Induction of mild hypothermia with infusion of cold (4 °C) fluid during ongoing experimental CPR

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Abstract

Introduction: Therapeutic hypothermia after resuscitation has been shown to improve the outcome regarding neurological state and to reduce mortality. The earlier hypothermia therapy is induced probably the better. We studied the induction of hypothermia with a large volume of intravenous ice-cold fluid after cardiac arrest during ongoing cardiopulmonary resuscitation (CPR).

Methods: Twenty anaesthetised piglets were subjected to 8 min of ventricular fibrillation, followed by CPR. They were randomized into two groups. The hypothermic group was given an infusion of 4 °C acetated Ringer’s solution 30 ml/kg at an infusion rate of 1.33 ml/kg/min, starting after 1 min of CPR. The control group received the same infusion at room temperature. All pigs received a bolus dose of vasopressin after 3 min of CPR. After 9 min, defibrillatory shocks were applied to achieve restoration of spontaneous circulation (ROSC). Core temperature and haemodynamic variables were measured at baseline and repeatedly until 180 min after ROSC. Cortical cerebral blood flow was measured, using Laser-Doppler flowmetry.

Results: All pigs had ROSC, except one animal in the hypothermic group. Only one animal in the hypothermic group died during the observation period. The calculated mean temperature reduction was 1.6 ± 0.35 °C in the hypothermic group and 1.1 ± 0.37 °C in the control group (p = 0.009). There was no difference in cortical cerebral blood flow and haemodynamic variables.

Conclusion: Inducing hypothermia with a cold infusion seems to be an effective method that can be started even during ongoing CPR. This method might warrant consideration for induction of early therapeutic hypothermia in cardiac arrest victims.

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Keywords: Hypothermia; Cardiac arrest; Cardiopulmonary resuscitation (CPR)

1. Introduction

Postischaemic–anoxic encephalopathy and permanent brain damage may follow initial successful resuscitation after cardiac arrest, despite general supportive measures, such as avoiding hypotension, hypoxaemia and hypovolaemia. Mild hypothermia, defined as 33 ± 1 °C body temperature [1], has been shown to reduce brain damage [2–4] and improve functional outcome [2] in several animal studies. In recent clinical trials, improved survival [5] and improved neurological outcome [5,6] were seen in patients treated with induced hypothermia.

The methods of decreasing core temperature have varied. In animal studies, cardiopulmonary bypass [7,8], cold aortic flush [9], external cooling [4,10] and peritoneal cooling [11] are some examples of the methods that have been used. Some studies have indicated that to achieve the most benefit from hypothermia, the therapy must be induced early after the insult [4,7] or may be even before the insult [12].

In the clinical setting, there is a need for a fast, simple method, not dependent on large numbers of specialised. Further perceived advantages are the possibility to induce therapy during pre-hospital care and a modest cost of the method. Clinical studies have been performed using external cooling with icepacks [6], forced cooled air [5] or a cooling helmet device [13]. The main problem with these methods is the slow decrease in core temperature, with icepacks measured to be 0.9 °C/h [6], 0.3 °C/h with forced cooled air [5] and
0.6 °C/h with a cooling helmet [13]. Consequently, there is a relatively long time-period between initiation of therapy and achievement of the goal temperature.

In a recent clinical study, hypothermia was induced using a rapid (30 min) intravenous infusion of a large volume (30 ml/kg) lactated Ringer’s solution at 4 °C [14]. The decrease in core temperature after fluid administration was 1.7 °C. The authors claimed improvements in mean arterial pressure, renal function and acid–base balance. This method has also been used directly after restoration of spontaneous circulation (ROSC), in the pre-hospital setting, without any serious adverse haemodynamic effects [15].

Outcome seems to be improved when cooling is initiated very early after cardiac arrest [7,16–18]. With this in mind, we hypothesised that induction of hypothermia would be feasible to start during ongoing CPR, using intravenous infusion of ice-cold solution.

2. Materials and methods

The design of this study and the care and handling of the animals were reviewed and approved by the Institutional Review Board for Animal Experimentation in Uppsala, Sweden.

2.1. Animal preparation

Twenty-two piglets of Swedish country breed of both genders were included in the study. They were 11–15-week-old and had a mean weight of 25.6 ± 0.7 kg. All animals were fasting with free access to water during the night before the experiment. The same supplier delivered them directly to the laboratory on the morning of the experiment. Anaesthesia was induced with an intramuscular injection of tiletamine and zolazepam 6 mg/kg, xylazine 2 mg/kg and atropine 0.04 mg/kg. A peripheral ear vein was cannulated for induction and maintenance of anaesthesia and for fluid administration. Morphine, 1 mg/kg and ketamine, 100 mg were given IV as a bolus injection. Anaesthesia was maintained by continuous intravenous infusion of 8 mg/kg/h of pentobarbitral, 0.25 mg/kg/h of pancuronium bromide and 0.5 mg/kg/h of morphine. Water losses were compensated for by a bolus infusion of 30 ml/kg of acetated Ringer’s solution during 1 h before the experiment and a continuous infusion of 2.5% glucose at a rate of 10 ml/kg/h during the entire experiment.

Tracheotomies were performed on the piglets and they were mechanically ventilated (Servo Ventilator 900C, Siemens-Elena, Solna, Sweden) with a 70/30 mixture of N2O/O2 during preparation. Volume-controlled ventilation was used and minute ventilation adjusted to maintain the arterial pCO2 within a range of 5.0–5.5 kPa (38–41 mmHg) and a PEEP of 5 cm H2O was applied.

For continuous measurement of cerebral cortical blood flow, a Laser-Doppler flow probe (Periflux® Laser-Doppler flow meter PF2B, Perimed, Stockholm, Sweden) was placed directly over the surface of the right frontal cortex through a burr hole, 1 cm anterior to the coronal suture and 1 cm lateral to the sagittal suture [19]. Laser-Doppler flowmetry is a method for continuous measurement of volume flow [20]. This technique is known to be highly suitable for the study of blood flow dynamics [21].

A pulmonary artery catheter (CritiCare Ohmeda®; 7 French) was inserted via the right external jugular vein for pressure monitoring. Catheters were also inserted into the right atrium (7 French) for drug administration and pressure monitoring, into the aortic arch via a branch of the right external carotid artery (18 gauge) for pressure monitoring and into the femoral artery (18 gauge) for blood sampling. Another catheter (3.8 French) was inserted into the left internal jugular vein and passed in a retrograde direction as far as possible towards the jugular bulb for blood sampling. This technique was used in order to allow continuous blood flow in the vein after insertion of the catheter [22].

2.2. Measurements

Standard lead II ECG, systemic arterial blood pressure, right atrial pressure and pulmonary artery blood pressure were monitored continuously (Marquette, Solar 8000, Hellege Systems, Freiburg, Germany) and recorded (Workbench 3.0, Strawberry Tree Inc., Sunnyvale, CA, USA). End-tidal CO2 was measured (CO2smoplus, Novametrix, Medical Market Inc., Lidingö, Sweden). Blood gases (ABL 300, Radiometer, Copenhagen, Denmark) and oxygen saturation (OSMi3, Radiometer, Copenhagen, Denmark) were repeatedly measured in arterial and jugular venous blood. Core temperature was measured continuously in the pulmonary artery and recorded repeatedly.

2.3. Experimental protocol

Nitrous oxide was discontinued after preparation of the animals and the piglets were ventilated with 30% O2 in air. After 45 min of no instrumentation or interventions, baseline values were obtained. Ventricular fibrillation (VF) was induced with a brief application of an alternating current shock of 40–60 V, administered by two subcutaneous needles. Cardiac arrest was defined as VF on the ECG and the loss of arterial pulsation. Ventilation was stopped at the same time. After 8 min of cardiac arrest, the piglets received mechanical closed-chest cardiopulmonary resuscitation (CPR) with a LUCAS device [23] and ventilation was resumed with 100% O2. The animals were randomised into two study groups with one group receiving an intravenous infusion of ice-cold (4 °C) acetated Ringer’s solution 30 ml/kg at a rate of 1.33 ml/kg/min starting after 1 min of CPR (hypothermic group). The total infusion time was thus 22 min, and 10.6 ml/kg was given during CPR equalling 35.3% of the total infusion amount. The fluid was given through infusion pumps to make sure that the predetermined rate was delivered. The control group received the same treatment with the exception that the solution was at room tempera-
ture (24.2 ± 0.3 °C). After 3 min of CPR, the animals were given an intravenous bolus of vasopressin 0.4 U/kg. CPR was then continued for another 6 min. After 9 min of CPR, one external defibrillatory shock of 200 J was administered. If this was unsuccessful, the energy level was raised to 360 J, and if needed, a bolus dose of adrenaline (epinephrine) (45 μg/kg) was given. Defibrillatory shocks were applied for a maximum of 5 min. If restoration of spontaneous circulation (ROSC) was not achieved during this time, CPR was discontinued. ROSC was defined as a pulsatile rhythm with a systolic aortic blood pressure of >60 mmHg maintained for at least 10 min.

In animals that received ROSC, FiO₂ was returned to 0.3 after 5 min of ROSC. If arterial pH was less than 7.20, 5 min after ROSC acidosis was corrected with a tri-buffer mixture (Tribonate®, Pharmacia & Upjohn, Stockholm, Sweden) of 1 mmol/kg and increased minute ventilation, aiming at an arterial pCO₂ of 5.0–5.5 kPa (38–41 mmHg). The animals were followed thereafter until 180 min after ROSC. There were no other interventions during the observation period.

2.4. Analysis and statistics

Unpaired t-test was used for comparing the total decrease in core temperature between the groups and for comparing baseline values. Paired t-test was used for comparing baseline values with mean values after stabilization following ROSC. By studying the graphs, this period to stabilization was designated as the period from 25 min after ROSC to the end of the experiment for all variables except cardiac output, and was between 30 min and the end of the experiment. All variables were analysed using repeated measure ANOVA for the two groups and the repeated recording time points to detect any differences between the groups. Values are expressed as mean ± 0.95 confidence interval where nothing else is indicated. Significance were detected at the p < 0.05 level. The statistical analyses were calculated using the programme STATISTICA (Statsoft, Scandinavia, Sweden).

3. Results

Of the 22 piglets used, two were excluded. One animal, which did not achieve ROSC, was found to have a hypoplastic heart at postmortem thoracotomy. The second animal was excluded because of an abnormal baseline temperature at 40 °C and suspected sepsis. Twenty animals (ten per group) followed the protocol and were used for analysis.

There were no significant differences in baseline physiological variables (Table 1) between the groups. ROSC was achieved in nine out of 10 animals in the hypothermic group and in all animals in the control group. One animal in the hypothermic group did not survive during the entire observation time (it died from cardiogenic shock 105 min after ROSC). All animals in the control group survived for 180 min after ROSC.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline variables, no significant group differences</th>
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<tbody>
<tr>
<td>Baseline variables</td>
<td>Hypothermic group</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.63 ± 0.47</td>
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<tr>
<td>Body weight (kg)</td>
<td>25.87 ± 0.84</td>
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<tr>
<td>MAP (mmHg)</td>
<td>100.3 ± 4.52</td>
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<tr>
<td>CPP (mmHg)</td>
<td>11.7 ± 1.18</td>
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<tr>
<td>DPAP (mmHg)</td>
<td>16.5 ± 2.98</td>
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<tr>
<td>MPAP (mmHg)</td>
<td>20.4 ± 3.04</td>
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<tr>
<td>Wedge (mmHg)</td>
<td>10.4 ± 1.18</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.8 ± 0.86</td>
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<tr>
<td>ET CO₂ (kPa)</td>
<td>5.53 ± 0.19</td>
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<tr>
<td>Hæmatocrit (%)</td>
<td>26.3 ± 1.18</td>
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<tr>
<td>CO₂-extraction rate (%)</td>
<td>18.9 ± 7.62</td>
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Note: All values are mean ± 1 confidence interval.

3.1. Core temperature

Core temperature decreased during the infusion time in both groups (Fig. 1). The time of infusion was 22 min. The maximal decrease of temperature in the hypothermic group was 1.62 ± 0.23 and 1.14 ± 0.23 °C in the control group. The difference in temperature reduction proved to be significant; p = 0.009.

3.2. Haemodynamic variables

There was no significant difference between the groups in any of the haemodynamic variables studied at base line, during CPR or after ROSC.

During CPR, the mean arterial pressure reached initial values of about 30% of baseline. After the vasopressin bolus, there was a rise in mean arterial pressure to values of 60–70% of baseline. Mean right atrial pressure (Fig. 2), mean pulmonary arterial pressure (Fig. 3), systolic right atrial pressure and systolic pulmonary arterial pressure, all increased during the same period. Diastolic pulmonary arterial pressure (Fig. 4) (as an equivalent to wedge pressure) decreased to negative values during CPR, as did the diastolic right atrial pressure.

Mean arterial pressure increased for about 10 min after ROSC, followed by a hypotensive period, and then adjustment at a level below baseline values. The mean difference was 38 mmHg between baseline values and values after stabilization after ROSC. This was a significant reduction, p = 0.000. Mean right atrial pressure (Fig. 2) after ROSC stabilised at an increased level with a mean difference of 4.5 mmHg, compared to baseline values which is a significant increase (p = 0.000). Mean pulmonary arterial pressure (Fig. 3) and diastolic pulmonary arterial pressure (Fig. 4), both showed a similar pattern with stabilisation at increased levels compared to baseline, p = 0.000012 and 0.00004. The mean differences compared to baseline were 4.8 and 6.5 mmHg, respectively.

Endtidal-CO₂ (end-tidal carbon dioxide, Et-CO₂, Fig. 5) was studied as an indirect marker of cardiac output (CO) during CPR. There was a decrease in the Et-CO₂ during...
3.3. Cerebral cortical blood flow and cerebral oxygen extraction rate

Cerebral blood flow is presented as a fraction of the baseline flow level before cardiac arrest, i.e. baseline is 1.0. Cerebral blood flow showed no significant differences between the groups (Fig. 7), but after ROSC, there was increased flow followed by adjustment at a level slightly lower than baseline. The mean difference from baseline to this level was 0.17 (relative value) which was significant; \( p = 0.047 \).
Concerning cerebral O$_2$-extraction rate (Fig. 8), both groups showed an increase in extraction rate during cardiac arrest, followed by a marked decrease during CPR. After ROSC, there was an increase, followed by a slow reduction down to values close to baseline values. The hypothermic group showed slightly reduced values after ROSC compared to the control group. However, this difference did not prove to be significant.

3.4. Hematocrit

In both groups, there was an initial rise in hematocrit after cardiac arrest with a mean increase of 2.7%, $p = 0.000$. This was followed by a small mean dilutional effect of 1.1% ($p = 0.008$) when comparing post-ROSC values (time-range from 30 to 180 min) with baseline values. There was no statistically difference between the groups.

4. Discussion

In this feasibility study, we found that induction of mild hypothermia with a cold (4°C) infusion, initiated during ongoing CPR, was successful without any major disadvantages regarding ROSC or haemodynamic variables. The study design included starting cooling during ongoing CPR, since...
The mean decrease in core temperature in the hypothermic group was 1.6 °C. In our control group, we also had a mean decrease in temperature of 1.1 °C. This was not a surprising finding, as the pigs were given an infusion at room temperature (22–24 °C), which is colder than the normal core temperature of pigs. The reason for choosing a room temperature infusion for the control group with infusion was that this is the ordinary temperature of infusions given to patients during resuscitation. To allow for evaluation of the pure effect of volume versus hypothermia, core-temperate infusions for the controls would have been preferred; however, this was not our main objective of the study.

Core cooling by central venous infusion of 4 °C solution has been shown by Rajek et al. to be an effective method of reducing core temperature in healthy volunteers [24]. They also concluded that the reduction in core temperature using this method was greater than would be expected if the change in body heat content were distributed in proportion to body mass.

In a recent study by Bernard et al. [6], induction of mild hypothermia with an ice-cold infusion was used on survivors after out-of-hospital cardiac arrest, with promising results.

One advantage of the method is that it is relatively fast, especially if compared to methods using external cooling. Our results with a reduction of 1.6 °C in 22 min correlated well with Bernard’s study, where the mean reduction in core
temperature was 1.7 °C in 30 min [14]. This should be compared to 0.3–0.9 °C/h reductions in different studies of external cooling [5,6,13,25]. Animal studies, using other methods of core cooling, such as cardiopulmonary bypass, cold aortic flush and cold peritoneal lavage have been effective in means of reducing body temperature, but might be too complex or too demanding on personnel to be suitable in the clinical setting.

Another advantage, if core-cooling is used as the only method of inducing and maintaining hypothermia is that, the rewarming period will be more controlled. If surface cooling is used, the peripheral tissues will be markedly reduced in temperature, and during cutaneous rewarming, there will be a core temperature afterdrop that can be hard to predict, and that must be overcome before an increase in core temperature can occur.

The animals had a mean baseline core temperature of 37.6 °C. A decrease of 1.6 °C gives us a core temperature of 36.0 °C. As the goal temperature for therapeutic mild hypothermia is usually set to 32–34 °C, this is not sufficient. Pigs have a slightly higher normal body temperature than humans and patients with cardiac arrest tend to lose warmth and reduce their temperature. In the clinical setting, we therefore believe that this method might very well prove to be sufficient for initiating hypothermia down to an adequate level, as shown by Bernard et al. [14]. Even if the goal temperature is not fully achieved, this is still a fast induction method, which can be used together with, for example, an external cooling method to reach the target temperature more quickly.

Our main concern regarding the use of a cold infusion as a method for inducing hypothermia during already ongoing...
CPR was the fear of side effects of volume loading of the haemodynamic system. Starting this kind of infusion during resuscitation had not been tried earlier. In nine out of 10 survivors in the hypothermic group and 10 out of 10 in the control group, we believe that volume loading during CPR was possible without any great haemodynamic side-effects. It could be argued that as the animals were receiving mechanical ventilation with a positive intrathoracic pressure, this in itself might hide the effects of cardiac failure and help to avoid pulmonary oedema. As mechanical ventilation is a part of the treatment of comatose patients, we do not believe that this is of any clinical implication.

In the study by Bernard et al. [14], the haemodynamic effects of volume expansion after ROSC were positive rather than negative. It is also believed that volume expansion and haemodilution reduce cerebral no-reflow and improve neurological outcome [26], or that haemodilution at least improves systemic haemodynamics and tissue perfusion [27]. Another aspect is the evidence indicating that the post-resuscitation phase resembles a sepsis-like syndrome [28] that might benefit from symptomatic volume treatment.

We could see a rise in mean pulmonary artery pressure and mean right atrial pressure during CPR that might reflect the volume loading of the inadequate heart, but as the diastolic pulmonary arterial pressure showed a marked decrease during the same time, we concluded that the rise in mean right atrial pressure and mean pulmonary arterial pressure, probably were not due to the loading of volume, but were rather a reflection of the intrathoracic pressures created by the mechanical CPR. This is also in accordance with previous results [29].

After ROSC, the mean right atrial pressure, the mean pulmonary arterial pressure and the diastolic pulmonary arterial pressures stabilised at significantly increased levels compared to baseline values. However, these alterations were not dramatically high and not at levels indicating severe cardiac failure. Cardiac output during CPR, as reflected by Et-CO₂, and conventional thermodilution after ROSC, followed the previously described pattern. Et-CO₂ showed an initial reduction during CPR, followed by a further reduction after 3 min of CPR. We believe that this is not an effect of the volume loading as, in time, it mirrors the bolus dose of vasopressin that was given. This is probably an effect of pulmonary vaso-constriction following vasopressin, and a reduction in Et-CO₂ indicates shunting to the systemic circulation. The reduction of cardiac output after ROSC is in line with previous observations by our group when no fluid has been administered.

In the clinical situation, inotropic drugs most often support patients after cardiac arrest; however, the animals in our study received no such treatment. Our measurements of cerebral perfusion (using laser doppler cerebral blood flow and cerebral O₂-extraction rate) gave no suspicion of any negative effects of the fluid bolus or of hypothermia.

This leads us to believe that the negative effects of volume loading on the circulation are quite small and can probably be disregarded. A remaining concern, however, is that we studied the insult on pigs with presumably healthy hearts before the insult, while most patients suffering cardiac arrest usually have a history of previous heart disease, and our study does not elucidate what impact that might have.

We used the LUCAS device [23] during CPR, as we wanted a user-independent method with standardisation of the chest compressions. Previous experimental studies have shown the LUCAS device to result in better haemodynamic variables, cerebral blood flow and ROSC, compared to standard external chest compressions during CPR [23]. Rubertsson S, Karlsten R. Improved cortical cerebral blood flow and end tidal CO₂ during experimental cardiopulmonary cerebral resuscitation with mechanical LUCAS chest compressions versus manual. Resuscitation, in press). Therefore, the use of the LUCAS device might have been beneficial for the outcome of our experiments. When using the LUCAS, our monitoring device was unable to-sample values for coronary perfusion pressure during CPR. Instead, we measured Et-CO₂ as an indirect measurement of cardiac output.

We measured the temperature in the pulmonary artery but not brain temperature directly, assuming that there should correlate (with cerebral temperature, lagging 0.6 °C behind pulmonary artery), according to a study by Ao et al. [30]. The reason for choosing core temperature instead of cerebral temperature was partly practical and partly because core temperature is the temperature measured during hypothermia treatment in the clinical setting. A problem of some concern is the questionable accuracy of the temperature of the solution, as it is infused to the animal. The cold solutions were taken from a refrigerator, with an inside temperature of 4 °C, immediately before the start of the infusion. The infusion bags were enclosed in icepacks to keep the solution cold during the infusion. We suspected that there could be a partial rewarming of the infusion as it passed through the infusion lines. Earlier investigations have shown that even with rapid infusions (over 100 ml/min), there is an increase in temperature of several degrees [31]. We measured the temperature of the solution at the end of the infusion lines, immediately before the connection to the animal, and found an increase in temperature to 8 ± 0.5 °C. Nevertheless, the animals were given a solution of much lower temperature than their natural core temperature, and there was a significant lowering of body temperature.

5. Conclusion

We conclude that the method of inducing therapeutic hypothermia with intravenous infusion of cold (4 °C) solution is a method that can be started during ongoing CPR, and that it has a fast and fairly good effect in terms of reducing body core temperature without any major haemodynamic disadvantages, at least in the experimental setting. The method is simple and inexpensive, and deserves to be tested in clinical circumstances to achieve a rapid and early
induction of hypothermia, thereby hopefully gaining further advantages from hypothermia therapy.

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