Clinical Paper

Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids[☆]

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ARTICLE INFO

ABSTRACT

Aim of the study: Application of mild hypothermia (32–33 °C) has been shown to improve neurological outcome in patients with cardiac arrest. However, hypothermia affects hemostasis, and even mild hypothermia is associated with bleeding and increased transfusion requirements in surgery patients. On the other hand, crystalloid hemodilution has been shown to induce a hypercoagulable state. The study aim was to elucidate in which way the induction of mild therapeutic hypothermia by a bolus infusion of cold crystalloids affects the coagulation system of patients with cardiac arrest.
Methods: This was a prospective pilot study in 18 patients with cardiac arrest and return of spontaneous circulation (ROSC). Mild hypothermia was initiated by a bolus infusion of cold 0.9% saline fluid (4 °C; 30 ml/kg/30 min) and maintained for 24 h. At 0 h (before hypothermia), 1, 6 and 24 h we assessed coagulation parameters (PT, APPT), platelet count and performed thrombelastography (ROTEM) after *in vitro* addition of heparinase.
Results: A total amount of 2528 ($\pm$528) ml of 0.9% saline fluid was given. Hematocrit ($p < 0.01$) and platelet count (-27%; $p < 0.05$) declined, whereas APTT increased (2.7-fold; $p < 0.01$) during the observation period. All ROTEM parameters besides clotting time (CT) after 1 h (-20%; $p < 0.05$) did not significantly change.
Conclusion: Mild hypothermia only slightly prolonged clotting time as measured by rotation thrombelastography. Therefore, therapeutic hypothermia initiated by cold crystalloid fluids has only minor overall effects on coagulation in patients with cardiac arrest.

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1. Introduction

Application of mild hypothermia (32–33 °C) improves neurological recovery and survival in patients with out-of-hospital cardiac arrest.[1,2] Based on the results of two large clinical trials the European Resuscitation Council recommends to cool all hospitalized survivors of cardiac arrest with shockable rhythms to 32–34 °C for 12–24 h.[3]

Infusion of 4 °C cold crystalloids is an appealing method to initiate therapeutic hypothermia: it is inexpensive, easy to perform and effective in lowering body temperature,[4] even in an out-of-hospital setting.[5] Most cardiac arrests are caused by acute coronary syndromes with pronounced activation of the coagulation system. The notion that hypothermia may impair hemostasis is especially relevant for these patients, as many of them are treated with antithrombotic drugs like heparins and aspirin. Even mild hypothermia is associated with bleeding and increased transfusion requirements in surgical patients.[6] On the other hand, induction of hypothermia with large amounts (30 ml/kg) of crystalloids causes hemodilution. Acute hemodilution caused by crystalloid infusion induces a hypercoagulable state detectable by whole blood thrombelastography.[7,8] Thrombelastography yields information on the cumulative effects of various blood components (e.g., coagulation factors, hematocrit, platelets, leukocytes)[9] involved in the coagulation process. It is also sensitive to the anti-coagulant effects of therapeutic hypothermia in surgery patients.[10]

Currently, it is unknown how induction of mild therapeutic hypothermia by infusion of cold saline solution affects coagulation in patients with cardiac arrest. We therefore conducted a prospective study in 18 cardiac arrest survivors and assessed hemostasis using heparinase-modified thrombelastography.

2. Methods

2.1. Study design and study subjects

This was a prospective pilot study in 18 patients after cardiac arrest admitted to the emergency department of a tertiary

care hospital. The study procedures were approved by our local Ethics Committee. Patients were eligible if they were comatose upon admission with a spontaneous circulation after resuscitation from non-traumatic, normothermic cardiac arrest of presumed cardiac etiology. Patients with one of the following criteria were excluded: age <18 and >85 years, pregnancy, clinical signs of pulmonary edema, severely reduced left ventricular function, coma possibly due to a cerebrovascular accident or head trauma, patients receiving any form of renal replacement therapy, diagnosed terminal illness and known coagulopathy including warfarin use or thrombocytopenia. Data documentation was performed according to the Utstein Style. Patients received the following standardized procedures: Foley catheters with incorporated temperature probes, arterial catheters, central venous catheters, and mechanical ventilation after intubation. Patients were sedated and anesthetized (midazolam, 0.2–0.25 mg/kg/h and fentanyl, 0.01 mg/kg/h) and neuromuscular blockade was induced by rocuronium (0.5 mg/kg bolus, continous infusion of 0.5 mg/kg/h) to prevent shivering until patients reached normothermia again. The target temperature was continuously monitored using a bladder temperature probe.

All patients received a standard anti-coagulation regimen consisting of a bolus of 60 IU/kg unfractionated heparin (UFH) (at most 4000 IU) followed by APTT guided continuous UFH infusion with a target APTT of 50–70 s.

2.2. Study interventions

We drew baseline (0 h) blood samples into citrated tubes (Vacutainer tubes, 3.8% citrate, Becton Dickenson) through a newly inserted arterial catheter. Thereafter, study patients received an intravenous bolus infusion of 30 ml/kg, 4 °C cold crystalloid solution (physiological saline or lactated Ringer's solution depending on the serum electrolytes measured in the first blood gas analysis) over 30 min via two large lumen peripheral catheters. The infusion was stopped in case of a temperature drop below our target temperature of 33 °C or clinical signs of pulmonary edema. One hour after start of infusion core temperature was re-assessed and another study blood sample (1 h) was drawn. Additional cooling with an endovascular cooling device (Icy catheter, CoolGard 3000, Alsius, Irvine, USA) was applied if the temperature had not dropped below 34 °C. To avoid fluid overload, repetition of cold infusions was limited to every 6 h and the dose was reduced to 10 ml/kg for all additional infusions. Further blood samples were collected 6 and 24 h after induction of mild therapeutic hypothermia.

2.3. Routine laboratory tests

Just before induction of mild therapeutic hypothermia (0 h) and 1, 6 and 24 h thereafter coagulation parameters (activated partial thromboplastin time and prothrombin time) as well as whole blood counts (e.g., platelets, leukocytes) were determined using a routine photometric coagulation analyzer and the SYSMEX XE-2100 hematology analyzer (Sysmex Corporation, Kobe, Japan).

2.4. ROTEM (modified rotation thrombelastogramm analyzer)

The principle of thrombelastography (TEG) and the ROTEM Coagulation Analyzer (Pentapharm, Munich, Germany) have been described in detail elsewhere.[11,12] Briefly, TEG measures shear elastic modulus during clot formation and subsequent fibrinolysis. The ROTEM uses a ball-bearing system for power transduction, which makes it less susceptible to mechanical stress, movement and vibration.

Before running the assay, we added 10 ml of heparinase to the citrated blood samples. Thereafter, samples were recalcified with 20 μl of $CaCl_2$ 0.2 M (Nobis, Endingen, Germany) and run.

Heparinase-modified thrombelastography is feasible despite anti-coagulation with heparin, which is present in most cardiac arrest patients. We did not add activators to the test system to keep conditions as physiological as possible and to quantify the intrinsic changes in coagulation during hypothermia. TEG was performed at 37 °C.

The following ROTEM parameters were analyzed: clotting time (CT; conventional thrombelastography: reaction time *r*), clot formation time (CFT; conventional thrombelastography: *k*-value), maximum clot firmness (MCF; conventional thrombelastography: MA) and maximum lysis (ML).

3. Data analysis

All data are expressed as means ± standard deviation (SD) unless otherwise stated. After repeated measures ANOVA, the Friedman ANOVA and the Wilcoxon signed rank test for post hoc comparisons were used. A two-tailed $p < 0.05$ was considered statistically significant. All statistical calculations were performed using commercially available statistical software (Statistica Version 6.1; Stat Soft, Tulsa, OK).

4. Results

Subject characteristics are presented in Table 1.

Most of our study subjects (78%) were male, and acute myocardial infarction was the predominant cardiac arrest cause (61%). Correspondingly, all patients received anti-coagulant therapy (Table 1). Seven patients (39%) received a primary percutaneous coronary intervention within the first 4 h after admission to the emergency room. None of the study patients received fibrinolytic therapy.

We administered a total volume of 2528 ± 52 ml crystalloid fluid within half an hour to induce hypothermia. Mean patient tem-

Table 1
Patient demographics ($n = 18$).

Age (y)	60 ± 14
Male sex (%)	14 (78%)
Origin of cardiac arrest	
Cardiac	14 (78%)
- Acute Myocardial Infarction (AMI)	11 (61%)
- No AMI	3 (17%)
Non-cardiac	4 (22%)
CPR related variables	
No flow time (min)	9 ± 23
Time from collapse to ROSC (min)	25 ± 21
Amount of epinephrine during CPR (mg)	1.7 ± 1.7
Defibrillations (*n*)	2.0 ± 1.6
Lactate on admission (mmol/l)	9.1 ± 5.8
pH-value on admission	7.20 ± 0.22
Laboratory values on admission	
Hemoglobin (g/dl)	12.9 ± 2.1
Platelet count ($\times 10^*9$/l)	223 ± 66
Leukocyte count ($\times 10^*9$/l)	13.0 ± 6.8
Fibrinogen (mg/dl)	407 ± 166
aPPT (s)	55 ± 34
PT (%)	76 ± 23
In-hospital therapy (during first 24 h)	
Aspirin, low dose	14 (78%)
Clopidogrel	8 (44%)
Heparin	8 (100%)
- Unfractionated heparin (UFH)	16 (89%)
- Low-molecular-weight heparin (LMWH)	2 (11%)

Data are given as numbers (percentages) or mean values (± standard deviation). No flow time = time from collapse to basic life support; ROSC = return of spontaneous circulation; APTT = activated partial thromboplastin time; PT = prothrombin time.
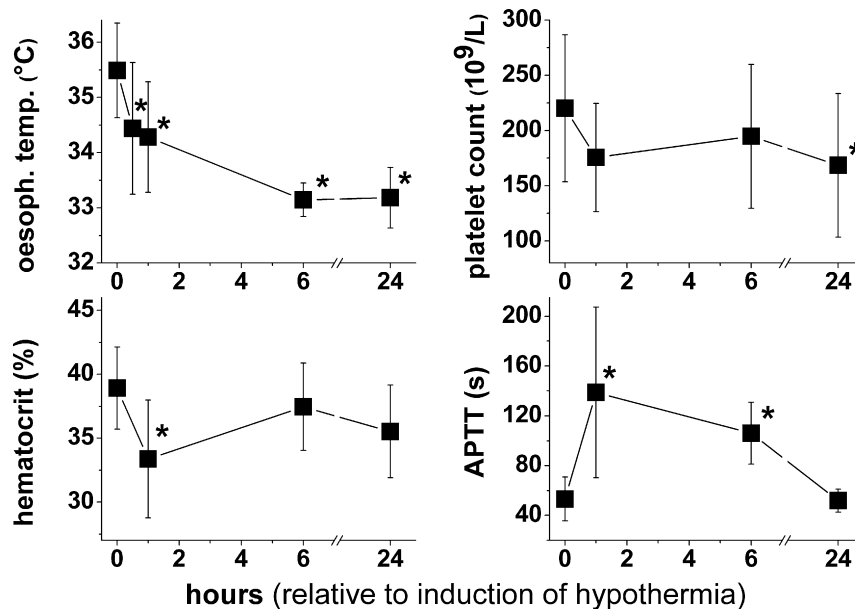
Fig. 1. Alterations of hematocrit, platelet count and APTT after initiation of mild therapeutic hypothermia by cold fluids. Data are presented as means (±SD), *$p < 0.02$ as compared to baseline.

perature at time of infusion was $35.5 \pm 0.9\,^\circ$C, which declined to $34.4 \pm 1.2\,^\circ$C after 30 min and to $34.3 \pm 1.0\,^\circ$C after 1 h ($p < 0.02$). Of all 18 patients, 16 (89%) required additional endovascular cooling to maintain hypothermia because either their temperature did not drop below $34.0\,^\circ$C ($n = 7$; 39%) or it increased again above $34.0\,^\circ$C ($n = 9$; 50%) within the first 6 h. The temperature course is presented in Fig. 1.

4.1. Infusion of cold fluids significantly altered coagulation parameters and whole blood counts

Intravenous bolus infusion of 30 ml/kg cold fluids led to a significant decrease in hematocrit after 1 h (-16%; $p < 0.02$; Fig. 1) due to hemodilution. Thereafter, hematocrit returned to baseline values. Platelet counts showed a steady decline (-27% after 24 h;

$p < 0.01$; Fig. 1). Due to heparins APTT increased 2.7-fold after 1 h ($p < 0.01$) and did not reach baseline values until 24 h thereafter (Fig. 1). Prothrombin time did not change over time (data not shown).

4.2. Infusion of cold fluids had only minor effects on thrombelastographic (ROTEM) parameters

Bolus infusion of cold fluids was associated with a significant prolongation of ROTEM CT (-20%; $p < 0.05$) 1 h after initiation of hypothermia, which returned to baseline thereafter. All other ROTEM parameters (CFT, MCF, ML) were not altered over time (Fig. 2).

None of the patients developed bleeding complications during the observation period.
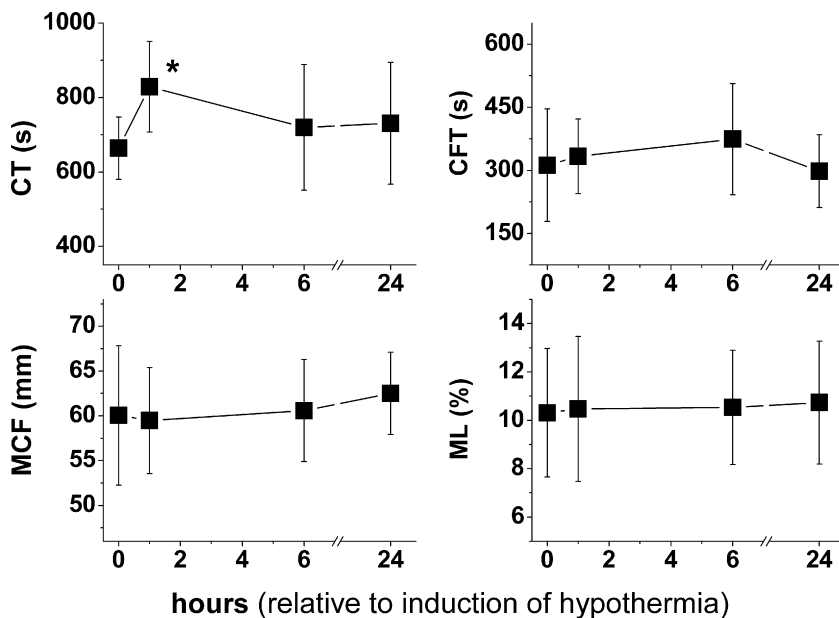

Fig. 2. Alterations of ROTEM parameters (CT, CFT, MCF, ML) after initiation of mild therapeutic hypothermia by cold fluids. Data are presented as means (±SD), *$p < 0.05$ as compared to baseline.

5. Discussion

We found that thrombelastographic parameters are only slightly affected during therapeutic hypothermia in cardiac arrest patients. The heparinase in this assay allows measurement of coagulation despite the presence of heparins in the samples. Solely, the time to clot formation (CT) was prolonged 1 h after induction of mild hypothermia. This finding is consistent with a prolonged clotting time observed in healthy volunteers[13] as well as in surgical patients after induction of hypothermia.[14] Hence, hypothermia-induced coagulation impairment predominates over coagulation activation due to crystalloid hemodilution in cardiac arrest patients.[15]

We observed no alteration of propagation of clot formation (CFT), lytic capacities of the clot (ML), or maximal clot firmness (MCF) in our study patients. MCF, which mainly depends on platelet count and function,[16] did not change despite a significant drop in platelet count and the administration of anti-thrombotic drugs to a majority of our study patients (Table 1). An explanation may be that most cardiac arrests were caused by acute myocardial infarction (Table 1), which is associated with pronounced platelet hyperfunction and coagulation activation.[17,18] On top of that, prolonged cardiac arrest and CPR can even further increase coagulation activation in humans.[19,20]

In line with our results, MCF was unaffected by hypothermia in patients undergoing cardiopulmonary bypass.[21] Furthermore, a reduction in clot firmness did not develop until 48 h of prolonged hypothermia in a canine model.[22]

Hemodilution has been shown to promote cerebral blood flow in various preclinical cardiac arrest trials.[23,24] Hence, induction of mild therapeutic hypothermia by bolus infusion of cold crystalloids may favorably affect outcome not only by cooling the patients but also by enhancing cerebral blood flow after ROSC.

A major limitation of our study is that we could not include a control group without mild hypothermia treatment. We believe this would have been unethical as mild therapeutic hypothermia represents standard medical care and is recommended for the treatment of cardiac arrest patients. It is therefore difficult for us to estimate the sole effect of hypothermia on whole blood coagulation. We rather measure the cumulative impact of cardiac arrest cause, medication and hypothermia treatment on whole blood clot formation.

One further important study limitation is that we performed thrombelastography at 37 °C and not at patient's temperature during hypothermia. Given that even mild hypothermia (32 °C) slightly impairs clot formation as measured by TEG[10] we might overestimate the speed of clot formation and therefore underestimate *in vivo* coagulation impairment.

6. Conclusions

Mild hypothermia only slightly prolonged clotting time as measured by rotation thrombelastography. Therefore, therapeutic hypothermia initiated by cold crystalloid fluids has only minor overall effects on coagulation in patients with cardiac arrest.

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