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Experimental paper

Ethyl pyruvate enhances intra-resuscitation hemodynamics in prolonged ventricular fibrillation arrest☆,☆☆

Brian P. Suffoletto*, David D. Salcido, Eric S. Logue, Timothy W. Caprio, James J. Menegazzi

University of Pittsburgh, Department of Emergency Medicine, 230 McKee Place, Suite 400, Pittsburgh, PA 15213, United States

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ABSTRACT

Aims: As the duration of untreated cardiac arrest increases, the effectiveness of standard therapies declines, and may be more harmful than helpful. We investigated the hemodynamic, metabolic and anti-inflammatory effects of Ringer's ethyl pyruvate solution (REPS) versus Ringer's solution (RS) in the acute model of prolonged porcine arrest.

Methods: Seventeen mixed-breed swine were induced into ventricular fibrillation (VF) and left untreated for 8 min. CPR was begun using a mechanical chest compression device at a rate of 100 per minute. At the onset of CPR, animals were randomly assigned to treatment with either 25 mL/kg of RS or 25 mL/kg of REPS containing 40 mg/kg of ethyl pyruvate, infused over 5 min in blinded fashion. CPR continued with administration of a drug cocktail at 2 min and the first rescue shock was delivered at minute 13 of VF. Animals having ROSC were supported with standardized care for 2 h.

Results: Both groups had 100% ROSC and 100% 2-h survival. The REPS group exhibited higher median CPP (27.3 mmHg) than the control group (16.5 mmHg) by 3 min of CPR, which continued throughout the duration of CPR ($p = 0.02$). The median time to hypotension following ROSC was 9.64 min in the REPS group and 7.25 min in controls ($p = 0.04$) and there was a non-significant trend of decreased use of vasopressors for the duration of resuscitation. There was no difference in systemic or cerebral metabolism between groups. There were non-significant trends of decreased IL-6, increased Il-10 and decreased mesenteric bacterial colony growth in those treated with REPS when compared to RS.

Conclusions: The administration of REPS with CPR significantly improved intra- and post-resuscitation hemodynamics in this swine model of prolonged cardiac arrest, but did not definitely change the metabolic or inflammatory profile during the acute resuscitation period.

1. Introduction

Cardiopulmonary resuscitation (CPR) supplies vital organs with blood flow during cardiac arrest and is necessary to achieve successful resuscitation once the collapse-to-shock interval exceeds the first few minutes.[1,2]

In addition to chest compressions, guidelines recommend administering vasoactive pharmacotherapy during CPR to increase coronary perfusion pressure.[3] As the duration of arrest approaches 10 min, the body enters the metabolic phase of cardiac arrest where the effectiveness of these therapies declines rapidly.[4,5]

Even when these therapies are effective at achieving return of spontaneous circulation (ROSC), post-cardiac arrest syndrome results in significant morbidity and mortality.[6,7] Reperfusion from whole-body ischemia has been shown to result in organ injury independent of ischemia.[8] Various mechanisms likely contribute to this process, including the release of circulating inflammatory modulators.[5] Additionally, gut mucosal translocation of gram-negative bacteria may result in endotoxin- and cytokine-induced suppression of myocardial function after defibrillation.[9]

Currently, there is no recommended therapy specific to the metabolic phase of cardiac arrest, but studies of delayed hypothermia suggest that injury can be mitigated during and even after reperfusion.[10,11] There are reports in animals of improved survival when a drug cocktail (including adrenaline (epinephrine), lidocaine, bretylium, and propanolol) was used in prolonged arrest,[12] and reports of successful human resuscitation from prolonged perioperative arrest when a glutamate/aspartate substrate-enriched blood cardioplegic solution was used in addition to extracorporeal circulation.[13] Other experimental studies have demonstrated improved post-resuscitation myocardial function after infusion of

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* Corresponding author. Tel.: +1 412 901 6892; fax: +1 412 647 6669.
E-mail address: suffolettobp@upmc.edu (B.P. Suffoletto).

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dobutamine,[14] however concern remains for worsening of ischemic injury given its β-activity. Ideally, one would be able to administer a pharmacotherapy that provides metabolic support during the intra- and post-resuscitation period, resulting in less systemic inflammatory response and less hemodynamic instability.

Pyruvate, a metabolic fuel that has been shown to exhibit antioxidant[15] and anti-inflammatory[16] properties, may be an ideal candidate to include in such pharmacotherapy. It has been shown to increase energy reserves and antioxidant defenses of the resuscitated myocardium[10] as well as to improve overall neurologic recovery from cardiac arrest in experimental models.[11] However, it has poor stability in solution and rapidly dimerizes into parapyruvate, a metabolic inhibitor.[17] Ethyl pyruvate (EP) is a lipophilic ethyl ester of pyruvate that is stable in aqueous solution and is classified as safe by the Food and Drug Administration. In addition, it has shown enhanced redox potential[18] and anti-inflammatory properties not seen in equimolar doses of pyruvate.[19] Using a randomized controlled experimental design in established porcine model of prolonged ventricular fibrillation (VF), we examined the effects of Ringer's ethyl pyruvate solution (REPS) versus Ringer's solution (RS) on hemodynamics (coronary perfusion pressure (CPP) during CPR, time to hypotension post-ROSC, dose of vasopressors), metabolism (cerebral oxygen extraction, glucose, base deficit) and inflammation (TNF-alpha, IL-6, IL-10, mesenteric lymph node bacteria count). We hypothesized that resuscitation with REPS would improve these parameters compared with RS in the porcine model of prolonged cardiac arrest.

2. Material and methods

The University of Pittsburgh Institutional Animal Care and Use Committee approved this investigation.

2.1. Animal preparation

Seventeen domestic mixed-breed swine of either sex, ranging in mass from 23 to 29 kg, were included in the study. Prior to the experiment, animals were randomized into two groups: the control group (9 animals), receiving 25 mL/kg of Ringer's solution (RS), and the REPS group (8 animals), receiving 25 mL/kg of Ringer's solution containing 40 mg/kg of ethyl pyruvate (0.28 mmol/kg). The solutions were made equitonic so as to control for the effect on oncotic pressure. The investigators performing the resuscitation were blinded to group assignment.

Animals were prepared in a standardized fashion. We sedated the animals with intramuscular ketamine (10.0 mg/kg) and xylazine (4.0 mg/kg). We obtained intravenous (IV) access via a peripheral ear vein via a 21 g catheter. We established a surgical plane of anesthesia using a rapid IV infusion of alpha-chloralose (50 mg/kg), and maintained this with a continuous infusion of the same (10 mg/kg/hr). We intubated the swine with a 5-0 cuffed endotracheal tube via direct laryngoscopy, and ventilated them using an Ohmeda 7000 ventilator (Ohmeda, BOC Health Care, Madison, WI). Ventilation began at a tidal volume of 15–18 cc/kg, a ventilatory rate of 12 breaths per minute, and an inspiration:expiration ratio of 50%. Ventilation was adjusted to maintain eucapnea (end-tidal carbon dioxide 35–45 mmHg), which was measured with a main-stream capnometer (Zoll M Series CCT). We measured core body temperature by placing an esophageal probe (Bi-Temp Temperature Monitor, Respiratory Supply Products, Inc., Irvine, CA) approximately 10 cm into the animals' esophagus. We placed three surface electrodes configured to correspond to a standard lead II electrocardiogram (ECG), and monitored this continuously. After establishing a surgical depth plane of anesthesia, we paralyzed the animals with pancuronium (4 mg initial bolus IV with additional 2 mg boluses as needed).

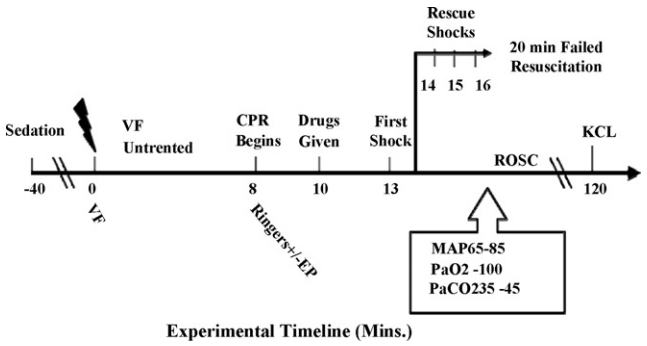

Fig. 1. Abbreviations: VF, ventricular fibrillation; CPR, cardiopulmonary circulation; MAP, mean arterial pressure; PaO_2, arterial pressure of oxygen; $PaCO_2$, arterial pressure of CO_2; ROSC, return of spontaneous circulation; EP, ethyl pyruvate; KCL, potassium chloride.

We then placed arterial and venous introducers (9 Fr) in the right femoral artery and vein and passed 7 Fr micro-manometer tipped pressure catheters (Mikro-Tip Catheter Transducers SPR-471A and SPC-370-S, Millar Instruments, Houston, TX) into the ascending aorta and right atrium. Correct positioning of the catheters was confirmed by interpretation of the pressure tracings. Arterial and venous pressures were monitored continuously with the same data acquisition system used to record the ECG. As well, we placed a 9F introducer into the right jugular bulb to measure cerebral oxygen extraction. We recorded the anesthesia time (which we defined as the time from the induction of anesthesia to the time VF was induced).

We induced VF by delivering a 3 s, 60 Hz, 100 mA alternating current externally across the thorax. We recorded the anesthesia time, which we defined as the time from the induction of anesthesia to the time VF was induced. After VF was induced, the animals were untreated for 8 min. After 8 min of VF, CPR was begun using a mechanical chest compression device (LUCAS), which gave compressions at a rate of 100 per minute, at a depth of 5 cm in the antero-posterior position, and a duty cycle of 50%. At the onset of CPR animals received either control or EP solution, infused over a 5 min period. After 2 min of CPR (minute 10 of VF) we gave adrenaline (0.10 mg/kg), vasopressin (40 U) and propranolol (0.1 mg/kg). CPR continued and the first rescue shock was delivered at minute 13 of VF. All shocks were 150 J biphasic waveform defibrillations. Animals having return of spontaneous circulation (ROSC) were followed for up to 2 h, and were supported with standardized care. The experimental endpoints were either 2 h survival or failed resuscitation. The experimental timeline can be seen in Fig. 1.

2.2. Acid–base chemistry

Arterial blood samples for blood gas analysis (~3 cc) were analyzed as soon as arterial access was established (baseline), after 12 min of untreated VF-, and after 30-, 60-, 90- and 120-min post-return of spontaneous circulation (ROSC) (i-STAT Portable Clinical Analyzer, Heska Corporation, Waukesha, WI).

2.3. Hemodynamic measurements

Hemodynamic measurements were acquired digitally at a sampling rate of 1000 points/s with a commercially available software package (Chart, v.5.3, ADInstruments, Castle Hill, Australia). CPP was defined as aortic diastolic pressure minus right atrial diastolic pressure and was determined at a time point 0.1 s just prior to the