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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—To evaluate how 4 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 4 different definitions of CVI were further analyzed.

Results—All 4 definitions were associated with greater number of days on MV & days on O\textsubscript{2}. The definition using a threshold blood pressure (BP) measurement alone was not associated with days to full feeding, days in the NICU or death. The definition based on treatment of CVI was associated with all 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

Introduction

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 transition to extra uterine life as well as unclear differences by gestational age (GA) and postnatal age. Furthermore, the relationship between specific blood pressure values with adequate organ perfusion is unknown. There are conflicting reports on the association of adverse outcomes with definitions of hypotension using variable blood pressure 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.\textsuperscript{1-3} However, in other reports, low blood pressure by different definitions is not associated with brain injury by
cranial ultrasounds. 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. In this infant population, clinicians will also use signs such as prolonged capillary refill, oliguria, and acidosis in addition to a threshold blood pressure to determine the best treatment. 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 4 different a priori definitions which included definitions based on low threshold blood pressure alone, low threshold blood pressure 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 1 of these definitions of CVI. We also found a higher incidence of adverse short term outcomes in those infants with any definition of CVI compared to those without CVI. The purpose of this study is to determine the specific association of 4 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 critically ill term and late preterm newborn infants had enrolled 647 infants in 2009 of whom 419 (65%) had cardiovascular insufficiency as defined by 1 of 4 definitions outlined in Table 1. The enrolled infants were ≥34 0/7 weeks gestational age, admitted to one of 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 including range checking, internal comparisons for logic violations and comparison of expected and observed values.

Short term outcomes were collected at 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 gestational age groups (< 37 weeks GA and ≥ 37 weeks GA). First, those with cardiovascular insufficiency by each definition were compared to those without cardiovascular insufficiency 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 O\textsubscript{2} were log-transformed and analyzed by linear regression to determine the relationships of each definition of cardiovascular insufficiency to the outcomes. For each definition, the model parameter estimate, which is the adjusted mean difference 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 2961 grams; 62% were male, 46% outborn and 55% delivered by cesarean section. Patient characteristics have been described in further detail previously.\textsuperscript{6} The mean (SD) systolic, diastolic and mean blood pressures just before the first fluid bolus was given were 53 (10.8), 30 (13.5) and 38 (9.8) mmHg, respectively, for infants <37 weeks GA; for infants ≥37 week, the mean values were 61 (13.9), 36 (11.2) and 44.2 (11.7) mmHg. 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 (adjusted mean difference (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 blood pressure measurement alone (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 cardiovascular insufficiency occurs in a high percentage (65%) of mechanically ventilated term and late preterm infants\textsuperscript{6} 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 4 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 blood pressure 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 blood pressure value alone is a poor measure of blood flow or risk for poor outcomes. However, surveys have suggested that up to 25% of neonatologists use a threshold blood pressure to determine when treatment is initiated. In our previous study, we found that 36% of infants with blood pressure <GA received no therapy, while 46% of those who received therapy had mean blood pressures greater than gestational age, suggesting that other factors besides blood pressure were used to decide treatment. Thus, we also evaluated a definition which included not only blood pressure but clinical 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, this is not a consistent finding. Similar to our study, there are reports in preterm infants showing no correlation of mortality with low blood pressure, as defined by mean BP < GA, and no association with PVL or IVH.

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 blood pressure, there is significantly higher mortality than those without low blood pressure (4.4% vs. 1.9%, p<0.05) and a much higher mortality rate (27%) if they present with low blood pressure plus an abnormal capillary refill.

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. In term infants, secondary analyses have shown that in infants with meconium aspiration, those receiving inotropes had a mortality rate of 68% compared to 15.7% in those who did not (p<0.001). In late preterm infants requiring respiratory support, the use of inotropes has also been associated with adverse neurological events (OR 3.2, 1.8-5.6, p<0.001 for prolonged seizures, brain atrophy, intracranial hemorrhage or stroke).

Although, we did not use a definition of CVI as a blood pressure less than the 5th percentile for age, we found that the mean systolic, diastolic and mean blood pressure at which fluid
boluses were initiated were near the 5th percentiles for age. A blood pressure normogram published by Kent et al shows the 5th percentiles means estimated to be 55 mmHg for the systolic, 30 for the diastolic and 40 for the mean in healthy term infants. At the highest gestational age in our study, a mean BP < 40 mmHg would be low per our definition of mean BP < GA. We found no increase in mortality in term infants with a mean BP < 40 mmHg, 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, blood pressure 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 pre-specified time range as possible. In the statistical analysis, important factors were adjusted for including birth weight, gestational age 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, we need a clinical definition of cardiovascular insufficiency which identifies the population of infant who are at greatest risk for adverse associated outcomes. These findings are important to the design of intervention studies aimed at treating hypotension or cardiovascular insufficiency 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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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Mr. Doug Kendrick (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

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Yale University, Yale-New Haven Children's Hospital (U10 HD27871, UL1 RR24139) – Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

References


Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CVI</td>
<td>cardiovascular insufficiency</td>
</tr>
<tr>
<td>ECHO</td>
<td>echocardiogram</td>
</tr>
<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>GA</td>
<td>gestational age</td>
</tr>
<tr>
<td>iNO</td>
<td>inhaled nitric oxide</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular hemorrhage</td>
</tr>
<tr>
<td>NICU</td>
<td>newborn intensive care unit</td>
</tr>
<tr>
<td>NIRS</td>
<td>near infrared spectroscopy</td>
</tr>
<tr>
<td>NRN</td>
<td>Neonatal Research Network</td>
</tr>
<tr>
<td>PVL</td>
<td>periventricular leukomalacia</td>
</tr>
<tr>
<td></td>
<td>CVI defined by 4 different definitions (A-D)</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>A</td>
<td>2 consecutive mean blood pressures (BP) less than gestational age (GA) in completed weeks (mean BP &lt; GA)</td>
</tr>
<tr>
<td>B</td>
<td>2 consecutive mean BP less than GA in completed weeks (mean BP &lt; GA) and at least 1 additional clinical sign * of CVI</td>
</tr>
<tr>
<td>C</td>
<td>Receipt of fluid bolus, inotrope or glucocorticoid</td>
</tr>
<tr>
<td>D</td>
<td>Receipt of inotropes</td>
</tr>
</tbody>
</table>

*Clinical sign: poor capillary refill (> 3 seconds), oliguria (urine output < 1ml/kg/hour over 6 hours) or serum bicarbonate < 18 and/or base deficit > 5
Table 2a
Incidence of outcomes for each definition of CVI in infants <37 weeks GA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No CVI(\dagger)</th>
<th>A. BP &lt; GA (\ast) P-value</th>
<th>B. BP &lt; GA + sign (\ast) P-value</th>
<th>C. Receipt of any therapy for CVI (\ast) P-value</th>
<th>D. Receipt of Inotropes (\ast) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA &lt; 37 weeks</td>
<td>N = 115</td>
<td>N = 102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>0 (0)</td>
<td>5 (4.9)</td>
<td>0.02</td>
<td>3 (6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Died within 7 days (%)</td>
<td>0 (0)</td>
<td>3 (2.9)</td>
<td>0.10</td>
<td>1 (2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Days on oxygen</td>
<td>4 [2, 8]</td>
<td>6 [3, 13]</td>
<td>0.02</td>
<td>8 [3, 15]</td>
<td>0.003</td>
</tr>
<tr>
<td>DoL at time of full nipple feeding</td>
<td>8 [6, 14]</td>
<td>12.5 [7, 21]</td>
<td>0.01</td>
<td>14 [7, 25]</td>
<td>0.01</td>
</tr>
<tr>
<td>Days in NICU</td>
<td>10 [6, 17]</td>
<td>16 [10, 33]</td>
<td>0.001</td>
<td>17 [11, 34]</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

CVI Cardiovascular insufficiency; DoL Day of life, GA gestational age; NICU Newborn intensive care unit

*P-Value is the comparison of the CVI definition group (in the column at the left) with the No CVI group.

\(\dagger\) No CVI by any of the four definitions.

\(\ast\) Receipt of any volume expander and/or inotropes aimed at improving CVI.

Data are presented as number (%) and median [25\(^{th}\) percentile, 75\(^{th}\) percentile].
### Table 2b
Incidence of outcomes for each definition of CVI in infants ≥37 weeks GA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No CVI†</th>
<th>A. BP&lt; GA</th>
<th>*P-value</th>
<th>B. BP&lt; GA + sign</th>
<th>*P-value</th>
<th>C. Receipt of any therapy for CVI</th>
<th>*P-value</th>
<th>D. Receipt of Inotropes</th>
<th>*P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA ≥37 weeks</td>
<td>N = 113</td>
<td>N = 145</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>3 (2.7)</td>
<td>11 (7.6)</td>
<td>0.15</td>
<td>10 (11.8)</td>
<td>0.2</td>
<td>13 (5.6)</td>
<td>0.34</td>
<td>9/92 (9.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Died within 7 days, n (%)</td>
<td>0 (0)</td>
<td>5 (1.9)</td>
<td>.07</td>
<td>4 (4.7)</td>
<td>.03</td>
<td>5 (2.2)</td>
<td>0.18</td>
<td>4/92 (4.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CVI Cardiovascular Insufficiency; DoL Day of life; GA Gestational Age; NICU Newborn Intensive Care Unit

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

*P-Value is the comparison of the CVI definition group (in the column at the left) with the No CVI group.

†No CVI by any of the four definitions.

‡Receipt of any volume expander and/or inotropes aimed at improving CVI.
### Table 3

Association of outcomes by definition of CVI

<table>
<thead>
<tr>
<th>Definition of CVI</th>
<th>A. BP&lt;GA</th>
<th>B. BP&lt;GA + sign*</th>
<th>C. Receipt of any therapy for CVI</th>
<th>D. Receipt of inotropes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMD</td>
<td>p-value</td>
<td>AMD</td>
<td>p-value</td>
</tr>
<tr>
<td>Days to full nipple feedings</td>
<td>0.099</td>
<td>0.26</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>Days in the NICU</td>
<td>0.79</td>
<td>0.22</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>0.15</td>
<td>0.02</td>
<td>0.27</td>
<td>0.001</td>
</tr>
<tr>
<td>Days on oxygen</td>
<td>0.23</td>
<td>0.003</td>
<td>0.26</td>
<td>0.006</td>
</tr>
<tr>
<td>Death Odds Ratio (95% CI)</td>
<td>2.3 (1, 6)</td>
<td>0.07</td>
<td>3.3 (1, 6)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

AMD Adjusted Mean Difference in Log BP Blood Pressure; CVI Cardiovascular Insufficiency; GA Gestational Age

* Sign of low systemic flow: capillary refill > 3 sec, urine output < 1cc/kg/hr, or serum bicarbonate < 18 and/or base deficit > 5. Bolded values are values which are significant at p<0.05.

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. The higher the AMD, the higher 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.