during a specific postnatal hour. Intermittent—rather than continuous—ABP recording and the use of multiple methods of measurement are also potential limitations. In addition, although most infants had a UAC placed shortly after birth, it typically takes several hours to establish invasive ABP monitoring. There were a significantly higher percentage of non-invasive ABP measurements in first few hours as compared with each later postnatal hour (data not shown). Hence, the observed drop in ABP over the first 4 postnatal hours may reflect a true decrease in ABP or may be due to a transition from oscillographic ABP measurements to invasive monitoring methods, as ABP values obtained from a UAC are lower in this population.[21]

This study demonstrates that ABP increases spontaneously during the first postnatal day for extremely preterm infants born ⩽26 weeks GA, with a wide range in ABP values at each postnatal hour. Although ABP values tend to increase with increasing GA, we observed significant overlap in ABP values across the entire GA range for this population of infants. Future studies of extremely preterm infant hemodynamics should consider these findings when evaluating the effectiveness of cardiovascular therapies. The effect of antihypotensive therapies on ABP was unpredictable—we found that ABP variably decreased, increased at a rate similar to untreated infants or increased more rapidly. This variability in response to therapies makes it difficult to assess their risks and benefits. A single criterion for institution of therapy—such as a numeric ABP cutoff—is not likely to reliably predict which infants will respond to or benefit from treatment. Until more information on these medications is available, a cautious approach to ABP management is warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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