Review

Clinical and translational aspects of hypothermia in major trauma patients: From pathophysiology to prevention, prognosis and potential preservation

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The human body strives at maintaining homeostasis within fairly tight regulated mechanisms that control vital regulators such as core body temperature, mechanisms of metabolism and endocrine function. While a wide range of medical conditions can influence thermoregulation the most common source of temperature loss in trauma patients includes: exposure (environmental, as well as cavity), the administration of i.v. fluids, and anaesthesia/loss of shivering mechanisms, and blood loss per se. Loss of temperature can be classified either according to the aetiology (i.e. accidental/spontaneous versus trauma/haemorrhage-induced temperature loss), or according to an unintended, accidental induction in contrast to a medically intended therapeutic hypothermia. Hypothermia occurs infrequently (prevalence < 10% of all injured), but more often (30–50%) in the severely injured. Hypothermia usually come together with and may aggravate acidosis and coagulopathy (the “lethal triad of trauma”), which again may be associated with a high mortality. However, recent studies disagree in the independent predictive role of hypothermia and mortality. Prevention of hypothermia is imperative through all phases of trauma care and must be an interest among all team members. Hypothermia in the trauma setting has attracted focus in the past from a pathophysiological, preventive and prognostic perspective; yet recent focus has shifted towards the potential for using hypothermia for pre-emptive and cellular protective purposes. This paper gives a brief update on some of the clinically relevant aspects of hypothermia in the injured patient.

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Introduction

The human body strives at maintaining homeostasis within fairly tight regulated mechanisms that control vital regulators such as core body temperature, mechanisms of metabolism and endocrine functions. These essential functions may demonstrate
just slight circadian oscillation under normal circumstances, such as temperature oscillation maintained between 2 and 4°C on a circadian basis. Regulation of temperature follows through a stimulus–feedback system that ensures either generation of heat (through muscle shivering) if temperature falls, or the removal of excess heat through generation of sweat and vasodilation (see mechanisms in Fig. 1). However, any disruption of the homeostatic mechanisms may blunt these otherwise tightly controlled mechanisms (e.g. bacterial infection leading to fever; or loss of consciousness leading to heat loss and failure to compensate through shivering). A major trauma insult on the human body is typically followed by deregulated mechanisms ranging from cellular and molecular mechanisms, to altered human physiology and single or multi-organ dysfunction. For severely injured bleeding patients the extreme form may be characterised as the "lethal triad of trauma" with acidosis, hypothermia and coagulopathy with a very high mortality even in the modern era of trauma management. Hypothermia in the trauma setting has attracted interest in the past from a pathophysiological, preventive and prognostic perspective, yet recent focus has shifted towards the potential for using hypothermia for pre-emptive and cellular protective purposes. This review gives an overview on current findings and results reported for hypothermia in trauma victims.

Definition, measurements and classification

Hypothermia is usually considered to be present in trauma patients with a body core temperature < 35°C. However, as no globally agreed classification of hypothermia exists, various cut-off values have been used for the definition of hypothermia, but most studies refer to hypothermia as either < 35°C or ≤ 35°C. In 2008, the ATLS redefined hypothermia parameters for trauma – for injured patients it is now < 36°C – for patients exposed such as in submersion injury, it remains < 35°C.

Notably, while recording body temperature is perceived as an everyday procedure and one of the most used ways of evaluating the general health condition, it may be associated with a considerable larger uncertainty than probably perceived by most clinicians. Temperature can be measured and monitored either by invasive means (by a pulmonary catheter, by probes in the oesophagus or bladder or by rectal probes) or by non-invasive techniques (oral, axillary, temporal artery and ear-based measurements). A number of factors may influence temperature measurements and interpretation, including human factors such as patients age and gender, choice of technique and location, measurement errors on the side of the user, or equipment errors based on technical or calibration issues. Considerable variation exists in measurement accuracy, but pulmonary artery measurements and rectal temperature appears to be fairly accurate and demonstrating good correlation for estimating core body temperature, usually with as little as ±0.1°C in variation. Probes inserted in the urinary bladder may also be an alternative, with temporal artery reading and axillary measurements being less reliable – with up to ±1°C in difference from invasively recorded measurements – although widely used in clinical practice. As novel and improved techniques develop it is hoped that more standardised and reliable measurements can be obtained.

Loss of temperature can be classified either according to the aetiology (i.e. accidental/spontaneous versus trauma-induced), or the mode of induction, such as an accidental drop of temperature in contrast to that of a medically intended use of therapeutic hypothermia. Usually one would consider hypothermia as either spontaneous or accidental when caused by an accident or insult per se (such as cold exposure) or therapeutic when used as a therapeutic means. While trauma-induced hypothermia may include an accidental component (exposure to cold weather) it is important to make clinical distinction between isolated accidental/spontaneous hypothermia and that of trauma-induced
hypothermia, as the accidental hypothermia has much better outcome, should receive prolonged resuscitation until core body temperature has been achieved, and as long- and short-term survivors have been described at extreme temperatures below 20 °C,17,18 with lowest core body temperature recorded at 13.7 °C.18 Notably, trauma patients do worse within both extremes of body temperature ranges, both in civilian and military injuries.19

Aetiology for hypothermia

Multiple factors may contribute to loss of temperature after an injury insult, and across all phases of trauma care (Fig. 2). In general, hypothermia after injury is induced either by environmental exposure,20 by the infusion of cold intravenous fluids, as a consequence of haemorrhagic shock or as a side effect of anaesthetic drugs affecting thermoregulation.5,21 One study of a physician-manned pre-hospital emergency service in London22 found a significant difference in body temperature between anaesthetised patients (n = 207) and non-anaesthetised patients (n = 287) for a difference in temperature (mean ± SD 35.0 ± 2.1 °C vs. 36.2 ± 1.0 °C, respectively; p < 0.001). This is in line with a recent pre-hospital, multicentre observational study that found 15% of trauma patients to be hypothermic, with severity of injury, environmental conditions and the medical care provided by EMS as significant risk factors for hypothermia.23

In-hospital factors may further aggravate loss of temperature; cavitary exposure during surgery should be noted as a source for temperature loss and associated mortality.7 Inaba et al.7 found that when compared to patients with normal temperature at the end of an operation, hypothermic patients had a significantly higher mortality (35% versus 8%; p < 0.001). With decreasing temperatures, there was a stepwise increase in mortality, and mortality was an independent predictor of mortality adjusted for other variables in this study. However, they did not report on the number of patients that were hypothermic before entering the operating room and stayed hypothermic; or the numbers who became hypothermic due to exposure in the operating room. Nonetheless, the dangers of temperature loss during surgery should be kept in mind.

A wide range of medical conditions can also influence thermoregulation. However, in civilian trauma, exposure, hypovolaemia and the infusion of cold fluids are likely the most important factors contributing to temperature loss in an injured individual. Notably, while studies have found no seasonal difference in the occurrence of hypothermia,20,22,24,25 others have found a positive association to winter time.29 Precautions should be taken during all seasons to prevent the further loss of temperature in the injured patient.

Prevalence of hypothermia after trauma

Accurately estimating the true occurrence of hypothermia in trauma patients is difficult because of inconsistent documentation of body core temperature,3,19,27–30 lack of a reference standard to measure body temperature, reported variable accuracy in measurement tools and inconsistent use of cut-off levels for defining hypothermia. However, many studies appear to agree on a body core temperature of <35 C as clinically relevant and as an important cut-off for hypothermia.4–26,8,9,28

The incidence of post-traumatic hypothermia has been investigated in a number of larger retrospective studies indicating that the prevalence of hypothermia on admission varies from 1 to 10% of all injured patients5,9,19,23,27,28,30 while not adjusted for injury severity. Indeed, hypothermia may be as common as every third severely injured (ISS ≥ 16) adult trauma patient.31 Larger database studies from the United States have found 5–9% of trauma patients to be hypothermic (defined as <35 °C).5,28 A National Trauma Databank (NTDB) study in >700,000 trauma patients found hypothermia in 1.6% of patients, with temperatures < 32 °C in only 802 patients (0.11%).27 The data mentioned above underscore that prevalence changes with the groups studied (with age-groups included/excluded; dependant on injury severity and,
the type of injuries) and, that hypothermia is not common in trauma patients overall, but might have detrimental effects in the most severely injured, e.g. ISS > 15 and higher.24

Physiologic effects of trauma-induced hypothermia

Mild heat loss is usually well-tolerated with compensatory pathophysiological changes to maintain temperature homeostasis.1 Responses to mild hypothermia include increased muscle tone and shivering (Fig. 1), as well as metabolic increases from the release of catecholamines and thyroxin. Below 32 °C, cardiac conduction disturbances become apparent; atrial fibrillation is not uncommon with core temperatures below 30 °C (Fig. 3). Notably, there is no artificial cut-off temperature where one event may or may not occur over another. Obviously the effects of hypothermia may be influenced by many factors, including other sustained injuries and the patient’s age and comorbidity. Fig. 3 gives an illustrative view of the potential danger areas when temperature decrease may lead to deranged physiological function. Below 28 °C, serious abnormal cardiac rhythms may occur. Below 28 °C, respiratory rates decrease and may stop, myocardial contractility is depressed, and the initial slowing of the heart and supraventricular arrhythmias may give way to ventricular fibrillation and, finally, asystole.32–35 Hypothermia decreases the enzymatic activity of clotting factors and impairs platelet function (Fig. 4). In addition, hypothermia inhibits fibrinogen synthesis.36,37 Trauma-induced shock results in anaerobic metabolism that can give way to reduced adenosine triphosphate (ATP) synthesis, resulting in the decreased hydrolysis of ATP to adenosine diphosphate (ADP) and hence decreased heat production.38 Previous data from animal research have shown that thermoregulation after injury is impaired as a result of a lowered hypothalamic temperature threshold for the onset of shivering, which results in either no shivering, or only slight shivering, observed at about 31 °C. Similarly, an impairment in the threshold for vasoconstriction may also occur after trauma. In addition to the effects of environmental exposure, trauma patients have reduced heat production due to low perfusion of the muscles and may experience increased heat loss because of radiation, conduction and evaporation from exposed body cavities if subject to surgery.21,38 Some authors have argued that within the most common temperature range of hypothermia seen in trauma patients (33–36 °C), isolated hypothermia probably has only a minimal clinical impact on haemostasis.38 Nonetheless, all means to prevent temperature loss should be introduced early on from the prehospital phase to reception in the emergency room.

Prognostic implications of trauma-induced hypothermia

Several past and current retrospective studies have shown an independent relationship between mortality and hypothermia after trauma.5,7,9,27,28,39–41 With non-survivors demonstrating a lower average body temperature, higher ISS, and an increased blood transfusion requirement. Some retrospective studies have shown an independent association with mortality in trauma patients with admission temperatures < 35 °C.9,26,27,28 Further, two recent publications from the Los Angeles area demonstrated an increased mortality in patients with TBI who had hypothermia on admission or the pre-hospital phase, suggesting this as an independent prognostics factor.22,42 However, results have not been consistent over time, as others have not confirmed the association with mortality.8,30,31,44 A recent large German study of >5000 patients did not find an independent predictive effect of hypothermia on mortality,8 rather it suggested that hypothermia is part of the detrimental physiological effects that come with severe injury and haemorrhage (and thus acidosis and coagulopathy). A more recent association between hypothermia and increased organ dysfunction, but not mortality,8 may indeed point...
to several factors: an increased awareness of hypothermia; better prevention to ameliorate further heat loss; but, also to the general advancement in critical care for the most severely wounded. As such, recent studies have proposed that hypothermia has no independent effect on mortality in different models, and likely mortality prediction was reflected in the co-existence of acidosis and coagulopathy.\textsuperscript{30,45,46}

Hypothermia may contribute to increased morbidity, including higher risk for organ dysfunction\textsuperscript{6} and as a risk-factor for surgical site infection in trauma laparotomies.\textsuperscript{3} Again, awareness and diligent screening for the current body temperature in injured patients is mandatory to detect, prevent and treat further temperature loss.\textsuperscript{47} This is important among all team members and needs attention alike other important tasks in the early work-up and management of the trauma patient.

Prevention/prophylaxis and treatment and of hypothermia

Prevention and treatment of hypothermia are often two of a kind – however, emphasis should be prevention firstly and treatment with further prevention once hypothermia has been diagnosed by screening the temperature. Modalities may range from simple, non-invasive, passive external warming techniques (such as, removal of cold, wet clothing; movement to a warm environment) to active external rewarming (e.g. insulation with warm blankets) to active core rewarming (e.g. warmed intravenous fluid infusions, heated humidified oxygen, body cavity lavage, and extracorporeal blood warming).

Only one randomised trial has been performed for active treatment to correct hypothermia.\textsuperscript{41} In the trial, no effect was demonstrated for survival, but those receiving standard rewarming (compared to invasive rewarming) had higher fluid requirements during the intensive care phase. There is considerable costs and use of resources needed to actively re-warm hypothermic trauma-patients with the latter technique, knowingly with no demonstrable clinical effect on outcome.

The proclamation “prevention is the best treatment” holds true also for hypothermia. Prevention of heat loss is usually easy to perform (in most cases), yet likely the most commonly forgotten measure in the care of the injured. Even in a major trauma centre in London the body temperature was only recorded in 38% of all trauma patients on admission.\textsuperscript{22} “If you don’t take a temperature you won’t find a fever” – likewise goes the saying for hypothermia and temperature loss undetected if temperature is not measured. Missing values of temperature is fairly frequent in reports from trauma databases, and a recently proposed collection of common core data points in trauma victims did not include temperature as a core variable.\textsuperscript{48} In light of the association with hypothermia and mortality, the lack of temperature as a core variable may be viewed as a failure. However, recent modelling of prognosis does not support hypothermia as a core variable.\textsuperscript{50} Be it right or wrong, this decision was derived from the consensus agreement among a large number of international researchers.\textsuperscript{49,50} It may be subject to future revisions.

Preventive measures should start in the pre-hospital phase for all trauma victims (Fig. 2). One study of healthy volunteers, showed that a combination of vapour tight layer and an additional dry insulating layer (called Hibler’s method) was the most efficient wrapping method to prevent heat loss, as shown by increased skin temperatures, lower metabolic rate and better thermal comfort.\textsuperscript{51} A small, randomised trial from northern Sweden demonstrated that in patients with mild hypothermia after trauma and a preserved shivering capacity, passive warming was effective in establishing a slow rewarming rate and in reducing cold discomfort during prehospital transportation.\textsuperscript{52} However, the addition of active warming using a chemical heat pad applied to the torso significantly improved thermal comfort and could potentially reduce the cold induced stress response. Obviously, awareness of cold exposure throughout all links in the ‘trauma chain of survival’ is crucial,\textsuperscript{53} and education and protocols for the entire team involved is essential.\textsuperscript{26,54}
Prophylactic and therapeutically induced hypothermia in trauma

Clinical experience of therapeutic hypothermia from cardiac arrest, stroke and newborn asphyxia have revealed prognostic difference in outcomes, with improved outcomes overall and for neurologic recovery with induced hypothermia under controlled conditions. Further, potential benefits from hypothermia have been suggested from elective surgery, and extrapolated from cellular effects demonstrated in in vitro studies. Extrapolation of the positive effects of clinically-induced therapeutic hypothermia used in cardiac arrest on the improved neurologic outcome have probably been most convincing, particularly for isolated injuries of the central nervous system. Additionally, recent findings in traumatic brain injury seem to indicate that hypothermia may have protective effects in selected victims. However, in contrast to the effects and expanding role seen in cardiac arrest survivors, the induction of therapeutic hypothermia after major injury remains a largely experimental option. Notably, controversies still persist in indications, initiation and depth of hypothermia for cardiac arrest. Recent reviews have explored the technical details concerning methods of inducing hypothermia, which are beyond the scope of this review.

Neuroprotective effect in TBI

The majority of evidence of the neuroprotective effects of mild to moderately induced hypothermia stem from animal research, and is currently undefined. The clinical role is as yet undefined and human studies are needed for better clarification of the actual therapeutic effect. Two recent North American studies demonstrated a detrimental outcome in (non-therapeutic induced, accidental) hypothermia and traumatic brain injury (TBI). The neuroprotective effects of therapeutic hypothermia in isolated types of injuries, most often TBI or spinal cord injuries (SCI), have currently revealed conflicting results in clinical trials. For TBI studies, the conflicting results are partly explained by different trial designs used by the investigators. Though, studies of hypothermia for patients with severe brain injury can be divided into either studies of hypothermia used to treat raised intracranial pressure or, studies were hypothermia is intended as a neuroprotective intervention to stop the biochemical inflammatory cascade after injury. Thus, immediate comparison of studies may be difficult and unwarranted. Further, underpowered studies and dubious subgroup analyses have contributed to the controversy in the past. However, larger clinical studies are underway. More recently, the randomised clinical trial ‘National Acute Brain Injury Study: Hypothermia II’ (NABIS II trial) failed to demonstrate any beneficial effect of early introduction of mild hypothermia in patients with TBI. However, the study has been criticised among others for rearming patients too early, which may have led to increased intracranial pressures and worse outcomes. Two ongoing trials may give additional answers on the therapeutic effect of hypothermia in patients with TBI. One is the European trial ‘EUROTHERM’ (Current Controlled Trials ISRCTN34555414) which aim for 1800 patients and is still recruiting with recruitment to be stopped in 2013. The EUROTHERM trial is a pragmatic, multi-centre RCT examining the effects of hypothermia at 32–35 °C and titrated to reduce intracranial pressure < 20 mmHg. Outcome will be examined on morbidity and mortality at 6 months after TBI. Further, a RCT initiated by the Australian and New Zealand Intensive Care Clinical Trials Group (ANZICS-CTG) named POLAR (Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury; Clinicaltrials.gov NCT00987698) is currently also recruiting patients and is estimated to complete recruitment by late 2013. Hopefully, the EUROTHERM and POLAR studies will cast new light on the potential benefit of hypothermia in TBI.

Hypothermia as a preserving mechanism in multisystem trauma

For multisystem trauma, the clinical experience of induced hypothermia is very limited, with only a case series of six patients reported with intended therapy-induced hypothermia for severe injuries suffering cardiac arrest. However, an abundance of animal research and evolving understanding of basic mechanisms are unfolding. From several animal experiments, it appears that cellular preservation mechanisms can be induced with therapeutic hypothermia. Notably some of these definitions are outside the range currently applicable for clinical use (i.e. deep, profound and ultra-profound hypothermia) as therapeutic hypothermia are classified into mild (33–36 °C), moderate (28–32 °C), deep (16–27 °C), profound (6–15 °C), and ultra-profound (<5 °C).

The mechanisms and approach to induce a rapid total body preservation, to allow for repair of injuries during metabolic arrest, then followed by controlled resuscitation defines the concept of ‘emergency preservation and resuscitation’ (EPR), recently reviewed in detail elsewhere. Extensive preclinical data suggest that in advanced stages of shock, rapid cooling can protect cells during ischaemia and reperfusion, decrease organ damage, and improve survival. However, it should be noted that induction of hypothermia is a double-edged sword. The practical application of therapeutic hypothermia is not trivial, and the treatment carries risks. Unless managed carefully, its induction can be associated with a number of complications. However, if the laboratory success of the groups working on therapeutic and mechanistic understanding of this can bring the knowledge for a safe transfer to the bedside, it may pose a considerable advance forward for severely injured patient having otherwise a poor chance of good outcome.

Conflict of interest statement

The authors have no conflicts of interests to declare related to the content or publication of this manuscript.

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