Original Article

Development of new equipment for intra-arrest brain cooling that uses cooled oxygen in the lungs: volunteer study

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Aims: Many experimental studies have reported that intra-arrest cooling during cardiac arrest is a promising treatment to mitigate brain injury. However, there is no clinically established method for cooling the brain during cardiac arrest. We hypothesized that, as blood flow in the lungs must be very slow during cardiopulmonary resuscitation, the blood could be cooled by ventilating the lungs with cooled oxygen like a radiator, and that this cooled blood would in turn cool the brain. The aim of this study was to develop equipment to cool oxygen for this purpose and to confirm its safety on a group of volunteers.

Methods: We developed new equipment that cools oxygen by running it through a vinyl chloride coil submerged in a bottle of water and frozen at −80°C. Using this equipment, seven volunteers were given oxygen by mask, and their blood pressure, heart rate, and peripheral saturation of oxygen were measured. The temperature in the mask was also measured.

Results: This equipment was able to decrease the temperature in the mask to −5°C at the Jackson Rees circuit for an oxygen flow of 10 L/min. Among the volunteer group, vital signs were unchanged and the temperature in the mask decreased from 30.1 ± 2.6°C (mean ± standard deviation) to 15.9 ± 9.6°C. No adverse effects were observed in the volunteers after experimentation.

Conclusion: We successfully developed new equipment to cool oxygen and established its safety in a volunteer study.

Key words: Brain protection, cardiac arrest, development of new equipment, intra-arrest lung cooling

INTRODUCTION

CLINICAL STUDIES HAVE found that treatment with mild therapeutic hypothermia (TH) after resuscitation from cardiac arrest (CA) improves neurological outcomes for patients.[1,2] The Hypothermia after Cardiac Arrest study reported that in the post-resuscitative hypothermia group 55% of patients had a favorable neurologic outcome, indicating a significant improvement with this treatment.[1] However, the alternative viewpoint of this study is that 45% of patients had an unfavorable outcome despite treatment with TH after resuscitation. An alternative strategy was needed to achieve greater improvement in outcomes for patients resuscitated after CA.

Several animal studies have suggested that the benefit to neurological outcome could be greatly increased if TH is started during cardiopulmonary resuscitation.[3–6] This strategy, so-called intra-arrest therapeutic hypothermia (IATH), has been developed in clinical practice using many kinds of equipment to conduct transnasal evaporative cooling,[7] cold saline and external cooling,[8] and pharyngeal cooling.[9] Although all these types of equipment could be proven to induce IATH in the clinical setting, they were not able to improve the outcome of patients after CA. Moreover, the International Liaison Committee on Resuscitation recommended against routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after return of spontaneous circulation (ROSC).[10] The development of other IATH equipment was required.

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Experimental studies in lung cooling using cold perfluorocarbons (PFC) were successful in inducing IATH and facilitating ROSC in a swine CA model.[11,12] These studies suggest that intra-arrest lung cooling (IALC) is a possible new strategy for IATH.

METHOD

Equipment to cool oxygen

WE NEEDED TO develop equipment to cool oxygen. Our approach to cool the oxygen was to use a vinyl chloride coil (BLT500; Toray Medical Co., Ltd., Tokyo, Japan) designed for warming blood during blood transfusion. The coil was placed in a 500-mL PET bottle (Fig. 1A) and covered with water. The bottle was then frozen to −80°C in a deep freezer (Fig. 1B). When we ran oxygen at a rate of 10 L/min into the coil and measured the temperature at its outflow point, it was approximately −5°C. Our next step was to establish a ventilation system using this equipment. We attached a bag valve mask (BVM) to this equipment with an oxygen flow of 10 L/min, but we were not able to successfully cool the oxygen with this method. We then used a Jackson Rees circuit, Mapleson D type (JN1609/3/002; Armstrong Medical, London, UK), to create a ventilation system. We tried to use one coil/bottle system by 10 L/min and failed to sufficiently decrease the temperature. Two sets of coil/bottle equipment, each administering oxygen at 10 L/min (20 L/min totally), were attached to the Jackson Rees circuit and a heat and moisture exchanger (352-5877Z; Covidien, Dublin, Ireland) with mask (Fig. 2). The temperature in the mask was measured three times and significantly decreased to −2.0 ± 7.1°C after 10 min and to 6.9 ± 4.0°C after 30 min (Fig. 3).

Volunteer study to confirm safety

This study was approved by the Clinical Research Institutional Review Board of Nihon University Hospital (RK-140314-2; Tokyo, Japan). Seven healthy volunteers (all male) of age 34.6 ± 6.0 years, height 168.9 ± 5.8, weight 63.0 ± 7.3 kg (mean ± standard deviation), and with no underlying medical problems participated in this study. Before testing began, all volunteers were fully briefed both verbally and in writing about the study aims and risks (minor side effects, e.g., dry mouth) and gave free and informed, consent in writing to participate in the research.

Each volunteer lay on the operating table in the supine position. His nose was pinched with a swimming nose clip to ensure that ventilation occurred only by mouth to avoid warming through the nose. A mask was fitted on to the volunteer's face and oxygen was administered at a flow rate of 10 L/min through each bottle (20 L/min totally) through both ports without the new equipment for 5 min. Each mask

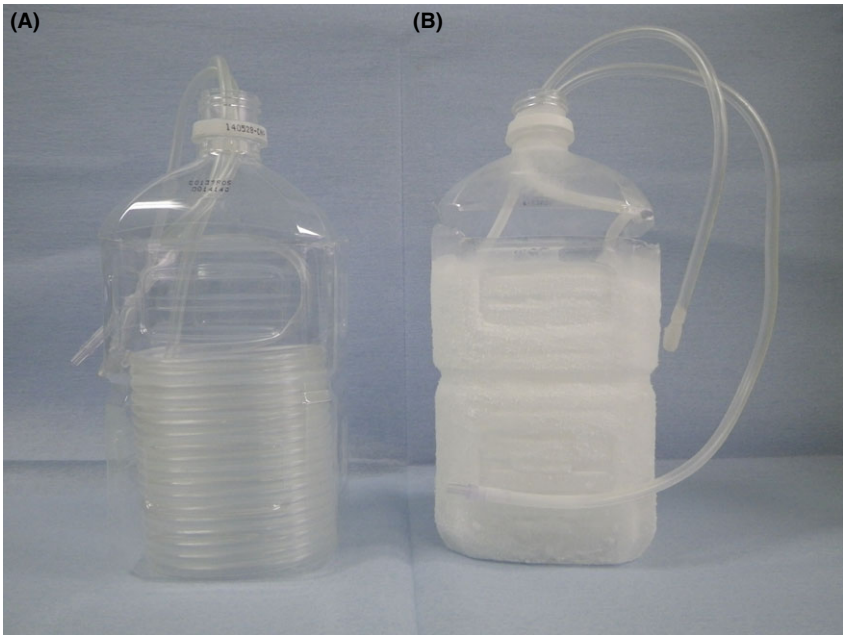

Fig. 1. Oxygen cooling equipment designed to cool the brain during cardiac arrest. A vinyl chloride coil is submerged in water in a 500-mL PET bottle (A) and frozen to −80°C (B).

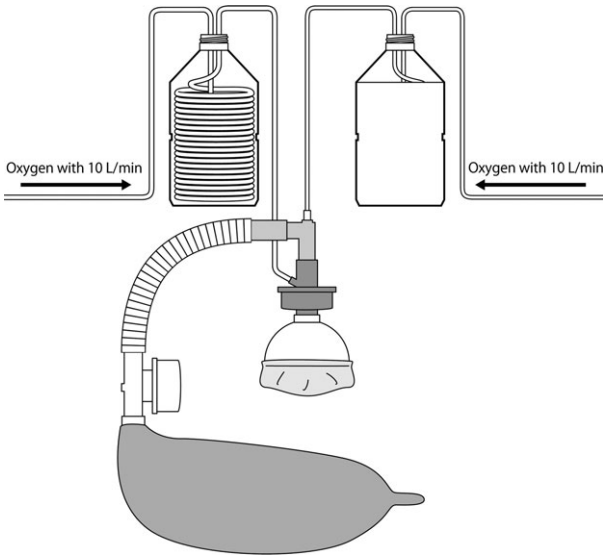

Fig. 2. Ventilation system designed to cool blood, and thus the brain, during cardiac arrest. The system uses two sets of coil/bottle equipment, each administering oxygen at 10 L/min, attached to a Jackson Rees circuit and a heat and moisture exchanger.

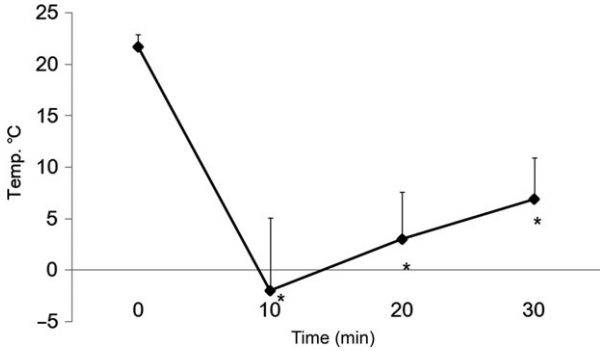

Fig. 3. Temperature changes in the breathing mask when using oxygen cooling equipment designed for use during cardiac arrest. The temperature in the mask significantly decreased once the equipment was attached. *$P < 0.05$ versus 0.

was fitted by head gear and in this setting some amount of oxygen was leaked. We then measured the temperature inside the mask. The new equipment was then attached to each oxygen port and we measured the temperature inside the mask over a period of 30 min.

We continuously monitored each volunteer's heart rate by electrocardiogram, peripheral saturation of oxygen (SpO_2) by pulse oximetry, and respiratory rate. We intermittently monitored indirect systolic blood pressure every 10 min using a medical monitor system (MU-651R; Nihonkohden,

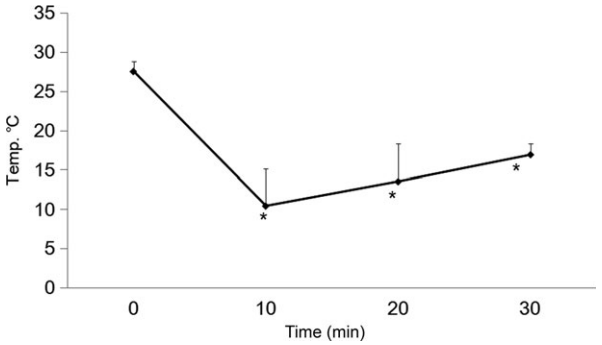

Fig. 4. Temperature changes in the breathing masks of volunteers when using oxygen cooling equipment designed for use during cardiac arrest. The temperature in the masks of the volunteers significantly decreased once this equipment was attached. *$P < 0.05$ versus 0.

Tokyo, Japan). Axillary temperature (T_{axi}) was recorded every 10 min using an electronic clinical thermometer (MC-1600W-HP; Omron Healthcare, Kyoto, Japan). Right tympanic temperature (T_{ty}) was measured continuously with a non-contact eardrum thermometer (CET-001; Nipro, Osaka, Japan). The temperature in the mask was also measured. We followed up on complications 1 week afterwards.

We analyzed the changes between the control (before the equipment was attached at 0 min) and every 10 min after it was attached using repeated ANOVA followed by Scheffe's test for multiple comparison (StatView version 5.0: SAS Institute Inc., Cary, NC, USA).

RESULTS

THE MEASUREMENTS FOR heart rate (b.p.m., 58.0 ± 13.0 at 0 min and 57.1 ± 11.9 at 30 min), systolic blood pressure (mmHg, 121.6 ± 20.0, 123.6 ± 21.6), respiratory rate (breaths/min, 14.6 ± 5.0, 16.0 ± 6.0), SpO_2 (%, 100.0 ± 0, 100 ± 0), T_{axi} (°C, 36.4 ± 0.5, 36.5 ± 0.3), and T_{ty} (°C, 36.6 ± 0.2, 36.5 ± 0.3) did not change significantly throughout the experiment from beginning to end. The temperature in the mask decreased significantly from 27.6 ± 1.3 to 10.5 ± 4.7°C at the 10 min mark after the equipment was attached and made a further significant decrease to 17.0 ± 1.4°C after 30 min (Fig. 4). We did not observe any cases of shivering in this study. No complications were observed in any of the volunteers 1 week after this experiment.

DISCUSSION

IN OUR PREVIOUS study, we developed equipment to cool oxygen and established a ventilation system with

this equipment to cool the lungs. In this volunteer study we were able to safely use this ventilation system to cool oxygen for 30 min.

Initially, the equipment failed to decrease temperature with the BVM system because heat was exchanged at the BVM and air was warmed. The change to the Mapleson D breathing system was a good choice for this experiment because the inlet for fresh gas flow was located just at the outlet of the system[13] and cooled air could blow into the mask without warming. We attempted to use a one coil/bottle system by 10 L/min and also failed to adequately decrease temperature. Next we used a two coil/bottle system with the Mapleson D breathing system and successfully decreased the temperature. The reason for this was the incomplete mask fitting, using head gear, and leakage of oxygen. It seems that high flow of cooled oxygen with leakage may avoid rebreathing and could decrease the temperature in the mask. In this setting, the safety of this system was confirmed by the volunteer study.

An experimental study reported that during CA with resuscitation by external chest compression, cardiac output decreased between 16% and 36% from before cardiac arrest.[14–16] Theoretically, in such a situation the blood flow should slow down and the time the blood remains in the organs should increase. Takeda *et al.*[17] posited this theory and established a pharyngeal cooling system to cool the brain by cooling the carotid artery.[9,17] As the lung has a very large area of alveoli, the efficacy of heat exchange may be better there than in other organs, working in the same way as an air cooling radiator. If the lungs can be cooled during CA when the blood flow is slow, the blood maybe cooled more efficiently. Following this theory, it was reasonable that T_{axi} and T_{ty} did not decrease in the present study, because the volunteers were not suffering CA.

One experimental study showed that pulmonary arterial temperature decreased through total liquid ventilation (TLV) with cold PFC (−15°C), and that a better ROSC ratio was achieved in the group treated with TLV with cold PFC than in the control group.[11] Another study reported that moderate hypothermia was achieved rapidly during CA with ventricular fibrillation and cardiopulmonary resuscitation using both a cold saline infusion and cold TLV using cold PFC (−15°C), but that ROSC was higher than the control only in the cold TLV group.[12] Therefore, TLV with cold PFC may be a form of IALC that can induce IATH, facilitate ROSC, and mitigate brain damage caused by CA. These findings suggest that lung cooling with cold oxygen may facilitate ROSC and mitigate brain damage by inducing IATH. Moreover, Tissier *et al.*[18] reported that TLV with cooled PFC can elicit rapid cardioprotective cooling during heart ischemia. Intra-arrest lung cooling may also protect the heart against ischemia during CA.

This study has some limitations. One question concerns the safety of cooled oxygen for the patient's lungs. Some resuscitation efforts have been carried out in very cold conditions for Out-of-hospital cardiac arrest (OHCA) but we have not been able to find any reports of severe lung damage resulting from ventilation with cooled ambient air in a cold climate. This information and our own study lead us to believe that ventilation of cooled oxygen is not dangerous. Another question concerns the advantage of this equipment over other devices that perform IATH through transnasal evaporative cooling or pharyngeal cooling. Our equipment may have more advantages because of its low cost, portability, and ease of use. However, our focus is to prove the efficacy of IALC with the new equipment for patients with CA, and further studies will be needed to assess the advantages of the different types of equipment available.

CONCLUSION

WE WERE ABLE to develop new equipment to cool oxygen and proved that it can be safely used on healthy volunteers to administer cooled oxygen. In order to test the efficacy of this equipment with IALC, it will be necessary to conduct a feasibility study with patients suffering CA.

CONFLICT OF INTEREST

NONE DECLARED.

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