TITLE:
The Effect of Chest Compression Location and Aortic Perfusion in a Traumatic Arrest Model

SHORT TITLE:
Chest Compression Location and SAAP

AUTHOR NAMES AND AFFILIATIONS:

Benjamin J. Barringer, MD[a]
Email: benjamin.j.barringer.mil@mail.mil

Maria G. Castaneda, MS[b]
Email: maria.g.castaneda7.ctr@mail.mil

Jason Rall, PhD[b]
Email: jason.m.rall.ctr@mail.mil

Joseph K. Maddry, MD[c]
Email: joseph.k.maddry.mil@mail.mil

Kenton L. Anderson, MD[d]
Email: kentona@stanford.edu

a. Joint Base Elmendorf-Richardson
Department of Emergency Medicine
5955 Zeamer Ave
Elmendorf AFB, AK 99506

b. CREST Research Program
Wilford Hall Ambulatory Surgical Center
2200 Bergquist Dr.
Lackland AFB, TX 78236

c. United States Air Force En-route Care Research Center
United States Army Institute of Surgical Research/59th MDW/ST
3698 Chambers Road
San Antonio, TX 78234

d. Stanford University School of Medicine
Department of Emergency Medicine
900 Welch Road, Ste 350
Palo Alto, CA 94304

CORRESPONDING AUTHOR:
Kenton L. Anderson, MD
Stanford University School of Medicine
Department of Emergency Medicine
900 Welch Road, Ste 350
Palo Alto, CA 94304
Fax: 650-723-0121
Tel: 650-723-0063
Email: kentona@stanford.edu

DECLARATIONS:
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DISCLAIMERS:

The views expressed are those of the author(s) and do not reflect the official views or policy of the Department of Defense or its components.

The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended.

ABSTRACT

Background: Recent evidence demonstrates that closed chest compressions directly over the left ventricle (LV) in a traumatic cardiac arrest (TCA) model improve hemodynamics and return of spontaneous circulation (ROSC) when compared to traditional compressions. Selective aortic arch perfusion (SAAP) also improves hemodynamics and controls hemorrhage in TCA. We hypothesized that chest compressions located over the LV would result in improved hemodynamics and ROSC in a swine model of TCA using SAAP.

Materials and Methods: Transthoracic echo was used to mark the location of the aortic root (Traditional location) and the center of the LV on animals (n=24) which were randomized to receive chest compressions in one of the two locations. After hemorrhage, ventricular fibrillation (VF) was induced to simulate TCA. After a period of ten minutes of VF, basic life support (BLS) with mechanical CPR was initiated and performed for ten minutes followed by advanced life support (ALS) for an additional ten minutes. SAAP balloons were inflated at minute 6 of BLS. Hemodynamic variables were averaged over the final two minutes of the BLS and ALS periods. Survival was compared between this SAAP cohort and a control group without SAAP (No-SAAP) (n=26).

Results: There was no significant difference in ROSC between the two SAAP groups (p=0.67). There was no ROSC difference between SAAP and No-SAAP (p=0.74).

Conclusions: There was no difference in ROSC between LV and Traditional compressions when SAAP was used in this swine model of TCA. SAAP did not confer a survival benefit compared to historic controls.

Keywords: Cardiopulmonary resuscitation; Trauma; Balloon Occlusion; Hemodynamics; Survival; Echocardiography

INTRODUCTION

Resuscitation of traumatic cardiopulmonary arrest (TCA) patients in the prehospital setting remains challenging and controversial. In the United States trauma is the leading cause of death for those less than 45 years of age, and subsequently the overall leading cause of life-years lost (1). Hemorrhage is the cause of up to 40% of those traumatic deaths (2-4). Non-compressible hemorrhage (NCH) poses an especially difficult management challenge; recent evidence demonstrates a mortality of up to 86% among patients with NCH - 88% of those died in the prehospital setting (5). In recent years, survival rates among TCA patients have increased despite a disregard for guidelines that recommend withholding cardiopulmonary resuscitation (CPR) (6-9). These improved survival rates are a result of traditional resuscitation techniques and do not take into consideration newer interventions such as resuscitative endovascular balloon occlusion of the aorta (REBOA) or selective aortic arch perfusion (SAAP). Older observational studies of TCA have reported survival rates lower than 3.7%, which led some authors to suggest that TCA resuscitation was futile (6-9). However, for reasons that are still unclear, more recent reports describe improved survival rates on par with non-traumatic cardiac arrest (NTCA); some of these reports suggest that earlier intervention may improve outcomes (10-15).

The use of traditional closed chest compressions in the resuscitation of TCA patients remains particularly debated since they only proved a small fraction of the cardiac output generated by open chest compressions, the additional forward blood flow they do provide may not confer any survival benefit, and they may cause additional traumatic injury (16, 17). For these reasons, resuscitative thoracotomy has traditionally served as the primary method for controlling NCH and increasing cardiac output via direct cardiac massage. Fortunately, there have been recent advancements that may allow improved TCA management, even in the prehospital setting, with less invasive techniques. Recent animal studies have demonstrated that chest compressions performed directly over the left ventricle (LV) improve hemodynamics and return of spontaneous circulation (ROSC) when compared to traditional compressions in both NTCA and TCA models – this method may be the closest approximation to open cardiac massage

that can be achieved without performing a thoracotomy (18,19). Additionally, REBOA has also been used in both NTCA and TCA to improve perfusion pressures and survival outcomes in both animal and human studies (20-25). SAAP is currently an experimental technique similar to REBOA in that it utilizes an endovascular balloon catheter to provide aortic occlusion, but SAAP catheters have a distal port that allows direct intra-aortic infusion of fluid and medications cephalad to the level of the occlusive balloon (Figure 1). One recent animal study demonstrated higher survival rates when comparing the use of SAAP to REBOA in the management of TCA (24). It is possible that improvements in ROSC and hemodynamics are additive when LV chest compressions and SAAP are combined during TCA.

We hypothesized that chest compressions located directly over the left ventricle (LV) would increase ROSC when compared with traditional compressions in a swine model of TCPA where SAAP was used in the resuscitation of all animals. Secondary analyses included an evaluation of short-term survival to 60 minutes, and hemodynamic and laboratory variables. We also conducted a secondary analysis comparing ROSC between this SAAP cohort and a historical TCA control cohort where resuscitation was performed without SAAP (No-SAAP).

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective, randomized blinded comparative investigation. This study was approved by the Institutional Animal Care and Use Committee for the U.S. Air Force 59th Medical Wing Clinical Investigation and Research Support (Lackland Air Force Base, TX). This facility animal care and use program is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Reporting adheres to the Animals in Research Reporting In Vivo Experiments (ARRIVE) guidelines (26). This study builds on prior NTCA and TCA models, and the methods used in this study are identical to a prior TCA model except for the use of SAAP (18, 19).

Animal Preparation

Twenty-four female Yorkshire swine weighing 25 kg to 32 kg were obtained 5 to 7 days before experimentation to allow acclimation to the facility. The animals were free from viral, bacterial, and parasitic pathogens as per the local vendor.

Pre-intervention animal care follows the protocol previously described (18,19). Animals were housed individually in 4x6foot cages with rubberized textured flooring in a temperature and humidity-controlled building with a 12-hour light/dark cycle set on a timer. Animals were allowed free access to water and were provided a maintenance diet (PMI Nutrition International, LLC, Brentweed, MO). Within 48 hours of arrival to the facility a physical exam of each animal was performed to evaluate for lesions and to ensure normal heart and lung sounds. Complete blood cell count and blood chemistry analysis were also performed. No pretreatment with any medications was performed.

All experiments were initiated during the morning hours. Animals were initially sedated with 20 mg/kg intramuscular ketamine; general anesthesia was subsequently induced with isoflurane (3-4.5%),mechanical ventilation initiated (Fabius GS; Draeger-Siemens, New York, NY) with a mixture of 60% oxygen and maintained on isoflurane (1–2.5%) with a tidal volume of 10 mL/kg at a respiratory rate of 12 minutes. End-tidal CO2 (ETCO2) was monitored by in-line waveform capnography, and the respiratory rate was adjusted to maintain an ETCO2 between 38 mm Hg and 42 mm Hg before induction of cardiac arrest. Continuous cardiac rhythm and heart rate were monitored by electrocardiography using standard limb leads. Peripheral capillary pulse oximetry (SpO2) was also monitored continuously. The anesthesia used in this experiment is standard for swine models. All other drugs, routes of administration, and timing of administration are those outlined in CPR guidelines (27, 28). Standard weight-based doses were used.

Interventions

Pre-experimental interventions follow the protocol previously described (18, 19). High fidelity, solid state micromanometer-tipped pressure transducers (Millar MPC-500; Millar Inc., Houston, TX) were

advanced through right internal jugular vein and right femoral artery into thoracic locations to measure continuous aortic and right atrial pressures respectively. A 9Fr SAAP catheter was advanced through the left femoral artery to Zone 1 of the descending thoracic aorta, just proximal to the diaphragm (Resusitech Inc., Menlo Park, CA). Fluoroscopy was used to position all catheters (Model Siremobile 2U C-arm, Siemens, Inc., Danvers, MA). Unfractionated heparin (100 μ/kg) was provided to prevent catheter clotting. Near infrared spectroscopy sensors were adhered to the scalp and the right flank to continuously monitor and record cerebral and renal regional oximetry (rSO2) respectively (INOVS 5100C Cerebral/Somatic Oximeter; Covidien, Minneapolis, MN). Once all catheters and sensors were in place, the animals were allowed to acclimate for 10 minutes, and each animal received a bolus of 15 mL/kg of 0.9% saline intravenously to replace overnight fasting fluid deficits.

Animals were placed in a v-shaped trough to eliminate lateral movements during chest compressions. At the onset of the 10-minute acclimatization period inhaled oxygen was decreased to 21%. During the 10-minute acclimatization period, transthoracic echocardiography (z.one ultra sp; Zonare Medical Systems, Inc., Mountain View, CA) was used to locate the aortic root (AR) and the center of the LV in two orthogonal planes (the parasternal long axis and parasternal short axis). The animals' skin was marked in the midsternum at the level of the AR to represent the traditional compression location and at the center of the LV to represent the LV compression location. A multiplane transesophageal (TEE) transducer (P8-3TEE; Zonare Medical Systems, Inc., Mountain View, CA) was used to obtain a midesophageal long axis (ME LAX) view of the heart. The TEE transducer was left in place for recording the area of maximal compression (AMC) during compressions.

Experimental Protocol

The experimental protocol was developed and used in prior work (19). Animals were randomly allocated to LV or Traditional chest compression groups. Allocation was performed using a commonly employed computer-generated randomization program (http://www.randomization.com) and blinding was employed by sealed envelope. Randomization was performed for all animals prior to the beginning of the study and the results for each animal were kept sealed until ventricular fibrillation (VF) had been induced. A graphic display of the general protocol is presented in Figure 2a, and a more detailed outline of the advanced life support (ALS) portion of the protocol is presented in Figure 2b.

During the hemorrhage period, 30% of each animals' blood volume was removed over a 20-minute period, as previously described, at a rate of 1.42 ml/kg/min for the first 7 minutes followed by a rate of 0.76 ml/kg/min over the remaining 13 minutes as previously described (19,29-31). Blood was removed from the carotid arterial line via aspiration with peristaltic pump and saved in a blood collection system containing citrate-phosphate-dextrose with Optisol red blood cell preservative solution (Terumo Corp., Tokyo, Japan). The collected blood was then placed in a blood warmer for subsequent experimental transfusion to the same animal.

Ventricular fibrillation (VF) was induced five minutes after the completion of hemorrhage to simulate TCA. VF was induced with a 3second 60Hz 100mA electric current delivered across the thorax (Model 1745A Power Supply; B&K Precision Corporation, Yorba Linda, CA) as previously described (32,33). VF was confirmed by ECG, the sudden loss of arterial pulsations, and an abrupt reduction of the systolic blood pressure to less than 25mmHg. The induction of cardiac arrest represented time zero during the experiment; mechanical ventilation and anesthesia were simultaneously discontinued at time zero. All animals remained in VF arrest without any intervention for a period of 10 minutes (Non-intervention period) as previously described (19). During the 10-minute Non-intervention period, the allocation to either the Traditional or LV compression groups was unblinded, and the center of the piston on the automatic mechanical compression device (AMCD) (Thumper 407CC; Michigan Instruments, Grand Rapids, MI) was lowered into place over the corresponding skin marking. Defibrillation pads were placed over the right and

left lateral chest and connected to a biphasic electronic defibrillator/monitor (Lifepak 20; Physio Control Inc., Redmond, WA).

Basic Life Support

After 10 minutes of cardiac arrest, basic life support (BLS), was initiated using the AMCD over the allocated position as previously described (19); compressions were delivered at a rate of 100 min^{-1}, at a depth of 5 cm, with a 50% duty cycle and a compression-ventilation ratio of 30:2. Compressions were briefly interrupted every 2 minutes to perform a rhythm analysis that lasted 2-5 seconds. During BLS, a 10-second video clip of the ME LAX view was saved for future review. A 10-minute interval of BLS without defibrillation was used as a practical approach because this duration of CPR is necessary to adequately compare CPR techniques (33). At 6 minutes into BLS (16 minutes of cardiac arrest) the SAAP balloon was inflated with 10mL of normal saline; this period of time was chosen to simulate the amount of time required to insert and inflate the balloon and to allow adequate time to compare CPR techniques before the other advanced life support interventions were initiated as outlined below.

Advanced Life Support

After 10 minutes of BLS, ALS was initiated, as previously described, with a 125-J (approximately 4 J/kg) biphasic waveform defibrillation attempt, resumption of mechanical ventilation with 100% oxygen, continuous compressions at the same rate and depth, and bolus transfusion of 500 mL of whole blood (WB) under 250 mm Hg of pressure (Fig. 2b) via the SAAP catheter. We elected to transfuse WB since WB is the resuscitation fluid that plasma, packed red blood cells, and platelets in a 1:1:1 ratio attempt to simulate, and fresh WB may be administered in tactical field care or elsewhere in combat theater when other blood products are not available or not effective (34,35). Although prior SAAP models have used pre-oxygenated blood, in this model the blood was not oxygenated prior to infusion to simulate blood products that are currently available in the clinical and prehospital settings and to determine if administering volume with

oxygen carrying capacity would have a benefit. Every two minutes compressions were interrupted for a rhythm analysis that lasted 2-5 seconds. If the rhythm was VF or VT, another 125J defibrillation attempt was provided and compressions were re-initiated. If the animal was in asystole or an organized rhythm, no defibrillation attempt was made and compressions were re-initiated; if an organized rhythm was present at a second consecutive rhythm analysis, compressions were only re-initiated if the animal did not meet criteria for ROSC. At the second and fourth ALS rhythm analyses, epinephrine (0.01mg/kg) followed by a 10mL normal saline flush was administered if the animal had not met criteria for ROSC. During the third and fifth ALS rhythm analyses, amiodarone (5mg/kg) followed by a 10mL normal saline flush was administered if the animal had not met criteria for ROSC and was in a defibrillation-appropriate rhythm (VF or VT).

Return of Spontaneous Circulation and Post-Resuscitation Care

Post-resuscitation care followed the previously described protocol (18, 19). Return of spontaneous circulation was defined as an organized rhythm with a sustained aortic systolic blood pressure greater than 60 mm Hg without any intervention for one minute during a scheduled rhythm check. If ROSC was attained, the animals were supported in a simulated intensive care setting until termination of the protocol at minute 60. After ROSC, mechanical ventilation was provided with the initial ventilator settings and 100% oxygen. Respiratory rate was adjusted to maintain an ETCO2 of 38–42 mmHg. Inhaled isoflurane was administered as necessary.

An epinephrine infusion was started as needed, at a rate of 0.1mcg/kg/min and titrated by 0.1mcg/kg/min every two minutes to a maximum of 2.0mcg/kg/min, to maintain an aortic systolic blood pressure (SBP) greater than 90mmHg. If the SBP rose above 120mmHg the epinephrine was titrated down by 0.1mcg/kg/min every two minutes. An amiodarone infusion (5mg/kg/hr) was started if the animal had received amiodarone during ALS.

Termination of the Protocol

Protocol termination has been described in prior work (18, 19). Animals were considered expired if the aortic SBP was less than 60mm Hg for 10 minutes after minute 30. Expired animals were euthanized with IV sodium pentobarbital (100mg/kg), and mechanical ventilation was terminated. Animals that did attain ROSC were supported until minute 60, to ascertain short-term viability; at this time all life support, including medication infusions and mechanical ventilation, were terminated and the remaining animals were euthanized. The euthanasia of animals for this study was in accordance with the AVMA Guidelines for the Euthanasia of Animals, 2013. No post-operative care was required given that the endpoint was euthanasia at the end of the study procedures..

Measurements

The same measurements used in prior work were also recorded and analyzed for this study (18, 19). Hemodynamic data (aortic systolic (AoS) and diastolic (AoD) blood pressure, right atrial systolic and diastolic blood pressure, SpO2, ETCO2, cerebral and renal regional oximetry) were continuously monitored; the 2-minute intervals at the end of each experimental period (baseline, post-hemorrhage, end of Non-intervention, end of BLS, end of ALS) were averaged and analyzed. Baseline for hemodynamic measurements was defined as the 2-minute interval immediately prior to hemorrhage. Post-hemorrhage was defined as the 2-minute interval immediately prior to time zero. End of non-intervention was defined as the two-minute interval immediately prior to initiation of BLS (systolic and diastolic blood pressures as well as SpO2 were not measurable during the Non-intervention period). Coronary Perfusion Pressure (CPP) was calculated as the difference between the end-diastolic aortic pressure and the simultaneous end-diastolic right atrial pressure.

Arterial blood gas (ABG) specimens were obtained at baseline (immediately prior to hemorrhage), post-hemorrhage (immediately prior to time zero), end of Non-Intervention, end of BLS, and end of ALS during the protocol.

The number of animals that attained ROSC in each group and the number of ROSC animals that

survived to 60 minutes was subsequently recorded. The total amount of epinephrine and amiodarone that each animal received were also recorded.

For the purpose of analyzing the difference in ROSC between this SAAP cohort and the historical No-SAAP control cohort, the number of animals that attained ROSC was recorded in both cohorts (19). Since the exact same animal model was used in both studies, except for the use of SAAP, we treated the comparison of SAAP versus No-SAAP as a single study with a factorial design.

Outcomes

The primary outcome was the difference in ROSC between the two experimental groups. Secondary outcomes included the difference in: 1) short-term, 60-minute survival, 2) hemodynamic variables, and 3) ABG variables between the Traditional and LV groups. In the secondary analysis between SAAP and No-SAAP cohorts, the outcome of interest was the difference in ROSC between cohorts.

Analysis

Means and standard deviations were calculated for measured variables of each treatment group across all time intervals. Shapiro-Wilk tests were used to test for normality. The treatment groups were compared on baseline weight and size, as well as the total amount of amiodarone and epinephrine administered using the nonparametric Wilcoxon/Mann-Whitney test. Differences in rates of survival were analyzed using Fisher's exact test. To control for within-subjects variation (due to repeated measures over time) and between-subjects variation (due to different treatment groups), a two-way repeated measures analysis of variance (ANOVA) was performed for the hemodynamic and ABG variables. The Greenhouse-Geisser correction was used to correct for violations of the assumption of sphericity, and the Bonferroni correction was applied for multiple comparisons. Statistical significance was defined as $p<0.05$, and 95% confidence intervals were provided.

Regarding sample size, based on prior data, 43% of animals were expected to attain ROSC (primary outcome) in the LV compressions and 0% in the Traditional group; at the $\alpha = 5\%$ significance level and with 80% power, a total sample size of 24 animals would be required (12 in each arm).

For comparisons within the SAAP and No-SAAP cohorts, p-values and confidence intervals were calculated using the Fisher Exact test. We assessed for interaction between compression type (LV or Traditional) and SAAP using a difference-in-differences comparison. The LV- Traditional risk differences were compared between the SAAP and No- SAAP cohorts using the Chi-square test. Pooled comparison of SAAP vs. No- SAAP used the Fisher exact test. All reported p-values are 2-sided.

RESULTS

There was no difference in the size of the animals or the baseline hemodynamic and laboratory measures between the Traditional and LV groups ($p>0.05$ for all measures) (Table 1). There was 100% agreement between the AMC by TEE review and location of AMCD placement ($\kappa = 1.0$, 95% CI 1.0-1.0).

The mean total dose of epinephrine was similar between the LV (0.50mg ± 0.17mg SD) and Traditional group (0.46 ± 0.23mg SD) ($p=0.34$). The mean total dose of amiodarone was also similar in the Traditional group (197mg ± 93.7 SD) compared to the LV group (188mg ± 131mg SD) ($p=0.28$).

Return of Spontaneous Circulation and Short-term survival

The number of animals that attained ROSC was not significantly higher in the LV group ($p=0.67$) (Table 2). All eight animals that attained ROSC did so during the ALS period (Traditional group: two at minute 24, and one at minute 30; LV group: one at minute 22, two at minute 26, and two at minute 30). In both groups, there was one animal that achieved ROSC that did not survive to the 60-minute point; the animal in the Traditional group did not maintain a blood pressure that satisfied ROSC criteria, and the LV animal converted back to VF one minute into the post-resuscitation period. A post-hoc sample size analysis determined that with the rates of ROSC demonstrated in Table 2, significance level set at $\alpha = 5\%$ and 80% power, an additional 66 animals (33 in each group) would be required to demonstrate a difference in ROSC between the LV and Traditional groups.

Hemodynamic and Laboratory Variables

The difference in the hemodynamic variables between the LV and traditional experimental groups are demonstrated in Table 3. The differences in the mean blood gas analysis variables between the LV and traditional experimental groups are demonstrated in Table 4. Detailed graphical representation of hemodynamic values across the entire resuscitative period are presented in Appendix A.

SAAP versus No-SAAP

Stratifying on Traditional versus LV compressions, the proportion with ROSC was 25% higher (Traditional) or 3% higher (LV) when SAAP was used (Table 5a). The test for interaction (difference in differences of 22%) was not statistically significant (p=0.343), permitting calculation of the pooled results in Table 5b. Comparing SAAP to No-SAAP, the proportion with ROSC was not different in the SAAP cohort (Table 5b).

DISCUSSION

In our study we did not detect a significant difference in ROSC when chest compressions were performed in two different locations in a swine model of traumatic cardiac arrest using SAAP with unoxygenated blood. Additionally, we demonstrated that chest compressions and SAAP with unoxygenated blood did not improve survival rates compared to chest compressions alone in the management of TCA. Further work is needed to evaluate whether utilizing oxygenated blood with SAAP would result in a difference between groups.

In prior work, our group demonstrated that LV compressions improve hemodynamics and ROSC compared to traditional compressions in both NTCA and TCA models without SAAP. In this model, which was identical to our prior TCA model except for the addition of the SAAP catheter, we did not find the difference in ROSC between the two groups to be significant. Although there was a trend toward improved ROSC, a larger study would be required to verify whether this trend is significant (our post-hoc sample size calculation suggests more than twice as many animals would be required). The hemodynamic measures

that most reliably predict ROSC and favorable clinical outcomes include ETCO2, AoD and CPP (36-40); Appendix A demonstrates that there was a trend toward higher values for all three of these variables in the LV group during the resuscitative period, especially during BLS, which may be contributing to the trend toward improved ROSC.

The lower-than-anticipated differences in ROSC and hemodynamics might be due, in part, to the SAAP catheters providing enough afterload during compressions that the location of compressions becomes less important in general. It is possible that the 3 animals that attained ROSC in the Traditional group, due to normal anatomic variation, had left ventricles that were located closer to the sternum so that traditional compressions, with the addition of SAAP, produced a similar hemodynamic response as the LV group. Our prior investigations suggest that without the support provided by SAAP those animals would likely not have attained ROSC either (18,19). In the young healthy swine that were used in this experiment, there was very little anatomic variation (Table 1), so even small anatomic differences could have large clinical implications. In the human model, where the size and anatomic variation of the heart is greater, we would expect that larger movements in chest compression location would be necessary to have similar clinical implications. Nonetheless, the addition of SAAP, in this TCA model, seems to have improved the performance of Traditional compressions and decreased the importance of chest compression location somewhat.

The lower-than-projected difference in hemodynamics and ROSC between the Traditional and LV groups may also be due, in part, to the unoxygenated blood that was administered directly into the aorta. We anticipated that the administration of blood volume with the potential for oxygen carrying capacity would override the temporary dilution of oxygenated blood in the systemic circulation; however, this was not the case. The administration of unoxygenated blood through the SAAP catheter likely had a greater effect on the lack of difference in ROSC between the SAAP and No-SAAP cohorts. In this SAAP cohort we elected to use unoxygenated blood since oxygenating blood prior to transfusion requires equipment that is not readily available in most emergency departments and prehospital settings, so the use of unoxygenated blood

is currently more clinically applicable. Alternatively, REBOA has been shown to have a survival benefit over No-REBOA in both investigational animal and observational human studies, and REBOA is currently available for clinical use in the hospital and some prehospital settings whereas SAAP is not (41-45). At this time it is more clinically feasible, and likely safer, to transfuse unoxygenated blood into the venous system with the use of REBOA for aortic occlusion when non-compressible exsanguination is below the diaphragm. Although oxygenating blood for SAAP transfusion in the prehospital setting may currently seem prohibitive, prehospital extracorporeal membrane oxygenation (ECMO), which is similar in complexity, for cardiac arrest has been performed suggesting that prehospital SAAP may be possible under the right circumstances (46). Furthermore, if the SAAP technique proves to be of benefit, it would not be difficult to incorporate the proper equipment into hospital settings such as the intensive care unit or the emergency department. Further work is necessary to determine whether there is a utility for SAAP with oxygenated blood for TCA in these settings.

Limitations

First, this animal model performed under laboratory conditions does not exactly reproduce the human experience during TCA. Swine are often used in TCA studies due to the anatomic and metabolic similarities to humans, however, there are some anatomic differences in the chest wall and heart which somewhat alter compression mechanics (47-50). Nonetheless, these anatomic differences do not diminish the importance that different compression locations have on hemodynamics during TCA. When considering replicating LV compressions in human patients, the only method of verifying the location of compressions with current technology is TEE. TEE has been used to verify the location of chest compression in human NTCA in a manner analogous to the methods used in this investigation (51-53); although the use of TEE has not been described in TCA to date, there are no barriers to its utilization when REBOA or SAAP are used for aortic occlusion rather than thoracotomy. Portable ultrasound machines are readily available in trauma centers for the focused assessment in trauma (FAST) exam; the use of TEE in

arrest only requires the addition of a single TEE transducer and approximately 4 hours of TEE-specific training for physicians that are already comfortable performing point-of-care transthoracic echocardiography (54,55). In the case of suspected intrathoracic hemorrhage, where resuscitative thoracotomy is necessary, TEE would not produce interpretable images due to the increased acoustic impedance caused by the introduction of air around the esophagus; however, in this scenario open cardiac massage would be the only viable option once the thoracotomy has been performed.

Second, in our experiment we induced VF arrest during class III hemorrhage which may not cause TCA in many instances. This was done to reduce the number of animals needed to detect a difference in ROSC. Further work will be done to determine if these differences persist in class IV hemorrhage. Third, this study only addressed VF as the initial cardiac rhythm after inducing hemorrhagic shock; one reason we chose to use VF in our model was to maintain uniformity between this study and our prior cardiac arrest studies (18,19). Although pulseless electrical activity (PEA) is the most common cardiac rhythm in TCA, our VF model also ensured that the animals were truly in a cardiac arrest state rather than simply in a profound shock state which is often the case in traumatic PEA (56,57). Our group has also developed a traumatic PEA model which will be used in future work to address this issue (58). Additionally, we only analyzed young healthy swine which may which may not be physiologically similar to all TCA patients; however, trauma is the leading cause of death for humans ages 1-44 suggesting that a young swine model is likely more reflective of human physiology than an older swine model (10). A sex difference in cardiac and cerebral injury following severe hemorrhage and VF has been also been demonstrated, so generalization to male subjects may not be possible (59).

CONCLUSIONS

Closed chest compressions directed over the LV did not result in a significantly higher rate of ROSC or short-term survival compared to chest compressions in the traditional location when SAAP with unoxygenated blood was used in this swine model of TCA, however, a larger study may demonstrate that

there is a difference. SAAP did not confer a survival benefit over No-SAAP when de-oxygenated blood was used during TCA; more work is needed to determine the potential role of SAAP with oxygenated blood in TCA.

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DISCLOSURE

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FIGURE LEGENDS

Figure 1. Selective Aortic Arch Perfusion catheter. Inlay: close-up view of inflated balloon and catheter tip. (photograph by J. Rall).

FIGURE 2. (a) Experimental protocol timeline; (b) Detailed ALS protocol timeline. *=rhythm check, BLS=Basic Life Support, ALS=Advanced Life Support, Post Resusc=Post Resuscitation, t=time, VF=ventricular fibrillation, ROSC=return of spontaneous circulation, J=joules, CPR=cardiopulmonary resuscitation, FiO2=fraction of inspired oxygen, mg-milligram, kg=kilogram, Epi=epinephrine, Amio=amiodarone, prn=as needed, gtt=infusion.

APPENDIX A. Hemodynamics during the resuscitative period.

Table 1. Baseline weight and size of animals

	Traditional (n=12)	**LV** (n=12)
Weight, kg	27.0 (3.52)	27.6 (3.93)
Vertical distance from sternal notch to aortic root, cm	8.85 (1.37)	8.64 (1.19)
Vertical distance from sternal notch to mid LV, cm	13.1 (1.12)	12.9 (1.30)
Lateral distance from sternum to mid LV, cm	2.54 (0.62)	2.27 (0.65)

Values given are mean (SD). No significant differences exist between groups on any of the listed measures at $p<0.05$. LV = left ventricle.

Table 2. Rates of survival

	Traditional (n=12)	**LV** (n=12)	**Relative Risk**	**95% CI**	**p-value**
ROSC	3 (25%)	5 (42%)	0.60	0.18-2.0	0.67
Survival to 60 minutes	2 (17%)	4 (33%)	0.50	0.11-2.2	0.64

Values given are n (%). ROSC = return of spontaneous circulation, LV = Left Ventricle, CI = Confidence Interval. Fisher's exact test used to determine p-value.

Table 3. Results of repeated measures ANOVAs for hemodynamic variables

	Traditional (n=12)	LV (n=12)	95% CI of Difference LL	95% CI of Difference UL	p-value
AoS, mmHg					
Baseline	102 (13.1)	103 (12.8)	-11.8	10.7	0.917
Post bleed	72.4 (12.6)	71.8 (12.1)	-11.1	9.78	0.896
End of BLS	109 (35.8)	104 (32.4)	-34.1	23.7	0.710
End of ALS	114 (48.9)	104 (53.5)	-54.6	34.2	0.639
AoD, mmHg					
Baseline	74.6 (13.3)	74.2 (11.9)	-11.4	10.4	0.930
Post bleed	50.8 (11.4)	48.8 (10.2)	-11.0	7.22	0.668
End of BLS	14.1 (10.8)	10.7 (17.0)	-15.6	8.56	0.553
End of ALS	27.2 (36.5)	34.3 (37.9)	-25.2	39.4	0.652
RAS, mmHg					
Baseline	11.1 (4.04)	13.4 (5.26)	-1.77	6.42	0.251
Post bleed	8.73 (3.82)	11.0 (3.22)	-0.78	5.33	0.137
End of BLS	88.4 (24.6)	125 (65.6)	-7.13	80.4	0.096
End of ALS	82.9 (65.9)	88.8 (96.8)	-66.7	78.4	0.869
RAD, mmHg					
Baseline	6.91 (3.33)	8.17 (4.64)	-2.28	4.79	0.468
Post bleed	4.18 (3.52)	5.25 (3.17)	-1.83	3.97	0.452
End of BLS	1.82 (8.53)	1.17 (9.97)	-8.74	7.43	0.869
End of ALS	8.55 (9.29)	7.83 (9.85)	-9.04	7.61	0.861
CPP, mmHg					
Baseline	67.8 (14.0)	65.9 (11.6)	-13.0	9.21	0.726
Post bleed	47.5 (13.5)	43.8 (10.5)	-14.2	6.76	0.470
End of BLS	13.5 (15.1)	9.67 (14.4)	-16.6	9.01	0.545
End of ALS	20.7 (37.7)	26.5 (34.2)	-26.3	37.8	0.713
SpO2, mmHg					
Baseline	97.1 (2.01)	96.5 (2.59)	-2.55	1.38	0.544
Post bleed	97.0 (2.40)	96.7 (2.61)	-2.59	2.00	0.793
End of BLS	60.4 (28.5)	66.8 (20.4)	-36.5	49.2	0.728
End of ALS	71.3 (33.5)	84.4 (19.4)	-19.6	45.8	0.397
ETCO2, mmHg					
Baseline	42.6 (3.56)	43.2 (3.09)	-2.20	3.45	0.650
Post bleed	36.7 (4.46)	36.00 (2.58)	-3.79	2.37	0.638
End Non-intervention	12.9 (9.04)	10.9 (11.84)	-16.7	12.8	0.772
End of BLS	16.7 (22.5)	31.1 (23.9)	-5.78	34.6	0.153
End of ALS	18.9 (10.7)	25.9 (13.5)	-3.33	17.3	0.174
Cerebral rSO2, %					
Baseline	66.8 (8.54)	65.5 (12.3)	-10.2	7.73	0.776
Post bleed	42.3 (16.9)	46.5 (18.9)	-11.0	19.3	0.574
End Non-intervention	26.8 (19.6)	33.3 (17.1)	-9.10	22.1	0.396
End of BLS	36.1 (17.1)	39.4 (14.7)	-10.1	16.8	0.613
End of ALS	41.9 (19.7)	42.3 (20.5)	-16.6	18.3	0.920
Renal rSO2, %					
Baseline	62.7 (8.72)	58.0 (3.54)	-10.1	0.76	0.088
Post bleed	49.1 (13.7)	46.9 (8.09)	-11.4	7.05	0.632
End Non-intervention	43.8 (14.1)	35.8 (9.23)	-17.7	1.78	0.104
End of BLS	43.2 (16.8)	33.6 (8.19)	-20.4	1.26	0.081
End of ALS	38.2 (16.4)	35.3 (10.1)	-14.2	8.48	0.605

*Significant difference, $p<0.05$; adjusted p-values for repeated-measures ANOVA are reported. Data are reported as mean (SD).

LV = left ventricle, LL = lower limit, UL = upper limit, HR=heart rate, Ao=aortic, RA=right atrial, S=systolic blood pressure, D=diastolic blood pressure, mmHg=millimeters of mercury, SpO2=peripheral capillary oxygen saturation, rSO2=regional oximetry, BLS = basic life support, ALS = advanced life support.

Table 4. Results of repeated measures ANOVAs for arterial blood gasses

	Traditional (n=13)	LV (n=13)	95% CI of Difference LL	95% CI of Difference UL	p-value
pH					
Baseline	7.39 (0.07)	7.41 (0.06)	-0.04	0.07	0.505
Post bleed	7.52 (0.05)	7.51 (0.05)	-0.05	0.04	0.764
End Non-intervention	7.47 (0.07)	7.45 (0.05)	-0.07	0.03	0.521
End of BLS	7.14 (0.07)	7.10 (0.06)	-0.10	0.02	0.173
End of ALS	7.14 (0.11)	7.17 (011)	-0.06	0.13	0484
pCO2					
Baseline	49.9 (7.89)	47.5 (12.0)	-11.0	6.16	0.564
Post bleed	37.0 (3.88)	37.8 (2.77)	-2.04	3.67	0.559
End Non-intervention	39.8 (5.99)	40.3 (9.26)	-6.05	7.16	0.862
End of BLS	69.4 (11.5)	66.2 (21.0)	-18.0	11.7	0.662
End of ALS	57.9 (23.4)	21.7 (16.4)	-24.2	11.8	0.483
pO2					
Baseline	182 (87.5)	146 (74.8)	-105	33.0	0.292
Post bleed	101 (16.4)	97.5 (24.9)	-21.0	14.8	0.722
End Non-intervention	74.6 (10.6)	67.2 (8.63)	-15.3	1.03	0.084
End of BLS	107 (31.4)	114 (53.8)	-31.7	45.7	0.709
End of ALS	132 (92.5)	148 (104)	-71.0	104	0.696

Data are reported as mean (SD). Adjusted p-values for repeated-measures ANOVA are reported.
pCO2 = partial pressure of carbon dioxide, pO2 = partial pressure of oxygen, BLS= basic life support, ALS = advanced life support

Table 5a. Rates of ROSC between Traditional and LV compressions

	Traditional (n=13 No-SAAP n=12 SAAP)	**LV** (n=13 No-SAAP n=12 SAAP)	**Difference**	**95 CI**	**p-value**
No-SAAP ROSC	0 (0.0%)	5 (39%)	5 (39%)	12-65	0.04*
SAAP ROSC	3 (25%)	5 (42%)	2 (17%)	-20-53	0.67

Table 5b. Rates of ROSC between SAAP and No-SAAP compressions

	SAAP (n=24)	**No-SAAP** (n=26)	**Difference**	**95 CI**	**p-value**
ROSC	8 (33%)	5 (19%)	3 (14%)	-18-32	0.74

Values given are n (%). *p-value less than 0.05

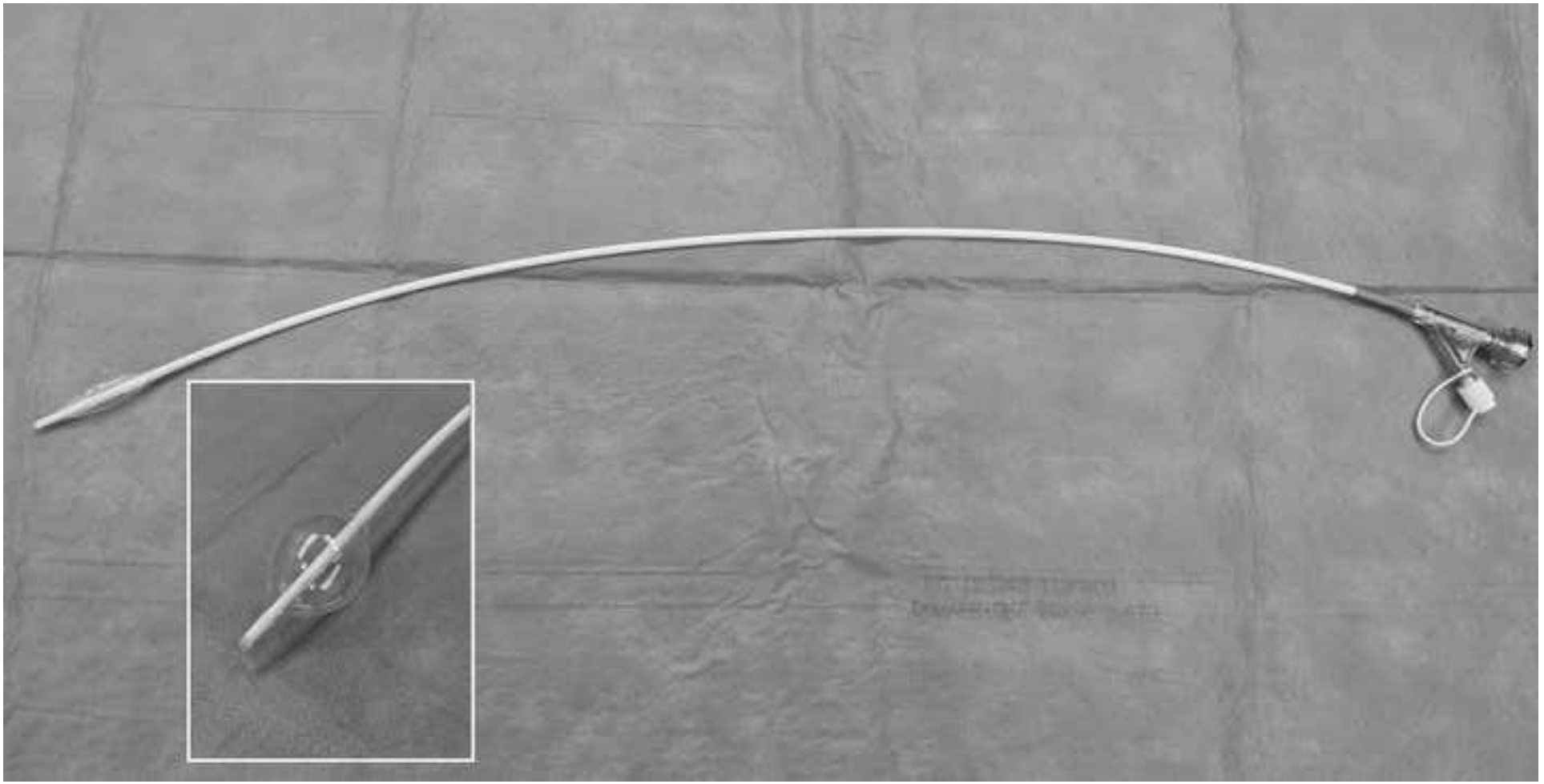

Figure 1 – SAAP catheter

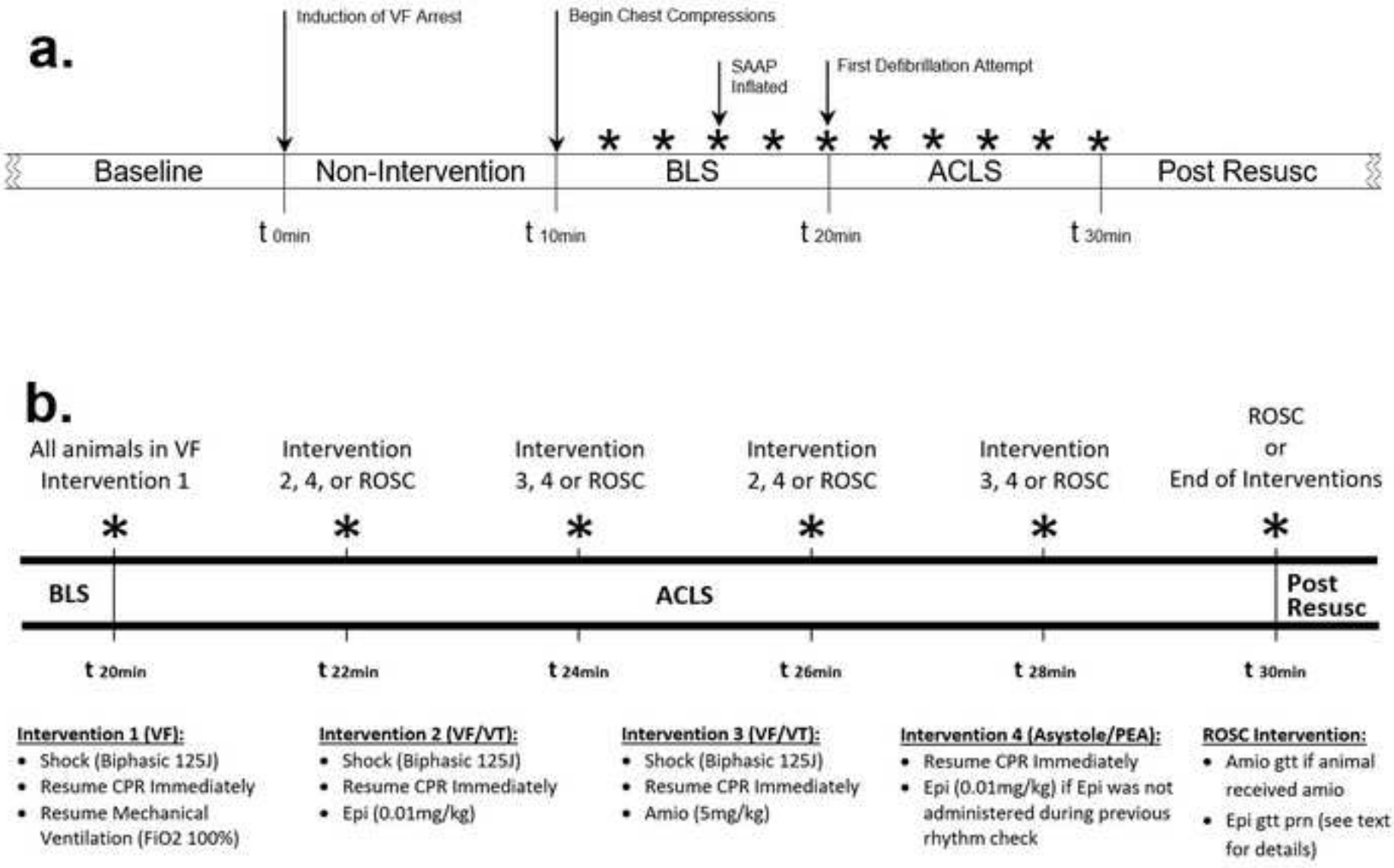

Figure 2 – Timeline