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Is Epinephrine Effective During Neonatal Resuscitation?

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Abstract

In the original research article published in *Pediatric Research*, Anderson et al provide valuable data from a placebo-controlled randomized trial on epinephrine in 12-hour-old piglets in cardiac arrest. In this commentary, we discuss briefly the existing evidence supporting use of epinephrine during neonatal resuscitation.

Epinephrine (adrenaline) is the only medication recommended by the International Liaison Committee On Resuscitation (ILCOR) during resuscitation in newborns with persistent bradycardia or asystole.¹ However, there are no randomized clinical trials investigating epinephrine use in the delivery room owing to its infrequent use during resuscitation (~0.05–0.06% of live births)², difficulty in predicting its need and ethical challenges. Retrospective studies and large multi-center observational studies and registries are providing valuable clinical data on survival and long-term neurodevelopmental outcomes.

Translational studies in animal models have significantly contributed to the evidence supporting epinephrine use in neonatal resuscitation. However, differences in animal species, age and related physiological changes, variations in induction of bradycardia and cardiac arrest and timing and route of epinephrine have led to differences in outcomes and results (figure 1). In a recent issue of the journal *Pediatric Research* Andersen et al have presented novel data from their randomized placebo-controlled trial evaluating epinephrine use in porcine neonatal cardiac arrest with a 6-hour follow-up and magnetic resonance imaging (MRI)/ magnetic resonance spectroscopy (MRS) of the brain.³ Epinephrine (0.01 mg/kg/

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dose) administered at 1 min after onset of resuscitation resulted in higher incidence of return of spontaneous circulation (ROSC) compared to placebo (epinephrine 10/13 vs placebo 4/12, RR 2.31; 95% CI: 1.09 to 5.77, $p = 0.047$). However, the authors observed no difference between the groups in median time-to-ROSC from initiation of resuscitation (epinephrine: 120 (113–211) vs placebo 153 (116–503) s, $p = 0.66$), and 6-hour survival (7/13 vs 3/12, $p = 0.23$), or lactate to N-acetyl aspartate (Lac/ NAA) ratio by MRS and composite outcome of death or abnormal MRI/MRS. The authors comment, “newborn animal models of cardiac arrest have failed to produce convincing evidence to support the use of epinephrine in neonatal resuscitation”. In this commentary, we review existing data on efficacy of epinephrine during neonatal resuscitation.

Data from clinical studies and animal studies:

Retrospective clinical studies^{2,4} show approximately 76% ROSC following epinephrine in the delivery room but only 44% survival to NICU discharge. Such sparse human evidence is of very low certainty demonstrating the limits of our current knowledge of epinephrine in neonatal resuscitation. In contrast, several studies in newly born lamb models show high rate of ROSC with epinephrine.^{5–7} These models induced asphyxia by umbilical cord compression, a clinically relevant cause of birth asphyxia, compared to endotracheal tube occlusion in postnatal piglets (figure 1). Newly born lambs have lung fluid that dilutes endotracheal epinephrine reducing the efficacy of first dose of epinephrine by endotracheal route (55%) as compared to umbilical venous catheter (UVC-82%).⁵ In 12-hour-old piglets, the lungs are no longer fluid-filled and are ventilated with air as the cardiopulmonary transition has already occurred prior to cardiac arrest. In addition, an open ductus arteriosus limits the build-up of diastolic blood pressure, a key determinant of coronary perfusion pressure during chest compressions (CC). In spite of this limitation, neonatal lambs in cardiac arrest have a high incidence of ROSC with very low diastolic pressures (< 10 mmHg) in contrast to studies from postnatal animal models³ and in children.

Variations in study design:

In addition to these physiological differences in species and age, variations in study design make comparison between neonatal animal studies difficult. Andersen et al defined cardiac arrest as mean blood pressure <20 mm Hg and heart rate (HR) < 60 bpm, and resuscitation was initiated 5 min after the above criteria were met (leading to asystole or pulseless electrical activity). In contrast to stricter definitions based on duration of asystole (HR=0) used in previous studies,⁶ it is possible that the definition used may lead to piglets with varying degrees of asphyxia included in the current study.

Optimizing chest compressions:

The Textbook of American Academy of Pediatrics-Neonatal Resuscitation Program (AAP-NRP) currently recommends synchronous 3:1 compression-to-ventilation ratio with approximately 90 CC and 30 breaths per min. Asynchronous CC and ventilation as in the Andersen et al study, is a deviation from current guidelines which they have acknowledged in their limitations. However, in animal models asynchronous CC provide a higher rate

(~120/min vs. 90/min with synchronous 3:1 compression-to-ventilation ratio) with increased blood flow and oxygen delivery to the brain.

The piglet model has an advantage with thoracic shape amenable to anteroposterior CC (figure 1) and is more suitable to study CC depth.⁸ Bruckner et al recently reported higher incidence and shorter time to ROSC with CC at 33–40% of anteroposterior thoracic diameter (0% ROSC with 12.5% depth, 75% with ¼ depth, 88% with 1/3 and 2/5th depth).⁸ The lamb chest is “keel-shaped” resulting in CC administered from the side with the lamb in a decubitus position.

Timing of epinephrine administration:

In clinical situations, every attempt should be made to deliver intravenous or intraosseous epinephrine as soon as possible if positive pressure ventilation (PPV) and CC are not effective in restoring HR.⁵ Administering an epinephrine dose at 1-min after onset of PPV and 30 s of CC is ideal but may be impractical in the delivery room as 5.4 ± 2.2 min are needed to place an emergent UVC and administer the first dose of epinephrine.² In animal studies, early epinephrine may potentially lead to unnecessary use in some animals who might have recovered spontaneously. Delaying epinephrine until 4–6 min of resuscitation is associated with ROSC prior to epinephrine in lambs,^{6,7} similar to clinical studies where only 40% of term infants (< 36 weeks) receiving CC for > 1-min receive epinephrine.^{9,10} Optimal interval between epinephrine doses warrants further study.

Route of epinephrine administration:

Intravenous (UVC inserted 2–4 cm below the skin) and intraosseous routes are effective in lamb models of neonatal cardiac arrest.^{3,5,11} Andersen et al do not specify the depth of UVC placement and in the absence of plasma epinephrine concentrations, one cannot be certain that piglets that failed to achieve ROSC received epinephrine in their general circulation. Additionally, the ductus venosus may begin to close, thus affecting the delivery of epinephrine through a low UVC in a 12-hour-old piglet.

Flush volume:

Andersen et al have acknowledged the use of 1-ml flush volume following UVC epinephrine may not have been adequate to propel epinephrine to the right atrium during CC.³ Based on studies in lambs with higher flush volume,⁶ AAP-NRP now recommends a 3-ml flush following intravenous and intraosseous epinephrine.

Epinephrine Dose:

A 0.01 mg/kg dose of epinephrine was used by Andersen et al for initial and repeat doses. We have previously shown higher incidence of ROSC and higher plasma epinephrine concentrations with larger dose of epinephrine (0.02 and 0.03 mg/kg). Recent studies with the use of 0.02 mg/kg of UVC epinephrine resulted in successful ROSC in 7/8 (87.5%) lambs with peak plasma epinephrine concentrations of 333 ± 79 ng/mL. Although plasma epinephrine concentrations are not good predictors of ROSC (233 ± 138 ng/mL vs 505 ± 556

ng/mL, $p=0.11$, in lambs that achieved ROSC vs no ROSC after 0.01 mg/kg epinephrine dose), they could still help determine if epinephrine entered the general circulation.⁶ Based on our current data from lambs, we concur with AAP-NRP and suggest 0.02 mg/kg as the initial dose of intravenous epinephrine.¹²

It is possible that the lack of difference in survival and brain imaging noted by Andersen et al is due to the severe asphyxia in this model. There is no published evidence that epinephrine administration is associated with changes in MRS/ MRI, although it may be associated with an increase in cerebral blood flow. Although Apgar score of 0 at 10-min was associated universally with poor outcomes in the pre-hypothermia era, Laptook et al showed better outcomes in 208 infants in a secondary analysis of neonates enrolled in cooling trials.¹³ Death or disability occurred in 76% (19/25) of infants with a 10-min Apgar score of 0, death occurred in 48%, and among 13 survivors, 7 (54%) had moderate-to-severe disability, and 6 (46%) did not, and in fact had a Mental Developmental Index (MDI) of 87 ± 9 (range: 73–100).¹³ A systematic review evaluating newborns requiring resuscitation beyond 10-min reported that 10.8% of the newborns survived without moderate-to-severe impairment.²² Further study of neurological outcomes after epinephrine is vital due to the worse neurological outcomes reported in adult out-of-hospital arrest and pediatric resuscitation.¹⁴

Andersen et al provide valuable data comparing epinephrine and placebo during neonatal resuscitation. We applaud the authors for moving beyond short-term outcomes in preclinical studies and evaluating brain MRI/MRS changes. However, based on the limitations mentioned in this commentary, in our opinion, these findings should not influence change in the current guidelines from ILCOR and AAP-NRP. Animal studies with longer (3–7 day) follow-up with MRI/MRS or brain histology studies are needed.¹⁵ Large multicenter observational studies and registries with long-term follow-up are warranted to assess the impact of epinephrine during resuscitation.

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Data availability statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Impact:

1. Review the currently available evidence supporting use of epinephrine during neonatal resuscitation.
2. Animal studies have helped investigators in understanding efficacy and pharmacokinetics of epinephrine in perinatal models of cardiac arrest.
3. As the only medication currently recommended in neonatal resuscitation for severe bradycardia and cardiac arrest, it is important to optimize its use to improve neonatal outcomes by investigating optimal dosing, route, timing and interval between epinephrine doses.

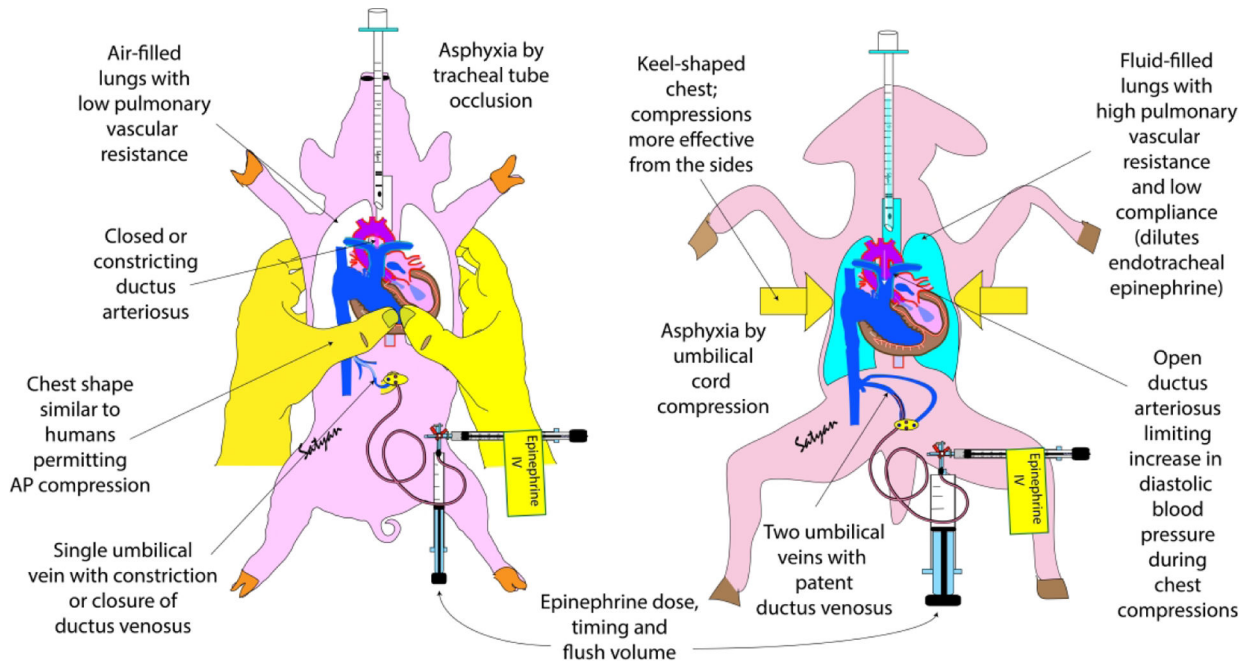


Figure 1: Differences between postnatal piglet (left) and perinatal lamb (right) models of asphyxial cardiac arrest.