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Cardiopulmonary resuscitation in hospitalized infants

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Abstract

Background—Hospitalized infants requiring cardiopulmonary resuscitation (CPR) represent a high-risk group. Recent data on risk factors for mortality following CPR in this population are lacking.

Aims—We hypothesized that infant demographic characteristics, diagnoses, and levels of cardiopulmonary support at the time of CPR requirement would be associated with survival to hospital discharge following CPR.

Study design—Retrospective cohort study.

Subjects—All infants receiving CPR on day of life 2 to 120 admitted to 348 Pediatrics Medical Group neonatal intensive care units from 1997 to 2012.

Outcomes measures—We collected data on demographics, interventions, center volume, and death prior to NICU discharge. We evaluated predictors of death after CPR using multivariable logistic regression with generalized estimating equations to account for clustering of the data by center.

Results—Our cohort consisted of 2231 infants receiving CPR. Of these, 1127 (51%) survived to hospital discharge. Lower gestational age, postnatal age, 5-min APGAR, congenital anomaly, and markers of severity of illness were associated with higher mortality. Mortality after CPR did not change significantly over time (Cochran–Armitage test for trend $p = 0.35$).

Conclusions—Mortality following CPR in infants is high, particularly for less mature, younger infants with congenital anomalies and those requiring cardiopulmonary support prior to CPR. Continued focus on at risk infants may identify targets for CPR prevention and improve outcomes.

Keywords

Cardiopulmonary resuscitation; Infants; Survival; Neonatal intensive care units

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1. Introduction

Cardiopulmonary resuscitation (CPR) is life-saving for infants suffering a cardiopulmonary arrest. Although an arrest is most likely to occur immediately after birth, CPR can also be required outside of the delivery room in the neonatal intensive care unit (NICU) [1]. Data on CPR risk factors and survival in the NICU are sparse, but small, single-center studies have suggested low survival following NICU CPR [1,2]. This finding contrasts sharply with the trend in improved overall survival of infants, particularly those of very low birth weight [3,4]. The reasons for low survival rate after NICU CPR are largely unknown.

Several studies of survival following CPR in infants have focused on, or included, delivery room CPR [5–8]. Studies focusing on NICU CPR are less common, and all have been limited by their small sample size and overall high mortality [1]. Because of these limitations, risk factors and associated survival following NICU CPR are poorly understood. This lack of understanding limits the ability of providers to identify infants at risk for CPR as well as to decide which infants should undergo CPR, how extensive CPR should be, and how best to counsel parents in the setting of CPR need.

The purpose of our study was to describe the risk factors associated with survival following infant CPR in the NICU. We hypothesized that infant demographic characteristics, diagnoses, and levels of cardiopulmonary support at the time of CPR requirement would be associated with survival to hospital discharge following CPR.

2. Material and methods

2.1. Study design and sample

We used a database derived from electronic medical records and daily progress notes generated by clinicians on all infants cared for by the Pediatrix Medical Group in 348 NICUs in North America from 1997 to 2012. Data on multiple aspects of care were entered into a shared electronic medical record to generate clinical documentation. Information on maternal history, demographics, medications, laboratory results, diagnoses, and procedures were then transferred to the Pediatrix clinical data warehouse for quality improvement and research purposes [9]. We included all infants discharged with documentation in their medical record of having received CPR between day of life 2 and 120, including those who died. We excluded infants with missing information on mortality at NICU discharge which includes infants transferred to another hospital. The study was approved by the Duke University Institutional Review Board (Fig. 1).

2.2. Study measurements

We defined CPR as any new episode of CPR that was documented in the medical record, and we counted the number of separate days during which an infant received CPR. We defined mortality as in-hospital mortality prior to discharge, maternal steroids as any steroid exposure during pregnancy regardless of number of doses, small for gestational age (SGA) as previously described, and congenital anomalies as any major anomaly as described in our study database [10]. We defined measures of cardiopulmonary support and other

interventions as the presence of or exposure to any of the following on a given day: any inotrope (epinephrine, dopamine, dobutamine, amrinone, milrinone, and norepinephrine), any mechanical ventilation (conventional or high-frequency ventilation), any fraction of inspired oxygen (FiO_2) $>30\%$, any pulmonary hypertension therapy (inhaled nitric oxide, sildenafil, bosentan, or epoprosterenol), or any central line (peripherally inserted central venous catheters, percutaneous or tunneled central venous lines, umbilical venous lines). We then evaluated cardiopulmonary support measures using 3 different methods: the use of each cardiopulmonary support measure on the day prior to CPR, the cumulative number of days each cardiopulmonary support measure was used prior to CPR, and the escalation of each cardiopulmonary support measure on the day prior to CPR. Escalation of inotropic and ventilator support, pulmonary hypertension therapy, central venous line, and FiO_2 was defined as new exposure to inotropes, initiation of mechanical ventilation or conversion from conventional to high frequency ventilation, new exposure to pulmonary hypertension therapy, insertion of central venous line, and an increase in $\text{FiO}_2 \geq 25\%$ (e.g., 25% to 50% FiO_2) on the day prior to CPR.

2.3. Statistical methods

The unit of observation for this analysis was an infant requiring CPR at least once between day of life 2 and 120. We excluded infants receiving CPR before day of life 2 to avoid CPR courses received in the delivery room or for ongoing resuscitation of birth depression, and after day of life 120 because of the small sample size and heterogeneous nature of infants hospitalized for >120 days. We used summary statistics including medians and 25th and 75th percentiles to describe continuous variables, and frequency counts and percentages to describe categorical variables. Continuous variables were categorized using clinically relevant cutoffs (gestational age [GA], birth weight [BW], and postnatal age [PNA]) or based on the distribution of our data (discharge year, center volume). We compared infant characteristics between survivors and non-survivors using chi-square tests of association and Wilcoxon rank sum tests analyzing trends over time using the Cochran–Armitage test.

We used multivariable logistic regression to evaluate the association between survival to NICU discharge following CPR and clinically relevant predictors. We used the method of generalized estimating equations to account for the clustered nature of the data by site. After performing modeling assumption diagnostics and assessments of collinearity, we included the following covariates in the final model: GA, SGA, 5-min APGAR score, inborn status, presence of any congenital anomaly, PNA on the day of CPR, discharge year, and inotropes, pulmonary hypertension therapy, mechanical ventilation, $\text{FiO}_2 > 30\%$, and presence of any central line on the day prior to CPR. We report odds ratios and 95% confidence intervals for mortality prior to NICU discharge, as well as predicted probability of death by GA group. We conducted all analyses using Stata 13.1 (College Station, Texas) and considered a $p < 0.05$ statistically significant.

3. Results

3.1. Infant characteristics

We identified 2231/887,910 (0.25%) infants who received CPR, of whom 2129/2231 (95%) received CPR on only 1 day (one event), 89/2131 (4%) received CPR on 2 days (2 events), and 13/2131 (1%) received CPR on 3 or more days (3 or more events). The overall survival to hospital discharge among all infants receiving CPR was 1127/2231 (51%). Median (25th, 75th percentile) GA, BW, and PNA on the day of first CPR was 29 weeks (25, 34), 1210 g (720, 2215), and 11 days (4, 27), respectively. Infants with CPR who survived to hospital discharge were more mature, had higher BW, and were older on the day of CPR compared to those who died (33 weeks [29, 35] vs. 26 weeks [24, 30], $p < 0.001$; 1844 g [1120, 2550] vs. 790 g [625, 1260], $p < 0.001$; and 13 days [6, 31] vs. 8 days [2, 22], $p < 0.001$; respectively). Survivors were less likely to be SGA and to suffer from a major congenital anomaly, and more likely to be inborn (Table 1). Survival was lowest in infants <1000 g BW (25%) and those <26 weeks GA (22%). Infants at the limit of viability, with a GA 22–24 weeks, had lower survival (18%) than all other GA groups. Median postnatal age at the time of death for non-survivors was 10 days (3, 26), with most infants dying shortly after CPR (median 1 day (0, 1) after receipt of CPR). CPR survivors were discharged at a median postnatal age of 29 days (13, 68), and later after CPR (median 6 days (2, 30) after receipt of CPR).

3.2. Cardiopulmonary support at time of CPR

Data on cardiopulmonary support prior to CPR were available for 2190/2231 (98%) infants. On the day prior to CPR, the majority of infants did not receive inotropic support (1778/2190 [81%]), more than two thirds did not have a central line in place (1566/2190 [72%]), and mechanical ventilation and supplemental $\text{FiO}_2 > 30\%$ were used in half of all infants (1108/2190 [51%] and 1087/2190 [50%], respectively). Infants receiving or initiated on any cardiopulmonary support the day prior to CPR were less likely to survive to hospital discharge (Table 2). Survivors to hospital discharge had lower pre-CPR median (25th, 75th percentile) cumulative days of inotropic support (0 [0, 0] vs. 1 [0, 3]), mechanical ventilation (0 [0, 4] vs. 5 [1, 15]), $\text{FiO}_2 > 30\%$ (1 [0, 4] vs. 3 [1, 11]), and presence of a central venous line (0 [0, 6] vs. 2 [1, 9]), than those who died (all $p < 0.001$).

3.3. Outcomes

The proportion of infants who survived to hospital discharge following CPR increased over time from 115/269 (43%) in 1997–2001 to 272/ 545 (50%) in 2010–2012, but the trend was not statistically significant ($p = 0.35$ from Cochran–Armitage test for trend). Further, survival was highest between 2002 and 2005. Results were similar after stratifying the analysis by GA (Fig. 2). Survival following CPR in NICUs with at least 50 events over the study period ranged from 8% to 96%, and did not differ significantly between NICU quartiles of CPR events ($p = 0.229$).

On multivariable analysis, less mature, lower BW, SGA, and younger infants at the time of CPR had higher mortality (Table 3). Infants with a diagnosis of congenital anomaly and those requiring cardiopulmonary support also had increased odds of dying, while the presence of a central line on the day prior to CPR was associated with decreased odds of

mortality after adjustment for covariates. The model predicted probability of death following CPR varied significantly by age and was highest for infants ≥ 28 weeks GA (Fig. 3). Significance of associations remained unchanged when modeling was repeated after inclusion of all CPR episodes performed in the first 120 days of life.

Extracorporeal membrane oxygenation (ECMO) was used in only 5/2231 ($<1\%$) infants following CPR. Of the 5 infants receiving ECMO, 1 infant who was 38 weeks GA and who required CPR on day of life 13 died prior to NICU discharge. The other 4 infants requiring ECMO survived to hospital discharge.

4. Discussion

We conducted the largest multicenter study to date of risk factors and outcomes associated with infant CPR outside of the delivery room. Overall survival was poor, particularly for less mature, lower BW, SGA, and younger infants, those suffering from a major congenital anomaly, and those requiring cardiopulmonary support prior to CPR. Further, CPR survival did not improve significantly over time.

CPR is a life-saving medical intervention for infants in cardiopulmonary arrest. The risk of cardiopulmonary arrest in infants is highest at birth in the delivery room. Because of this, most studies of risk factors and outcomes include infants requiring delivery room CPR. The largest delivery room CPR study conducted to date enrolled 1664 infants ≥ 1500 g BW treated at a Vermont Oxford Network participating hospital in 1994–1996 and reported an overall mortality of 38% [5]. This mortality is consistent with more recent, smaller, single-center studies and is significantly lower than the mortality that we report following CPR receipt in the NICU. The largest previous study of CPR in the NICU included 83 infants 508–4500 g BW treated at a single teaching hospital from 1981 to 1983 [11]. Overall survival was 14% at hospital discharge and 8% at 1-year follow-up. Survival to discharge was similarly low (16%) in a study of 49 infants <1500 g BW requiring CPR while treated at a single NICU in 1985 [6].

More recent single-center studies have reported even lower hospital survival rates after NICU CPR ($<10\%$), but these studies included only infants ≥ 750 g or ≥ 1500 g BW [2,12]. Survival was higher in our cohort (50%), likely because of the inclusion of all infants requiring CPR, with nearly half of our cohort >1500 g BW. Survival was lower (32%) for the 1281 infants ≥ 1500 g BW included in our cohort, although this remains higher than previous reports. We can only speculate as to why survival in our cohort was higher overall, but limited information about the nature of CPR received and its duration in our database may have lead us to capture less severe or shorter CPR episodes associated with improved outcomes. Survival following either delivery room or NICU CPR has been consistently higher in more mature or higher BW infants [2,5]. This was also the case in our study, but we observed highest survival rates (86%) in the 33–36 weeks GA cohort, with somewhat lower survival in infants >36 weeks GA (62%). We hypothesize that selection bias may explain this finding: most full-term infants do not require NICU admission unless they suffer from a pre- or postnatal diagnosis, while several near-term (33–36 weeks GA) infants may be admitted simply for monitoring. This is supported by the fact that in our study, infants

>36 weeks GA were more likely to suffer a congenital anomaly compared to those 33–36 weeks GA (14% vs. 8%).

Mortality prediction in hospitalized infants has been the focus of several studies [13–16]. Our results and others show the significant impact of NICU CPR on infant survival. A meta-analysis of 1515 infants from 5 NICU CPR studies reported a very significant odds ratio for mortality in infants requiring NICU CPR compared to controls (OR from random effects model: 54.82 [95% confidence interval 15.44–194.63]) [1]. This result should be interpreted with caution given the overall small sample size for a meta-analysis and the heterogeneity of the 5 included studies ($I^2 = 78\%$) [17]. Nevertheless, the difference in the odds of mortality between infants with and without NICU CPR is higher than any other reported risk factor for hospital mortality.

We found several risk factors associated with increased mortality following CPR. In addition to characteristics present at birth, infants requiring more cardiopulmonary support at the time of CPR were more likely to die. These findings suggest that sicker infants requiring more support have worse outcomes after CPR, and these findings are consistent with previous studies that have identified need for inotropic support, lower urine output, and preceding laboratory anomalies such as creatinine elevation as risk factors for mortality after CPR [11]. The relationship between underlying illnesses, need for cardiopulmonary support, and survival following CPR is complex.

At the heart of the problem is the physiologic mechanism leading to cardiopulmonary arrest and the goal of CPR. The goals of CPR are to restore cardiopulmonary functions through a series of targeted interventions, including securing airway patency, oxygenation and ventilation, and the mechanical or pharmacologic restoration of cardiac output [18]. CPR is not intended to directly alter the function of other organs or reverse underlying illnesses responsible for the cardio-pulmonary arrest. Infants requiring cardiopulmonary support prior to CPR may suffer from more severe, progressive diseases such as overwhelming sepsis or pulmonary failure, which may not be reversible. It is intuitive that the inability to reverse the process resulting in cardio-pulmonary failure significantly reduces survival after CPR, and explains why our data show lower survival in infants requiring increased support. On the other hand, infants who suffer a cardiopulmonary arrest and undergo CPR due to an acutely reversible process, such as a pneumothorax, pleural or pericardial effusion, or even displacement of an existing endotracheal tube, will likely survive CPR following corrective action to reverse the underlying arrest cause.

In our cohort, the cause of arrest in infants not requiring cardio-pulmonary support prior to CPR was unclear, and the cohort likely consisted of a significant number of infants with acutely reversible processes. However, acutely reversible processes may also occur as complications from the use of cardiopulmonary support. In a retrospective study of 29 infants requiring CPR while intubated, at least 3 cases were due to acute complications including improper endotracheal tube position and pneumothoraxes [19]. The retrospective nature of our study does not allow us to infer causality, but differences in survival by diagnosis and levels of cardiopulmonary support are consistent with the hypothesis that etiology of cardiopulmonary arrest is an essential predictor of CPR outcome. An alternative

explanation for our finding could be that a clinician's ability to identify an infant at risk for CPR is relatively poor.

The strengths of our study include its large sample size, the diversity of infants and NICUs included, and the availability of daily clinical data, including cardiopulmonary support and diagnoses in the Pediatrix Clinical Data Warehouse. We were thus able to include infant demographics and cardiopulmonary support as predictors of CPR survival. In addition, we were able to identify absence of major congenital anomalies and presence of a central venous line as factors associated with improved survival. Our findings are representative of a large proportion of NICUs in the United States and cover almost 20 years of medical practice [9]. This wealth of data allowed us to describe trends in outcomes over time and the differences across NICUs. Our study is primarily limited by its data source, which is based on a shared electronic health record and has not undergone the development and scrutiny of a prospective clinical trial database. This limitation may affect data validity. Most importantly, we were not able to identify the mechanism leading to cardiopulmonary arrest and need for CPR. Another limitation of our study was the lack of information about the specific CPR interventions received. Differences in outcomes have been reported in infants receiving more extensive CPR, defined by either CPR duration, multiple CPR events on the same day, or receipt of specific interventions including drug administration, defibrillation, or others [11,12]. We were unfortunately only able to identify whether an infant received CPR, but not CPR duration, number of CPR events on a given day, or specific interventions. Our inability to provide a detailed CPR description may also affect the interpretation of temporal trends, as changes in resuscitation guidelines over time may distort our comparisons. These limitations highlight the need for future well-designed prospective observational studies of NICU CPR focusing on the collection of data on CPR etiology and interventions, preferably following the Utstein-style reporting guidelines recommended by the American Heart Association and the European Resuscitation Council among others [18]. Lastly, while our study provides new and valuable insight into survival after infant CPR, our analysis did not focus on post-CPR interventions such as hypothermia, timing to restoration of normal hemodynamics, hyperglycemia, and other factors which may have affected outcomes.

In conclusion, we found a 51% survival rate following NICU CPR in infants. We identified several risk factors associated with worse outcomes, including demographic characteristics and need for cardiopulmonary support prior to CPR. Survival did not improve significantly over time. Our findings highlight the significant impact of NICU CPR on outcomes and provide guidance for parental counseling, and for the design of future trials of specific interventions.

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Abbreviations

BW	Birth weight
CPR	Cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
FiO₂	Fraction of inspired oxygen
GA	Gestational age
NICU	Neonatal intensive care unit
PNA	Postnatal age
SGA	Small for gestational age

Fig. 1.
Study flow diagram.

Fig. 2.
Mortality following cardiopulmonary resuscitation by gestational age and discharge year.

Fig. 3. Predicted probability of death (with 95% confidence interval) following cardiopulmonary resuscitation by gestational age.

Table 1

Demographics and clinical characteristics of infants requiring cardiopulmonary resuscitation.

	Survived (N = 1127)	Died (N = 1104)	p
	N (%)	N (%)	
Gestational age (weeks)			<0.001
<26	130 (22)	461 (78)	
26–28	141 (32)	298 (68)	
29–32	251 (67)	125 (33)	
33–36	413 (81)	97 (19)	
>36	191 (62)	115 (38)	
Birth weight (g)			<0.001
<1000	240 (25)	719 (75)	
1000–1499	175 (54)	147 (46)	
1500–2499	415 (79)	109 (21)	
2500–3499	232 (69)	106 (21)	
>3499	62 (74)	22 (26)	
Small for gestational age	172 (39)	270 (61)	<0.001
Male	623 (50)	616 (50)	0.84
5-min APGAR			<0.001
0–3	35 (23)	114 (77)	
4–6	116 (29)	278 (71)	
7–10	937 (59)	664 (41)	
Inborn	891 (53)	793 (47)	<0.001
Caesarean section	677 (48)	725 (52)	0.02
Antenatal steroids	523 (47)	590 (53)	0.001
Any congenital anomaly	41 (26)	116 (74)	<0.001
Number of days with CPR reported			<0.001
1	1104 (52)	1025 (48)	
2	20 (22)	69 (78)	
3	3 (25)	10 (75)	
Postnatal age at CPR (days)			<0.001
7	350 (40)	519 (60)	
8–14	241 (54)	202 (46)	
15–28	217 (54)	185 (46)	
28–120	319 (62)	198 (38)	
Discharge year			<0.001
1997–2001	115 (43)	154 (57)	
2002–2005	425 (59)	298 (41)	
2006–2009	315 (45)	379 (55)	
2009–2012	272 (50)	273 (50)	

Abbreviation: CPR, cardiopulmonary resuscitation.

Table 2

Cardiopulmonary support prior to requiring cardiopulmonary resuscitation.

	All (N = 2190)	Survived (N = 1116)	Died (N = 1074)	p
	N	N (%)	N (%)	
<i>Support on the day prior to CPR</i>				
Inotropes	412	54 (13)	358 (87)	<0.001
Mechanical ventilation	1108	204 (18)	904 (82)	<0.001
FiO ₂ > 30%	1087	258 (24)	829 (76)	<0.001
Pulmonary hypertension therapy	34	10 (29)	24 (71)	0.01
Central venous line	624	180 (29)	444 (71)	<0.001
<i>Support escalated on the day prior to CPR</i>				
Inotropes	97	7 (7)	90 (93)	<0.001
Mechanical ventilation	46	12 (26)	34 (74)	0.001
FiO ₂ increased by >25%	174	26 (15)	148 (85)	<0.001
Pulmonary hypertension therapy	15	1 (7)	14 (93)	0.001
Central venous line	22	4 (18)	18 (82)	0.002

Abbreviations: CPR, cardiopulmonary resuscitation; FiO₂: fraction of inspired oxygen.

Table 3

Adjusted odds of mortality following cardiopulmonary resuscitation.

	Adjusted OR (95% CI)
Gestational age (weeks)	
25	2.82 (1.95–4.08)
26–28	2.88 (1.99–4.19)
29–32	1.67 (1.15–2.43)
33–36	0.93 (0.66–1.30)
37	Reference
Antenatal steroids	0.98 (0.79–1.23)
Small for gestational age	1.42 (1.14–1.80)
Postnatal age at CPR (days)	
7	2.02 (1.67–2.91)
8–14	2.21 (1.64–2.99)
15–28	1.71 (1.28–2.28)
28–120	Reference
5 minute APGAR	
0–3	1.70 (1.14–2.52)
4–6	1.40 (1.09–1.79)
7–10	Reference
Inborn	0.98 (0.76–1.25)
Any major congenital anomaly	2.69 (1.74–4.16)
Inotropic support	1.61 (1.22–2.12)
Mechanical ventilation	3.42 (2.59–4.50)
FiO ₂ > 30%	1.96 (1.55–2.48)
Pulmonary hypertension therapy	0.54 (0.28–1.07)
Presence of central venous line	0.63 (0.49–0.80)
Discharge year	
1997–2001	0.46 (0.32–0.66)
2002–2005	0.66 (0.50–0.87)
2006–2009	0.97 (0.75–1.25)
2009–2012	Reference

Abbreviations: CPR, cardiopulmonary resuscitation; FiO₂: fraction of inspired oxygen.