

Clinical paper

Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors[☆]

Claudius Jacobshagen^{*}, Anja Pax, Bernhard W. Unsöld, Tim Seidler, Stephan Schmidt-Schweda, Gerd Hasenfuss, Lars S. Maier

Department of Cardiology and Pneumology, Georg-August-University, Göttingen, Germany

ARTICLE INFO

Article history:

Received 17 February 2009

Received in revised form 24 May 2009

Accepted 18 June 2009

Keywords:

Hypothermia

Cardiac arrest

Resuscitation

Respiratory function

ABSTRACT

International guidelines for cardiopulmonary resuscitation recommend mild hypothermia (32–34 °C) for 12–24 h in comatose survivors of cardiac arrest. To induce therapeutic hypothermia a variety of external and intravascular cooling devices are available. A cheap and effective method for inducing hypothermia is the infusion of large volume, ice-cold intravenous fluid. There are concerns regarding the effects of rapid infusion of large volumes of fluid on respiratory function in cardiac arrest survivors. We have retrospectively studied the effects of high volume cold fluid infusion on respiratory function in 52 resuscitated cardiac arrest patients.

The target temperature of 32–34 °C was achieved after 4.1 ± 0.5 h (cooling rate 0.48 °C/h). During this period 3427 ± 210 mL ice-cold fluid was infused. Despite significantly reduced LV-function (EF $35.8 \pm 2.2\%$) the respiratory status of these patients did not deteriorate significantly. On intensive care unit admission the mean PaO₂ was 231.4 ± 20.6 mmHg at a F_iO₂ of 0.82 ± 0.03 (PaO₂/F_iO₂ = 290.0 ± 24.1) and a PEEP level of 7.14 ± 0.31 mbar. Until reaching the target temperature of ≤ 34 °C the F_iO₂ could be significantly reduced to 0.63 ± 0.03 with unchanged PEEP level (7.23 ± 0.36 mbar). Under these conditions the PaO₂/F_iO₂ ratio slightly decreased to 247.5 ± 18.5 ($P = 0.0893$). Continuing the saline infusion to achieve a body temperature of 33 °C, the F_iO₂ could be further reduced with unchanged PEEP.

The infusion of large volume, ice-cold fluid is an effective and inexpensive method for inducing therapeutic hypothermia. Resuscitation from cardiac arrest is associated with a deterioration in respiratory function. The infusion of large volumes of cold fluid does not cause a statistically significant further deterioration in respiratory function. A larger, randomized and prospective study is required to assess the efficacy and safety of ice-cold fluid infusion for the induction of therapeutic hypothermia.

© 2009 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Survival after out-of-hospital cardiac arrest remains low worldwide, averaging 6% or less.^{1,2} Even after return of spontaneous circulation (ROSC) the overall prognosis has not improved since 1953.³ The National Registry of Cardiopulmonary Resuscitation (NRCPR) reported in 2006 that among 19,819 adults who regained ROSC, in-hospital mortality was 67%.⁴ Furthermore, among survivors the neurologic outcome is often poor.^{5,6} Mild hypothermia (32–34 °C for 12–24 h) is the only therapy applied in the post-cardiac arrest setting that has been shown to significantly improve neurologic recovery and survival rates.^{7–9} Hypothermia reduces

oxygen consumption and other multi-factorial chemical and physical mechanisms that lead to reperfusion cell damage. Despite compelling data and inclusion in resuscitation guidelines (ILCOR 2005)⁵ therapeutic hypothermia is still underused as a post-cardiac arrest treatment, reaching less than 30% of all resuscitated patients in Europe and the United States.^{10–12} Major concerns are that the specialized cooling devices are technically too difficult or expensive.^{11,12} An inexpensive and effective alternative is the infusion of large volume, ice-cold intravenous fluid.^{13,14} Impaired myocardial function in resuscitated patients^{14,15} does however raise concerns about inducing pulmonary oedema by rapid infusion of large fluid volumes. We have studied the effects of a rapidly infused high volume of ice-cold fluid on respiratory function in patients resuscitated after cardiac arrest.

2. Methods

We retrospectively analyzed the data from 52 patients that were treated with mild hypothermia after cardiac arrest. Patients were

[☆] A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2009.06.032.

^{*} Corresponding author at: Department of Cardiology and Pneumology, Heart Center/Georg-August-University, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany. Tel.: +49 551 39 6380; fax: +49 551 39 22953.

E-mail address: jacobshagen@med.uni-goettingen.de (C. Jacobshagen).

included when their records were available and all study relevant data (baseline characteristics, the amount of infused intravenous fluid, the body core temperature, the blood gas values, the ventilator settings and the timings of post-cardiac arrest interventions) were documented. Patients were excluded when they died before the target temperature was reached. Cardiac arrest was defined as being unconscious as a result of a sudden pulseless collapse; ROSC was a return of a spontaneous palpable pulse. Except for trauma, all causes of cardiac arrest were considered, such as ventricular fibrillation, asystole and pulseless electrical activity (PEA). Out-of-hospital as well as in-hospital cardiac arrest patients were included. Patients were eligible if they were 18 years and older. All patients received intensive care interventions as recommended by ILCOR.^{5,16} The trachea was intubated and central venous access was established in all patients. Invasive blood pressure, heart rate and pulse oximetry data were monitored continuously. Core temperature was measured continuously by a bladder temperature probe (Foley catheter) or intravascularly if a pulmonary-artery catheter was placed. Haemodynamic support with inotropic agents (dobutamine, epinephrine, levosimendan) or vasopressors (norepinephrine, vasopressin) or mechanical devices (intraortic balloon pump or microaxial LV-assist device) was used as indicated to reach a mean arterial blood pressure of 80 mmHg. Arterial blood gas values, corrected for temperature, were frequently obtained to adjust the ventilator to maintain a partial pressure of arterial oxygen (PaO₂) of 100 mmHg and a partial pressure of arterial carbon dioxide (PaCO₂) of 40 mmHg. Left ventricular systolic function was assessed at admission by echocardiography in biplane standard views. Hypothermia was induced in all patients that remained unconscious after ROSC. Patients were routinely cooled for 24 h. After an initial evaluation of neurological status, all patients received intravenous sedation (midazolam and fentanyl or propofol and sufentanil). To prevent shivering, paralysis was induced by intravenous administration of pancuronium (8 mg every 2 h) during the 24 h cooling period. Patients were cooled with different internal and external devices. In addition, all patients received a large volume of ice-cold (2–4 °C), intravenous fluid (0.9% sodium chloride or a balanced electrolyte fluid). Since resuscitation guidelines recommend starting cooling as soon as possible, different cooling methods were combined.⁵ Emergency room, catheterization laboratory and intensive care units were equipped with refrigerators capable of storing several 1-L bags of 0.9% sodium chloride or crystalloid fluids at 2–4 °C. Each litre was rapidly infused through a peripheral or a central intravenous line, 18-gauge or larger. If available a pressure bag inflated to 300 mmHg was used. Cooling by cold intravenous fluid was administered even during diagnostic or therapeutic procedures such as percutaneous coronary intervention (PCI) or computed tomography (CT) scan. The target temperature of 33 °C was maintained for 24 h while the patient continued to be sedated and paralyzed to prevent shivering. After 24 h the patient was rewarmed passively and cautiously (0.25–0.5 °C/h). Sedation was stopped at a core temperature of 35 °C.

We systematically reviewed the patient's records with respect to the baseline characteristics, the amount of infused intravenous fluid, the body core temperature, the blood gas values, respiratory function, echocardiography results and the timings of post-cardiac arrest interventions.

2.1. Statistical analysis

All values are presented as mean ± SEM. Differences between values at defined body temperatures were evaluated for statistical significance by use of ANOVA followed by Tukey post-test analysis. The correlation between the PaO₂/FiO₂ ratio and the amount of intravenous fluid was evaluated by a linear regression

Table 1
Baseline characteristics.

Total no. of patients	52
Male sex no. (%)	38 (73)
Female sex no. (%)	14 (27)
Age (year)	61.3 ± 2.3
Initial cardiac rhythm	
Ventricular fibrillation or tachycardia no. (%)	30 (58)
Asystole no. (%)	11 (21)
Pulseless electrical activity no. (%)	9 (17)
Not reported no. (%)	2 (4)
Diagnosis or cause of cardiac arrest	
Myocardial infarction no. (%)	18 (35)
Primary arrhythmia (CAD and reduced EF) no. (%)	8 (15)
Primary arrhythmia (other cardiomyopathy) no. (%)	8 (15)
Pulmonary embolism no. (%)	4 (8)
Other no. (%)	13 (27)
Initial LV ejection fraction (%)	35.8 ± 2.2
Maximum NSE value (μg/L)	57.7 ± 11.1

no: number; LV: left ventricular; CAD: coronary artery disease; EF: ejection fraction; NSE: neuron-specific enolase.

analysis. The significance level was set at 0.05. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

3. Results

3.1. Baseline characteristics

We retrospectively analyzed the data of 52 cardiac arrest patients that were admitted to the University Heart Center of Goettingen between July 2005 and December 2008. The average age of the enrolled patients was 61.3 ± 2.3 years (range, 18–89 years). Most patients presented with ventricular fibrillation (58%) as the initial cardiac rhythm; 21% of the patients had asystole, 17% PEA. The predominant cause of cardiac arrest was acute myocardial infarction (35%) followed by primary arrhythmias in patients with ischemic heart disease (15%) or other cardiomyopathies (15%). Echocardiographic examination was performed as soon as possible after admission in 46 of the 52 patients. A significantly reduced systolic left ventricular function (LV) with an initial ejection fraction (EF) of 35.8 ± 2.2% (range, 10–65%) was documented. In 16 patients follow up echocardiography showed improvement in LV function over time (EF 47.8 ± 2.6%). The average peak plasma level of neuron-specific enolase (NSE) as a prognostic marker of neurological recovery was 57.7 ± 11.1 μg/L (range, 15.5–403.1 μg/L) during the first 5 days after ROSC. The in-hospital mortality was 32.6%. 35 of 52 patients were discharged alive. The detailed baseline characteristics are presented in Table 1.

3.2. Cooling parameters

The average time interval from admission to our hospital to intensive care unit (ICU) arrival was 95.6 ± 9.0 min (Table 2). The main reasons for this delay were procedures such as coronary angiography with or without PCI (56%) or CT scans (8%). Since cooling was started in the emergency room and continued during the interventions such as PCI, the initial core temperature (bladder temperature probe) on ICU arrival was already 35.3 ± 0.2 °C. The target temperature of ≤34 °C was achieved 4.1 ± 0.5 h after admission to the ICU. A total volume of 3427 ± 210 mL of ice-cold intravenous fluid had been infused when a temperature of ≤34 °C was achieved. To achieve a body temperature of 33 °C a total volume of 3800 ± 275 mL cold fluid was administered.

Table 2
Cooling parameters.

Time interval from ER admission to arrival ICU (min)	95.6 ± 9.0
Reason for delay	
Coronary angiography and/or intervention no. (%)	27 (56)
CT scan no. (%)	4 (8)
Echocardiography no. (%)	11 (21)
Others no. (%)	16 (31)
Initial body temperature at arrival ICU (°C)	35.3 ± 0.2
Total volume of ice-cold intravenous fluid	
Until body temperature 34 °C (mL)	3427 ± 210
Until body temperature 33 °C (mL)	3800 ± 275
Time interval from arrival ICU to target temperature	
To 34 °C (h)	4.1 ± 0.5
To 33 °C (h)	6.6 ± 0.7
Cooling velocity (°C/h)	0.48 ± 0.1

ICU: intensive care unit; no: number; CT: computer tomography.

3.3. Respiratory data

With respect to the initially assessed impaired contractility (EF 35.8 ± 2.2%) we analyzed the impact of high volume fluid load on the respiratory function in these patients (Table 3). On ICU admission the patients partial pressure of arterial oxygen (PaO₂) was 231.4 ± 20.6 mmHg with a fraction of inspired oxygen (FiO₂) of 0.82 ± 0.03 and a positive end-expiratory pressure (PEEP) of 7.14 mbar (range, 5–14 mbar). The PaO₂/FiO₂ ratio was 290.0 ± 24.1 (range, 55–725). Until reaching the target temperature of ≤34 °C the FiO₂ could be significantly reduced to 0.63 ± 0.03 (*P* < 0.05, Fig. 1A) with an almost unchanged PEEP level of 7.23 ± 0.36 mbar (range, 5–14 mbar; Fig. 1B). Despite intravenous infusion of 3427 ± 210 mL ice-cold fluid the PaO₂/FiO₂ ratio slightly but not significantly decreased to 247.5 ± 18.4 (range, 57–607.5; Fig. 2A). The mean change in PaO₂/FiO₂ ratio was −42.6 ± 21.3 (range, −436.4 to 333.2). Continuing the infusion of ice-cold intravenous fluid to achieve a body temperature of 33 °C the FiO₂ could be further reduced to 0.56 ± 0.03 without significantly increasing the PEEP level (Fig. 1). The PaO₂/FiO₂ ratio slightly but not significantly decreased to 224.3 ± 16.3 (range, 63–443.3; *P* = 0.0893; Fig. 2A). The mean change in PaO₂/FiO₂ ratio was −51.2 ± 24.4 (range, −355.3 to 183). Fig. 2B demonstrates that the volume of infused cold fluid and the PaO₂/FiO₂ ratio do not correlate significantly in a range between 1000 and 7500 mL (*r*² = 0.06, not significant). Furthermore, there was no significant correlation between the change in PaO₂/FiO₂ ratio and the amount of infused volume (*r*² = 0.02, not significant; Fig. 2C). Finally, there was no significant correlation between the change in PaO₂/FiO₂ ratio and LV-function (*r*² = 0.01, not significant; Fig. 2D).

4. Discussion

In the present study, we demonstrate that the rapid infusion of large volume, ice-cold intravenous fluid is an effective, and inexpensive procedure for the induction of therapeutic hypothermia.

Table 3
Ventilator parameters and blood gas values during induction of therapeutic hypothermia.

Variable	Admission ICU	34 °C	33 °C
FiO ₂	0.82 ± 0.03	0.63 ± 0.03	0.56 ± 0.03
PEEP (mbar)	7.14 ± 0.31	7.23 ± 0.36	7.50 ± 0.46
PaO ₂ (mmHg)	231.4 ± 20.6	141.3 ± 10.0	112.9 ± 8.4
PaO ₂ /FiO ₂	290.0 ± 24.1	247.5 ± 18.4	224.3 ± 16.3

FiO₂: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; PaO₂: partial pressure of arterial oxygen.

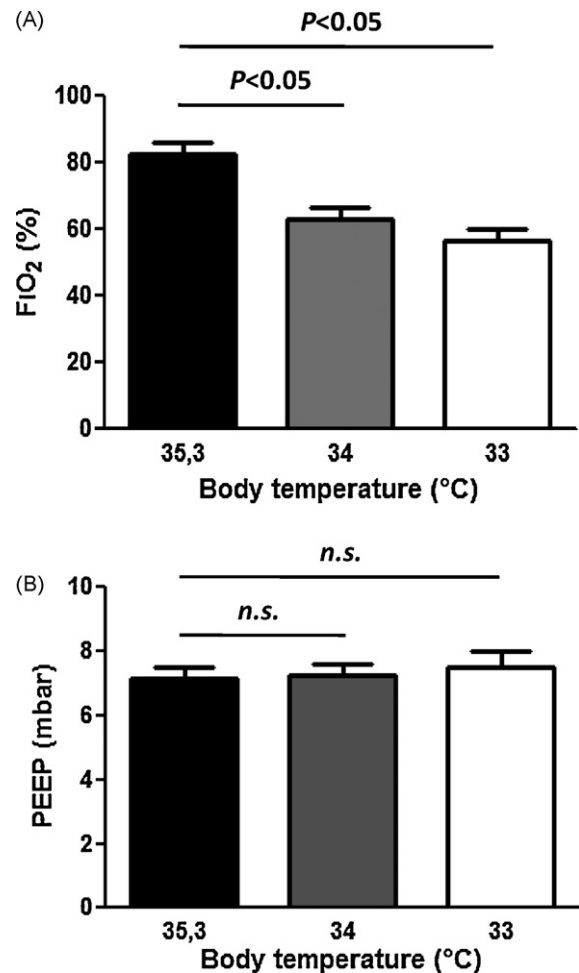


Fig. 1. Ventilator parameters during induction of therapeutic hypothermia on arrival at the intensive care unit (35.3 °C), at 34 °C and 33 °C. (A) Fraction of inspired oxygen (FiO₂) at the different body temperatures. (B) Positive end-expiratory pressure (PEEP) at the different body temperatures. n.s.: not significant.

Our results show that patients resuscitated from cardiac arrest have a decrease in the PaO₂/FiO₂ ratio. Systematic analysis of the correlation between the amount of infused fluid and the respiratory parameters indicate that despite significantly reduced left ventricular function high volumes of ice-cold intravenous fluid do not cause a statistically significant further deterioration in respiratory function after cardiac arrest.

This is in line with other studies reporting that there is no evidence for pulmonary edema in cardiac arrest patients treated with ice-cold saline.^{8,13,14,17} This is surprising, since myocardial dysfunction is a common feature in patients after cardiac arrest.^{14–16} Via echocardiography, we measured an initial ejection fraction (EF) of 35.8% in patients after cardiac arrest. Kim et al. reported a mean EF of 34.1%,¹⁴ and studies with invasive hemodynamic measurements showed a significantly reduced cardiac index in cardiac arrest patients.⁷ Furthermore, it has been shown that therapeutic hypothermia could decrease cardiac output, which is most likely caused by an increased systemic vascular resistance.⁷ On the other hand, there is evidence that mild hypothermia improves contractility in human myocardium¹⁸ and stabilizes ejection fraction.¹⁴ In the present study a follow up echocardiography was performed in 16 patients demonstrating an improved LV function over time (EF 47.8 ± 2.6%). It might be speculated whether this positive effect on myocardial function contributes to the fluid tolerance in patients after cardiac arrest.

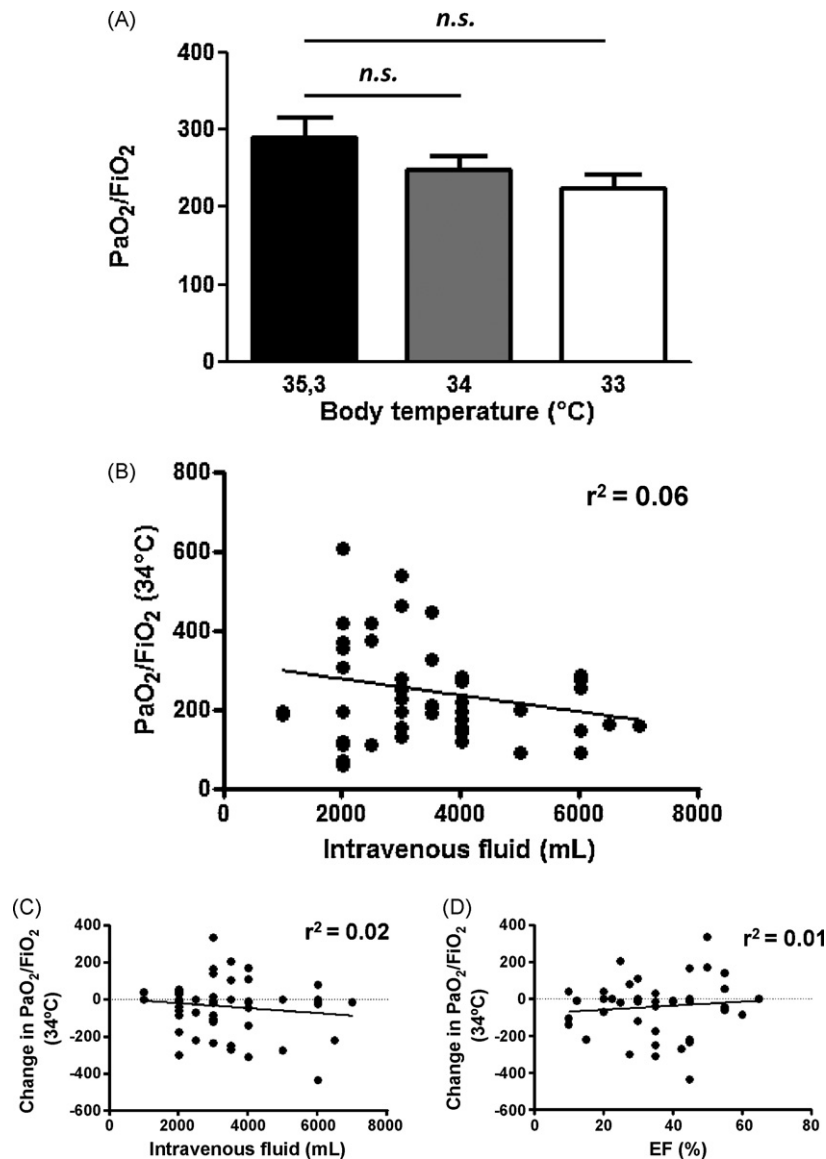


Fig. 2. Impact of therapeutic cooling and large volume of ice-cold intravenous fluid on the PaO₂/FiO₂ ratio. (A) PaO₂/FiO₂ ratio at the different body temperatures. (B) PaO₂/FiO₂ ratio in correlation with the amount of ice-cold intravenous fluid. $r^2 = 0.06$, n.s.: not significant. (C) Correlation between change in PaO₂/FiO₂ ratio and the amount of ice-cold intravenous fluid. $r^2 = 0.02$, n.s.: not significant. (D) Correlation between change in PaO₂/FiO₂ ratio and patients LV ejection fraction (EF). $r^2 = 0.01$, n.s.: not significant.

Moreover, it has been shown that the whole-body ischaemia and reperfusion during cardiac arrest and resuscitation causes a “sepsis-like”-syndrome with systemic inflammation, endothelial injury, impaired vasoregulation, high levels of circulating cytokines, the presence of endotoxin in plasma and generalized activation of immunologic and coagulation pathways.^{16,19–21} As in septic shock,^{22,23} it has been shown in cardiac-arrest patients that 3.5–6.5 L of intravenous crystalloid is required in the first 24 h after ROSC to maintain right atrial pressures in the range of 8–13 mmHg.^{15,16,24} This indicates a high fluid demand in post-cardiac arrest patients. Therefore, cooling by rapid infusion of large volume, ice-cold intravenous fluid represents an essential component of the hemodynamic support in the post-cardiac arrest patient which is crucial for the perfusion of the post-ischaemic brain.¹⁶

ILCOR recommends that therapeutic hypothermia should be part of a standardized treatment strategy for comatose survivors of cardiac arrest.^{5,16} However, no cooling method is specified. Animal studies demonstrate a benefit of very early cooling either during CPR or shortly after ROSC.^{25–27} Therefore, it is recommended that mild hypothermia is initiated as soon as possible.^{5,16} Several

methods have been proposed to induce rapid hypothermia, including the use of cooling blankets, placement of intravascular heat exchange catheters and cooling helmets.^{28–31} However, each has limitations, especially for use in the prehospital setting or in the catheterization laboratory. It has been shown that infusion of large volume, ice-cold intravenous fluid is an attractive option to easily and rapidly induce mild hypothermia^{13,14} even in the field.¹⁷ In the present study, we confirm that the infusion of large volume, ice-cold intravenous fluid rapidly induces mild hypothermia. We demonstrate that the concomitant volume expansion does not significantly worsen the respiratory situation in these patients. However, rapid infusion of ice-cold fluids is an excellent method to induce therapeutic hypothermia, but it cannot be used alone to maintain hypothermia for 24 h.³² In addition, other cooling methods are required to keep the body temperature constantly between 32 and 34 °C. This is best achieved with special external or internal cooling devices that include continuous temperature feedback to maintain the target temperature.^{16,29–31} However, less expensive methods, such as cold, wet blankets placed on the torso and around the extremities or ice packs combined with ice-cold fluids, can also

be effective,^{7,16} considering that these methods may be more time consuming for nursing staff and could result in greater temperature fluctuations.^{16,33}

Rapid infusion of cold crystalloids has been shown to decrease platelet count and to increase prothrombin time,¹⁴ probably due to plasma dilution. Therefore, it might be hypothesized that the infusion of cold fluid could affect the coagulation and immune system more than other cooling methods. Most importantly, the water and electrolyte balance in the post-ischaemic brain has not been monitored and although studies in trauma patients demonstrated no relationship between intravenous fluid administration and cerebral edema after head injury,^{34,35} randomized prospective trials are necessary to compare the different cooling methods with respect to neurologic outcome and survival.

This study has a number of limitations. Due to the retrospective data collection it cannot be excluded that physicians slowed the infusion of fluids or stopped fluids as they noticed a deterioration in respiratory function. The mean PaO₂/FiO₂ ratio in our study population was 290 at admission indicating an acute lung injury (defined as PaO₂/FiO₂ ratio <300).³⁶ Furthermore, a number of patients presented a PaO₂/FiO₂ ratio of <200, consistent with ARDS³⁶ as a consequence of the massive systemic inflammatory response syndrome and the impaired myocardial function in patients after cardiac arrest.^{16,19} Therefore, all patients were ventilated with a lung protective strategy using tidal volumes of ≤6 mL/kg body weight and a plateau pressure of ≤30 cm H₂O as recommended.^{16,37} However, it has to be acknowledged that the PaO₂/FiO₂ ratio decreased slightly – although not significantly ($P=0.0893$) – during fluid administration. Noteworthy, there was no significant correlation between the amount of infused fluid and the PaO₂/FiO₂ ratio. Certainly, respiratory parameters of all resuscitated patients should be monitored continuously and it cannot be recommended to continue the rapid infusion of high volumes cold fluid if the PaO₂/FiO₂ ratio decreases seriously (oxygen saturation <94%), jeopardizing the oxygenation status of the resuscitated brain.

The infusion of large volume, ice-cold fluid is an effective and inexpensive method for inducing therapeutic hypothermia. Resuscitation from cardiac arrest is associated with a deterioration in respiratory function. The infusion of large volumes of cold fluid does not cause a statistically significant further deterioration in respiratory function. A larger, randomized and prospective study is required to assess the efficacy and safety of ice-cold fluid infusion for the induction of therapeutic hypothermia.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Acknowledgements

Dr. Maier is funded by the Deutsche Forschungsgemeinschaft (DFG) through grants for a Clinical Research group KFO155 (MA 1982/2-1) and a Heisenberg grant (MA 1982/4-1), as well as by the Deutsche Gesellschaft für Kardiologie (DGK) by a Hengstberger grant.

References

- Fredriksson M, Herlitz J, Nichol G. Variation in outcome in studies of out-of-hospital cardiac arrest: a review of studies conforming to the Utstein guidelines. *Am J Emerg Med* 2003;21:276–81.
- Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300:1423–31.
- Stephenson Jr HE, Reid LC, Hinton JW. Some common denominators in 1200 cases of cardiac arrest. *Ann Surg* 1953;137:731–44.
- Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006;295:50–7.
- International Liaison Committee on Resuscitation. Proceedings of the 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2005;67:157–341.
- Longstreth Jr WT. Brain resuscitation after cardiopulmonary arrest. *Acta Anaesthesiol Belg* 1988;39:115–9.
- 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.
- The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
- Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Mullner M. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005;33:414–8.
- Wolfrum S, Radke PW, Pischon T, Willich SN, Schunkert H, Kurowski V. Mild therapeutic hypothermia after cardiac arrest—a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. *Resuscitation* 2007;72:207–13.
- Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006;34:1935–40.
- Abella BS, Rhee JW, Huang KN, Vanden Hoek TL, Becker LB. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. *Resuscitation* 2005;64:181–6.
- Bernard S, Buist M, Monteiro O, Smith K. 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.
- Kim F, Olsufka M, Carlom D, et al. Pilot study of rapid infusion of 2 L of 4 °C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005;112:715–9.
- Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002;40:2110–6.
- Neumar RW, Nolan JP, Adrie C, et al. Post-Cardiac Arrest Syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008;118:2452–83.
- Kim F, Olsufka M, Longstreth Jr WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 °C normal saline. *Circulation* 2007;115:3064–70.
- Weisser J, Martin J, Bisping E, et al. Influence of mild hypothermia on myocardial contractility and circulatory function. *Basic Res Cardiol* 2001;96:198–205.
- Adrie C, diB-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a “sepsis-like” syndrome. *Circulation* 2002;106:562–8.
- Adrie C, Laurent I, Monchi M, Cariou A, Dhainau JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care* 2004;10:208–12.
- Geppert A, Zorn G, Karth GD, et al. Soluble selectins and the systemic inflammatory response syndrome after successful cardiopulmonary resuscitation. *Crit Care Med* 2000;28:2360–5.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- Bion J, Jaeschke R, Thompson BT, Levy M, Dellinger RP. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008;34:1163–4.
- Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73:29–39.
- Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109:2786–91.
- Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. 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.
- Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006;113:2690–6.
- Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: Cohort study and Bayesian approach. *Stroke* 2006;37:1792–7.
- Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation* 2001;51:275–81.
- Felberg RA, Krieger DW, Chuang R, et al. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. *Circulation* 2001;104:1799–804.

31. Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation* 2004;62:143–50.
32. Kliegel A, Janata A, Wandaller C, et al. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007;73:46–53.
33. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006;34:S490–4.
34. Schmoker JD, Shackford SR, Wald SL, Pietropaoli JA. An analysis of the relationship between fluid and sodium administration and intracranial pressure after head injury. *J Trauma* 1992;33:476–81.
35. Ramming S, Shackford SR, Zhuang J, Schmoker JD. The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. *J Trauma* 1994;37:705–13.
36. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–24.
37. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–8.