Medical Science & Healthcare Practice
ISSN 2573-0371 (Print) ISSN 2573-038X (Online)
Vol. 3, No. 2, 2019
www.scholink.org/ojs/index.php/mshp

# Effects of Endotracheal Administration of Epinephrine in Cardiac Arrest of Adult and Pediatric Swine

Steven Kertes[1], Valentina Fillman[2], Brandon Krawczyk[1], Logan Hirsch[1], Allison Martin[1], Phillip Noble[1], Thomas M. Clark[1], Aleczander Battelle[1], Joseph O'Sullivan[3] & Don Johnson[1*]

[1] US Army Graduate Program in Nursing Anesthesia, Fort Sam Houston, San Antonio, TX, USA

[2] Mennonite College of Nursing. Illinois State University, Normal, IL, USA

[3] The Geneva Foundation, Tacoma, WA, USA

[*] Don Johnson, arthurjohnso@gmail.com

Received: July 4, 2019 Accepted: September 9, 2019 Online Published: September 16, 2019

doi:10.22158/mshp.v3n2p34 URL: http://dx.doi.org/10.22158/mshp.v3n2p34

***Abstract***

***BACKGROUND:*** *Few studies have investigated the effects of hypovolemia on area under the curve (AUC) and the return of spontaneous circulation (ROSC) comparing adults and children in cardiac arrest.*

***AIMS:*** *To compare the epinephrine endotracheal (ET) administration relative to AUC, rate, time to, and odds of achieving ROSC between hypovolemic adult and pediatric cardiac arrest models.*

***METHODS****: This was an experimental study using male Adult ET and Pediatric ET swine. Pediatric ET pigs (N=7) weighed 20-30 kg representing the average weight for a child between 5 and 6 years of age. Adult ET pigs (N=7) weighed 60 to 80 kg. All were exsanguinated 35% of their blood volume. Swine were put into arrest for 2 minutes. Cardiopulmonary resuscitation (CPR) was initiated for 2 minutes; epinephrine was then administered. Blood samples were collected over 5 minutes.*

***RESULTS****: No significant difference occurred in AUC between the groups ($p > 0.05$). The Pediatric ET group had higher rates of ROSC and a shorter time to ROSC ($p < 0.05$). Pediatric ET group had a 15 times greater odds of achieving ROSC compared to the Adult ET group.*

***CONCLUSION****: Based on the results of this study, we recommend epinephrine administration via ET within the pediatric arrest model, but not for the adult.*

***Keywords***

*endotracheal, epinephrine, cardiac arrest, hypovolemia*

## 1. Introduction

### *1.1 Need for Study*

Each year, trauma results in the death of over 5 million individuals worldwide and expected to be over

8 million each year by 2020 (Kauvar, Dubick, Walters, & Kragh, 2018; Kauvar, Miller, & Walters, 2018). Death from hemorrhage represents more than 60,000 deaths per year in the United States and 1.9 million deaths worldwide with 1.4 million of which result from physical trauma (Lozano et al., 2012). Hemorrhage is the leading cause of cardiac arrest from trauma in both civilian and military sectors (Dowling et al., 2016; Eastridge et al., 2012; Kelly et al., 2008; Lozano et al., 2012; Schauer, April, et al., 2018; Schauer, Naylor, et al., 2018). Hemorrhage can lead to hypovolemic shock and subsequent cardiac arrest. Research has consistently demonstrated that survivability decreases when drug administration is delayed: The chance of survival is decreased for every minute of delay in administering resuscitation drugs (Hansen et al., 2018). Therefore, vascular access is essential in increasing the probability of return of spontaneous circulation (ROSC).

*1.2 Need for Vascular Access*

In a cardiac arrest situation, the victim's veins have collapsed, especially in hypovolemic shock, making intravenous access (IV) difficult and very time consuming even for the most skilled clinician particularly for a child in arrest. Early administration of epinephrine increases the chance for ROSC and decreases neurological complications among pediatric resuscitation patients in out-of-hospital and in-hospital settings (Andersen et al., 2015; Hansen et al., 2018). Furthermore, Donnino et al. found that delayed administration of epinephrine was associated with less chance of survival cardiac arrest. They compared cardiac arrest in pediatric patients and found that the time to epinephrine administration of five minutes or less had a significantly higher rate of ROSC compared to time to epinephrine administration of longer than 5 minutes (Donnino et al., 2014). Likewise, Khera et al. found that the odds of death with delayed epinephrine administration for patients in cardiac arrest were 58% higher than those who received the drug in the first 5 minutes (Khera, Chan, Donnino, Girotra, & American Heart Association's Get With The Guidelines-Resuscitation, 2016). Further, Zuercher et al. showed a significant improvement in survival, better neurological outcome, and better 24-hour survivability when epinephrine was given earlier (Zuercher et al., 2011). In two separate studies, Burgert et al. and Orlowski et al. found that the absorption of epinephrine was highly variable and unreliable in an adult hypovolemic model (Burgert et al., 2019; Orlowski, Gallagher, & Porembka, 1990; Orlowski, Porembka, Gallagher, Lockrem, & VanLente, 1990). However, these studies did not include a pediatric model.

*1.3 Cardiac Arrest Guidelines*

The American Heart Association (AHA) and the European Resuscitation Council recommend that if IV is not accessible, intraosseous (IO) and endotracheal (ET) routes be used in order of preference. For the individual in cardiac arrest, the recommendation for a pediatric patient is 0.1 mg/Kg and 2 mg for the adult patient to be repeated between 3 and 5 minutes (Link et al., 2015; Neumar et al., 2015; Perkins et al., 2015; Soar et al., 2015).

*1.4 Research Questions*

Few studies that have examined the effects of ET route in either the adult or child or investigated the

effects of hypovolemia on area under the curve (AUC) and ROSC. AUC refers to the bioavailability of drug concentration in blood plasma versus time. We speculated that differences in AUC may affect the rate of ROSC in a hypovolemic cardiac arrest model in pediatrics and adults.

The following research questions guided this study:

1) Are there significant differences in AUC when epinephrine is administered in hypovolemic adult and pediatric cardiac arrest models?

2) Are there significant differences in the occurrence AUC, rate, time to, and odds of achieving ROSC when epinephrine is administered in hypovolemic adult and pediatric cardiac arrest models?

## 2. Method

### *2.1 Design*

This study was a prospective, randomized, between-subjects, experimental design, which compared AUC, ROSC, time to ROSC, and odds of ROSC in a hypovolemic adult to a hypovolemic pediatric cardiac arrest model. The investigation was approved by the Institutional Animal Care and Use Committee of the Naval Medical Research Unit-San Antonio. The study was conducted at the Naval Medical Research Unit-San Antonio which is an approved laboratory facility.

### *2.2 Subjects*

Two groups of adult and pediatric male Yorkshire-cross, s*us scrofa,* swine were used for the study. For the Pediatric ET group (N =7), we used swine that weighed 20 and 30 kg, representing the average weight for a male child between the ages of five and six years. For the Adult ET group (N=7), we used swine that weighed 60 to 80 kg which approximates the average weight of an adult, male human (Gordon et al., 2015; Gordon C., 2015). The rationale for using male pigs was to avoid any potential hormonal effects. Also, the cardiovascular, pulmonary, and bone physiology are very similar to humans (Hannon, Bossone, & Wade, 1990; Swindle, Makin, Herron, Clubb, & Frazier, 2012).

### *2.3 Veterinary Care and Housing*

Housing and care of the swine were in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals (National Research Council, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, & Institute for Laboratory Animal Research, 2011). They were housed in separate enclosures in the same room for social interaction. A comprehensive health assessment was completed on the swine to ensure a good state of health. Swine were fed antibiotic-free feed and received tap water *ad libitum*. The swine did not receive solid food after midnight before the experiment but received water until anesthetic induction.

### *2.4 Animal Preparation*

Swine were premedicated with an intramuscular injection of Telazol (4.4 mg/kg), (Tiletamine/Zolazepam, Fort Dodge Animal Health, Fort Dodge, IA, USA). General anesthesia was induced with inhaled isoflurane (2% to 5%) in 100% oxygen as the carrier gas. After ET intubation, we reduced the isoflurane concentration to a maintenance dose of between 1% and 2%. Ventilation was

achieved with 8-10 mL/kg tidal volume at a rate of 10-14 breaths per minute with an Aestiva 5 anesthesia machine (Datex-Ohmeda, Madison, WI, USA). Heart rate (HR), electrocardiography (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation ($SpO_2$), end-tidal capnography ($ETCO_2$) and body temperature (ºC) were continuously observed using a Datex-Ohmeda Cardiocap 5 monitoring system (GE Healthcare, Helsinki, Finland).

The left carotid artery and left femoral artery were surgically exposed and arterial catheters placed and secured in both sites. The left carotid arterial line was used for continuous arterial blood pressure monitoring. Both the carotid and femoral arteries were cannulated with an 8.5 French x 10 cm central venous catheter (Arrow International, Reading, PA, USA). The investigators used the femoral arterial line for exsanguination, blood specimen collection, and continuous monitoring of cardiac output (CO) and stroke volume (SV) using a Vigileo hemodynamic monitor (Edwards Lifesciences, Irvine, CA, USA). The swine's body temperature was maintained at ≥ 36 °C using an under-body circulating water blanket (Gaymar Industries, Orchard Park, NY, USA) and a forced air warming system (3M Inc., St. Paul, MN, USA).

*2.5 Experimental Procedures*

After a 15-minute stabilization period, we created a Class III hemorrhage by exsanguinating 35% of each swine's estimated blood volume by using controlled suction of the femoral artery catheter. Blood volume was calculated using a factor of 70 mL/kg of body weight. For example, a 70 kg swine has a blood of 4900 mL and 35% represented 1715 mL. We used a Thermal Industries of Florida electronic scale (Thermal Industries of Florida, Owatonna, MN, USA) to measure the amount of exsanguinated blood. The scale was zeroed according to the manufacturer's instructions with a collection canister in place. The scale is accurate and precise within 0.5%. Suction was applied and regulated toexsanguinate approximately 100 mL of blood per minute.

Following exsanguination, we used a method we developed that ran an electric current that was passed through the swine's heart to induce cardiac arrest (Burgert, Johnson, Garcia-Blanco, Craig, & O'Sullivan, 2015). Anesthesia was discontinued, and after two minutes of arrest without intervention, we used the Mechanical Compression Device, Model 1008 (Michigan Instruments, Grand Rapids, MI, USA) and administered mechanical chest compressions at 100 compressions per minute. Mechanical ventilations were delivered at a rate of 8 to 10 per minute (1 breath every 5-6 seconds). These procedures were consistent with AHA guidelines (Link et al., 2015; Neumar et al., 2015; Perkins et al., 2015; Soar et al., 2015). Chest compressions quality was confirmed by observing the arterial pressure and capnographic waveforms. The rationale for two minutes of arrest without intervention was to replicate the minimum amount of time to start cardiopulmonary resuscitation (CPR) in a real scenario.

After four minutes of cardiac arrest, we disconnected the anesthesia circuit from the ET. We then lifted the swine's head 45 degrees and administered 0.1 mg/kg (1 mg/mL) for each of the pediatric subjects and 2 mg of epinephrine for each of the adult subjects. The epinephrine was diluted in 8 mL 0.9% normal saline. Following administration of epinephrine, we administered four tidal volume breaths

administered using a bag valve ventilation device followed by lowering of the swine's head and reconnecting the anesthesia circuit to the ET. After administration of epinephrine, we collected blood samples (10 mL) at 30, 60, 90, 120, 150, 180, 240, and 300 seconds from the left femoral arterial line. Prior to collecting each sample, we aspirated and discarded 8 mL of blood to avoid any residual epinephrine in the tubing from the previous time. We then collected the sample and irrigated the arterial line with 10 mL of saline to clear the line and maintain patency. Using the AHA Guidelines, we defibrillated every two minutes starting at three minutes after and repeated epinephrine administration every four minutes until ROSC (de Caen et al., 2015a, 2015b).

After 15 minutes, the exsanguinated blood was administered. The rationale for 15 minutes was this would be the approximate time to type and cross and acquire the blood for transfusion. The study was terminated if ROSC was not achieved in thirty minutes and continued for thirty minutes for subjects that achieved ROSC

*2.6 Sample Analyses*

The samples were placed in lithium heparin collection tubes after each collection and centrifuged immediately (Thermo Fisher Scientific, Waltham, MA, USA). The samples were immediately frozen to a temperature of –80 °C in a laboratory freezer. Once all the data were collected, we thawed the samples. A technician who was blinded to group assignment analyzed the data using High-Performance Liquid Chromatography with Tandem Mass Spectrometry, the industry standard for determining concentration of drugs in the serum.

*2.7 Sample Size Estimation*

The investigators used data from similar, previous studies and calculated a large effect size of 0.6 (Adams, Blouin, & Johnson, 2016; Fulkerson et al., 2016; Johnson et al., 2015; Johnson et al., 2016; Loughren et al., 2014; Wong et al., 2016). Using an $\alpha$ of 0.05, an effect size of 0.6, and a power of .80, we determined a sample size of 14 (N = 7 per group) was needed. Power analysis was performed using G*Power 3.1 for Windows (Heinrich Heine University, Dusseldorf, Germany).

*2.8 Statistical Analyses*

The SPSS Statistics Software package, version 22 (IBM, Armonk, NY, USA) was used for data analysis. Means, standard deviations (SD), and standard error of the means (SEM) were calculated for the groups receiving epinephrine. Significance was indicated by a p value $< 0.05$. A Multivariate Analysis of Variance (MANOVA) was used to determine if there were significant differences between the groups relative to the pretest data, AUC, and time to ROSC. A Chi-Square Test was used to determine if there were differences in the rate of ROSC between the Pediatric ET and Adult ET groups. The odds of ROSC for each group were compared using MedCalc for Windows, version 17.9 (MedCalc Software, Ostend, Belgium).

## 3. Results

All swine enrolled in the study completed the experiment. However, detectable plasma epinephrine levels were found in only two of seven Adult ET group. There were no significant differences in pretest data by group in either pediatric and adult groups (weight, amount of hemorrhage, HR, SBP, DBP, MAP, CO, SV, and temperature) indicating the groups were equivalent on these variables ($p > 0.05$). There were large differences in AUC between the Pediatric ET and Adult ET groups); however, there was no statistical differences ($p = .199$) (See Figure 1). The reasons there was no statistically significant difference was because of the number of detectable plasma levels and the large variability particularly in the Adult ET group. ROSC occurred in 6 out of 7 and 2 out of 7 in the Pediatric ET and Adult ET groups respectively. Chi -Squared test indicated that the Pediatric ET group had a significant higher rate of ROSC compared to the Adult ET group ($p = 0.031$) (See Figure 2). A MANOVA indicated significantly shorter mean times to ROSC in the Pediatric ET group compared to the Adult ET group ($p = 0.01$) (See Figure 3). The Pediatric ET group had a 15 times greater odds of achieving ROSC compared to the Adult ET group.

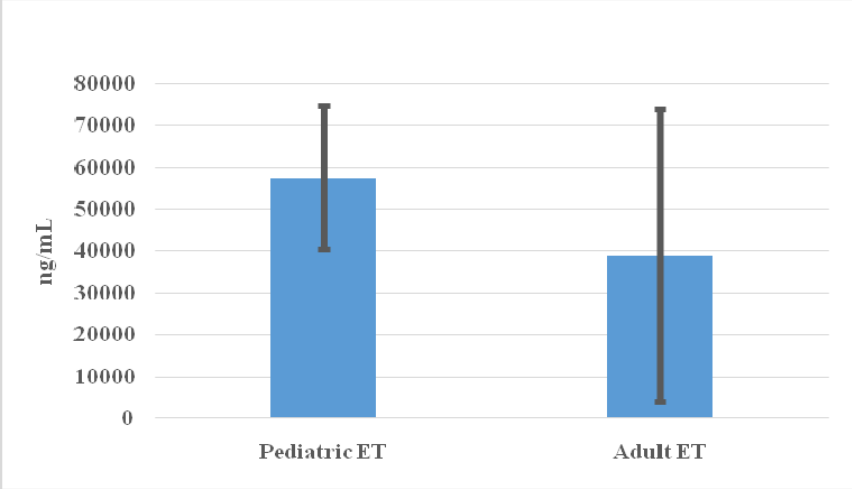


**Figure 1. AUC ± SEM by Group**

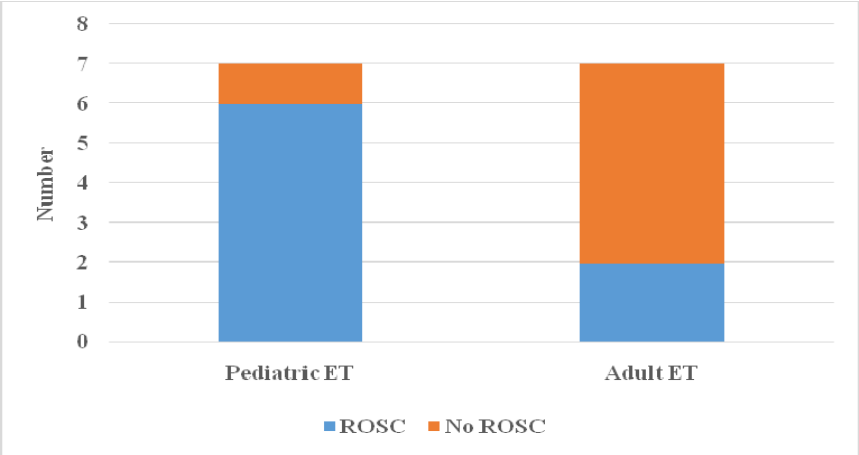


**Figure 2. Rate of ROSC by Group**

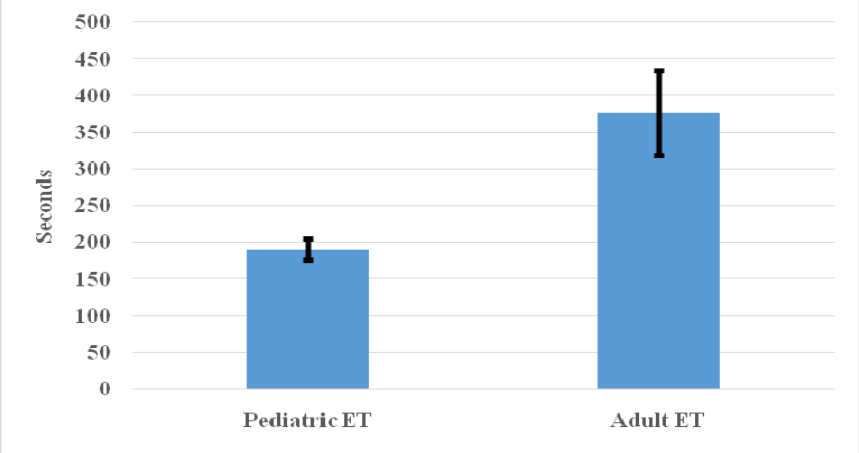


**Figure 3. Comparison of Mean Times ± SEM to ROSC**

## 4. Discussion

*4.1 Summary of Results*

The purpose of this study was to compare the AUC, rate, time to, and odds of achieving ROSC in the Pediatric ET and Adult ET groups of hypovolemic cardiac arrest. There were no statistically significant differences in AUC but large differences that may have translated to the greater odds of ROSC in the Pediatric ET group compared to the Adult ET group. The Pediatric ET group had significant higher rate of ROSC and a shorter time to ROSC compared to the Adult ET group. The Pediatric Group had 15 times greater odds of achieving ROSC compared to the Adult ET group.

*4.2 Comparison of Previous Studies*

Our study expands an early study by Orlowski et al., who found significant differences with ET verses IV epinephrine in hypovolemic adult models. This study expanded their research with pediatric models with the addition of investigating AUC and using the recommended epinephrine dosages (Orlowski, Gallagher, et al., 1990). Our study supports the findings of Burgert et al. and Orlowski et al. in that the

absorption of epinephrine was highly variable and unreliable in the adult (Burgert et al., 2019; Orlowski, Gallagher, et al., 1990; Orlowski, Porembka, et al., 1990). Our study expanded on their findings with the addition of a pediatric group. We support the findings of Lin et al. who used a retrospective analyses of both normovolemic and hypovolemic individuals aged 19 and younger. They found greater rates of ROSC with early administration epinephrine in both a normovolemic and hypovolemic (Lin et al., 2019). The difference in our study was that we used prospective, rigorously-design of pediatric swine ranging in age from an equivalent five to six years of age, whereas they used a retrospective design with individuals 19 years or younger (Lin et al., 2019). Our study also supports the findings of Manisterski et al. who studied the efficacy of epinephrine in the ET route during cardiopulmonary resuscitation. However, while their study found significance with 0.3mg/kg, our study used 0.1mg/kg, which is current AHA guidelines. They observed vital sign changes but did not investigate the occurrence of ROSC (Manisterski et al., 2002). Our study supports the findings of Hansen et al. who found that faster epinephrine delivery in an arrest situation the greater the odds of achieving ROSC. This study expanded Hansen's research in that we examined AUC of epinephrine and narrowed the age from five to six years of age whereas he investigated individuals <18 years of age (Hansen et al., 2018).

*4.3 Speculated Reasons for Differences*

We speculate that the reason we found a higher rate and odds of achieving ROSC in the Pediatric ET group was the dosage differences between adult and pediatric models. In the child, we administered 0.1 mg/Kg compared to 2 mg in the adult which translated to approximately 0.02 mg/Kg in an average sized male. The higher dose for the Pediatric ET group resulted in higher AUC levels and subsequent higher rates, faster time and greater odds of ROSC compared to the Adult ET group. Our findings support that of Niemann, et al. who found that doubling the dose of ET epinephrine administration for the adult does not increase the rate of ROSC (Niemann & Stratton, 2000; Niemann, Stratton, Cruz, & Lewis, 2002). Our study also supports Wagner et al. who found that higher dosages for ET administration of epinephrine was required compared to vascular access (Wagner et al., 2018).

## 5. Limitations

The greatest limitation of our study was the small sample size; however, we had enough power to find a difference in rate, time to ROSC and odds of ROSC between the Pediatric ET and Adult ET groups. Although the Pediatric ET group had larger AUC compared to the Adult ET group, the results were not statistically significant. With a larger sample size, we probably would have had enough power to find a statistical significance. Another limitation was that the investigators were not blinded, but the individual who performed the HPLC analyses was. Although the investigators were not blinded, we rigorously adhered to the protocol. Another limitation is that the findings may not be generalizable to humans, but the cardiovascular and pulmonary physiology are very similar to humans and are considered an excellent model for this type of research (Hannon et al., 1990; Swindle et al., 2012). Another potential limitation was the study continued for only 30 minutes after ROSC. Dumas et al. and Lin et al. found negative

effects of epinephrine in long-term neurological survivability (Dumas et al., 2014; Lin et al., 2019). Future studies need to expand the time after ROSC to determine the long-term effects.

## 6. Conclusion

Based on the findings of this study, we recommend the use of the ET route administration of epinephrine for hypovolemic pediatric patients who are in cardiac arrest. With each minute delay of epinephrine delivery, there is a 9% decrease in survivability (Hansen et al., 2018). Studies show that it may take as much as 49 minutes to start an IV. Leidel et al. found IV failure rates were from 10 to 40% in patients not in arrest and that the average time for obtain IV access was 2.5 to 16 minutes and in extreme cases as long as 55 minutes in critically ill patients who were not in arrest (Leidel et al., 2009). Hence, the ET route should be considered as a first choice for a pediatric patient: ET intubation can be placed in less than 30 seconds by an experienced provider (White et al., 2012). We do not recommend the use of the ET route administration of epinephrine in the adult. Only two out of seven subjects had detectable epinephrine levels and only two achieved ROSC.

## References

Adams, T. S., Blouin, D., & Johnson, D. (2016). Effects of tibial and humerus intraosseous and intravenous vasopressin in porcine cardiac arrest model. *Am J. Disaster Med*, *11*(3), 211-218. https://doi.org/10.5055/ajdm.2016.0241

Andersen, L. W. et al. (2015). Time to Epinephrine and Survival After Pediatric In-Hospital Cardiac Arrest. *JAMA, 314*(8), 802-810. https://doi.org/10.1001/jama.2015.9678

Burgert, J. M., Johnson, A. D., Garcia-Blanco, J. C., Craig, W. J., & O'Sullivan, J. C. (2015). An Effective and Reproducible Model of Ventricular Fibrillation in Crossbred Yorkshire Swine (Sus scrofa) for Use in Physiologic Research. *Comp Med*, *65*(5), 444-447.

Burgert, J. M., Johnson, A. D., O'Sullivan, J. C., Blalock, W. J., Duffield, B. C., Albright, B. P., … Rauch, J. W. (2019). Pharmacokinetic effects of endotracheal, intraosseous, and intravenous epinephrine in a swine model of traumatic cardiac arrest. *Am J. Emerg Med*. https://doi.org/10.1016/j.ajem.2019.02.035

de Caen, A. R., Berg, M. D., Chameides, L., Gooden, C. K., Hickey, R. W., Scott, H. F., … Samson, R. A. (2015a). Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation, 132*(18 Suppl 2), S526-542. https://doi.org/10.1161/CIR.0000000000000266

de Caen, A. R., Berg, M. D., Chameides, L., Gooden, C. K., Hickey, R. W., Scott, H. F., … Samson, R. A. (2015b). Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Reprint). *Pediatrics, 136 Suppl 2*, S176-195. https://doi.org/10.1542/peds.2015-3373F

Donnino, M. W. et al. (2014). Time to administration of epinephrine and outcome after in-hospital

cardiac arrest with non-shockable rhythms: Retrospective analysis of large in-hospital data registry. *BMJ*, *348*, g3028. https://doi.org/10.1136/bmj.g3028

Dowling, M. B., Chaturvedi, A., MacIntire, I. C., Javvaji, V., Gustin, J., Raghavan, S. R., … Narayan, M. (2016). Determination of efficacy of a novel alginate dressing in a lethal arterial injury model in swine. *Injury*, *47*(10), 2105-2109. https://doi.org/10.1016/j.injury.2016.05.003

Dumas, F., Bougouin, W., Geri, G., Lamhaut, L., Bougle, A., Daviaud, F., … Cariou, A. (2014). Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *J. Am Coll Cardiol*, *64*(22), 2360-2367. https://doi.org/10.1016/j.jacc.2014.09.036

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *J. Trauma Acute Care Surg*, *73*(6 Suppl 5), S431-437. https://doi.org/10.1097/TA.0b013e3182755dcc

Fulkerson, J., Lowe, R., Anderson, T., Moore, H., Craig, W., & Johnson, D. (2016). Effects of Intraosseous Tibial vs. Intravenous Vasopressin in a Hypovolemic Cardiac Arrest Model. *West J. Emerg Med*, *17*(2), 222-228. https://doi.org/10.5811/westjem.2015.12.28825

Gordon, C. B. C., Bradtmiller, B., Parham, J., Barrientos, P., & Paquette, S. (2015). Anthropoetric survey of US Army personnel: Methods and summary statistics. *US Army Natick Soldier Research*, 225-226.

Gordon, C., Blackwell, C., Bradtmiller, B., Parham, J., Barrientos, P., Paquette, S., … Kristensen, S. (2015). *Anthropometric Survey of US Army Personnel: Methods and Summary Statistics*. Natick, MA.: US Army Natick Soldier Research, Development and Engineering Center.

Hannon, J. P., Bossone, C. A., & Wade, C. E. (1990). Normal physiological values for conscious pigs used in biomedical research. *Laboratory animal science*, *40*(3), 293.

Hansen, M. et al. (2018). Time to Epinephrine Administration and Survival From Nonshockable Out-of-Hospital Cardiac Arrest Among Children and Adults. *Circulation*, *137*(19), 2032-2040. https://doi.org/10.1161/CIRCULATIONAHA.117.033067

Johnson, D., Garcia-Blanco, J., Burgert, J., Fulton, L., Kadilak, P., Perry, K., & Burke, J. (2015). Effects of humeral intraosseous versus intravenous epinephrine on pharmacokinetics and return of spontaneous circulation in a porcine cardiac arrest model: A randomized control trial. *Ann Med Surg (Lond), 4*(3), 306-310. https://doi.org/10.1016/j.amsu.2015.08.005

Johnson, D., Giles, K., Acuna, A., Saenz, C., Bentley, M., & Budinich, C. (2016). Effects of tibial intraosseous and IV administration of vasopressin on kinetics and survivability in cardiac arrest. *Am J. Emerg Med*, *34*(3), 429-432. https://doi.org/10.1016/j.ajem.2015.11.027

Kauvar, D. S., Dubick, M. A., Walters, T. J., & Kragh, J. F., Jr. (2018). Systematic review of prehospital tourniquet use in civilian limb trauma. *J. Trauma Acute Care Surg*, *84*(5), 819-825. https://doi.org/10.1097/TA.0000000000001826

Kauvar, D. S., Miller, D., & Walters, T. J. (2018). Tourniquet use is not associated with limb loss

following military lower extremity arterial trauma. *J. Trauma Acute Care Surg*, *85*(3), 495-499. https://doi.org/10.1097/TA.0000000000002016

Kelly, J. F., Ritenour, A. E., McLaughlin, D. F., Bagg, K. A., Apodaca, A. N., Mallak, C. T., … Holcomb, J. B. (2008). Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J. Trauma*, *64*(2 Suppl), S21-26; discussion S26-27. https://doi.org/10.1097/TA.0b013e318160b9fb

Khera, R. et al. (2016). Hospital Variation in Time to Epinephrine for Nonshockable In-Hospital Cardiac Arrest. *Circulation*, *134*(25), 2105-2114. https://doi.org/10.1161/CIRCULATIONAHA.116.025459

Leidel, B. A., Kirchhoff, C., Bogner, V., Stegmaier, J., Mutschler, W., Kanz, K. G., & Braunstein, V. (2009). Is the intraosseous access route fast and efficacious compared to conventional central venous catheterization in adult patients under resuscitation in the emergency department? A prospective observational pilot study. *Patient Saf Surg*, *3*(1), 24. https://doi.org/10.1186/1754-9493-3-24

Lin, Y. R., Wu, M. H., Chen, T. Y., Syue, Y. J., Yang, M. C., Lee, T. H., … Li, C. J. (2019). Time to epinephrine treatment is associated with the risk of mortality in children who achieve sustained ROSC after traumatic out-of-hospital cardiac arrest. *Crit Care*, *23*(1), 101. https://doi.org/10.1186/s13054-019-2391-z

Link, M. S., Berkow, L. C., Kudenchuk, P. J., Halperin, H. R., Hess, E. P., Moitra, V. K., … Donnino, M. W. (2015). Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, *132*(18 Suppl 2), S444-464. https://doi.org/10.1161/CIR.0000000000000261

Loughren, M. J., Kilbourn, J., Worth, K., Burgert, J., Gegel, B., & Johnson, D. (2014). Comparison of muscle paralysis after intravenous and intraosseous administration of succinylcholine in Swine. *J. Spec Oper Med*, *14*(2), 35-37.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., … Memish, Z. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, *380*(9859), 2095-2128.

Manisterski, Y., Vaknin, Z., Ben-Abraham, R., Efrati, O., Lotan, D., Berkovitch, M., … Paret, G. (2002). Endotracheal epinephrine: A call for larger doses. *Anesth Analg*, *95*(4), 1037-1041. https://doi.org/10.1097/00000539-200210000-00045

National Research Council, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, & Institute for Laboratory Animal Research. (2011). *Guide for the care and use of laboratory animals*. Washington, D.C.: National Academies Press.

Neumar, R. W., Shuster, M., Callaway, C. W., Gent, L. M., Atkins, D. L., Bhanji, F., … Hazinski, M. F. (2015). Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for

Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, *132*(18 Suppl 2), S315-367. https://doi.org/10.1161/CIR.0000000000000252

Niemann, J. T., & Stratton, S. J. (2000). Endotracheal versus intravenous epinephrine and atropine in out-of-hospital "primary" and postcountershock asystole. *Crit Care Med*, *28*(6), 1815-1819. https://doi.org/10.1097/00003246-200006000-00022

Niemann, J. T., Stratton, S. J., Cruz, B., & Lewis, R. J. (2002). Endotracheal drug administration during out-of-hospital resuscitation: Where are the survivors? *Resuscitation*, *53*(2), 153-157. https://doi.org/10.1016/S0300-9572(02)00004-7

Orlowski, J. P., Gallagher, J. M., & Porembka, D. T. (1990). Endotracheal epinephrine is unreliable. *Resuscitation*, *19*(2), 103-113. https://doi.org/10.1016/0300-9572(90)90033-B

Orlowski, J. P., Porembka, D. T., Gallagher, J. M., Lockrem, J. D., & VanLente, F. (1990). Comparison study of intraosseous, central intravenous, and peripheral intravenous infusions of emergency drugs. *Am J. Dis Child*, *144*(1), 112-117. https://doi.org/10.1001/archpedi.1990.02150250124049

Perkins, G. D. et al. (2015). European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. *Resuscitation*, *95*, 81-99. https://doi.org/10.1016/j.resuscitation.2015.07.015

Schauer, S. G., April, M. D., Naylor, J. F., Maddry, J. K., Arana, A. A., Dubick, M. A., … Pusateri, A. E. (2018). Prehospital Application of Hemostatic Agents in Iraq and Afghanistan. *Prehosp Emerg Care*, *22*(5), 614-623. https://doi.org/10.1080/10903127.2017.1423140

Schauer, S. G., Naylor, J. F., April, M. D., Fisher, A. D., Cunningham, C. W., Fernandez, J. R. D., … Bebarta, V. S. (2018). Prehospital Resuscitation Performed on Hypotensive Trauma Patients in Afghanistan: The Prehospital Trauma Registry Experience. *Mil Med*. https://doi.org/10.1093/milmed/usy252

Soar, J. et al. (2015). Part 4: Advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*, *95*, e71-120. https://doi.org/10.1016/j.resuscitation.2015.07.042

Swindle, M. M., Makin, A., Herron, A. J., Clubb, F. J., & Frazier, K. S. (2012). Swine as models in biomedical research and toxicology testing. *Veterinary pathology*, *49*(2), 344. https://doi.org/10.1177/0300985811402846

Wagner, M., Olischar, M., O'Reilly, M., Goeral, K., Berger, A., Cheung, P. Y., & Schmolzer, G. M. (2018). Review of Routes to Administer Medication During Prolonged Neonatal Resuscitation. *Pediatr Crit Care Med*, *19*(4), 332-338. https://doi.org/10.1097/PCC.0000000000001493

White, M. C., Marsh, C. J., Beringer, R. M., Nolan, J. A., Choi, A. Y., Medlock, K. E., & Mason, D. G. (2012). A randomised, controlled trial comparing the Airtraq optical laryngoscope with conventional laryngoscopy in infants and children. *Anaesthesia*, *67*(3), 226-231. https://doi.org/10.1111/j.1365-2044.2011.06978.x

Wong, M. R., Reggio, M. J., Morocho, F. R., Holloway, M. M., Garcia-Blanco, J. C., Jenkins, C., &

Johnson, A. D. (2016). Effects of intraosseous epinephrine in a cardiac arrest swine model. *J. Surg Res*, *201*(2), 327-333. https://doi.org/10.1016/j.jss.2015.11.015

Zuercher, M., Kern, K. B., Indik, J. H., Loedl, M., Hilwig, R. W., Ummenhofer, W., … Ewy, G. A. (2011). Epinephrine improves 24-hour survival in a swine model of prolonged ventricular fibrillation demonstrating that early intraosseous is superior to delayed intravenous administration. *Anesth Analg*, *112*(4), 884-890. https://doi.org/10.1213/ANE.0b013e31820dc9ec