Induced hypothermia does not impair coagulation system in a swine multiple trauma model

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Juliane Mohr, MD, Steffen Ruchholtz, MD, Frank Hildebrand, MD, Sascha Flohé, MD, Michael Frink, MD, Ingo Witte, MD, Matthias Weuster, MD, Matthias Fröhlich, MD, Martijn van Griensven, PhD, Claudia Keibl, VMD, *and* **Philipp Mommsen, MD,** *Marburg, Germany*

BACKGROUND: Accidental hypothermia, acidosis, and coagulopathy represent the lethal triad in severely injured patients. Therapeutic hypothermia however is commonly used in transplantations, cardiac and neurosurgical surgery, or after cardiac arrest. However, the effects of therapeutic hypothermia on the coagulation system following multiple trauma need to be elucidated.

METHODS: In a porcine model of multiple trauma including blunt chest injury, liver laceration, and hemorrhagic shock followed by fluid resuscitation, the influence of therapeutic hypothermia on coagulation was evaluated. A total of 40 pigs were randomly assigned to sham (only anesthesia) or trauma groups receiving either hypothermia or normothermia. Each group consisted of 10 pigs. Analyzed parameters were cell count (red blood cells, platelets), pH, prothrombin time (PT), fibrinogen concentration, and analysis with ROTEM and Multiplate.

RESULTS: Trauma and consecutive fluid resuscitation resulted in impaired coagulation parameters (cell count, pH, PT, fibrinogen, ROTEM, and platelet function). During hypothermia, coagulation parameters measured at 37°C, such as PT, fibrinogen, thrombelastometry measurements, and platelet function, showed no significant differences between normothermic and hypothermic animals in both trauma groups. Additional analyses of thrombelastometry at 34°C during hypothermia showed significant differences for clotting time and clot formation time but not for maximum clot firmness. We were not able to detect macroscopic or petechial bleeding in both trauma groups.

CONCLUSION: Based on the results of the present study we suggest that mild hypothermia can be safely performed after stabilization following major trauma. Mild hypothermia has effects on the coagulation system but does not aggravate trauma-induced coagulopathy in our model. Before hypothermic treatment can be performed in the clinical setting, additional experiments with prolonged and deeper hypothermia to exclude detrimental effects are required. (*J Trauma Acute Care Surg*. 2013;74: 1014–1020. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Multiple trauma model; hemorrhagic shock; therapeutic hypothermia; coagulation; pig.

Patients with multiple injuries are predisposed for the development of accidental hypothermia, which is defined as body core temperature less than 35°C. With up to 66% of these patients have hypothermia at time of admission.[1–3] Having potentially detrimental pathophysiologic effects on different organ systems, accidental hypothermia seems to be associated with an increased risk for posttraumatic complications, such as multiple-organ dysfunction syndrome, and worse survival.[4–8] In this context, hypothermia-induced coagulopathy represents one of the most serious consequences of accidental hypothermia after major trauma. Following major trauma, clinically relevant coagulation disorders seem to occur at a body core temperature less than 34°C, while hypothermia-induced coagulopathy is partially compensated by trauma-induced hypercoagulability greater than 34°C.[9] Hypothermic coagulopathy comprises a dysfunction of the cellular and plasmatic coagulatory system, depending on the severity of accidental hypothermia.[2,10] Up to a body core temperature of 33°C, cellular coagulation disorders with reversible thrombocytopenia and thrombocytopathy could be observed.[9,11,12] An additional clinically relevant plasmatic coagulopathy with diminished thrombin and fibrin formation occurs at a body temperature less than 33°C.[12,13] The impact of hypothermia on the fibrinolytic activity is still controversially discussed. A hypothermia-related activation of fibrinolysis caused by a reduced secretion of antifibrinolytic mediators (e.g., plasminogen activator inhibitor, α-2-antiplasmin) as well as a decreased fibrinolytic activity has been described.[14,15] As a result of these anticoagulatory effects, an increased blood loss and transfusion requirements in the presence of accidental hypothermia has been reported in several clinical trials.[10,16,17] In contrast to the negative effects of accidental hypothermia, therapeutic hypothermia is used in cardiosurgical and neurosurgical interventions as well as after cardiac arrest owing to the hypothermia-related decrease of cellular metabolism and apoptosis without any coagulation disorders.[18] Although a diminished hemostatic function was reported during therapeutic induced hypothermia in healthy pigs,[13] further experimental

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From the Trauma Department (J.M., S.R., M.F.), University of Giessen-Marburg, Marburg; Trauma Department (F.H., P.M.), Hannover Medical School, Hannover; Trauma Department (S.F., I.W.), University of Düsseldorf, Düsseldorf; Trauma Department (M.W.), University of Schleswig-Holstein, Kiel; Trauma Department (M.F.), University of Aachen, Aachen; and Experimental Trauma Surgery (M.V.G.), Technical University Munich, Munich, Germany; and Ludwig Boltzmann Institute for Experimental and Clinical Traumatology (M.V.G., C.K.), Vienna, Austria.

The study was presented at the (1) Congress of European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Berlin, 2012; and (2) Congress of German Association for Orthopaedics and Traumatology (DKOU), Berlin, 2012.

Address for reprints: Juliane Mohr, MD, Department of Trauma, Hand and Reconstructive Surgery, University Hospital Giessen and Marburg GmbH, Marburg, Baldingerstraße, 35043 Marburg; email: mohrj@med.uni-marburg.de.

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studies found neither impaired coagulation or increased blood loss after isolated splenic laceration nor elevated transfusion requirements after isolated hemorrhage, depending on the induction of therapeutic hypothermia.[19–21] However, the effects of therapeutic induced hypothermia on the coagulation system have never been investigated in a combined trauma model mimicking the clinical situation of severely injured patients. In conclusion, it remains unclear whether therapeutic induced hypothermia could also be used in patients with multiple injuries after initial resuscitation and operative bleeding control to get the benefit of the possible cellular and organ protective effects but without incurring coagulation disorders and a consecutively increased risk for secondary bleeding complications. Therefore, the present experimental study aimed to investigate the coagulation function in a porcine multiple trauma model and to evaluate the effects of therapeutic induced hypothermia on the coagulatory system within this setting.

MATERIALS AND METHODS

Animal Care

The animal protocol review board of the City Government of Vienna, Austria, approved all experimental procedures in accordance with the Guide for the Care and Use of Laboratory Animals as defined by the National Institutes of Health. The experiments were performed in 40 male pigs (German domestic pigs, Muenichsthal) aged 12 weeks to 16 weeks and weighing 26 kg to 36 kg. The animals were fasted overnight, and water was available ad libitum. The animals were randomly assigned into sham groups receiving only anesthesia and trauma groups, in which blunt chest injury, liver laceration, and hemorrhagic shock were induced. The animals of sham and trauma groups (each consisting of 10 animals, in summary 40 animals) were subjected either to normothermia or to mild hypothermia of 34°C. In total, four study groups were generated as follows:

1. Sham-normothermia (sham-norm [SN])
2. Sham-hypothermia (sham-hyp [SH])
3. Trauma-normothermia (trauma-norm [TN])
4. Trauma-hypothermia (trauma-hyp [TH])

Premedication and Anesthesia

Premedication and anesthesia were induced with an intramuscular application of Zoletilmixture (xylazin 146 mg, ketamin 125 mg, butorphanol 25 mg, tiletamin 50 mg, zolazepam 50 mg, in total 10 mL) in a dose of 1 mL per 15 kg. Animals were kept in a supine position. After endotracheal intubation and during preparation, anesthesia administration was initially performed with isoflurane 1.5% plus rocuronium bromide (1 mg/kg/h) and sufentanyl (0.008 mg/kg/h) intravenously via ear vein. General anesthesia was maintained during the entire study period as total intravenous anesthesia with 2% midazolame plus rocuronium bromide (1 mg/kg/h) and sufentanyl (0.008 mg/kg/h).

Preparation Period

Animals were kept in a supine position. Ventilation was performed with volume-controlled ventilation (Draeger, Primus, Danvers, MA) to obtain normocapnia with FIO_2 30%, tidal volume of 10 mL/kg per body weight, 20 breaths per minute, positive end expiratory pressure of 3 mm Hg, $Paco_2$ of 35 mm Hg to 45 mm Hg, and end-tidal CO_2 of 4.5% to 5.5%. Respiratory parameters, for example, $Paco_2$ and Pao_2 were monitored continuously and adjusted if required to keep oxygenation and ventilation on a physiologic level. The management of fluids was performed following the experimental protocol with crystalloids (Ringer, 309 mosmol/L, Fresenius Kabi GmbH, Graz, Austria) 10 mL/kg per hour. Saline-filled catheters were placed by preparing arteries and veins for medical substitution as well as measuring hemodynamic parameters. Urinary output was monitored via urinary catheter (Cystofix, Braun, Melsungen, Germany). Sham animals were only anaesthetized and received preparation of arterial, venous, and urinary lines.

Induction of Multiple Injuries, Resuscitation, and Hypothermia

As shown in Figure 1, multiple injuries were induced at baseline. Blunt chest trauma was induced by a bolt of cattle killing cartridges (9 × 17, Dynamit Nobel AG, Troisdorf, Germany), shot on a panel at the right dorsal, lower chest in inspiration. After laparotomy, two cuts into the right upper liver lobe were performed with a self-made sharp four edges scalpel. After 30 seconds of uncontrolled bleeding, the liver was packed, followed by photographic documentation. Finally, pressure-controlled hemorrhage was induced by withdrawing blood (maximum of 45% of total blood volume) until a mean (SD) arterial blood pressure of 30 (5) mm Hg was reached. Hemorrhagic shock was maintained for 1.5 hours.

Fluid resuscitation using colloids (HES 130/4, 6%, Voluven, 308 mOsm/L, Fresenius Kabi GmbH) and crystalloids (Ringer, 309 mOsm/L, Fresenius Kabi GmbH) in a 1:8 ratio was performed with four times the shed blood volume during a period of 1 hour. Fluid administration was monitored and analyzed in comparison with the urinary output for fluid balance.

After resuscitation, normothermia was maintained over the entire study period, or mild hypothermia of 34°C was

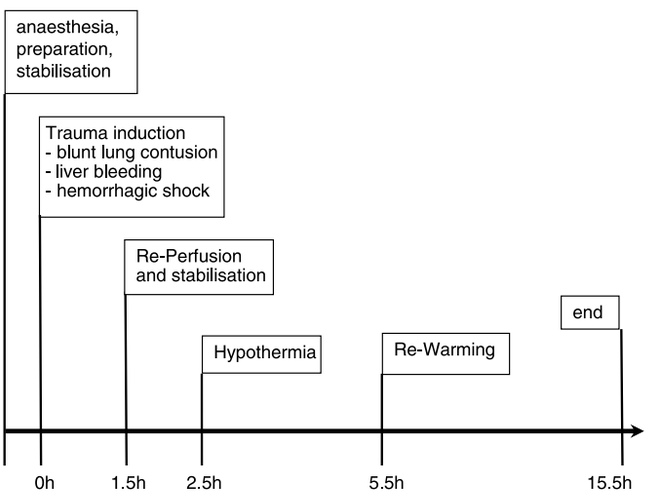

Figure 1. Timeline. Trauma hypothermia porcine model. Duration, 15.5 hours. *Arrow* indicates measurements and blood samples.

induced via venous Icy catheter using the CoolGard3000 (ZOLL Circulation, Inc., Sunnyvale, CA). After 3 hours of therapeutic hypothermia, rewarming with a target temperature of 37°C to 39°C was performed, also using the aforementioned catheter.

Animals were sacrificed 15.5 hours after trauma induction.

Protocol for Blood Sampling and Measurement of Hemostatic Parameters

Blood samples were taken from the femoral arterial line after removal of 10 mL blood. For coagulation parameters (e.g., prothrombin time [PT], fibrinogen) samples were drawn into 4 mL citrate tubes (Vacuette, Greiner-Bio One, Frickenhausen, Germany) and analyzed with the Sysmex CA automated coagulation analyzer 1500 (Siemens, Marburg, Germany). Cell count (e.g., red blood cells, platelets) and hemoglobin measurement were performed from 1-mL EDTA tubes (Vacuette, Greiner-Bio One) with the Celldyn 3700 SL (ABBOTT Diagnostics Division, ABBOTT Ges m.b.H, Vienna, Austria) following the manufacturer's instructions. Samples for thrombelastometry (ROTEM, Pentapharm, Munich, Germany) were taken into 2-mL citrate tubes (Vacuette, Greiner-Bio One) and for platelet aggregation studies into 3-mL hirudin tubes (Verum Diagnostica GmbH, Munich, Germany).

Coagulation measurements (PT, fibrinogen) and analyses with Multiplate (ADPtest, COLtest) were performed at 37°C. Thrombelastometry measurements (exTEM, fibTEM) were performed at 37°C as well as at 34°C during hypothermia.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 statistical software for Windows (version 5.03, GraphPad Software Inc., La Jolla, CA). Gaussian distribution was ascertained using the Kolmogoroff-Smirnov test. Differences between groups were analyzed using Student's *t* test. Statistical significance was considered at $p < 0.05$. Results are presented as mean (SD).

RESULTS

Cell Count and pH

Following trauma induction (T 1.5 hours), no significant differences in cell count parameters were observed in trauma groups as compared with respective baseline values in control groups (Table 1). Fluid resuscitation (T 2.5 hours) resulted in a comparable impairment of cell count in both trauma groups as compared with sham groups, with a decreased number of red blood cells, platelets, and hemoglobin. There were no significant differences during and after hypothermia between both trauma groups as well as between both sham groups (T 5.5 hours, Table 1).

At the beginning of the experiment, pH values of all groups were comparable (Table 1). Following trauma, pH values significantly decreased for trauma groups compared with sham groups (T 1.5 hours, Table 1). The pH value continuously decreased for both trauma groups (T 15.5 hours, Table 1) until the end of the observation period. We did not detect any differences between trauma and sham groups during the experiment ($p > 0.05$, Table 1).

Coagulation Parameters

Before induction of trauma, no differences of coagulation parameters were present between groups studied. Following trauma, coagulation parameters significantly decreased in trauma groups, which were more pronounced for PT and fibrinogen (T 1.5 hours, Fig. 2*A* and *B*). PT stabilized in both trauma groups at a low level during the whole observation period (Fig. 2*A*). Systemic fibrinogen levels were restored in trauma groups, reaching initial concentrations at the end of the study period (Fig. 2*B*). For analyzed coagulation parameters, differences between trauma groups and sham groups were not significant. Furthermore, hypothermia had no influence on coagulation (T 5.5 hours, Fig. 2*A* and *B*).

TABLE 1. Mean (SD) for Cell Count and pH Over Time

	Group	T 0	T 1.5 h	T 2.5 h	T 5.5 h	T 9.5 h	T 15.5 h
Red blood cells, $\times 10^9$/L	SN	5.4 (0.5)	5.8 (0.7)	5.7 (0.9)	5.6 (0.7)	5.3 (0.6)	4.9 (0.5)
	SH	5.1 (0.6)	5.7 (0.5)	5.3 (0.8)	5.6 (0.9)	4.9 (0.4)	4.6 (0.6)
	TN	5.5 (0.5)	5.5 (0.3)	3.1 (0.4)*	4.2 (0.3)*	4.0 (0.3)*	3.9 (0.6)*
	TH	5.3 (0.5)	5.4 (0.4)	3.0 (0.3)	4.3 (0.6)	4.0 (0.5)	3.8 (0.5)
Hemoglobin, g/dL	SN	9.7 (0.7)	10.5 (1.1)	10.0 (1.0)	10.0 (1.0)	9.3 (1.0)	8.7 (0.9)
	SH	9.4 (0.9)	10.3 (0.7)	9.7 (1.1)	10.0 (1.2)	8.8 (0.5)	8.4 (0.9)
	TN	9.7 (1.0)	9.7 (0.5)	5.5 (0.8)*	7.5 (0.5)*	7.2 (0.5)*	6.8 (1.0)*
	TH	9.4 (1.1)	9.5 (0.4)	5.3 (0.6)	7.8 (1.0)	7.2 (0.8)	6.8 (0.8)
Platelets, $\times 10^6$/L	SN	341.2 (118.2)	345.4 (118.4)	322.5 (116.4)	282.5 (125.6)	272.0 (135.2)	241.8 (108.6)
	SH	364.5 (71.6)	360.8 (75.3)	327.9 (69.8)	286.6 (60.2)	269.6 (48.1)	233.7 (46.6)
	TN	348.7 (97.5)	362.3 (95.5)	233.2 (69.4)	260.4 (78.6)	231.1 (80.8)	183.6 (74.2)
	TH	338.9 (58.2)	324.6 (63.4)	188.3 (36.1)	235.4 (57.2)	202.3 (39.9)	169.1 (31.5)
Arterial pH	SN	7.45 (0.03)	7.55 (0.03)	7.48 (0.03)	7.45 (0.03)	7.43 (0.02)	7.45 (0.03)
	SH	7.46 (0.02)	7.54 (0.03)	7.49 (0.02)	7.43 (0.05)	7.43 (0.02)	7.44 (0.04)
	TN	7.45 (0.02)	7.39 (0.07)*	7.29 (0.05)*	7.35 (0.04)*	7.35 (0.06)*	7.27 (0.09)*
	TH	7.45 (0.04)	7.38 (0.06)	7.32 (0.07)	7.34 (0.04)	7.31 (0.10)	7.28 (0.14)

*$p < 0.001$, significant differences compared TN with SN. No significant differences between trauma groups and sham groups.
T 0, baseline; T 1.5 h, after shock; T 2.5 h, after resuscitation; T 5.5 h, during hypothermia; T 9.5 h, after rewarming; T 15.5 h, at the end of the experiment.

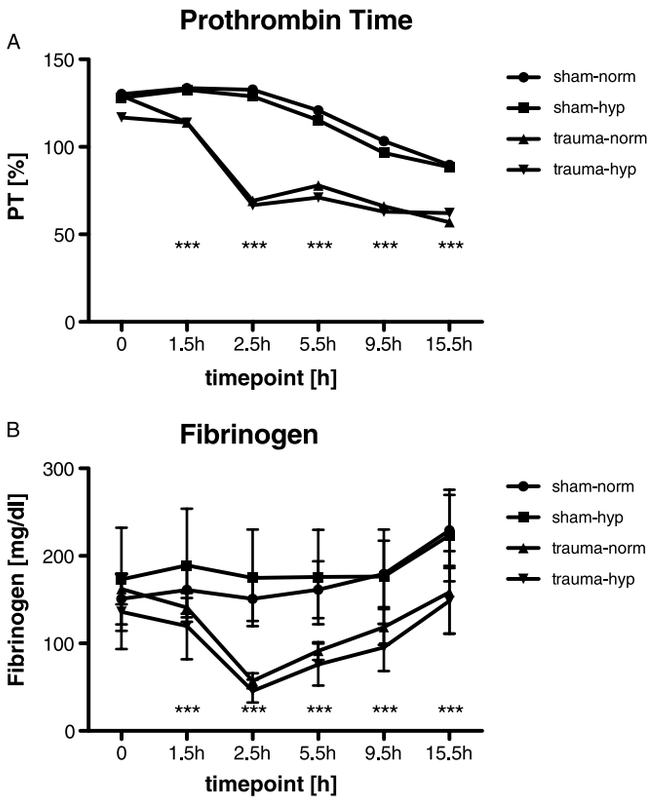

Figure 2. *A* and *B*, Mean (SD) for coagulation parameters PT and fibrinogen (T 0, baseline; T 1.5 hours, after shock; T 2.5 hours, after resuscitation; T 5.5 hours, during hypothermia; T 9.5 hours, after rewarming; T 15.5 hours, at the end of the experiment). Significant differences for TN compared with control group at the same time point (***$p < 0.001$). No significant differences between sham groups as well as trauma groups. SDs for PT were very small, so that they were not represented.

ROTEM

Baseline values for thrombelastometry measurements were comparable for all groups.

Clotting time (CT) was significantly prolonged for TN following resuscitation as compared with SN (T 2.5 hours, Fig. 3*A*). CT further decreased in both trauma groups until 5.5 hours following trauma at approximately 45 seconds and remained stable afterward (Fig. 3*A*). No difference between TN and TH animals was observed ($p > 0.05$).

Clot formation time (CFT) was comparable in both trauma groups before trauma induction (TN vs. TH, 43.4 [6.9] seconds vs. 45.6 [7.2] seconds; $p > 0.05$). Following resuscitation, CFT was significantly prolonged in TN as compared with SN (T 2.5 hours, Fig. 3*B*). While CFT initially recovered, an increase in both trauma groups was observed until the end of the investigation without reaching statistical significance (Fig. 3*B*). Hypothermia did not influence CFT at any time point.

Maximum clot firmness (MCF) significantly decreased in TN and TH until 18 mm after resuscitation. After stabilization, MCF was constant around 25 mm for both trauma groups through the investigation period (Fig. 3*C*). Compared with that of the SN group, MCF was significant decreased following resuscitation in the trauma groups (Fig. 3*C*). There were no effects of hypothermia on MCF.

There were no significant differences between sham groups for CT, CFT, and MCF values (Fig. 3).

In addition, thrombelastometry analyses for SH and TH at 37°C and 34°C during hypothermia (T 5.5 hours) were performed. In both hypothermic study groups, significant differences were shown between analytic procedures at 34°C and 37°C for CT and CFT, while no differences were revealed for MCF (Fig. 4).

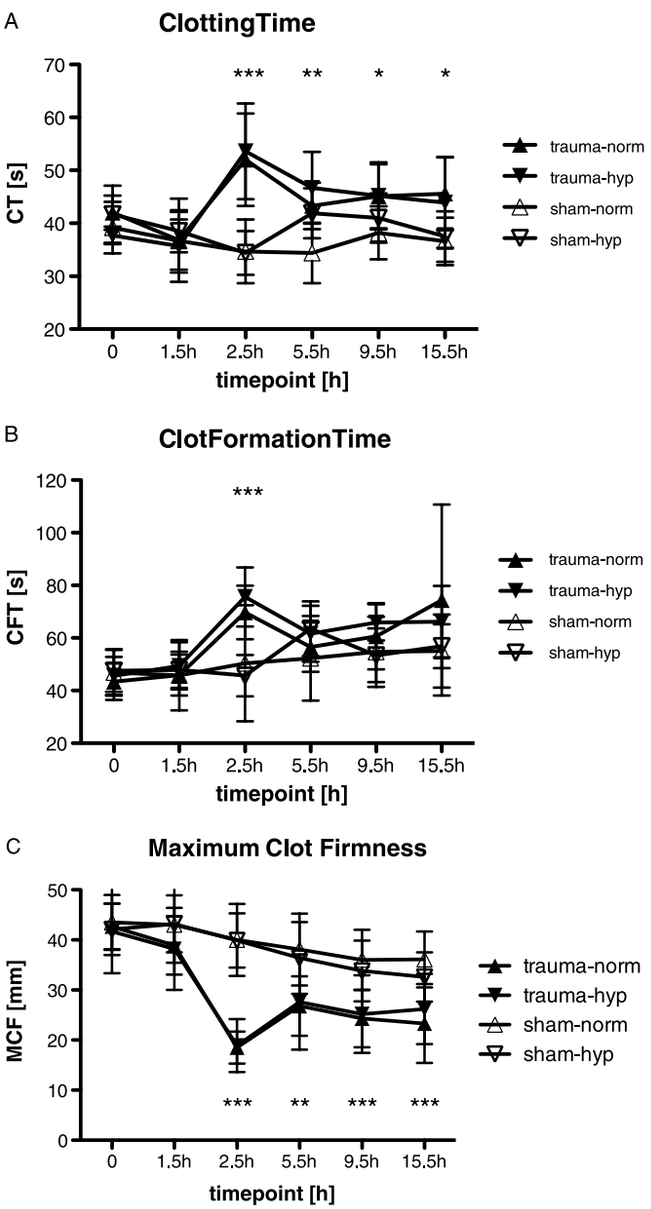

Figure 3. *A–C*, Thrombelastometry measurements at 37°C (T 0, baseline; T 1.5 hours, after shock; T 2.5 hours, after resuscitation; T 5.5 hours, during hypothermia; T 9.5 hours, after rewarming; T 15.5 hours, at the end of the experiment). Significant differences compared TN with SN: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. No significant differences between sham groups as well as trauma groups.

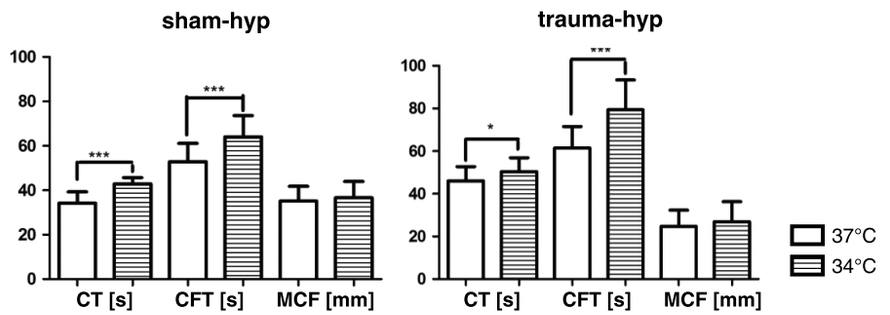

Figure 4. Thrombelastometry measurements for SH and TH at 34°C and 37°C only during hypothermia (T 5.5 hours). The effects of temperature on enzymatic kinetics. Significant differences, *$p < 0.05$ and ***$p < 0.001$.

When comparing ROTEM analyses at 37°C, no significant differences could be demonstrated between hypothermic and normothermic trauma groups (Fig. 3).

Platelet Function

Before trauma induction, all animals had comparable platelet function. Following trauma induction, analyses of platelet function (Multiplate) showed a significant decrease regarding the area under curve for ADPtest in TN compared with SN (T 1.5 hours: SN, 52.7 [23.3] U vs. TN, 33.0 [10.2] U; $p = 0.03$). The lowest platelet function was revealed following resuscitation for trauma groups with significant differences compared with SN (Fig. 5; T 2.5 hours: SN, 54,6 [23.4] U vs. TN, 21.9 [12,4]; $p = 0.001$). The decrease was present until the end of the resuscitation phase and remained stable afterward without differences between trauma groups (Fig. 5)

There were no differences between sham groups.

COLtest showed no differences for every group at any time point (data not shown).

There was no influence of hypothermia between sham or trauma groups ($p > 0.05$).

Macroscopic Results

Before rewarming, careful exploration of the injured liver was performed. We were not able to detect macroscopic or petechial bleeding in both trauma groups

DISCUSSION

It is already known that accidental hypothermia combined with acidosis and coagulopathy in trauma patients is associated with an increased mortality.[10,16,17] In contrast, induced hypothermia is commonly used as a therapeutic approach following cardiac arrest or during neurosurgical and cardiosurgical interventions without bleeding complications. Clinical studies showed that induced hypothermia after cardiac arrest improved clinical outcome owing to decreased metabolism and reduced rate of apoptosis.[18] We suggest that induced hypothermia can also be therapeutically used in trauma patients after initial stabilization without bleeding complications.

In the present study, we investigated the impact of induced therapeutic hypothermia on coagulation parameters in a porcine multiple trauma model.[22] The aim of the present study was to evaluate the impact of induced hypothermia on coagulation parameters measured by "conventional" parameters (PT, fibrinogen) and more innovative methods (thrombelastometry, Multiplate) following major trauma.

Trauma and consecutive fluid resuscitation resulted in impaired coagulation parameters. Induced hypothermia did not deteriorate coagulation parameters.

We stabilized pigs during the resuscitation period before starting induced hypothermia. For hemodynamic stabilization, fluid administration was performed. In accordance with the German guideline regarding treatment of severe injuries, we only used a minor quantity of colloidal infusion since negative effects on the coagulation system following severe shock is described.[23] Acidosis was controlled by artificial ventilation. Significant acidosis persisted in both trauma groups until the end of the experiment, which may be explained by pulmonary impairment owing to lung injury performed.[22] Following fluid resuscitation, a moderate coagulopathy was detected. Since pigs have a hypercoagulability coagulation system compared with human coagulation, we do not have to stabilize coagulation with blood products in this experimental model. Regarding coagulation parameters, this severe trauma model simulates the situation after admission to the intensive care unit. Following the resuscitation period and after hemodynamic stabilization, a controlled hypothermia was induced.

After establishment of the described trauma model, all animals survived the observation period in all experimental groups.

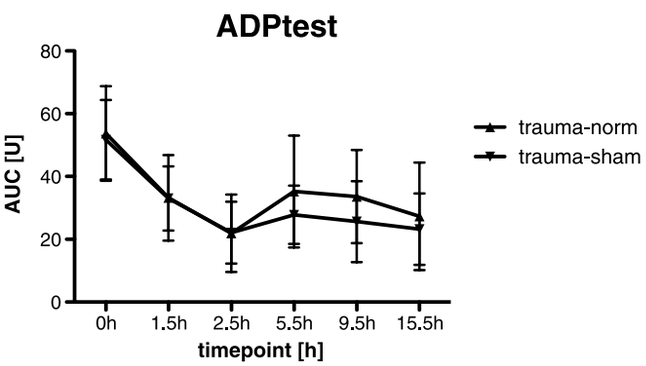

Figure 5. Mean (SD) for ADPtest of platelet function (T 0, baseline; T 1.5 hours, after shock; T 2.5 hours, after resuscitation; T 5.5 hours, during hypothermia; T 9.5 hours, after rewarming; T 15.5 hours, at the end of the experiment).

Red blood cells, platelets, hemoglobin, and PT decreased over time also in sham groups, which may be caused by catheter insertion and blood sampling.

During hypothermia, coagulation parameters measured at 37°C, such as PT, fibrinogen, thrombelastometry measurements and platelet function, showed no significant differences between normothermic and hypothermic animals in both trauma groups. In the current literature, only a few studies examined coagulation in experimental hemorrhagic shock models. George et al.[24] compared different levels of hypothermia in a porcine model of hemorrhagic shock showing a decreased mortality for severe hypothermia at 33°C without significant effects on coagulation activity at 37°C (partial thromboplastin time, international normalized ratio). This is in accordance with our results demonstrating no influence of hypothermia on prothrombin time or systemic fibrinogen levels. However, our results revealed a significant effect of controlled hypothermia in thrombelastometry measurements at 34°C. CT and CFT were prolonged in hypothermic animals, while clot firmness was comparable. The effect of hypothermia on thrombelastometry was investigated in several studies. Confirming our results, the initial CT and clotting rapidity was prolonged in healthy pigs, with an induced hypothermia of 32°C, while clot strength was not affected. In contrast to our results, the authors could detect a decrease in fibrinogen and thrombin synthesis, which may be related to the longer hypothermia period of 7 hours as compared with 2.5 hours in the present study. Heinius et al.[14] and Martini et al.[25] investigated the impact of hypothermia (32°C) on coagulation in a swine hemorrhagic shock model. Thrombelastography measurements were performed at body temperature. Both reported significant changes in CT and CFT but no differences in cloth strength during hypothermia, which is in accordance with our results. Interestingly, we observed these effects in trauma as well as in sham groups. Since hypothermia influences enzymatic kinetics but not the product quantity, a prolongation of the enzymatic reaction could be expected, while the final product should not be affected. Thus, the results of the present study suggest the treatment of hypothermia by rewarming; coagulation factors should only be substituted if a systemic decrease is present.

In another study, significant differences for prothrombin time and partial thromboplastin time of hypothermia-induced coagulopathy in an experimental hemorrhagic shock model in pigs were documented. While coagulation impairment was corrected by shed blood transfusion in normothermic animals, these effects could not be seen in hypothermic pigs. The authors conclude that hypothermia and shock have additive effects on hemodynamics and coagulation and that both need to be addressed.[26] However, it remains questionable if shed blood replacement is an appropriate treatment for coagulation disorders under hypothermic conditions.

In our study, platelet function investigated by ADPtest and COLtest did not show any difference between normothermic and hypothermic animals following trauma as well as in sham animals. Investigations of platelet function, performed with the impedance aggregometer Multiplate at multiple test temperatures, demonstrated no influence on platelet aggregation in mild hypothermic patients.[27] Watts et al.[10] showed a slowed enzyme activity and decreased platelet function in trauma patients with a core temperature less than 34°C. To the best of our knowledge, the current study is the first report on the impact of hypothermia on platelet function in an animal trauma model.

Rebleeding is described after restoration of the arterial pressure and blood flow.[28,29] To date, the influence of hypothermia on rebleeding was only evaluated in a model of uncontrolled hemorrhage in rats.[30] The authors could clearly demonstrate more severe rebleeding in animals treated with hypothermia of 30°C for 90 minutes. In contrast, at the end of the hypothermia period, a careful examination of the liver did not detect any macroscopically bleeding or oozing of injured livers in the present study. These divergent results may be explained by the deeper hypothermia used by the other authors. Moreover, it is questionable to what extent the results of experiments with rodents may be transferred to large animal models or even the clinical situation. In a clinical study, Tuma et al.[31] reported about a case series of five acute trauma patients who were managed with induced hypothermia of 32°C to 34°C for 24 hours after cardiac arrest. Confirming our observations, the authors described no obvious bleeding complications related to cooling.

Nevertheless, there are several shortcomings of this animal study. The study was conducted in anesthetized animals. The physiologic response to pain may have an impact on hemostasis and is not considered in the present study. Hemorrhage was limited to a maximum of 45% of total blood volume owing to additional injuries (blunt lung injury, liver incision). However, the model used in this study simulates the clinical situation shown by decreased pH and hemoglobin values. In addition, we reached similar physiologic results after reperfusion as compared with another study.[32] Coagulation parameters after reperfusion are comparable with the human situation at intensive care unit admission after cardiopulmonary stabilization of patients with moderate hemorrhage despite pH and hemoglobin levels, suggesting a more severe hemorrhage. This may be explained by the better coagulation in pigs as compared with that in humans.[33] Nevertheless, pigs are commonly used for coagulation studies in experimental polytrauma models.[26,34,35]

The results of the present study suggest that mild hypothermia can be safely performed after stabilization following major trauma. Mild hypothermia affects the coagulation system but does not aggravate trauma-induced coagulopathy in our model. Before hypothermic treatment can be performed in the clinical setting, additional experiments with prolonged and deeper hypothermia to exclude detrimental effects are required.

AUTHORSHIP

All authors have participated sufficiently in this work and take public responsibility for the content.

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DISCLOSURE

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