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Incidence, management and outcomes of cardiovascular insufficiency in critically ill term and late preterm newborn infants

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Abstract

Objective—To characterize the incidence, management and short term outcomes of cardiovascular insufficiency (CVI) in mechanically ventilated newborns, evaluating 4 separate pre-specified definitions.

Study Design—Multicenter, prospective cohort study of infants ≥34 weeks gestational age (GA) and on mechanical ventilation during the first 72 hours. CVI was prospectively defined as either (1) mean arterial pressure (MAP) <GA; (2) MAP<GA + signs of inadequate perfusion; (3) any therapy for CVI; or (4) inotropic therapy. Short term outcomes included death, days on ventilation, oxygen, and to full feedings and discharge.

Results—Of 647 who met inclusion criteria, 419 (65%) met ≥1 definition of CVI. Of these, 98% received fluid boluses, 36% inotropes and 17% corticosteroids. Of treated infants, 46% did not have CVI as defined by a MAP < GA ± signs of inadequate perfusion. Inotrope therapy was associated with increased mortality (11.1% vs. 1.3%; $P < 0.05$).

Conclusion—More than half of the infants met at least one definition of CVI. However, almost half of the treated infants met none of the definitions. Inotropic therapy was associated with increased mortality. These findings can help guide the design of future studies of CVI in newborns.

Keywords

blood pressure; cardiovascular insufficiency; mechanical ventilation; inotrope; fluid bolus; glucocorticoid; outcomes; newborn

INTRODUCTION

Hypotension is commonly diagnosed and treated in mechanically ventilated term and late preterm newborn infants; however, a specific definition for hypotension in the neonatal population, its incidence, and its consequences are essentially unknown. Despite an often unknown etiology and the lack of documented correlation between blood pressure and organ or tissue perfusion, the diagnosis of hypotension often prompts a cascade of therapies in the critically ill newborn.[1] Volume expanders are usually the first line treatment for newborns with hypotension, followed by inotropic agents.[2] In one large, retrospective study of infants

>34 weeks gestation, 60% received volume expanders and 35% received inotropes for a diagnosis of hypotension.[3] In addition, glucocorticoids are increasingly used to treat hypotension in the critically ill term infant.[4] The actual frequency of use and outcomes associated with glucocorticoid administration in this population are currently unknown.

The lack of a clear definition of hypotension and the absence of data regarding incidence, treatment and associated outcomes in this population significantly impedes the ability to design rigorous large clinical trials of therapies aimed at treating this condition. Therefore, we designed a multi-center observational study to address these gaps in knowledge by (1) characterizing the population of term and late preterm infants receiving mechanical ventilation for respiratory failure in the first 3 postnatal days, (2) using a broader descriptive term, cardiovascular insufficiency (CVI), to describe the incidence and treatment approaches to CVI and (3) evaluating the utility of 4 different definitions of CVI to predict short term adverse outcomes.

METHODS

We performed a multicenter, prospective, observational cohort study of CVI in critically ill term and late preterm newborn infants. Infants ≥34 0/7 weeks gestational age admitted to one of 16 Neonatal Research Network (NRN) centers in 2009 who were intubated and mechanically ventilated for respiratory failure for at least 1 hour within the first 72 hours after birth were eligible for inclusion. Infants electively intubated for surgery were excluded, as were infants with hypotension resulting from documented acute maternal and/or fetal hemorrhage within 24 hours prior to delivery, and those with a known diagnosis of major congenital heart disease, moderate or severe hypoxic ischemic encephalopathy (HIE), pituitary hypoplasia, congenital adrenal hyperplasia, congenital diaphragmatic hernia, omphalocele or chromosomal disorder.

Clinical data were collected by trained research coordinators, and all analyses were performed at the Network 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.

Infant and maternal clinical and demographical data were collected from the medical record. Data regarding administration of inhaled nitric oxide (iNO), surfactant and/or extracorporeal membrane oxygenation (ECMO) in the first 72 hours of age were also collected. Prospectively defined short term outcomes included death, days on mechanical ventilation, days on oxygen, days to full enteral nipple feedings, and length of stay; these data were collected at time of death, discharge, transfer, or at 60 days if the infant was still in the hospital.

Four definitions of CVI were established *a priori*, as illustrated in Figure 1. Definition A: 2 consecutive mean arterial blood pressures (MAP) lower than the infant's gestational age in completed weeks at birth. This definition was included because of its presumed prevalent

use, and because published nomograms have shown that the lower limit of 80% confidence intervals for MAP is greater than the gestational age in the first 72 hours.[5-7]

Definition B: definition A plus at least one of the following signs of inadequate perfusion: capillary refill time >3 seconds, oliguria (urine output <1ml/kg/hour over 6 hours), or serum bicarbonate <18 and/or base deficit >5. Definition C: receipt of any therapy for CVI, including fluid bolus, inotropic therapy or glucocorticoid. Definition D: receipt of inotropic therapy, including dopamine, dobutamine, or epinephrine. The definition of CVI as receipt of treatment with fluid, steroids or inotropes is based on previously published operational definitions of hypotension.[3,8]

For infants who received volume expanders, inotropes or glucocorticoids, data were collected on age and blood pressure (measured by non-invasive oscillometry and/or transduced in-line arterial catheters) nearest the time of initiation if available in chart, stated reason for initiation, dosing, duration and type of therapy. Inotropic drug exposure was measured as total days of therapy and as peak dose in 6-hour time periods over the first 72 hours of age. The median of 12 (6-hour time blocks × 12= 72 hours) inotrope peak doses was calculated and then averaged over the first 72 hours of age. The mean peak dose was calculated by using the following inotropic score, which has been used previously in ill patient populations[9]: Dopamine (mcg/kg/min) × 1, plus dobutamine (mcg/kg/min) ×1, plus epinephrine (mcg/kg/min) × 100, plus phenylephrine (mcg/kg/min) × 100, plus noradrenaline (mcg/kg/min) × 100.

Waiver of consent was approved by the institutional review boards at 14 NRN sites. At 2 other sites, infants were enrolled after parental written informed consent was obtained.

Statistical Analysis

This study was time-limited to a 9-month enrollment period, was designed to explore the incidence of CVI in this population and was not hypothesis-driven. However, we calculated a sample size to test the null hypothesis that <25% of mechanically ventilated newborns have CVI as defined by receipt of vasopressors/inotropic agents to confirm an estimate of infants with CVI, based on previous findings.[2] At least 494 infants were required to achieve 80% power to detect a difference of 5% (30% of infants given inotropes instead of 25%) using a 1-sided binomial test with a Type I error rate of 0.05.

Analysis was performed on data that was complete. Three infants were missing fully completed characteristic data and were not included. Patient characteristics were evaluated by comparing CVI rates by any definition, by use of any inotrope (definition D), and by no CVI. Short term outcomes for infants with CVI by any definition and by the definition of receipt of any inotrope were compared to those without CVI using continuity-adjusted chi-square test. P values less than 0.05 were considered statistically significant. *A priori*, sub-group analysis was planned based on gestational age strata of <37 vs. ≥ 37 weeks.

RESULTS

Enrollment

During the 9-month study period, 830 infants ≥34 0/7 weeks gestational age at 16 NRN centers were intubated and mechanically ventilated for respiratory failure for at least 1 hour during the first 72 postnatal hours. Of these, 183 were subsequently excluded because they had one or more exclusion criteria (Figure 1). Of the 647 infants included in the analyses, 65% met at least one of the definitions of CVI (Figure 1).

Patient characteristics

Infants with CVI by any definition (N=419) vs. no CVI (N=228) were more mature at birth (37.3 vs. 36.8 weeks, p=0.008), more likely to be intubated in the delivery room (32% vs. 24%, p=0.045), receive iNO (24.8 % vs. 1.3%, p<0.0001) and/or ECMO (5.7% vs. 0%, p<0.001), but did not differ in gender, race, ethnicity, rates of prenatal steroid administration or cesarean section, Apgar scores, receipt of chest compressions or epinephrine in the delivery room, or outborn vs. inborn status.

Demographics stratified by late preterm and term groups are shown in Table 1, separated into those with CVI by any definition and those without. Late preterm infants who received inotropes were more likely to have received intubation (42% vs. 21%, p=0.01) and chest compressions at delivery (9.8% vs. 2.1%, p=0.04), and more often received iNO (37% vs. 3%, p<0.0001) or ECMO (9.8 %vs. 0.4%, p=0.002) than infants with no CVI by any definition. Term infants who received inotropes vs. those who did not have CVI by any definition were more likely to be inborn than outborn (76% vs. 49%,<0.0001), and were more likely to receive iNO (71% vs. 7.2%, p=<0.0001), surfactant (65% vs. 27%, p=<0.0001) or ECMO (17% vs. 1.4%, p=<0.0001).

The most common diagnoses recorded in the medical chart included suspected sepsis (71.1%), respiratory distress syndrome (67.9%), persistent pulmonary hypertension (19.3%), patent ductus arteriosus (15.9%), pneumothorax or pneumomediastinum (14.7%), meconium aspiration syndrome (13.9%), and pneumonia (10%).

Incidence of cardiovascular insufficiency and relationship to receipt of therapy

Among included infants, 247 (38%) had CVI by Definition A (2 MAP readings < GA). Of these infants, 55% (n=135) also had at least one sign of impaired perfusion including oliguria, metabolic acidosis or poor capillary refill (Definition B). Over half of the study population (371/647; 57%) met Definition C (fluid infusion, inotrope or steroid therapy). Of these infants, 36% (n=135) received inotropes (Definition D).

Figure 2 shows the general relationships between these 4 definitions of CVI. Notably, of infants who received any therapy (Definition C), 46% (172) did not meet either Definition A or B. As shown in Figure 2, each different definition described a different population – overlapping but not identical. Only 24 infants (3.7% of 647 enrolled infant) met criteria for all 4 definitions.

Therapies received

The fluid most commonly used for volume expansion was normal saline (87.6%), followed by packed red blood cells (19.3%), and fresh frozen plasma (13.5%). Of 135 infants receiving inotropic agents, 94.1% received dopamine, 30.4% dobutamine, 25.2% epinephrine and 3.7% milrinone. Of infants receiving inotropic therapy, 96% also received a fluid bolus. Of the 64 infants who received steroids, 60 received hydrocortisone and 4 received dexamethasone. Fifty-six (88%) of the infants who received steroids also received inotropes. Two centers reported no steroid use.

Timing of initiation and duration of therapies

The first dose of any therapy was given at a median age of 5 hours. In the first 7 days of age, a median [25th percentile - 75th percentile] of 81 [40 - 189] ml/kg of volume boluses was administered, of which 93% was given in the first 72 hours. Inotropes were received for median of 2 [1 - 4] days. Over the first 72 hours, the inotrope peak dose in each 6-hour time period was a median of 5 [2 – 10] mcg/kg/min. For hydrocortisone, the median total dose given was 7.1 [4- 13.8] mg/kg in the first 72 hours and 13.6 mg/kg [4 - 26] total over a median of 4 [1 - 8] days. Of the infants treated for CVI, the majority (62%) had a mean blood pressure >38 mmHg at the time of initial receipt of therapy (mean 41.6 ± 11.2 mmHg).[10] The timing and duration of therapies administered and reasons for administering are stratified by gestational age group in Table 2.

Association with short term outcomes

Infants with CVI by any definition had significantly worse outcomes than those without CVI except for death in the term infants (Table 3). Those who received an inotropic agent (Definition D) had a higher incidence of all adverse outcomes than infants who did not have CVI.

DISCUSSION

In this study of mechanically ventilated term and late preterm infants, we found that a majority (57%) of these infants were treated for presumed CVI within the first 72 hours. However, infants with “hypotension” classified by an often-used definition of MAP<gestational age did not always receive therapy. This suggests that either clinicians are not aware that infants are meeting this threshold definition or that clinicians take other factors into consideration when deciding to initiate fluid, inotropic or steroid therapy. Therefore, blood pressure alone is unlikely to be a useful entry criterion for studies evaluating therapy for CVI. Conversely, infants who received inotropic therapy had significantly worse short term outcomes, including a much higher mortality rate, suggesting that a clinical decision to employ inotropic therapy may define an appropriate high-risk group for inclusion in future studies.

Our findings are similar to a recent large retrospective study of respiratory failure in late preterm and term infants.[3] Defining CVI as receipt of therapy, Clark reported that of newborn infants >34 weeks gestation who required mechanical ventilation within 72 hours, 60% received volume expanders and 35% received vasopressors. In our population, 56%

received volume expanders and 21% received vasopressors. In our study, the most common treatment pattern began with fluid boluses (predominantly normal saline) followed by inotropic agents (predominantly dopamine), and subsequently hydrocortisone. This treatment strategy is similar to the current guideline and recommendations by the American College of Critical Care Medicine and to the findings of surveys of treatment in preterm infants.[11,12]

No blood pressure threshold has been shown to consistently or accurately identify low blood flow or risk for poor outcomes in this population, nor has treatment of blood pressure been shown to improve outcomes.[6] However, a threshold blood pressure continues to be frequently used to initiate treatment.[12] Surveys suggest that over 25% of neonatologists rely on blood pressure values alone, and most used a mean blood pressure <GA as the threshold for therapy.[12] In our study, however, 36% of infants with blood pressure <GA received no therapy, while 46% of those who received therapy did not have a MAP less than gestational age, suggesting that many neonatologists use other factors in addition to blood pressure to decide upon treatment. To explore other possible contributing factors, we prospectively evaluated the use of an additional definition, “low blood pressure *and* signs of low blood flow.” Addition of this definition still did not correlate with the decision to institute therapy or with increased mortality.

We are not aware of any published randomized trials of outcomes following inotrope therapy in term and late preterm newborns. Observational studies have reported an increased risk of adverse neurological events and of death in newborns who received vasopressors compared to those who did not[3,13] These increased adverse outcomes could be due to the underlying disease, inadequate perfusion prior to therapy, the therapy itself, or other factors. No long term outcome studies have been published to confirm safety or benefit of any inotrope in neonates.

Furthermore, there have been no randomized controlled trials of glucocorticoid therapy to treat or prevent CVI in term and late preterm infants. The few trials in preterm infants have shown improved blood pressure, decreased administration of vasopressors, reduced days on vasopressors and decreased use of volume therapy compared to placebo.[14,15] Despite this lack of information for term infants, clinicians in 14 of the 16 study centers administered steroids for the treatment of hypotension.

This study was intentionally limited in its scope. Although a power analysis was performed to ensure adequate numbers were enrolled to confirm the incidence of hypotension, this was not a hypothesis-driven study for comparisons between groups. We did not analyze differences between blood pressures measurements by oscillatory vs. arterial line methods; however, a recent report found good agreement between these two methods.[16] This study also did not collect data on the utilization of newer modalities for determining blood flow and perfusion, such as near-infrared spectroscopy (NIRS) or bedside functional echocardiogram.[17,18] in the future, such tools may help evaluate the contributions of underlying diseases, clinical factors, and treatments to outcomes in this population.

In conclusion, more than half of the mechanically ventilated term and late preterm infants in this study received therapy for suspected CVI. At the same time, many who met a widely used definition of CVI (mean BP <GA) were not treated, and many treated infants did not have a mean BP<GA or documented signs of low systemic blood flow. Receipt of inotropic therapy appeared to define the highest risk group. The results of this study will inform the design of future randomized controlled trials of treatment(s) for cardiovascular insufficiency in these critically ill patients.

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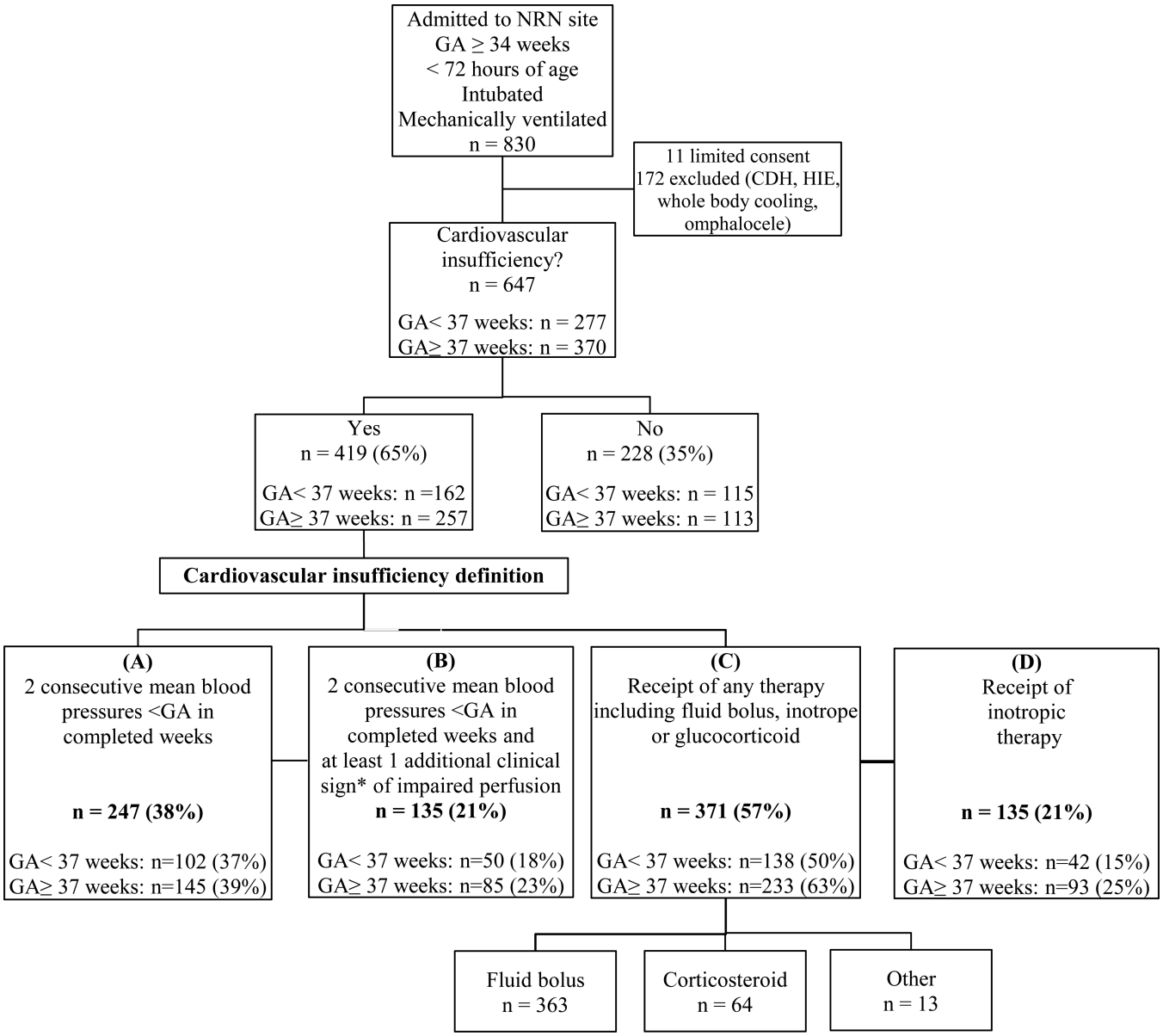

Figure 1.

*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

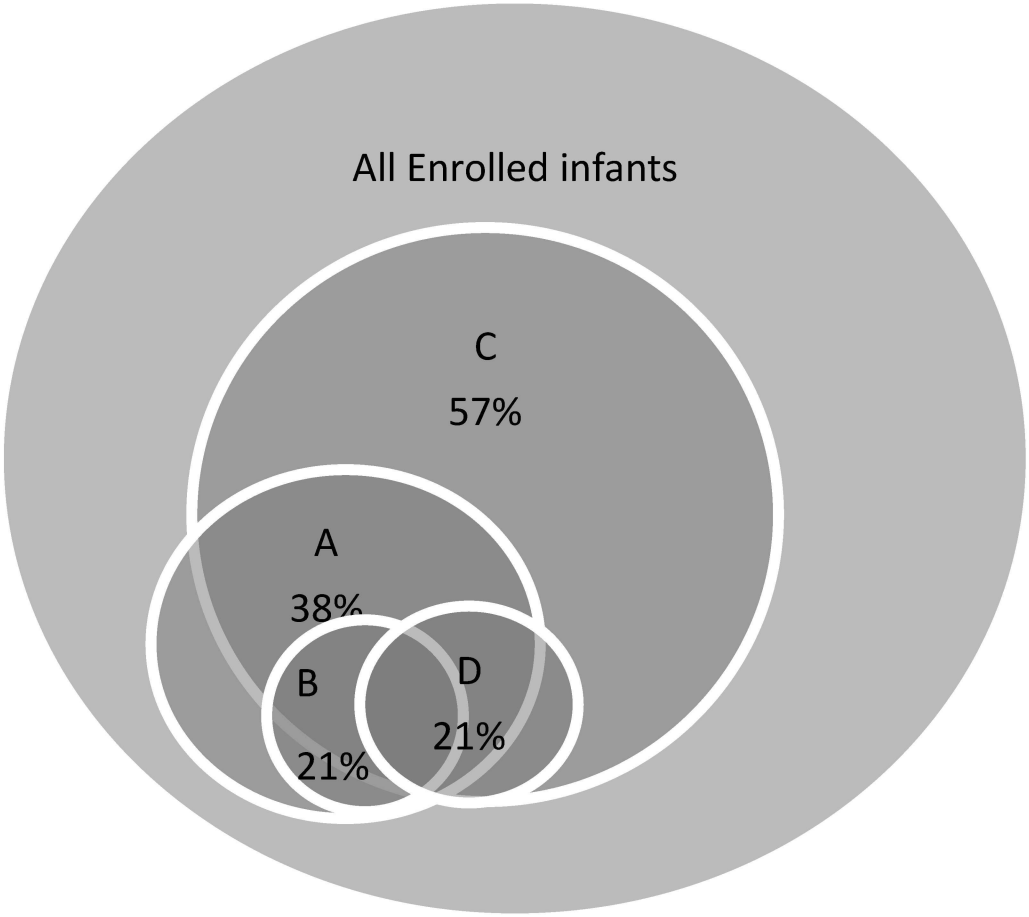

Figure 2.

Percent (%) is number of infants with the each definition divided by total number of infants enrolled. Of the 112 infants who met criteria for Definition A, 36% (40) received no therapy. Of those who met either Definition A or B (low mean blood pressure ± clinical signs of low blood flow), 19% (48) were not treated. Of infants who received inotropic agents (Definition D), 30% (40) did not have CVI by Definition A and 47% (64) did not meet Definition B. Of the infants who received fluid expansion, 46% (166) did not have CVI by Definition A and 65% (237) did not meet definition B.

Table 1

Patient characteristics by cardiovascular insufficiency (CVI) vs. no CVI by any study definition

Patient Characteristic	GA <37 weeks				GA ≥37 weeks			
	All Infants (n=277)	CVI (n=162)	No CVI (n=115)	P value*	All Infants (n=370)	CVI (n=257)	No CVI (n=113)	P value*
Prenatal steroids, n (%)	40 (15)	22 (14)	18 (16)	0.75	3 (0.8)	2 (0.8)	1 (0.9)	1.00
Birth weight, mean (SD), g	2570 (528)	2567 (558)	2573 (483)	0.92	3254 (591)	3228 (602)	3315 (565)	0.19
GA, mean (SD), weeks	35 (0.8)	35.1 (0.8)	35.0 (0.8)	0.29	38.6 (1.3)	38.6 (1.4)	38.7 (1.2)	0.88
Apgar <3 (5 min), n (%)	11(4)	8 (4.9)	3 (2.7)	0.53	29 (7.9)	20 (7.9)	9 (8.0)	1.00
Delivery room								
Intubation, n (%)	67 (24.2)	48 (29.6)	19 (16.5)	0.02	122 (33)	86 (33.5)	36 (31.9)	0.86
Chest compression, n (%)	9 (3.2)	8 (4.9)	1 (0.9)	0.09	17 (4.6)	13 (5.1)	4 (3.5)	0.71
Epinephrine, n (%)	2 (0.7)	2 (1.2)	0 (0)	0.51	5 (1.4)	5 (1.9)	0 (0)	0.33
Cesarean section, n (%)	158 (57)	87 (53.7)	71 (61.7)	0.23	200 (54.1)	133 (51.8)	67 (59.3)	0.40
Male, n (%)	166 (59.9)	92 (56.8)	74 (64.3)	0.25	232 (62.7)	159 (61.9)	73 (64.6)	0.70
Black race, n (%)	48 (18)	26 (16.7)	22 (19.8)	0.62	82 (22.9)	52 (20.6)	30 (28.3)	0.15
Hispanic, n (%)	34 (14.3)	24 (16.2)	10 (11.1)	0.37	65 (19.6)	41 (17.7)	24 (24.2)	0.22
Outborn, n (%)	133 (48)	82 (50.6)	51 (44.3)	0.36	164 (44.3)	102 (39.7)	62 (54.9)	0.01
Inhaled NO, n (%)	22 (7.9)	20 (12.3)	2 (1.7)	0.003	85 (23)	84 (32.7)	1 (0.9)	<.0001
ECMO, n (%)	5 (1.8)	5 (3.1)	0 (0)	0.08	19 (5.1)	19 (7.4)	0 (0)	0.01
Surfactant use, n (%)	181 (65.3)	92 (56.8)	89 (77.4)	0.001	133 (35.9)	106 (41.2)	27 (23.9)	0.002

GA gestational age; ECMO extracorporeal membrane oxygenation; NO nitric oxide

*P value, any CVI vs. no CVI within each gestational age group

Table 2

Timing and duration of administered therapies and recorded reasons on medical chart for administration

	All (n = 371)		Volume expanders (n = 363)		Inotropes (n = 135)		Steroids (n = 64)	
	GA < 37 weeks (n = 138)	**GA ≥ 37 weeks (n = 233)**	**GA < 37 weeks (n =135)**	**GA ≥ 37 weeks (n = 228)**	**GA < 37 weeks (n = 42)**	**GA ≥ 37 weeks (n = 93)**	**GA < 37 weeks (n = 18)**	**GA ≥ 37 weeks (n = 46)**
Hours of age at 1st dose, median [interquartile range]	4 [1, 16]	6 [2, 21]	4 [1, 16]	5 [2, 21]	18 [10, 25]	15 [9, 31]	33 [14, 44]	25 [13, 45]
Days of tx received, median [interquartile range]	NA	NA	NA	NA	2 [1, 4]	2 [1, 5]	4 (2, 8)	5 [1, 9]
BP at 1st dose of tx mean (SD), mmHg	38 (10)	44 (12)	38 (10)	44 (12)	35 (8)	41 (11)	41 (10)	44 (10)
Mean BP < GA, n (%)	52 (44)	53 (33)	53 (46)	52 (33)	23 (61)	35 (50)	4 (25)	12 (32)
Reason for administration, n (%)								
Low BP	NA	NA	64 (47)	88 (39)	35 (83)	72 (77)	10 (56)	29 (63)
Poor perfusion/CR <3s	NA	NA	60 (44)	94 (41)	20 (48)	39 (42)	7 (39)	11 (24)
Low urine output	NA	NA	15 (11)	36 (16)	5 (12)	9 (10)	2 (11)	3 (7)
Replace metabolic loss	NA	NA	5 (4)	8 (4)	0 (0)	1 (1)	0 (0)	3 (7)
Metabolic acidosis	NA	NA	22 (16)	38 (17)	6 (14)	7 (8)	0 (0)	3 (7)
Tachycardia	NA	NA	7 (5)	6 (3)	2 (5)	1 (1)	0 (0)	2 (4)
Response to ECHO	NA	NA	1 (1)	1 (0.4)	1 (2)	0 (0)	0 (0)	0 (0)
Poor renal perfusion	NA	NA	1 (1)	4 (2)	1 (2)	5 (5)	1 (6)	2 (4)
Raise systolic BP in PPHN	NA	NA	2 (2)	7 (3)	4 (10)	17 (18)	4 (22)	5 (11)
Unknown	NA	NA	20 (15)	44 (19)	1 (2)	6 (7)	3 (17)	5 (11)

BP, blood pressure; ECHO, Echocardiogram; GA, gestational age; CR, capillary refill; No, number; SD standard deviation; PPHN persistent pulmonary hypertension; tx, therapy

Not all infants had a blood pressure recorded or collected around the time of initial therapy administration

Table 3

Short term outcomes, stratified by gestational age, median (interquartile range)

	All infants	No CVI	CVI By any definition	Received inotrope*	P value†
GA < 37 weeks	**n = 277**	**n = 115**	**n = 162**	**n = 42**	
Death	3%	0%	6%	14%*	0.03
Days of age at death	9 (4, 16)	NA	9 (4, 16)	4 (3, 16)	NA
Days intubated and on mechanical ventilator	2 (2, 5)	2 (2, 4)	3 (2, 7)	7 (4, 11)*	0.0001
Days on oxygen	5 (2, 9)	4 (2, 8)	6 (3, 11)	11 (4, 16)*	0.03
Days of age at time of full nipple feeding	9 (6, 17)	8 (6, 14)	12.5 (7, 21)	21 (10, 27)*	0.001
Days in NICU	12 (8, 25)	10 (6, 17)	15 (9, 29)	16 (10, 34)*	0.001
GA ≥ 37 weeks	**n = 370**	**n = 113**	**n = 257**	**n = 93**	
Death	4%	3%	5%	10*	0.44
Days of age at death	13 (2, 46)	48 (30, 60)	10 (2, 18)	12 (2, 18)*	0.10
Days intubated and on mechanical ventilator	3 (2, 8)	2 (1, 4)	4 (2, 10)	10 (4, 13)*	<.0001
Days on oxygen	5 (2, 10)	3 (1, 5)	7 (2, 13)	11 (8, 19)*	<.0001
Days of age at time of full nipple feeding	8 (5, 15)	6 (3, 9)	10 (6, 17)	14 (10, 26)*	<.0001
Days in NICU	12 (7, 21)	8 (5, 15)	14 (8, 24)	17 (11, 35)*	<.0001

CVI cardiovascular insufficiency; NICU Newborn intensive care unit; GA gestational age

*Significant at P<0.05 vs. no CVI

†P value for CVI by any study definition vs. no CVI