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Experimental paper

Anaesthetic *Postconditioning at the Initiation of CPR Improves Myocardial and Mitochondrial Function in a Pig Model of Prolonged Untreated Ventricular F*ibrillation☆

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ABSTRACT

Background: Anaesthetic *post*conditioning (APoC) attenuates myocardial injury following coronary ischaemia/reperfusion. We hypothesised that APoC at the initiation of cardiopulmonary resuscitation (CPR) will improve post resuscitation myocardial function along with improved mitochondrial function in a pig model of prolonged untreated ventricular fibrillation.
Methods: In 32 pigs isoflurane anaesthesia was discontinued prior to induction of ventricular fibrillation that was left untreated for 15 min. At the initiation of CPR, 15 animals were randomised to controls (CON), and 17 to APoC with 2 vol% sevoflurane during the first 3 min CPR. Pigs were defibrillated after 4 min of CPR. After return of spontaneous circulation (ROSC), isoflurane was restarted at 0.8–1.5 vol% in both groups. Systolic and diastolic blood pressures were measured continuously. Of the animals that achieved ROSC, eight CON and eight APoC animals were randomised to have their left ventricular ejection fraction (LVEF%) assessed by echocardiography at 4 h. Seven CON and nine APoC were randomised to euthanasia 15 min after ROSC to isolate mitochondria from the left ventricle for bioenergetic studies.
Results: ROSC was achieved in 10/15 CON and 15/17 APoC animals. APoC improved haemodynamics during CPR and post-CPR LVEF%. Mitochondrial ATP synthesis, coupling of oxidative phosphorylation and calcium retention capacity were improved in cardiac mitochondria isolated after APoC.
Conclusions: In a porcine model of prolonged untreated cardiac arrest, APoC with inhaled sevoflurane at the initiation of CPR, is associated with preserved mitochondrial function and improved post resuscitation myocardial dysfunction.
Approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center (protocol number 11-05).
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1. Introduction

With an estimated 350,000 patients per year in the United States alone[1] and a survival rate of only 3–16%,[2] out-of-hospital cardiac arrest (OHCA) continues to be a significant cause of neurologic[3] and cardiac[4] morbidity and mortality. We have recently shown that ischaemic *post*conditioning at the initiation of standard[5] or sodium nitroprusside-enhanced cardiopulmonary resuscitation (CPR)[6]

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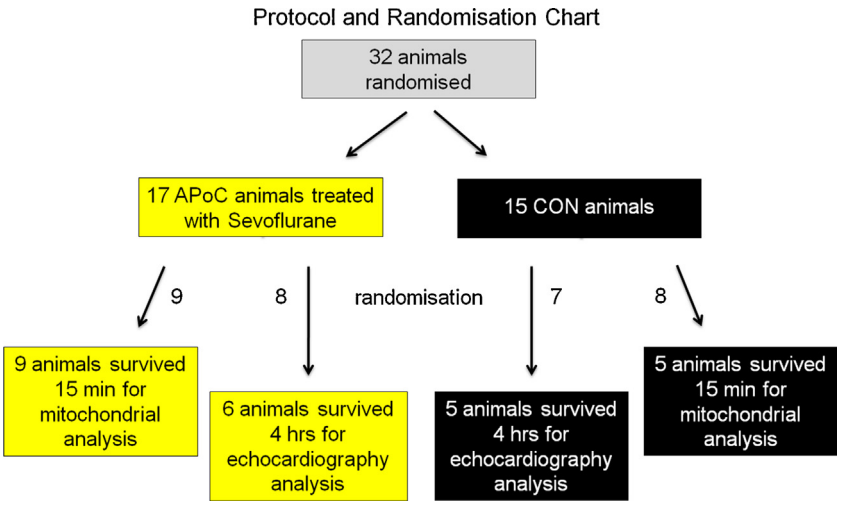

Fig. 1. Protocol and randomisation chart. Animals were initially randomised to either be treated as controls (CON) or to receive inhaled 2 vol% sevoflurane at the initiation of CPR for 3 min with each breath (anaesthetic postconditioning, APoC). Animals were further randomised to either 15 min survival before euthanasia for mitochondrial analysis or to 4 h survival for left ventricular function by echocardiography and serum biomarkers of myocardial injury assessment. The number of surviving animals is stated in each box.

significantly improved neurologically intact survival following 15 min of untreated ventricular fibrillation (VF) and concomitant global ischaemia in a porcine model of cardiac arrest. CPR was augmented by the use of an active compression/decompression (ACD) device[7] and an impedance threshold device (ITD).[8] *Post*conditioning was achieved by three to four 20-s pauses during the first 3 min of CPR.

Alternatively, myocardial *post*conditioning can also be achieved by pharmacological means. Volatile anaesthetics have been shown to attenuate myocardial injury following coronary ischaemia/reperfusion (IR) in isolated hearts[9] as well as in vivo,[10] and can be administered by ventilation. In contrast, an intravenous (IV) drug would require establishing IV access and could therefore be administered only significantly *after* initiation of CPR in the OHCA setting as delaying CPR to reach a therapeutic level at the *initiation* of CPR is not feasible.

In this investigation we tested the hypotheses that the volatile anaesthetic sevoflurane given for 3 min immediately at the initiation of CPR can (a) improve early post-resuscitation cardiac mitochondrial function and (b) improve post-resuscitation left ventricular function in a pig model of prolonged untreated VF.

2. Materials and methods

This study conformed to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press 2011) and was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center (protocol number 11-05). All experiments were performed on isoflurane-anaesthetised female Yorkshire farm pigs weighing an average of 38.2 ± 2.1 kg.

2.1. Preparation

Our protocol has been described in detail.[5] After endotracheal intubation, an anaesthesia machine (Narkomed 4A, Dräger, Telford, PA, USA) was used to ventilate the animals with a tidal volume of 10 ml kg^{-1}, starting at a respiratory rate of 10–18 min^{-1} and on room air supplemented with O_2, all titrated to achieve normocapnia and an O_2 saturation ≥95%. Until induction of VF, general anaesthesia was maintained with inhaled isoflurane 0.8–1.5 vol% end-tidal measured by a gas analyser (Datex-Ohmeda Capnomac; GE Healthcare, Waukesha, WI, USA) and at a fresh gas flow of 2 litres min^{-1}; isoflurane was restarted after return of spontaneous circulation (ROSC) following VF and CPR. A warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, MN, USA) was used to maintain body temperature at 37.5 ± 0.5 °C. Arterial blood was sampled for blood gas analysis (Gem 3000, Instrumentation Laboratories, Lexington, MA, USA) at five time points: at baseline, at the end of CPR, and 5 min, 15 min and 1 h after ROSC. Micromanometer-tipped catheters (Mikro-Tip Transducer, Millar Instruments, Houston, TX, USA) were used to continuously record central aortic (AoP) and right atrial (RAP) pressures. During CPR, coronary perfusion pressure (CPP) was calculated as the difference between AoP and RAP during diastole (spontaneously beating) or decompression (CPR). Systolic (SBP) and diastolic (DBP) blood pressure was derived from AoP. CPR compression force, rate, and depth were controlled and continuously recorded during all experiments to assure that all groups received identical CPR quality.

2.2. Experimental protocol

When arterial O_2 saturation on room air was ≥95%, and endtidal CO_2 was stable between 35 and 42 mmHg for 5 min, a direct intracardiac current was used to induce VF. Thirty-two (32) animals were used (Fig. 1). Seventeen (17) animals were randomised to the APoC group and received inhaled sevoflurane for the first 3 min of CPR at an endtidal concentration of 2.0 ± 0.2 vol% (1 minimal alveolar concentration), a clinically relevant concentration shown to significantly improve haemodynamic outcome in a rat model of cardiac arrest and resuscitation.[11] Fifteen (15) animals were randomised to the control (CON) group and did not receive any anaesthetic during CPR.

Within the APoC group, 9 of 9 randomised animals were euthanised 15 min after ROSC in order to assess mitochondrial function and reperfusion injury, and 8 animals were randomised to be kept alive for 4 h to echocardiographically assess left ventricular function (see below) and biomarkers of cardiac injury. Only 6 animals of the latter group survived the full 4 h. These 6 and the