# Effects of Endotracheal Epinephrine on Pharmacokinetics and Survival in a Swine Pediatric Cardiac Arrest Model

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**Objectives:** The aim of this study was to compare the endotracheal tube (ET) and intravenous (IV) administration of epinephrine relative to concentration maximum, time to maximum concentration, mean concentration over time (MC), area under the curve, odds, and time to return of spontaneous circulation (ROSC) in a normovolemic pediatric cardiac arrest model.
**Methods:** Male swine weighing 24–37 kg were assigned to 4 groups: ET (n = 8), IV (n = 7), cardiopulmonary resuscitation (CPR) + defibrillation (CPR + Defib) (n = 5), and CPR only (n = 3). Swine were placed arrest for 2 minutes, and then CPR was initiated for 2 minutes. Epinephrine (0.1 mg/kg) for the ET group or 0.01 mg/kg for the IV was administered every 4 minutes or until ROSC. Defibrillation started at 3 minutes and continued every 2 minutes for 30 minutes or until ROSC for all groups except the CPR-only group. Blood samples were collected over a period of 5 minutes.
**Results:** The MC of plasma epinephrine for the IV group was significantly higher at the 30- and 60-second time points ($P = 0.001$). The ET group had a significantly higher MC of epinephrine at the 180- and 240-second time points ($P < 0.05$). The concentration maximum of plasma epinephrine was significantly lower for the ET group (195 ± 32 ng/mL) than for the IV group (428 ± 38 ng/mL) ($P = 0.01$). The time to maximum concentration was significantly longer for the ET group (145 ± 26 seconds) than for the IV group (42 ± 16 seconds) ($P = 0.01$). No significant difference existed in area under the curve between the 2 groups ($P = 0.62$). The odds of ROSC were 7.7 times greater for the ET versus IV group. Time to ROSC was not significantly different among the IV, ET, and CPR + Defib groups ($P = 0.31$).
**Conclusions:** Based on the results of this study, the ET route of administration should be considered a first-line intervention.

**Key Words:** cardiac arrest, epinephrine, endotracheal, pharmacokinetics

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Cardiac arrest in both adults and children is one of the leading causes of morbidity and mortality with more than 356,500 occurrences outside of the hospital each year.[1] Approximately 6000 hospitalized and 9500 out-of-hospital children receive cardiopulmonary resuscitation (CPR) per year just in the United States.[2–5] Over 6 million children die each year. Approximately 900,000 children in the age group of 5–14 years of age died in 2017.[6] These deaths were from illnesses, injuries, electrocution, and drowning. Regardless of the cause, rapid administration of epinephrine increases survival and decreases neurological complications among pediatric resuscitation patients both in- and out-of-hospital settings.[7,8] There is a 9% decrease in the odds of survival for every minute delay in epinephrine administration in patients with nonshockable rhythms.[7–10] Obtaining vascular access is frequently challenging and time-consuming among pediatric patients because children have smaller vessels and increased amounts of subcutaneous fat compared with adults.[11]

The American Heart Association's Pediatric Advanced Life Support (PALS) guidelines recommend epinephrine be given in order of preference by intravenous (IV), intraosseous (IO), or the endotracheal (ET) route of administration.[12–14] However, these recommendations are based on limited animal studies and expert opinion. Pinto et al[15] stressed that pharmacokinetic data were lacking relative to the use of ET route of administration and emphasized that guidelines cannot be established by expert opinion and few studies. They concluded that additional, prospective studies are urgently needed.[15]

The ET route of administration provides rapid access to the vascular space and rapid access to the cardiac tissue because of the anatomical relationship between the pulmonary and cardiac circulation. The initial concentration of epinephrine from the pulmonary circulation may be sufficient to facilitate survival. However, it has not been shown whether this route is effective in resulting in return of spontaneous circulation (ROSC) in a normovolemic, pediatric cardiac arrest model.

The following research questions guided the study:

1. Are there significant differences in maximum plasma concentration ($C_{max}$), time to maximum concentration ($T_{max}$), mean concentration (MC) of plasma epinephrine over time, and area under the curve (AUC) when epinephrine is administered by IV or ET routes?
2. Are there significant differences in the frequency and odds of the occurrence of return of ROSC in the ET, IV, CPR + defibrillation (CPR + Defib), and CPR-only groups?
3. Are there significant differences in the time to ROSC among ET, IV, CPR + Defib, and CPR-only groups?

## METHODS

### Study Design and Selection of Subjects

This was a prospective (within and between) subjects design approved by the Institutional Animal Care and Use Committee supporting the Naval Medical Research Unit–San Antonio. Twenty-five (n = 25) juvenile male castrated swine, *Sus scrofa* (20–35 kg), were placed into 4 groups: IV, ET, CPR + Defib, and CPR only. The sequence of using each animal was determined by assignment using a random number generator (https://www.random.org). The weight range is analogous to the average weight of a 5- to 6-year-old male child. Castrated male subjects were used to avoid potential hormonal effects. We reduced animal usage by decreasing the sample size of the CPR + Defib and CPR-only groups by using relevant historical data. To maintain consistency and health, we used subjects procured from Oak Hill Genetics, Ewing, IL, a supplier of purpose-bred swine to research facilities.

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## Veterinary Care and Housing

All swine were housed and cared for in accordance with the Animal Welfare Act and Regulations and the Guide for the Care and Use of Laboratory Animals. Swine were allowed to acclimate to the holding areas for 3 days before commencement of the study. During that time, veterinarians evaluated them to be in good general health and free of disease. All animals were fed antibiotic-free swine diet and received ad libitum tap water. Animals were allowed social interaction with conspecifics until the procedure day. Twelve hours before the anesthesia, animals were not permitted solid food but were allowed access to water. We made the assumption that all the subjects were normovolemic because each had moist mucus membranes and appropriate skin turgor determined by the veterinarians. In addition, all the pigs were allowed access to water until the experiment.

## Animal Preparation

Animals were premedicated with 4.4 mg/kg Telazol (tiletamine/zolazepam; Fort Dodge Animal Health, Fort Dodge, IA) intramuscularly and buprenorphine SR (sustained release) at 4 μg/kg subcutaneously. General anesthesia was induced with inhaled isoflurane at 1%–5% in 100% oxygen. After ET placement, isoflurane was maintained between 1% and 2%. Subjects were ventilated at 8–10 mL/kg tidal volume at a rate of 10–14 breaths per minute with a Dräger anesthesia machine. Heart rate (HR), mean arterial pressure (MAP), oxygen saturation ($O_2$), end-tidal capnography, and body temperature (Temp) were monitored continuously using the Dräger monitoring system.

For each pig, vascular access was achieved with an 18-guage percutaneous catheter placed in the auricular vein. Patency was maintained with lactated Ringers solution at a rate of 50 mL/h. The left carotid and femoral arteries were cannulated with 8.5F × 10 cm central venous catheters (Arrow International, Reading, PA) using an open surgical approach and secured in place. Carotid lines provided continuous arterial blood pressure monitoring, whereas femoral lines were used for blood sampling and continuous monitoring of cardiac output (CO) and stroke volume (SV) using a Vigileo hemodynamic monitor (Edwards Lifesciences, Irving, CA). A forced-air patient warming system (Bair Hugger; 3M, St Paul, MN) was used to maintain Temp at or above 36°C. For those subjects achieving ROSC, we monitored HR, CO, SV, MAP, Temp, SBP, DBP, and $O_2$ every 5 minutes for a total of 30 minutes (6 times). A mean and SD was calculated for each pig for the 30 minutes (6 times) and then by group.

## Experimental Procedures

After a 15-minute stabilization, we passed an electric current through the swine's heart to induce ventricular fibrillation, a procedure developed by the investigators.[16] Anesthesia was discontinued, and 2 minutes of arrest without intervention was implemented to replicate an usual delay in treatment. A mechanical compression device (Model 1008; Michigan Instruments, Grand Rapids, MI) administered mechanical chest compressions at 100 compressions per minute. Manual ventilations were delivered at a rate of 6 to 10 per minute. The quality of chest compressions was confirmed by observing the arterial pressure and capnographic waveforms. After 4 minutes of cardiac arrest, we disconnected the anesthesia circuit from the ET, lifted the subject's head 45 degrees, and administered the American Heart Association's PALS recommended dose of epinephrine (0.1 mg/kg; 1 mg/mL) for each subject in the ET group. The epinephrine was diluted in 8 mL 0.9% normal saline. Four volume capacity breaths were administered using a bag valve. The IV group received epinephrine (0.01 mg/kg; 1 mg/mL). The CPR + Defib and CPR-only groups were not administered epinephrine. Serial blood specimens (10 mL) were collected from the left femoral arterial line at 30, 60, 90, 120, 150, 180, 240, and 300 seconds after epinephrine administration. Before each specimen collection, we aspirated and discarded 8 mL of blood to avoid any residual epinephrine in the tubing from the previous time. At the conclusion of each specimen collection, 10 mL of 0.9% normal saline was injected into the arterial line to clear the line and to maintain patency. We defibrillated at PALS recommended energy levels every 2 minutes starting at 3 minutes for the IV, ET, and CPR + Defib groups.[12–14] For the IV and ET groups, we continued epinephrine administration every 4 minutes and defibrillation every 2 minutes until ROSC.[12–14] For the purposes of this study, ROSC was defined as a SBP of at least 60 mm Hg and a palpable femoral pulse for 30 minutes. At the end of 30 minutes, those subjects were euthanized. If ROSC occurred, the time was documented. For all subjects, if ROSC was not achieved within 30 minutes, the study was terminated (Table 1).

Blood specimens were placed in lithium heparin collection tubes and centrifuged immediately (Thermo Fisher Scientific, Waltham, MA) for 15 minutes at 1800 g. Separated plasma was pipetted into duplicate 2 mL microcentrifuge vials and frozen to a temperature of −80°C. Blood specimen analysis for epinephrine was performed using high-performance liquid chromatography with tandem mass spectrometry and performed on samples collected only after the first dose of epinephrine.

## Statistical Analyses

The SPSS Statistics Software package, version 22 (IBM, Armonk, NY) was used for data analyses. Means, standard deviations (SD), and standard errors of the mean (SEM) were calculated for the IV and ET groups. A 1-way multivariate analysis of variance (ANOVA) was used to determine if there were significant differences among the groups relative to pretest data, HR, CO, SV, MAP, Temp, SBP, DBP, and $O_2$ after ROSC, $C_{max}$, $T_{max}$, and time to ROSC. A repeated-measures ANOVA with pairwise

**TABLE 1.** Summary of Intervention After Stabilization

| Activity | Place in Arrest | Start CPR | Administer Epinephrine | Collect Samples | Defibrillate | Administer Epinephrine | Monitor | Those Without ROSC |
|---|---|---|---|---|---|---|---|---|
| Time | After arrest, there is no activity for 2 min. | At the 2 min mark, CPR is started for 2 min. | At the 4 min mark, epinephrine is given over 5 s. | 30, 60, 90, 120, 150, 80, 240, and 300 s after epinephrine administration | Start at 7 min after arrest and repeat every 2 min or until ROSC | After initial epinephrine repeat dose every 4 min until ROSC | Monitor subjects who achieve ROSC for 30 min | Continue with epinephrine every 4 min and defibrillation every 2 min for a period of 30 min |

**TABLE 2.** Data After ROSC

| | Means and SD for Data Collected Over 30 min After ROSC | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Groups** | **HR** | **SBP** | **DBP** | **MAP** | **CO** | **SV** | **$O_2$** | **Temp** |
| ET group | 105 ± 7 | 116 ± 9 | 62 ± 8 | 88 ± 8 | 8 ± 4 | 89 ± 11 | 99 ± 1 | 37.5 ± 0.8 |
| IV group | 108 ± 9 | 119 ± 10 | 67 ± 8 | 92 ± 11 | 9 ± 4 | 90 ± 10 | 98 ± 2 | 37.9 ± 0.9 |
| CPR + Defib group | 113 ± 9 | 117 ± 9 | 65 ± 8 | 90 ± 13 | 7 ± 4 | 86 ± 5 | 98 ± 2 | 37.7 ± 0.7 |

comparisons was used to determine if there were statistical differences among the groups relative to the MC of epinephrine at each specimen collection time point. Fisher exact test was used to determine if there were differences in the incidence of ROSC among groups. An odds ratio was used to determine the chances for ROSC (https://www.medcalc.org/calc/odds_ratio.php). For all statistical analyses, significance was indicated by a $P$ value <0.05. When a significant difference was found using multivariate ANOVA and repeated-measures ANOVA, the least significant difference post hoc test was used to find where the difference was.

## Sample Size Estimation

The investigators used the means and standard deviations of $C_{max}$, $T_{max}$, and plasma MC over time from similar pharmacokinetic studies and calculated a medium effect size of 0.6.[17,18] Using an alpha of 0.05, an effect size of 0.6, and a power of 0.80, it was determined a sample size of 8 was needed in the ET and IV groups. Power analysis was performed using G*Power 3.1 for Windows (Heinrich Heine University, Dusseldorf, Germany).

# RESULTS

All swine completed the study except 1 subject in the IV group that was ill and excluded. There were no significant differences in pretest data by group (weight, HR, SBP, DBP, MAP, CO, SV, $O_2$, or Temp), indicating the groups were equivalent on these variables ($P > 0.05$). There was no significant difference in HR, SBP, DBP, MAP, CO, SV, $O_2$, or Temp by group over a 30-minute period for subjects achieving ROSC ($P > 0.05$) (Table 2). The investigators acknowledge that the preoperative medications and anesthesia may have altered the SBP; however, all subjects were exposed to the same medications. There were no statistically significant differences in the baseline SBP ($P = 0.28$). The means and SD in mm Hg of the baseline SBP were IV (92 ± 8), ET (88 ± 9), CPR + Defib (94 ± 9), and CPR (97 ± 9).

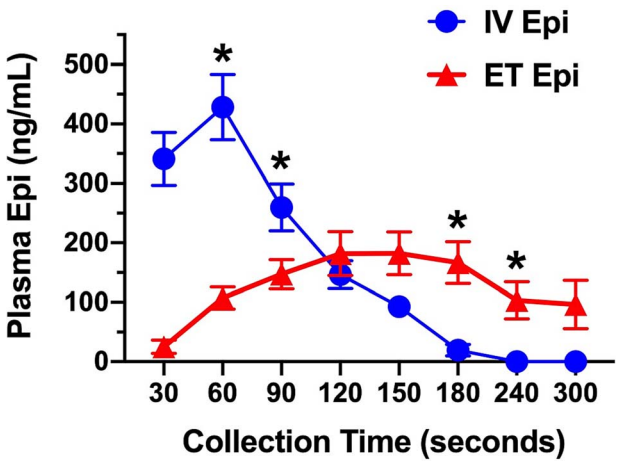


**FIGURE 1.** Mean ± SE of plasma epinephrine in nanograms per milliliter.

## Epinephrine Pharmacokinetics

The time courses of mean plasma epinephrine concentration were markedly different for the IV and ET groups. The MC of plasma epinephrine for the IV group was significantly higher at the 30- and 60-second time points ($P = 0.001$). By contrast, the ET group had a significantly higher MC of epinephrine at the 180- and 240-second time points ($P < 0.05$) (Fig. 1).

The $C_{max}$ of plasma epinephrine was significantly lower for the ET group (195 ± 32 ng/mL) than for the IV group (428 ± 38 ng/mL) ($P = 0.01$) (Fig. 2A). The $T_{max}$ was significantly longer for the ET group (145 ± 26 seconds) than for the IV group (42 ± 16 seconds) ($P = 0.01$) (Fig. 2B). There was no significant difference in AUC between the 2 groups ($P = 0.62$) (Fig. 2C). All the pharmacokinetics results represent the time after the first dose of epinephrine.

## Return of Spontaneous Circulation

There was no significant difference in the incidence of ROSC between the ET (8 of 8) and IV (5 of 7) routes of epinephrine administration ($P = 0.20$). There was a significant difference between the ET and CPR + Defib (2 of 5) groups ($P = 0.04$). The difference in the incidence of ROSC between the IV administration of epinephrine and CPR + Defib groups was not statistically significant ($P = 0.37$) (Fig. 3). None of the CPR-only group achieved ROSC (data not shown).

The time to ROSC was not significantly different among the IV, ET, and CPR + Defib groups ($P = 0.31$). The means and SD for time in seconds to ROSC for the IV, ET, and CPR + Defib groups were 398 ± 170, 372 ± 163, and 413 ± 32, respectively. The odds of achieving ROSC were 7.7 times greater in the ET group versus the IV group.

# LIMITATIONS

As with all animal models, the results may not be generalizable to humans; however, the cardiovascular and pulmonary systems of swine are similar to humans and appropriate for this study.[19–21] The sample size was small, but we had enough power to find significant differences. The investigators were not blinded to group assignment. Because of the obvious nature of route of administration, rapid sample collection at specific time points, and requirement for constant hemodynamic monitoring, all data collection occurred without blinding. However, strict adherence to protocols was achieved. The individual determining pharmacokinetics of epinephrine was blinded as to group assignment. Most pediatric cardiac arrests are because of hypoxia, and the initial heart rhythm is asystole. This swine study applies to previously anesthetized ventilated subjects with ventricular fibrillation. Volatile inhaled agents are used initially but are discontinued immediately after cardiac arrest. Volatile agents are restarted and titrated according to BP after ROSC. However, it must be noted that our

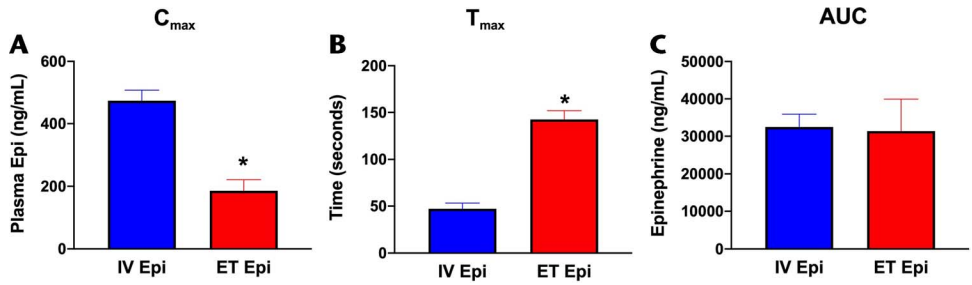


**FIGURE 2.** A, $C_{max}$ comparison IV versus ET. B, $T_{max}$ comparison IV versus ET. C, AUC comparison IV versus ET.



results are specific and only applies to our swine model using anesthesia precode and ventricular fibrillation, and no other inference to any other arrest circumstances can be made based on the provided data.

## DISCUSSION

Epinephrine was administered by IV (0.01 mg/kg) or ET (0.1 mg/kg) route. The doses of epinephrine administered were according to American Heart Association's PALS guidelines.[12–14] The time courses of MC epinephrine concentration were markedly different for the IV and ET routes of administration. However, there was no difference between the ET and IV groups in the AUC, a measure of total systemic exposure to epinephrine. Endotracheal administration of epinephrine was as effective as IV administration of epinephrine in the restoration of ROSC in this normovolemic pediatric cardiac arrest model; however, the odds of ROSC were 7.7 times greater in the ET versus IV groups indicating clinical significance. The ET route of administration of epinephrine may be considered as an effective administration route for the pediatric patient in cardiac arrest, especially in situations in which IV catheterization is difficult or time-consuming.

### Epinephrine Pharmacokinetics

The time courses of MC of epinephrine concentration were markedly different for the IV and ET routes of administration. Plasma epinephrine concentrations after IV administration peaked within the first 60 seconds; plasma epinephrine concentrations after ET administration rose more gradually and peaked at 145 seconds. The $C_{max}$ after ET administration was approximately half of that after IV administration. Given the differences in the pharmacokinetics of plasma epinephrine with respect to $C_{max}$ and $T_{max}$ between IV and ET administration, it is important to note that there was no significant difference in the AUC, a measure of total systemic exposure to the drug between groups.

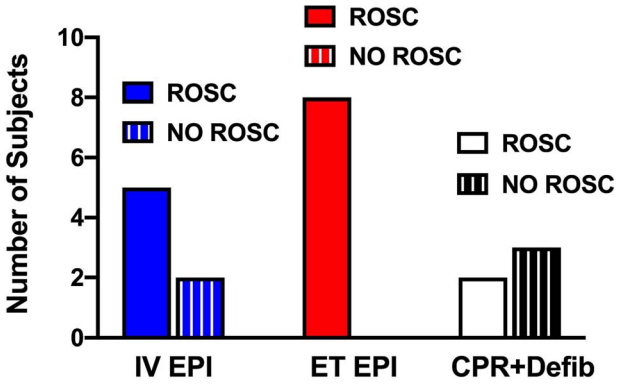


**FIGURE 3.** Comparison of ROSC by group.

We previously examined the pharmacokinetics of ET and IV administered epinephrine in a hypovolemic pediatric cardiac arrest model.[17] In comparison to the normovolemic model, the time courses of plasma epinephrine after ET and IV administration were similar in the hypovolemic model.[17] We found no significant difference in the $C_{max}$, $T_{max}$, MC, or AUC between ET and IV groups in the hypovolemic model. The time course of ET administered epinephrine was similar in the hypovolemic and normovolemic models. However, the time to maximum plasma concentration of IV administered epinephrine was greater in the hypovolemic model (111 ± 14 seconds) than in the normovolemic model[17] The delay in peak epinephrine concentration after IV administration in the hypovolemic model when compared with the normovolemic model may reflect poor circulation at the peripheral site of administration, that is, auricular vein.

### Return of Spontaneous Circulation

In the present study, there was no statistically significant difference in the incidence of ROSC between the ET and IV routes of epinephrine administration. However, there was a clinical significance: the ET group had 100% compared with 71.4% of the IV group achieve ROSC. Time to ROSC was similar for the IV and ET groups. Given the differences in the pharmacokinetics of plasma epinephrine with respect to $C_{max}$ and $T_{max}$ between IV and ET routes of administration, our data suggest that ROSC may be dependent on total systemic exposure to the drug in normovolemic pediatric cardiac arrest.

We previously determined the incidence of ROSC and time to ROSC between ET and IV routes of epinephrine administration in a hypovolemic pediatric cardiac arrest model.[17] There was no significant difference in the incidence of ROSC between the ET and IV routes of epinephrine administration, indicating that ET administration of epinephrine is as effective as IV administration in achieving ROSC in hypovolemic pediatric cardiac arrest. However, the time to ROSC in the ET group was significantly faster than the IV group in this hypovolemic pediatric cardiac arrest model.[17] The faster onset of ROSC after ET administration may be due to the anatomic relationship between the pulmonary and cardiac circulation, and reduced circulation at the peripheral site of IV administration.

To the best of our knowledge, there are no other reports of epinephrine plasma pharmacokinetics and the incidence of ROSC after ET administration of epinephrine in pediatric cardiac arrest models. There are a few reports of studies of ET administration in neonatal cardiac arrest models, which indicate that the absorption of ET epinephrine is low and delayed in neonates.[22,23] These findings are perhaps not surprising given the specialized pulmonary anatomy and physiology necessary to facilitate atmospheric breathing after parturition.[24] Retrospective review of clinical data suggests that previously recommended ET epinephrine doses (0.01–0.03 mg/kg) are

often ineffective during neonatal resuscitation, and that additional research regarding optimal dosing is needed.[25,26]

In adult animal models, the ET route of epinephrine administration has been shown to be unreliable and not reproducible in either the normovolemic or hypovolemic animals.[27–29] In a human study comparing the effects of ET and IV epinephrine on arterial pressure or heart rate, low doses of ET epinephrine had no hemodynamic effects. The authors concluded that recommended ET dose of twice the IV dose would likely be ineffective for the treatment of cardiac arrest.[30] We previously examined plasma epinephrine pharmacokinetics and the incidence of ROSC after ET and IV routes of administration in a hypovolemic adult cardiac arrest model.[18] The absorption of the recommended dose of epinephrine (2 mg, approximately 0.02 mg/kg) was highly variable compared with IV epinephrine (2 mg). Only 2 of 7 subjects achieved ROSC.[18] Future studies will expand upon the existing literature by investigating the pharmacokinetics and ROSC of weight-based dosing of ET epinephrine and ROSC in both a normovolemic and hypovolemic adult cardiac arrest model. Our previous data show that the IO devices are also effective for epinephrine administration in a normovolemic pediatric cardiac arrest model. Future studies should compare the IO versus IV administration of epinephrine.

## CONCLUSIONS

Endotracheal administration of epinephrine may be considered an effective route of administration for the normovolemic pediatric patient in cardiac arrest, especially in situations in which IV catheterization is difficult or time-consuming. Skilled anesthesia practitioners surveyed by the authors estimate that it would take approximately 15–25 seconds to intubate a child. Studies show that intubation time is approximately 34 seconds compared with a lengthier time for gaining IV access, and that it may take as much as 49 minutes to start an IV. Leidel et al[31–33] found IV failure rates were from 10% to 40% in adult patients not in arrest and that the average time for obtain IV access was 2.5 to 16 minutes. In extreme cases, the average time for obtaining IV access was as long as 55 minutes in critically ill adult patients who were not in arrest.[31–33] Obtaining vascular access is frequently challenging and time-consuming among pediatric patients. Therefore, more time-conserving routes need to be investigated. The critical time that is saved may translate into a greater likelihood of achieving ROSC for pediatric patients experiencing cardiac arrest.

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