Protection and treatment of hypothermia in prehospital trauma care

- with emphasis on active warming

Peter Lundgren

Department of Surgical and Perioperative Sciences
Umeå University, Sweden

In collaboration with the Deparment of Clinical and Experimental Medicine, Linköping University

To be continued …

ABSTRACT

Background: In prehospital trauma care active warming is recommended to aid in protection from further cooling. However, scientific evidence of the effectiveness of active warming in a clinical setting is scarce. Also, evaluating the effectiveness of active warming, especially in harsh ambient conditions, by objective measures, is difficult.

Objective: To evaluate the effectiveness of field applicabe heat sources (**I**) and to evaluate active warming intervention in a prehospital clinical setting (**II** and **III**).

To evaluate reliability and validity of the Cold Discomfort Scale (CDS), a subjective judgement scale for assessment of the thermal state of patients in a cold environment (**IV**).

Methods: In a laboratory trial, non-shivering hypothermic subjects (n=5), were cooled in 8 ℃ water followed by spontaneous warming, a charcoal heater, two flexible hot-water bags or two chemical heat pads, all applied to the chest and upper back (**I**). Oesophageal temperature, skin temperature, heat flux, oxygen consumption, respiratory rate and, heart rate were measured.

In two clinical randomized trials, shivering patients during road and air ambulance transport (**II**) and during field treatment (**III**) were randomized to either passive warming alone (n=22 and n=9) or to passive warming with the addition of a chemical heat pad (n=26 and n=11). Body core temperature, respiratory rate, heart rate, blood pressure (**II**) and the patients' subjective sensation of thermal comfort (**II** and **III**) were measured.

In a laboratory trial, shivering subjects were exposed to – 20 ℃ (n=22). The CDS was evaluated regarding reliability, defined as test-retest stability, and criterion validity, defined as the ability to detect changes in cold discomfort due to changes in cumulative cold stress (**IV**).

Results: In non-shivering hypothermic subjects postcooling afterdrop was significantly less for the chemical heat pads, but not for the hot water bags and the charcoal heater, compared to spontaneous warming (**I**). Temperature drop during the entire warming phase was significantly less for all the heat sources respectively, compared to spontaneous warming (**I**).

During road and air ambulance transport, ear canal temperature was significantly increased and cold discomfort significantly decreased, both in patients assigned to passive warming only, and in patients assigned to additional active warming (**II**). During field treatment, cold discomfort was significantly reduced in patients assigned to additional active warming, but remained the same in patients assigned to passive warming only (**III**).

Weighted kappa coefficient, describing test-retest stability, was 0.84 (**IV**). CDS ratings were significantly increased during each 30 minutes interval (**IV**).

Conclusion: In non-shivering hypothermic subjects, heat sources were effective to attenuate afterdrop, when providing high heat content over a large surface area and effective to continue to increase body core temperature when providing sustained high heat content. In shivering trauma patients, adequate passive warming were sufficient treatment to prevent afterdrop, to slowly increase body core temperature, and to reduce cold discomfort. If inadequate passive warming, additional active warming was required to reduce cold discomfort. The CDS, a subjective judgement scale for assessment of the thermal state of patients in a cold environment seemed to be reliable regarding test-retest stability and valid regarding ability to detect change in cumulative cold stress.

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals:

I   Lundgren JP, Henriksson O, Pretorius T, Cahill F, Bristow G, Chochinov A, Pretorius A, Bjornstig U, Giesbrecht GG. Field Torso Warming Modalities: A Comparative Study Using a Human Model. Prehosp Emerg Care 2009,3:371-378.

II   Lundgren P, Henriksson O, Naredi P, Bjornstig U. The effect of active warming in prehospital trauma care during road and air ambulance transportation - a clinical randomized trial. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2011 19:59.

III Lundgren P, Henriksson O, Naredi P, Bjornstig U. The Effect of Active Warming on Cold Discomfort in Field Treatment of Trauma Patients – a Clinical Randomized Trial. Manuscript.

IV Lundgren P, Henriksson O, Kuklane K, Holmér I, Naredi P, Bjornstig U. Validity and Reliability of the Cold Discomfort Scale - a Subjective Judgement Scale for Assesssment of the Thermal State of Patients in a Cold Environment. Manuscript.

Original papers were reprinted with approval from the publishers.

SAMMANFATTNING

Bakgrund: En skadad person löper stor risk att bli nedkyld, men redan innan allmän nedkylning är ett faktum, aktiveras kroppens försvarsmekanismer i form av sammandragning av ytliga blodlärl för att minska värmeförlusterna samt huttring för att öka värmeproduktionen. Detta innebär, förutom ett ökat obehag, en stor fysiologisk belastning för kroppen som kan vara ödesdiger i kombination med andra yttre skador. Om allmän nedkylning ändå inträffar medför detta ökad blödningsbenägenhet, vätskeförluster och risk att drabbas av livshotande hjärtrytmrubbningar. Allmän nedkylning i samband med allvarliga kroppsskador har visat sig vara en negativ prognostisk faktor associerad med ökad dödlighet. Vid omhändertagande på skadeplats samt under transport in till sjukhus är det således av yttersta vikt att skydda skadade patienter mot ytterligare nedkylning och åtgärder för att förhindra detta är prioriterade. Isolering mot yttre påverkan av väta, blåst och kyla utgör grunden för behandling. Därtill rekommenderas i såväl nationella och internationella riktlinjer att någon form av extern värmekälla ska tillföras patienten redan på skadeplats och under transport som komplement till isolering i syfte att minska den fysiologiska belastningen på kroppen.

De förhållanden som råder utanför sjukhus sätter begränsningar avseende möjligheter att adekvat mäta hur kylan påverkar patienten. Det är svårt att med tillförlitliga medel mäta central kroppstemperatur på skadeplats eller under transport til sjuhus och det är än svårare att under dessa omständighetrer objektivt mäta graden av huttring.

Syfte: Utvärdering av extern värmetillförsel på skadeplats samt under transport, avseende inverkan på fysiologisk samt även psykologisk belastning på kroppen. Specifikt var syftet att, under kontrollerade former i laboratorium, utvärdera och jämföra effekt av fältmässigt anpassad materiel för värmetillförsel (studie I) och att i kliniska situationer (studie II och III) utvärdera utvärdera effekten av sådan materiel, som tillägg till ordinarie behandling med isolering. Utöver detta var syftet även att utvärdera en alternativ mätmetod i form av en skala för subjektiv skattning av upplevelse av kyla, Cold Discomfort Scale (CDS), i syfte att kunna bedöma graden av kylapåverkan redan tidigt i förloppet.

Metod: I ett laboratorium exponerades forskningspersoner (n = 5) för kyla i form av 8 °C vatten, för att därefter erhålla behandling med en varm sovsäck och en av fyra olika behandlingsmetoder; en kolbricketdriven värmare, kemiska värmekuddar, varmvattensäckar, alternativt ingen värmebehandling alls (studie I). Försökspersonernas huttring hämmades med läkemedel. Central kroppstemperatur, värmeöverföring, syrgasförbrukning som ett mått på huttring samt andnings- och hjärtfrekvens mättes

I två kliniska studier av behandling på skadeplats (studie II) och behandling under transport till sjukhus (studie III) randomiserades lindrigt skadade patienter till antingen ordinarie behandling med endast isolering (n = 22 och n = 9) eller till behandling ordinarie med tillägg av extern värmekälla (n = 26 och n = 11).

Kroppstemperatur, andningsfrekvens, hjärtfrekvens och blodtryck (studie II) samt patienternas upplevelse av kyla (studie III) mättes.

Forskningspersoner (n = 22) exponerades vid två upprepade tillfällen med identiska förutsättningar för - 20 ℃ i 60 minuter. CDS utvärderades för reliabilitet avseende test-retest stabilitet och för kriterievaliditet, definierad som förmåga att mäta skillnad i kumulativ kylapåverkan.

Resultat: Under förhållanden där forskningspersonernas huttring hämmades med läkemedel sjönk kroppstemperaturen mindre, avseende lägsta uppmätta kroppstemperatur (afterdrop), vid behandling med de kemiska värmekuddarna, men inte vid behandling med varmvattensäckar eller kolbrickettdriven värmare, jämfört med ingen värmebehandling alls. Under hela behandlingsfasen, sjönk kroppstemperaturen mindre vid behandling med såväl de kemiska värmekuddarna, varmvattensäckarna som den kolbricketdrivna värmaren.

Under transport till sjukhus ökade patienternas centrala kroppstemperatur, samtidigt som deras upplevelse av kyla minskade signifikant både vid behandling med endast ordinarie isolering och vid behandling med tillägg av extern värmekälla (studie II).

På skadeplats och under inledande transport utomhus minskade patienternas upplevelse av kyla signifikant vid behandling med tillägg av extern värmekälla till ordinarie isolering, men den kvarstod däremot oförändrad vid behandling med endast isolering.

Viktad kappa koefficient, som mått på test-retest stabilitet, var 0.84. CDS visade signifikant ökad niva för upplevelse av kyla vid jämförelse av mätningar med 30 minuters mellanrum.

Slutsats: Externa värmekällor som tillförde mycket värmeenergi över en stor kontaktyta var effektiva för att minska afterdrop och under förutsättning att de tillför denna värmeenergi under lång tid, även effektiva för att påbörja uppvärmning vid behandling av patienter som har nedsatt huttringsförmåga. Avseende patienter som har bibehållen huttringsförmåga var adekvat mängd isolering tillräckligt för att motverka afterdrop, påbörja uppvärmning, och minska upplevelsen av kyla, men då isoleringen, utifrån rådande omgivningsförhållanden, inte var adekvat krävdes tillägg av extern värmekälla för att minska upplevelsen av kyla. Subjektiv skattning av upplevelse av kyla enligt CDS uppvisade både god reliabilitet avseende test-retest stabilitet och god validitet avseende förmåga att påvisa skillnad i kumulativ kylapåverkan.

CONTENTS

ABBREVIATIONS

ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
ANOVA	Analysis of Variance
C	Celsius
CDS	Cold Discomfort Scale
CI	Confidence interval
EMS	Emergency Medical Services
ICAR	International Commission for Alpine Rescue
IQR	Interquartile range
NRS	Numerical Rating Scale
PLSD	Protected Least Significant Differences
SaR	Search and Rescue
SD	Standard deviation
VAS	Visual Analoude Scale
VRS	Verbal Rating Scale

INTRODUCTION

In a prehospital rescue scenario, cold exposure poses a considerable risk for injured or ill patients. Admission hypothermia is associated with worse outcome and higher mortality in trauma patients (1-8). The cold induced stress response will also render considerable thermal discomfort which might increase the experience of pain and anxiety, even in still normothermic patients (9). In Sweden the average temperature in January during the period 1961 – 90 were between – 16 ºC in the northern part and – 1 ºC in the southern part of the country (10). In such environment, protection and treatment of hypothermia in prehospital trauma care is vitally important.

During the period 2001 – 2010, the median annual incidence of fatal accidental hypothermia in Sweden (about 9,5 million inhabitants) was 48 (range 37 – 63) (11). Hypothermia due to cold exposure as the primary cause (primary hypothermia) mainly affects two groups of patients; one group of elderly, most of them chronic abusers and under the influence of alcohol, and another group of younger, sober persons, performing outdoor leisure and sporting activities (12).

Although primary hypothermia is a rare diagnosis, secondary hypothermia, as a complication of systemic disorders, including trauma and sepsis, is common. In trauma patients, the overall medical condition and the administration of analgesic or anaesthetic drugs act to impair thermoregulatory mechanisms (13-16). In addition, wet clothing, contact with cold surfaces, large bleedings and administration of cold intravenous fluids contribute to the cold stress. Reported hypothermia incidence in the prehospital setting or upon arrival to hospital varies over a wide range (1, 4-8, 17-19). Severity of injury, the presence of haemorrhagic shock, prehospital induction of anaesthesia and protracted evacuation are predictive variables of admission hypothermia (1-5, 18, 20-22), reported hypothermia incidence is therefore dependent on inclusion criteria of the trauma registers and also dependent on whether hypothermia is being defined as body core temperature < 35 ºC or < 36 ºC. In one retrospective study using the US National Trauma Data Bank including more than 700000 patients, Martin et al. (4) found an hypothermia (< 35 ºC) incidence of about 2 %, whereas Helm et al (18), in a prospective study including 302 trauma patients treated during primary helicopter rescue missions, found a hypothermia (< 36 ºC) incidence of about 50%.

Induced hypothermia diminishes complications due to ischemia reperfusion injury during elective surgery (23). In laboratory studies, hypothermia has been shown to have beneficial effects during and after hemorrhagic shock and traumatic brain injury (23-25). The reduced physiological stress due to shivering prevention in induced hypothermia, compared to the increased physiological stress in accidental hypothermia, has been suggested a reason for these beneficial effects (23). In the clinical setting a few retrospective (19, 22) and prospective (17) observational

studies, investigating a total of about 1200 trauma patients, have found no difference in adjusted mortality for hypothermic versus normothermic patients. However, other retrospective (1, 3-8) as well as prospective (2) observational clinical studies, investigating more than 750000 trauma patients have revealed that hypothermia remains an independent determinant of mortality.

Accordingly, effective prehospital field protection and treatment of hypothermia, is considered vitally important to improve the medical condition upon admission to hospital, and active warming in the field is considered one important part of such treatment (13-15, 26-32). Because the heat sources need to be portable and easily handled by Search and Rescue (SaR) or Emergency Medical Services (EMS) personnel, there are limited treatment options in the field and during prehospital transport. Chemical heat pads, hot water bottles, carbon-fiber resistive heating blankets, and charcoal fuelled heat pacs are commonly used and advised (13, 14, 26, 28, 29, 32). There are some laboratory studies (33-37) evaluating such field-applicable devices (portable, not requiring external electrical power supply), but to this author's knowledge, only two randomized clinical trials have evaluated the effectiveness of such heat sources in the field (38, 39).

As part of primary trauma care, it is important to have accurate measures to evaluate the thermoregulatory state of the patient, both upon arrival of the rescue personnel and during prehospital treatment and transport. In the field, especially in harsh ambient conditions, this is often hard to achieve (14, 15). Measuring body core temperature as well as skin temperature might be difficult and measuring oxygen consumption to assess shivering is, in most clinical scenarios, not possible. Thus, alternative measures, such as subjective judgement scales for assessment of the thermal state of patients, might be of considerable importance in such scenarios, both for an initial assessment of the patient and for evaluation of the treatment provided. The judgement scales must be reliable and valid.

This thesis primarily focuses on protection and treatment of hypothermia in prehospital trauma care, the emphasis being evaluation of active warming intervention regarding impact on thermoregulation. Subjective judgement scales for assessment of the thermal state of patients in a cold environment is also studied.

Historical notes

Throughout history, accidental hypothermia is perhaps best documented in military history, where harsh ambient conditions have played a major role for the outcome of numerous military campaigns. The list is long and distinguished.

Hannibal lost about 20000 of his 46000 soldiers in 218 B.C when crossing the Pyrenees and Alps on his way towards Rome.

In 1718 Carl Gustaf Armfeldt and his army were caught in a blizzard crossing the mountains on their return from Norway to Sweden. Only 1700 of the 5100 soldiers survived.

In 1812 Napoleon lost much of his army because of the cold while attempting to invade Moscow.

During the First World War 115000 British soldiers suffered local cold injuries or trench foot.

During the Second World War 200000 German soldiers were disabled because of cold injuries.

When writing about hypothermia from a historical perspective, it is also important to mention the horrible crimes committed under the guise of medical experiments on prisoners in German concentration camps during World War II. To establish the most effective treatment for victims of immersion, Germans conducted hypothermia experiments at the Dachau concentration camp in 1942 and 1943. Immediately after, the American Chief of Counsel for War Crimes prepared a 228 page report after investigating the records of the experiments. This report, referred to as the Alexander report (author: the American psychiatrist Leo Alexander), was cited by some authors during the first decades after the war. This is considered by most authors, including this author, strongly, ethically reprehensible. In addition, citations are inappropriate on scientific grounds (40) [Berger 1990].

Definitions of hypothermia

Traditionally, hypothermia has been defined as body core temperature < 35 ℃ and further classified into levels of severity based on the physiological changes that occur because of decreased body core temperature (13-16). The levels are mild (32 – 35 ℃), moderate (28 – 32 ℃), severe (20 – 28 ℃), and profound hypothermia (< 20 ℃). These definitions were introduced to describe hypothermia resulting from environmental exposure. However, more recently, due to the poor prognosis of the combination of trauma and hypothermia, a revised classification has been developed for use in trauma care (27). In this classification, hypothermia is defined as body core temperature < 36 ℃ and subsequently as 34 – 36 ℃ for mild, 32 – 34 ℃ for moderate, and < 32 ℃ for severe hypothermia. Furthermore, in this context, it is

important to stress that thermoregulatory responses are induced long before body core temperature declines below the level defined as hypothermia. Beyond the two classifications mentioned above, to be more applicable in a prehospital rescue scenario, yet another method of staging hypothermic patients is recommended by the International Commission for Alpine Rescue (ICAR) (28). Using this method, degree of consciousness, presence or absence of shivering, cardiac activity, and body core temperature are taken into consideration when deciding hypothermia level. Table 1.1.

Table 1. Classifications of hypothermia based on body core temperature.

Hypothermia level (ICAR level)	Traditional classification	Trauma classification	ICAR classification
Mild (I)	35 – 32 ºC	36 – 34 ºC	35 – 32 ºC
Moderate (II)	32 – 28 ºC	34 – 32 ºC	32 – 28 ºC
Severe (III)	28 – 20 ºC	< 32 ºC	28 – 24 ºC
Profound (IV)	< 20 ºC		24 – 15 ºC
(V)			< 15 ºC

Cold exposure

The human body maintains an average core temperature near 37 °C in various thermal conditions (41). However, extreme thermal exposure as well as certain medical conditions can lead rapidly to dangerous deterioration of body core temperature. Because the speed of chemical reactions vary with temperature and because the enzyme systems of the body have narrow temperature ranges in which their function is optimal, normal body function depends on finetuned temperature regulation. A deviation of about 2 °C above or below normal body core temperature is well tolerated but a deviation of about 3 °C begins to threaten normal body function.

Thermoregulatory mechanisms are not fully developed until after puberty and from about seventy years of age thermoregulatory capacity is decreased, having the consequence that children and elderly are more vulnerable to cold stress (41).

There are also differences between men and women (41). Women, as a group, have, compared to men, a greater surface-area-to-mass ratio, a greater percentage of subcutaneous and total body fat, a greater resting vasoconstriction in hands and feet, a higher setpoint for cutaneous vasodilation and onset of sweating, and also cyclic hormonal changes that influence thermoregulation. However, when individual differences are accounted for, thermoregulatory gender differences are negligible.

Heat exchange

The human body maintains core temperature by a fine balance between heat gain and heat loss. When heat gain equals heat loss, a state of thermoneutrality exists, but if heat loss exceeds heat gain, there is a risk of whole body cooling and hypothermia (13, 14, 16, 41-43).

Factors governing heat exchange can be described by the heat balance equation:

$$H_{tot} = \pm H_d \pm H_c \pm H_r \pm H_e$$

where

H_{tot} = total metabolic heat production
H_d = conductive heat exchange
H_c = convective heat exchange
H_r = radiative heat exchange
H_e = evaporative heat exchange

Total metabolic heat production, which is about 70 W/m^2 (basal metabolism) in a resting 70 kg man, increases with voluntary physical activity and involuntary muscle contractions (shivering).

Conductive heat exchange means heat transfer by direct contact to a surrounding medium, for example air, water, or solid ground (13, 41, 44, 45). The amount of heat flow is dependent on physical characteristics of the surrounding medium, temperature gradients, and the contact surface area. Air conducts heat poorly. Water conducts heat approximately twenty five times, and metals up to ten thousand times, greater than air.

Convective heat exchange means heat transfer by movements of the boundary layer of the surrounding medium (air or water) (13, 41, 44, 45). The amount of heat exchange is mainly dependent on the relative velocity of the surrounding medium.

Radiative heat exchange means heat transfer by infrared electromagnetic waves to objects, for example, cold stone walls of a building (13, 41, 44, 45). The amount of heat transfer is dependent on the physical characteristics of the objects and temperature gradients.

Evaporative heat exchange means heat transfer from evaporation of water on the skin surface or the respiratory tract, where the amount of heat exchange is dependent on the amount of water evaporated (13, 41, 44, 45).

Heat loss is caused primarily by convection, which is greatly increased by wind or movements (13, 41, 44, 45). To a smaller extent, heat is also lost through radiation to cold objects in the surrounding environment, or to the clear sky, and by

evaporative and convective heat loss from the airways. Sweating and evaporative heat loss from the skin is often minimal in cold environments, but could be considerable in cases of wet clothing or skin due to immersion or previous physical activity. In addition, if immersed, lying on the ground or in direct contact with a cold surface, conductive heat loss will be significant.

Thermophysiological reactions to cold exposure

Thermal receptors are widely distributed, especially in the skin, but also in the abdominal viscera, the spinal cord, extrahypothalamic as well as hypothalamic portions of the brain (13, 16, 41-43). The information from both peripheral and central receptors is integrated in the preoptic nucleus – anterior hypothalamic area of the brain, which is considered the center of thermoregulation. In response to cooling of peripheral or central receptors or both peripheral and central receptors, a sympathetic mediated thermoregulatory response is evoked, rendering vasoconstriction to preserve heat within the body core and shivering to increase endogenous metabolic heat production.

Vasoconstriction is primarily due to the closing of the arteriovenous anastomoses of the hands and feet resulting in decreased blood flow in the entire extremity (13, 41, 42). During full vasoconstriction, blood flow through the fingers and toes can decrease up to one hundredfold, from 80 -90 ml/min/100ml of tissue during full vasodilation to 0,5 – 1,0 ml/min/100ml of tissue during massive vasoconstriction (13). In addition to central regulation, tissue cooling directly affects vasoconstriction by increasing cutaneous blood vessel sensitivity to cathecolamines.

In shivering, thermogenesis is due to involuntary and unsyncronized muscle contractions (13, 41, 42). At maximum shivering, endogenous heat production can be increased by as much as five times from resting levels (46). In mild hypothermia (32 – 35 ℃), thermoregulatory responses are still intact, but if body core temperature declines even further, thermoregulation, and thereby shivering, starts to fail and at about 30 - 32 °C the shivering response is lost.

As a consequence of cold-induced peripheral vasoconstriction, temperature in peripheral parts of the body starts to decline long before body core temperature is affected (14, 41). Following substantial cold exposure, there is temperature equalization between the warm body core and the cold peripheral parts, contributing to a continuous fall in body core temperature, designated the afterdrop phenomenon. Main contributing factors are conductive temperature equilibration between the colder periphery and the warmer body core and circulatory changes involving counter current cooling of warm blood circulating cold, previously vasoconstricted peripheral tissues. The magnitude of the afterdrop, which can be considerable and amount to several degrees, is dependent on temperature gradients in the tissues, peripheral circulation, and endogenous heat production.
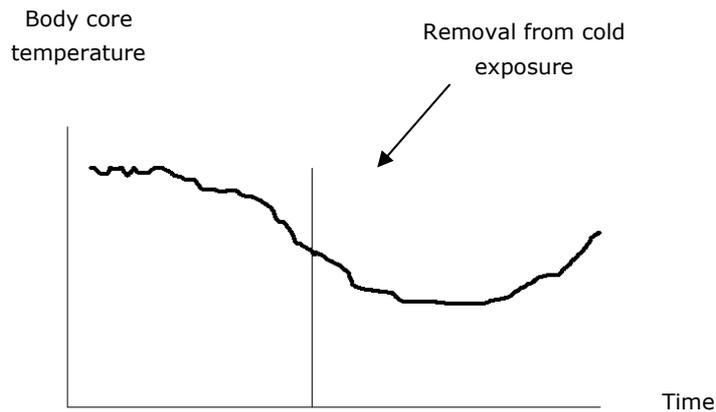
Figure 1. Afterdrop.

In trauma patients, thermoregulation is often impaired, resulting in an increased vulnerability to cold exposure (13, 14, 16, 41). Injuries to the nervous system might affect both vasoconstriction and shivering because of both central and peripheral effects. Muscle injuries locally affect shivering ability. The administration of analgesics, anaesthetics or both induces vasodilation and impedes shivering. Although lipid and protein work as alternative fuels to carbohydrates in shivering thermogenesis, malnutritive states reduce shivering capacity.

Psychological reactions to cold exposure

Psychological reactions to cold exposure is divided into thermal comfort or discomfort and thermal sensation, where the fomer drives behaviour, while the latter drives autonomic thermoregulation, described above (47). However, in clinical reality it is difficult to differentiate between those modalities. Because of thermal comfort is driven by both physiological and psychological variables, whereas thermal sensation is driven by only physiological variables, in this thesis, psychological reactions to cold exposure is described as thermal comfort.

According to the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE), thermal comfort is described as a state of mind that expresses satisfaction with the surrounding environment. Physiological variables affecting thermal comfort include information from brain, body core and skin temperature sensors as well as vasoconstriction and shivering (48-52). The psychological variables include previous experience with cold exposure, state of mind, social context, and behaviour (53).

Patophysiology and clinical presentation of hypothermia

The following section outlines, the pathophysiological reactions and clinical picture due to cold stress and hypothermia. In this context, attentiveness to the occurrence of considerable individual differences is important. There are also differences dependent on whether hypothermia has developed rapidly (acute hypothermia) or over a longer period (chronic hypothermia) (14).

Respiratory and cardiovasculatory changes. In response to the cold-induced sympathetic mediated thermoregulatory stress response, respiratory and cardiac work is increased. Shivering thermogenesis increases oxygen demand and peripheral vasoconstriction raises systemic blood pressure which further escalates cardiac workload. (13, 16, 41, 42, 46).

As body core temperature declines, spontaneous depolarization of the pacemaker cells of the sinus node decreases, resulting in atropine-resistant bradycardia (16). Because hypothermia increases duration of action potentials, and because the His-Purkinje system of the heart is more sensitive to cold than the myocardium itself, decelerated conduction might cause re-entry currents, resulting in ventricular arrhythmias. PR, QRS, and QT intervals are prolonged (54-56). However, not pathognomonic of hypothermia, Osborn or J-waves, a distinctive deflection occuring at the QRS-ST junction, are common in hypothermic patients. Osborn waves might pose a diagnostic difficulty, because they, when pronounced, resemble the elevation of the ST segment also seen in transmural myocardial infarction. Atrial as well as ventricular arrhythmias are encountered at body core temperatures below 32 °C and spontaneous ventricular fibrillation is seen below 25 °C (15). The risk of developing cardiac arrhythmias is increased by hypovolemia, tissue hypoxia, electrolyte and acid balance disturbances, as well as rough handling of the hypothermic patient.

In chronic hypothermia, peripheral vasoconstriction, resulting in increased central blood volume, will lead to fluid extravasation and tissue oedema, including lung oedema and also to increased diuresis due to raised renal perfusion pressure (14). Thus, patients exposed to prolonged cold stress should be considered hypovolemic, which is important to account for when peripheral circulation returns to normal during rewarming.

As for the heart rate, respiratory rate also declines with body core tempreature. In severely hypothermic patients, breathing may be hard to detect since it is very slow and shallow.

Neurological changes. The cold-induced sympathetic mediated stress response results in an initial increase in cerebral metabolism, but as body core temperature drops by more than 1 °C, cerebral metabolism will decline (15). This will result in an increasingly deteriorated mental status, presented as impaired memory and judgement, slurred speech, and decreased level of consciousness. Most patients are unconscious at a body core temperature below 30 °C (16).

Muscle performance in the extremities is impaired both because of local tissue cooling as a consequence of vasoconstriction and neurological malfunction. These combined effects pose a substantial risk for development of local cold injuries (57, 58).

Blood chemistry changes. Haematocrit and also blood viscosity rises because of fluid extravasation and increased diuresis (15, 16). Platelet count is lowered due to bone marrow depression and sequestration in the spleen and liver. Platelet adhesion and aggregation is impaired. Coagulation enzyme activity is reduced to a level equivalent to 50 % of clotting factor deficiency at temperatures below 33 °C (59, 60). Already mild hypothermia induces a general coagulopathy (61, 62) which can be reversed by active warming (63).

Leukopenia, also due to bone marrow depression and sequestrian of leukocytes in the spleen and liver, together with a general immune system depression, weakens the resistance to infections(16).

Serum electrolytes fluctuate over time and with body core temperature during cooling and rewarming (14, 16). Hypokalaemia due to an intracellular redistribution of potassium, as well as hyperkalaemia, due to assumed cellular membrane dysfunction, is seen. Hyponatremia is common in chronic hypothermia due to osmolar diuresis.

Neutral pH varies with temperature and rises with body core cooling (14). Respiratory alkalosis due to initial hyperventilation is common after sudden immersion in cold water. This is followed by respiratory and metabolic acidosis due to respiratory depression and also ketogenesis and lactate formation from shivering, reduced cardiac output and tissue hypoxia due to impaired peripheral circulation.

Initially, blood glucose level rises because of glycogenolysis caused by the cold-induced stress response (14, 16). During prolonged cold stress glycogen stores will be depleted and hypoglycaemia might develop due to shivering and the cold-induced glycosuria.

Prehospital protection and treatment of hypothermia

Actions to reduce cold stress and prevent further heat loss are an important and integrated part of prehospital trauma care. Initial measures should be taken to shelter, remove wet clothing, and insulate the patient from ambient weather conditions and ground chill. Adequate windproof and waterproof insulation ensembles (passive warming) are imperative. In addition, depending on the physiological status of the patient including body core temperature, available resources and expected duration of evacuation, the application of heat (active warming) is recommended by most authors as protection from further cooling during treatment and transport to definitive care (13-15, 28-32). In a prehospital setting the primary objective of active warming is to reduce cold stress and further

cooling, not to rewarm the patient. Available, field applicable, heat sources all have limited heating capacity, rendering rapid rewarming in the field impossible. Too rapid rewarming, implying possible development of fluid, acid-base or electrolyte imbalances that would be difficult to control in the field, is therefore not considered a problem (14, 15, 29).

Several studies on mildly hypothermic shivering subjects have found that exogenous skin heating attenuates shivering heat production by an amount equivalent to the heat donated (34, 37, 64). Thus, in a mildly hypothermic, shivering patient, active external rewarming generally does not decrease afterdrop or increase the rewarming rate more than shivering thermogenesis. However, thermogenesis from shivering during passive warming alone can result in significant anaerobic metabolism and lactic acidosis, and active external warming might therefore present treatment advantages of decreased respiratory and cardiac workload, preserved substrate availability, and increased comfort. Overall, additional active warming should be considered also when treating mildly hypothermic trauma patients.

When shivering is diminished or absent, as in moderate to severe hypothermia, or is otherwise impaired because of the overall medical condition of the patient, active external or internal warming is required. Otherwise afterdrop will continue and little or no warming will occur (35, 36, 65, 66).

Active external warming

To be field applicable, warming modalities need to be portable and require no external electrical power supply. In a report summarizing survey responses from from 41 Mountain Rescue Association teams (67) the active warming methods most frequently used were warm IV fluids, chemical heat pads, body-to-body warming, charcoal heaters, and warm air or oxygen inhalation. Some of these methods are extensively studied, others are not. Regardless of the warming method, most of the studies are laboratory studies, only a few have been conducted in a prehospital environment, which might be a considerable limitation when making decisions about prehospital trauma care.

In the following section, field applicable warming methods, i.e. warming methods that are portable and require no external electrical power supply, are described.

Exercise. Moderately to severly hypothermic patients are likely to be physically and metabolically exhausted and have an altered level of consciousness. In these patients, movements might also induce ventricular fibrillation (13-16). Thus, excercise is not a treatment alternative. However, in mild hypothermia, increasing endogenous heat production by exercise has been suggested for warming purposes.

In one study on subjects cooled to 33 °C, Giesbrecht et al. (34) found that the post cooling rewarming rate for exercise was significantly higher than for shivering, but not higher than for external heat. However, exercise, as well as external heat,

significantly increased both length and amount of afterdrop compared to shivering, resulting in no difference between the three treatment alternatives regarding total recovery time. In another study on shivering subjects, Giesbrecht et al (68) postponed exercise until afterdrop was complete and found that during exercise there was a second afterdrop of similiar, but not greater, magnitude as during the initial shivering period.

Body-to-body warming. Direct body-to-body contact with a minimally clothed euthermic heat donor used to be widely recommended for warming hypothermic patients in the field (69-71). As it is also shown for other active external heat sources (34, 37), body-to-body warming has no beneficial effect on body core warming compared to shivering thermogenesis alone (64, 72). However, if shivering is diminished or absent, as in moderate to severe hypothermia, or otherwise impaired because of the overall medical condition of the patient, heat donated by body-to-body contact will, as other external heat sources, increase heat gain (36).

Heat packs. Warm water bottles, chemical heat pads, or the HeatPac®; a charcoal heater (Normeca AS, Oslo, Norway), are widely used (67) for active external warming in the field. Such devices are portable and easy to handle for the rescue personnel, but heat content is limited. In order facilitate heat transfer, heat sources should be applied in proximity (precautions should be taken to avoid burn injuries) to the skin on areas with high heat transfer such as the chest (36), neck, axillae, and groins.

In mildly hypothermic shivering subjects, laboratory studies of the Heat Pac® (34, 37) have shown no beneficial effect on body core rewarming compared to shivering thermogenesis alone. This is in accordance with studies on other active external warming modalities (64, 72). In one laboratory study on human subjects, where shivering was suppressed pharmacologically to resemble moderate to severe hypothermia, the HeatPac® was significantly more efficient than body-to-body rewarming in minimizing afterdrop and facilitating body core rewarming (36). The HeatPac® consists of a combustion chamber, charcoal fuel, and a branched; reinforced, but flexible, heating duct and produces 250 W of heat. It is placed on the patient's chest and the heating ducts are applied dorsally over the shoulders and then anteriorly under the axillae crossing over the lower chest. Total skin contact surface area of the chamber (23 × 12 × 6 cm, 1100 g) and ducts is about 1500 cm2. Because there are no clinical studies using the HeatPac®, practical aspects, such as ignition of the charcoal fuel in field conditions and the potential risk of the charcoal fuel burning in proximity to or even inside vehicles, has not been evaluated. However, a safety concern regarding carbon monoxide contamination has been presented (37).

In a prehospital clinical randomized trial by Watts et al (39), chemical heat pads were applied in at least two locations (on top of the head, under the patient against the lower back, or under either axilla with the hot pack against the chest wall) This treatment was compared to five other treatment alternatives (no intervention, passive rewarming, reflective blankets, warmed IV fluids, and warmed IV fluid plus

reflective blanket). Trauma patients who received hotpack warming showed a mean increase in body core temperature during transport (0.7 °C) (measure of variation not reported), while all other groups (no intervention, passive warming, reflective blankets, warmed IV fluids, warmed IV fluid plus reflective blanket) showed a mean decrease in temperature during transport (- 0.2 °C to - 0.4 °C), the difference was statistically significant. The chemical heat pad Hot Cycle 1 (Sign Manufacturing Corporation, Fairfield CA) is activated by breaking an internal chamber and it reaching a temperature of 54.5 °C. To avoid burn injuries of the skin the chemical heat pads were rolled in towels before application.

Resistive heating. In a laboratory study on human subjects by Greif et al (35), where shivering was suppressed pharmacologically to resemble moderate to severe hypothermia, a carbon-fiber resistive heating blanket was evaluated. Both total body heat content and body core rewarming rate were increased compared to passive warming alone. In contrast to the passive warming group that presented a small, although not statistically significant afterdrop, there was no afterdrop in the carbon-fiber resistive heating blanket group. The carbon-fiber resistive heating blanket measures 80 x 200 cm, with the actively heated section being 40 x 148 cm. The batteries weigh 0.5 kg, each lasting 30 – 40 minutes.

In a prehospital clinical randomized trial by Kober et al (38)[Kober 2001] the same carbon-fiber resistive heating blanket was compared to passive warming alone. In trauma patients receiving passive warming alone mean body core temperature decreased by 0.4 °C/h (95% CI; 0.3 – 0.5 °C/h), whereas in patients receiving additional carbon-fiber resistive heating, mean body core temperature increased by 0.8 °C/h (95% CI; 0.7 – 0.9 °C/h), the difference between groups being statistically significant.

Inhalation warming. The effectiveness of inhalation rewarming has been somewhat equivocal. In some studies (73-76), beneficial effects on body core temperature have been reported, whereas in other (37, 77, 78), including one study on non-shivering human subjects (66), no body core warming advantages have been found. Benefits of inhalation warming such as rehydration, stimulation of mucociliary activity in the respiratory tract and direct heat transfer from the upper airways to the hypothalamus, brain stem, and other brain structures have been suggested (75).

Warm intravenous fluids. Intravenous fluids should be heated to 40 - 42 °C during hypothermia resuscitations (32). Cold fluid resuscitation of hypovolemic patients can induce hypothermia, infusion warming devices are therefore mandatory during massive volume resuscitations (79, 80).

Prehospital monitoring

To have accurate measures to evaluate the thermal state of patients in the prehospital setting is vitally important. In the field, especially in harsh ambient conditions, this is often hard to achieve (41). Adequate measurements of body core temperature as well as skin temperature might be difficult to obtain (14, 41), and measuring oxygen consumption for assessment of shivering is, in most rescue scenarios, not possible.

Thus, alternative measures such as subjective judgement scales for assessment of the patient's thermal state might be of considerable importance, both for an initial assessment of the patient and for evaluation of the treatment provided.

Body core temperature

The temperature of the pulmonary artery is considered the best reference temperature for deep body core temperature (41). However, pulmonary artery catheterization is not an option in the field.

In the following section, non-invasive generally accepted sites for measuring body core temperature are listed, all of various degrees of usefulness in the field.

Oesophagus. Oesophageal temperature is obtained by placing a temperature probe into the distal portion of the oesophagus, usually via nasal passage, to the level of the heart (81). The proximity of the oesophagus to the descending aorta and the left auricle is the anatomical basis for an accurate measurement of deep body core temperature. It is an accurate method for deep body core temperature (82, 83). However, this method is, for educational and practical reasons, also not an option in many prehospital rescue scenarios.

Closed ear canal. Closed ear canal temperature is obtained by placing a temperature probe in the mid to distal portion of the ear canal, which is then sealed from the ambient environment by insulation covering the ear. The proximity of the ear canal to the internal carotid artery makes it an ideal site for measuring body core temperature. This method has been shown to correlate well with oesophageal temperature (84, 85). Although these results are mainly based on data from indoor operating theatre environments, Walpoth et al. (84) have shown that, if properly sealed from the ambient air, closed ear canal temperature is also reliable in sub-zero and wind conditions. As the reliability of closed ear canal temperature is dependent on positioning within the ear canal, there is a risk of false low recordings. However, if measurements are made over a period of time with the probe left in position in the ear canal, which is standard procedure, temperature change over that period of time should be reliable.

Tympanic membrane. Tympanic membrane temperature is obtained by reflecting infrared electromagnetic waves from the tympanic membrane and the ear canal. It is a simple field applicable method but has been shown not reliable (86-88).

Rectum. Rectal temperature is an accurate method for measuring deep body core temperature in steady state conditions (41). However, when deep body core temperature changes, there is a delay in rectal temperature change.

Urinary bladder. Urinary bladder temperature is an accurate method for measuring deep body core temperature and as many patients need a urinary catheter, the catheter can be used for measuring temperature (89).

Oral cavity. Oral temperature is obtained by placing the probe in the sublingual pocket which is well perfused. Provided that the patients can keep their mouths closed, it is a simple field applicable method, but has also been shown not reliable (88).

Subjective judgement scales for assessment of the thermal state of the patient

The most common single item judgement scales are Visual Analouge Scales (VAS), Numerical Rating Scales (NRS) and Verbal Rating Scales (VRS). A VAS consists of a visual line, usually 100 mm long, where the ends of that line are labeled with descriptions for the extremes of the studied modality. The respondent places a mark on the line representing his or her level of experienced intensity in relation to the described extremes. Instead of a visual line, a NRS consists of a range of numbers, usually 0 – 10, and a VRS consists of a list of words or phrases, describing various degrees of the studied modality.

The international standard BS EN ISO 10551:2001 (90) outlays general principles for construction of subjective judgement scales for assessment of the influence of the environment on the thermal state of the patient. These general principles, mainly used for indoor or near isothermal environments, recommend symmetrical 7 to 9-degree rating scales comprising a central indifference point and two times 3 or 4 degrees of increasing intensity for both hot and cold. The two most well-known scales are the Bedford scale (91) and the ASHRAE scale (92). In 1936 Bedford (91) collected data on almost 2000 industrial workers to correlate subjective judgements of their thermal comfort to objective measurements of the thermal environment. The responses of the workers were measured according to a seven degree VRS, called the Bedford scale, and to be able to use statistics on the data, numerical values were assigned to the different levels of the scale. In 1971 Rohles et al. (92) collected data on 1600 college students to correlate subjective judgement of thermal comfort to ambient air temperature, humidity, length of exposure and gender. The scale developed for those studies is also a VRS, called the ASHRAE scale.

OBJECTIVES

The overall objective of this thesis was to evaluate prehospital active external warming intervention regarding impact on thermophysiological and psycological reactions. Reliability and validity of the Cold Discomfort Scale (CDS), a subjective judgement scale for assessment of the thermal state of patients in a cold environment was also studied.

Specific objectives were to evaluate:

the warming effectiveness of three different portable heat sources, none of them requiring external electrical power supply, and spontaneous warming (control condition) regarding their impact on post-cooling body core temperature including afterdrop in a laboratory setting (study I).

external warming intervention, using a previously evaluated (study I) heat source as additional treatment to a standard protocol of passive warming in a prehospital clinical setting, both during transport and treatment in a heated road ambulance or helicopter (study II) and during outdoor field treatment and transport (study III), regarding impact on body core temperature (study II) and thermal comfort (study II and III).

the CDS, a subjective judgement scale for assessment of the thermal state of patients in a cold environment, regarding reliability, defined as test – retest stability, and criterion validity, defined as ability to detect changes in cumulative cold stress (study IV)
.

METHODS

Because of small study populations, especially in the laboratory studies, where study populations also are relatively homogenous, the limited external validity must be considerd when conclusions are drawn based on the results of these studies.

Table 2. Overall methods.

	Study I	Study II	Study III	Study IV
Environment	Laboratory	Prehospital transport	Prehospital scene of injury	Laboratory
Study design	Experimental controlled trial	Randomized clinical trial	Randomized clinical trial	Experimental controlled trial
Study population	n = 5	n = 48	n = 20	n = 22
Intervention	Comparison of three different heat sources and spontaneous warming	Passive warming alone vs. Passive warming + active warming	Passive warming alone vs. Passive warming + active warming	
Primary outcome	Body core temperature	Body core temperature, cold discomfort	Cold discomfort	Cold discomfort
Statistical analysis	Non-parametric statistics	Non-parametric statistics	Non-parametric statistics	Non-parametric statistics

Laboratory trials

Measurements on shivering subjects

Study design
The CDS was evaluated in a laboratory environment regarding reliability, defined as test-retest stability and criterion validity, which is defined as the ability to detect changes in cold discomfort due to changes in cumulative cold stress (study IV). Twentytwo healthy subjects participated in two trials each, on two separate occasions, at about the same time of day, approximately one week apart. Conditions were identical during both trials, subjects were exposed to -20 °C for 60 minutes wearing only light clothing. CDS ratings were recorded every five minutes, both during 10 minutes of base line data collection and during the 60 minutes of cold exposure. The CDS is a subjective judgement scale for assessment of the thermal state of patients in a cold environment. It is designed as a NRS, where the subjects assess the thermal state of their whole body, not specific body parts, and provide integer values from 0 to 10, where 0 means not being cold at all and 10 means being unbearably cold.

Statistical analysis
Pre-study calculations indicated a minimal sample size of 18 to detect a difference in Cold Discomfort Scale ratings of 2 or more IQR; 2) presupposed 80% statistical power at an α-level of 0.05. Reliability of the CDS was analysed for test-retest stability using weighted kappa coefficient, comparing median CDS ratings between the two trials. This included all the measurements made every five minutes and also, separately, every single measurement.

Criterion validity was analysed by comparing median CDS ratings over a moving 30 minutes interval (5-35 minutes; 10-40 minutes; 15-45 minutes etc) using Wilcoxon signed ranks test. Statistical significance was defined as $p < 0.05$, and, in analysis of criterion validity, after correction for multiple comparisons according to Bonferroni as $p < 0.008$ (two-sided).

Methodological considerations
Because the test and retest were conducted in a laboratory environment, ambient conditions were controlled and identical for both the test and retest. Subjects also served as their own controls. However, it is always difficult to achieve identical conditions in a test-retest design when measuring subjective parameters. Even though all arrangements are made to match, the subjects might react differently to the same cold exposure at two different occasions. There might also be a habituation which can either increase or decrease the sensitivity to the exposure.

Evaluation of criterion validity is dependent on how it is defined and conclusions about criterion validity therefore, must be based on that definition. It might

sometimes be hard to appraise if the chosen definition is relevant, which then complicates interpretation of results.

In this study, criterion validity was defined as the ability to detect changes in cold discomfort due to changes in cumulative cold stress by subjects exposed to -20 °C wearing only light clothing, over a moving 30-minute interval. The time interval was chosen based upon what, under prevailing conditions, was appraised a clinically significant change in cumulative cold stress. A moving 30-minute interval was chosen in attempt to cover early as well as late changes within the evaluation period of 60 minutes.

Measurements on non-shivering hypothermic subjects

Study design
In a laboratory environment, three different portable exogenous heat sources, none of them requiring external electrical power supply, and spontaneous warming (control condition) were compared (study I). Five human subjects participated in four trials each, one trial for every condition, thereby serving as their own controls. To mimic moderate to severe hypothermia and also to achieve equal conditions of endogenous heat production for each condition, shivering was suppressed pharmacologically using a human model previously evaluated in several studies (36, 65, 66). An initial cooling phase, in which subjects were exposed to 8 ° C water for 10-30 minutes, was followed by a 120-minutes treatment phase including passive warming with the addition of either one of three exogenous heat sources or spontaneous warming. Prior to the trials, 30 mg of orally administered buspirone, and during the last 10 minutes of the cooling phase, and also if needed during rewarming, intravenously administered meperidine to a maximum cumulative dose of 3,5 mg/kg, was used to supress shivering. Oesophageal temperature (81-83), skin heat transfer, skin temperature, oxygen consumption, respiratory rate and heart rate were continuously monitored and recorded during the trials. The exogenous heat sources applied to the chest and upper back, were a charcoal heater, HeatPac®, (Normeca AS, Oslo, Norway), two chemical heating pads (Dorcas AB, Skattkarr, Sweden) and two flexible water bags (Mountain Safety Research, Seattle, WA) each filled with 2 litres of 55 °C water replenished every 20 minutes.

Statistical analysis
Continuous data, considered normally distributed, were initially compared using repeated measures analysis of variance (ANOVA). If statistical significance was revealed, Student´s t-test for pair-wise post hoc analysis with Fisher's protected least significant difference (PLSD) for multiple comparisons test was used to identify and quantify differences between individual conditions. Statistical significance was defined as $p < 0.05$ (two-sided).

Methodological considerations

The human model, in which shivering is suppressed pharmacologically, is designed to thermophysiologically mimic a scenario of moderate to severe hypothermia. It has been evaluated in several studies (36, 65, 66). Beyond the ability to evaluate different treatment alternatives in a thermophysiologically hypothermic subject, which, for safety reasons, would otherwise be impossible, this model also makes comparisons between treatment alternatives almost perfectly fair regarding influence of endogenous heat production. This is because endogenous heat production is kept at a constantly low rate and also is controlled for. If there are differences in endogenous heat production, this will be revealed and impact on the overall result will be possible to analyse.

The human model for severe hypothermia eliminates and controls for shivering. However, it does not account for other physiological or psychological changes that come with moderate to severe hypothermia such as, respiratory, circulatory, neurological, and blood chemistry changes.

In this study, because of safety considerations, the amount of meperidine administered to inhibit shivering was limited to a cumulative dose of 3.5 mg/kg for each trial. Therefore, the cooling phase had to be adjusted for the subjects' body composition, resulting in a relatively longer cooling phase in subjects with a higher percentage of body fat. However, because subjects served as their own control and the cooling phase was identical for each subject for all conditions, this should have very limited impact on the results.

Parametric statistical tests were used for ratio and interval scale data, despite small study population, because data were considered normally distributed. However, considering the small study population, the use of parametric statistics is controversial and therefore, results are also presented for non-parametric statistics using Friedman test and Wilcoxon signed rank test instead of ANOVA and PLSD respectively.

Clinical trials

Study design

In two randomized clinical trials, chemical heat pads (Dorcas AB, Skattkarr, Sweden), the same chemical heat pads as previously evaluated on non-shivering subjects (study I) were used to evaluate the impact of active warming on thermoregulation in mildly hypothermic trauma patients with preserved shivering capacity during transport and treatment in a heated road ambulance or helicopter (study II) or during outdoor field treatment and transport by ski patrol units (study III). Sequential trauma patients, age ≥ 18 years, who had sustained an outdoor injury, were enrolled. Patients were excluded if initial level of consciousness was affected, (Glasgow Coma Scale < 15), if duration of transport or treatment was expected to be shorter than 10 minutes, if active warming already had been initiated,

if they had been taken indoors for more than 10 minutes before ambulance or ski patrol unit arrival or had an initial cold discomfort rating ≤ 2.

If enrolled, patients were randomized to either passive warming with blankets according to an existing protocol alone (study II: n = 22, study III n = 9) or to passive warming with blankets according to the existing protocol with the addition of one chemical heat pad applied on the anterior chest (study II: n = 26: study III: n = 11). In study II, after loading into the ambulance or helicopter, initial measurements of closed ear canal temperature (84, 85), respiratory rate, heart rate, blood pressure, and patients' subjective sensation of thermal comfort according to the CDS were made. In study III, at the scene of injury, an initial measurement of patients' subjective sensation of thermal comfort according to the CDS was made. In both studies initial measurements were made before eventual application of the chemical heat pad. Measurements were then continuously made every 30 minutes and at the receiving hospital (study II), first aid centre or EMS unit arrival (study III).

Statistical analysis

Pre-study sample size calculations, estimating a difference in body core temperature of ≥ 0.5 °C and in CDS ratings of ≥ 2 between the two intervention groups, an alpha of 0.05 and a beta of 0.10 revealed a minimum study population of 42 patients. This was for both studies II and III since CDS was the restricting variable.

For comparison between groups the Mann Whitney U test was used for interval and ordinal data and Chi square or Fisher's exact test for nominal data. In addition, CDS ratings were characterized as increased, unchanged or decreased and the difference between groups was analysed using Fisher's exact test. For comparisons within groups, Wilcoxon signed rank test was used for interval and ordinal data. Statistical significance was defined as $p < 0.05$ (two-sided).

Methodological considerations

The rescue personnel used the standard protocol for all patients; participation in the studies involved no interfering instructions. Application of the chemical heat pad to the anterior thorax for those assigned to additional active warming was the only difference between groups. This study design thus enables a fair comparison between study groups. The active warming intervention being evaluated in a proper environment must also be considered a great strength of the study. A laboratory environment results in a high degree of control when conducting the study, including control of evaluated intervention and recordings. This might be more difficult to achieve in a prehospital clinical setting and it is important to be aware of such possible sources of errors when interpreting results. Although, if considered, that must not entail a limitation.

Closed ear canal temperature (84, 85) was used for measurement of body core temperature. Because the absolute value of closed ear canal temperature is somewhat dependent on placement within the ear canal, those values might not be

completely accurate. However, if the ear canal is properly insulated from the ambient environment and if the temperature sensor is kept in the same place during the entire trial, recordings of temperature changes will be accurate.

CDS was used for assessment of thermal comfort. The reliability (defined as test – retest stability) and criterion validity (defined as ability to detect an increase in cumulative cold stress) of CDS is discussed below.

In study II, fourteen day and night manned road ambulance units and one helicopter ambulance unit participated during the entire, or part, of an inclusion period of two and a half years. There are 125 000 inhabitants in the catchment area of the participating ambulance units and, due to tourism, the population increases during winter time. In study III, ski patrols from three ski resorts in the northern parts of Sweden participated in the study during two consecutive winter seasons. There were a total number of 1 803 000, person-ski days during that period. Still, the study population was relatively small, which might be due to several factors. The compliance of the rescue personnel to include patients in the study might have been low. The doctors in charge of the studies, Lundgren and Henriksson, visited every unit about twice a year and above that carried out monthly phone calls to make sure the study proceeded as planned, but that might not have been adequate.

The inclusion and exclusion criteria were also somewhat narrow, which also might have had an influence on the size of the study population. Reports from the ambulance personnel indicated that many of the patients injured outside had already been moved inside, while waiting for the ambulance to arrive and, due to long distances, the time limit of ten minutes of indoor stay or active warming treatment was exceeded. Reports from ski patrol units indicated that many of the patients injured and in need of treatment on the ski slopes were rapidly transported to an indoor medical facility, thereby outdoor treatment and transport time were less than the required 10 minutes.

Patients having an initial CDS rating of ≤ 2 were also excluded since they were not considered cold stressed.

However, presented inclusion and exclusion criteria were considered necessary to limit the study population to those actually considered cold stressed, even if some patients who also could have been considered cold stressed might have been left out, and the resulting consequenses was a small study population.

Study II was terminated when the required number of included patients had been reached according to prestudy sample size calculation. Statistical analysis of outcome variables was performed until the second measurement, at an average of 26 $\pm$ 7 minutes, since at that point, all 48 subjects were included, whereas at the third measurement, performed at an average of 58 $\pm$ 5 minutes only 12 subjects remained.

Study III was terminated before the required number of included patients had been reached according to pre-study sample size calculations, since differences in CDS between groups proved to be larger than expected when making those calculations.

CDS data was considered ordinal scale data. In study II, non-parametric statistics wass used also for interval scale data as the study population was small.

RESULTS

Reliability and criterion validity of the Cold Discomfort Scale

In total, forty-four trials were completed; all twenty-two subjects participated in two trials each. Median CDS increased from 0 (IQR; 0 – 0) during base line to 7 (IQR; 5 – 7) at the end of the first trial (test) and to 6 (IQR; 5 – 7) during the second trial (retest) (Figure 2).
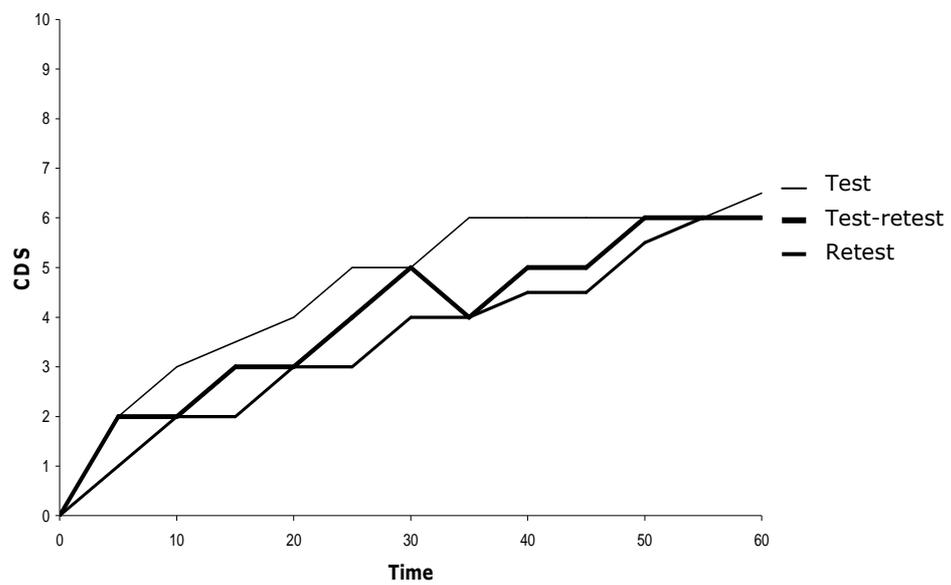

Figure 2. Median CDS ratings of test (n = 22), retest (n = 22) and merged median CDS ratings of test-retest (n = 22).

Reliability analysed for test-retest stability, using weighted kappa coefficient, which included all the measurements made every five minutes, was 0.84 and separated for every single measurement between 0.48 and 0.86 (Table 3).

Table 3. Test-retest stability of CDS ratings at 5 minutes intervals.

Time (min)	Test * (n=22)	Re-test * (n=22)	Weighted kappa coefficient** (n=22)
5	2 (1.25 - 3)	1 (1 - 2)	0.56 (0.25 - 0.86)
10	3 (2 - 3)	2 (1 - 2)	0.48 (0.20 - 0.77)
15	3.50 (3 - 4)	2 (1.25 - 3.75)	0.56 (0.31 - 0.81)
20	4 (3.25 - 4)	3 (2 - 4)	0.60 (0.38 - 0.83)
25	5 (4 - 5)	3 (2.25 - 4.75)	0.53 (0.30 - 0.76)
30	5 (4 - 6)	4 (3 - 5)	0.68 (0.48 - 0.87)
35	6 (4 - 6)	4 (3 - 5)	0.64 (0.40 - 0.88)
40	6 (4 - 6)	4.5 (6 - 4)	0.70 (0.49 - 0.90)
45	6 (4.25 - 6)	4.5 (6 - 4)	0.72 (0.51 - 0.92)
50	6 (5 - 7)	5.5 (5 - 7)	0.76 (0.57 - 0.96)
55	6 (5.25 - 7)	6 (5 - 7)	0.86 (0.72 - 1.0)
60	6.5 (5.25 - 7)	6 (5 - 7)	0.85 (0.81 - 0.99)

Values are median (IQR) * and weighted kappa coefficient (95% CI) **.

Criterion validity analysed by comparing median CDS ratings (n = 22) over a moving 30-minute interval, revealed that CDS ratings were significantly increased during each 30-minute interval (5-35 minutes; 10-40 minutes;15-45 minutes etc) (Table 4).

Table 4. CDS ratings change over a 30 minutes moving interval.

Time (min)	Test and retest*(n=22)	Test and retest**(n=22)	Wilcoxon signed rank test
5 vs. 35	2 (1 - 2.25)	5 (3.75 - 6)	P < 0.001
10 vs. 40	2 (2 - 3)	5.5 (4 - 6)	P < 0.001
15 vs. 45	3 (2 - 4)	6 (4 - 7)	P < 0.001
20 vs. 50	4 (2 – 4)	6 (5 - 7)	P < 0.001
25 vs. 55	4 (3 - 5)	6 (5 - 7)	P < 0.001
30 vs. 60	5 (3 - 6)	6 (5 - 7)	P < 0.001

Values are median (IQR).
*First time in interval, **second time in interval.

Effectiveness of exogenous heat sources for active warming intervention in non-shivering hypothermic subjects

Metabolic heat production increased from 116 ± 17 W (mean $\pm$ SD) during baseline to 195 ± 51 W during the last 10 minutes before meperidine injection. Meperidine suppressed shivering and heat production returned to 114 ± 21 W during the first 40 minutes of treatment and subsequently fell to 97 ± 17 W throughout the remaining 80 minutes of treatment (Figure 3). There were no significant differences in metabolic heat production for the different conditions either during the cooling or the treatment phase.
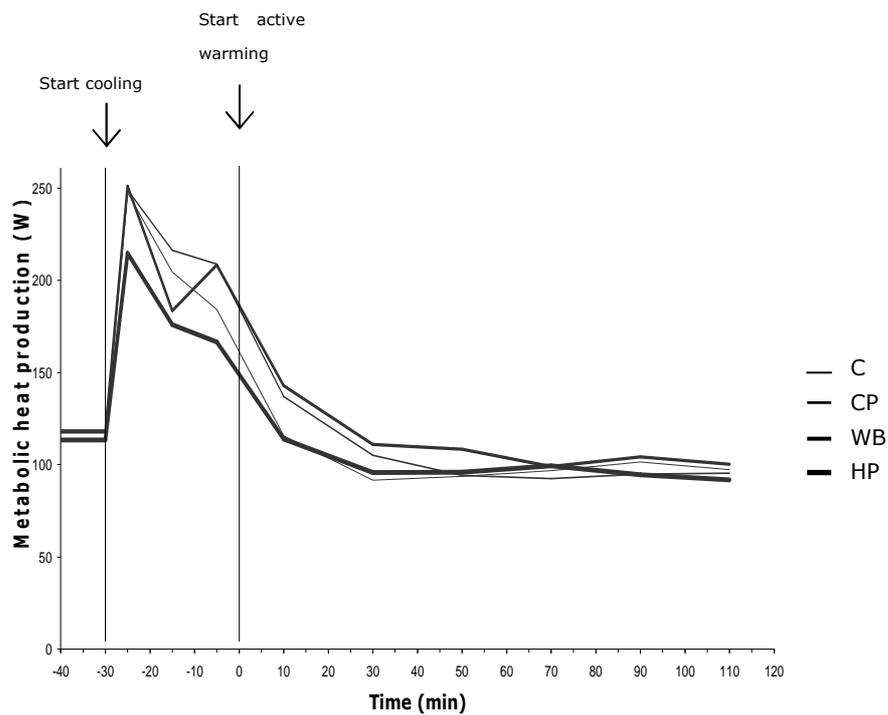
Figure 3. Mean metabolic heat production during four warming protocols (n=5).
WB = Hot water bags; CP = Chemical heat pads; HP = Charcoal heater;
C = Spontaneous warming.

Parametric statistics: The post-cooling afterdrop was significantly less for the chemical heat pads and the hot water bags, but not for the charcoal heater, compared to spontaneous warming. Time to temperature nadir and temperature drop during the entire treatment phase (0 to 120 minutes) was significantly less for all three heat sources compared to spontaneous warming.

Non parametric statistics: The postcooling afterdrop was significantly less for the chemical heat pads, but not for the hot water bags or the charcoal heater, compared to spontaneous warming. Time to temperature nadir and temperature drop during the entire treatment phase (0 to 120 minutes) was significantly less for all three heat sources compared to spontaneous warming. (Table 5)

Table 5. Post-cooling body core temperature and time to temperature nadir during treatment phase.

	Spontaneous warming (n=5)	Charcoal heater (n=5)	Chemical heat pads (n=5)	Hot water bags (n=5)
Maximum temperature drop (afterdrop) amount (°C)	-2.2 (0.3)	-1.9(0.5)	-1.5 (0.4) [a]	-1.6 (0.2)
Time to temperature nadir	88 (38)	53 (31) [a]	46 (23) [a]	44 (23) [a]
Total temperature drop amount (°C)	-1.7 (0.8)	-1.1 (0.6) [a]	-0.9(0.7) [a]	-0.6 (0.6) [a]

Values are mean (± SD).
*Significantly less than spontaneous warming[a] (Wilcoxon signed rank test, $p < 0.05$).
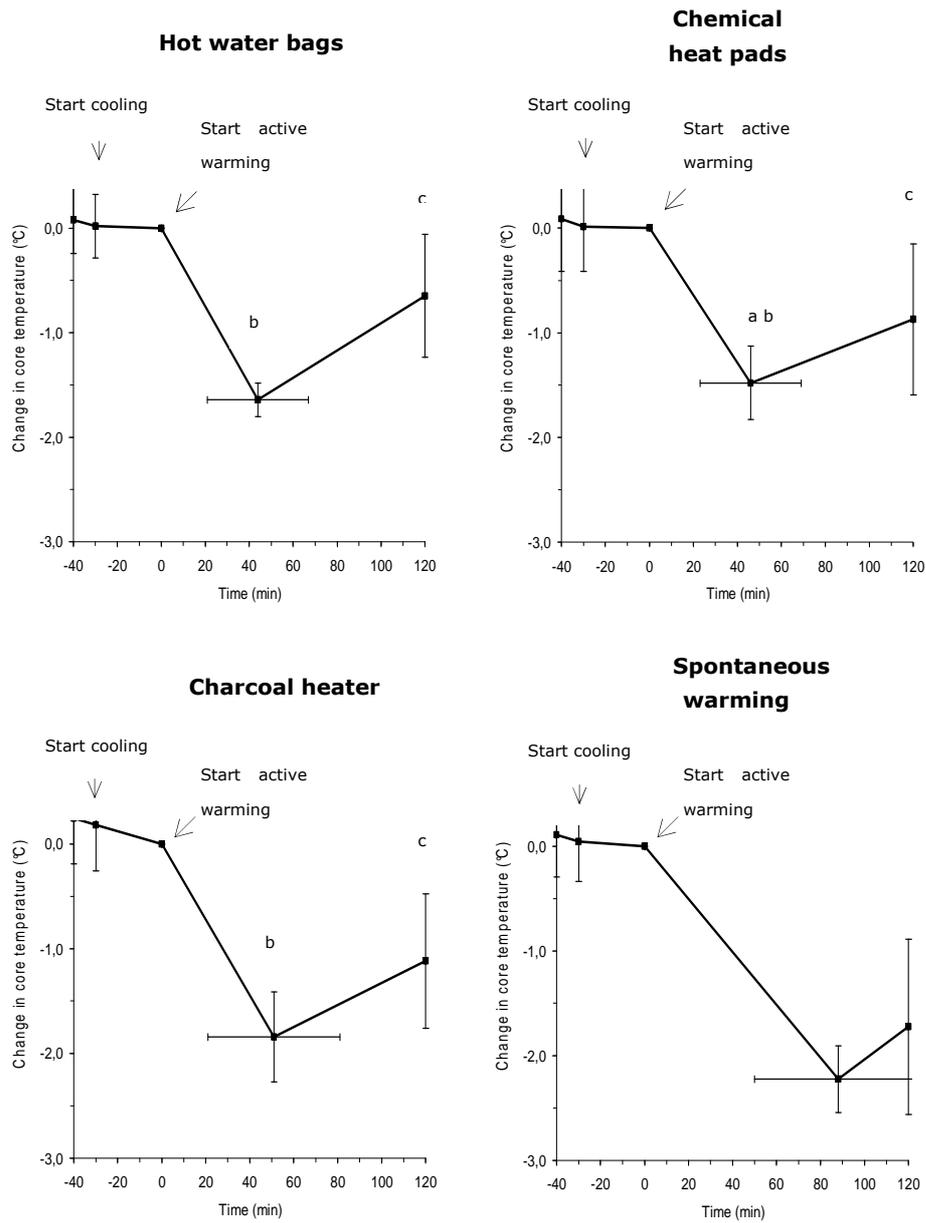
Figure 4. Body core temperature change for each condition (mean; SD; n = 5).
[a] Afterdrop amount, [b] time to temperature nadir and [c] total temperature drop amount significantly less than spontaneous warming (Wilcoxon signed rank test, $p < 0.05$).

Effectiveness of active warming intervention in shivering trauma patients

The mean time from injury to the arrival of ambulance personnel arrival was 64 (95 % CI; 41 – 88) minutes in patients assigned to passive warming only and 81 (95 % CI; 61 – 101) minutes in patients assigned to additional active warming with no significant differences between the two groups.

During road and air ambulance transport ear canal temperature was significantly increased and CDS ratings was significantly decreased, both in patients assigned to passive warming only, and in patients assigned to additional active warming (Table 6).

Table 6. Body core temperature and cold discomfort within treatment groups during prehospital transport.

		1st measurement	2nd measurement
Passive warming (n = 22)	Body core temperature	35.1 (34.7 – 35.5)	36.0 (35.7 – 36.3)*
	Cold discomfort	5 (4 – 7)	3 (0 – 5)*
Active warming (n = 26)	Body core temperature	35.6 (35.2 – 36.0)	36.4 (36.1 – 36.7)*
	Cold discomfort	7 (5 – 8)	2 (1 – 3)*

Values are mean (95% CI) or median (IQR).
* Significantly different from first measurement (Wilcoxon signed rank test, p < 0.05).

However, when change in cold discomfort was characterized as increased, unchanged or decreased, 15 out of 21 in the group assigned to passive warming only presented a decrease in CDS rating, whereas all 26 patients in the group assigned to additional active warming presented a decrease in CDS ratings. This difference in CDS rating change between groups was statistically significant (p < 0.05).

The time from injury to ski patrol arrival was 11 ± 7 minutes (mean ± SD) in patients assigned to passive warming only and 16 ± 9 minutes in patients assigned to additional active warming, with no significant differences between the two groups.

During field treatment, CDS ratings were significantly reduced in patients assigned to additional active warming, but remained the same in patients assigned to passive warming only (Table 7).

Table 7. Cold discomfort within treatment groups during prehospital field treatment.

	1st measurement	2nd measurement
Passive warming (n = 9)	5 (2 – 5)	5 (3 – 6)
Active warming (n = 11)	4 (3 – 8)	1 (0 – 3)*

Values are median (IQR).
* Significantly different from first measurement (Wilcoxon signed rank test, $p < 0.05$).

In addition, when change in cold discomfort was characterized as increased, unchanged, or decreased, 9 of 11 patients assigned to additional active warming presented a decrease in cold discomfort and two remained at their initial cold discomfort whereas only 3 of 9 patients assigned to passive warming alone presented a decrease in cold discomfort; one remained at initial cold discomfort and 5 presented an increase in cold discomfort, this difference in cold discomfort change between groups being statistically significant ($p < 0.05$).

DISCUSSION

Active external warming

Admission hypothermia is an independent risk factor associated with worse outcome in trauma patients, retrospective (1, 3-8) as well as prospective (2) observational clinical studies have revealed that hypothermia remains an independent determinant of mortality after correction for severity of injury. Actions to reduce cold exposure and prevent further heat loss are therefore an important and integrated part of prehospital trauma care. Active warming is by most authors recommended to aid in protection from further cooling during treatment and transport to definitive care (13-15, 28-32). Prehospital active external warming treatment, aims primarily at reducing further heat loss and to counteract the post cooling afterdrop.

Exogenous heat sources for active warming intervention

Chemical heat pads and warm water bottles are commonly used and advised for prehospital active warming treatment. However, unlike the HeatPack® charcoal heater, these heat sources have never before been evaluated regarding their impact on thermoregulation in non-shivering hypothermic subjects. Although all the evaluated heat sources were applied on the chest and upper back, providing their heat content conductively to the skin and underlying tissues, they displayed some important differences that affected warming effectiveness.

Chemical heat pads were most effective in attenuating afterdrop amount. This was most likely due to their high initial heat delivery to a relatively large surface area. The charcoal heater, also with a high initial heat production but a relatively small surface area, had less effect on afterdrop amount compared to spontaneous warming than the chemical heat pads.

The charcoal heater, like the hot water bags (replenished every 20 minutes), provided high continuous heat delivery. The heat delievery of the chemical heat pads declined over time. Therefore, the charcoal heater also, like the chemical heat pads and the warm water bottles, presented a significant difference in body core temperature change over the entire warming phase, compared to spontaneous warming. Thus, all heat sources presented a statistical significant lower body core temperature drop compared to spontaneous warming during the warming phase and this is also in accordance with findings of large afterdrop amounts and little or no warming, when exogenous heat is left out (35, 36, 65, 66).

In summary, heat sources applied on the chest and upper back were effective to attenuate afterdrop when providing high heat content over a large surface area, and

effective to continue to increase body core temperature when providing sustained high heat content.

However, it could be discussed whether recorded differences in body core temperature of about 1˚C is clinically relevant. Nevertheless, prehospital active warming aims primarily at reducing heat loss and to reverse a continuing fall in body core temperature. Thus, especially at critical temperature levels at about 30 ˚C where the heart becomes susceptible to arrhythmias, every degree might be important or even lifesaving.

All of the evaluated warming modalities are portable, require no external power supply and are easily used by laypersons, Search and Rescue (SaR) personnel, or Emergency Medical Services (EMS) crew members without significant training. They are suitable for different clinical scenarios.

The charcoal heater, which is lightweight and provides heat over 8–12 hours, has advantages in protracted evacuation and rescue operations because of sustained heat production.

Water bags, which often are lightweight and easy to bring during backcountry excursions are better suited for scenarios in which the patient will remain on the scene of the accident waiting for evacuation, because an external heat source and significant effort are required for replenishing the water bags.

Chemical heating pads, although heavier and requiring more space than the other modalities can be easily transported in a vehicle such as in ground or air ambulance units. As they are effective in reversing the initial fall in body core temperature, they might prove valuable for initial thermal stabilization of a cold patient, and if replaced at sufficient intervals, also for continuous heat delivery.

Effectiveness of active warming intervention in a prehospital clinical setting

Passive warming according to standard treatment protocol was effective in preventing afterdrop and slowly increasing body core temperature during transport to definitive care (study II). Additional active warming composed no beneficial effect on body core temperature in this study on cold stressed trauma patients with an initial body core temperature of about 35°C and preserved shivering capacity. This is in accordance with previous laboratory studies on mildly hypothermic shivering subjects, where exogenous skin heating has been shown to attenuate shivering heat production by an amount equivalent to the heat donated (34, 37, 64, 72). Passive warming was also effective in reducing cold discomfort. However, only 2/3 of the patients assigned to passive warming, whereas all patients assigned to additional active warming presented a decrease in cold discomfort during transport. This beneficial effect on thermal comfort by application of a chemical heat pad to the upper torso is probably explained by a combination of reduction of shivering thermogenesis and increased skin temperature.

Contrary to this study, two other randomized clinical trials found a decrease in body core temperature with passive warming only, whereas with additional active warming using either resistive heating blankets (38) or multiple chemical heat pads (39), body core temperature was increased during transport. Because effective passive warming requires adequate insulation materials in relation to ambient conditions and intact shivering thermogenesis, differences regarding these factors might explain differences between studies.

During field treatment additional active external warming rendered improved thermal comfort, whereas passive warming alone did not (study III).

This is a difference compared to study II, where passive warming alone was enough to reduce cold discomfort, even though additional active warming was even more efficient. In both studies, the number of blankets used for passive warming was about the same, but in study II, the evaluation was conducted during treatment and transport in a heated ambulance or helicopter, whereas in study III evaluation was conducted during treatment and transport in the outdoors. This probably resulted in a greater cold stress during the evaluation period for patients in study III than in study II, and thereby, probably also in increased shivering thermogenesis and lower skin temperature. Although, an equal amount of insulation was present in both studies, the realative cold stress seemed to be greater in study III. If cold stress increases, demands on shivering thermogenesis during passive warming also increases. In a scenario with trauma patients injured on the ski slopes, where extensive shivering might be harmful, additional active warming seemed to be beneficial.

Increased thermal comfort of patients in both study II and study III indicates a beneficial effect on thermoregulation of additional active warming compared to passive warming alone. This is most probably due to an increase of skin temperature and to a reduction in demands on shivering thermogenesis and also consistent with previous studies demonstrating that exogenous skin heating attenuates shivering by an amount equivalent to the heat donated (34, 37, 64, 72).

Future research

Clinical randomized trials presented in this thesis indicate beneficial thermophysiologic effects from active warming intervention. However, since body core temperature remains stable if shivering and adequate passive warming are intact, these results were based on subjective judgements of included patients. Clinical studies, that, besides body core temperature, also investigate other objective parameters and early predictors of cold induced stress, such as oxygen consumption, are desirable.

Although probably due to different degrees of severity of injuries of included patients as well as different heat sources and different amounts of passive warming,

results from these and the few prior studies on active warming intervention in a prehospital clinical setting (38, 39) are diverging. Therefore, and also because all studies are relatively small, more and larger studies are desirable.

Future prehospital studies should also address more severely injured patients suffering from moderate or severe hypothermia to evaluate effects of active warming intervention regarding requirements of hospital treatment, morbidity and mortality.

Prehospital monitoring

To have accurate measures to evaluate the thermal state of patients in the prehospital setting is vitally important. In the field, especially in harsh ambient conditions, this is often hard to achieve (14, 41). Thus, alternative measures to body core temperature, skin temperature, and oxygen consumption, such as subjective judgement scales for assessment of the patient's thermal state, might be of considerable importance in such scenarios, both for an initial assessment of the patient and for evaluation of the treatment provided. Such assessment of the thermal state of the patient might also be an early predictor of cold stress, and therefore may be used to evaluate the risk of developing hypothermia.

It is important not to underestimate evaluation of the patient's subjective experience of medical care. Improved thermal comfort might have the potential of relieving psychological stress such as the experience of pain and anxiety (9), which might comprise a considerable physiological stress to the patient by increasing respiratory and cardiovascular workload.

Reliability and criterion validity of the Cold Discomfort Scale

In a laboratory setting the test-retest stability of median CDS ratings showed moderate to very good agreement. CDS ratings were generally somewhat higher during test compared to retest, this difference might be a result of a decreased sensitivity to the cold exposure from previous experience, and therefore being less anxious, about exposure to the cold the second time, compared to the first time. This tendency to habituation from repeated exposure might be a weakness of reliability of the CDS. However, there was only one week between test and retest and if a longer period would have passed between test and retest, reliability might have been even better.

Criterion validity, when defined as the ability to detect changes in cold discomfort due to increased cumulative cold stress from 30 minutes in - 20°C wind still conditions, was good. CDS ratings proved to be statistical significantly increased for every 30 minutes of cold exposure. However, during the last 20

minutes it seemed that CDS ratings did not increase as much as during the first 40 minutes. This tendency to habituation during exposure might be an indication of a limitation to detect differences in cumulative cold stress when cold exposure is protracted.

Bedford (91) and also Rholes (92) evaluated subjective judgement scales for assessment of the thermal environment regarding construct validity, trying to correlate subjective judgements of thermal comfort to objective measurements of the thermal environment. Different from that, the CDS is evaluated for criterion validity, defined as the ability to detect changes in cold discomfort due to changes in cumulative cold stress, and therefore should be used to monitor changes in cold discomfort over time. The CDS can not be used to measure and rank the level of cold stress the patients are exposed to and that is the reason, why it is not possible to make any comparisons between CDS ratings at different occasions.

Future research

This study is the first to evaluate reliability and criterion validity of a subjective judgement scale for assessment of the thermal state of patients in an extreme cold environment. Further studies including larger study populations, to confirm these results would be desirable. Evaluating the CDS in different ambient conditions and when using warming intervention would also be desirable.

CONCLUSION

Active external warming

Active external warming is recommended for protection from further cooling and treatment of hypothermia in prehospital trauma care.

In non-shivering hypothermic subjects, heat sources applied on the chest and upper back were effective to attenuate afterdrop, when providing high heat content over a large surface area and effective to continue increasing body core temperature when providing sustained high heat content.

In cold stressed, shivering trauma patients, adequate passive warming was sufficient treatment to prevent afterdrop and slowly increase body core temperature. Adequate passive warming also seemed sufficient to reduce cold discomfort, even though additional active warming was even more efficient. When passive warming was inadequate, additional active warming was required to reduce cold discomfort.

Prehospital monitoring

In a prehospital rescue scenario subjective judgement scales might be a valuable measure for assessment of the thermal state of conscious patients.

The Cold Discomfort Scale, a subjective judgement scale for assessment of the thermal state of patients in a cold environment seemed to be reliable, regarding test-retest stability, and valid, regarding ability to detect change in cumulative cold stress.

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