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Clinical paper

Targeted temperature management using the "Esophageal Cooling Device" after cardiac arrest (the COOL study): A feasibility and safety study

Antoine Goury[a], Florent Poirson[a], Ulriikka Chaput[b], Sebastian Voicu[a], Pierre Garçon[a], Thomas Beeken[a], Isabelle Malissin[a], Lamia Kerdjana[a], Jonathan Chelly[a,c], Dominique Vodovar[a], Haikel Oueslati[a], Jean Michel Ekherian[a], Philippe Marteau[b], Eric Vicaut[d], Bruno Megarbane[a,e], Nicolas Deye[a,f,*]

[a] *Réanimation Médicale & Toxicologique, Hôpital Lariboisière, AP-HP, Paris Cedex 10, France*
[b] *Hépato-gastro-entérologie, Hôpital Saint-Antoine, AP-HP, Paris, France*
[c] *Clinical Research Unit—Groupe Hospitalier Sud Île de France, 77000 Melun, France*
[d] *Unité de Recherche Clinique, Hôpital Fernand Widal, AP-HP, Paris Cedex 10, France*
[e] *INSERM UMRS-1144, Paris, France*
[f] *INSERM U942, Hôpital Lariboisière, Paris, France*

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ABSTRACT

Background: Targeted temperature management (TTM) between 32 and 36 °C is recommended after out-of-hospital cardiac arrest (OHCA). We aimed to assess the feasibility and safety of the "Esophageal Cooling Device" (ECD) in performing TTM.

Patients and methods: This single-centre, prospective, interventional study included 17 comatose OHCA patients. Main exclusion criteria were: delay between OHCA and return of spontaneous circulation (ROSC) >60 min, delay between sustained ROSC and inclusion >360 min, known oesophageal disease. A TTM between 32 and 34 °C was performed using the ECD (Advanced Cooling Therapy, USA) connected to a heat exchanger console (Meditherm III®, Gaymar, France), without cold fluids' use. Primary endpoint was feasibility of inducing, maintaining TTM, and rewarming using the ECD alone. Secondary endpoints were adverse events, focusing on potential digestive damages. Results were expressed as median (interquartiles 25–75).

Results: Cooling rate to reach the Target Temperature (33 °C-TT) was 0.26 °C/h [0.19-0.36]. All patients reached the 32–34 °C range with a time spent within the range of 26 h [21–28] (3 patients did not reach 33 °C). Temperature deviation outside the TT during TTM-maintenance was 0.10 °C [0.03–0.20]. Time with deviation >1 °C was 0 h. Rewarming rate was 0.20 °C/h [0.18–0.22]. Among the 16 gastrointestinal endoscopy procedures performed, 10 (62.5%) were normal. Minor oeso-gastric injuries (37.5% and 19%, respectively) were similar to usual orogastric tube injuries. One patient experienced severe oesophagitis mimicking peptic lesions, not cooling-related. No patient among the 9 alive at 3-month follow-up had gastrointestinal complains.

Conclusion: ECD seems an interesting, safe, accurate, semi-invasive cooling method in OHCA patients treated with 33 °C-TTM, particularly during the maintenance phase.

Introduction

Targeted temperature management (TTM) has been shown to improve outcome in comatose patients successfully resuscitated after out-of-hospital cardiac arrest (OHCA) [1,2]. TTM between 32 °C and 36 °C is recommended by international guidelines [3–5]. Many methods can be used to induce and maintain TTM [6,7]. Invasive procedures, such as endovascular or intraperitoneal cooling, and non-invasive procedures, such as ice packs, fans, cold

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* Corresponding author at: Medical ICU, Inserm U942, Hôpital Lariboisière, 2 rue Ambroise Paré, Assistance Publique des Hôpitaux de Paris, 75010, Paris, France.
E-mail addresses: nicolas.deye@aphp.fr, n.deye@orange.fr (N. Deye).

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air blankets, or surface cooling pads are available. Endovascular cooling seems the most effective method to quickly induce and accurately maintain TTM [8,9]. However, no firm differences were observed regarding outcome between endovascular devices and surface cooling methods in large randomized clinical trials. Moreover, the endovascular method is expensive and could be associated with a higher rate of minor side-effects [8]. Recently, peritoneal cooling has demonstrated an impressive capacity to quickly induce cooling, but its potential beneficial effect on outcome cannot be firmly confirmed [10].

The "Esophageal Cooling Device" (ECD™, Advanced Cooling Therapy Inc., Chicago, Illinois, USA) is a new heat exchanger device placed in the oesophagus to provide highly efficient heat transfer to the patient. As a semi-invasive internal device, ECD could potentially improve the effectiveness of TTM and minimize the risks of invasive methods. Mathematical models and animal studies strongly support the efficacy and safety of the ECD [11–13]. In 2 series recently published, potential side-effects of ECD were not precisely evaluated [14,15]. Additionally, ECD was always associated with other cooling methods such as the use of large volume of cold fluids, despite that this cooling method is no longer recommended according to recent international guidelines [16].

Our prospective observational study aimed to assess the feasibility and safety (by focusing on oesophageal and gastric injuries) of this new oesophageal device used as a sole cooling method for inducing and maintaining cooling in OHCA patients treated with a 33 °C-TTM.

Methods

Study design and population

This single-centre, prospective, open, and interventional clinical study evaluated the feasibility (efficacy) and safety of the ECD in patients successfully resuscitated after OHCA and treated with TTM.

Inclusion criteria were the following: patients aged over 18 years successfully resuscitated after OHCA, with sustained return of spontaneous circulation (ROSC) (i.e. palpable pulse maintained for >20/minutes), hospitalised in the intensive care unit (ICU), comatose (not obeying to verbal command), and treated with TTM targeted to 32–34 °C (corresponding to therapeutic hypothermia: TH).

Exclusion criteria were the following: age <18 years, patients with previous oesophageal disease (oesophageal trauma, oesophagectomy, known cirrhosis, oesophageal varices, previous swallowing disorders or dysphagia, achalasia, known ingestion of acidic or caustic poisons), patients with less than 40 kg of body mass, pregnancy, terminal disease or "do not resuscitate order", unsustained ROSC (impossibility to maintain stable ROSC), or unstable haemodynamic conditions defined as intractable severe cardiogenic shock or immediate need for extra-corporeal life support (ECLS) that could lead to multi-organ failure and early-onset death (less than 48 h after collapse), accidental hypothermia or hypothermia <30 °C on admission, prolonged delay between cardiac arrest (CA) and ROSC (i.e. time to ROSC more than 60 min), prolonged delay between ROSC and inclusion (more than 360 min), conscious patient (obeying to verbal command before starting TTM), severe bleeding or diathesis or uncontrolled haemorrhage before inclusion, oesophageal bleeding before ECD insertion, pre-existing severe conductive disorder requiring pacing, ECD or console not available at inclusion.

Specific TTM protocol

The ECD is a multilumen silicone heat exchanger connected to an external heat exchanger console (Medi-therm III®, Gaymar distributed by Gamida, France) and placed by the physician in the oesophagus to provide heat transfer (Supplemental Figs. S1 and S2). Circulating water temperature is controlled and determined by automatic feedback according to core patient's temperature.

TTM was initiated as soon as possible after inclusion and designed as follows: a target temperature (TT) of 33 °C was maintained for at least 24 h after the start of the procedure. No cold fluid infusions were allowed during the whole TTM phase. After the maintenance phase, patients were rewarmed actively to normothermia with a controlled rewarming speed ≤0.5 °C/h. ECD was removed after at least 48 h following ROSC achievement. Normothermia was secondarily maintained after ECD's removal within 72 h after ROSC using basic and external means if necessary.

Other treatments

All patients received standard intensive care for resuscitation after CA according to local protocol, to national, and international guidelines as previously described [3,17]. Specifically, a systematic strategy of research of CA aetiology was initially performed, with coronary angiogram in first line and/or brain CT-scan or chest-CT scan depending on clinical context. During TH, sedation and analgesia were performed with continuous infusion of midazolam or propofol, and sufentanil. Neuromuscular blockade was performed using atracurium to favour cooling and prevent shivering.

Data collection and endpoints

Prehospital data collection followed the Utstein criteria [18]. Initial temperatures were initially measured via tympanic and naso-pharyngeal temperature sensors in the prehospital field and the catheterization laboratory respectively. Continuous temperature's measurement was performed using a bladder temperature probe (Foley urinary catheter with tip thermistor, Tyco Healthcare, Plaisir, France). From the start of TTM until ECD removal, core temperature was monitored following an hourly basis. All temperature data for analyses are defined in the Supplemental Table S1.

The list of all side-effects collected in our study is available in the Supplemental Table S2. Potential gastrointestinal side-effects were strictly monitored: dysphagia, odynophagia, and oesophageal injury diagnosed by a gastroenterologist blinded to patient's treatment and outcome. A complete upper gastrointestinal tract endoscopy (oesophageal, gastric, and duodenal examination) was systematically performed by an independent gastroenterologist just after ECD's removal to describe the presence/absence of mucosal necrosis according to the Zargar classification used for caustic injuries, and the presence/absence of oesophagitis signs using the Savary-Miller classification (Supplemental Tables S3 and S4) [19,20].

The primary endpoint of our study was the feasibility of inducing and maintaining TH, and of rewarming using the ECD alone (specifically the cooling rate, rewarming rate, and percentage of time outside the 33 °C-TT during the TTM period).

Secondary endpoints were the evaluation of adverse events focusing on potential oeso-gastric lesions related to the cooling device. A phone interview was systematically performed in survivors at the end of the 3 months of follow-up to check the absence of odynophagia or pain during swallowing. Moreover, if severe oesophageal or gastric damage was observed, an endoscopy was performed at 1 month to control the complete recovery of gastrointestinal injuries.

Ethical approval

The protocol was approved by the French national ethical review board (*CPP Ile-de-France VI*, CPP/79-14, ID RCB 2014-AO1145-42),

and the study was conducted according to the principles of the Declaration of Helsinki. According to French law, informed consent was waived until the patient was able to consent, and consent was secondarily obtained for all patients with favorable neurological outcome. The study was declared at ClinicalTrials.gov (Identifier: NCT02327871) and at the French "Food and Drug Administration" (*Agence Nationale de Sécurité du Médicament et des Produits de Santé:* N°DDPT/DMTECH/KB/2014-AO1145-42).

Statistical analysis

Since this was a pilot study a sample size of at least 15 patients was calculated based on local feasibility considering all end-points and exclusion criteria. Analyses were made in patients who received the ECD cooling. Unsuccessful attempts to use the ECD were listed. Quantitative parameters were expressed as median and quartiles (25th–75th percentiles). Categorical parameters were expressed as frequencies and percentages. Quantitative parameters were analysed with non-parametric tests, considering the number of patients included. For categorical parameters, percentages and their two-sided 95% confidence intervals were calculated. Correlation tests were performed using the Pearson test. All tests were 2-sided with a 5% significance level and performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Patients

Between December 2014 and March 2016, CA was the cause of hospitalisation in ICU in 173 patients (Fig. 1). Excluding 155 patients with at least one exclusion criteria, 18 patients were enrolled. In one patient, the treatment was aborted because of a device failure, with a silicone lumen dysfunction leading to inability of the cold fluid to circulate inside the ECD. Finally, 17 patients were included and cooled with the ECD. General characteristics are described in Table 1. Characteristics of patients after hospital admission and during ICU hospitalisation are reported in Table 2.

Cooling

Temperature characteristics are summarized in Table 3. Delay to initiation of cooling with ECD after ROSC was 5 h [4–6]. All patients reached 34 °C whereas 14 patients (82%) reached the 33 °C-TT. Cooling rate to reach 33 °C-TT was 0.26 °C/hour [0.19-0.36]. The time spent in the TH range between 32 °C and 34 °C during the maintenance phase was 26 h [21–28]. Temperature deviation out of the 33 °C-TT was 0.10 °C [0.03–0.20]. The time with deviation >1 °C versus the 33 °C-TT was 0 h [0–0]. Five patients among those reaching the 33 °C-TT (36%) experienced an episode of minor temperature deviation >0.5 °C versus the TT. Only one patient, experiencing multi-organ failure leading to ECLS implementation and renal replacement therapy presented a deviation superior to 1 °C. Distribution of temperature during the TTM phase is depicted in Fig. 2.

Adverse events

Side-effects possibly related to the cooling method are described in Table 4. No patients died during cooling. One patient developed a refractory shock related to recurrent ventricular fibrillations with a core temperature of 31.8 °C leading to ECLS implantation and early rewarming. Three patients (17.5%) needed transfusions not ECD-related.

All patients received upper gastrointestinal tract endoscopy performed immediately after ECD removal, except one patient experiencing early death. Among the 16 endoscopic procedures performed, 10 (62.5%) were strictly normal. Endoscopic procedures showed for 6 patients (37.5%) minor gastric injuries according to Zargar classification. Within these 6 patients, 1 patient (6%) experienced a severe ulcerous oesophagitis mimicking peptic injuries not firmly related to the ECD, and 3 patients (19%) presented minor oesophagitis injuries according to Savary and Miller classification. No significant digestive bleeding was observed and no local haemostatic procedure was required.

Anticoagulation therapy and anti-platelet strategies were respectively given in 3 patients (18%) and 9 patients (53%) during the TTM period (Supplemental Tables S5 and S6). Fifteen patients (88%) received prophylactic treatment with proton pomp inhibitor. All patients with gastrointestinal injuries diagnosed by endoscopy were secondarily given an increase of proton pomp inhibitor treatment using a twice-daily dose therapy. Finally, during the phone interview performed in all survivors at the end of follow-up, no odynophagia or other gastrointestinal symptoms were reported. For the patient experiencing the severe oesophagitis, the endoscopic control at 1 month showed a perfect recovery.

Additional endpoints and outcomes

No correlations were observed between cardiovascular parameters, severity scores, and cooling parameters (Supplemental Table S7). No correlations were observed between cardiovascular parameters, severity scores, and oeso-gastric injuries (Supplemental Table S8). Of the 17 patients included, 9 patients (53%) survived

Table 1
Patient General Characteristics at Baseline and in the Prehospital Phase.

Characteristic	n = 17
Age, y	59.5 [54–65]
Male sex, n (%)	14 (82)
Body mass index, kg/m2	26.6 [21.2–28.4]
Previous cardiovascular disease, n (%)	8 (47)
Hypertension	4 (23.5)
Coronary disease	2 (12)
Heart failure	2 (12)
Diabetes mellitus, n (%)	4 (23.5)
Immune suppression, n (%)	1 (6)
Chronic respiratory disease, n (%)	4 (23.5)
Tobacco	7 (41)
Previous treatment with proton pump inhibitor	4 (23.5)
Alcohol abuse	4 (23.5)
Liver cirrhosis	1 (6)
Location of arrest: home, n (%)	8 (47)
Location of arrest: public place, n (%)	9 (53)
Witnessed arrest, n (%)	17 (100)
Bystander CPR, n (%)	9 (53)
Basic life support provided by first rescuers, n (%)	17 (100)
Automated external defibrillation (shockable rhythm)	9 (53)
No automated defibrillation (no shockable rhythm)	8 (47)
First documented cardiac rhythm (ALS), n (%)	
Ventricular fibrillation/Ventricular tachycardia	2 (12)
Pulseless activity	1 (6)
Asystole	9 (53)
Glasgow Coma Scale score	3 (100)
Blood glucose, mmol/L	10.5 [7.6–11.9]
No flow, min	5.0 [2.5–8.5]
Low flow, min	20.0 [13.5–30.0]
Adrenaline (total intravenous bolus dose), mg	1 [0–2]
Fluid loading (prehospital field), n (%)	8 (47)
Cold intravenous fluids (prehospital field), n (%)	2 (11.8)
Shock before inclusion, n (%)	14 (82.3)

Abbreviations: ALSadvanced cardiac life support provided by the medical team; CPRcardiopulmonary resuscitation; No flow timethe delay between collapse (or the time of emergency call in non-witnessed cardiac arrests) and the first CPR; low flow timethe delay between the first CPR and the return of spontaneous circulation; shockthe need for continuous infusion of catecholamines.
All patients were intubated and mechanically ventilated on the scene of the out-of-hospital cardiac arrest.

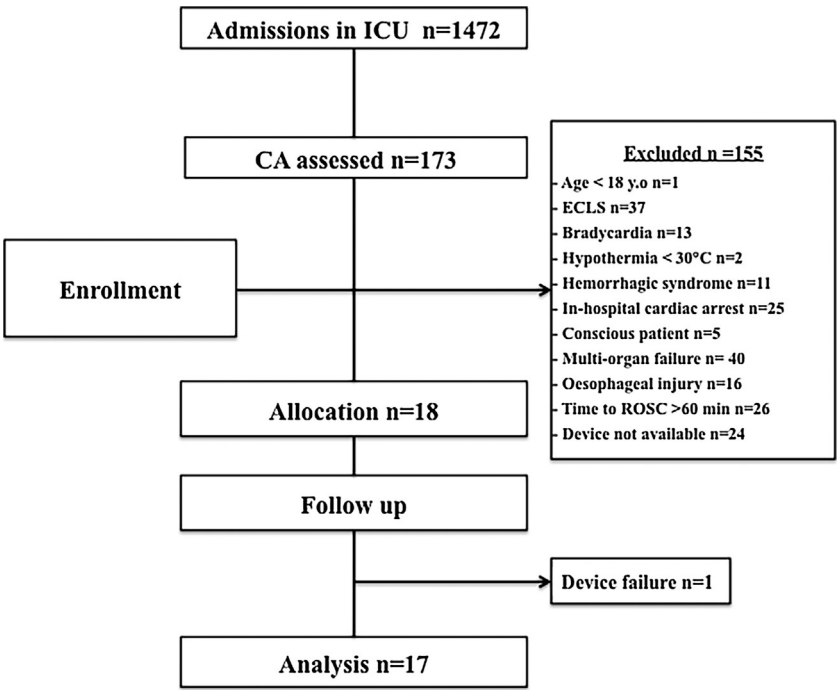

Fig. 1. Flow chart of the study.
Abbreviations: ICU, intensive care unit; CA, cardiac arrest; ECLS, extracorporeal life support; ROSC, return of spontaneous circulation.
The following previous oesophageal injuries were excluded (n = 16): oesophageal trauma and/or oesophagectomy, known cirrhosis and/or oesophageal varices, known ingestion of acidic or caustic poisons, oesophageal bleeding before ECD insertion.

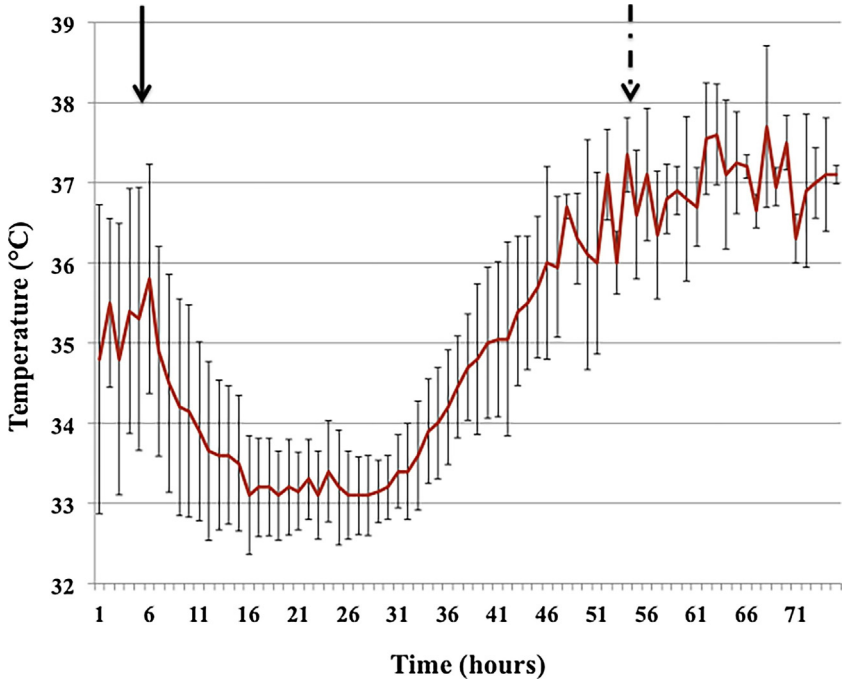

Fig. 2. Temperature distribution during the targeted temperature management (TTM) phase.
ECD = "Esophageal cooling device".
Solid line arrow: ECD introduction (median time: H5)
Dotted line arrow: ECD removal (median time: H55).

without major neurological sequelae at day 180 (Supplemental Table S9).

Discussion

To the best of our knowledge, we herein report the first largest prospective study evaluating a new oesophageal cooling device as the sole method to correctly implement TTM in OHCA patients, and to accurately maintain TTM. Moreover, this is the first study with an independent safety analysis of potential gastrointestinal injuries systematically evaluated after ECD removal, and showing that most patients (93.5%) presented no or minor gastrointestinal injuries not cooling-related.

Table 2
Patient General Characteristics After Hospital Admission and During Hospitalization in the Intensive Care Unit.

Characteristic	n = 17
Cardiac cause(s) responsible for CA, n (%)	11 (65)
Arrhythmia	9 (53)
Acute coronary syndrome	9 (53)
Pulmonary embolism	2 (12)
Respiratory cause(s) responsible for CA, n (%)	6 (35)
Brain and/or chest CT-scan	11 (65)
Coronary angiography, n (%)	15 (88)
Acute coronary occlusion, n (%)	8 (47)
PCI, n (%)	8 (47)
Successful PCI[a], n (%)	7 (87.5)
Stenting, n (%)	8 (47)
Intra-aortic balloon pump, n (%)	0 (0)
Initial echocardiographic LVEF, %	40 [30–60]
Pacing, n (%)	0 (0)
Extracorporeal life support, n (%)	1 (6)
Cold intravenous fluids at catheterization lab	7 (41)
Initial renal failure, n (%)[b]	
Risk	4 (23.5)
Injury	3 (17.5)
Failure	2 (11.5)
Renal replacement, n (%)	3 (17.5)
SAPS II	69 [61–75]
Seizures assessed on EEG, n (%)	1 (6)
Awake patients, n (%)[c]	9 (53)
Mechanical ventilation duration, days	6 [5–8]
Tracheostomy, n (%)	0 (0)
Decision to limit treatment(s), n (%)	6 (35)
Delay to first treatment limitation decision, days	7 [7–7]
Brain death, n (%)	1 (6)
Multi-organ failure, n (%)	1 (6)
Duration of hospitalization in ICU, days	7 [5–9]
Time alive out of ICU within 28 d	1 [0–18]

Abbreviations: CA, cardiac arrest; EEG, electroencephalogram; ICU, intensive care unit; LVEF, left ventricular ejection fraction; CT: computer tomography; PCI, percutaneous coronary intervention (angioplasty); SAPS II, simplified acute physiological score II.

[a] n = 8 data available.

[b] Renal failure occurring within the first day after admission according to RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease).

[c] Defined as Glasgow Coma Scale score ≥ 9 during the ICU stay.

Table 4
Main side-effects possibly related to the ECD or the cooling itself (i.e, Main Potential Cooling-Related Complications).

Characteristics	n = 17
Difficulties to insert ECD[a]	1 (6)
Myocardial infarction post ROSC	1 (6)
Bradycardia <30/min[b]	1 (6)
Refractory arrhythmia	1 (6)
Death related to TH	0 (0)
Early Onset Pneumonia[c]	14 (82)
Late Pneumonia	3 (17.5)
Anemia needing transfusion[d]	3 (17.5)
Oesophagitis (according to the Savary and Miller Classification)[e]	4 (25)
Minor injuries (grade I and II)	3 (19)
Major injuries (grade III, IV and V)	1 (6)
Gastritis (according to the Zargar Classification)[e]	6 (37.5)
Minor injuries (grade 1 and 2)	6 (37.5)
Major injuries (grade 3)	0 (0)

Abbreviations;: ECD, "esophageal cooling device"; ROSC, return to spontaneous circulation; TH, therapeutic hypothermia.

[a] ECD inadvertently positioned in the oral cavity (transient unability to descend into the oesophagus) but secondarily replaced using laryngoscopy.

[b] resulting from ECD or cooling itself, and recovering completely without need of pacing after early rewarming.

[c] Most of these pneumoniae were aspiration pneumoniae without obvious relationship with the ECD.

[d] One patient during the ECLS setting, one patient with respect to neuroprotection and according to guidelines (low hemoglobin level), and one patient because of major bleeding related to hemothorax related to CPR-traumatism (patient initially treated with thrombolysis for a CA related to pulmonary embolism).

[e] n = 16 endoscopy data available; one patient did not have this procedure because of hemodynamic instability and early death related to post-CA refractory shock.

Cooling

TTM between 32 °C and 36 °C is recommended to improve neurological outcome in OHCA patients [3–5]. Presently, endovascular cooling seems the most effective method regarding TH induction and TT maintenance [8,9]. The ability of the ECD to induce cooling, maintain and rewarm accurately critically ill patients has been demonstrated in previous pilot studies [11,14,15,21]. Only two series reported the use of ECD in the field of CA [14,15]. However, ECD was always associated with other cooling methods: basic cooling with ice packs and blankets and large volume of cold fluids. This could explain that cooling rates were higher in those studies as

Table 3
Temperature characteristics.

Characteristic	n = 17
Prehospital temperature[a], °C	35.5 [34.9–36.1]
Temperature at the catheterization laboratory[b], °C	35.5 [34.9–36.2]
Initial temperature on admission to the ICU, °C	35.4 [34.3–35.9]
Delay to start ECD cooling, h after ROSC	5 [4–6]
Temperature ≤34 °C reached, n (%)	17 (100)
Time from ROSC to temperature ≤34 °C, h	9 [7–15]
TT (33 °C) reached, n (%)	14 (82)
Time from ROSC to 33 °C-TT[c], h	15 [10–17]
Cooling rate[c], °C/h	0.26 [0.19–0.36]
Time with deviation >1 °C vs. the 33 °C-TT (after reaching the TT and before rewarming)[c], h	0 [0–0]
Percentage of time with deviation >1 °C vs. the 33 °C-TT (after reaching the TT and before rewarming)[c], %	0.0 [0.0–0.0]
Time with deviation >0.5 °C vs. the 33 °C-TT (after reaching the TT and before rewarming)[c], h	0 [0–3]
Percentage of time with deviation >0.5 °C vs. the 33 °C-TT (after reaching the TT and before rewarming)[c], %	0.0 [0.0–14.3]
Temperature deviation from the 33 °C-TT during the maintenance phase[c], °C	0.10 [0.03–0.20]
Hypothermia duration, h	26 [21–28]
Time to reach 37 °C after the maintenance phase[c,d], h	16 [12–20]
Rewarming rate to reach 37 °C temperature[c], °C/h	0.20 [0.18–0.22]
Time between ECD insertion and removal, h	50 [42–56]

Abbreviations: CA, cardiac arrest; ECD, "esophageal cooling device"; ICU, intensive care unit; ROSC, return of spontaneous circulation; TT, target temperature (33 °C).
All temperatures are expressed as °C and measured using a bladder catheter with a thermistor probe, except the initial temperatures measured with a tympanic method.

[a] n = 9 data available.

[b] n = 7 data available.

[c] n = 14 data interpretable (i.e. patients reaching the 33 °C-TT).

[d] Delay between the time when the hypothermia maintenance was effectively stopped and time when the first temperature of 37 °C was recorded.

compared to our study where ECD was used alone. In our study, no patients received cold fluids to reach the 33 °C-TT, partly explaining the relatively prolonged time to reach 34 °C and 33 °C. Other factors such as specific thermodynamic rules or the automatic feedback and algorithm delivered by the Medi-Therm® system could also explain our global ECD performances during the induction phase. Our prolonged delays to start cooling (5 h) and to reach the TT (9 h) can be explained by the ECD's insertion procedure and our diagnostic methods systematically performed before ICU admission: percutaneous coronary intervention in 15 patients (88%), and brain and chest-CT scan in 11 patients (65%). To date, excluding ECMO, the fastest method of cooling seems the automated peritoneal lavage with cold fluid with an impressive rate of cooling of 14 °C/hour [10], but this relatively invasive method must be evaluated in larger comparative studies. In the Icerea study [8], a mean cooling rate of 0.39 °C/h was reported in the endovascular group versus 0.27 °C/h in the basic surface cooling group, close to our cooling rate of 0.26 °C/h. However in our study 100% of patients reached the 32–34 °C range, as compared with 97% for the endovascular group and 91% for the external cooling group in the Icerea study.

During the maintenance phase, with an overall temperature deviation of only 0.1 °C, the ECD as sole method of cooling showed in our study an excellent ability to precisely maintain the 33 °C-TT for most patients, except for one who experienced a deviation >1 °C out of this TT. Our observed time spent with a deviation >1 °C of 0.0 h [0.0–0.0] compares favourably with those measured for endovascular devices of 1 h [0–2] and for basic external methods of 5.5 h [2.0–10.0] [8]. Thus, ECD demonstrated here a high ability to accurately maintain the 33 °C-TT during the whole maintenance phase, similar to best advanced cooling devices with a percentage of time out the 32–34 °C target of 0% [0–0]. This seems more accurate than the one described in the Markota's study with the ECD showing a higher percentage of time out the 32–34 °C target of 6.5% [0–29] [14]. This difference could be explained by a large use of cold fluid infusions in this study, which didn't allow a precise maintenance of the TT.

According to recent publications, a strict maintenance of the TT between 32 °C and 36 °C is as important as a fast cooling rate to better optimize TTM [9,22]. Future large studies are warranted to compare ECD with other cooling methods such as peritoneal or endovascular devices for their ability to precisely control the TTM phase.

Oeso-gastric evaluations

Frequency of mucosal upper digestive tract injuries diagnosed by endoscopy in critically ill patients can reach 75% to 100% [23,24]. This contrasts with a prevalence of clinically digestive bleeding of 1.5% [25]. Patients hospitalised in neurocritical care or in cardiac ward seem more vulnerable to stress-related ulcer gastrointestinal bleeding [26,27]. Gastrointestinal injuries and gut dysfunctions are extremely frequent after CA [28]. Additionally, naso or orogastric tube can lead to oeso-gastric lesions either by direct mechanic injuries (erosion or suction) [29], or by increasing risk of reflux [30].

Studies using ECD in animal models did not describe any oesophageal injuries after necropsy and histological examinations [13]. To date, no studies evaluated oeso-gastric damages in humans when using ECD. In our study, patients presented many risk factors of gastrointestinal injury: ischaemia-reperfusion, shock, mechanical ventilation, neurological injury, coagulopathy, dual antiplatelet therapy, and high SAPSII score. However, no patient suffered from clinically significant gastrointestinal bleeding. Endoscopy was mostly normal (62.5%). Characteristics and localizations of most minor injuries were similar to those observed with usual orogastric silicon tubes, as described in a previous study [31]. Only one patient presented a severe ulcerous peptic oesophagitis, likely related to usual risks factors rather than directly ECD-induced.

A prophylactic proton pomp inhibitor treatment was also largely used because of absence of initial enteral feeding. Feeding was started after ECD removal (when ECD was replaced by a standard oro-gastric tube), despite that another recent study showed that ECD had the same capacity for delivering drugs and feeding [32]. This could have influenced our results. However, no significant injuries were found in the 2 patients without prophylactic proton pomp inhibitor treatment. Finally, no associations were found between oeso-gastric injuries and general parameters such as the time spent with ECD.

Other safety parameters

Pneumonia was here relatively frequent during hospitalisation. Most of them were aspiration pneumonia without obvious connection with the ECD. Furthermore, our results are similar to those found in recent studies [33,34].

Limitations

The number of patients enrolled in the present study was limited. However, our aim was feasibility and safety of the device, and not to show outcome improvement when using ECD. Global outcomes of our patients seemed similar to those currently described in literature [9,35–37]. Additionally, previous publications trying to demonstrate outcome improvement using advanced devices failed to prove firm clinical differences with larger cohorts. As the time spent with ECD was arbitrary fixed to at least 48 h in order to systematically obtain endoscopic evaluations, we cannot assume if ECD could strictly maintain normothermia up to 72 h. However, our study suggests that ECD can safely perform a precise 33 °C-TTM for at least 55 h. It was difficult to perform a blinded study with systematic endoscopy performed in a control group not treated with ECD, mainly for ethical reasons, as endoscopy is an invasive procedure with potential complications [38].

Futures perspectives

Considering the results of the Nielsen's study [39], ECD could be an interesting device to implement a 36 °C-TTM, because this internal device seems very efficient to correctly maintain the TT without need of supplemental device generating potential complications (vascular, peritoneal. . .). Moreover, our study shows that ECD could be an "intermediate" device, between intravascular invasive device and non-invasive surface cooling, due to its semi-invasive properties and its performances for precisely maintain TTM. Finally, in burned patients needing precise TTM, this device could find a place avoiding central lines and skin damage [21].

Conclusions

ECD can be an interesting semi-invasive method of cooling in OHCA patients. Although it seems slower than endovascular devices to reach the 33 °C-TT, ECD demonstrated an impressive ability to accurately maintain the TT during the TTM phase. Using systematic endoscopy showing no or minor injuries in 93.5%, no severe oeso-gastric injuries could be directly ECD-related. Further studies will be necessary to define the precise place of this safe and interesting device within the cooling strategies in critically ill patients needing TTM.

Conflicts of interests

All authors declare that they have no financial and non-financial competing interests in relation with this paper. Eric Vicaut report

personal fees from honorarium for speeches given at symposia, and received funding from Boehringer Ingelheim® outside the submitted work. Nicolas Deye declared speaker and travel fees from Bard and Zoll companies outside the submitted work. Additionally, none of the authors have received any financial compensation for this research. No specific research grant was obtained for performing this study. The contribution of Advanced Cooling Therapy, Chicago, Illinois, USA, was limited to provision of all esophageal Cooling Devices free-of-charge used in this study. Sylvain Thuaudet, IST-Cardiology, Le Fresne-Camilly, France, distributing ECD in France, provided the Meditherm III Console (Gamida, France) for the whole duration of the study.

Authors' contributions

All authors have made substantive intellectual contributions to the study: substantial contributions in acquisition of data, analysis and interpretation of data, and/or drafting or revising the manuscript. Details are as follows: AG's participation: patient enrolment, ECD insertion, bedside nurse orientation, follow up of the patients, acquisition of data, analysis and interpretation of data, statistics, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and general study supervision; FP's participation: patient enrolment, ECD insertion, bedside nurse orientation; UC's participation: endoscopy realization, acquisition and interpretation of data, analysing and supervision; PG's participation: patient enrolment, ECD insertion, bedside nurse orientation; TB's participation: patient enrolment, ECD insertion, bedside nurse orientation; LK's participation: patient enrolment, ECD insertion, bedside nurse orientation; SB's participation: patient enrolment, ECD insertion, bedside nurse orientation; IM's participation: patient enrolment, ECD insertion, bedside nurse orientation; JC's participation: substantial contributions to conception and design; DV's participation: substantial contributions to conception and design; OH's participation: patient enrolment, ECD insertion, bedside nurse orientation; PM's participation: endoscopy supervision; EV's participation: study design, statistics management, critical revision of the manuscript for important intellectual content; BM's participation: organization of patients' care and ICU team management; ND's participation: study concept and design, declaration of the present study to ANSM, IRB, and NCT, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content, and general study supervision. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2017.09.021.

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