Published in final edited form as:

Resuscitation. 2016 June ; 103: 41–48. doi:10.1016/j.resuscitation.2016.03.015.

Energy Conserving Chemical Defibrillation of Ventricular Fibrillation: A Randomized Two Phase Controlled Blinded Trial

Keith A. Marill, M.D., David D. Salcido, Ph.D., Matthew L. Sundermann, M.S., Allison C. Koller, B.S., and James J. Menegazzi, Ph.D.

Department of Emergency Medicine, University of Pittsburgh School of Medicine

Abstract

Objectives—Potassium cardioplegia-induced transient asystole may conserve myocardial energy, foster chemical defibrillation, and improve VF arrest outcome. A trial of potassium infusion with or without calcium reversal was conducted to test for improvement in intra-arrest VF waveform and post-ROSC hemodynamics.

Methods—Eighteen swine were randomized to three treatment arms in two phases. VF was electrically induced and untreated for four minutes. The animals then received six minutes of mechanical CPR. Blinded investigators infused two study medicines peripherally during this interval. One group received 1.5 mEq/kg KCl with CPR initiation followed three minutes later by CaCl 10% infusion 0.12 cc/kg, the second group received 1.5 mEq/kg KCl without CaCl, and the third group received placebo infusions. Ten minutes post VF initiation, defibrillation was performed, as appropriate, followed by ACLS for continued arrest or observation for 30 minutes if ROSC. AMSA change from before to 5 minutes post study drug infusion was compared with nonparametric statistics. MAP post ROSC was compared using mixed linear regression analysis.

Results—Average normalized AMSA change was -0.15 , -0.63 , and $+0.27$ in the KCl, KCl+CaCl, and placebo groups, respectively ($p=0.01$). Three KCl+CaCl animals developed on organized rhythm chemically without electrical defibrillation. One, 3, and 4 animals in the KCl, KCl+CaCl, and placebo groups, respectively, survived post ROSC. Post ROSC, MAP decreased 1.8 mm Hg (95% CI -1.4 to 5.1) per minute less in the KCl+CaCl group compared to placebo.

Conclusions—Chemical defibrillation and ROSC are possible post potassium-induced asystole. Potassium followed by calcium reversal, but not potassium alone, led to ROSC and post-ROSC hemodynamics comparable to recommended therapy.

Address for correspondence: Iroquois Building, Suite 400A, 3600 Forbes Avenue, Pittsburgh, PA 15261, United States.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Previous Presentation:

8th Mediterranean Emergency Medicine Congress, Rome, Italy, September 10, 2015. American Heart Association Resuscitation Science Symposium (RESS), Orlando, FL, November 7, 2015.

Conflicts of interest statement: None

Disclosures: The LUCAS device that was used in this experiment was loaned to Dr. Menegazzi by Joilife. None of the authors have any financial interest in Joilife. The Zoll monitor-defibrillator that was used in this experiment was loaned to Dr. Menegazzi. None of the authors have any financial interest in Zoll. The authors have nothing else to disclose in relation to this particular investigation.

Keywords

ventricular fibrillation; sudden cardiac death; heart arrest; potassium; calcium

Introduction

VF is characterized by unsynchronized myocardial contraction with inadequate cardiac output. Myocardial energy expenditure exceeds supply, and if untreated, myocardial activity predictably decays to an asystolic state.^{1,2} Innovative advances that emphasize rapid uninterrupted chest compressions have been made to maximize energy substrate delivery to the fibrillating myocardium.³ Less research focus has been placed on minimizing myocardial energy expenditure.

Myocardial energy demand is routinely minimized during cardiac bypass surgery by infusing the heart with a cold cardioplegic potassium solution to arrest contractions.⁴ Multiple investigators have studied extended potassium cardioplegia combined with cardiopulmonary bypass to treat or reverse refractory arrest and associated ischemia after cardiac surgery.⁵⁻⁸ Treatment with combined cardiopulmonary bypass and potassium cardioplegia has also been studied for induced VF without surgery.⁹ Provision of cardiopulmonary bypass during the treatment of spontaneous cardiac arrest is feasible, but challenging.¹⁰

VF is associated with higher energy expenditure than a non-contracting heart.^{11,12} Lee, et al. induced cardiac standstill with potassium infusion during CPR without cardiopulmonary bypass in a porcine model of VF arrest.¹³ They observed an improvement in: the number of countershocks, doses of epinephrine, and duration of CPR in the group that received 0.9 mEq/kg of potassium infused into the right atrium at the start of CPR. Expanding on this work, they found similar beneficial effects when lidocaine 1.2 mg/kg was infused along with potassium 0.9 mEq/kg at the start of CPR.¹⁴ They also observed chemical defibrillation in 4 of the 8 treated animals.

We sought to determine whether potassium cardioplegia infusion into a peripheral vein with or without subsequent calcium reversal improves outcome in a porcine model of VF arrest. The primary outcomes analyzed were: 1) the intra-arrest change in AMSA from immediately before potassium or placebo infusion to 5 minutes post infusion, and 2) post-arrest MAP dynamics in those animals that achieved ROSC. AMSA is a quantitative waveform measurement associated with successful defibrillation, ROSC, and survival.^{15,16} Secondary outcomes were collected in four domains including: CPP, serum electrolyte measurements, the proportion of survivors and the time and number of shocks until ROSC, and the electrocardiographic characteristics of resulting organized rhythms.

Methods

Study Design and Population

This was a two-phase randomized, blinded, three arm controlled trial of potassium infusion with or without subsequent calcium infusion in a swine model of VF arrest. This study was

approved by the **BLINDED** Institutional Animal Care and Use Committee (protocol 14033398), and was performed in compliance with the Guide for the Care and Use of Laboratory Animals.¹⁷ Eighteen female mixed-breed domestic swine (*Sus scrofa*) with mean mass of 26.0 kg were used. Only female swine were used to minimize confounding from possible sex-based variations in animal response.

Study Protocol

The animals were sedated with intramuscular ketamine (10 mg/kg) and xylazine (4 mg/kg). We then established IV access via a peripheral ear vein using a 20g catheter. We established a surgical plane of anesthesia using a rapid IV infusion of fentanyl (0.05 mg/kg), and maintained this with a continuous titrated infusion of the same (0.03-0.100 mg/kg/hr).

The animals were intubated by direct laryngoscopy with a 5-0 cuffed endotracheal tube. They were ventilated with FiO₂ 21% at 12-16 breaths per minute using an Ohmeda 7000 ventilator (Ohmeda, BOC Health Care, Madison, WI). Eucapnia was maintained as measured with a mainstream capnometer (Capnostat, Respironics Novamatrix, Inc., Wallingford, CT). Core body temperature was measured with an esophageal probe. The animals' forelimbs were shaved, and three surface electrodes configured to correspond to a standard Lead II ECG were placed. The ECG signal was passed through a 50 Hz lowpass Powerlab preamplifier and digitized at 1000 samples/second (Powerlab 16/30 Model ML880, ADInstruments, Dunedin, New Zealand).

The animals were paralyzed with vecuronium (4 mg initial bolus IV with additional 2 mg boluses as needed). Micromanometer-tipped catheters (Millar, Inc., Houston, TX) were introduced into the descending aorta and right atria via 9Fr. introducers placed by cut-down in the right femoral artery and vein, respectively. Arterial and venous pressures were monitored continuously with the same data acquisition system used to record the ECG. Serial arterial blood gas and electrolyte measurements were taken via the femoral artery introducer per protocol (Portable Clinical Analyzer, I-Stat, Heska Corp. Wakesha, WA).

One investigator (ACK) prepared the experimental potassium chloride cardioplegic, calcium chloride reversal, or normal saline (NS) control weight-based infusion agents using a computer randomization scheme. She assisted data collection but made no resuscitation decisions or actions. All other investigators were blinded to the identity of the infusion agent throughout the experiment.

A schematic of the final experimental protocol is shown in Figure 1. VF was induced transthoracically by delivering a three second, 60 Hz, 100 mA alternating current. VF was confirmed by examination of the ECG and arterial waveform tracings. After 4 minutes of untreated VF arrest, the experimental agent, 1.5 mEq/kg potassium chloride in a volume of approximately 20 cc, was infused into a peripheral ear IV in two groups, and the third group received identical appearing normal saline (NS) placebo. Simultaneously, closed-chest CPR was started using mechanical compressions with a LUCAS device (Jolife AB / Physio-Control, Lund, Sweden) at a rate of 100 compressions/minute and asynchronous mechanical ventilation with 100% FiO₂ was resumed. Chest compressions were halted for 7 seconds at

the end of each minute beginning after infusion of the experimental agent to allow rhythm observation and recording without interference.

This study was originally designed to compare potassium infusion alone to placebo. It became apparent after the first 5-10 animals that outcomes were generally poor. It was suspected potassium was not dissipating sufficiently rapidly to allow a return to satisfactory cardiac electrophysiologic function. An amendment was submitted and approved by the IACUC to add a third arm to the trial to include active reversal of the hyperkalemic effect with calcium chloride. Dosing was comparable to that used clinically on a weight basis. The experiment was thus effectively performed in two phases: an initial blinded randomized comparison of KCl versus placebo (total 10 animals), and a second phase with blinded randomized comparison of KCl alone, KCl+CaCl₂, and placebo (total 8 animals). An expanded randomization scheme was produced to accommodate the second phase. Allocation was necessarily unbalanced in the two experimental phases, but all animals were randomized between one or both treatment arms and placebo.

For the second phase of the experiment, seven minutes after VF induction, calcium chloride 10% solution 0.12 cc/kg with total volume approximately 3 cc was infused into a peripheral vein in one potassium group, and the other two groups received comparable NS placebo. Simultaneously, 1 mEq/kg sodium bicarbonate was infused in the central venous catheter in all animals. If the animal achieved ROSC after the first (potassium) or second (calcium) experimental agent infusion, then CPR was stopped. ROSC was defined as a persistent perfusing rhythm with systolic aortic blood pressure of at least 60 mm Hg for at least 10 consecutive minutes.

Ten minutes after VF induction the animal was assessed for a shockable rhythm. Biphasic defibrillation with 150 Joules was provided as appropriate via bilateral chest paddles coated with electrode gel. If the animal demonstrated a nonperfusing rhythm based on arterial waveform, then standard advanced cardiac life support (ACLS) measures were begun including: continued mechanical chest compressions and ventilations, 0.015 mg/kg epinephrine infusion every 3 minutes beginning with the first shock, and rhythm check for possible defibrillation every 2 minutes. This protocol was continued for 10 minutes or until the animal achieved ROSC.

If the animal failed to achieve ROSC within 20 minutes of the initial VF induction, resuscitation efforts were ceased. If the animal achieved ROSC, then the animal was observed for 30 minutes post ROSC. Heart rate, arterial and venous blood pressure (BP), and electrocardiographic rhythm tracing were monitored continuously. If the animal developed a mean arterial pressure (MAP) less than 50 mm Hg, then norepinephrine pressor infusion was initiated with titrated dosing to maintain blood pressure above MAP 50 mm Hg. A low BP treatment threshold was chosen to allow maximal observation and comparison prior to intervention. The animal was euthanized after the observation period with a rapid IV infusion of 40 mEq KCl.

Measurements

AMSA was calculated using a 3 second ECG strip epoch obtained 20 seconds after VF induction and then during the 7 second cessation of chest compressions each minute beginning just before the first experimental infusion. AMSA was computed as described by Povoas and Bisera¹⁸ by taking the fast Fourier transform (FFT) of the detrended time signal epoch using MATLAB R2014a (Mathworks, Natick, MA), and band-pass filtering between 4 and 48 Hz in the frequency domain. The amplitude of the FFT for each frequency was multiplied by the frequency value and summed. CPP was recorded as the average difference between the aortic and central venous pressure over 200 milliseconds just before the onset of chest compressions and then after the final compression at the start of each 7 second pause or during diastole for those animals that achieved ROSC. ABG and electrolytes were measured before and at 4, 7, and 10 minutes post VF induction. ABG potassium values greater than 9.0 mmol/L are read as ">9.0" and were given a value of 10.0 for subsequent calculations. Electrocardiographic QRS interval was measured in all animals with an organized rhythm 11 minutes post VF induction which was 1 minute after the first possible defibrillation. The proportion of survivors in each group and the time until ROSC and number of shocks required was recorded. The hemodynamics of surviving animals including the MAP and mean heart rate measured over 5 seconds were measured every minute for 30 minutes after ROSC or until initiation of norepinephrine. Measurements were made automatically within Labchart (ADInstruments, Sydney, Australia), and MAP was determined by taking the mean for each cardiac cycle and then taking the mean of these values for each 5 second epoch. MAP serves as a surrogate marker of LV function in this experiment, though it may be confounded by a host of factors such as vascular tone, adrenergic treatment, and heart rate.

Analysis

Data was placed in an Excel 2010 database (Microsoft, Redmond, WA) and exported for data analysis in SPSS 22 (IBM, Armonk, NY) except as noted. For each animal, AMSA was normalized to a value of 1 at 4 minutes post VF induction, just before study drug infusion. The difference in normalized AMSA from 4 to 9 minutes post VF onset was compared between the three groups using the nonparametric Kruskal-Wallis test. The second data point was chosen 1 minute before initial defibrillation at 10 minutes to avoid any interference that might be caused by unplugging monitors and preparing for defibrillation. If a significant difference among groups was found, then the Mann-Whitney U and Hodges-Lehmann estimate of median shift were used for pairwise comparisons. Other comparisons of interval data were made using the same method, and comparisons of dichotomous data (survival) were made using Fishers exact test and the Feeman-Halton extension for three groups. For pairwise comparisons, assuming a standard deviation of 0.25 within each experimental group, a meaningful normalized mean difference of 0.5, power 0.8, type I error 0.05, and a two-tailed test, 6 animals were required in each group to detect a difference in the change in AMSA five minutes post initial study drug infusion.

Random-effects mixed linear regression was used to assess MAP post-ROSC until study completion or norepinephrine infusion. This model was made with SAS 9.4 (SAS Institute, Cary, NC). The dependent variable was MAP. Multiple serial measurements were clustered

for each animal, and the individual animals and their time=0 intercept were represented by two random variables. Five fixed independent variables included: time after ROSC, MAP 1 minute post ROSC and its interaction with time, and treatment group and its interaction with time. A similar technique was used to model CPP between 5 and 10 minutes post VF induction and excluding measurements after ROSC. The dependent variable was CPP and fixed variables in this parsimonious model included: time after VF induction, and measurement post KCL or CaCl infusion.

This study was designed to yield ROSC and survival for the majority of animals by limiting the duration of untreated VF arrest to 4 minutes, thus allowing a comparison of both intra-arrest parameters and hemodynamics post-ROSC. The study was also designed to maximize the beneficial effect of potassium cardioplegia, if any, by infusing it at the start of chest compressions and continuing chest compression for 6 minutes prior to defibrillation.

Results

Eighteen animals in 3 groups of 6 were studied. The Table provides the progression of rhythms, AMSA, and CPP as a function of minutes post VF induction for all animals. The mean change in normalized AMSA from immediately before study drug infusion to 5 minutes later for the 14 animals still in VF was -0.15 in the KCl group, -0.63 in the KCl +CaCl group, and +0.27 in the placebo group (Figure 2). The 3 distributions differed, ($p=0.01$), and both potassium groups were significantly different from placebo on pairwise testing. CPP decreased 4.7 mm Hg per minute (95% CI 2.9 to 6.5) from minutes 5 to 10 post VF induction and there was no significant effect after KCl -3.4 mm Hg (95% CI -18.5 to 11.8) or CaCl 1.2 mm Hg (95% CI -9.3 to 11.7) infusions.

Figure 3 depicts the trajectories of serum potassium, calcium, and pH. Eleven minutes after VF induction and 1 minute after the first possible defibrillation, 7 animals across the 3 groups demonstrated organized electrical activity. Mean QRS duration in the KCl, KCl +CaCl, and placebo groups was 155, 100, and 62.5 milliseconds (msec), respectively, and these were not statistically different, ($p=0.43$).

One animal in the KCl group, three in the KCl+CaCl group, and four in the placebo group achieved ROSC, ($p=0.36$), (Figure 4). The average times to ROSC were 16.5, 9.3, and 10.5 minutes, respectively, ($p=0.14$). Two of three KCl+CaCl animals that achieved ROSC did so chemically prior to any electrical therapy. Figure 5 demonstrates the progressive ECG and arterial waveform changes for one of these animals. The average number of shocks received prior to initial ROSC in the KCl, KCl+CaCl, and placebo groups was 3, 0.67, and 1.25, ($p=0.21$). Two animals in the KCl+CaCl group that did not achieve ROSC did spontaneously develop an organized rhythm. One of these demonstrated a narrow complex rhythm at 150 BPM 8 minutes post VF induction and appeared to have an appropriate waveform but was hypotensive with MAP 30. The animal was untreated for 2 minutes before pressor infusion initiation. Chest compressions were resumed 1 minute after pressor infusion but the animal could not be resuscitated.

One animal in the KCL, 3 in the KCl+CaCl, and 4 in the placebo group survived post ROSC. MAP decreased an average 2.8 mm Hg (95% CI 0.9 to 4.7) every minute post ROSC across all 8 animals (Figure 6). The coefficient for the interaction term (treatment group*time) comparing KCl+CaCl to placebo was 1.8 (95% CI -1.4 to 5.1). MAP decreased 1.8 mm Hg per minute less in the KCl+CaCl group compared to placebo.

Discussion

Decreasing wasteful energy expenditure for a controlled interval to improve cardiac arrest outcome is a tantalizing concept. Myocardial preservation is accomplished in cardiac surgery most commonly by infusing the heart with a cold potassium cardioplegic solution. Rapid hypothermia is not currently feasible for most cardiac arrests, but rapid asystole induction with potassium infusion can be achieved with peripheral IV access. Our goal was to ascertain whether potassium-induced asystole with presumed myocardial energy conservation leads to a measureable improvement in cardiac arrest parameters.

We confirmed that it is possible to achieve ROSC post potassium-induced asystole during VF arrest. However, we failed to corroborate the Korean group findings of Lee, et al.¹³ as our experiment does not demonstrate evidence of a beneficial effect from infusion of a potassium plegic solution alone early in VF arrest. The change in AMSA was significantly worse in the KCl treatment group. Only 1 animal achieved ROSC.

A third arm was added to this study providing CaCl 3 minutes after KCl infusion to reverse the myocardial effects of the hyperkalemic state. Animals in the third arm demonstrated chemical defibrillation as previously observed,^{13,14} and the proportion with ROSC and their hemodynamics post ROSC were comparable to the placebo group. In essence, this approach provides both an “off” and “on” switch for myocardial contractile activity, and resumption of organized activity is accomplished without the trauma of electrical defibrillation.²⁰ We are unaware of any other pharmacologic agents that similarly defibrillate the heart.

In our study, transient asystole and depressed AMSA occurred within 1-2 minutes and lasted for 1-2 minutes in virtually all animals that received KCl infusion (Table). VF recurrence and variably poor AMSA recovery occurred in all animals treated with KCl alone. However, 4 of 6 animals treated with KCl + CaCl resumed organized electrical activity before or coincident with calcium infusion. Three KCl+CaCl animals went on to survival without the benefit of pressors (Figure 6).

Hyperkalemia did not dissipate 6 minutes after KCl infusion at the time of defibrillation based on serum potassium measurements. Persistently depressed AMSA scores and an inability to form an organized perfusing rhythm may have been partly due to untreated hyperkalemia. Calcium as a single agent rapidly counteracts the electrophysiologic effects of hyperkalemia.²¹ It is possible that calcium infusion alone provided benefit irrespective of prior potassium infusion, but calcium infusion has not demonstrated consistent benefit in multiple studies of cardiac arrest.²²

Sodium bicarbonate was infused in our experiment 7 minutes after VF onset to counteract anticipated acidosis post potassium infusion and as recommended by ACLS guidelines. A

reversal of the trend toward decreasing pH was observed in all study groups at the next measurement 3 minutes later (Figure 3b). However, sodium bicarbonate alone does not substantially lower or counteract elevated serum potassium.^{23,24}

We have performed a proof of concept experiment demonstrating potassium cardioplegia followed by calcium reversal can successfully resuscitate electrical phase VF. This represents a promising line of research for a condition that strikes hundreds of thousands of victims annually and has stubbornly resisted any therapeutic survival benefit beyond timely CPR and electrical defibrillation. It could prove most useful for: patients with prolonged down times in the circulatory or metabolic phases of VF arrest, the roughly 20% of VF cases refractory to electrical defibrillation,²⁵ patients in VF storm, possibly in concert with extracorporeal membrane oxygenation (ECMO), or even PEA. Nevertheless, many questions remain. If KCl + CaCl is beneficial, is this due to transient energy conservation, electrical defibrillation elimination, or other? Is it beneficial for more prolonged arrest? What would be the optimal dosing and timing of KCl and CaCl infusions? How can those with subsequent pseudo-PEA be most successfully resuscitated?

Limitations of this study include the use of an electrically-induced model of VF, and a limited animal number. This necessitated the use of surrogate interval data primary outcomes including AMSA and post-arrest MAP instead of the critical clinical dichotomous outcome, survival.

AMSA is firmly established as a predictor of defibrillation success,^{15,16,18} though its use has not been validated in abnormal potassium states, and it may be confounded by beta blockade and other therapies that lower energy utilization.¹⁹ Blinding could have been threatened by observation of the electrocardiographic tracing necessary to direct the resuscitation or by nonverbal cues from the single unblinded investigator.

We made two experimental errors that limit our results. As noted, one KCl+CaCl animal was inadvertently left untreated for 2 minutes after return of an organized rhythm with inadequate BP. The arterial catheter pressure readings had to be recalibrated in one animal treated with placebo, and thus this animal with falling BP was treated prematurely with norepinephrine prior to reaching a true MAP of 50 mm Hg (Figure 6).

Conclusions

Infusion of 1.5 mEq/kg potassium plegic solution by peripheral IV caused 1-2 minutes of transient asystole in a porcine model of electrically-induced VF arrest. Potassium cardioplegia followed by rapid calcium reversal, but not potassium alone, can lead to prompt chemical defibrillation with ROSC and survival comparable to recommended therapy. This novel therapeutic approach merits further investigation for more prolonged VF.

Acknowledgement

The authors are grateful to Dr. Clif Callaway for his encouragement and assistance with study design.

The project described was supported by Award Number 5K12HL109068 (KAM) from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Abbreviations

VF	ventricular fibrillation
CPR	cardiopulmonary resuscitation
AMSA	amplitude spectrum area
ROSC	return of spontaneous circulation
BP	blood pressure
MAP	mean arterial pressure
CPP	coronary perfusion pressure
ABG	arterial blood gas
ECG	electrocardiogram
IV	intravenous

References

1. Kohn RM. Myocardial Oxygen Uptake During Ventricular Fibrillation and Electromechanical Dissociation. *Am J Cardiol.* 1963; 11:483–6. [PubMed: 14034236]
2. Hallstrom AP, Eisenberg MS, Bergner L. The persistence of ventricular fibrillation and its implication for evaluating EMS. *Emerg Health Serv Q.* 1982; 1:41–9. [PubMed: 10258551]
3. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA.* 2010; 304:1447–54. [PubMed: 20924010]
4. Chambers DJ, Fallouh HB. Cardioplegia and cardiac surgery: pharmacological arrest and cardioprotection during global ischemia and reperfusion. *Pharmacol Ther.* 2010; 127:41–52. [PubMed: 20398698]
5. Lazar HL, Buckberg GD, Manganaro AJ, et al. Reversal of ischemic damage with secondary blood cardioplegia. *J Thorac Cardiovasc Surg.* 1979; 78:688–97. [PubMed: 491722]
6. Ovrum E, Tangen G, Holen EA, Ringdal MA, Istad R. Conversion of postischemic ventricular fibrillation with intraaortic infusion of potassium chloride. *Ann Thorac Surg.* 1995; 60:156–9. [PubMed: 7598579]
7. Watanabe G1, Yashiki N, Tomita S, Yamaguchi S. Potassium-induced cardiac resetting technique for persistent ventricular tachycardia and fibrillation after aortic declamping. *Ann Thorac Surg.* 2011; 91:619–20. [PubMed: 21256336]
8. Almdahl SM, Damstuen J, Eide M, Mølsted P, Halvorsen P, Veel T. Potassium-induced conversion of ventricular fibrillation after aortic declamping. *Interact Cardiovasc Thorac Surg.* 2013; 16:143–50. [PubMed: 23115100]
9. Liakopoulos OJ, Allen BS, Buckberg GD, et al. Resuscitation after prolonged cardiac arrest: role of cardiopulmonary bypass and systemic hyperkalemia. *Ann Thorac Surg.* 2010; 89:1972–9. [PubMed: 20494058]
10. Arlt M, Philipp A, Voelkel S, Graf BM, Schmid C, Hilker M. Out-of-hospital extracorporeal life support for cardiac arrest-A case report. *Resuscitation.* 2011; 82:1243–5. [PubMed: 21536364]
11. Berglund E, Monroe RG, Schreiner GL. Myocardial oxygen consumption and coronary blood flow during potassium-induced cardiac arrest and during ventricular fibrillation. *Acta Physiol Scand.* 1957; 41:261–8. [PubMed: 13497774]

12. McKeever WP, Gregg DE, Canney PC. Oxygen uptake of the nonworking left ventricle. *Circ Res.* 1958; 6:612–23. [PubMed: 13573592]
13. Lee HY, Lee BK, Jeung KW, et al. Potassium induced cardiac standstill during conventional cardiopulmonary resuscitation in a pig model of prolonged ventricular fibrillation cardiac arrest: a feasibility study. *Resuscitation.* 2013; 84:378–83. [PubMed: 22940601]
14. Kook Lee B, Joon Lee S, Woon Jeung K, et al. Effects of potassium/lidocaine-induced cardiac standstill during cardiopulmonary resuscitation in a pig model of prolonged ventricular fibrillation. *Acad Emerg Med.* 2014; 21:392–400. [PubMed: 24730401]
15. Povoas HP, Weil MH, Tang W, Bisera J, Klouche K, Barbatsis A. Predicting the success of defibrillation by electrocardiographic analysis. *Resuscitation.* 2002; 53:77–82. [PubMed: 11947983]
16. Ristagno G, Mauri T, Cesana G, et al. Azienda Regionale Emergenza Urgenza (AREU) Research Group. Amplitude spectrum area to guide defibrillation: a validation on 1617 patients with ventricular fibrillation. *Circulation.* 2015; 131:478–87. [PubMed: 25466976]
17. Institute of Laboratory Animal Research. Commission on Life Sciences. National Research Council; Guide for the Care and Use of Laboratory Animals. <http://www.nap.edu/catalog/5140.html> [March 5, 2015]
18. Povoas HP, Bisera J. Electrocardiographic waveform analysis for predicting the success of defibrillation. *Crit Care Med.* 2000; 28(11 Suppl):N210–1. [PubMed: 11098949]
19. Sherman L, Niemann J, Youngquist ST, Shah AP, Rosborough JP. Beta-blockade causes a reduction in the frequency spectrum of VF but improves resuscitation outcome: A potential limitation of quantitative waveform measures. *Resuscitation.* 2012; 83:511–6. [PubMed: 21996018]
20. Walcott GP, Killingsworth CR, Ideker RE. Do clinically relevant transthoracic defibrillation energies cause myocardial damage and dysfunction? *Resuscitation.* 2003; 59:59–70. [PubMed: 14580735]
21. Chamberlain MJ. Emergency treatment of hyperkalemia. *Lancet.* 1964; 1:464–7. [PubMed: 14102248]
22. Neumar RW, Otto CW, Lonk MS, et al. Part 8: Adult Advanced Cardiovascular Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010; 122:S729–S767. [PubMed: 20956224]
23. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. *Am J Kidney Dis.* 1996; 28:508–14. [PubMed: 8840939]
24. Kim HJ. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. *Nephron.* 1996; 72:476–82. [PubMed: 8852501]
25. Sakai T, Iwami T, Tasaki O, et al. Incidence and outcomes of out-of-hospital cardiac arrest with shock-resistant ventricular fibrillation: Data from a large population-based cohort. *Resuscitation.* 2010; 81:956–61. [PubMed: 20653086]

Figure 1.
Schematic timeline of the experimental trial design.

Figure 2.
Boxplots of AMSA as a function of treatment group 9 minutes post VF induction.

Figure 3.
Serum K, Ca, and pH dynamics as a function of treatment group.

ROSC and survival

Figure 4.
ROSC, survival, and norepinephrine infusion as a function of treatment group.

Example of electrocardiographic (blue) and blood pressure (red) tracings in an animal that received KCl infusion 4 minutes and CaCl infusion 7 minutes post VF induction

Figure 5.

Example electrocardiographic and associated blood pressure tracings as function of time in a KCl + CaCl animal. VF at 4 minutes post VF induction is followed by asystole 1 minute later after KCl infusion. A progressively improved and narrowing organized rhythm resumes after asystole and CaCl infusion 7 minutes post VF induction.

Figure 6.
MAP trajectory as a function of time in surviving animals.

Cardiac rhythm, normalized AMSA, and CPP as a function of time and treatment group

Table

Study Drug	Minutes post VF induction	KCl infusion				CaCl infusion				First Defibrillation										30 minute post ROSC observation:			
		0.3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Norepi for MAP<50	Norepi onset time		
KCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	pulseless VT	pulseless VT	pulseless VT	pulseless VT	pulseless VT	pulseless VT	asystole	brady PEA	asystole	asystole				
	AMSA	0.92	1.00	0.07	0.67	1.35	0.86	0.82	0.83	1.92	-	1.23	1.38	1.38	1.62	0.09	1.28	0.07	0.05				
	CPP		-4.9	32.9	17.3	7.3	6.9	5.3	5.9	12.1	1.7	0.2	4.1	0.7	-0.2	0.1	-4.0	-3.5	-1.9				
KCl	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF	asystole	brady pea	VF	VF	asystole	asystole	asystole	asystole	asystole	asystole				
	AMSA	1.27	1.00	0.86	0.62	0.66	0.86	0.79	-	0.17	1.07	0.71	0.83	0.09	0.11	0.14	0.09	0.10	0.38				
	CPP		16.6	22.2	25.0	23.4	19.0	17.2	14.0	13.0	13.4	13.6	14.4	13.0	13.3	13.1	13.1	13.0	12.8				
KCl	Rhythm	VF	VF	VF	asystole	asystole	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	trans pulse	VF	VF				
	AMSA	1.32	1.00	1.62	0.27	0.28	0.83	0.68	0.84	0.90	1.11	0.97	0.94	2.73	0.96	1.24	1.18	0.91	0.78				
	CPP		11.1	37.2	38.7	72.6	34.2	29.8	28.0	30.7	33.9	29.1	34.2	31.4	27.3	27.6	31.2	27.1	30.3				
KCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	VF	VF	PEA	pseudo PEA	pseudo PEA	pseudo PEA - >ROSC	SVT	SVT	SVT	SVT	Yes	39		
	AMSA	1.28	1.00	0.06	1.14	1.46	1.07	0.83	2.63	0.81	0.79	2.19	1.78	2.48	3.26	2.67	1.81	1.75	1.91				
	CPP		-7.6	22.0	3.5	0.0	-5.0	2.0	5.9	10.8	10.4	7.6	8.0	11.7	14.0	36.4	86.0	103.6	124.0				
KCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	VF	VF	VF	pulseless VT	PEA	PEA	PEA	PEA	PEA	PEA				
	AMSA	1.40	1.00	0.11	0.56	0.71	0.53	0.64	0.46	0.58	0.51	0.78	0.66	1.52	1.54	-	1.13	1.07	0.90				
	CPP		16.2	83.4	38.5	29.8	26.0	22.2	25.9	26.4	26.0	23.9	24.3	22.8	19.2	18.4	16.8	14.9	14.8				
KCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	PEA	PEA	PEA	PEA	brady PEA	asystole	asystole	asystole	asystole	asystole				
	AMSA	1.15	1.00	0.17	0.70	1.51	1.48	1.37	1.54	1.46	2.18	1.61	1.60	1.04	0.17	0.17	0.17	0.16	0.16				
	CPP		6.7	45.5	24.7	24.7	22.8	21.6	17.6	22.8	14.7	17.3	19.9	19.7	19.6	21.3	20.8	20.0	21.2				
KCl/CaCl	Rhythm	VF	VF	no pause	Asystole	pseudo PEA	pulseless VT	pulseless VT	VF	VF	VF-> asystole	asystole	pulseless VT -> PEA	PEA	VF	VF	VF	VF	VF				
	AMSA	0.76	1.00	-	0.25	0.31	0.41	0.44	2.71	0.32	0.44	0.26	1.53	1.74	0.38	0.41	0.34	0.34	0.33				
	CPP		-3.1	36.9	27.2	11.9	8.8	8.7	6.5	6.5	4.3	4.2	1.0	-1.7	-2.1	-4.1	-5.4	-7.7	-8.4				
KCl/CaCl	Rhythm	VF	VF	asystole	pseudo PEA	pseudo PEA	SVT	SVT	afib	pseudo PEA	VF	VF->asystole	brady PEA	asystole	asystole	asystole	asystole	asystole	asystole				
	AMSA	6.00	1.00	0.42	1.08	1.31	0.95	1.33	0.98	0.65	0.66	0.81	3.91	0.88	0.40	0.38	0.40	0.42	0.42				
	CPP		3.1	-3.8	-34.7	-43.8	-57.2	-56.2	-58.7	-49.5	-96.1	-61.1	-69.6	0.6	1.9	1.7	1.9	2.2	2.4				
KCl/CaCl	Rhythm	VF	VF	no pause	pseudo PEA	pseudo PEA	pseudo PEA	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	No			
	AMSA	1.18	1.00	-	0.79	0.72	1.32	1.30	1.33	1.43	1.17	1.09	1.10	1.05	1.10	1.23	1.21	1.22	1.29				
	CPP		-5.0	55.3	62.3	53.0	70.1	98.6	103.0	101.6	106.3	100.1	93.5	88.1	86.6	86.4	86.7	85.6	88.1				
KCl/CaCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	VF	VF->ROSC	sinus	sinus	afib	sinus	sinus	sinus	afib	afib	No			
	AMSA	0.88	1.00	0.39	0.52	0.45	0.49	0.46	0.56	0.45	0.61	0.72	0.64	0.64	0.74	0.63	0.70	0.99	0.92				
	CPP		4.6	61.1	28.2	23.6	15.5	16.2	14.8	27.7	21.3	24.0	29.5	27.7	33.8	54.5	40.0	49.4	33.7				
KCl/CaCl	Rhythm	VF	VF	asystole	VF	VF	VF	VF	VF	Fine VF	Fine VF	Fine VF	Fine VF	Fine VF	PEA	VF	VF	asystole	asystole				
	AMSA	2.12	1.00	0.37	0.78	0.35	0.42	0.28	-	0.33	0.60	0.23	0.27	0.16	0.32	0.17	0.19	0.15	0.17				

Study Drug	Minutes post VF induction	KCl Infusion			CaCl Infusion			First Defibrillation			11	12	13	14	15	16	17	18	19	20	30 minute post ROSC observation:	
		0.3	4	5	6	7	8	9	10	11											Norepi for MAP≤50	Norepi onset time
KCl/CaCl	CPP		4.2	56.8	14.4	7.3	3.7	3.9	2.6	2.1		2.9	0.9	-0.6	-1.0	-3.2	-5.9	-6.4	-8.3	-8.6		
	Rhythm	VF	VF	asystole	PEA	SVT	SVT	SVT	SVT	afib		afib	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	No	
	AMSA	1.28	1.00	0.29	1.25	1.47	1.08	1.74	1.15	0.87	0.83	0.83	0.78	0.82	0.82	0.82	0.77	0.84	0.71	0.80		
Placebo	CPP		19.3	37.2	53.8	87.8	134.5	137.6	143.9	131.7	126.2	121.6	120.1	119.1	112.8	112.8	113.1	112.4	110.7	106.1		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF	asystole		asystole	asystole	asystole	asystole	asystole	asystole	asystole	asystole	asystole		
	AMSA	0.99	1.00	1.91	1.40	1.26	1.07	0.86	0.57	0.27	0.18	0.13	0.13	0.12	0.57	0.13	0.14	0.12	0.18	0.28		
Placebo	CPP		-4.1	58.8	54.2	57.4	30.8	20.3	15.0	-1.4	-6.6	-8.4	-9.9	-9.3	-8.7	-8.7	-8.8	-8.9	-7.9	-8.6		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF->ROSC	SVT	SVT	SVT	SVT	Trigeminy	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Yes	24
	AMSA	0.88	1.00	1.32	1.47	1.67	1.50	1.36	1.19	2.96	3.50	3.43	2.33	1.17.7	1.39	1.19	1.16	1.13	0.98	0.90		
Placebo	CPP		17.6	53.5	44.1	40.7	36.7	29.5	31.5	109.3	118.2	122.1	117.7	125.9	119.6	119.6	117.9	114.4	108.0	102.4		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF		
	AMSA	1.25	1.00	1.37	1.44	1.46	1.31	1.40	1.36	1.15	1.41	1.21	1.30	1.30	0.89	0.79	0.55	0.45	0.42	0.34		
Placebo	CPP		-11.6	10.4	12.3	5.7	0.6	1.2	1.3	8.8	8.5	-1.5	1.1	-4.5	-6.5	-6.5	-11.1	-11.5	-12.8	-12.5		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF	VF	VF->ROSC	SVT	SVT	SVT	Afib	Afib	Afib	Afib	Afib	Afib	No	
	AMSA	1.13	1.00	1.44	1.55	1.45	1.53	1.39	1.24	1.38	1.26	2.40	1.99	132.6	2.59	1.63	1.72	2.06	1.65	1.80		
Placebo	CPP		10.1	47.8	35.8	33.7	29.6	32.0	31.1	31.6	41.9	133.2	132.6	123.1	110.8	110.8	112.6	119.7	102.3	91.2		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF->ROSC	SVT	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	sinus	Yes	24
	AMSA	1.37	1.00	0.95	1.64	1.65	1.37	1.51	8.56	0.95	1.78	1.66	1.76	1.76	1.74	1.36	1.32	1.26	1.19	1.08		
Placebo	CPP		-3.4	31.6	27.2	19.3	19.6	12.2	12.5	68.9	99.3	103.1	99.9	96.7	95.1	95.1	89.8	85.1	70.6	59.7		
	Rhythm	VF	VF	VF	VF	VF	VF	VF	VF->afib	VF	VF->afib	VF	VF->ROSC	SVT	SVT	SVT	sinus	sinus	sinus	sinus	Yes	30
	AMSA	0.93	1.00	1.12	1.28	1.50	1.43	1.08	1.22	1.27	1.54	1.13	1.11	2.86	1.96	1.96	2.33	2.38	2.02	2.17		
	CPP		11.9	42.6	36.7	37.3	45.3	42.0	39.9	43.6	37.6	33.7	45.0	126.1	106.0	106.0	91.7	87.8	94.3	95.5		

Pulseless VT is defined as a regular wide complex rhythm with rate> 120 BPM and MAP<50 mm Hg. Pseudo PEA is defined as organized electrical activity with rate<120 BPM and associated aortic arterial pressure deflections with MAP<50 mm Hg. PEA is defined as organized electrical activity with no discernible aortic arterial waveform.