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Experimental paper

Reperfusion injury protection during Basic Life Support improves circulation and survival outcomes in a porcine model of prolonged cardiac arrest

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ABSTRACT

Objective: Ischemic postconditioning (PC) using three intentional pauses at the start of cardiopulmonary resuscitation (CPR) improves outcomes after cardiac arrest in pigs when epinephrine (epi) is used before defibrillation. We hypothesized PC, performed during basic life support (BLS) in the absence of epinephrine, would reduce reperfusion injury and enhance 24 h functional recovery.
Design: Prospective animal investigation.
Setting: Animal laboratory
Subjects: Female farm pigs ($n = 46$, 39 ± 1 kg).
Interventions: Protocol A: After 12 min of ventricular fibrillation (VF), 28 pigs were randomized to four groups: (A) Standard CPR (SCPR), (B) active compression-decompression CPR with an impedance threshold device (ACD-ITD), (C) SCPR + PC (SCPR + PC) and (D) ACD-ITD CPR + PC. Protocol B: After 15 min of VF, 18 pigs were randomized to ACD-ITD CPR or ACD-ITD + PC. The BLS duration was 2.75 min in Protocol A and 5 min in Protocol B. Following BLS, up to three shocks were delivered. Without return of spontaneous circulation (ROSC), CPR was resumed and epi (0.5 mg) and defibrillation delivered. The primary end point was survival without major adverse events. Hemodynamic parameters and left ventricular ejection fraction (LVEF) were also measured. Data are presented as mean ± SEM.
Measurements and Main Results: Protocol A: ACD-ITD + PC (group D) improved coronary perfusion pressure after 3 min of BLS versus the three other groups (28 ± 6, 35 ± 7, 23 ± 5 and 47 ± 7 for groups A, B, C, D respectively, $p = 0.05$). There were no significant differences in 24 h survival between groups.
Protocol B: LVEF 4 h post ROSC was significantly higher with ACD-ITD + PC vs ACD-ITD alone ($52.5 \pm 3\%$ vs. $37.5 \pm 6.6\%$, $p = 0.045$). Survival rates were significantly higher with ACD-ITD + PC vs. ACD-ITD alone ($p = 0.027$).
Conclusions: BLS using ACD-ITD + PC reduced post resuscitation cardiac dysfunction and improved functional recovery after prolonged untreated VF in pigs.
Protocol number: 12-11.

Introduction

Despite years of research to improve survival after out-of-hospital cardiac arrest (OHCA), survival with good neurologic outcome remains poor.[1] Recently, new investigations have examined the relationship between outcomes and the method by which blood flow is reintroduced to the body after a prolonged period of ischemia. In many clinical scenarios, the reperfusion process itself can cause injury. Reperfusion injury is proportional to the duration of ischemia and the way blood flow is reintroduced after prolonged ischemia. Reperfusion injury can cause up to 50% of the total damage induced by myocardial infarction in animal models[2–4].

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There are multiple ways to reduce reperfusion injury: most involve modulation of this process with drugs that affect the reperfusion injury salvage kinase (RISK) pathway or mitochondrial permeability transition pore, or both.[4] Re-introduction of blood flow with "controlled pauses" is a non-pharmacological means to protect the myocardium and the brain from ischemia reperfusion injury in clinical scenarios of regional ischemia during ST elevation myocardial infarction and stroke.[4–6] This concept is called "ischemic post-conditioning" (PC).[7] PC using three intentional 20 s pauses at the initiation of CPR improves hemodynamics and neurologically intact survival after prolonged ventricular fibrillation in porcine models of cardiac arrest.[8,9] In previous studies with PC, epinephrine was always used before the first defibrillation attempt.

The aim of the study was to assess if PC used during the Basic Life Support (BLS) phase of CPR would provide better cerebral and myocardial protection against reperfusion injury and facilitate functional recovery after prolonged untreated VF compared to CPR alone.

Methods

This study was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center. All animal care was compliant with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals (protocol number: 12-11). All studies were performed by a qualified, experienced research team in Yorkshire female farm bred pigs weighing 39 ± 1 kg. A certified and licensed veterinarian assured the protocols were performed in accordance with the National Research Council's Guidelines.

Preparatory phase

The aseptic surgical preparation, anesthesia, data monitoring and recording procedures used in this study have been previously described.[10,11] Animals were fasted overnight. Intramuscular ketamine (10 mL of 100 mg mL^{-1}) was used for sedation followed by inhaled isoflurane (0.8–1.2%). Pigs were intubated with a size 7.0 endotracheal tube then ventilated with room air, using an anesthesia machine (Narkomed, Telford, Pennsylvania), with a tidal volume of 10 ml kg^{-1} and a respiratory rate adjusted to continually maintain a PaCO2 of 40 mmHg and PaO2 of 80 mmHg (blood oxygen saturation > 95%). Normothermia was maintained with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota). Central aortic blood pressure was recorded continuously with a Millar catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX, USA) placed in the descending thoracic aorta. A second Millar catheter was inserted in the right atrium via the right external jugular vein. An ultrasound flow probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, New York) was placed in the left common carotid artery to quantify carotid blood flow (ml min^{-1}). Animals received an intravenous heparin bolus (100 units kg^{-1}). Arterial blood gases (Gem 3000, Instrumentation Laboratory) were obtained at baseline, 15, 30, 60 and 4 h after return of spontaneous circulation (ROSC). Electrocardiograms were continuously recorded. Hemodynamic data were continuously monitored and recorded (BIOPAC MP 150, BIOPAC Systems, Inc., CA, USA). Coronary perfusion pressure (CPP) was calculated as the difference between aortic and right atrial pressures during the decompression phase. End tidal carbon dioxide ($ETCO_2$), tidal volume, minute ventilation, and blood oxygen saturation were continuously measured (COSMO Plus, Novametrix Medical Systems, Wallingford, Connecticut). ROSC was defined using the Utstein guidelines for uniform reporting in animal research as maintenance of systolic pressure of ≥60 mm Hg for ≥10 consecutive minutes.[12]

Experimental protocol

Following the surgical preparation VF was induced by delivering direct intra-cardiac current via a temporary pacing wire. STD-CPR and ACD-CPR were performed with a pneumatically driven automatic piston device (Pneumatic Compression Controller, Ambu International, Glostrup, Denmark) as previously described.[13] During STD-CPR, uninterrupted chest compressions were performed at a rate of 100 compressions/min, with a 50% duty cycle and a compression depth of 25% of the anteroposterior chest diameter. After each compression, the chest wall was allowed to fully recoil passively. With ACD-CPR, after each compression, the chest was actively pulled upwards with a suction cup attached to the skin with a decompression force of ∼20 lbs.[13,14]

Concurrently with ACD-CPR, an impedance threshold device (ITD, ResQPOD TM, Advanced Circulatory Systems, Roseville, MN, USA) with a resistance of 16 mmHg was attached to the endotracheal tube. After the period of intentional pauses, when positive pressure breaths were delivered only during the pauses, asynchronous positive pressure ventilations were delivered with room air (FiO2 of 0.21) with a manual resuscitator bag. The tidal volume was maintained at ∼10 mL kg^{-1} and the respiratory rate was 10 breaths min^{-1}.

Protocol A

Following 12 min of untreated ventricular fibrillation, 28 pigs were randomized to receive CPR during the BLS period as follows:

1) Group A: Standard CPR (SCPR)
2) Group B: ACD-ITD CPR
3) Group C: SCPR plus PC (SCPR-PC)
4) Group D: ACD-ITD CPR plus PC (ACD-ITD + PC)

PC groups initially received 20 s of CPR (SCPR or ACD-ITD) without positive pressure breaths followed by a 20 s pause of compressions followed by another 20 s of CPR and the cycle was repeated for a total of three pauses. Three positive pressure breaths were delivered during each pause, with each breath delivered over 1 s and 6 s between each breath. After 2.75 min of BLS, the first defibrillation effort was delivered with 275-J biphasic shocks.

If ROSC was not achieved, defibrillation was delivered every 2 min thereafter during CPR. Epinephrine was administered in all animals without ROSC as a 0.5 mg (∼15 μg kg^{-1}) bolus at 4 min together with 25 mg of amiodarone. In addition, during this Advanced Life Support (ALS) phase we used an active form of the intrathoracic pressure regulation therapy rather than the ITD, which generated a continuous negative intrathoracic pressure of -9 mmHg between each positive pressure breath.[15,16] All animals received oxygen at 4 l min^{-1} rate during ALS.

Protocol B

The two groups with the best survival results in Protocol A were selected. After 15 min of untreated VF, 18 pigs were randomized to receive BLS augmented with ACD-ITD CPR or ACD-ITD CPR plus controlled pauses (Fig. 1). Controlled pauses, ventilations, and the CPR method were performed as in Protocol A. Unlike Protocol A, the BLS period in Protocol B was 5 min in duration, after which the first defibrillation shock was delivered. If ROSC was not achieved, defibrillation shocks were delivered every 2 min thereafter during CPR. Epinephrine was administered in all groups in a 0.5 mg (∼15 μg kg^{-1}) bolus at 6 min together with 25 mg of amiodarone. Similar to Protocol A, an active form of the ITD that provided continuous negative intrathoracic pressure was used during the ALS phase.