Resuscitation 81 (2010) 943–949

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Safety and feasibility of nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest☆

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ARTICLE INFO

Article history:
Received 9 December 2009
Received in revised form 13 April 2010
Accepted 28 April 2010

Keywords:
Cardiac arrest
Hypothermia
Cooling devices

ABSTRACT

Aim: Mild therapeutic hypothermia improves survival and neurologic recovery in primary comatose survivors of cardiac arrest. Cooling effectivity, safety and feasibility of nasopharyngeal cooling with the RhinoChill device (BeneChill Inc., San Diego, USA) were determined for induction of therapeutic hypothermia.

Methods: Eleven emergency departments and intensive care units participated in this multi-centre, single-arm descriptive study. Eighty-four patients after successful resuscitation from cardiac arrest were cooled with nasopharyngeal delivery of an evaporative coolant for 1 h. Subsequently, temperature was controlled with systemic cooling at 33 °C. Cooling rates, adverse events and neurologic outcome at hospital discharge using cerebral performance categories (CPC; CPC 1 = normal to CPC 5 = dead) were documented. Temperatures are presented as median and the range from the first to the third quartile.

Results: Nasopharyngeal cooling for 1 h reduced tympanic temperature by median 2.3 (1.6; 3.0) °C, core temperature by 1.1 (0.7; 1.5) °C. Nasal discoloration occurred during the procedure in 10 (12%) patients, resolved in 9, and was persistent in 1 (1%). Epistaxis was observed in 2 (2%) patients. Periorbital gas emphysema occurred in 1 (1%) patient and resolved spontaneously. Thirty-four of 84 patients (40%) patients survived, 26/34 with favorable neurological outcome (CPC of 1–2) at discharge.

Conclusions: Nasopharyngeal evaporative cooling used for 1 h in primary cardiac arrest survivors is feasible and safe at flow rates of 40–50 L/min in a hospital setting.

1. Introduction

Sudden cardiac arrest is a major cause of death in the western world, and the estimated number of out-of-hospital cardiac arrest cases is 300,000/year in the US. The median rate of survival to hospital discharge in the US is 7.9%.[1] Favorable outcome of patients admitted to the hospital range between 11% and 48%,[2,3] indicating a large number of patients that die after successful resuscitation during the hospital stay, or develop sustained severe brain damage. Two randomized controlled trials[4,5] have demonstrated that mild therapeutic hypothermia (32–34 °C) for 12–24 h improves neurologic recovery and survival after cardiac arrest. The European Resuscitation Council and The American Heart Association recommend mild hypothermia for unconscious adult patients resuscitated from cardiac arrest due to ventricular fibrillation.[6,7] Animal data suggest that a delay in cooling may negate its beneficial effects,[8] and a study by Wolff et al. demonstrated that early achievement of hypothermia is a determinant of favorable outcome

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2010.04.027.

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doi:10.1016/j.resuscitation.2010.04.027

in patients after cardiac arrest.[9] Cooling methods are needed which can be applied early after restoration of spontaneous circulation (ROSC) and cool efficiently.

The RhinoChill device (BeneChill Inc., San Diego, USA) allows evaporative cooling by spraying an inert liquid coolant into the nasal cavity. The liquid evaporates instantaneously, thereby removing heat. The coolant is a proprietary perfluorochemical. Perflourochemicals are a family of chemicals that are both chemically and biologically non-reactive. These chemicals are among the least toxic compounds known. They cannot reach appreciable concentrations in tissues of air-exposed animals since they have limited ability to dissolve in biological media. They are highly volatile and have a high air–blood partition coefficient, which facilitates their rapid elimination through pulmonary expiration should any of it remain in the body after exposure (more information is available via 3M Specialty Materials. Robust summaries and test plan: perfluorocompounds, C5–C18; revised summaries. EPA Report 201-14684B, Aug 2003). The cooling and safety profile associated with the specific perfluorochemical used in the coolant has been determined by Wolfson et al. in a sheep model,[10] where no damage to the epithelial surface could be detected. The nasal cavity with its proximity to the cerebral circulation, basal brain regions and the brain stem offers an approach that might cause preferential brain cooling. The device has been tested in a pig model of prolonged ventricular fibrillation cardiac arrest during cardiopulmonary resuscitation (CPR). After 10 min of cardiac arrest, cooling and CPR were begun simultaneously. Jugular vein temperature, which was used as surrogate for brain temperature, dropped from 38.1 °C to 34.2 °C within 5 min of CPR.[11] Pigs and sheep however differ considerably to humans in their ratio between the size of their nasal cavity and their brain. We hypothesized that nasal evaporative cooling is safe and feasible in patients after cardiac arrest and successful resuscitation, and effective in inducing systemic mild therapeutic hypothermia.

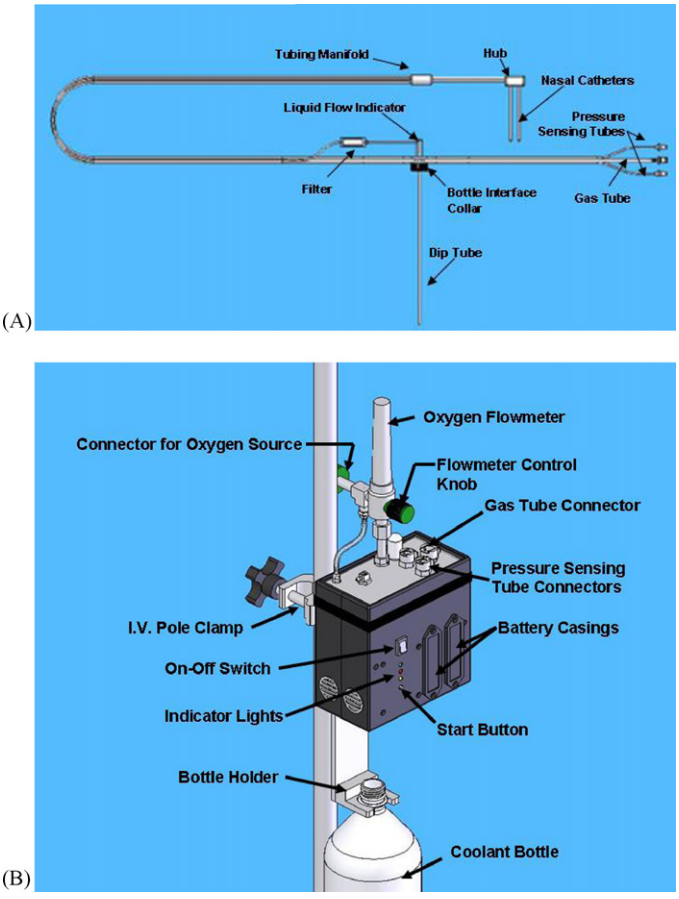

Fig. 1. A, tubing set; B, control unit.

2. Methods

2.1. Study design

The primary aim of this prospective, multi-center, single-arm observational study was to demonstrate safety, feasibility and cooling effectivity of nasopharyngeal evaporative cooling in comatose patients after successful resuscitation from cardiac arrest. Primary endpoints were cooling rate, time needed to achieve mild hypothermia (34 °C) and target temperature (33 °C), and the evaluation of possible side effects of evaporative cooling in the nasopharynx and elsewhere. The secondary endpoints were survival rate and neurologic outcome at hospital discharge.

2.2. Setting

Eleven European intensive care units and emergency departments participated. Local Ethics Committees of each centre approved the protocol. All patient files were monitored by an external institute. Monitoring visits were performed by a sponsor designee conversant in the local language and regulations. Periodic site visits were made to monitor the progress of the clinical investigation. Data were collected by independent data managers and compared with the case report forms. Compliance with the investigation plan, and appropriate device use and accountability were reviewed per International Conference on Harmonization–Good Clinical Practices guidelines. Findings of noncompliance or required modifications were reviewed with the investigator and disclosed in a written monitoring report to the study sponsor. Study monitoring functions were carried out per ISO 14155 regulations concerning the conduct of clinical investigations of medical devices in human subjects. Consent was obtained from the patients after they regained consciousness or from the next relatives. In case of consent denial, data were not used.

2.3. Patient selection

Patients were included after successful resuscitation from cardiac arrest, irrespective if the presenting rhythm was ventricular fibrillation (VF), ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. Inclusion was done if investigators trained on the device were on duty. Patients were included if they were over 18 years of age, did not obey any verbal command at any time after ROSC and prior to initiation of cooling. If under sedation prior to cardiac arrest, patients were included if they received external chest compressions for any duration. Further inclusion criteria were a tympanic temperature >34 °C and an oxygen saturation >95% on 50% oxygen. Patients were excluded from the study if trauma occurred in the circumstance of cardiac arrest, or if they suffered from severe bleeding. If a barrier inhibited correct placing of intra nasal catheters (e.g. septum deviation, skull base fracture), patients were excluded. Further exclusion criteria were terminal disease, pregnancy and a known coagulopathy (except therapeutically induced).

2.4. Interventions

The RhinoChill device (Fig. 1) consists of the tubing set, the control unit, and the coolant bottle. The tubing set delivers oxygen and coolant to the patient. The catheters are fully inserted through the nostrils and have spray ports on their dorsal surface. The coolant is nebulized by close contact with oxygen at the spray ports. A bat-

tery operated control unit controls coolant flow rate and acts as an over-pressure shut-off valve. The patient pressure safety circuitry switches the system to a standby mode if the pressure in either nasal cavity exceeds 60 cm H_2O. Coolant delivery is maintained at a constant ratio to oxygen flow such that cooling level is controlled by setting the oxygen flow rate between 0 and 80 L/min.

Cardiac arrest and CPR-data were recorded according to Utstein style.[12] Patients received sedation, analgesia, muscle paralysis and other medication according to local standard protocols (Table 5). Nasopharyngeal cooling was initiated as soon as practical after patient's assessment for inclusion. After inserting the intranasal catheters, the nostrils remained uncovered to allow venting of vaporized coolant. The bed was kept at 0° to further reduce the risk of aspiration, and the FiO_2 was kept at 1.0 during RhinoChill use. Tympanic temperature (ThermoScan Pro 4000, Braun GmbH, Kronberg, Germany) and one core temperature [esophageal (Nellcor Mon-a-therm® General Purpose Sensor, 12 Fr, Mallinckrodt, St. Louis, MO, USA), arterial blood temperature (PiCCO System, Pulsion Medical System, Munich, Germany), bladder temperature (Ruesch Sensor®, Serie 400 Silicone, Willy Ruesch AG, Kernen, Germany) or rectal temperatures (Philips Medical Systems, NA, USA)] were measured and recorded continuously. The oxygen flow was started and gradually moved up to 60–80 L/min. The patient's mouth was kept open to provide venting of the coolant vapor. After the occurrence of a device related adverse event (described below), the flow rate was reduced to 40–50 L/min. The coolant bottle was exchanged as necessary. During the cooling period, constant check of skin-condition was required in order to avoid nasal or facial frostbite. Cooling was discontinued if signs of tissue freezing were observed, or the control unit detected over-pressure, or if the target temperature was reached (stop temperature was tympanic 33 °C in all centers except one, which used a stop temperature of esophageal 34 °C).

Because of the use of high gas flow rates in a relatively vulnerable area, the device as sole cooling method was assessed for at least 1 h, if none of the indications for an interruption of cooling described above were observed. At the end of the 1-h cooling phase, the method used for further systemic cooling was at the discretion of the participating center; some centers continued with the RhinoChill device until target temperature (33 °C) or until availability and initiation of an alternative cooling method. Target temperature was maintained for 12–24 h. Chest X-rays were performed after cooling, and at 24 h, 48 h and after 7 days if the initial X-ray showed signs of coolant aspiration (diffuse patchy, cotton–wool infiltrates bilaterally).

2.5. Outcome measures

Neurologic outcome was assessed using a cerebral performance category (CPC) score (CPC 1 = conscious and alert with no or slight disability; is able to work and lead a normal life; may have minor psychological or neurological deficits like mild dysphasia or non-incapacitating hemiparesis; CPC 2 = conscious and alert with moderate disability; sufficient cerebral function for part-time work in a sheltered environment; independent in activities of daily life (dressing, travelling with public transportation, and preparing food); CPC 3 = conscious with severe disability; depends on others for daily support because of impaired brain function; includes a wide variety of cerebral abnormalities from ambulatory with severe memory disturbance or dementia, to paralytic and able to communicate with eyes; CPC 4 = comatose or in a persistent vegetative state; no verbal or psychological interactions with environment; CPC 5 = certified brain dead or dead); a CPC score of 1 or 2 was considered good, while a CPC score of 3 or 4 was rated as poor functional outcome. Adverse events (AEs; serious and non-serious) for all enrolled patients were collected from time of enrollment until discharge from hospital. The possible device relation of AEs was rated as follows: *Unrelated* – AE is due to the underlying disease; *probably unrelated* – minimal or no temporal relationship to the use of the investigational device and/or a more likely alternative etiology exists; *probably related* – a strong temporal relationship is present and another etiology is unlikely; *definitely related* – a strong temporal relationship is present and another etiology is highly unlikely.

Olfactory function was evaluated in patients surviving to discharge. The Cross-Cultural Smell Identification Test (CC-SIT) was used to determine whether patients experienced persistent olfactory damage.[13] The CC-SIT is a 12-item self-administered micro-encapsulated odorant test for measuring olfactory function.

Table 1
Patient characteristics.

Factors measured	Result
Out-of-hospital cardiac arrest, *n* (%)	56 (67)
Aetiology presumed cardiac, *n* (%)	56 (67)
Time to first CPR attempts (min), median (IQR)	3 (0; 8)
Time to resuscitation by EMS (min), median (IQR)	5 (2; 10)
Duration from cardiac arrest to ROSC (min), median (IQR)	20 (14; 30)
Duration of CPR (min), median (IQR)	17 (10; 25)
Bystander basic life support, *n* (%)	50 (60)
Initial rhythm PEA/EMD, *n* (%)	12 (14)
Initial rhythm VF/VT, *n* (%)	37 (44)
Initial rhythm asystole, *n* (%)	34 (41)
Initial rhythm unknown, *n* (%)	1 (1)

2.6. Primary data analysis

Descriptive statistics were performed. Continuous variables are presented as median and 25–75% interquartile range. Binary variables are presented as number and percentage. Cooling rate for the nasopharyngeal cooling method was derived from each patient's original data by dividing the difference between baseline temperature and the temperature at the end of 1 h of cooling. A comparison between tympanic cooling rates at high and low oxygen flow rates during cooling was done with the Mann–Whitney *U* test.

3. Results

3.1. Patient characteristics

Between September 2007 and August 2008, 84 patients were enrolled. Age was 71 (63; 79) years, body mass index 26 (24; 29), 64 (76%) patients were male. None of the patients who regained consciousness denied consent or was lost to follow-up. Patient characteristics and resuscitation data are presented in Table 1.

3.2. Cooling effectivity

Cooling was initiated 90 (68; 125) min after collapse, 70 (41; 96) min after ROSC and 35 (17; 73) min after arrival in the emergency department. Duration of nasopharyngeal cooling was 60 (50; 90; range 25–195) min, 3.5 (2.0; 4.0) L coolant per-patient was used. Cooling data are given in Table 2 and Fig. 2. Tympanic temperature was measured in 82 patients, the median tympanic cooling rate was 2.3 (1.6; 3.0) °C in 1 h of nasopharyngeal cooling. Core temperature was measured in 84 patients as arterial ($n = 17$), esophageal ($n = 19$), bladder ($n = 26$) and rectal ($n = 22$) temperature, composite core cooling rate was 1.1 (0.7; 1.5) °C/h during nasopharyngeal cooling. Core cooling rates were split into slow reacting peripheral core temperature measurement sites (bladder, rectal) and fast reacting central core temperature measurement sites (esophageal, arterial). Cooling rate for central core temperature measurement ($n = 36$) was 1.4 (0.9; 2.0) °C/h, for peripheral temperature mea-

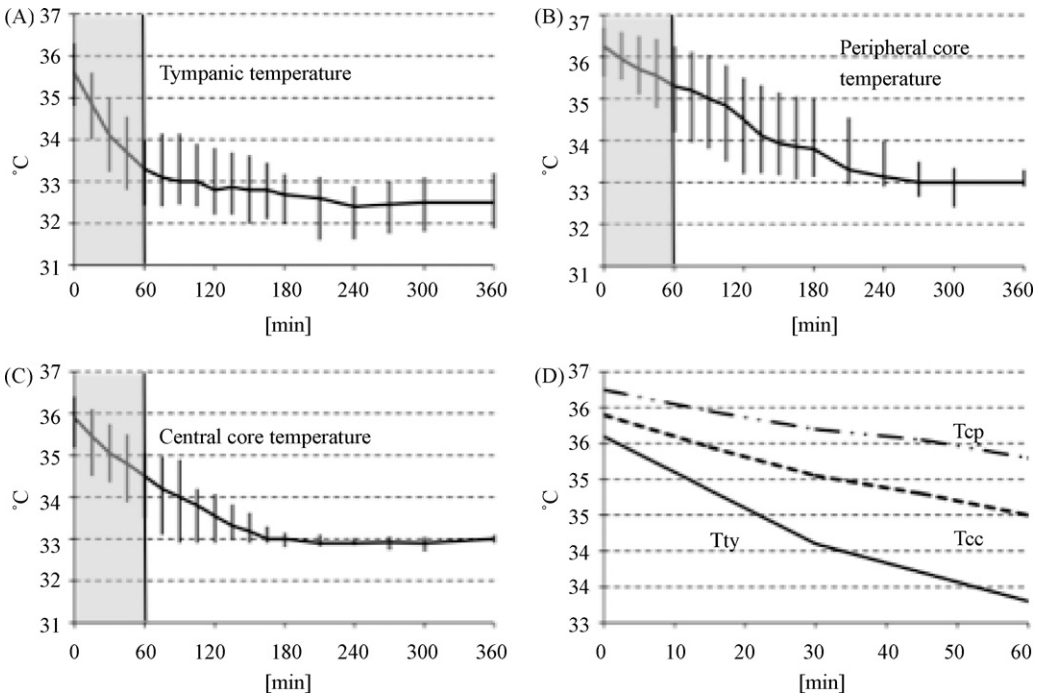

Fig. 2. A–C, temperatures (median and range from first to third quartile) during 6 h from start cooling; A, tympanic temperature ($n = 82$); B, central core temperature ($n = 36$) (composite from arterial, $n = 17$, and esophageal, $n = 19$, temperatures); C, peripheral core temperature ($n = 48$) (composite from bladder, $n = 26$, and rectal, $n = 22$, temperatures); shaded gray indicates times of RhinoChill cooling. Vertical line indicates median RhinoChill cooling time. D, median temperatures during first hour of RhinoChill cooling; Tty, tympanic temperature; Tcc, central core temperature; Tcp, peripheral core temperature.

surement 0.9 (0.5; 1.2) °C/h ($p = 0.001$). After the observation of a severe device related adverse event at the oxygen flow rate of 60–80 L/min, the flow rate used during the cooling procedure was lowered to 40–50 L/min. This had no significant effect on the tympanic cooling rate (high flow 2.3 °C/h vs. low flow 2.3 °C/h, $p = 0.89$). Eighteen patients were cooled with the reduced flow rate. After reduction of the flow rate, no more serious device related adverse events were observed, 2 patients showed reversible cold-related nasal discoloration. Additional systemic cooling was used in 79/84 patients. Cooling was discontinued in 5 patients because of death, a decision to withdraw intensive care, embolectomy in massive PE, or at the discretion of the treating physician. The systemic methods used were endovascular cooling in 43 patients (Icy catheter and CoolGard 3000, Alsius Corp., Irvine, CA, USA), and a variety of surface cooling methods in 36 patients (Arctic Sun, Medivance Incorporated, Louisville, CO, USA, $n = 5$; Blanketroll Cincinnati Sub-Zero, Cincinnati, OH, USA, $n = 5$; cold packs, PINO GmbH Hamburg, $n = 8$; CritiCool, MTRE Advanced Technologies Ltd., Southampton, PA, USA, $n = 2$; Emcoolspad, Emcools, Vienna, Austria, $n = 2$; Medi-Therm II, Gaymar Industries Inc., Orchard Park, NY, USA, $n = 2$; generic surface cooling methods, $n = 12$).

Table 2
Cooling procedure.

Times associated with cooling procedure	Result
Arrival ED to initiation of nasopharyngeal cooling (min), median (IQR)	35 (17; 73)
ROSC to start nasopharyngeal cooling (min), median (IQR)	70 (41; 96)
Collapse to start nasopharyngeal cooling (min), median (IQR)	90 (68; 125)
Duration of RhinoChill use (min), median (IQR)	60 (50; 90)
Start RhinoChill to tympanic 34 °C (min), median (IQR)	27 (14; 58)
Start RhinoChill to tympanic 33 °C (min), median (IQR)	60 (36.5; 117.5)
Start RhinoChill to core 34 °C (min), median (IQR)	52 (26; 86)
Start RhinoChill to core 33 °C (min), median (IQR)	180 (120; 285)
ROSC to tympanic 33 °C (min), median (IQR)	120 (92; 189)
ROSC to core 33 °C (min), median (IQR)	262 (187; 370)
Target tympanic 33 °C reached with RhinoChill alone *n* (%)	55/76 (66%)
Target core 33 °C reached with RhinoChill alone *n* (%)	16/80 (19%)

3.3. Outcome

Thirty-four of 84 patients (40%) survived, 26/34 (76%) with favorable neurological outcome (CPC of 1–2) at discharge. Of 37 patients with VF as presenting rhythm, 21 (57%) survived, 16/21 (76%) with favorable neurological outcome at discharge. Of 46 patients with asystole or PEA as presenting rhythm, 13 (28%) survived, 9/13 (69%) with favorable outcome. Patients with CPC 1 or 2 ($n = 26$) were significantly younger than those having a poor neurological outcome (CPC 3–5, $n = 58$) (65 ± 13.7 vs. 72 ± 10.4 years, $p = 0.017$). Outcome assorted by study center is presented in Table 5.

3.4. Safety

The RhinoChill device was safe with regards to overcooling. The lowest core temperature observed during application of the device was 31.2 °C, the lowest tympanic temperature 29.4 °C, with a corresponding core temperature of 35.8 °C. Systemic adverse events were consistent with the patient population being treated. Adverse events related to the device were observed in 13 out of 84 patients (16%) (Table 3). One of those was serious. In a patient with cardiogenic shock, tissue damage of nose and cheeks due to freezing occurred. The tissue damage persisted until death due to cardiac failure 36 h later during reversal of hypothermia. In 9 patients signs of aspiration on chest X-ray were observed. None of those showed patchy, diffuse, or dense infiltrates described in cases of liquid coolant aspiration.

Table 3
Device related adverse events.

	Total incidence	Resolved	Sequelae
Device related events	15/84 (16%)		
Nasal discoloration	10/84 (11%)	10 (11%)	
Cold-induced tissue damage	1/84 (1%)	0	1 (1%)
Epistaxis	2/84 (2%)	2 (2%)	0
Coolant in sinus	1/84 (1%)	1 (1%)	0
Periorbital gas emphysema	1/84 (1%)	1 (1%)	0

Table 4
Patients in whom RhinoChill cooling was halted early.

Patients No.	Description
00–03	37 min into cooling, the patient's arterial pressure and pulse oximetry readings dropped, and he went into cardiac arrest due to PEA. Cooling was halted during resuscitation of the patient. Autopsy findings showed that the subject had extensive 3-vessel coronary artery disease (all were occluded) and a very large ventricular infarct.
00–06	30 min into cooling, the patient's nose tip appeared white and stiff. Cooling was halted, and the patient's nose color returned to normal within the hour.
04–07	175 min into cooling, the patient developed bilateral periorbital subcutaneous emphysema. Crepitations were present bilaterally. Extraocular muscles were not affected. Cooling was halted, and the emphysema resolved within 24 h without intervention.
14–01	45 min into cooling, the patient's pulse oximetry reading fell to 77. Cooling was halted at this time. Chest X-ray findings were consistent with the known fact that the patients had aspirated gastric contents prior to study enrollment.
15–05	Over an hour into cooling, the patient's nose tip appeared white and stiff. Cooling was halted, and the patient's nose returned to normal with an hour.

One patient died during the cooling procedure (Table 4). Autopsy showed occlusion of all three coronary arteries and a large ventricular infarct. No sign of coolant aspiration could be found. The infarct was deemed to be responsible for the death and the adverse event was rated as "probably not device related".

For assessment of olfactory function, the CC-SIT was administered to patients with favorable neurologic recovery following discharge, if they were willing to cooperate. Twenty-six patients were discharged with minimal neurological deficit. Eleven of these patients took the CC-SIT under the supervision of one of the clinical researchers at the time of discharge or at a follow-up appointment. The remaining 15 patients were discharged prior to local approval of the protocol amendment, and therefore did not complete this assessment. All patients scored within the normal range for smell identification for their age and gender.

4. Discussion

In this observational study the RhinoChill device effectively lowered tympanic and core temperatures in patients after cardiac arrest. The device proved feasible in an emergency department setting, and safe during 1 h use, with the exception of persistent tissue damage in 1 patient at the high oxygen flow rate of 60–80 L/min. At the lower oxygen flow rate of 40–50 L/min, no persistent cold-related tissue damage was observed. Importantly, this reduction in flow rate did not affect the cooling rate. Essential safety measures that prevent tissue damage include uncovering the face and keeping the mouth open during cooling, so that coolant vapor can escape from mouth and nostrils. No evidence was obtained that the coolant might have caused lung damage following aspiration. Smell tests demonstrated that cooling via the nasal cavity did not affect the olfactory epithelium. The mortality rate of 60% was not unexpected for this unselected patient population, and good neurologic recovery was observed in a comparably high percentage.

Cooling the body via the nasal cavity raises questions regarding interpretation of temperature measurements. A higher tympanic than systemic cooling rate might indicate preferential brain cooling. On the other hand, tympanic temperature might be influenced by local cooling of tissue adjacent to the ear canal, without corresponding temperature changes in the brain.[14] Direct brain temperature measurement is ethically not possible in cardiac arrest patients, however, and the exact relation between tympanic and brain temperature during the cooling procedure is unknown. Measurement of core temperature in addition to tympanic temperature is important, as tympanic temperatures as low as 29.4 °C were observed with core temperatures within the therapeutic range. Reacting to tympanic temperatures would have obviated effective cooling. Differences were also observed between central (arterial and esophageal temperature) and peripheral (bladder and rectal temperature) core temperatures. This might be clinically relevant during fast cooling, where central core temperature reacts faster to changes than peripheral temperature, while being less prone to external influences than tympanic temperature. A rapid tympanic cooling rate with the RhinoChill device had been expected, the comparably high central core-cooling rate (1.4 °C/h) exceeded expectations. Surface cooling methods using large body areas for heat exchange allow cooling rates between 1.2 °C/h[15] and 3.4 °C/h,[16] the surface cooling method used in the landmark trail by the European Hypothermia after Cardiac Arrest (HACA) Study Group achieved 0.3 °C/h.[4] Infusion of 30 mL/kg cold lactated Ringer's solution over 30 min reduced temperature by 1.7 °C in a study by Bernard et al.[17] but with cold fluids alone many patients do not reach target temperature. Future studies could combine ice cold fluids with the RhinoChill device, for both methods can be implied rapidly in an emergency setting.

Cooling was initiated median 35 min after arrival in the ED in this study, and could be started earlier if no study related procedures needed to be fulfilled prior to cooling. While intravascular cooling methods require sterile catheter placement by a trained physician, the device can be started by just inserting the nasal catheter. Because of its independence of power supply, out-of-hospital cooling with the RhinoChill device seems feasible, too, and will be evaluated in a randomized trial [the ongoing PRINCE (Pre-ROSC Intranasal Cooling Effectiveness)-trial, ClinicalTrials.gov Identifier: NCT00808236].

Compared to other surface cooling methods, nasopharyngeal cooling uses a relatively small area for heat exchange. This might have lead to the side effects described above, but it enables easy combination with other methods and early application of the device. Clinical outcome studies comparing early vs. delayed cooling would be needed to confirm animal data about the importance of early and rapid cooling. If early and rapid cooling of the brain would enhance the neuroprotective effects of hypothermia after cardiac arrest, combining established methods like cold intravenous fluids and surface cooling with the RhinoChill device would offer a powerful approach to cooling.

A temperature gradient between brain and body core during nasopharyngeal cooling might allow differentiated temperature management. Covaciu et al. maintained a temperature gradient of 1.8 °C between brain and esophageal temperature with nasal cooling using a nasal balloon catheter perfused with cold saline and external body heating in pigs.[18] Selective brain cooling might yield less systemic side effects compared to systemic hypothermia. This may be applied in patients who otherwise do not qual-

Table 5
Anesthesia protocols, cooling data and patient outcome assorted by study center.

Centers	*n*	Anesthesia protocol	Muscle paralysis	Time interval collapse to cooling (min)	RhinoChill cooling in 1st h (Tty, °C/h)	Start cooling to Tty 33 °C (min)	Start cooling to Tcore 33 °C (min)	Good neurologic recovery
1	15	Midazolam/fentanyl	Yes	132 (106; 219)	2.9 (2.4; 4.4)	20 (14; 47)	80 (48; 173)	5/15
2	10	Propofol/sufentanil	Yes	75 (51; 90)	2.3 (2.0; 3.5)	65 (45; 115)	120 (103; 195)	3/10
3	22	Propofol/sufentanil	No	80 (68; 118)	2.3 (1.3; 2.8)	50 (37; 78)	233 (163; 373)	8/22
4	2	Midazolam/fentanyl	Yes	78; 60	2.1; 5.3	312, 135	312, 150	2/2
5	8	Propofol/sufentanil	2/8	100 (75; 125)	2.1 (0.7; 2.5)	140 (70; 225)	358 (213; 326)	4/8
6	5	Propofol/sufentanil	No	55 (47; 98)	1.6 (1.3; 2.8)	173 (60; 178)	178 (173; 465)	1/5
7	9	Midazolam/fentanyl	No	54 (31; 80)	3.2 (2.1; 4.1)	30 (26; 37)	98 (77; 195)	0/9
8	2	Propofol/fentanyl	No	160; 440	2.0; 3.0	77; 35	105; 200	1/2
9	1	Propofol	Yes	n.a.	1.1	62	100	0/1
10	3	Midazolam/fentanyl or propofol/fentanyl	Yes	175; 97; 72	2.0; 2.2; 1.7	n.a.	285; 315; 135	2/3
11	7	Midazolam/morphine	No	100 (95; 106)	2.8 (1.7; 3.6)	55 (38; 91)	146 (39; 219)	0/7

ify for systemic cooling (e.g. post-operative patients with risk of bleeding). Outcome studies comparing the local cooling effects of nasopharyngeal cooling to conventional surface cooling methods are needed to confirm this.

Unfortunately a variety of different cooling methods were added to nasopharyngeal cooling for systemic cooling, which makes comparison difficult. While the time to target temperature differed greatly, the cooling rate with the RhinoChill device was consistent between centers (see Table 5). Another limitation of the study lies in different protocols for anesthesia (listed in Table 5) and temperature measurement in the participating centers. Shivering in patients not receiving muscle relaxation might influence cooling rates. However, this early after cardiac arrest and under deep sedation, in none of the patients shivering was observed during the use of the device.

It is a limitation that cooling with the RhinoChill device was only for 1 h. Safety and feasibility of prolonged or intermittent use of the device for maintenance of hypothermia has to be tested in another clinical study.

5. Conclusion

Nasopharyngeal cooling for 1 h using the RhinoChill device is effective in reducing core temperature in cardiac arrest survivors. The method device is safe at oxygen flow rates of 40–50 L/min. Clinical studies will have to confirm safety and feasibility of the device for more prolonged use.

Conflict of interest statement

BeneChill Inc. supported the participating centres with a per-patient-support used for medical supplies and personnel for data processing. This conflict of interest applies for all authors and co-authors. Dr. Andreas Janata received a travel grant and support for manuscript preparation from BeneChill Inc. Denise Barbut is co-founder of BeneChill Inc., intellectual property holder and stockholder. Becky Inderbitzen is an employee of BeneChill Inc.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;27, 119:480–486.
2. Becker LB, Smith DW, Rhodes KV. Incidence of cardiac arrest: a neglected factor in evaluating survival rates. Ann Emerg Med 1993;22:86–91.
3. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997;30:1500–5.
4. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
5. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
6. Nolan J. European Resuscitation Council guidelines for resuscitation 2005. Section 1. Introduction. Resuscitation 2005;67(Suppl. 1):S3–6.
7. Guidelines 2005 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2005;112(Suppl.):III-1–III-136.
8. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348–58.
9. Wolff B, Machill K, Schumacher D, et al. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol 2009;133:223–8.
10. Wolfson MR, Malone DJ, Wu J, et al. Intranasal perfluorochemical spray for preferential brain cooling in sheep. Neurocrit Care 2008;8:437–47.
11. Tsai MS, Barbut D, Tang W, et al. Rapid head cooling initiated coincident with cardiopulmonary resuscitation improves success of defibrillation and post-resuscitation myocardial function in a porcine model of prolonged cardiac arrest. J Am Coll Cardiol 2008;51:1988–90.

12. Cummins RO. The Utstein style for uniform reporting of data from out-of-hospital cardiac arrest. Ann Emerg Med 1993;22:37–40.
13. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope 1996;106:353–6.
14. Crowder CM, Tempelhoff R, Theard MA, et al. Jugular bulb temperature: comparison with brain surface and core temperatures in neurosurgical patients during mild hypothermia. J Neurosurg 1996;85:98–103.
15. Haugk M, Sterz F, Grassberger M, et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation 2007;75:76–81.
16. Uray T, Sterz F, Janata A. Surface cooling with a new cooling-blanket for rapid induction of mild hypothermia in humans after cardiac arrest: a feasibility trial. Resuscitation 2006;69:93.
17. Bernard S, Buist M, Monteiro O, et al. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003;56:9–13.
18. Covaciu L, Allers M, Enblad P, et al. Intranasal selective brain cooling in pigs. Resuscitation 2008;76:83–8.