Use of Initial Endotracheal Versus Intravenous Epinephrine During Neonatal Cardiopulmonary Resuscitation in the Delivery Room: Review of a National Database

Cecilie Halling, MD, FAAP[1], Sara Conroy, PhD[2,3,4], Tia Raymond, MD, MBA, FAAP, FAHA, FCCM[5], Elizabeth E. Foglia, MD, MA, MSCE[6], Mary Haggerty, DO, FAAP[6], Linda L. Brown, MD MSCE, FAAP[7,8], and Myra H. Wyckoff, MD, FAAP[9], for the American Heart Association's Get With The Guidelines–Resuscitation Investigators

Objective To assess whether initial epinephrine administration by endotracheal tube (ET) in newly born infants receiving chest compressions and epinephrine in the delivery room (DR) is associated with lower rates of return of spontaneous circulation (ROSC) than newborns receiving initial intravenous (IV) epinephrine.

Study design We conducted a retrospective review of neonates receiving chest compressions and epinephrine in the DR from the AHA Get With The Guidelines-Resuscitation registry from October 2013 through July 2020. Neonates were classified according to initial route of epinephrine (ET vs IV). The primary outcome of interest was ROSC in the DR.

Results In total, 408 infants met inclusion criteria; of these, 281 (68.9%) received initial ET epinephrine and 127 (31.1%) received initial IV epinephrine. The initial ET epinephrine group included those infants who also received subsequent IV epinephrine when ET epinephrine failed to achieve ROSC. Comparing initial ET with initial IV epinephrine, ROSC was achieved in 70.1% vs 58.3% (adjusted risk difference 10.02; 95% CI 0.05-19.99). ROSC was achieved in 58.3% with IV epinephrine alone, and 47.0% with ET epinephrine alone, with 40.0% receiving subsequent IV epinephrine.

Conclusions This study suggests that initial use of ET epinephrine is reasonable during DR resuscitation, as there were greater rates of ROSC compared with initial IV epinephrine administration. However, administration of IV epinephrine should not be delayed in those infants not responding to initial ET epinephrine, as almost one-half of infants who received initial ET epinephrine subsequently received IV epinephrine before achieving ROSC. *(J Pediatr 2024;271:114058)*.

Neonatal resuscitation in the delivery room (DR) remains rare, with most infants successfully transitioning from fetal to neonatal life with no additional resuscitative efforts required beyond the initial steps of warming, stimulation, repositioning and, if needed, suctioning.[1] Just less than 10% require additional resuscitative support, usually in the form of positive pressure ventilation (PPV).[2,3] Less than 1% of newborns receive extensive resuscitation in the form of chest compressions with or without epinephrine.[4] If, after PPV and initial attempted ventilation corrective steps, the heart rate remains <100 beats per minute (bpm), an alternate airway is recommended, preferably in the form of an endotracheal tube (ET), with a supraglottic airway as an acceptable alternative.[4] Chest compressions are only recommended if the heart rate remains less than 60 bpm despite 30 seconds of effective PPV, with consideration for emergent umbilical venous catheter (UVC) placement at this time. If the heart rate remains less than 60 bpm after 60 seconds of chest compressions and adequate PPV, the administration of epinephrine (ideally via the intravenous [IV] route) is recommended every 3-5 minutes by the 2020 American Academy of Pediatrics/American Heart Association (AHA) Neonatal Resuscitation Program.[1,4-6]

AHA	American Heart Association	HR	Hazard ratio
bpm	Beats per minute	IV	Intravenous
CPR	Cardiopulmonary resuscitation	PPV	Positive pressure ventilation
DR	Delivery room	RD	Risk difference
ET	Endotracheal tube	ROSC	Return of spontaneous circulation
GWTG-R	Get With The Guidelines–Resuscitation	UVC	Umbilical venous catheter

From the [1]Division of Neonatology, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University, Columbus, OH; [2]Center for Perinatal Research and the Ohio Perinatal Research Network, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [3]Department of Pediatrics, College of Medicine, The Ohio State University, Columbus, OH; [4]Biostatistics Resource at Nationwide Children's Hospital, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [5]Department of Pediatrics, Cardiac Critical Care, Medical City Children's Hospital, Dallas, TX; [6]Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; [7]Department of Emergency Medicine, Alpert Medical School of Brown University, Hasbro Children's Hospital, Providence, RI; [8]Department of Pediatrics, Alpert Medical School of Brown University, Hasbro Children's Hospital, Providence, RI; and [9]Division of Neonatal-Perinatal Medicine, Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, TX

https://doi.org/10.1016/j.jpeds.2024.114058

Since 2006, the Neonatal Resuscitation Program has recommended administering epinephrine preferentially via the umbilical vein,[5] with the ET listed as an alternate route. Only a few studies[7-10] have reported on the use and efficacy of ET vs IV epinephrine during neonatal cardiopulmonary resuscitation (CPR) in the DR. Two were single-center retrospective studies from the same center that showed a significantly greater proportion of infants achieving return of spontaneous circulation (ROSC) with IV epinephrine compared to ET epinephrine.[7,8] A systematic review highlights the lack of evidence currently available for route and dosing of epinephrine in neonatal patients.[11] The dosage interval for epinephrine is every 3-5 minutes if the heart rate remains less than 60 bpm, although an IV dose should be given as soon as umbilical access is obtained if the response to ET epinephrine has been inadequate.[1,4] This may result in ET epinephrine and IV epinephrine being given in very close proximity. In addition, an infant may receive several different combinations of epinephrine, such as single or multiple doses of ET epinephrine followed by single or multiple doses of IV epinephrine. This can complicate the understanding of ET and IV epinephrine efficacy.

The objective of this study was to investigate the use of epinephrine in the newly born infant receiving chest compressions and epinephrine in the DR. We hypothesized that initial ET epinephrine is given more frequently than IV epinephrine and is associated with lower rates of ROSC compared to those receiving initial IV epinephrine.

Methods

Study Design and Sample

This retrospective cohort study used the AHA's Get With The Guidelines-Resuscitation (GWTG-R) registry. This is a large, national, multicenter prospective database of in-hospital cardiac arrest. Hospitals participating in the registry voluntarily submit clinical information regarding medical history, hospital care, and outcomes of consecutive patients hospitalized for cardiac arrest using an online, interactive case report form and Patient Management Tool (IQVIA). IQVIA serves as the data-collection tool (through their Patient Management Tool, or PMT) and coordination center for the AHA/American Stroke Association Get With The Guidelines programs. The registry uses Utstein-style[12] definitions for all patient variables and outcomes to facilitate uniform reporting across institutions. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Participating hospitals may use the registry to query the database for the purposes of quality improvement and to benchmark their results for resuscitation practice and patient outcomes. Data accuracy is ensured through certification of data abstractors and uses standardized software with data checks for accuracy and completeness. Its design has been previously described in detail (www.heart.org/resuscitation). This study was exempt from review by Nationwide Children's Hospital Institutional Review Board.

The study cohort included newly born infants from 142 centers who received chest compressions and at least 1 dose of epinephrine in the DR with data submitted to the GWTG-R registry between October 2013 and July 2020 (**Figure 1**). The primary analysis estimated rates of ROSC based on the initial route of epinephrine administered and did not consider the route of subsequent epinephrine doses. As a result, rates of ROSC reported in both groups include those infants who received subsequent IV epinephrine before achieving ROSC. Neonates were excluded if they had (1) no gestational age data, (2) gestational age less than 22 weeks, (3) missing time or date of birth, (4) missing time of first dose epinephrine, or (5) time to first epinephrine dose was not within 30 minutes of birth. The 30-minute cut off was chosen to include only the initial resuscitation in the DR. Time to first epinephrine dose was defined as minutes from birth to the time epinephrine was administered. ROSC was defined as no further need for chest compressions for greater than 20 minutes (heart rate remaining greater than 60 bpm). This was indicated in the dataset as an infant surviving the CPR event. Time to ROSC was defined as the time period from the start of chest compressions to the time ROSC was achieved. No ROSC was defined as those infants that died in the DR after cessation of resuscitative efforts.

Statistical Analysis

Maternal, infant, and resuscitation characteristics were stratified by type of epinephrine received for the first dose without consideration of route of subsequent doses (initial ET epinephrine vs initial IV epinephrine) and summarized with count (percent) for categorical variables and median (IQR) for continuous variables. Following STROBE[13] guidelines, inferential measures and *P* values are not included for descriptive characteristics. The primary outcome was ROSC in the DR. However, some infants received multiple doses of only ET, only IV, or both types of epinephrine. Therefore, secondary outcomes of interest were rates of ROSC after the initial epinephrine dose, time to ROSC, 24-hour survival, survival to hospital discharge, and time to first dose of epinephrine. A final summary included the number and type of additional epinephrine doses infants received.

For ROSC and survival outcomes, risk differences (RDs) and 95% CIs were estimated from logistic regression models using average marginal effects to assess the difference in proportion of infants who survived by initial route of epinephrine received. Time to ROSC was analyzed using competing risks survival analysis with a proportional subdistribution hazards regression model defining no ROSC as the competing event.[14,15] This model provides estimates of the hazard ratio (HR) to compare the difference in time to ROSC between the 2 strategies over the

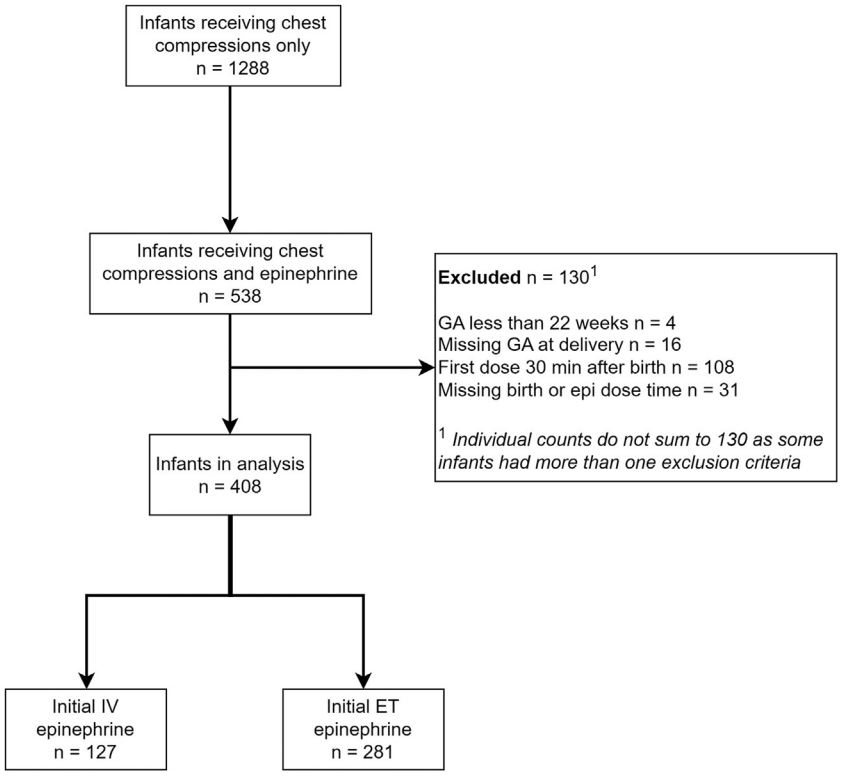

Figure 1. Study sample flow diagram providing counts and reason for exclusion from the final study sample. *GA*, gestational age.

entire follow-up period. The HR represents the rate per minute of achieving ROSC or not. Time to first epinephrine dose was analyzed using Cox proportional hazards regression. All infants in this study received a first dose of epinephrine, so there were no competing risks and no censored observations for time to first dose. The HR represents the rate per minute of infants receiving their first dose of epinephrine. Plots of the cumulative incidence for both time to ROSC and time to first dose epinephrine and tables of the estimated incidence of ROSC at 5, 10, 15, and 20 minutes are presented.

For all analyses, adjusted models are controlled for gestational age at delivery as a potential confounder. An additional post-hoc subgroup analysis among infants who received initial ET epinephrine compared ROSC after the first dose for infants born less than 34 weeks to those at least 34 weeks of gestational age using a Pearson χ^2 test. Confounding control was limited as additional variables that may affect the route of epinephrine received are likely influenced by hospital protocol, physician comfort at quickly placing an emergent UVC, and the size of the team present for the resuscitation, and these variables are not available in the registry. Although many different sites contribute to the registry, 90 sites submitted data for the 408 infants included in the analysis, with number of infants ranging from 1 to 30 per site. We were not able to assess similarities or differences in hospital protocol, as no other site information was made available to us. Statistical analyses were conducted using the statistical software R.[16]

Results

Between October 2013 and July 2020, a total of 1288 infants from 142 sites were entered into the GWTG-R registry as having received chest compressions. Of these, 538 infants received at least 1 dose of epinephrine. Of those, 408 infants from 90 sites met the inclusion criteria (**Figure 1**), with 281 infants receiving initial ET epinephrine and 127 infants receiving initial IV epinephrine in the DR.

Maternal, delivery, and infant baseline characteristics grouped by initial ET vs initial IV epinephrine in the DR are found in **Table I**. Overall, median gestational age of the 408 infants was 31.1 [IQR, 26, 37] weeks and median birth weight was 1.9 [IQR, 0.79, 3.13] kg. Those infants receiving initial ET epinephrine tended to be slightly larger (2.0 kg vs 1.6 kg) and had slightly higher gestational age (32.4 weeks vs 30.0 weeks). Singleton deliveries and maternal and delivery complications were similar between the 2 groups. A greater percentage of those receiving initial ET epinephrine were born via emergent cesarean delivery (79.8% vs 66.7%) and were more likely to have a cord pH of less than 7.01, as well as lower 1-minute Apgar scores. Those receiving initial ET epinephrine were more likely to be asystolic than those who received initial IV epinephrine (41.0% vs 31.9%).

ROSC and survival results after initial ET vs IV epinephrine are presented in **Table II**. ROSC was achieved in 197 of 281 (70.1%) neonates who received initial ET epinephrine

Table I. Maternal, delivery, and infant baseline characteristics and outcomes stratified by initial ET vs initial IV epinephrine in the delivery room

Characteristics	Overall (n = 408)	Initial ET epinephrine (n = 281)	Initial IV epinephrine (n = 127)
Weight, kg,* median (IQR)	1.86 (0.79, 3.13)	2.00 (0.84, 3.23)	1.61 (0.75, 2.75)
Gestation, wk, median (IQR)	31.1 (26.0, 37.0)	32.4 (26.0, 37.2)	30.0 (25.6, 36.0)
Less than 34 wk	237 (58.09%)	151 (53.74%)	86 (67.72%)
Female†	199 (49.01%)	146 (52.14%)	53 (42.06%)
Prenatal care	352 (86.27%)	247 (87.90%)	105 (82.68%)
Singleton	389 (95.34%)	268 (95.37%)	121 (95.28%)
At least 1 maternal complication‡	154 (43.87%)	110 (45.08%)	44 (41.12%)
At least 1 delivery complication	94 (23.04%)	64 (22.78%)	30 (23.62%)
At least 1 fetal congenital anomaly§	100 (24.51%)	78 (27.76%)	22 (17.32%)
Nonreassuring fetal heart tracing	186 (68.38%)	123 (65.78%)	63 (74.12%)
Fetal monitoring¶ (external or internal)			
Delivery mode**	85 (75.89%)	63 (79.75%)	22 (66.67%)
Emergent cesarean delivery	21 (18.75%)	13 (16.46%)	8 (24.24%)
Vaginal, instrumental	6 (5.36%)	3 (3.80%)	3 (9.09%)
Vaginal/spontaneous/VBAC/scheduled cesarean delivery	97 (59.15%)	60 (52.17%)	37 (75.51%)
Cord pH††, 7.01 or greater	97 (59%)	60 (52%)	37 (76%)
Apgar scores, median (IQR)			
1 min‡‡	0 (0, 1)	0 (0, 1)	1 (0, 1)
5 min§§	1 (0, 2)	1 (0, 2)	1 (0, 2)
10 min¶¶	1 (1, 4)	1 (0, 4)	1 (1, 3)
Meconium-stained fluid	32 (7.84%)	22 (7.83%)	10 (7.87%)
Neonatal outcomes			
Heart rate***			
Bradycardia: heart rate <60 bpm	180 (61.86%)	118 (59.00%)	62 (68.13%)
Asystole	111 (38.14%)	82 (41.00%)	29 (31.87%)
Total number epinephrine doses received, median (IQR)	2 (1, 4)	2 (1, 4)	1 (1, 3)

VBAC, vaginal birth after cesarean.
*36 infants had missing data on birth weight; 25 in ET first, 11 in IV first.
†2 infants had missing data on sex; 1 in ET first, 1 in IV first.
‡57 infants had missing data on maternal complications, 37 ET first, 20 IV first.
§18 infants had missing fetal complications; 12 ET first/only, 6 IV only.
¶136 infants had missing data on fetal monitoring; 94 ET first, 42 IV first.
**296 infants were missing data on delivery mode; 202 ET first, 94 IV first.
††244 infants were missing pH levels; 166 ET first, 78 IV first.
‡‡38 were missing 1-minute Apgar; 33 ET first/only, 5 IV first.
§§37 missing 5-minute Apgar; 32 ET first/only, 5 IV first.
¶¶62 missing 10-minute Apgar; 48 ET first, 14 IV first.
***Missing 117, 36 for IV and 81 for ET.

(includes those infants subsequently receiving IV epinephrine) and 74 of 127 (58.3%) neonates who received initial IV epinephrine (adjusted RD 10.02%; 95% CI 0.05-19,99: P = .045). The adjusted RD was similar for 24-hour survival: (9.79%; 95% CI –0.38 to 19.95: P = .058) and survival to hospital discharge: (adjusted RD 8.52%; 95% CI −1.37 to 18.40: P = .096). After just 1 dose of either ET or IV epinephrine, rates of ROSC were similar between groups: 34.2% in ET epinephrine compared with 36.2% for IV epinephrine (adjusted RD –2.91%; 95% CI –13.00 to 7.18: P = .570).

Figure 2 shows the cumulative incidence curves for time to ROSC with competing risk of no ROSC (**Figure 2**A) and time to first dose (**Figure 2**B). The tables in **Figure 2** provide the percent of infants from each group who received the first dose of epinephrine or have achieved ROSC at specific time points during the CPR event. **Figure 2**A presents the cumulative incidence curves for time to achieve ROSC and the competing risk of not achieving ROSC (defined by the duration of CPR) stratified by route of initial epinephrine dose. This figure is truncated at 60 minutes, as only 18 infants had a duration of CPR longer than 60 minutes (see **Supplementary Figure 1** Online; available at www.jepds.com for details). These curves show the rates of ROSC and account for the changing denominator over time. Median time to ROSC, the time corresponding to when 50% of the infants in the given epinephrine group achieved ROSC, was 12 minutes in the initial ET group and 9 minutes in the IV group. Overall, the adjusted HR of ROSC comparing initial ET group with the initial IV group was 1.3 (95% CI 0.97-1.69: P = .083); however, the incidence curves cross. The ROSC curve has a steeper slope in the first 15 minutes, then starts to flatten out, with few infants achieving ROSC after the initial 15 minutes of the event. The curve for infants not achieving ROSC is much flatter in the beginning, which is expected, given resuscitation efforts don't typically stop after a few minutes. This plot does not account for the repeated doses of epinephrine, when they occurred, and what route they were given. Median time to first dose of epinephrine, the time corresponding to when 50% of the infants in the given epinephrine group had received the first dose of epinephrine, was 6 minutes for the initial ET group and 8 minutes for the initial IV group. The overall time was shorter for the ET group (adjusted

Table II. RD, HR, and 95% CI for primary and secondary outcomes

Outcomes	Initial ET Epinephrine	Initial IV Epinephrine	Unadjusted estimate ([95% CI], *P* value)	Adjusted* estimate ([95% CI], *P* value)
	Percent (count)	Percent (count)	RD	
Primary				
ROSC†	70.11 (197/281)	58.27 (74/127)	11.84 ([1.73-21.95], .020)	10.02 ([0.05-19.99], .045)
Secondary				
ROSC after first dose	34.16 (96/281)	36.22 (46/127)	−2.06 ([−12.09 to 7.97], .686)	−2.91 ([−13.00 to 7.18], .570)
Survive 24 h	59.79 (168/281)	47.24 (60/127)	12.54 ([2.14-22.95], .019)	9.79 ([−0.38 to 19.95], .058)
Survive to discharge	44.73 (123/275)	32.80 (41/125)	11.93 ([1.81-22.04], .025)	8.52 ([−1.37 to 18.40], .096)
	Median time to event (95% CI)		HR	
Time to ROSC‡	12 (10, 15)	9 (8, 12)	1.33 ([1.01-1.75], .043)	1.28 ([0.97-1.69], .083)
Time to first dose§	6 (5, 7)	8 (7, 10)	1.61 ([1.30-1.99], <.001)	1.60 ([1.29-1.99], <.001)

*Adjusted for gestational age at delivery.
†169 received only ET epinephrine, of whom 132 achieved ROSC. 113 received IV epinephrine after ET epinephrine, of whom 65 achieved ROSC.
‡Median time to ROSC is the event-specific time corresponding to when 50% of the infants in the given epinephrine group achieved ROSC.
§Median time to first dose is the time corresponding to when 50% of the infants in the given epinephrine group had received the first dose of epinephrine.

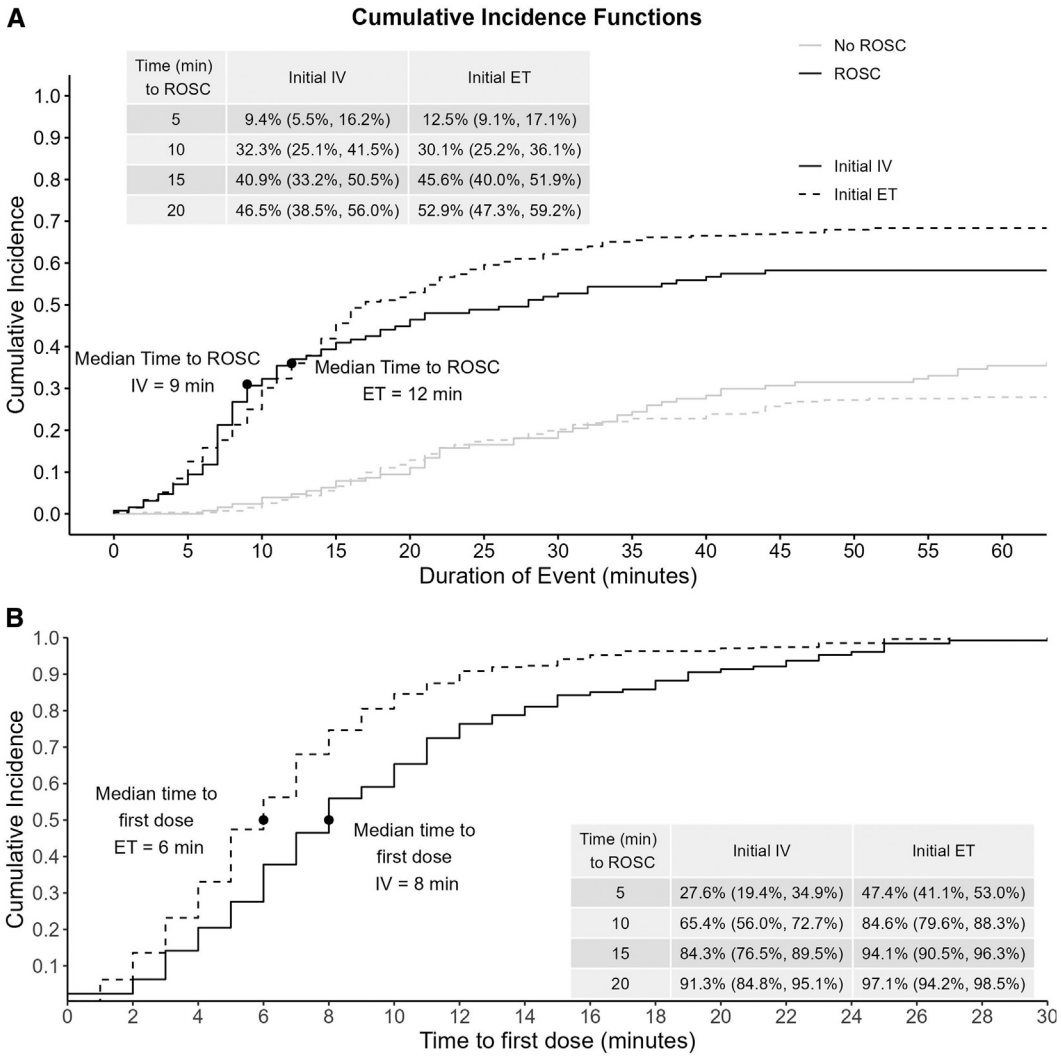

Figure 2. **A,** Cumulative incidence plots of time to ROSC (*black lines*) or no ROSC (*gray lines*) comparing infants who received IV epinephrine first (*solid lines*) vs ET epinephrine first (*dashed lines*). **B,** Cumulative incidence of time to first dose epinephrine comparing infants who received IV epinephrine first (*solid lines*) vs ET epinephrine first (*dashed lines*).

HR 1.60; 95% CI 1.29-1.99: $P < .001$], Figure 2B). Of the 281 infants who received initial ET epi, 80% (104/130) who were born 34 weeks of gestational age or more achieved ROSC compared with 62% (93/151) born less than 34 weeks of gestational age ($P < .001$).

Figure 3 depicts a more specific breakdown of ET and IV epinephrine dose administration and ROSC. Of the 127 infants receiving initial IV epinephrine, 74 infants (58.3%) achieved ROSC. Of the 281 neonates receiving ET epinephrine initially, 132 (47.0%) achieved ROSC with only ET epinephrine (single and multiple doses), 37 (13.2%) did not achieve ROSC and did not receive IV epinephrine, and 112 (39.9%) subsequently received IV epinephrine. Of these 112 neonates who received IV epinephrine after an initial dose of ET epinephrine, 65 (58.0%) achieved ROSC whereas the remaining 47 (42.0%) did not achieve ROSC.

Discussion

Our retrospective multicenter study reports data from 408 newborns receiving epinephrine during DR-CPR. This study suggests the initial use of ET epinephrine is reasonable during DR-CPR, as there were greater rates of ROSC compared with initial administration of IV epinephrine. However, administration of IV epinephrine should not be delayed in infants not responding to an initial dose of ET epinephrine, as almost one-half of those infants subsequently received IV epinephrine before achieving ROSC.

Greater-level evidence on the use and efficacy of epinephrine in the DR is scarce. Pediatric studies exist[17,18]; however, these studies do not accurately depict the unique transitional circulatory physiology present in the newly born infant with fluid filled lungs and high pulmonary pressures with a patent ductus arteriosus and foramen ovale.[19] Neonatal guidelines for the use of epinephrine in the DR are largely based on animal studies suggesting greater ET epinephrine doses (0.05-0.1 mg/kg) are needed to achieve the same epinephrine concentrations and hemodynamic responses as 0.01 mg/kg IV epinephrine.[20-22] In fetal sheep, absorption of ET epinephrine at birth (0.1 mg/kg) was low and delayed while UVC epinephrine (0.03 mg/kg) rapidly achieved high plasma concentrations resulting in greater rates of ROSC.[22] Few studies have compared ET and IV epinephrine in newborn infants in the DR. These were small, single-center retrospective cohort studies[7-10]; the 2 largest (50 and 47 newborns included) came from the same institution and suggested that ET epinephrine was often ineffective at achieving ROSC compared with IV epinephrine.[7,8] A systematic review including these studies as well as 2 smaller studies concluded that ET and IV routes of epinephrine administration resulted in similar survival outcomes.[11] However, given the small numbers, there is need for further investigation of the use of ET vs IV epinephrine in the DR.

In our large multicenter retrospective cohort study, 66% of all infants receiving chest compressions and epinephrine in the DR achieved ROSC. This illustrates that ROSC is achieved in most infants requiring extensive resuscitation in the DR, in keeping with other DR-CPR studies.[3,23] Focusing on

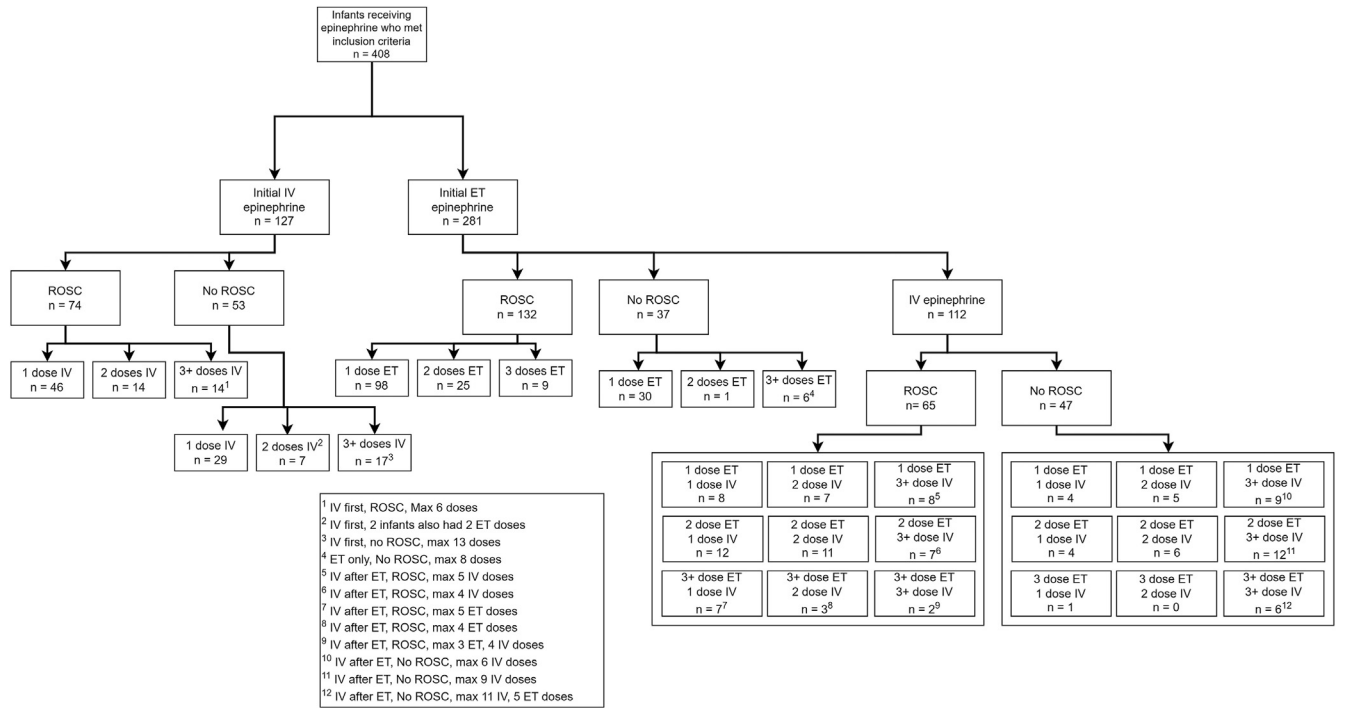

Figure 3. Details of delivery route (ET vs IV epinephrine) and number of epinephrine doses given in the DR for the 408 infants who met inclusion criteria.

administering epinephrine via the most efficacious route during DR-CPR could help maximize the number of infants achieving ROSC following extensive resuscitation in the DR and might decrease end-organ damage in survivors. The current cohort demonstrates a greater rate of ROSC in those infants initially receiving ET epinephrine rather than initial IV epinephrine. The initial ET epinephrine group, however, includes infants who also received subsequent IV epinephrine after failing to respond to ET epinephrine. As illustrated in **Figure 3**, 58.3% of infants achieved ROSC after IV epinephrine alone (includes single and multiple doses) whereas 47.0% of infants achieved ROSC with ET epinephrine alone (single and multiple doses), suggesting that infants have a greater likelihood of achieving ROSC after the administration of IV epinephrine. After failing to respond to initial ET epinephrine, ROSC was subsequently achieved in 58.0% of the 112 infants receiving IV epinephrine. Of note, 37 infants not achieving ROSC received ET epinephrine only. When epinephrine is administered via the IV route, it is delivered directly into the circulation. Epinephrine absorption via the ET tube is potentially less reliable as the result of an unknown amount of drug remaining in the ET tube and upper airways, the dilutional effect the drug will have once entering the fluid filled newborn lungs, and the unknown amount that will reach the heart as the result of high pulmonary pressures and inconsistent pulmonary blood flow in the newly born asphyxiated patient.[8] Because of this uncertainty and supported by our findings, it is reasonable to administer at least one IV dose (or intraosseous if a UVC cannot be obtained) of epinephrine before cessation of resuscitative efforts.

In our cohort, infants initially receiving ET epinephrine received the first dose faster than those infants receiving initial IV epinephrine (6 minutes vs 8 minutes). This is not surprising, as it is not uncommon for infants to receive ET epinephrine initially while awaiting completion of emergent UVC placement. Numerous pediatric studies have shown improvement in survival outcomes with epinephrine given at less than 5 minutes after onset of cardiopulmonary arrest.[16,23,24,25] However, among infants who achieved ROSC, this occurred faster if they initially received IV epinephrine (9 minutes) compared with ET epinephrine (12 minutes). This is important as prolonged resuscitation (longer than 10 minutes) has been associated with greater rates of mortality and greater risk for neurodisability.[26] In addition, infants who received initial IV epinephrine achieved ROSC with fewer doses of epinephrine compared with infants who received initial ET epinephrine. This is likely explained by the initial ET epinephrine group often requiring subsequent IV dose(s) before achieving ROSC. Multiple doses of epinephrine during pediatric CPR have been associated with decreased odds of ROSC,[3] decreased odds of survival at 24 hours[27] and to hospital discharge, and increased risk of hemodynamic instability (arrhythmias, rebound tachycardia, hypertension) after ROSC.[28,29] Interestingly, the rate of ROSC after one dose of ET or IV epinephrine was similar in the current cohort (34% vs 36%), highlighting the need for further studies investigating optimal initial dosages of both ET and IV epinephrine.

The current study was a review of a large national resuscitation registry and as such, numerous limitations were present. Missing data points in vital areas (gestational age, time of birth, time to first epinephrine dose, epinephrine route) resulted in numerous exclusions (130 of the 538 infants receiving epinephrine in the DR). In addition, we were not able to control for additional confounders because of missing data. Adjusting for gestational age did move the estimated risk differences closer to the null and future observational studies interested in a causal interpretation will need to collect and include all confounders in the statistical models. Information on actual epinephrine dosage given was available; however, there was no consistency in how the dosage was reported, some centers reporting mL/kg, some reporting mg/kg, and some reporting actual total dosage given. Although epinephrine dosing information would have been useful, we could not guarantee the accuracy of this information and therefore chose not to report it. Another limitation was the lack of information available regarding participating centers, information regarding number of deliveries per year for each center or number of level 3 or level 4 neonatal intensive care units participating or number of academic or private institutions was not available to us. Finally, given the limited data available in the literature, an informative power calculation was not possible a priori; however, these results could help inform future randomized clinical trials as well as additional observational studies.

In conclusion, in a large multicenter retrospective cohort of neonates receiving chest compressions and epinephrine in the DR, a greater percentage achieved ROSC after initial ET epinephrine compared with those receiving initial IV epinephrine; however, many received IV epinephrine before achieving ROSC. When including single and multiple doses, a greater percentage of infants achieved ROSC with only IV epinephrine compared with only ET epinephrine. Initial use of ET epinephrine during DR-CPR should not delay the administration of IV epinephrine in those infants not responding to initial ET epinephrine. Further studies investigating the optimal dosage of ET and IV epinephrine during DR-CPR are needed to potentially maximize rates of ROSC during DR-CPR. ■

CRediT authorship contribution statement

Cecilie Halling: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Sara Conroy:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Tia Raymond:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Elizabeth E. Foglia:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Mary Haggerty:** Writing – review & editing. **Linda L. Brown:** Writing – review & editing, Writing – original draft,

Methodology, Conceptualization. **Myra H. Wyckoff:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

This research was supported by the Ohio Perinatal Research Network (OPRN) at Nationwide Children's Hospital. OPRN is supported by the Center for Perinatal Research at Nationwide Children's hospital. Funding is provided by the Abigail Wexner Research Institute at Nationwide Children's Hospital. The authors have no conflicts of interest relevant to this article to disclose.

Get With the Guidelines–Resuscitation Pediatric Research Task Force: Anne-Marie Guerguerian, MD, PhD, FRCPC, FAAP, FAHA; Caitlin E. O'Brien, MD, MPH; Ericka L. Fink, MD, MS, Javier J. Lasa, MD, FAAP; Joan S. Roberts, MD, Lillian Su, MD; Linda L. Brown, MD, MSCE; Maya Dewan, MD, MPH; Melania M. Bembea, MD, MPH, PhD; Monica Kleinman, MD; Noorjahan Ali, MD, MS, FAAP; Punkaj Gupta, MBBS; Robert M. Sutton, MD, MSCE; Ron Reeder, MS, PhD; and Todd Sweberg, MD MBA.
The Get With The Guidelines–Resuscitation program is provided by the American Heart Association.

Submitted for publication Dec 19, 2023; last revision received Mar 27, 2024; accepted Apr 11, 2024.

Reprint requests: Cecilie Halling, MD, FAAP, Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205. E-mail: Cecilie.halling@nationwidechildrens.org

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