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Experimental paper

The effect of 50% compared to 100% inspired oxygen fraction on brain oxygenation and post cardiac arrest mitochondrial function in experimental cardiac arrest☆

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ABSTRACT

Background and aim: We hypothesised that the use of 50% compared to 100% oxygen maintains cerebral oxygenation and ameliorates the disturbance of cardiac mitochondrial respiration during cardiopulmonary resuscitation (CPR).
Methods: Ventricular fibrillation (VF) was induced electrically in anaesthetised healthy adult pigs and left untreated for seven minutes followed by randomisation to manual ventilation with 50% or 100% oxygen and mechanical chest compressions (LUCAS®). Defibrillation was performed at thirteen minutes and repeated if necessary every two minutes with 1 mg intravenous adrenaline. Cerebral oxygenation was measured with near-infrared spectroscopy (rSO_2, INVOS™5100C Cerebral Oximeter) and with a probe (NEUROVENT-PTO, RAUMEDIC) in the frontal brain cortex (PbO_2). Heart biopsies were obtained 20 min after the return of spontaneous circulation (ROSC) with an analysis of mitochondrial respiration (OROBOROS Instruments Corp., Innsbruck, Austria), and compared to four control animals without VF and CPR. Brain rSO_2 and PbO_2 were log transformed and analysed with a mixed linear model and mitochondrial respiration with an analysis of variance.
Results: Of the twenty pigs, one had a breach of protocol and was excluded, leaving nine pigs in the 50% group and ten in the 100% group. Return of spontaneous circulation (ROSC) was achieved in six pigs in the 50% group and eight in the 100% group. The rSO_2 ($p = 0.007$) was lower with FiO_2 50%, but the PbO_2 was not ($p = 0.93$). After ROSC there were significant interactions between time and FiO_2 regarding both rSO_2 ($p = 0.001$) and PbO_2 ($p = 0.004$). Compared to the controls, mitochondrial respiration was decreased, with adenosine diphosphate (ADP) levels of 57 (17) pmol s^{-1} mg^{-1} compared to 92 (23) pmol s^{-1} mg^{-1} ($p = 0.008$), but there was no difference between different oxygen fractions ($p = 0.79$).
Conclusions: The use of 50% oxygen during CPR results in lower cerebral oximetry values compared to 100% oxygen but there is no difference in brain tissue oxygen. Cardiac arrest disturbs cardiac mitochondrial respiration, but it is not alleviated with the use of 50% compared to 100% oxygen (Ethical and hospital approvals ESAVI/1077/04.10.07/2016 and HUS/215/2016, §7 30.3.2016, Funding Helsinki University and others).

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Introduction

According to current resuscitation guidelines, patients should be ventilated with the maximal feasible inspired oxygen concentration during cardiopulmonary resuscitation (CPR) [1]. After return of spontaneous circulation (ROSC), when oxygenation can be reliably monitored with peripheral pulse oximetry (SpO_2) or arterial blood gas (ABG) analysis, the inspired oxygen should be titrated to the lowest possible level to achieve an arterial oxygen saturation of 94–98%, with the intention to avoid hypoxia as well as hyperoxia, both of which are potentially harmful in the post-ischemic state following cardiac arrest (CA) [2]. Animal studies suggest that high arterial blood oxygen concentrations during reperfusion increase oxidative stress, worsening post-ischemic neuronal damage and adversely affecting the activity of the myocardial mitochondria [3–7]. Ventilation with lower fractions of oxygen during CPR might decrease the incidence of immediate hyperoxia after ROSC, but it is unclear if the use of lower oxygen fractions is enough to maintain adequate brain tissue oxygenation during CPR [5].

Means to non-invasively measure cerebral oxygenation during CPR include cerebral oximetry using near-infrared spectroscopy (NIRS), which estimates regional cerebral oxygen saturation (rSO_2) [8]. This enables continuous monitoring of brain oxygen saturation, and may capture oxygen delivery even without a pulsating rhythm, rendering it feasible during CPR [9]. However, its role in guiding CPR interventions has yet to be established. Invasive measurement of brain tissue oxygen is used in Neurocritical care, but it is not applicable in clinical CPR, unless the probe is in place prior to cardiac arrest [10].

In this randomised experimental animal study, we compared the effect of 100% and 50% oxygen fractions on cerebral oxygenation during and after CPR and their effects on the mitochondrial function of the myocardium. We hypothesised that the use of 50% oxygen during CPR would be enough to maintain brain oxygenation during CPR, and this would decrease the incidence of extreme hyperoxia after ROSC. In addition we hypothesised that cardiac arrest disturbs cardiac mitochondrial function and the use of 50% oxygen would alleviate the disturbance of the respiratory function of the cardiac mitochondria [11].

Material and methods

This is an experimental animal study performed in healthy adult pigs. The study plan was approved by the Finnish National Animal Experiment Board (ESAVI/1077/04.10.07/2016) and by the hospital board (HUS/215/2016, §7 30.3.2016). The study was conducted in the Research and Development Unit of Helsinki University Hospital, Helsinki, Finland, between March and June 2016. The study adhered to the ARRIVE guidelines, and a checklist is included in the Electronic Supplementary Material (ESM) [12].

Preparation and monitoring

We included twenty healthy landrace pigs of both genders, weighing 26–38 kg, for the interventional part and four control pigs for the assessment of the effect of cardiac arrest on cardiac mitochondrial function. The control pigs were kept under general anaesthesia but did not have CA or CPR. Prior to the procedural day, the animals had free access to food and water. Thirty minutes before the procedure, the animals were pre-medicated with a mixture of ketamine (600 mg), atropine (1 mg) and medetomide (2 mg) injected intramuscularly. A peripheral vein of the ear was cannulated, and an infusion of Ringer's acetate (Ringer-Acetat Baxter, Baxter Medical, Kista, Sweden) was started. The pigs were anesthetised with intravenous (IV) propofol (dose 20–100 mg) and fentanyl IV (100–200mcg) but without the use of paralytics. Anaesthesia was maintained with a continuous propofol infusion (20 mg/ml, 5–25 ml/h). The pigs were intubated (endotracheal tube size 6.0) and mechanically ventilated (Servo Ventilator 900C; Siemens-Elema, Solna, Sweden) with 21% oxygen (O_2) during the pre-arrest period. The ventilation targeted an end tidal carbon dioxide (etCO2) level of 5%.

The internal jugular vein was cannulated using Seldinger's technique, and an introducer catheter (Arrow, size 7, French) was inserted for medications, venous blood sampling and pacemaker catheter insertion. A temporary balloon-tipped pacing wire was inserted, and correct placement in the right ventricular wall was confirmed by initiating pacing (Medtronic 5348 Single Chamber Temporary Pacemaker) and confrming the presence of multiple ventricular beats on the electrocardiogram (ECG). The femoral artery was prepared surgically and cannulated with a vascular sheath (Arrow, size 7, length 15 cm) for invasive blood pressure measurement and for obtaining arterial blood samples. Oxygenation was monitored with pulse oximetry (SpO_2) attached to the pigs' tails. ABGs were measured with a point-of-care device (i-STAT System, Abbott Laboratories, Princeton, NJ).

Ventilation parameters such as tidal volume, respiratory pressure and inspired fractions of oxygen were monitored using a spirometry flow (D-Lite, GE Healthcare, USA) sensor connected to an airway module (GE DATEX OHMEDA). Haemodynamic and respiratory variables were measured and analysed using an AS/3 Monitor (Datex-Ohmeda AS/3, GE Healthcare, Helsinki, Finland) and stored on a computer using data collection software (iCentral® and S/5 Collect®, GE Healthcare, Helsinki, Finland). An oesophageal temperature probe was inserted, and a temperature of 38–39 °C was targeted to correspond the normal temperature of the pig, using an external radiant heater and a warming mattress [13].

Cerebral oximetry and brain tissue oxygen

Cerebral oximetry was monitored with near-infrared spectroscopy (INVOS™ 5100C Cerebral Oximeter, Somanetics Inc., Troy, MI, USA), fixed on the left side of the pigs' foreheads. For invasive brain tissue oxygen measurement, a cranial burr hole was performed on the right side of the forehead. A line was drawn from the orbit to the crossing of the parietal and midline sutures, and the location of the burr hole was at the second third from the orbit. A bolt kit was placed securely in the burr hole, and the dura was perforated. A probe (NEUROVENT-PTO, RAUMEDIC, Helmbrechts, Germany) was inserted and secured approximately 1 cm below the dura into brain tissue. The probe enables measurement of parenchyma intracerebral pressure and oxygen partial pressure. A data logger (MPR2 logO Datalogger, RAUMEDIC, Helmbrechts, Germany) was used for storing data.

Experimental procedures

Prior to the induction of ventricular fibrillation (VF), a baseline blood gas analysis was performed and sedation was ceased. VF was induced with a 4 V electrical current. The pigs were not ventilated during CA. After induction of CA, the pigs were randomised with sealed envelopes into two groups: ventilation during CPR with either 100% oxygen or 50% oxygen. At 7 min mechanical chest compressions (LUCAS™ Chest Compression System, Lund, Sweden) were initiated. Manual bag valve ventilation (LAERDAL Silicone Resuscitator, Norway) was started, with a frequency of 10/min with supplemental oxygen flow. The oxygen flow was titrated to achieve an inspired fraction of oxygen (FiO_2) of approximately 50% or 100% (2–15 l/min) using continuous information obtained with the flow sensor (D-lite, Gas sampler and flow sensor, Ge Healthcare) between the endotracheal tube and ventilation bag and the