Resuscitation 84 (2013) 1051–1055

Contents lists available at ScienceDirect

Resuscitation

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

Clinical paper

Rapid induction of mild therapeutic hypothermia by extracorporeal veno-venous blood cooling in humans☆

Christoph Testori[a], Michael Holzer[a], Fritz Sterz[a], Peter Stratil[a], Zeno Hartner[d], Francesco Moscato[b,c], Heinrich Schima[b,c,d], Wilhelm Behringer[a,*]

[a] Department of Emergency Medicine, Medical University of Vienna, Austria
[b] Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria
[c] Ludwig-Boltzmann-Cluster for Cardiovascular Research, Vienna, Austria
[d] Department of Cardiac Surgery, Medical University of Vienna, Austria

ARTICLE INFO

Article history:
Received 9 January 2013
Received in revised form 20 February 2013
Accepted 6 March 2013

Keywords:
Cardiac arrest
Induced hypothermia
Cardiopulmonary resuscitation (CPR)
Heart arrest
Resuscitation
Return of spontaneous circulation

ABSTRACT

Aim: Mild therapeutic hypothermia is beneficial in patients successfully resuscitated from non-traumatic out-of-hospital cardiac arrest. The effect of fast induction of hypothermia in these patients remains to be investigated. The aim of this study was to evaluate the efficacy and safety of extracorporeal veno-venous blood cooling in humans successfully resuscitated from cardiac arrest.
Methods: We performed an interventional study in patients after successful resuscitation from cardiac arrest admitted to the emergency department of a tertiary care centre. The extracorporeal veno-venous circulation was established via a percutaneously introduced double lumen dialysis catheter in the femoral vein, and a tubing circuit and heat exchanger. A paediatric cardiopulmonary bypass roller pump and a heater-cooler system were used to circulate the blood. Main outcome measures were feasibility, efficacy, and safety.
Results: We included eight consecutive cardiac arrest patients with a median oesophageal temperature of 35.9 °C (interquartile range 34.9–37.0). A median time of 8 min elapsed (interquartile range 5–15 min) to reach oesophageal temperatures below 34 °C, which reflects a cooling rate of 12.2 °C/h (interquartile range 10.8 °C/h to 14.1 °C/h). The predefined target temperature of 33.0 °C was reached after 14 min (interquartile range 8–21 min). No device or method related adverse events were reported.
Conclusion: Extracorporeal veno-venous blood cooling is a feasible, safe, and very fast approach for induction of mild therapeutic hypothermia in patients successfully resuscitated from cardiac arrest.

1. Background

Mild therapeutic hypothermia is a recommended therapy in patients successfully resuscitated from non-traumatic out-of-hospital cardiac arrest.[1] Animal data indicate that early and fast cooling after restoration of spontaneous circulation is essential.[2–5] Prospective randomized[6,7] and retrospective non-randomized clinical trials[8–13] show conflicting results concerning the benefit of early and fast cooling. One reason for the conflicting results in these studies might be the lack of a fast and reliable cooling method.[14] For a future definite trial to investigate the need for early and fast cooling, it would be essential to have a very rapid and reliable cooling device. With surface cooling of the trunk, skin temperature has to be reduced substantially first, in order to achieve a mild hypothermic core temperature. Current surface cooling devices are limited to cooling rates of 3.3 °C/h maximum.[15] Cardiopulmonary bypass, once vessel access is achieved, is an effective tool to rapidly decrease whole-body temperature,[16] but its clinical use is limited to certain hospitals. Novel endovascular cooling devices, using cold fluid pumped through a catheter inserted into the superior or inferior vena cava, are already used clinically[17,18] reaching cooling rates up to 4.8 °C/h.[19] Two animal studies using veno-venous blood-shunt-cooling described a theoretical cooling rate of 40.4 °C/h in small dogs (approximately 25 kg), and 8.2 °C/h in human sized pigs (approximately 70 kg).[20,21] The aim of this study was to evaluate the efficacy and safety of this promising cooling technique with extracoroporeal veno-venous blood cooling in humans successfully resuscitated from cardiac arrest.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2013.03.013.

* Corresponding author at: Universitätsklinik für Notfallmedizin, Medizinische Universität Wien, Allgemeines Krankenhaus der Stadt Wien, Währinger Gürtel 18-20/6D, 1090 Wien, Austria.
E-mail address: wilhelm.behringer@meduniwien.ac.at (W. Behringer).

0300-9572/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.resuscitation.2013.03.013

2. Methods

This was a prospective interventional study in a cohort of eight consecutive patients admitted to the emergency department of a tertiary care centre. The study was conducted according to the principles of the declaration of Helsinki (Version 4, 2004) and was approved by the local ethical review board. The requirement of informed consent at the time of inclusion into the study was waived in accordance with the guidelines of good clinical practice and Austrian laws and regulations. In case of survival and favourable outcome the participant was asked to provide written informed consent. If the patient did not regain consciousness, the legal representative had to consent.

2.1. Study setting and population

Consecutive patients with an age of 18–75 years successfully resuscitated from witnessed or non-witnessed out-of-hospital cardiac arrest (irrespective of the first monitored cardiac rhythm) and remaining comatose (Glasgow coma scale lower than 8) after restoration of spontaneous circulation were included in the study. Exclusion criteria were cardiac arrest due to trauma or intracranial bleeding, terminal illness before cardiac arrest, a known pre-existing coagulopathy, and pregnancy.

2.2. Study objectives and endpoints

The primary objective of this explorative study was to evaluate the efficacy and safety of extracorporeal veno-venous blood cooling in patients successfully resuscitated from cardiac arrest. Target temperature was 33 °C oesophageal temperature. Secondary endpoints were survival up to six month and best neurologic outcome within six month. Neurologic outcome was evaluated in terms of Pittsburgh cerebral performance categories (Category 1: conscious and normal, without disability; Category 2: conscious with moderate disability; Category 3: conscious with severe disability; Category 4: comatose or vegetative state; Category 5: death).

2.3. The veno-venous cooling system

The extracorporeal veno-venous circulation was established via a percutaneously introduced double lumen dialysis catheter (Double Lumen EXTRA FLOW short term, 14 french, length 20 cm, Joline GmbH, Germany) in the femoral vein, and a tubing circuit (Safeline Treatment, Maquet Cardiopulmonary AG, Germany) and heat exchanger (Plegiox, Maquet Cardiopulmonary AG, Germany). A paediatric cardiopulmonary bypass roller pump and a heater-cooler system (CAPS, Computer Aided Perfusion System, Stöckert Instruments, Germany) were used to circulate the blood with a flow of 200 ml/min. The priming volume of the total circuit was 100 ml. The tubing and heat exchanger were heparin-coated. System pressure was measured prior and after the heat exchanger. Alarm systems were installed to stop the pump and occlude the circuit if the pressure is outside the predefined limits, or if the ultrasonic bubble detector indicated the presence of air.

2.4. Temperature control and monitoring

Temperature on admission was measured with an infrared tympanic thermometer (Ototemp LighTouch®, Exergen Corporation, MA, USA). Further temperature measurements were made with two oesophageal temperature probes (Mon-a-therm® General Purpose, 12 french, Mallinckrodt Medical Inc., St. Louis, MO, USA) as the main temperature site. One probe was connected to the monitor and the other one to the cooling device. Blood temperature was measured at the outflow connector of the heat exchanger. A urine bladder temperature probe (Foley catheter, Medtronic Electronics Inc. Parker, CO, USA) was used for additional temperature monitoring. An arterial catheter was placed in the radial or femoral artery for continuous invasive blood pressure monitoring and blood sampling. ECG, peripheral oxygen saturation, end-tidal CO_2, and respiratory rate as standardized intensive care monitoring was established.

With initiation of the veno-venous circulation, blood was cooled with the heat exchanger water temperature set to 10 °C until an oesophageal temperature of 33.5 °C was reached. Once the oesophageal temperature of 33.5 °C was reached, the three-state temperature remote control algorithm (heat-off-cool) of the heater-cooler system was activated to keep the oesophageal temperature automatically at 33 °C for 6 h. The time of device application was limited, because the heat exchanger was only certified for a period of 6 h. After this time period cooling was switched to a standard surface cooling method (Arctic Sun Temperature Management System, Bard Medical, CO, USA) for maintaining hypothermia up to a cumulative time of 24 h and for controlled rewarming with a rate of 0.4 °C/h.

2.5. Treatment

We used midazolam with a dose of 0.125 mg/kg/h and fentanyl 0.002 mg/kg/h, titrated as clinically indicated to achieve an adequate level of sedation and analgesia. To avoid shivering, a continuous infusion of rocuronium was given until oesophageal temperature reached 35 °C during rewarming.

Arterial saturation of was kept >95% e.g. paO_2 100–150 mmHg; ventilation was set to maintain normocapnia with a partial pressure of CO_2 between 35 and 45 mmHg. Arterial pH was kept between 7.3 and 7.5. Electrolytes were substituted if necessary and kept in normal ranges. Mean arterial blood pressure was kept >60 mmHg. Pressure drops were treated primarily with crystalloid fluids or hydroxyl ethyl starch. If sufficient blood pressure control was not achieved with fluids alone, vasopressors (i.e. norepinephrine) were used. Serum blood glucose was kept between 110 and 180 mg/dl.

Laboratory data analyses were performed as clinically indicated, but at least on admission as well as 6, 12, 24 and 48 h after return of spontaneous circulation. Arterial blood-gas analyses were performed at least every 4 h during the first 24 h.

2.6. Safety variables and measurements

All adverse events (serious and non-serious) for all enrolled patients were collected from the time of enrolment until discharge from hospital.

Serious adverse events included, but were are not limited to: re-arrest due to arrhythmias or heart failure, major bleeding, (i.e. intracranial haemorrhage, spontaneous bleeding, bleeding at any instrumented site, retroperitoneal bleeding, or bleeding associated with a drop in haemoglobin of >5.0 g/dl), emergency or urgent cardiac surgery and stroke.

A non-serious adverse event was accounted in case of minor bleeding (gross haematuria or hematemesis, observed blood loss associated with a drop in haemoglobin of 3–5 g/dl, or no evidence of bleeding but a drop in haemoglobin of 3–5 g/l), signs of haemolysis (2× rise in free haemoglobin and lactate dehydrogenase), and pneumonia (signs of infiltration in chest X-ray with elevation of C-reactive protein, fibrinogen, or white blood cells).

2.7. Data analysis

Continuous variables are given as mean ± standard deviation, or as median and interquartile range, if not normally distributed. Nominal data are given as counts and percentage of total number.