TITLE:
Effects of left ventricular compressions in a traumatic pulseless electrical activity model

SHORT TITLE:
LV compressions in traumatic PEA

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DECLARATIONS:
The authors report no conflicts of interest in this work.

AUTHOR CONTIRBUTIONS:
Each of the authors listed below have made substantial contributions in each of the following areas: (1) J.C.E., J.D.M. and K.L.A. contributed to conceiving and designing the study; (2) J.C.E., J.D.M., M.G.C., S.M.B., and K.L.A. contributed to collecting the data or analyzing and interpreting the data. (3) J.C.E, J.K.M, and K.L.A contributed to writing the manuscript or providing critical revisions that are important for the intellectual content and (4) J.C.E., J.D.M., M.G.C., S.M.B., J.K.M., and K.L.A. contributed to approving the final version of the manuscript.

DISCLAIMERS:
The views expressed are those of the authors 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: Prehospital cardiopulmonary resuscitation has commonly been considered ineffective in traumatic cardiopulmonary arrest (TCA) because traditional chest compressions do not produce substantial cardiac output. However, recent evidence suggests that chest compressions located over the left ventricle produce greater hemodynamics when compared to traditional compressions. We hypothesized that chest compressions located directly over the left ventricle would improve return of spontaneous circulation (ROSC) and hemodynamics, when compared to traditional chest compressions, in a swine model of traumatic pulseless electrical activity (PEA).

Materials and Methods: Transthoracic echocardiography was used to mark the location of the aortic root (traditional compressions), and the center of the left ventricle (LV) on animals (n=34) which were randomized to receive chest compressions in one of the two locations. Animals were hemorrhaged to MAP<20 to simulate traumatic PEA. After five minutes of PEA, 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. Hemodynamic variables were averaged over the final two minutes of BLS and ALS periods.

Results: Six of the left ventricle group (35%) achieved ROSC compared to eight of the aortic root group (47%) (p=0.73). There was an increase in aortic systolic blood pressure (p<0.01), right atrial systolic blood pressure (p<0.01) and right atrial diastolic blood pressure (p=0.02) at the end BLS.

Conclusions: In our swine model of traumatic PEA, chest compressions performed directly over the left ventricle improved blood pressures during BLS, but not ROSC.

Keywords: Cardiopulmonary resuscitation; Cardiac arrest; Trauma; Hemodynamics; Survival; Echocardiography

INTRODUCTION

In the United States traumatic injury is the leading cause of death for those less than 45 years of age; the premature deaths of so many relatively young patients is the overall leading cause of life-years lost (1). Unfortunately, the resuscitation of traumatic cardiac arrest (TCA) patients in the pre-hospital setting remains somewhat contested. Early observational studies reported almost negligible survival rates among resuscitated TCA patients which led some investigators to propose that resuscitation was ineffectual (2-5). More recent publications have described improved survival rates on par with non-traumatic out-of-hospital cardiac arrest; some of these reports also provide evidence that earlier intervention may also improve outcomes (6-14).

Traditional closed chest compressions have been at the center of the discussion surrounding pre-hospital TCA resuscitation. While only providing a small fraction of the cardiac output generated by open chest compressions, traditional closed chest compressions also have the potential to cause further traumatic injury (15, 16). However, 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 non-traumatic cardiac arrest (NTCA) and TCA models – this method may be the closest approximation to open cardiac massage that can be achieved without performing a thoracotomy (17, 18). These animal models used ventricular fibrillation (VF) as the cardiac arrest rhythm, yet the most common presenting rhythm in TCA is pulseless electrical activity (PEA) (13, 19). Traumatic PEA is often due to the profound hypovolemia that accompanies catastrophic trauma rather than cardiac arrhythmia, therefore, outcomes from traumatic PEA may vary substantially from other TCA rhythms such as VF (profound hypovolemia in TCA is

sometimes referred to as pseudo-PEA because there is no true electromechanical dissociation (EMD)).

We hypothesized that chest compressions located directly over the LV would increase return of ROSC when compared to traditional compressions in a swine model of traumatic PEA. Secondary analyses included an evaluation of hemodynamic and laboratory variables as well as short-term survival to 60 minutes between the two groups.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective, randomized comparative investigation approved by our Institutional Animal Care and Use Committee. The housing of animals and the performance of the study took place in the Animal Care Facility at our institution. All procedures involving animals complied with the regulations and guidelines of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the American Association for Accreditation of Laboratory Animal Care. Reporting adheres to the Animals in Research Reporting In Vivo Experiments (ARRIVE) guidelines (20). This study builds on prior work, and the methods used in this study are derived from prior TCA and traumatic PEA models (18, 21).

Animal Preparation

Thirty-four Yorkshire swine weighing 25-32kg were obtained 5-7 days before experimentation to allow acclimation to the facility. Per the vendor, the animals were free from viral, bacterial and parasitic pathogens.

Pre-intervention animal care follows the protocol previously described (17, 18, 21). Animals were housed individually in 4x6 foot 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, USA). 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. A complete blood cell count and blood chemistry analysis were also performed. No pre-treatment with any medications was performed.

All experiments were initiated during the morning hours. Animals were initially sedated with 20mg/kg intramuscular ketamine; general anesthesia was subsequently induced with isoflurane (3-4.5%), and mechanical ventilation initiated (Fabius GS; Draeger-Siemens, New York, NY) with a mixture of 60% oxygen and isoflurane (1-2.5%) with a tidal volume of 10mL/kg at a respiratory rate of 12 min^{-1}. End-tidal CO2 (ETCO2) was monitored by in-line waveform capnography, and the respiratory rate was adjusted to maintain an ETCO2 between 38 and 42 mmHg prior to induction of cardiac arrest. Continuous cardiac rhythm and heart rate were monitored by electrocardiography (ECG) 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 (22, 23). Standard weight-based doses were used.

Interventions

Pre-experimental interventions follow the protocol previously described (17, 18, 21). 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. Unfractionated heparin (100u/kg) was provided to prevent catheter clotting. Near infrared spectroscopy (NIRS) 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 (TTE) (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 mid-sternum 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 mid-esophageal 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 (18, 21). 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). Randomization was performed for all animals prior to the beginning of the study and the results for each animal were kept sealed until the hemorrhage period was complete and the animals were considered to be in PEA. A graphic display of the general protocol is presented in Figure 1a, and a more detailed outline of the advanced life support (ALS) portion of the protocol is presented in Figure 1b.

During the hemorrhage period, blood was removed via the carotid arterial line via aspiration with a 60mL syringe at a predetermined rate (3mL/kg/min) as previously described and saved in a blood collection system containing citrate-phosphate-dextrose with Optisol red blood cell preservative solution (Terumo Corp., Tokyo, Japan) (21). The collected blood was then placed in a blood warmer for subsequent experimental transfusion to the same animal.

Because palpable pulses are not reliable in swine, once the animals had reached a sustained mean arterial pressure ≤20 mmHG for at least 1 min without intervention, the ventilator was removed, and the animals were considered to be in PEA (Figure 1). The induction of PEA represented time zero during the experiment. All animals remained in PEA without any intervention for a period of 5 minutes (Non-intervention period) as previously described (21). During the 5-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) in case the animals converted to VF or ventricular tachycardia (VT) during the experiment.

Basic Life Support

After the 5-minute Non-intervention period, Basic Life Support (BLS), was initiated using the AMCD over the allocated position as previously described (18, 21); compressions were delivered at a rate of 100 min^{-1}, at a depth of 5cm, with a 50% duty cycle and a compression-ventilation ratio of 30:2. Compressions were briefly interrupted every two 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 was used as a practical approach because this duration of CPR is necessary to adequately compare CPR techniques (24).

Advanced Life Support

After 10 minutes of BLS, advanced life support was initiated, as previously described, including resumption of mechanical ventilation with 100% oxygen, continued compressions at the same rate and depth, and bolus transfusion of the whole blood (WB) that was removed during the hemorrhage under 250 mmHg of pressure (Figure 1b) (21). 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 a tactical field care or elsewhere in combat theater when other blood products are not available or not effective (25, 26). Every two minutes compressions were interrupted for a rhythm analysis that lasted 2-5 seconds. If the rhythm was VF or VT, a 125 Joule defibrillation attempt would be 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 (0.01 mg/kg) followed by a 10 mL normal saline flush was administered if the animal had not met criteria for ROSC. During the third and fifth ALS rhythm analyses, amiodarone (5 mg/kg) followed by a 10 mL 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 follows the previously described protocol (17, 18, 21). 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 0.1 mcg/kg/min and titrated by 0.1mcg/kg/min every two minutes to a maximum of 2.0 mcg/kg/min, to maintain an aortic systolic blood pressure (SBP) greater than 90 mmHg. If the SBP rose above 120 mmHg the epinephrine was titrated down by 0.1 mcg/kg/min every two minutes.

Termination of the Protocol

Protocol termination has been described in prior work (17, 18, 21). Animals were considered expired if the aortic SBP was less than 60 for 10 minutes after minute 30. Expired animals were euthanized with 100 mg/kg sodium pentobarbital, 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 American Veterinary Medical Association Guidelines for the Euthanasia of Animals (27). No post-operative care was required given that the endpoint was euthanasia at the conclusion of study procedures.

Measurements

The same measurements used in prior work were also recorded and analyzed for this study (18, 21). Hemodynamic data (aortic systolic (AoS) and diastolic (AoD) blood pressure, right atrial systolic (RAS) and diastolic (RAD) 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.

The 10-second TEE video recordings were randomly compiled into a file that was independently assessed at the conclusion of all data collection by an investigator who is certified in TEE and blinded to the remainder of the data. This investigator rated the AMC in each video as being over the LV or AR.

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.

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 preliminary data, 50% of animals were expected to attain ROSC (primary outcome) in the LV compressions and 10% in the Traditional group; at the $\alpha = 5\%$ significance level and with 80% power, a total sample size of 34 animals would be required (17 in each arm).

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) (Tables 1, 2 & 3). The mean total blood loss during the hemorrhage period was similar between the Traditional (1,370 ± 298 mL SD) and LV groups (1,430 ± 187 mL SD) ($p=0.614$).

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 Traditional (0.64 ± 0.32 mg SD) and the LV groups (0.65 mg ± 0.30 mg SD) ($p=0.923$). Seven of the animals in the Traditional group converted to VF during the BLS period, and eight of the LV group converted to VF during the BLS period. The mean total dose of amiodarone was similar between the Traditional group (194 ± 83.2 mg SD) and the LV group (265 ± 26.2 mg SD) ($p=0.162$).

Return of Spontaneous Circulation and Short-term survival

The number of animals that attained ROSC was not significantly different between experimental groups (p=0.73) (Table 2). Three of the fourteen animals that attained ROSC did so during the BLS period (Traditional group: one at minute 11; LV group: one at minute 7, one at minute 13), the remaining eleven animals attained ROSC during the ALS period (Traditional group: two at minute 17, three at minute 21, one at minute 23 and one at minute 25; LV group: three at minute 21, one at minute 23) and all animals that attained ROSC survived to 60 minutes. Considering only the animals that remained in PEA and did not convert to VF, there was no difference in ROSC rates nor survival; seven (70%) in the Traditional group and six (67%) of the LV group attained ROSC and survived to 60 minutes (p=1.00).

Hemodynamic and Laboratory Variables

The difference in the hemodynamic variables between the LV and Traditional experimental groups are demonstrated in Table 3. Of note, the AoS, RAS and RAD were all higher among the LV group at the end of BLS, but these trends did not persist to the end of the ALS period. 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 (minutes 5-25) are presented in Appendix A.

DISCUSSION

In our study, there was an increase in blood pressures (AoS, RAS, RAD) at the end of the BLS period, yet this increase in blood pressure did not result in an improvement of ROSC or short term-survival in a swine model of traumatic PEA arrest.

Although performing chest compressions directly over the LV during TCA may be the nearest approximation to open chest compressions that is possible in the pre-hospital setting, LV compressions did not confer a survival benefit in our traumatic PEA model. Prior radiologic and echocardiographic investigations have suggested that the current traditional location for chest compressions, in the center of the chest, might not be optimal because that is not where the heart is situated (22, 23, 28-30); subsequent work has shown that hemodynamic measures do indeed improve when chest compressions are performed more caudally where the heart is more frequently located and the chest wall is more compliant (31, 32). Our group has also previously demonstrated that hemodynamic measures and ROSC can be improved by placing chest compressions directly over the left ventricle in NTCA and TCA models using VF as the cardiac arrest rhythm (17, 18). Since PEA is much more common than VF in TCA, we used a PEA model in this study that was almost identical to our prior VF studies (differences included a more profound hemorrhage, a shorter non-intervention period, and no electrical induction of VF) and found that some improvement in blood pressures in the LV group persisted in the PEA model, but a subsequent increase in ROSC and survival was not demonstrated (18, 21).

The smaller difference in ROSC and survival between experimental groups in this PEA model compared to the prior traumatic VF model are most likely multifactorial; however, the greatest contribution to this disparity is likely the organized cardiac activity that is present in the PEA model. It is instructive to point out that in the prior VF model, survival was similar in the LV group (38%) and much lower in the Traditional group (0%) when compared to this PEA

model (Table 2). With the presence of organized cardiac activity in the PEA model, there is already intrinsic cardiac output and forward blood flow, so it is possible that improvement of oxygen carrying capacity with blood replacement may become a more important determinant of survival than the improvement of hemodynamics with augmented (LV) chest compressions. Conversely, if a PEA model with EMD could be performed, it is possible that outcomes in the LV group would again be higher than the Traditional group as they were in VF model since there would be no intrinsic cardiac output; however, to date there are no reproducible traumatic EMD models which allow outcome measures, so this hypothesis is currently not verifiable. Only a few small studies have documented the presence or absence of cardiac activity using ultrasound during traumatic PEA; these works have cited the presence of cardiac activity in PEA to be between 19-24% (10, 33). Organized cardiac activity in traumatic PEA is associated with ROSC and survival, and this is the model we attempted to approximate in this laboratory study (10, 33).

In this PEA model, blood volumes were also much lower than in the prior traumatic VF model which may have contributed to the difference between ROSC and survival rates between the models as well. In this PEA model the average blood loss was 80% compared to 33% in our prior VF arrest models. With only 20% blood volume remaining during BLS, an improvement in cardiac output with augmented chest compressions is less likely to have as pronounced an effect on outcomes.

Further investigation needs to be performed on the utility of chest compressions in the pre-hospital setting for TCA, especially when PEA is the presenting rhythm. We have presented evidence that blood pressures improve with chest compressions, especially LV compressions, during BLS when blood is not available. There is also ample human evidence to suggest that closed chest compressions in the pre-hospital setting contribute to survival among TCA patients

(6-9, 14). However, more work needs to be done to elucidate whether there is a survival benefit to chest compressions in the pre-hospital setting or whether blood administration alone is enough during traumatic PEA, especially when organized cardiac activity is present.

Limitations

First, this animal model 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 (34-36). Nonetheless, these anatomic differences do not diminish the importance that different compression locations have on hemodynamics during TCA. Second, this study only addressed PEA as the initial cardiac rhythm. Prior work has already addressed VF as the initial rhythm. It is likely that these results would also vary from true EMD or asystole as the presenting rhythm, but those animal models have yet to be developed. Additionally, we only analyzed young healthy swine which may not be physiologically representative of the entire TCA population. However, trauma is the leading cause of death for humans ages 1-44 suggesting that a younger swine model is likely more reflective of human TCA physiology than an older swine model (5).

CONCLUSIONS

Closed chest compressions directed over the LV resulted in higher blood pressures (AoS, RAS, RAD) but did not result in a significantly higher rate of ROSC or short-term survival compared to chest compressions in the traditional location in this swine model of traumatic PEA.

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DISCLOSURE

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FIGURE LEGENDS

FIGURE 1. (a) Experimental protocol timeline; (b) Detailed ALS protocol timeline. *=rhythm check, NI=Non-Intervention, 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.