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Experimental paper

Early coronary revascularization improves 24 h survival and neurological function after ischemic cardiac arrest. A randomized animal study☆

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ABSTRACT

Background: Survival after out-of-hospital cardiac arrest (OHCA) remains poor. Acute coronary obstruction is a major cause of OHCA. We hypothesize that early coronary reperfusion will improve 24 h-survival and neurological outcomes.
Methods: Total occlusion of the mid LAD was induced by balloon inflation in 27 pigs. After 5 min, VF was induced and left untreated for 8 min. If return of spontaneous circulation (ROSC) was achieved within 15 min (21/27 animals) of cardiopulmonary resuscitation (CPR), animals were randomized to a total of either 45 min (group A) or 4 h (group B) of LAD occlusion. Animals without ROSC after 15 min of CPR were classified as refractory VF (group C). In those pigs, CPR was continued up to 45 min of total LAD occlusion at which point reperfusion was achieved. CPR was continued until ROSC or another 10 min of CPR had been performed. Primary endpoints for groups A and B were 24-h survival and cerebral performance category (CPC). Primary endpoint for group C was ROSC before or after reperfusion.
Results: Early compared to late reperfusion improved survival (10/11 versus 4/10, $p = 0.02$), mean CPC (1.4 ± 0.7 versus 2.5 ± 0.6, $p = 0.017$), LVEF (43 ± 13 versus $32 \pm 9\%$, $p = 0.01$), troponin I (37 ± 28 versus 99 ± 12, $p = 0.005$) and CK-MB (11 ± 4 versus 20.1 ± 5, $p = 0.031$) at 24-h after ROSC. ROSC was achieved in 4/6 animals only after reperfusion in group C.
Conclusions: Early reperfusion after ischemic cardiac arrest improved 24 h survival rate and neurological function. In animals with refractory VF, reperfusion was necessary to achieve ROSC.

1. Introduction

Sudden out-of-hospital cardiac arrest (OHCA) remains a serious public health problem associated with very poor hospital survival rates. Steady but small progress has been made over the last 50 years and survival rates from cardiopulmonary resuscitation (CPR) have remained relatively stable over the past half century.[1] In the best emergency medical systems in the world overall survival does not exceed 15% for all presenting rhythms. Under optimal conditions patients presenting with a shockable rhythm have >50% chance of survival with good neurological outcome.[2,3] Although less than 30% of patients presenting with out of hospital cardiac arrest have a shockable rhythm, this subset represents 90% of the patients that leave the hospital with good neurological function.[4–6]

Acute coronary obstruction is a major cause of cardiac arrest.[7] A large proportion of patients that present with shockable rhythms such as ventricular fibrillation and tachycardia (VF/VT) have significant coronary artery disease.[8–10] Although early primary percutaneous intervention and revascularization has been associated with improved odds for survival in observational studies, there are no randomized data in humans to support the practice, both for STEMI or NSTEMI patients.[7]

We hypothesize that early revascularization will improve post-resuscitation hemodynamic stability and lead to improved 24-h

Abbreviations: ACD, active compression decompression; ACLS, advanced cardiac life support; CK-MB, creatine kinase-MB; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ITD, impendence threshold device; OHCA, out of hospital cardiac arrest; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

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survival with good neurological function. We further hypothesize that in refractory ventricular fibrillation due to an occluded coronary artery the only way to achieve return to spontaneous circulation is to successfully perform coronary revascularization and establish reperfusion. In order to answer those two questions, we utilized a highly reproducible left anterior descending coronary artery myocardial infarction porcine model of cardiac arrest and resuscitation.[11]

2. Materials and methods

All studies were performed by a qualified, experienced research team in 27 Yorkshire female farm pigs weighing 36 ± 4 kg. The protocol was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation. All animals received treatment and care in compliance with the 1996 Guide for the Care and Use of Laboratory Animals by the National Research Council in accordance with the United States Department of Agriculture Animal Welfare Act, Public Health Service Policy, and the American Association for Accreditation of Laboratory Animal Care.

2.1. Preparatory phase

The anesthesia, surgical preparation, data monitoring, and recording procedures used in this study have been described previously.[12] Briefly, we employed aseptic surgical conditions, using initial sedation with intramuscular ketamine (7 mL of 100 mg/mL, Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) followed by inhaled isoflurane at a dose of 0.8–1.2%. Pigs were intubated with a size 7.0 endotracheal tube. The animal's bladder temperature was maintained at 37.5 ± 0.5 °C with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, MN). Central aortic blood pressure was recorded continuously with a micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments, Houston, TX) catheter placed at the beginning of the descending thoracic aorta. A second Millar catheter was inserted in the right atrium via the right external jugular vein. All animals received an intravenous heparin bolus (100 units/kg) and 500 units of heparin every hour until surgical repair was completed. An ultrasound flow probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, NY) was placed to the right internal carotid artery to record blood flow (mL/min). The animals were then ventilated with room air, using a volume-control ventilator (Narcomed, Telford, PA), with a tidal volume of 10 mL/kg and a respiratory rate adjusted to continually maintain a PaCO2 of 40 mmHg and PaO2 of 80 mmHg (blood oxygen saturation >95%), as measured from arterial blood (Gem 3000, Instrumentation Laboratory, Lexington, MA) to adjust the ventilator as needed. Surface electrocardiographic tracings were continuously recorded. All data were recorded with a digital recording system (BIOPAC MP 150, BIOPAC Systems, CA). End-tidal CO_2 ($ETCO_2$), tidal volume, minute ventilation, and blood oxygen saturation were continuously measured with a respiratory monitor (CO_2SMO Novametrix Medical Systems, Wallingford, CT).

2.2. Measurements and recording

Thoracic aortic pressure, right atrial pressure, ETCO2, and carotid blood flow (CBF) were continuously recorded. Coronary perfusion pressure during CPR was calculated from the mean arithmetic difference between right atrial pressure and aortic pressure during the decompression phase. Carotid artery blood flow was reported in mL/s.

2.3. Coronary artery occlusion methodology[11]

Under fluoroscopic guidance, a 6F short AL 0.75 guide catheter was used to engage the left main coronary artery. Using a non-hydrophilic 0.014-in guidewire, we advanced an over-the-wire 3.0–3.5 × 12-mm balloon into the left anterior descending coronary artery (LAD) and placed it after the first diagonal regardless of the size of the vessel or distal territory. Continuous limb and 2 precordial ECG tracings were recorded. The average time from the guide catheter engagement of the left main to balloon inflation was 6 ± 1.5 min and not different between groups.

2.4. Experimental protocol

After the surgical preparation was complete, oxygen saturation on room air was >95% and $ETCO_2$ was stable between 35 and 42 mmHg for 5 min. Total LAD occlusion, as described above, was induced via balloon inflation. After 5 min, ventricular fibrillation (VF) was induced by delivering intracardiac current via a temporary pacing wire (St. Jude Medical, Minnetonka, MN) and was left untreated for 8 min. The ventilator was disconnected from the endotracheal tube. All but one animal had electrical induction of VF. One animal in group A had spontaneous VF at minute 4 of LAD occlusion.

Active compression decompression (ACD) CPR was performed with a pneumatically driven automatic piston device (Pneumatic Compression Controller, Ambu International, Glostrup, Denmark) as previously described.[13] An impedance threshold device (ITD-16) (ResQPOD, Advanced Circulatory Systems, Inc., Minneapolis, MN) was used to provide ACD + ITD CPR.[4]

During 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 were provided. Asynchronous positive-pressure ventilations were delivered with room air (FiO_2 of 0.21) with a manual resuscitator bag. The tidal volume was maintained at ~10 mL/kg and the respiratory rate was 10 breaths/min.

Following 8 min of untreated VF and 3 min of CPR (simulating basic life support), epinephrine was administered in a 0.5 mg (~15 μg/kg) bolus at minute 3 of CPR. Cardioversion shocks were delivered with 200 J every 3 min and advanced cardiac life support (ACLS) was continued until either return of spontaneous circulation (ROSC) was achieved or 15 min of CPR were performed unsuccessfully.

If ROSC was achieved within 15 min, the animals were randomized to either 45 min (group A) or 4 h (group B) of total mid-LAD occlusion before reperfusion. In both groups, the primary end-points were 24-h left ventricular ejection fraction (LVEF) and survival with good neurological function. We chose 45 min of occlusion since in our porcine model that period of time gives on average about 50% of infarction size to area at risk. The infarction size expressed as a percentage of the area at risk is not related to the site of occlusion in this model.[14] For longer duration of occlusion (e.g. >90 min) the ratio of infarction to area at risk approaches >70% and reperfusion offers no or minimal benefit.[11] We chose this time in order to simulate early access (<4 h human equivalent) to the catheterization laboratory for patients with ST elevation myocardial infarction when benefits from revascularization are clinically observed.[15–17]

If ROSC was not achieved within 15 min, pigs were included in the refractory VF (group C) and ACLS was continued up to a total of 45 min of LAD occlusion. Defibrillation and epinephrine as well as amiodarone were given per AHA 2010 guidelines.[18,19] Amiodarone (20 mg) was administered bolus intravenously after the third unsuccessful shock cycle. If VF was refractory another bolus