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Authors

Lakshminrusimha, Satyan
Shankaran, Seetha
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et al.

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Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy—Antecedent Characteristics and Comorbidities

Satyan Lakshminrusimha[1], **Seetha Shankaran**[2], **Abbot Laptook**[3], **Scott McDonald**[4], **Martin Keszler**[3], **Krisa Van Meurs**[5], **Ronnie Guillet**[6], **Sanjay Chawla**[2], **Beena G. Sood**[2], **Sonia Bonifacio**[5], **Abhik Das**[7], and **Rosemary D. Higgins**[8]

[1]University of California at Davis, Sacramento, CA

[2]Wayne State University, Detroit, MI

[3]Brown University, Providence, RI

[4]RTI International, Research Triangle Park, NC

[5]Stanford University, Palo Alto, CA

[6]University of Rochester, Rochester, NY

[7]RTI International, Rockville, MD

[8]NICHD, Bethesda, MD

Abstract

Objective—To determine the characteristics of term infants with persistent pulmonary hypertension of the newborn (PPHN) associated with moderate or severe hypoxic ischemic encephalopathy (HIE).

Methods—We compared infants with and without PPHN enrolled in 2 randomized trials of therapeutic hypothermia: the induced hypothermia trial of cooling to 33.5°C for 72h vs normothermia, and the “usual-care” arm (33.5°C for 72h) of the optimizing cooling trial.

Results—Among 303 infants with HIE from these two studies, 67 (22%) had PPHN and 236 (78%) did not. We compared infants with PPHN with those without PPHN. The proportion of patients treated with therapeutic hypothermia was similar in PPHN and no-PPHN groups (66% vs. 65%). Medication use during resuscitation (58 vs. 44%), acidosis after birth (pH: 7.0±0.2 vs. 7.1±0.2), severe HIE (43 vs. 28%), meconium aspiration syndrome (39 vs. 7%), pulmonary hemorrhage (12 vs. 3%), culture-positive sepsis (12 vs. 3%), systemic hypotension (65 vs. 28%),

Corresponding author: Satyan Lakshminrusimha, MD, Department of Pediatrics, UC Davis, 2516 Stockton Blvd, Sacramento CA 95817, Phone: 9167345178, slakshmi@ucdavis.edu.

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iNO therapy (64 vs. 3%) and ECMO (12 vs. 0%) were more common in the PPHN group. Length of stay (26±21 vs. 16±14 d) and mortality (27 vs. 16%) were higher in the PPHN group.

Conclusions—PPHN is common among infants with moderate/severe HIE and is associated with severe encephalopathy, lung disease, sepsis, systemic hypotension, and increased mortality. The prevalence of PPHN was not different between those infants receiving therapeutic hypothermia at 33.5°C in these two trials (44/197 = 22%) compared with infants receiving normothermia in the induced hypothermia trial (23/106 = 22%).

Keywords

hypoxia; acidosis; asphyxia; cooling

Moderate hypothermia (33.5°C) is neuroprotective in infants who suffer from perinatal hypoxic-ischemic encephalopathy (HIE). The American Academy of Pediatrics[1] and Neonatal Resuscitation Program[2] support whole-body or selective head cooling for neonates with moderate to severe HIE. Persistent pulmonary hypertension of the newborn (PPHN) was reported in 6–25% neonates with HIE enrolled in the clinical trials of head and whole body cooling.[3–5] and is higher than the incidence of PPHN in the general population (1.9 per 1000 live births).[6] The definition of PPHN in these trials was variable and based on clinical features, presence of hypoxemic respiratory failure, echocardiography or use of inhaled nitric oxide (iNO).

There are several potential mechanisms causing hypoxemic respiratory failure and PPHN in asphyxiated newborn infants.[7] Fetal hypoxemia, meconium aspiration syndrome (MAS), sepsis, ventricular dysfunction and acidosis can increase pulmonary vascular resistance (PVR) and result in PPHN. Among fatal cases of PPHN secondary to MAS, 10/11 infants had evidence of remodeling of intraacinar pulmonary arteries at autopsy contributing to increased PVR.[8, 9]

In the first NICHD (Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, Maryland) - NRN (Neonatal Research Network) trial (induced hypothermia-IH), moderate hypothermia to 33.5°C was not associated with an increase in the incidence of PPHN or the need for iNO and extracorporeal membrane oxygenation (ECMO) compared with the normothermia group (25% vs 22%). In the optimizing cooling strategies trial (OC), the incidence of PPHN among infants cooled to 33.5°C was 20%. However, in the OC trial where neonates were randomly assigned to 4 combinations of duration and depth of cooling, whole body hypothermia to 32°C for duration of 72 or 120 hours was associated with an increased use of iNO and ECMO, compared with infants randomized to the 33.5°C cooling for either 72 or 120 hours.[10] Currently, moderate hypothermia with a core temperature of 33.5°C for 72 hours initiated within 6 hours of birth is recommended for newborns with moderate or severe HIE.[1, 211]

Our primary objective was to determine the clinical characteristics and comorbidities before delivery, intrapartum and during the hospital course prior to discharge that were associated with PPHN in term neonates with moderate to severe HIE. We hypothesized that lung disease (e.g. MAS, pulmonary hemorrhage), sepsis and cardiac dysfunction would be more

common in neonates with HIE who also had PPHN, and that infants with PPHN would have a lower PaO_2 at baseline, higher rate of severe encephalopathy, and higher mortality. We also evaluated the use of iNO and ECMO in infants with PPHN and compared the mortality between infants with and without PPHN. We used prespecified data collected from two randomized controlled trials, IH and OC. Because prolonged (120 h) and deeper cooling (32°C) are not standard of care, we excluded infants enrolled in these arms from the OC trial.

Methods

This study was a secondary analysis of data from the NICHD Induced Hypothermia Trial (IH- NCT00005772, 2000–2003) and the "usual care" arm (33°C for 72h) of the optimizing cooling strategies trial (OC-NCT01192776, 2010–2013). For both trials, infants were screened if they were of gestational age of ≥36 weeks and were admitted to the NICU at <6 hours of age, with an admitting diagnosis of acute perinatal asphyxia, neonatal depression, encephalopathy and/or fetal acidemia. Infants were evaluated according to physiologic criteria and a neurologic examination. Eligibility criteria included pH of ≤7.0 or base deficit of ≥16 mmol/L in cord blood or during the first 1 hour after birth. If, during this interval, the pH was between 7.01 and 7.15, the base deficit was between 10 and 15.9 mmol/L, or an arterial blood gas value was not available, then additional criteria were required (an acute perinatal event and either a 10-minute Apgar score of ≤5 or assisted ventilation for ≥10 minutes from birth). Once these criteria were met, all infants underwent a standardized neurologic examination, performed by a certified physician. Encephalopathy was defined as ≥1 moderate or severe signs in at least 3 of the 6 categories. The number of moderate or severe signs determined the degree of encephalopathy; if signs were distributed equally, then the designation was based on the level of consciousness. Moderate or severe encephalopathy or seizures qualified infants for the trials.

The diagnosis of PPHN was based on clinical signs consistent with this diagnosis and echocardiographic evidence of pulmonary hypertension (i.e., no structural heart disease; positive indication of elevated pulmonary arterial pressure; and/or flattened ventricular septum).[12] The centers were instructed to obtain and report blood gases at patient's actual temperature. The interpretation of echocardiograms, ventilator management, use of iNO and ECMO was as per individual center practices. The distribution of patients in various arms of these trials is shown in Figure 1.

Statistical analyses

Maternal characteristics (including intrapartum complications and mode of delivery), baseline neonatal characteristics, respiratory variables, mortality, length of stay, and associated organ dysfunction were analyzed for differences among babies with and without PPHN using chi- square or Fisher's exact tests for categorical variables and t-tests for continuous variables.

Logistic and linear regression analyses were also conducted for mortality and length of stay to compare outcomes for babies with and without PPHN, while adjusting for severity of

HIE. All reported *P* values are 2-sided and not adjusted for multiple comparisons; a p-value of less than 0.05 was considered statistically significant. The statistical software used was SAS (SAS Institute, Cary, North Carolina) version 9.4.

Results

The induced hypothermia (IH) trial enrolled 208 infants ≥36 weeks' gestation at birth with moderate to severe HIE.[13] In this trial, 102 infants were assigned to the whole-body hypothermia group (target esophageal temperature of 33.5°C for 72h) and 106 were assigned to the normothermia group (Figure 1). The optimizing cooling strategies trial (OC) randomized 364 infants to four arms with differing core target temperature and duration of therapeutic hypothermia: 33.5°C for 72h, 32°C for 72h, 33.5°C for 120h and 32°C for 120h. Only the 95 subjects from 33.5°C for 72h arm of the OC trial were included in the present analysis. In total, 303 infants (208 from IH and 95 from OC trial) were evaluated.

Sixty-seven patients (22%) had a diagnosis of PPHN. Twenty-three of 106 (21.7%) from the normothermia arm of the IH trial, 25 of 102 (24.5%) from hypothermia arm of IH trial and 19 of 95 (20%) from the usual care arm of the OC trial had PPHN. Maternal characteristics, antepartum, intrapartum and postnatal course during intervention and prior to discharge were compared between the PPHN group (n=67) and the no-PPHN group (n=236).

Maternal characteristics and intrapartum complications are shown in Table I. Maternal hypertension was less common in the PPHN group. All the other maternal parameters were similar between PPHN and no-PPHN groups. Uterine rupture was less common in the PPHN group. Membranes were intact in more subjects in the PPHN group compared with no-PPHN group. Among mothers with rupture of membranes (ROM) prior to delivery, the duration of ROM (either spontaneous or induced) was significantly shorter in PPHN group. Seventy percent of infants (213/303) were delivered by emergent cesarean delivery; there was no difference between PPHN and no-PPHN groups. Neonatal and delivery room resuscitation characteristics were similar in both groups and are shown in Table 2 The majority of the 303 infants with moderate to severe HIE required resuscitation in the delivery room. Spontaneous respirations were delayed beyond 10 minutes in 181 of 286 infants (63.3%). The use of medications for resuscitation was more frequent in the PPHN group. Other resuscitative measures were performed at a similar frequency between the 2 groups (Table 2).

The first postnatal gas showed significantly lower pH in the PPHN group. More infants with PPHN group were classified as having severe HIE based on the neurologic examination performed at < 6 hours of postnatal age compared with the no-PPHN group (Table 2). The age at randomization was similar between the groups. Out of the 303 infants, 106 infants assigned to the control (normothermia group) arm of the IH trial were not treated with therapeutic hypothermia. The percentage of infants undergoing hypothermia was similar in PPHN and no-PPHN groups (Table 2). Sepsis with a positive blood culture was more common among infants with PPHN. The organisms isolated from blood culture are shown as footnotes in Table 3. Underlying pulmonary pathology was more common in infants with PPHN compared with the no-PPHN group (Table 3).

Meconium aspiration syndrome (MAS) and pulmonary hemorrhage were more commonly observed in patients with PPHN. The use of high frequency ventilation was more common among infants with PPHN. Infants with PPHN were treated with higher F_IO_2 at baseline and throughout the period of intervention (Figure 2, A) to maintain PaO_2 similar to the no-PPHN group (Figure 2, B) (Figure 2 available at www.jpeds.com).

The cord pH was similar between the 2 groups. The pH on the first postnatal gas and at baseline was significantly lower in the PPHN group (Figure 3, A). PCO2 on the cord gas was not reported and was significantly higher on the first postnatal gas in the PPHN group. There was no difference in PCO_2 levels between the 2 groups at baseline and during the intervention period (Figure 3, B) (Figure 3 available at www.jpeds.com).

As expected, use of iNO was more frequent among infants with PPHN (Table 3). The specific indication for this therapy was not collected. Inhaled NO was used in 64% of infants with PPHN and 12% were placed on ECMO. Seven infants with moderate HIE in the no-PPHN group received iNO and 6 of them were on $F_IO_2 \geq 0.8$ and 4 died. These infants had hypoxemic respiratory failure but PPHN was not confirmed by echocardiogram. Four of these infants were in the control arm of the IH trial and 3 were in the usual care arm of the OC trial.

Systemic hypotension, cardiomegaly, cardiac dysfunction, use of volume expanders and inotropes were more common in the PPHN group (Table 3). The duration of inotrope therapy was more prolonged in the PPHN group. Oliguria and renal dysfunction were similar between groups (27 vs. 22% in PPHN vs. no-PPHN groups). There was no significant difference in neurological status at the time of hospital discharge among survivors between the 2 groups (Table 3).

Among the 67 patients with PPHN, 8 (12%) received ECMO and 7 survived. Five patients died secondary to PPHN and/or MAS (including one death after ECMO) and fourteen infants with PPHN had support withdrawn due to poor neurologic prognosis. Mortality was significantly higher in the PPHN group compared with no-PPHN group by unadjusted analysis (Table 3). When adjusted for severity of HIE, mortality was no longer significantly different in the PPHN group (adjusted OR: 1.52, 0.76–3.02 – p=0.24), suggesting potential confounding between PPHN and baseline severity of HIE. Among infants with moderate HIE, mortality was significantly higher (OR 2.73, 1.01–7.39, p=0.048) in the PPHN group (18%) compared with no-PPHN group (8%). Mortality was significantly higher with severe HIE (38%) and was not influenced by the presence of PPHN (38% mortality in both groups, OR 0.98, 0.40–2.41, p=0.96). The causes of death are listed in Table 3 and no significant differences were evident between the 2 groups. Among all infants, and among survivors to discharge, the length of stay was significantly prolonged in the PPHN group compared with no-PPHN group (Table 3) after correcting for severity of HIE.

Discussion

We analyzed prespecified, prospectively collected data evaluating PPHN among infants with moderate to severe HIE. In our study, PPHN was observed in 22%of neonates with moderate

to severe HIE. We found an association between comorbidities such as severe acidosis (first postnatal gas and at baseline), use of medications during delivery room resuscitation, underlying pulmonary pathology (meconium aspiration syndrome and pulmonary hemorrhage), hypercarbia on the first postnatal gas, high FiO_2 at baseline and presence of PPHN. Inhaled NO was used among approximately two-thirds and ECMO in 12% of infants with moderate/severe HIE and PPHN. Coexisting PPHN increased mortality among neonates with HIE.

We observed some differences in PPHN associated with HIE compared with that observed in general neonatal populations.[14, 1516] Black race, maternal diabetes, and maternal hypertension have been associated with increased PPHN in general neonatal populations[1516], but this association was not evident in the current analysis.

Interestingly, uterine rupture was less common (3% vs. 13%) among infants with PPHN. We speculate that uterine rupture is an acute, symptomatic event leading to immediate recognition, rapid delivery and prompt resuscitation and hence less likely to be associated with PPHN. However, we acknowledge that this difference could be due to small number of PPHN patients in our study.

The majority of infants with moderate or severe HIE required delivery room resuscitation. However, the increased use of medications during resuscitation of PPHN vs. the no-PPHN infants with HIE suggests a common association of these factors with severe HIE. Fetal hypoxemia associated with severe HIE exacerbates pulmonary vasoconstriction.[17] In addition, epinephrine is a pulmonary vasoconstrictor and may theoretically exacerbate PPHN.

We also found that the incidence of MAS and pulmonary hemorrhage was significantly more common in the PPHN vs. the no-PPHN group. Sarkar et al similarly demonstrated a high incidence of preexisting comorbidities such as parenchymal lung disease and perinatal stressors in patients with HIE developing PPHN.[18] Recently, Yum et al described a high incidence of MAS in patients with HIE and PPHN.[19] Randomized trials and epidemiological studies have demonstrated the association between these respiratory pathologies and PPHN in general neonatal populations (16,20) Infants with HIE with associated respiratory pathology should be closely monitored for clinical and echocardiographic signs of PPHN.

As expected, increased acidosis on the first postnatal gas and at baseline was associated with PPHN. Both groups had a low cord gas pH of 6.9 ± 0.2. The no-PPHN group corrected the acidosis (7.1 ± 0.2 on the first postnatal gas and 7.33 ± 0.15 at baseline- mean time 4.9h after birth) while the PPHN infants remained acidotic during the first six postnatal hours (7.0 ± 0.2 on the first postnatal gas-mean time 1.3h after birth and 7.25 ± 0.21 at baseline). Blood pH and PCO_2 levels (corrected for body temperature) normalized by 24 h of intervention and were similar between both groups. Persistent acidosis, especially pH ≤7.25 is associated with hypoxic pulmonary vasoconstriction and PPHN.[21]

The mortality associated with PPHN and moderate/severe HIE in our study (27%) is considerably higher than that reported in the general neonatal population. The California database reported a mortality of 7.6% among infants with PPHN,[16] and Konduri et al

reported mortality of 8.5% in infants with moderate PPHN treated with iNO.[20] In the current study, 17 of the 50 infants(34%) treated with iNO died, including 7 with hypoxemic respiratory failure without echocardiography to confirm PPHN,. Hypoxemic respiratory failure and PPHN associated with HIE and treated with iNO appears to have higher mortality compared with other causes of PPHN.

Adult animal studies have shown that hypothermia elevates PVR,[22] and in 1–3 day old neonatal lambs, decreasing body temperature from 40 to 30°C increased pulmonary arterial pressure from 29 to 40 mmHg.[23] However, a meta-analysis of 4 major clinical trials involving 614 infants did not demonstrate an increased risk of PPHN with hypothermia in patients with HIE (typical RR 1.36; 95% CI 0.94–1.97), with no significant heterogeneity of treatment effect ($I^2 = 0\%$).[12] We speculate that moderate hypothermia (33.5°C) induces mild pulmonary vasoconstriction in human infants with HIE. It is also possible that blood pressure, oxygenation and acid-base balance are closely monitored in patients undergoing therapeutic hypothermia in these trials, preventing exacerbation of PPHN.

In addition to pulmonary vasoconstriction, HIE can be associated with cardiac dysfunction[25, 26]. Myocardial dysfunction can lead to secondary pulmonary venous hypertension. Hypothermia in neonatal lambs increased inferior vena caval pressure (central venous pressure) from 5 to 9 mmHg and the left ventricular end-diastolic pressure from 8 to 25 mmHg.[23] Cardiac dysfunction can be multifactorial – myocardial ischemic injury during asphyxia, increased right ventricular afterload due to PPHN, and reduced venous return secondary to high pressure from the ventilator.[7] Systemic hypotension, cardiac dysfunction on echocardiogram and cardiomegaly were more common in PPHN compared with the no-PPHN group; all of which increase the risk for right-to-left shunting in patients with PPHN.

There are several caveats to this study. The IH trial recruited patients from July 2000 to May 2003[13] and the OC trial between October 20, 2010 and November 27, 2013[10]. Changes in clinical management between 2003 and 2010 may have influenced our findings. The definition of baseline differed slightly between the 2 trials. For the IH trial, baseline was defined as time of randomization in the non-cooled group and time infant was placed on cooling blanket in the cooled group. For the OC trial, baseline was defined as the time of randomization; keeping in mind that the time of baseline and induction of cooling could be the same for some infants, and for other infants clinical cooling would have been initiated before randomization. The sample size of infants with PPHN was small and we could not adjust for the year and center of enrollment. We did not record fluid balance and exact indications for volume and inotropes. Finally, the exact time of diagnosis of PPHN and indication and time at initiation of inhaled NO and ECMO were not recorded.

In summary, PPHN is commonly associated with HIE, particularly when lung disease (such as MAS and pulmonary hemorrhage), postnatal acidosis, culture-positive sepsis, systemic hypotension and cardiac dysfunction are present. The prevalence of PPHN was not different between those infants receiving therapeutic hypothermia at 33.5°C in the IH (25%) and OC trials (25%) compared with normothermia in the IH trial (22%). The mortality for PPHN increases when associated with HIE. We recommend development of evidence-based

protocols for the management of PPHN during therapeutic hypothermia at 33.5°C for infants with moderate to severe HIE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 Scott A. McDonald (DCC Statistician) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues, the infants, and their parents who agreed to take part in this study. The investigators, in addition to those listed as authors, who participated in this study are listed in the Appendix (available at www.jpeds.com).

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ABBREVIATIONS AND ACRONYMS

ECMO	extracorporeal membrane oxygenation
HIE	hypoxic ischemic encephalopathy
iNO	inhaled nitric oxide
MAS	meconium aspiration syndrome
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PPHN	persistent pulmonary hypertension of the newborn

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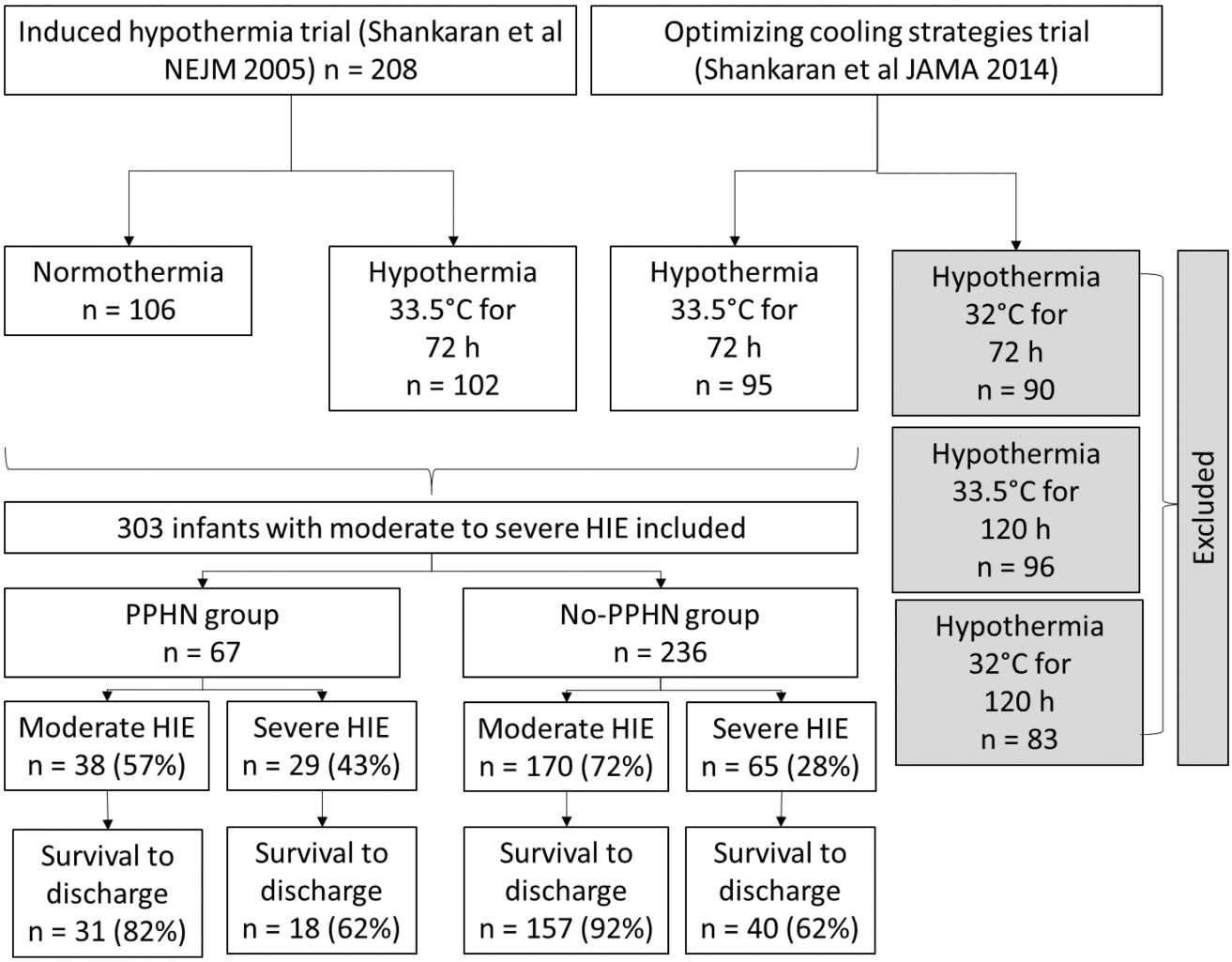

Figure 1.

Flow chart depicting the source of subjects and classification based the presence of persistent pulmonary hypertension of the newborn (PPHN - clinical and echocardiographic) and severity of hypoxic-ischemic encephalopathy (HIE). *one patient in the no-PPHN group did not have the severity of HIE documented and is missing from the reminder of the flow-chart.

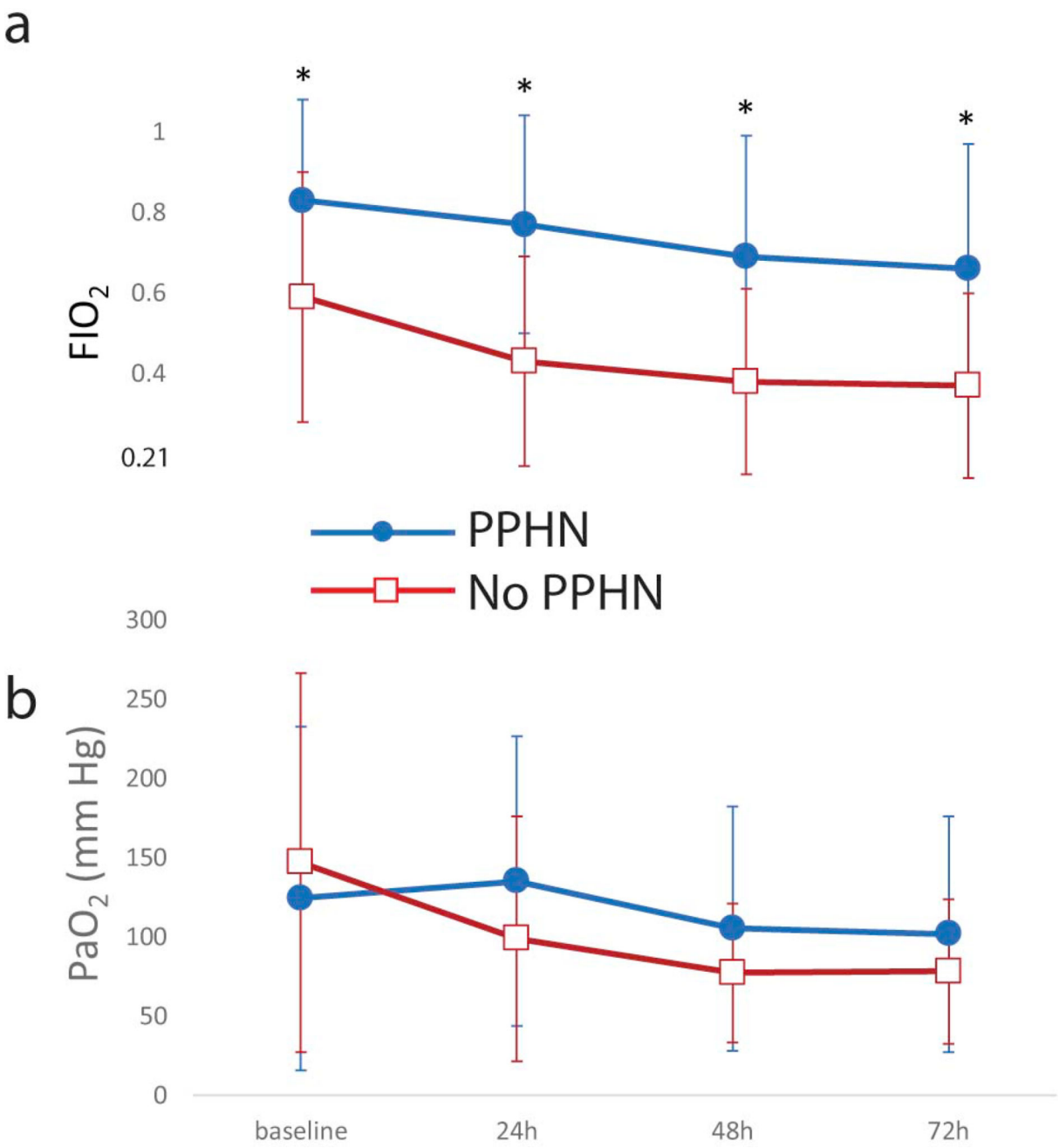

Figure 2. (online only). Oxygenation at baseline and during 72h of intervention: PPHN (closed blue circles) vs. no-PPHN (open red squares)

Changes in F_IO_2, and arterial PO_2, at baseline and during 72 hours of intervention (based on randomization to normothermia or hypothermia) in 67 infants with PPHN (black circles) and 236 infants without PPHN (open squares). * $p < 0.05$ compared with no-PPHN group. Data are shown as mean ± standard deviation.

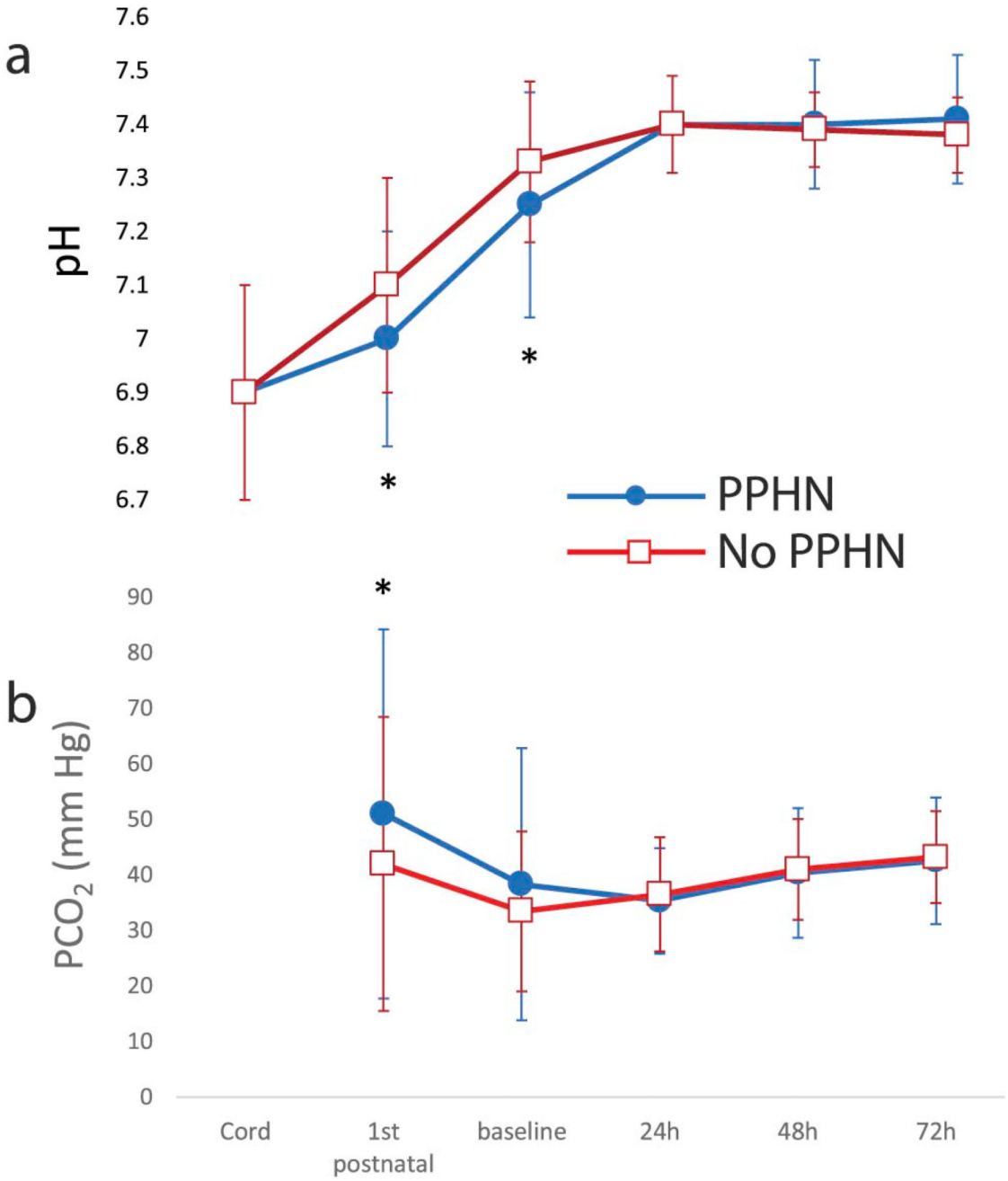

Figure 3. (online only). Acid-base balance at birth, during the postnatal period prior to intervention and during 72h of intervention

Changes in pH and PCO_2 on cord gas, first postnatal gas, baseline and during 72 hours of intervention (based on randomization to normothermia or hypothermia) in 67 infants with PPHN (blue closed circles) and 236 infants without PPHN (open red squares). * $p < 0.05$ compared with no-PPHN group. Data are shown as mean ± standard deviation. PCO_2 levels were not reported/collected on cord gases.

Table 1

Maternal Characteristics, intrapartum complications and mode of delivery in patients with and without PPHN associated with moderate to severe HIE.

Characteristics	PPHN (n=67)	No PPHN (n=236)
Maternal status		
Age	27.5 ± 5.7	27.5 ± 6.2
Race		
Black	29 (43%)	72 (31%)
White	36 (54%)	150 (64%)
Other	2 (3%)	14 (6%)
Marital status: Married	34 (52%)	130 (56%)
Maternal education: < High School	11 (22%)	55 (29%)
Gravida	2 (1–3)	2 (1–3)
Parity	2 (1–3)	2 (1–3)
Complications during pregnancy		
Hypertension	4 (6%)*	38 (16%)
Antepartum hemorrhage	7 (10%)	35 (15%)
Thyroid dysfunction	0 (0%)	6 (3%)
Diabetes	8 (12%)	18 (8%)
Intrapartum complications		
Fetal decelerations	53 (79%)	174 (74%)
Cord prolapse, rupture, compression	9 (13%)	44 (19%)
Uterine rupture	2 (3%)*	30 (13%)
Maternal pyrexia (> 37.6°C)	7 (10%)	23 (10%)
Shoulder dystocia	5 (8%)	21 (9%)
Maternal hemorrhage	6 (9%)	21 (9%)
Rupture of membranes (spontaneous or induced)		
No rupture	11 (17%)	17 (8%)
≤ 18 h	48 (76%)	181 (83%)
> 18 h	4 (6%)	19 (9%)
Mean (SD)	4.4 ± 8.4* (N=49)†	7.7 ± 11.5 (N=190)†

Characteristics	PPHN (n=67)	No PPHN (n=236)
Mode of delivery: emergency cesarean delivery	52 (78%)	161 (68%)

Data shown as n (%), mean ± standard deviation or median (inter-quartile range)

*Significant at $p<0.05$

†The 'n' in parentheses indicates that these data (exact duration of ROM) are available for some infants only.

Table 2

Baseline neonatal characteristics at < 6 hours of postnatal age.

Neonatal characteristics	PPHN (n=67)	No-PPHN (n=236)
Outborn	31 (46%)	121 (51%)
Male	38 (57%)	131 (56%)
Gestational age at birth (weeks)	38.7 ± 1.8	38.8 ± 1.5
Apgar score ≤ 5		
5 min after birth	60 (90%)	208 (89%)
10 min after birth	46 (77%)	162 (78%)
Birth weight, g	3304 ± 695	3339 ± 575
Length, cm	50.3 ± 2.9	50.8 ± 3.1
Head circumference, cm	34.0 ± 1.6	34.1 ± 1.8
Delivery room resuscitation		
Oxygen use	66 (99%)	229 (97%)
Bag and mask ventilation	63 (94%)	227 (96%)
Chest compressions	40 (60%)	126 (54%)
Intubation	63 (94%)	205 (87%)
Medications	39 (58%) *	104 (44%)
Time to spontaneous respiration, > 10 min	44 (70%)	137 (61%)
Cord blood		
pH	6.9 ± 0.2 (N=47)	6.9 ± 0.2 (N=175)
Base deficit, mEq/L	18.9 ± 8.3 (N=39)	17.8 ± 8.0 (N=144)
First postnatal blood gas		
Age at 1st postnatal blood gas, h	1.30 ± 1.07 (N=63)	1.20 ± 1.08 (N=224)
pH	7.0 ± 0.2 (N=66) *	7.1 ± 0.2 (N=232)
PCO_2	51.0 ± 33.2 * (N=65)	42.0 ± 26.4 (N=230)
Base deficit, mEq/L	19.1 ± 7.0 (N=60)	17.4 ± 7.8 (N=208)
Severity of HIE at < 6 h of age		
Moderate	38 (57%) *	170 (72%)
Severe	29 (43%) *	65 (28%)

Neonatal characteristics	PPHN (n=67)	No-PPHN (n=236)
Age at baseline, h	4.88 ± 1.60 (N=67)	4.51 ± 1.73 (N=236)
Age at randomization, h	4.7 ± 1.1	4.5 ± 1.2

Data shown as n (%) or mean ± standard deviation

* Significant at $p<0.05$

Table 3

Respiratory, cardiovascular and neurological variables, length of stay and mortality among patients with HIE with and without PPHN

	PPHN (n=67)	No-PPHN (n=236)
Pulmonary pathology		
Meconium aspiration syndrome	26 (39%) *	17 (7%)
Pulmonary hemorrhage	8 (12%) *	7 (3%)
Sepsis †	8 (12%) *	7 (3%)
Early-onset Sepsis (before completion of intervention)	2 (3%)[a]	3 (1%)[b]
Late-onset Sepsis (after completion of intervention)	8 (12%)[c]*	6 (3%)[d]
Respiratory therapy		
Percentage on high frequency ventilation		
• At baseline	11 (17%) *	13 (6%)
• 24h	11 (17%) *	9 (5%)
• 48h	10 (17%) *	5 (4%)
• 72h	13 (24%) *	4 (4%)
Therapy with iNO	43 (64%) *	7 (3%)
ECMO	8 (12%) *	0 (0%)
Pulmonary outcomes at discharge ‡		
Ventilator	0/46 (0%)	0/193 (0%)
Oxygen	1/46 (2%)	7/193 (4%)
Cardiovascular morbidity		
Systemic hypotension	43 (65%) *	65 (28%)
Cardiomegaly	10 (15%) *	3 (1%)
Cardiac failure	4 (6%)	7 (3%)
Cardiac dysfunction by echo	18 (27%) *	11 (5%)
Arrhythmia	2 (3%)	4 (2%)
Cardiovascular support		
Volume expanders	54 (81%) *	159 (67%)

	PPHN (n=67)	No-PPHN (n=236)
Median time given (hours from birth)	4.77 (3.20–6.70)	4.45 (2.95–5.78)
Inotropic support	53 (79%) *	99 (42%)
Median time given (hours from birth)	5.15 (4.18–10.1)	5.48 (3.82–8.17)
Median time stopped (hrs from birth)	80.9 (62.8–82.6) *	61.0 (34.5–81.3)
Neurological status		
Neurological exam at discharge – Normal/Mild	43 (93%)	164 (91%)
– Moderate	3 (7%)	17 (9%)
– Severe	0 (0%)	0 (0%)
Abnormal hearing test results (if performed)	10/43 (23%)	23/175 (13%)
MRI – abnormal	23 (53%)	104 (56%)
MRI – cranial hemorrhage	7 (16%)	18 (10%)
Seizures – At randomization	19 (28%) *	102 (43%)
– During treatment	29 (49%) *	64 (30%)
– At discharge	2 (4%)	5 (3%)
– At any time	41 (68%)	137 (63%)
Anticonvulsant therapy – At baseline	22 (33%)	77 (33%)
– During intervention	49 (77%) *	117 (52%)
– At discharge	13 (28%)	67 (35%)
– At any time	52 (83%) *	137 (64%)
Length of stay and mortality		
Number of patients undergoing therapeutic hypothermia	44 (66%)	153 (65%)
Length of stay (survivors)	33.7 ± 19.7 *	17.5 ± 13.5
Length of stay (all infants)	26.0 ± 21.3 *	16.4 ± 14.3
Death in hospital	18 (27%) *	38 (16%)
Cause of death –		
Proven sepsis	0	2 (0.8%)
Asphyxial brain injury	10 (15%)	30 (13%)
Multi-organ failure	2 (3%)	1 (0.4%)
MAS	1 (1.5%)[e]	1 (0.4%)
PPHN	4 (6%)	0
Other	0	3 (1.3%)[f]
Missing data	1 (1.5%)	1 (0.4%)

Data shown as n (%) or mean ± standard deviation

[*] Significant at $p<0.05$

[†] Two infants in the PPHN group and two in the no-PPHN group had both early and late onset sepsis

[‡] data on home respiratory support (oxygen, ventilator) is missing in 8 infants

[a]. The organisms isolated from blood culture for two infants with PPHN and early onset sepsis: Streptococcus Group B (n=1) and Pseudomonas aeruginosa (n=1)

[b]. The organisms isolated from blood culture for three infants without PPHN and early onset sepsis: Streptococcus Group B (n=2) and Staphylococcus coagulase negative (n=1)

[c]. The organisms isolated from blood culture for eight infants with PPHN and late onset sepsis: Streptococcus Group B (n=2), Serratia marcescens and coagulase-negative Staphylococcus (n=1); Pseudomonas aeruginosa (n=1); Hemophilus Influenzae (n=1); Staphylococcus epidermis or coagulase-negative (n=3);

[d]. The organisms isolated from blood culture for six infants without PPHN and late onset sepsis: Streptococcus Group B (n=2), Staphylococcus aureus (n=1), Staphylococcus epidermis or other coagulase negative species (n=2), Streptococcus viridans and Neisseria sp. (n=1)

[e]. One infant – cause of death was listed as MAS and asphyxial brain injury

[f]. One infant – pulmonary hemorrhage and disseminated intravascular coagulation (DIC); two infants listed as multiorgan failure and asphyxial brain injury