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Experimental paper

Sodium nitroprusside enhanced cardiopulmonary resuscitation improves short term survival in a porcine model of ischemic refractory ventricular fibrillation☆,☆☆

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ABSTRACT

Introduction: Sodium nitroprusside (SNP) enhanced CPR (SNPeCPR) demonstrates increased vital organ blood flow and survival in multiple porcine models. We developed a new, coronary occlusion/ischemia model of prolonged resuscitation, mimicking the majority of out-of-hospital cardiac arrests presenting with shockable rhythms.
Hypothesis: SNPeCPR will increase short term (4-h) survival compared to standard 2015 Advanced Cardiac Life Support (ACLS) guidelines in an ischemic refractory ventricular fibrillation (VF), prolonged CPR model.
Methods: Sixteen anesthetized pigs had the ostial left anterior descending artery occluded leading to ischemic VF arrest. VF was untreated for 5 min. Basic life support was performed for 10 min. At minute 10 (EMS arrival), animals received either SNPeCPR (n = 8) or standard ACLS (n = 8). Defibrillation (200J) occurred every 3 min. CPR continued for a total of 45 min, then the balloon was deflated simulating revascularization. CPR continued until return of spontaneous circulation (ROSC) or a total of 60 min, if unsuccessful. SNPeCPR animals received 2 mg of SNP at minute 10 followed by 1 mg every 5 min until ROSC. Standard ACLS animals received 0.5 mg epinephrine every 5 min until ROSC. Primary endpoints were ROSC and 4-h survival.
Results: All SNPeCPR animals (8/8) achieved sustained ROSC versus 2/8 standard ACLS animals within one hour of resuscitation (p = 0.04). The 4-h survival was significantly improved with SNPeCPR compared to standard ACLS, 7/8 versus 1/8 respectively, p = 0.0019.
Conclusion: SNPeCPR significantly improved ROSC and 4-h survival compared with standard ACLS CPR in a porcine model of prolonged ischemic, refractory VF cardiac arrest.

Introduction

Current resuscitation interventions for the approximate 380,000 patients who suffer out-of-hospital cardiac arrest (OHCA) each year in the United States result in an average functionally favorable survival rate ranging from 6 to 15%.[1] Most do not survive or get admitted to the hospital, and most are pronounced dead in the field. However, 25–30% of patients present with the shockable rhythms of ventricular fibrillation and/or tachycardia (VF/VT)[2–5] and this subset of the arrest population experiences survival rates ranging from 30 to 50%.[1–3] Thus, the VF/VT population represents the overwhelming proportion (up to 85%) of OHCA survivors.[6]

Irrespective of the presence or absence of ST elevation on the post-resuscitation 12-lead electrocardiogram (ECG), the VF/VT OHCA population has been shown to have a high prevalence (~60%) of acute coronary occlusion and/or coronary artery

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☆☆ All studies were performed with approval from the Institutional Animal Care Committee of the University of Minnesota (protocol 1508-32926A).
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ischemia.[7–12] This prevalence is even higher for the 50–70% of patients with refractory VF/VT.[7–12] Recognizing this underlying, potentially reversible cause for refractory VF/VT, the Minnesota Resuscitation Consortium established the first organized refractory VF/VT protocol in the nation. The protocol includes optimizing OHCA CPR hemodynamics using mechanical CPR devices, facilitating early emergency medical services (EMS) transport to the cardiac catheterization laboratory (CCL), delivering emergent percutaneous coronary intervention (PCI), and providing effective hemodynamic support using intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) before and/or after PCI procedures. Preliminary experience with this approach demonstrates a functionally favorable survival rate of 50%, despite prolonged CPR and resuscitation efforts.[7]

Sodium nitroprusside enhanced CPR (SNPeCPR) has been shown to improve CPR generated blood flow to the heart and brain,[13–17] improve cardiac function after pulseless electrical activity (PEA) and VF arrest, and cerebral recovery in prolonged CPR and prolonged untreated VF porcine models of cardiac arrest.[14,15,18]

We hypothesized that during prolonged resuscitation for ischemic refractory VF, the use of SNPeCPR advanced cardiac life support (ACLS) would lead to a higher return of spontaneous circulation (ROSC) rate and survival. To test this hypothesis, we developed a porcine model of severe refractory ischemic VF with ostial left anterior descending (LAD) balloon occlusion and CPR. In this model, return of spontaneous circulation (ROSC) in animals treated with standard ACLS is rare during coronary occlusion, simulating very closely the clinical presentation of patients treated in the CCL by the Minnesota Resuscitation Consortium refractory VF/VT protocol.[7]

Methods

This study was approved by the Institutional Animal Care and Use Committee of the University of Minnesota. 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 (40 ± 2 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 are part of our approved protocols. 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 $PaCO_2$ of 40 mmHg and PaO_2 of at least 80 mmHg (blood oxygen saturation > 95%). Normothermia was maintained with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota). Post resuscitation therapeutic hypothermia (34 °C) was achieved by the use of Blanketrol cooling blanket (Cincinnati Sub Zero). 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. Animals received an intravenous heparin bolus (100 units/kg).

Heparin is necessary to avoid intracoronary and intra-aortic thrombosis due to the presence of coronary guide catheters, coronary dilation balloons and wires. Arterial blood gases (Gem 3000, Instrumentation Laboratory) were obtained at baseline, and then every 5 min until 45 min, and then every hour starting at 1 h until death or sacrifice at 4 h. Electrocardiograms were continuously recorded. Hemodynamic data were continuously monitored and recorded (LabVIEW, National Instruments). Coronary perfusion pressure (CPP) was calculated as the difference between diastolic blood pressure and right atrial pressure. End tidal carbon dioxide ($ETCO_2$), tidal volume, minute ventilation, and blood oxygen saturation were continuously measured (COSMO Plus, Novametrix Medical Systems, Wallingford, Connecticut).

Experimental protocol

After the animals were prepared in the manner described above, percutaneous femoral arterial sheaths were placed. The left coronary artery was engaged using an AL 0.75 short tip guide catheter. A coronary guidewire was placed in the distal LAD and a 4.0 × 16 mm balloon was inflated in the ostial portion of the LAD before the first diagonal. The majority of the animals (13/16) developed ventricular fibrillation spontaneously. If the animal did not arrest spontaneously within 5 min, VF was induced via electrical stimulation in the right ventricle (via the right external jugular vein access). Ventricular fibrillation was left untreated for 5 min to simulate the average arrival time of first responders in our state of Minnesota. At 5 min of VF, basic life support (BLS) was initiated with chest compressions, using an automated system in which we determine the precise depth of compression and decompression. The compression decompression duty cycle was 50%, the rate was 100/min and the target depth was 20% of the antero-posterior thoracic diameter at the mid sternal level. All animals received automated active compression decompression (ACD) + impedance threshold device (ITD) CPR regardless of group assignment.[2] At that point, animals were randomized based on a computer-generated list, to be treated

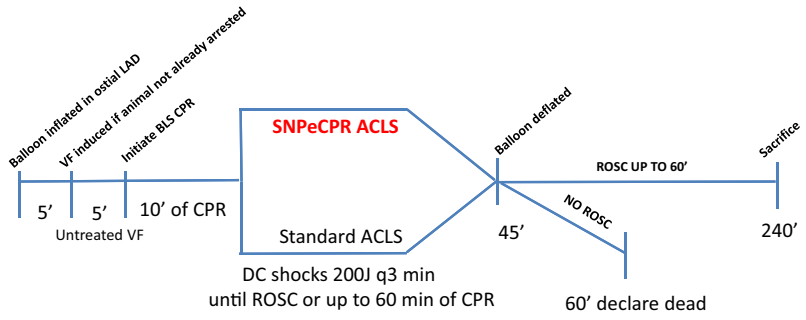

Fig. 1. Study protocol.
LAD: left anterior descending artery; VF: ventricular fibrillation; BLS: basic life support; CPR: cardiopulmonary resuscitation; SNPeCPR: sodium nitroprusside enhanced CPR; ACLS: advanced cardiac life support; DC: direct current; J: joules; ROSC: return of spontaneous circulation.