Clinical Paper

Feasibility study of immediate pharyngeal cooling initiation in cardiac arrest patients after arrival at the emergency room[☆]

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ABSTRACT

Aim: Cooling the pharynx and upper oesophagus would be more advantageous for rapid induction of therapeutic hypothermia since the carotid arteries run in their vicinity. The aim of this study was to determine the effects of pharyngeal cooling on brain temperature and the safety and feasibility for patients under resuscitation.

Methods: Witnessed non-traumatic cardiac arrest patients (n = 108) were randomized to receive standard care with (n = 53) or without pharyngeal cooling (n = 55). In the emergency room, pharyngeal cooling was initiated before or shortly after return of spontaneous circulation by perfusing physiological saline (5 °C) into a pharyngeal cuff for 120 min.

Pharynx
Selective cooling
Intra-arrest cooling

Results: There was a significant decrease in tympanic temperature at 40 min after arrival ($P = 0.02$) with a maximum difference between the groups at 120 min ($32.9 \pm 1.2\,°C$, pharyngeal cooling group vs. $34.1 \pm 1.3\,°C$, control group; $P < 0.001$). The return of spontaneous circulation (70% vs. 65%, $P = 0.63$) and rearrest (38% vs. 47%, $P = 0.45$) rates were not significantly different based on the initiation of pharyngeal cooling. No post-treatment mechanical or cold-related injury was observed on the pharyngeal epithelium by macroscopic observation. The thrombocytopaenia incidence was lower in the pharyngeal cooling group ($P = 0.001$) during the 3-day period after arrival. The cumulative survival rate at 1 month was not significantly different between the two groups.
Conclusions: Initiation of pharyngeal cooling before or immediately after the return of spontaneous circulation is safe and feasible. Pharyngeal cooling can rapidly decrease tympanic temperature without adverse effects on circulation or the pharyngeal epithelium.

1. Introduction

Mild hypothermia is known to ameliorate poor neurological outcomes after resuscitation in humans,[1,2] with clinical[3] and laboratory[4] data suggesting that early achievement of hypothermia is one of the most important factors for good neurological outcomes. However, rapid intravenous infusion of cold fluid, which is considered the technique for the fastest induction of hypothermia, may increase rearrest rates even after return of spontaneous circulation (ROSC) initiation.[5] Furthermore, nasal cooling, which is used for intra-arrest cooling, may cause serious epistaxis and periorbital emphysema.[6] Therefore, a technique that can be initiated before or shortly after ROSC without adverse effects is needed.

The bilateral common carotid arteries run near the pharynx and upper oesophagus. Therefore, cooling the pharyngeal region decreases brain temperature by cooling the blood in the carotid artery.[7] We developed a pharyngeal cooling system in which cold saline (5 °C) is perfused into a pharyngeal cuff. The pharyngeal cooling can be initiated before or shortly after ROSC. In a cardiac arrest animal model, pharyngeal cooling was initiated simultaneously with chest compression without having adverse effects on ROSC and pharyngeal epithelium.[7,8]

The primary aim of the present study was to determine the safety and feasibility of pharyngeal cooling in patients with non-traumatic cardiac arrest; the effects of particular interest were ROSC success and rearrest rates. The second aim was to identify the complications associated with the use of pharyngeal cooling, e.g., mechanical damage or cold-related injury to the pharyngeal epithelium. The third aim was to determine the effects of cooling on the tympanic and core temperatures during the initial 2-h period after arrival at the hospital.

2. Methods

2.1. Study design

This study was a multicentre, randomized, controlled clinical trial performed in 19 emergency medical centres in Japan between June 2009 and October 2013. The protocol was determined by a scientific advisory committee, in which emergency departments from seven universities in the Chugoku–Shikoku area in Japan participated, and was approved by the institutional review board of each participating centre. This study is registered at http://www.umin.ac.jp/ctr/index.htm (UMIN000002224 and UMIN000008506).

Originally, the present study was financially supported by the Ministry of Health, Labour and Welfare of Japan and was intended to determine the effect of pharyngeal cooling on tympanic temperature. In July 2010, the institutional review board at Okayama University Medical School recommended discontinuation of this work because of the apparent decrease in tympanic temperature

in the pharyngeal cooling group. In December 2011, after approval by the institutional review board, the research was resumed to examine the effect of pharyngeal cooling on survival with the same protocol and was supported by Daiken Medical Co. Although the sample size (108 cases) was much smaller than the size required to evaluate survival (692 cases), the study was terminated owing to the end of the planned experimental period.

Written, informed consent was obtained before enrolment when the family of the patient was present. However, if the family of the patient could not be located, the need for written, informed consent was waived, and consent was obtained as soon as possible. Randomization assignments were generated with block sizes of 4 in a 1:1 allocation to groups receiving standard care with or without pharyngeal cooling. The emergency physician in each participating centre checked the eligibility of patients and, when a patient was eligible, telephoned the allocation centre.

2.2. Patients

The eligibility criteria included the following: aged 16–89 years and witnessed cardiogenic cardiac arrest or witnessed non-cardiogenic cardiac arrest with resuscitation by medical personnel, including emergency services, within 15 min after collapse. Both in-hospital and out-of-hospital cardiac arrests were included. The exclusion criteria included the following: traumatic cardiac arrest, core body temperature <34 °C upon arrival at the emergency room, or pharyngeal or oesophageal disorder.

2.3. Treatments

Patients were resuscitated according to the 2005 or 2010 American Heart Association (AHA) Guidelines, depending on the date of admission. Immediately after arriving at the emergency room, pharyngeal cooling was initiated during chest compression or immediately after ROSC, if ROSC was achieved before arrival, and continued for 2 h unless the tympanic temperature decreased to <32 °C. Although it was encouraged to initiate whole body cooling following 2 h of pharyngeal cooling, the decision regarding timing and the technique were up to each facility based on their current standard care practice, i.e. infusion of cold fluid, ice pack, body surface cooling, or percutaneous cardiopulmonary support. Resuscitation measures were continued for at least 30 min after arrival at the emergency room.

2.4. Pharyngeal cooling

The pharyngeal cooling system (Daiken Medical Co., Osaka, Japan) was composed of a disposable pharyngeal cooling cuff (size #4 for 50–70 kg body weight) and circulator (Fig. 1). The cuff was made of vinyl chloride, designed to fit the upper oesophagus and pharynx and inserted using a manoeuvre similar to that for a
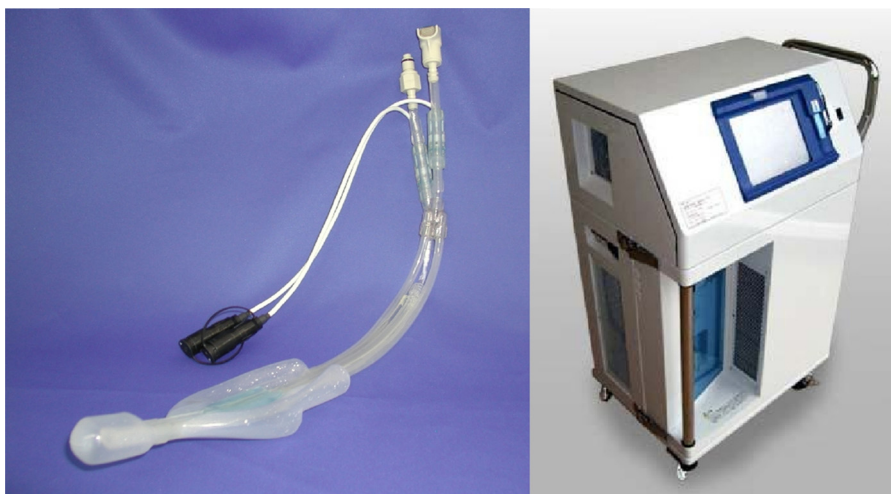
Fig. 1. Pharyngeal cooling cuff (left) and circulator (right). Physiological saline (5 °C) is initially supplied to the oesophageal cuff through the inflow tube, where temperature is continuously monitored, and subsequently fills the pharyngeal cuff before being discharged through bilateral outlets. The bilateral outlets are connected to an outflow tube, where pressure is continuously monitored. According to a pilot study, intra-cuff pressures at the oesophageal and pharyngeal cuffs were 8 cm H_2O and 6 cm H_2O higher than the pressure monitored at the outlet tube, respectively. The intra-cuff pressure at the pharyngeal cuff was controlled at 50 cm H_2O. The cuff is made from vinyl chloride, has passed biological safety tests, and tolerates up to 200 cm H_2O of intra-cuff pressure.

supraglottic airway device after securing the airway by tracheal intubation. Physiological saline cooled to 5 °C was perfused into the cuff at a rate of 500 ml min^{-1} and pressure of 50 cm H_2O. Intra-cuff pressure and perfusate temperature were continuously monitored at the outlet and the inlet tubes, respectively; the information was transmitted to the circulator for automatic feedback. After the pharyngeal cooling cuff was removed, the epithelium of the middle pharynx was visually examined.

2.5. Recordings

Bilateral tympanic temperatures were measured using thermistor thermometers (TM400, Covidien Japan, Tokyo) while the external auditory canals were insulated with adhesive wrapping material.[9] Rectal or bladder temperature was recorded as core body temperature. For the patients who survived for more than 24 h, the incidence of adverse events following resuscitation (systemic inflammatory response syndrome (SIRS), acute lung injury, bacteraemia, decrease in platelets (<50,000 mm^{-3}), and coagulopathy (activated partial thromboplastin time >50 s or prothrombin time-international normalized ratio >1.5) was recorded for 72 h. Survival was determined at 1 month.

2.6. Data management

Tympanic temperature was automatically recorded into a data logger for both groups. Each participating centre sent a datasheet and an electronic file containing tympanic temperature to a data management centre where all changes in history were logged and inspected by external parties (Data Inspection Committee).

2.7. Statistical analysis

The summary values for numerical variables are expressed as median and interquartile range or as mean ± standard deviation, while those for categorical variables are reported as counts and frequencies. Differences between the control and pharyngeal cooling groups were analysed using the Mann–Whitney U test for continuous variables and χ^2 analysis for categorical variables. Changes in temperature were analysed by two-factor ANOVA followed by Scheffe's test for multiple comparisons. Adjusted odds ratios (ORs) for ROSC and rearrest were estimated using multiple logistic

regression analyses. Adjusted relative risks (RRs) for survival at 1 month were estimated using the Cox proportional-hazards model. Of the covariates listed in Table 1, important covariables selected using the stepwise method were put into the model. These statistical analyses were performed using a general purpose statistical software package, StatFlex Ver. 6.0 (Artech Co., Osaka, Japan). Two-tailed tests were performed with $\alpha = 0.05$.

3. Results

The total experimental period was 37 months. Of the 4435 patients that were brought to the emergency room for resuscitation during that time, 818 patients met the inclusion criteria (Fig. 2). Owing to a shortage of human resources in the critical care department, 705 patients were not enrolled, at the discretion of their treating physician ($n = 680$) or for other, unknown reasons ($n = 25$). With the 113 patients that were enrolled, randomization was performed for intention-to-treat analysis ($n = 57$, control group; $n = 56$, pharyngeal cooling group). After randomization, 2 patients were excluded from the control group owing to the absence of family ($n = 2$), resulting in 55 patients for analysis. In the treatment group, 3 patients were excluded owing to low body temperature (<34.0 °C, $n = 1$), non-witnessed cardiac arrest ($n = 1$), and absence of family ($n = 1$), resulting in 53 patients for analysis.

The baseline characteristics of the two groups are shown in Table 1. The majority of the patients suffered out-of-hospital cardiac arrest, except for one patient in the control group and two patients in the treatment group ($P = 0.54$). The proportion of male patients was significantly lower in the pharyngeal cooling group (47%) than in the control group (67%, $P = 0.03$). Time from collapse to arrival of the emergency medical service was significantly shorter in the control group (median 7 min; range, 4–10 min) than the pharyngeal cooling group (9 min; range, 5–11 min; $P = 0.02$) (Table 1). The ROSC success rate, rearrest rate, adrenaline (epinephrine) dose, and number of DC shocks were comparable between the two groups. Multiple logistic regression analysis identified an initial rhythm of asystole (OR = 0.3, $P = 0.01$) as a significant factor for ROSC failure and cardiogenic cardiac arrest as a significant factor for rearrest (OR = 3.6, $P = 0.02$). The initiation of pharyngeal cooling did not have a significant effect on ROSC failure (OR = 1.3, $P = 0.58$) or rearrest (OR = 0.8, $P = 0.60$).

Table 1
Baseline characteristics of the patients with non-traumatic cardiac arrest, compared between the control and pharyngeal cooling groups.

	Control (n = 55)	Treatment (n = 53)	P value
Age (years)	72 (64–78)	72 (62–81)	0.64
Male sex	37 (67)	25 (47)	0.03
Witnessed by: EMS	8 (15)	6 (11)	0.62
Others	47 (85)	47 (89)	0.62
Bystander CPR	29 (55)	29 (58)	0.74
Location of arrest: out of hospital	54 (98)	51 (96)	0.61
In hospital	1 (2)	2 (4)	0.61
Initial rhythm: VF or pulseless VT	16 (29)	13 (25)	0.59
PEA	25 (45)	19 (36)	0.31
Asystole	13 (24)	20 (38)	0.11
Unknown	1 (2)	1 (2)	0.98
Cause of arrest: cardiogenic cardiac arrest	30 (56)	27 (52)	0.71
Number of defibrillation attempts	0 (0–2)	0 (0–1)	0.24
Adrenaline dose (mg)	4(1–6.5)	3 (1–6)	0.39
Spontaneous circulation on arrival at emergency room	11 (20)	13 (25)	0.57
Achieved ROSC	36 (65)	37 (70)	0.63
Rearrest	17 (47)	13 (38)	0.45
Time from collapse to EMS arrival	7 (4–10)	9 (5–11)	0.02
Time from collapse to emergency room arrival (min)	31 (23–38)	32 (25–38)	0.58
Time from collapse to the first ROSC	33 (21–39)	32 (17–42)	0.65

Continuous variables are presented as medians and interquartile ranges, and categorical variables are reported as frequencies.
EMS, emergency medical service; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation.

3.1. Pharyngeal cooling

Pharyngeal cooling was initiated at 12 min (7–22 min) after arrival at the emergency room and was continued for 80 min (30–120 min) (Table 2). Twenty-four patients (45%) underwent pharyngeal cooling during chest compression (intra-arrest cooling), and 29 patients (55%) underwent pharyngeal cooling shortly after ROSC (median, 17 min; range, 10–24 min) (Supplemental data 1). After pharyngeal cooling, no mechanical damage or cold injury was observed on the pharyngeal epithelium by macroscopic observation.
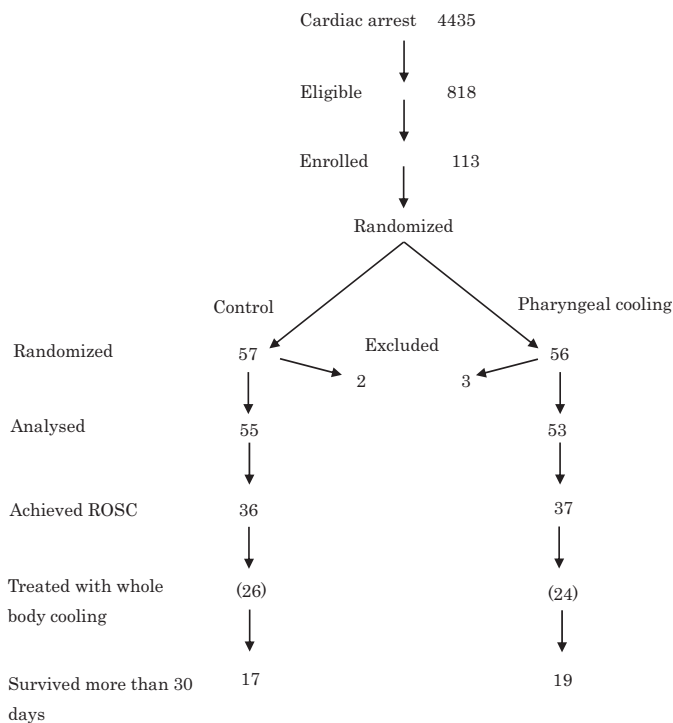
ROSC, return of spontaneous circulation

Fig. 2. Flow of participants from recruitment to analysis.

Table 2
Use of pharyngeal cooling and whole body cooling within each group (control and pharyngeal cooling groups).

| Cooling measures	Control (n = 55)	Treatment (n = 53)	P value
Pharyngeal cooling			
Number of patients, n	–	53	–
Onset time from arrival at emergency room, min	–	12 (7–22)	–
Infusion of cold fluid			
Number of patients, n	7	5	0.61
Onset from arrival at emergency room, min	21 (5.5–23)	2 (0–6)	0.07
Body surface cooling using a water blanket and gel-coated pad			
Number of patients	19	18	0.88
Onset time from arrival to emergency room, min	110 (97–185)	83 (63–124)	0.15
Number of patients who underwent initiation of body surface cooling within 2 h after arriving at the emergency room, n	9	11	0.57
Ice pack			
Number of patients	1	2	0.60
Onset time from arrival at emergency room, min	290	70, 78 in each	–
Percutaneous cardiopulmonary support			
Number of patients	1	0	0.32
Onset time from arrival to emergency room, min	67	–	
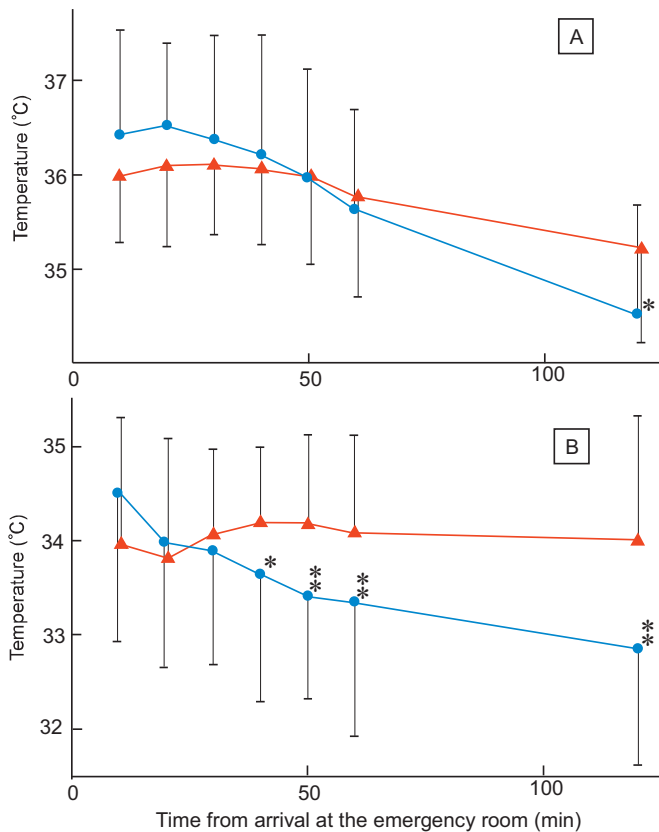
Fig. 3. (A) Changes in body temperature. (B) Changes in tympanic temperature. Blue circles indicate the temperature in the pharyngeal cooling group. Red triangles indicate the temperature in the control group. *P < 0.05 compared to the control group; **P < 0.01 compared to the control group.

3.2. Changes in temperature

Body temperature started to decrease gradually ($0.02\,°C\,min^{-1}$) at 30 min after arrival at the emergency room (Fig. 3A). At 120 min after arrival, the decrease in body temperature was significantly different between the two groups ($35.3 \pm 1.0\,°C$, control group vs. $34.5 \pm 1.1\,°C$, pharyngeal cooling group; $P = 0.02$).

In contrast, the tympanic temperature dramatically decreased by $0.6\,°C$ ($0.06\,°C\,min^{-1}$) during the first 10 min after arrival at the emergency room (Fig. 3B). However, it decreased only $0.06\,°C$ during the next 10 min. The tympanic temperature was significantly different between the groups ($34.1 \pm 1.1\,°C$, control group vs. $33.7 \pm 1.4\,°C$, pharyngeal cooling group; $P = 0.02$) at 40 min after arrival and reached the maximum difference ($34.1 \pm 1.3\,°C$, control group vs. $32.9 \pm 1.2\,°C$, pharyngeal cooling group; $P < 0.001$) at 120 min.

3.3. Whole body cooling

Whole body cooling was performed according to each centre's criteria in 26 patients in the control group and 24 patients in the pharyngeal cooling group (Table 2). Intravenous infusion of cold fluid was initiated in seven patients in the control group at 21 min (5.5–23 min) after arrival at the emergency room and five patients (vs. control group, $P = 0.61$) in the pharyngeal cooling group at 2 min (0–6 min, $P = 0.07$) after arrival. However, changes in temperature in the patients who did not receive an intravenous infusion of cold fluid were similar to those of the entire sample (Supplementary data 2).

Table 3
Complications during the first 3 days in patients with non-traumatic cardiac arrest who survived more than 24 h, compared between the control and pharyngeal cooling groups.

	Control ($n = 23$)	Treatment ($n = 26$)	P value
SIRS (%)	13 (57)	8 (31)	0.07
ALI (%)	4 (17)	4 (15)	0.85
Bacteraemia (%)	5 (22)	3 (12)	0.34
Thrombocytopaenia (%)	4 (17)	0 (0)	0.03
Coagulopathy (%)	9 (39)	4 (15)	0.06

SIRS, systemic inflammatory response syndrome; ALI, acute lung injury.

3.4. Adverse events

During the first 3 days, the incidences of SIRS, acute lung injury, bacteraemia, and coagulopathy tended to be lower in the pharyngeal cooling group, and the incidence of thrombocytopaenia was significantly lower in the pharyngeal cooling group ($P < 0.001$) (Table 3).

3.5. Prognosis

The cumulative survival rate during the 1-month period after cardiac arrest was not significantly different between the two groups (RR = 0.79, 95% confidence interval [CI] = 0.49–1.28, $P = 0.34$).

4. Discussion

In the present study, tympanic temperature was measured as an indicator of brain temperature; changes in tympanic temperature have been reported to be very similar to changes in brain surface and core brain temperatures during pharyngeal cooling in monkeys.[8] The tympanic temperature decreased by $0.6\,°C$ during the first 10 min in the pharyngeal cooling group followed by a decrease of only $0.06\,°C$ in the next 10 min. The mechanism for this marked change is uncertain; a possible explanation is an increase in the number of patients who successfully achieved ROSC and/or recovered blood pressure, because during chest compression, arterial blood passes slowly through the cervical region and could efficiently exchange heat with the pharyngeal cooling cuff. It has been shown previously in monkeys that the fastest decrease in brain temperature during pharyngeal cooling was in animals with low blood pressure owing to unstable circulatory conditions following ROSC.[8]

The severity of systemic inflammation is an important factor for post cardiac arrest syndrome (PCAS),[10] which influences survival following resuscitation. In the present study, the incidence rates of SIRS (57%, control group vs. 31%, pharyngeal cooling group, $P = 0.07$) and coagulopathy (39% vs. 15%, $P = 0.06$) tended to be lower in the pharyngeal cooling group during the first 3 days, while the thrombocytopaenia incidence (17% vs. 0%, $P = 0.03$) was significantly lower in the pharyngeal cooling group. The brain is rich in tissue thromboplastin,[11] and the severity of coagulopathy is considered an indication of brain damage[12]; therefore, these favourable results in the pharyngeal cooling group may indicate attenuation of brain damage.

One of the most important factors causing neuronal damage during ischaemia is glutamate,[13] which is released in the first few minutes after ischaemic onset[4] and rapidly diminishes after ROSC.[4] Hypothermia stops the release of glutamate[14]; therefore, intra-arrest hypothermia could attenuate glutamate-initiated neuronal damage.[4] A prospective observational study demonstrated that the initiation of intra-arrest hypothermia (32–$34\,°C$) using percutaneous cardiopulmonary support to out-of-hospital cardiac arrest patients significantly improved neurological outcomes 1 and 6 months after the collapse.[15]

No mechanical damage was observed on the pharyngeal epithelium after treatment. This is likely owing to the guided insertion of the cuff into the centre of the pharynx and oesophagus, resulting in equal pressure exerted on the top of the pharyngeal cooling cuff, which is hollow for contact with the tracheal tube during insertion. Moreover, the insertion manoeuvre for the pharyngeal cooling cuff is similar to that for insertion of a supraglottic airway device, with which emergency physicians are familiar and likely to insert in a cautious manner.

In addition, the pharyngeal epithelium did not show signs of cold-induced injury, which can be initiated by two different mechanisms. The first is the formation of ice crystals in the extracellular space, and the other is progressive formation of chilblain by release of inflammatory mediators at temperatures >0 °C.[16] Chilblain is usually observed at the fingertips, where blood flow is severely limited in a cold environment. However, the formation of ice crystals is unlikely since the perfusate temperature was controlled at 5 °C. It was also unlikely that the latter mechanism was induced in the pharynx, where blood flow is abundant. However, to avoid the possibility of cold-induced damage, the duration of pharyngeal cooling was limited to 2 h after onset.

Neuropathy of the pharynx could also occur with pharyngeal cooling. There have been case reports of recurrent laryngeal nerve palsy[17] and hypoglossal nerve palsy[18] occurring after the use of supraglottic airway devices, which are similar in shape to a pharyngeal cooling cuff. To avoid these neuropathies, it is recommended to inflate supraglottic airway devices to <60 cm H_2O.[19] Therefore, in the present study, the intra-cuff pressure was controlled at 50 cm H_2O.

This study has certain limitations. First, physicians were not blinded to the treatment assignment. Therefore, the treatment group may have received more extensive treatment during resuscitation. However, since the adrenaline dose and number of DC shocks were similar in both groups, we believe that the physicians provided similar treatment regardless of the treatment assignment. Second, although 818 patients met the inclusion criteria, 705 patients were not enrolled, primarily owing to manpower limitations in the critical care department. Because the randomization was performed after the enrolment and exclusion after enrolment was limited (two patients in the control group and three patients in the treatment group), we believe that the limited enrolment does not affect the data quality. Third, initiation of whole body cooling (26 patients in the control group and 24 patients in the treatment group) was not controlled by the experimental protocol but determined by each participating centre. Therefore, longitudinal changes in temperature represent the effects of both pharyngeal cooling and whole body cooling. However, the differences between the two groups likely represent the effects of pharyngeal cooling, given that whole body cooling was initiated at a similar rate in both groups (Table 2).

5. Conclusions

In conclusion, it appears that the initiation of pharyngeal cooling is safe and feasible before and shortly after ROSC in the emergency room. Tympanic temperature significantly decreased in a short period of time without damage to the pharyngeal epithelium or effects on the ROSC success and rearrest rates.

Conflict of interest statement

Okayama University and Daiken Medical Co. (Osaka, Japan), who provided funding for this study, hold patents related to the pharyngeal cooling device. The pharyngeal cooling device was manufactured by Daiken Medical Co., by which the laboratory is partially funded and Mr. Hashimoto and Mr. Tsuji are employed. The other authors have not received any individual benefits other than academic recognition.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2014.09.014.

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