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EXPERIMENTAL PAPER

Rapid non-invasive external cooling to induce mild therapeutic hypothermia in adult human-sized swine☆

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Therapeutic hypothermia;
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Summary
Aim of the study: Mild therapeutic hypothermia is a promising new therapy for patients resuscitated from cardiac arrest. Early and fast induction of hypothermia seems to be crucial for best results. The aim of the study was to investigate the feasibility and safety of a new surface cooling method using cold metal plates.
Subjects and methods: Twelve adult human-sized swine (79 ± 9 kg) were cooled from 38 to 33 °C brain temperature. The skin surface was covered with −20 °C metal plates (M), as compared to ice packs, alcohol rubs, and fans used in a control group (C). Each method was tested during spontaneous circulation and, after re-warming, during cardiac arrest. Temperatures were recorded continuously. Data are given as mean ± standard deviation or as median (interquartile range), if not normally distributed. Comparisons between the treatment groups were performed with the independent samples *t*-test, or the Mann—Whitney rank-sum test.
Results: During spontaneous circulation, cooling rates were 9.3 ± 1.4 °C/h (M), and 6.1 ± 1.4 °C/h (C) ($p = 0.003$); no skin lesions were observed. During cardiac arrest, cooling rates were 4.1 °C/h (1.8—4.8) (M), and 3.7 °C/h (3.1—5.3) (C) ($p = 0.9$); no skin lesions were observed.
Conclusion: Cooling with cold metal plates was an effective method for rapid induction of mild therapeutic hypothermia in adult human-sized swine during spontaneous circulation, without any signs of skin damage. This new surface-cooling device, independent of energy supply during use, should be further investigated.

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Introduction

Mild therapeutic hypothermia is a promising new therapy for patients resuscitated from cardiac arrest,[1–4] and has been recommended in the latest resuscitation guidelines by the European Resuscitation Council,[5] and the American Heart Association.[6] Therapeutic mild hypothermia might also be beneficial after stroke,[7,8] traumatic brain injury,[9,10] and myocardial infarction.[11,12] To achieve best possible outcome, early and rapid induction of hypothermia is essential.[13–19] The main challenge in the clinical scenario remains the immediate induction of mild hypothermia.

In recent years, several non-invasive external[1–3,8–10,20–22] and invasive[12,23–29] cooling strategies for induction of mild hypothermia were investigated. The main disadvantage of invasive blood cooling techniques out-of-hospital. Moreover, invasive cooling methods using a femoral central venous access bear the risk of complications of vascular catheterisation such as thrombosis, infection,[30,31] and bleeding.[32] Hypothermia per se presents a relevant but reversible cause generating haemorrhagic diathesis.[33–35] External cooling techniques have the advantage of being less invasive. However, most of them, such as cooling tents,[1] blankets,[7,8,10,21] helmets,[3,20] fluid pads,[9,11,21] mere ice packs,[2,9] or a combination of some of these techniques are impractical for out-of-hospital use. They all depend on energy supply, while ice packs or cooling helmets have only limited cooling capacity.

We sought a cooling method featuring a simple and non-invasive device that can be easily applied to patients and is independent from an energy source during cooling. With it, mild hypothermia might be induced by paramedics or even bystanders already during cardiac arrest, or immediately after successful resuscitation. The aim of this study was to explore a new external surface-cooling device fulfilling these requirements. We tested the feasibility and safety of the device operating with cold metal, compared to controls cooled with ice packs, alcohol rubs, and fans, in adult human-sized swine during spontaneous circulation and during cardiac arrest.

Methods

The experimental protocol was approved by our institutional animal investigation committee. Animal care and handling were according to National Institutes of Health guidelines and were performed by qualified personnel and supervised by veterinarians. All facilities and transportation comply with the current legal requirements and guidelines. Twelve female swine (Pietrain × German domestic breed, 60—92 kg) were used after a 7-day period of quarantine and observation at the local animal care facility. The animals were fasted 12 h before the experiment with free access to water.

Anaesthesia, preparation, and monitoring

After intramuscular (IM) premedication with midazolam 1 mg/kg, acepromacin 1.75 mg/kg, piritramide 15 mg, and atropine sulphate 0.5 mg, swine were transferred to an operating room. A peripheral venous catheter was placed in an ear vein. Before tracheal intubation (tracheal tube size 8), propofol was given as an initial bolus injection of 200 mg, followed by boluses of 40 mg until intubation was possible. After intubation, swine were ventilated via a respirator (Servo 300, Siemens, Germany) with a tidal volume of 10 ml/kg, positive end-expiratory pressure of 5 cm H_2O, and FiO_2 of 0.3. The respiratory rate was adjusted to achieve a Pa_{CO_2} of 4.7—5.3 kPa, and was kept constant thereafter during cooling.

For anaesthesia throughout the experiment, intravenous (IV) propofol (20 mg/(kg h)), and IM piritramide (60 mg every 2 h) were used. For paralysis, rocuronium was given (bolus of 0.6 mg/kg, continuous IV infusion of 0.6 mg/(kg h)). Saline 0.9% was infused at a rate of 5 ml/(kg h). ECG electrodes and a pulse oxymeter were attached for heart rate (HR) and oxygen saturation (SpO_2) monitoring.

For brain temperature (T_{br}) measurement, two temperature probes (Biosys, Vienna, Austria) were inserted into the parietal lobes through symmetrical burr holes, centered at 1.0 cm from the sagittal suture and 1.0 cm behind the coronal suture, to a depth of 2.0 cm under the dura mater. Bladder temperature (T_{bl}) was measured with a Foley catheter (Ruesch Sensor Ch 12, Ruesch, Kernen, Germany). Tympanic (T_{ty}) and oesophageal (T_{es}) temperatures were measured with a contact thermistor (Mon-a-therm General Purpose Critical Care Temperature Probes, Mallinckrodt Medical Inc., Northampton, UK). An arterial catheter was inserted by Seldinger technique into the left brachial artery for arterial pressure (AP) measurements and blood sampling at baseline and after cooling during spontaneous circulation. A pulmonary artery catheter (Edwards, Irvine, CA) was advanced by Seldinger technique via the right internal jugular vein for measurements of central venous pressure (CVP) and pulmonary artery temperature (T_{pa}). For re-warming, two venous bypass cannulas (Medtronic®, 17 F, right side: 50 cm, left side: 20 cm) were introduced into both femoral veins via surgical cut-down. After insertion of the cannulae, 10,000 IU of unfractioned heparin were given intravenously, and repeated if necessary by monitoring the activated clotting time.

All monitored haemodynamic and respiratory variables and temperatures were stored in a computerised data management system (VIPDAS, Biosys, Vienna, Austria). Arterial blood gas analysis including acid—base values, electrolytes (Pa_{CO_2}, Pa_{O_2}, pH, base excess, bicarbonate, K^+, Na^+, Ca^{++}, Cl^-, glucose, lactate) and haemoglobin was performed at the given time points mentioned above with a blood gas analyser (AVL 995 Hb, Roche Diagnostics).

Hypotension was treated with intravenous infusion of hydroxyethyl starch or, if necessary, with continuous infusion of noradrenaline [norepinephrine] to maintain a mean arterial pressure (MAP) of more than 60 mmHg.

Cooling device with cold metal

This external cooling device consisted of multiple metallic cooling plates in different sizes (prototype provided by Emcools, Emergency Medical Cooling Systems AG, Vienna, Austria). These plates were pre-cooled to −20 °C until shortly before the experiment, and kept at this temperature in commercially available isolated cool boxes. Experiments