Laboratory Research

The effect of body weight on the induction of mild hypothermia in a rabbit model of asphyxia cardiac arrest

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Objective  To investigate the effect of body weight on the induction of mild hypothermia in a rabbit model of asphyxia cardiac arrest.

Methods  Twenty-four rabbits were randomized into two groups: the ice bag group and the intravenous 4°C saline group. Cardiac arrest was induced and after 3 minutes of cardiac arrest, cardiopulmonary resuscitation was begun. Simultaneously, mild hypothermia was induced by putting an ice bag over the abdomen or infusion of 4°C saline via an ear vein. A 2°C decrease of rectal temperature was considered as the completion of hypothermia induction. Induction times were recorded, compared, and analyzed with respect to body weight.

Results  All rabbits had restoration of spontaneous circulation (ROSC) and ROSC lasted during the experiment. Induction time in the ice bag group was significantly shorter than that in the intravenous 4°C saline group (22.8 ± 4.7 min VS 42.5 ± 4.0 min, P< 0.001). Induction time significantly correlated with body weight in the ice bag group (Pearson Correlation: r=0.725, P=0.029), but not in the intravenous 4°C saline group (Pearson Correlation: P=0.418).

Conclusions  In a rabbit model, induction of mild hypothermia with an ice bag is faster than with intravenous 4°C saline; induction time positively correlates with body weight when an ice bag is used, but not when intravenous 4°C saline used. The effect of body weight should be considered when choosing an appropriate method to achieve early induction of mild hypothermia (J Geriatr Cardiol 2010; 7:161-165).

Keywords  Cardiac arrest; cardiopulmonary resuscitation; mild hypothermia; body weight

Introduction

The efficacy of mild hypothermia in improving neurological outcomes after out-of-hospital cardiac arrest has been well established and recommended.1-7 Earlier induction of mild hypothermia after cardiac arrest may yield greater benefit,8-11 even at the expense of a short delay in resuscitation.12 Several methods can be used to induce mild hypothermia, but they differ in terms of safety, efficiency and feasibility.6,13 Methods using ice bags and intravenous 4°C fluids are safe, efficient and feasible, and have the added advantage that they can be used during transportation of a patient in an ambulance.5,8,10,14,15 For out-of-hospital cardiac arrest, to begin inducing mild hypothermia in ambulances is early enough. Induction of mild hypothermia with intravenous 4°C fluids is faster than with ice bags in large animals or adult patients.16 Out-of-hospital cardiac arrest patients may range from small infants to obese adults. However, little is known about the effect of body weight on the induction of mild hypothermia, especially when the body weight is low. So we determine here the effect of body weight on the induction of mild hypothermia with the use of an ice bag and intravenous 4°C saline in a rabbit model of asphyxia cardiac arrest.

Methods

This study was approved by the animal investigation committee of Wuhan University and was performed in accordance with National Institutes of Health guidelines for ethical animal research.

Animal preparation

Rabbits of both sexes with varying weights (1000-2500 g, mean 1736 g). All rabbits were fasted overnight, but had free access to water. Rabbits were anesthetized with pentobarbital (30 mg/kg) administered via a 24-gauge catheter inserted into an ear vein. Then they were immobilized on a surgical board in supine position. The trachea was surgically exposed and incised. An endotracheal tube was inserted and secured by ligature. The other end of the endotracheal tube was connected to a volume-controlled small animal ventilator (DW-3000, Huaibei Zhenghua Biologic Apparatus Facilities Ltd., Anhui, China). Tidal volume was set at 20 ml/kg and respiratory frequency at 50 breaths/minute with room air.17 A heparinized saline-filled 16-gauge catheter was inserted from carotid artery into aorta artery to measure aortic pressure (AP). Needle-probe electrocardio-
gram data and AP were monitored via a PC-based data acquisition system (BL-420F, The Chengdu Technology and market Co Ltd, Chengdu, China). The core temperature was measured with a rectal thermoprobe (Adult Esophageal/Rectal Resusable Temperature Probe 21075A, Philips Medical Systems, Massachusetts, USA) connected to a monitor (IntelliVue MP30, Philips Medical Systems, Massachusetts, USA). Rabbits were assigned to the ice bag group or intravenous 4°C saline group by the flip of a coin. Ear vein access was established in the second ear of rabbits assigned to the intravenous 4°C saline group.

Experimental protocol

After a 5-minute equilibration period, baseline temperature was recorded, the endotracheal tube was clamped in expiratory phase and the ventilator was stopped. Cardiac arrest was defined as loss of aortic pulsations and AP below 10 mmHg. Time 0 was defined as 3 minutes of cardiac arrest. At time 0, the endotracheal tube was unclamped, the ventilator was restarted and chest compressions were started with the heel of one hand on the middle of the sternum at a rate of 120 compressions/minute guided by audio. The compressions were performed by the same investigator with equal duration of compression-relaxation, and maximal depth was approximately 30% of anterioposterior diameter when the chest was fully-recoiled. At time 0, the temperature was recorded and induction of mild hypothermia was started. In the ice bag group, a 30 cm by 20 cm plastic bag filled with 1 kg crushed ice was transversely put over the upper abdomen. In the intravenous 4°C saline group, 1 ml/kg/min 4°C saline was pumped through the second ear vein access using a pressure pump (FRESENIUS VIAL OPTIMA VS, Brittan Healthcare Group (Pty) Ltd, Kempton Park, South Africa) with 4°C saline bags kept in the refrigerator during pumping.

Restoration of spontaneous circulation (ROSC) was defined spontaneous pulsations with a systolic AP over 60 mmHg. Sustained ROSC was defined as ROSC lasting for more than 5 minutes. After 2 minutes, compressions were stopped to check whether ROSC was achieved. If it was, no further compressions were given. If it was not, compressions were restarted, and 200 μg/kg epinephrine and 200 μg/kg atropine were administered followed by a 5ml-saline flush. Epinephrine and atropine were administered every 5 minutes, and atropine was administered a maximum of 3 times. We checked every 2 minutes for achievement of ROSC.

The endpoint was the completion of mild hypothermia induction, defined as when temperature was decreased by 2°C. Primary outcome was the induction time needed to reach endpoint. The study was carried out in an air-conditioned room with ambient temperature of 22-24°C. In our pilot study, we found the baseline temperature in most rabbits was 37.0 to 37.5°C. One rabbit with a temperature below 37°C was excluded; rabbits with a temperature above 37.6°C were cooled to 37.6°C with gloves filled with cold water before beginning equilibration.

In pilot experiments, we cooled four rabbits and monitored the rectum temperature using the method described above. We also monitored the aorta temperature using an arterial thermodilution catheter (PV2015L20N, PULSION Medical Systems AG, Munich, Germany) inserted from carotid artery connected to the monitor with a cable (Temperature Interface cable M1643A, Philips Medical Systems, Massachusetts, USA). The rectal and aorta temperatures showed close similarity (Figure 1), justifying that rectal temperature monitoring would be sufficient.

Statistical analysis

All data are given as mean ± SD (standard deviation). Comparisons between the two groups were made using Unpaired Student’s t-Test. Pearson correlation was used to examine the association between induction time and body weight. Linear regression was used to fit curves. All statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, USA). Two-tailed P< 0.05 was considered statistically significant.

Results

Twenty-eight rabbits were used: 3 rabbits died during preparation and 1 was excluded because its baseline temperature was 36.8°C. The remaining 24 rabbits were equally randomized into two groups: the ice bag group and the intravenous 4°C saline group. Baseline characteristics (Table 1) including body weight, temperature, heart rate, and systolic aortic pressure were statistically indistinguishable between groups, as was temperatures at time 0. All rabbits had restoration of spontaneous circulation and restoration of spontaneous circulation lasted during the experiment. Times to achieve ROSC did not differ significantly between groups. Rapid cooling was achieved in both groups, and cooling is faster in the ice bag group than in the intravenous 4°C.
The mean induction time (22.8 ± 4.7 min) in the ice bag group was significantly shorter (P<0.001) than that (42.5 ± 4.0 min) in the intravenous 4°C saline group. There was a significant correlation between induction time and body weight in the ice bag group (Pearson Correlation: r = 0.725, P = 0.029) (Figure 2). However, no significant correlation was observed between induction time and body weight in the intravenous 4°C saline group (Pearson Correlation: P= 0.418).

Discussion

The main conclusions of this study are that in a rabbit model, induction of mild hypothermia with an ice bag is faster than with intravenous 4°C saline; and induction time positively correlates with body weight when an ice bag is used, but not when intravenous 4°C saline is used (Figure 2).

When a cold pad or ice bags were used to induce mild hypothermia, the reduction rate of core temperatures seems to decrease with the increase of body weight. The reduction rate of core temperatures in mice is 3.0-4.7°C/min (19, 20), in rats is 0.2-0.3°C/min (9, 21), in pigs is 4.2°C/h(22) and in adult humans is 0.9°C/h(2). Our results of the ice bag saline group. The mean induction time (22.8 ± 4.7 min) in the ice bag group was significantly shorter (P<0.001) than that (42.5 ± 4.0 min) in the intravenous 4°C saline group. There was a significant correlation between induction time and body weight in the ice bag group (Pearson Correlation: r = 0.725, P = 0.029) (Figure 2). However, no significant correlation was observed between induction time and body weight in the intravenous 4°C saline group (Pearson Correlation: P= 0.418).

**Table 1 Group characteristics during baseline, arrest and resuscitation period (n=12 per group)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ice bag group</th>
<th>intravenous 4°C</th>
<th>saline group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>1735 ± 319</td>
<td>1738 ± 500</td>
<td>0.988</td>
<td></td>
</tr>
<tr>
<td>Tembaseline (°C)</td>
<td>37.3 ± 0.2</td>
<td>37.2 ± 0.2</td>
<td>0.333</td>
<td></td>
</tr>
<tr>
<td>HRbaseline (bpm)</td>
<td>262 ± 18</td>
<td>253 ± 16</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>SAPbaseline (mmHg)</td>
<td>95.4 ± 14.3</td>
<td>87.9 ± 11.0</td>
<td>0.168</td>
<td></td>
</tr>
<tr>
<td>MAPbaseline (mmHg)</td>
<td>84.4 ± 12.4</td>
<td>75.9 ± 13.7</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>Tem0 (°C)</td>
<td>36.8 ± 0.3</td>
<td>36.7 ± 0.3</td>
<td>0.240</td>
<td></td>
</tr>
<tr>
<td>TROSC (min)</td>
<td>5.00 ± 1.3</td>
<td>4.3 ± 0.8</td>
<td>0.156</td>
<td></td>
</tr>
</tbody>
</table>

In large animals or adult patients, intravenous 4°C fluids at a rate of about 1 ml/kg/min is effective to induce mild hypothermia in approximately 30 minutes, and it is also safe and feasible before or after establishing hemodynamic stabilization (Table 2). Our results of the intravenous 4°C saline group correlated with these results, where a reduction of 2°C in 42.5 minutes when 4°C saline was infused at a rate of 1 ml/kg/min. From rabbit to adult patients, induction time seems irrespective of body weight, when intravenous 4°C fluids are used to induce mild hypothermia.

In adults, surface cooling using ice bags, usually takes 2 hours to reach mild hypothermia, while intravenous 4°C fluids can induce mild hypothermia in approximately 30 minutes. We found in a rabbit model, induction mild hypothermia with an ice bag is faster than with intravenous 4°C saline; induction time positively correlates with body weight when an ice bag is used, but not when intravenous 4°C saline is used. We suppose that a key body weight exists, where induction of mild hypothermia will be faster with an ice bag. Because of a narrow range of body weight in rabbits, we were not able to find the key weight. Rapid and early induction of mild hypothermia depends on the method chosen and the subjects of the study. Our results suggest the effect of body weight should be considered when choosing an appropriate method to achieve early induction of mild hypothermia in a clinical setting.

Bernard S reported a case of hypothermia induced during CPR using 40ml/kg 4°C lactated Ringer's infused in 20 minutes at a rate of 150 ml/min. Further investigations are needed to test its safety and to establish the optimal infusion volume and rate. Kliegel A et al. argued cold infusions are effective for induction of hypothermia after cardiac arrest.
but not for maintenance.27 They also proved the efficacy and safety of intravenous 4°C fluids for induction of hypothermia after cardiac arrest preceding further cooling and maintenance of hypothermia by specialized endovascular cooling.28 So intravenous 4°C fluids can be used to bridge prehospital and in-hospital interventions.

The end-point mean temperature of all the rabbits was 34.7°C, which was above the upper limit of mild hypothermia used in several trials and experiments. But it was used by the Peter Safar21,28-31 Due to a higher baseline temperature in animals, a 2°C decrease is sufficient for an adequate level of hypothermia in the clinical setting.16

There may be one concern that the weight of the ice bag may crush the rabbit. However, the longer side of the plastic bag used in our study is about 3 times as long as the lateral abdominal diameter of the rabbit, so much of the weight of the ice actually lies on the surgical board. Our study has some limitations. First, healthy animals were used, and cardiac arrest was caused by clamping the trachea. Second, the study was not blind to investigators. Third, rabbits that were precooled with gloves filled with cold water were not sub-analyzed or removed. Forth, no sedatives and paralytic agents were administered. Fifth, our results may not apply to other animal models with larger body weight or to humans. Our results are not enough evidence for guidance in selecting a method for the induction mild hypothermia in humans from the angle of body weight.

Conclusions
In a rabbit model, induction of mild hypothermia with an ice bag is faster than with intravenous 4°C saline; induction time positively correlates with body weight when the ice bag is used, but not when intravenous 4°C saline is used. Body weight is a determining factor in early achievement of ice bags-induced mild hypothermia. Further studies are needed to investigate the effect of body weight on the induction of mild hypothermia in other animal models with larger body weight and in humans.

Table 2 Experiments and trials using intravenous 4°C fluids to induce mild hypothermia

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Subjects (n)</th>
<th>Mean Weight</th>
<th>Timing</th>
<th>4°C Fluids Therapy</th>
<th>Core Temp. Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordmark J et al. (2005)(16)</td>
<td>pig (9)</td>
<td>26 kg</td>
<td>during CPR</td>
<td>30ml/kg acetated Ringer's solution in 22 minutes</td>
<td>1.6°C</td>
</tr>
<tr>
<td>Bernard S et al. (2003)(23)</td>
<td>human (22)</td>
<td>NA</td>
<td>comatose after OHCA</td>
<td>30ml/kg lactated Ringer's solution in 30 minutes</td>
<td>1.7°C</td>
</tr>
<tr>
<td>Kim F et al. (2005)(24)</td>
<td>human (17)</td>
<td>82Kg</td>
<td>comatose after OHCA</td>
<td>2L saline in 30minutes</td>
<td>1.4°C</td>
</tr>
<tr>
<td>Bruel C et al. (2008)(15)</td>
<td>human (33)</td>
<td>NA</td>
<td>during ALS</td>
<td>2L saline in 30minutes</td>
<td>2.1°C</td>
</tr>
</tbody>
</table>


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Reference


