

Definitions of Cardiovascular Insufficiency and Relation to Outcomes in Critically Ill Newborn Infants

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Abstract

Background We previously reported on the overall incidence, management, and outcomes in infants with cardiovascular insufficiency (CVI). However, there are limited data on the relationship of the specific different definitions of CVI to short-term outcomes in term and late preterm newborn infants.

Objective This study aims to evaluate how four definitions of CVI relate to short-term outcomes and death.

Study Design The previously reported study was a multicenter, prospective cohort study of 647 infants ≥ 34 weeks gestation admitted to a Neonatal Research Network (NRN) newborn intensive care unit (NICU) and mechanically ventilated (MV) during their first 72 hours. The relationship of five short-term outcomes at discharge and four different definitions of CVI were further analyzed.

Results All the four definitions were associated with greater number of days on MV and days on O₂. The definition using a threshold blood pressure (BP) measurement alone was not associated with days of full feeding, days in the NICU or death. The definition based on the treatment of CVI was associated with all the outcomes including death.

Conclusions The definition using a threshold BP alone was not consistently associated with adverse short-term outcomes. Using only a threshold BP to determine therapy may not improve outcomes.

Keywords

- ▶ blood pressure
- ▶ cardiovascular insufficiency
- ▶ outcomes
- ▶ newborn
- ▶ infant

The association of early hypotension with adverse outcomes in the neonate has been difficult to characterize. Reasons include the lack of a specific clinical definition of hypotension in the neonatal period during the transition to extrauterine life as well as unclear differences by gestational age (GA) and postnatal age. Furthermore, the relationship between specific blood pressure (BP) values with adequate organ perfusion is unknown. There are conflicting reports on the association of adverse outcomes with definitions of hypotension using variable BP thresholds. In some reports, there is an association of variably defined hypotension in preterm infants with intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, hearing deficits, and neurodevelopmental delay.¹⁻³ However, in other reports, low BP by different definitions is not associated with brain injury by cranial ultrasounds.⁴ Although considerably less is known about how different definitions of hypotension in critically ill-term or late-preterm infants relate to adverse outcomes, there are reports of increased neurological events (seizures, brain atrophy, intracranial hemorrhage, or stroke) and chronic lung disease in association with the use of inotropes.⁵ In this infant population, clinicians will also use signs such as prolonged capillary refill, oliguria, and acidosis in addition to a threshold BP to determine the best treatment.⁶ However, it is unknown how well these signs correlate with adverse short-term outcomes.

We previously reported on the incidence and management of cardiovascular insufficiency (CVI) using four different a priori definitions which included definitions based on low-threshold BP alone, low-threshold BP in conjunction with signs of low blood flow, inotrope use or the use of any therapy (volume expanders or inotropes) aimed at improving blood flow by clinicians. We found that 65% of all late-preterm and term infants who were intubated and mechanically ventilated

within 72 hours of birth met at least one of these definitions of CVI.⁶ We also found a higher incidence of adverse short-term outcomes in those infants with any definition of CVI compared with those without CVI. The purpose of this study is to determine the specific association of four different definitions to adverse short-term outcomes. Such knowledge is vital in designing future clinical trials.

Methods

The original multicenter, prospective, observational cohort study of CVI in the critically ill-term and late-preterm newborn infants had enrolled 647 infants in 2009 of whom 419 (65%) had CVI as defined by one of four definitions outlined in **Table 1**.⁶ The enrolled infants were $\geq 34^{0/7}$ weeks GA, admitted to one of the 16 Neonatal Research Network (NRN) centers and were intubated and receiving mechanical ventilation for at least 1 hour within the first 72 postnatal hours. Infants electively intubated for surgery were excluded, as were infants with hypotension resulting from documented acute maternal and/or fetal hemorrhage within 24 hours before delivery, and those with a known diagnosis of major congenital heart disease, moderate or severe hypoxic ischemic encephalopathy, pituitary hypoplasia, congenital adrenal hyperplasia, congenital diaphragmatic hernia, omphalocele, or chromosomal disorder. Waiver of consent was approved by the institutional review board at 14 NRN sites; for 2 other sites, infants were enrolled after parental written informed consent was obtained.

Clinical data were collected by trained research coordinators and all analyses were performed by the NRN Data Coordinating Center (RTI International, Research Triangle Park, NC). Data were entered remotely with electronic submission and scrutinized with quality control procedures,

Table 1 CVI defined by four different definitions (A–D)

		Incidence N = 419
A	Two consecutive mean BP less than GA in completed weeks (mean BP < GA)	n = 247 38%
B	Two consecutive mean BP less than GA in completed weeks (mean BP < GA) and at least one additional clinical sign ^a of CVI	n = 135 21%
C	Receipt of fluid bolus, inotrope, or glucocorticoid	n = 371 57%
D	Receipt of inotropes	n = 135 21%

Abbreviations: BP, blood pressure; CVI, cardiovascular insufficiency; GA, gestational age.

^aClinical signs: poor capillary refill (> 3 seconds), oliguria (urine output < 1 mL/kg/h over 6 hours) or serum bicarbonate < 18 and/or base deficit > 5.

including range checking, internal comparisons for logic violations, and comparison of expected and observed values.

Short-term outcomes were collected at the time of death, discharge, transfer, or at 60 days if the infant was still in hospital (whichever came first), and included death, days to full enteral nipple feedings, days of mechanical ventilation, and supplemental oxygen and days in the newborn intensive care unit (NICU).

Statistical Analysis

Infants were stratified into two GA groups (< 37 weeks GA and ≥ 37 weeks GA). First, those with CVI by each definition were compared with those without CVI by any definition using continuity-adjusted chi-square test. Second, continuous outcomes of days to full nipple feedings, in the NICU, mechanically ventilated, and on O₂ were log-transformed and analyzed by linear regression to determine the relationships of each definition of CVI to the outcomes. For each definition, the model parameter estimate, which is the adjusted mean difference (AMD) between the two levels of the definition, and its *p*-value were calculated. The higher this estimate, the more the definition contributed to a larger outcome. Death was analyzed by logistic regression. All outcomes were modeled with birth weight, GA, Apgar score at 5 minutes, gender, delivery room intubation, iNO use, race, and center. *p*-Values less than 0.05 were considered statistically significant.

Results

Of 647 infants enrolled, 419 met at least one of the definitions of CVI. The mean GA was 37.1 weeks and birth weight was 2,961 g; 62% were males, 46% were outborn, and 55% were delivered by cesarean section. Patient characteristics have

been described in further detail previously.⁶ The mean (SD) systolic, diastolic, and mean BPs just before the first fluid bolus was given were 53 (10.8), 30 (13.5), and 38 (9.8) mm Hg, respectively, for infants < 37 weeks GA; for infants ≥ 37 weeks, the mean values were 61 (13.9), 36 (11.2), and 44.2 (11.7) mm Hg. For each definition, the incidence of each outcome is shown in ►Table 2. For each definition, the outcomes were first compared between those with the CVI definition to those without CVI by each definition. Using chi-square testing, infants with CVI by any definition had significantly worse outcomes than those without CVI except for death in the term infants (►Table 2).

Each definition was then explored for its relationship to each adverse outcome after adjustment for covariates and expressed as the model parameter estimate (AMD) with its associated *p*-value (►Table 3). The higher the AMD, the more likely the definition contributed to a worse outcome. The definition utilizing mean BP measurement alone (definition A) was associated with days on oxygen and days on mechanical ventilation, but was not associated with days to full nipple feeding, length of stay in the ICU, or mortality. Definition B (definition A plus signs of low blood flow) was associated with more days on oxygen, days on mechanical ventilation, and increased mortality, but not with days to full feeds and length of NICU stay. Receipt of any therapy (definition C) was associated with all short-term adverse outcomes including death. The receipt of any inotrope (definition D) was significantly associated with all short-term outcomes and had the highest adjusted odds ratio for death.

Discussion

Clinical CVI occurs in a high percentage (65%) of mechanically ventilated term- and late-preterm infants⁶ and it is important to understand the association of CVI with adverse short- and long-term outcomes. As part of a prospective observational study of the incidence and management of hypotension in term- and late-preterm infants, we evaluated the relationship of four different definitions of CVI to distinctly measurable outcomes at discharge. We found that while all definitions were associated with more days on oxygen and days on mechanical ventilation, the definition using only a specific BP cutoff (mean BP < GA) was not associated with days to full nipple feedings, days in the NICU, or death after adjustment for confounders. Receipt of therapy for CVI (definition C), including boluses, inotropes, and/or steroids, was associated with all short-term adverse outcomes and infants receiving inotropic therapy had the highest mortality rate.

This study supports previous investigations that have demonstrated a BP value alone is a poor measure of blood flow or risk for poor outcomes.⁷ However, surveys have suggested that up to 25% of neonatologists use a threshold BP to determine when treatment is initiated.⁸ In our previous study, we found that 36% of the infants with BP < GA received no therapy, while 46% of those who received therapy had mean BPs greater than GA, suggesting that other factors besides BP were used to decide treatment. Thus, we also evaluated a definition which included not only BP but clinical

Table 2 Incidence of outcomes for each definition of CVI in infants < 37 weeks and ≥ 37 weeks GA

Outcome	No CVI ^a	BP < GA	p-Value ^b	BP < GA	p-Value ^b	Receipt of any therapy for CVI ^c	p-Value ^b	Receipt of inotropes	p-Value ^b
GA < 37 wk	N = 115	N = 102		N = 50		N = 138		N = 42	
Death (%)	0 (0)	5 (4.9)	0.02	3 (6)	0.03	9 (6.5)	0.01	6 (14.3)	0.0003
Died within 7 d (%)	0 (0)	3 (2.9)	0.10	1 (2)	0.30	4 (2.9)	0.13	4 (9.5)	0.01
Days intubated and on ventilator	2 (2, 4)	3.5 (2, 7)	< 0.0001	5 (2, 11)	< 0.0001	3.5 (2, 7)	< 0.0001	7 (4, 11)	< 0.0001
Days on oxygen	4 (2, 8)	6 (3, 13)	0.02	8 (3, 15)	0.003	6.5 (3, 11)	0.01	10.5 (4, 16)	< 0.0001
DoL at time of full nipple feeding	8 (6, 14)	12.5 (7, 21)	0.01	14 (7, 25)	0.01	14 (7, 22)	< 0.0001	20.5 (10, 27)	0.001
Days in NICU	10 (6, 17)	16 (10, 33)	0.001	17 (11, 34)	0.0004	16.5 (10, 29)	< 0.0001	16 (10, 34)	0.01
GA ≥ 37 wk	N = 113	N = 145		N = 85		N = 233		N = 93	
Death, n (%)	3 (2.7)	11 (7.6)	0.15	10 (11.8)	0.2	13 (5.6)	0.34	9/92 (9.8)	0.06
Died within 7 d, n (%)	0 (0)	5 (1.9)	0.07	4 (4.7)	0.03	5 (2.2)	0.18	4/92 (4.4)	0.04
Days intubated and on ventilator	2 (1, 4)	4 (2, 10)	< 0.0001	8 (2, 13)	< 0.0001	4 (2, 10)	< 0.0001	9.5 (4, 13)	< 0.0001
Days on oxygen	3 (1, 5)	8 (3, 13)	< 0.0001	9 (5, 16)	< 0.0001	8 (3, 13)	< 0.0001	11 (8, 19)	< 0.0001
DoL at time of full nipple feeding	6 (3, 9)	10 (7, 18)	< 0.0001	10 (7, 17)	< 0.0001	10 (6, 19)	< 0.0001	14 (10, 26)	< 0.0001
Days in NICU	8 (5, 15)	12 (8, 22)	< 0.0001	14 (9, 26)	< 0.0001	14 (9, 27)	< 0.0001	17 (11, 35)	< 0.0001

Abbreviations: CVI, cardiovascular insufficiency; DoL, day of life; GA, gestational age; NICU, newborn intensive care unit.

Note: Data are presented as number (%) and median (25th percentile, 75th percentile).

^aNo CVI by any of the four definitions.

^bp-Value is the comparison of the CVI definition group (in the column at the left) with the no CVI group.

^cReceipt of any volume expander and/or inotropes aimed at improving CVI.

Table 3 Association of outcomes by definition of CVI

Definition of CVI	BP < GA		BP < GA ^a		Receipt of any therapy for CVI		Receipt of inotropes	
	AMD	p-Value	AMD	p-Value	AMD	p-Value	AMD	p-Value
Days to full nipple feedings	0.099	0.26	0.18	0.09	0.29	0.001	0.38	0.003
Days in the NICU	0.79	0.22	0.11	0.14	0.29	< 0.0001	0.23	0.01
Days on mechanical ventilation	0.15	0.02	0.27	0.001	0.30	< 0.0001	0.48	< 0.0001
Days on oxygen	0.23	0.003	0.26	0.006	0.27	0.001	0.57	< 0.0001
Death odds ratio (95% CI)	2.3 (1, 6)	0.07	3.3 (1, 8)	0.01	3.9 (1, 14)	0.04	4.6 (2, 13)	0.003

Abbreviations: AMD, adjusted mean difference in log; BP, blood pressure; CI, confidence interval; CVI, cardiovascular insufficiency; GA, gestational age; NICU, neonatal intensive care unit.

Note: The data (except for death) are presented as the adjusted mean difference between the presence and absence of the specific hypotension definition and the associated p-value. Higher the AMD higher is the association between the definition and the outcome. The covariates include birth weight, GA, Apgar score at 5 minutes, gender, delivery room intubation, iNO use, race, and center.

^aSign of low systemic flow: capillary refill > 3 s, urine output < 1 mL/kg/h, or serum bicarbonate < 18 and/or base deficit > 5.

Bold values are significant at $p < .005$.

signs of low blood flow and found no significant increase in association with short-term outcomes.

There are a limited number of studies in the term newborn population with which to compare our findings. In preterm infants, although some investigators have reported an association between variably defined hypotension and adverse short term outcomes such as PVL, IVH, necrotizing enterocolitis, and renal impairment in preterm infants,^{9–15} this is not a consistent finding. Similar to our study, there are reports in preterm infants showing no correlation of mortality with low BP, as defined by mean BP < GA,^{4,16–18} and no association with PVL or IVH.^{4,17,18}

There are limited studies to compare our results using the definition, mean BP < GA plus a sign of low blood flow. In pediatric patients presenting to the emergency room with cardiovascular dysfunction defined by a low BP, there is a significantly higher mortality than those without low BP (4.4 vs. 1.9%, $p < 0.05$) and a much higher mortality rate (27%) if they present with low BP plus an abnormal capillary refill.¹⁹

The receipt of inotropes was used as a definition of CVI and this definition has been associated with increased mortality in newborn infants. Consistent with our results, preterm infants receiving inotropes have been shown to have worse outcomes, including death, IVH, and retinopathy of prematurity.^{20,21} In term infants, secondary analyses have shown that in infants with meconium aspiration, those receiving inotropes had a mortality rate of 68% compared with 15.7% in those who did not ($p < 0.001$).²² In late-preterm infants requiring respiratory support, the use of inotropes has also been associated with adverse neurological events (odds ratio 3.2, 1.8–5.6, $p < 0.001$ for prolonged seizures, brain atrophy, intracranial hemorrhage, or stroke).⁵

Although, we did not use a definition of CVI as a BP less than the 5th percentile for age, we found that the mean systolic diastolic, and mean BP at which fluid boluses were initiated were near the 5th percentiles for age. A BP nomogram published by Kent et al shows the 5th percentiles mean

estimated to be 55 mm Hg for the systolic, 30 mm Hg for the diastolic, and 40 mm Hg for the mean in healthy term infants.²³ At the highest GA in our study, a mean BP < 40 mm Hg would be low, as per our definition of mean BP < GA. We found no increase in mortality in term infants with a mean BP < 40 mm Hg, the 5th percentile for a term infant.

The major strength of this study is that it provides information in a population with a high incidence of CVI but in whom associated short-term outcomes are relatively understudied. Although the study was prospective, it is limited by its observational design. In addition, BP measurements and vital signs were not performed as part of this study, but instead performed by the clinical team. The study coordinators collected the data from the chart as close the prespecified time range as possible. In the statistical analysis, important factors were adjusted for including birth weight, GA, and center, but did not include adjusting for disease and overall severity of illness.

A better understanding of CVI and its effect on short-term outcomes is imperative as more than half of the mechanically ventilated term- and late-preterm infants receive therapy for CVI. Until we can better utilize newer modalities to more accurately determine blood flow and perfusion, such as near-infrared spectroscopy or bedside functional ECHOs,^{24,25} we need a clinical definition of CVI, which identifies the population of infants who are at greatest risk for adverse associated outcomes. These findings are important to the design of intervention studies aimed at treating hypotension or CVI in newborn infants.

The receipt of inotropic therapy appears to define a group at high risk for adverse outcomes, including death. This can provide vital baseline information to inform the development of future clinical trials.

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