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The precision of target temperature management in comatose survivors of cardiac arrest - a quality assessment

Degree Project in Medicine

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List of abbreviations

ACS - Acute coronary syndrome

ALS - Advanced life support

AMI – Acute myocardial infarction

ATP - Adenosine triphosphate

BBB - Blood brain barrier

CA - Cardiac arrest

CABG - Coronary artery bypass grafting

CAG - Coronary angiography

CBF - Cerebral blood flow

CHF - Congestive heart failure

CI - Cardiac index

CPC - Cerebral performance scale

CPR - Cardiopulmonary resuscitation

CT - Computed tomography

ECG - Electrocardiogram

EEG - Electroencephalogram

EMS - emergency medical service

ERC - European resusciation council

ICP - Intracranial pressure

ICU - Intensive care unit

IHCA - In-hospital cardiac arrest

IQR - Interquartile range

MAD - Mean absolute deviation

MAP - Mean arterial pressure

MOF - Multiple-organ failure

MRI – Magnetic resonanse imaging

NO - Nitric oxide

OHCA - Out of hospital cardiac arrest

PCAS - Post-cardiac arrest syndrome

PCBI - Post-cardiac arrest brain injury

PCI - Percutaneous cardiac intervention

PCMD - Post-cardiac arrest myocardial dysfunction

PiCCO - Pulse contour cardiac output catheter

RCT - Randomized controlled trial

ROS - Reactive oxygen species

ROSC - Return of spontaneous circulation

SD - Standard devation

SEP – Somatosensory evoked potential

SIRR - Systemic ischemia/reperfusion response

SIRS - Systemic inflammatory response syndrome

SOP – Standard operation protocol

TH - Therapeutic hypothermia

TTM - Target temperature mangagement

UCG - Echocardiography

WLST - Withdrawal of life-sustaining therapy

Abstract

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Title: The precision of target temperature management in comatose survivors of cardiac arrest - a quality assessment

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Introduction: To mitigate reperfusion cerebral injury secondary to cardiac arrest (CA), post-resuscitation target temperature management (TTM) is applied. TTM generally includes 24h of hypothermia followed by controlled normothermia.

Objective: To evaluate the precision of TTM at Sahlgrenska University Hospital by assessing potential deviations from protocol quality requirements as well as identifying potential areas of improvement.

Method: 2 historical cohorts of 45 patients treated by TTM 2011-2013 and 76 patients treated by TTM 2018-2020 were included. Outcome measures as to precision of TTM were time from return of spontaneous circulation [ROSC] to target temperature, temperature variability during hypothermia (mean absolute deviation [MAD]) and incidence of fever (T≥38.5°C). Comparison between study groups was used to evaluate the change in precision over time and a comparison of the 2018–2020 data to current literature was made to assess the precision compared to international standards.

Results: Time from ROSC to target temperature 33°C was significantly shorter in the 2018-2020 study group (mean 6h38min) than in the 2011-2013 study group (mean

10h6min). Variability was significantly lower in the 2018-2020 study group (average MAD [mean absolute deviation] 0.23°C) than in the 2011-2013 study group (average MAD 0.47°C). Fever incidence during normothermia phase was significantly lower in the 2018-2020 study group (11%) than in the 2011-2013 study group (29%).

Conclusion: Overall, precision of TTM at Sahlgrenska University Hospital as to timing, variability and fever incidence had improved over time and was in line with reported data from the largest studies of TTM today.

Key words: Target temperature management, cardiac arrest, fever

1. Background

1.1 Cardiac Arrest

1.1.1 Epidemiology

Out of hospital cardiac arrest (OHCA) represents a substantial health concern globally. In Europe an overall incidence of 56 (range: 21-91) cases per 100,000 population per year was reported in a large international prospective multicenter registry-based study published in 2020(1). Among 37,054 cases of OHCA studied across Europe, cardiopulmonary resuscitation (CPR) was initiated in 68% (n=25,171) of whom 33% (n=8189) achieved return of spontaneous circulation (ROSC). Of the patients achieving ROSC, 22% (n=1809) survived to hospital discharge indicating the overall survival rate 5% after cardiac arrest and 8% among those who received CPR(1). The results from this study are largely in line with other comprehensive epidemiological studies on OHCA, e.g. another large global multicenter registry-based study of emergency medical service (EMS) treated OHCA reported incidences between 30.0-97.1 per 100 000 population per year and a survival to hospital discharge rate of 3.1-20.1%(2).

Reported incidence and outcome vary substantially between countries and different parts of the world(2). The cause of scattered results in epidemiological studies is multifactorial and can to some extent be attributed to variability in patient population, reporting method, pre-hospital elements and potentially different methods of OHCA care(3).

The high incidence and generally poor prognosis of cardiac arrest (CA) makes it a leading cause of death in developed countries and has prompted intense research(4).

The causes of CA are commonly divided into cardiac and non-cardiac. Non-cardiac causes include traumatic and hypoxic CA. A recent publication concluded that cardiac causes historically might have been overestimated, however also identifying acute coronary syndrome (ACS) as the most prevalent cause of OHCA. The second most common etiology reported was respiratory failure(5).

1.1.2 Pre-hospital elements of cardiac arrest

Several pre-hospital circumstances are known to affect outcome from CA, the most important being; place of CA, whether the CA arrest was witnessed or not, if bystander CPR was given, if bystander defibrillation was performed, first presenting cardiac rhythm, time from CA to advanced life support (ALS) and emergency medical service (EMS) response time. These factors have for long been targets for improvement strategies, ranging from optimizing EMS response times to teaching CPR in schools. As these elements are associated with outcome, they represent potential confounders in studies of CA, why they are registered according to specified "Utstein" criteria, a set of international guidelines to facilitate uniform reporting of CA (2, 6, 7). An initial shockable rhythm, bystander CPR, shorter EMS response time, shorter time to ALS and shorter no-flow time are all associated with better outcome as to survival(8-10).

1.1.3 Post-cardiac arrest syndrome

The pathophysiological process responsible for the poor prognosis after resuscitation from CA is multifaceted. It extends beyond the global ischemic tissue and organ damage initially occurring during circulatory cessation. Additional cerebral injury is caused during and after reperfusion. This pathophysiological process is labeled the post-cardiac arrest syndrome (PCAS)(3). PCAS encompasses 4 key elements which will be addressed separately. These are 1) post-cardiac arrest brain injury (PCBI), 2) post-cardiac arrest myocardial dysfunction (PCMD), 3) systemic ischemia/reperfusion response (SIRR) and 4) persistent precipitating pathology(6).

1.1.3.1 Post-cardiac arrest brain injury

With its restricted tolerance of ischemia and unique reperfusion response, the brain constitutes the most vulnerable organ after suffering CA. The pathophysiological process is divided into a primary injury phase caused by the immediate cessation of oxygen supply to the brain and a secondary phase occurring after resuscitation. PCBI is the most common cause of mortality in

OHCA-treated patients in the intensive care unit (ICU), comprising around 65% of the cases(11). PCBI also accounts for neurological sequalae among survivors, ranging from mild cognitive dysfunction to unresponsive vegetative states. In addition to brain death and cognitive dysfunction, clinical manifestations of PCBI include myoclonus, seizures and coma (3).

During the primary phase, immediate cessation of oxygen supply to the brain leads to neuronal ischemia and rapid cell death. Depletion of nutrients with following cerebral glycopenia causes a metabolic crisis, aggravating neuronal injury and cell death. As adenosine triphosphate (ATP) depletes, energy dependent ion channels cease to function, causing an increased intracellular [Na^+], leading to cytotoxic edema. Anaerobic metabolism leads to lactate accumulation and intracellular acidosis. Furthermore, intracellular influx of Ca^{2+} activates lytic enzymes and induces mitochondrial dysfunction, further depleting ATP. Ultimately, apoptotic enzymes are activated(12).

The secondary phase begins as reperfusion occurs, through effective CPR and/or when ROSC is achieved. The pathophysiological processes of the secondary phase are mainly focused on the balance of oxygen consumption and supply(12).

During reperfusion, an initial phase of hyperemia is often followed by a state of hypoperfusion, known as the cerebral no-reflow phenomena. During the hyperemia phase, excessive levels of oxygen in the reperfused tissue result in reactive oxygen species (ROS) formation, causing oxidative damage and ultimately neuronal damage and cell death. This has triggered a debate as to what place oxygen should have in the treatment of PCBI, no uniform standpoint has been established although some unanimity is found in that both excessive hyper- and hypo-oxygenation can be injurious(13). As numbers of activated neutrophils accumulates, additional neuronal damage occurs(14).

Mechanisms causing the no-reflow state include endothelial dysfunction. Nitric oxide (NO) production decreases, causing vasoconstriction. Decreased anticoagulant function in the presence of abnormal activation of coagulation pathways causes diffuse microthrombi to

form(12, 14). The microthrombi formation leads to microcirculation disturbances, increasing cerebrovascular resistance and reducing cerebral blood flow (CBF).

Blood-brain barrier (BBB) loss of patency causes extravasation of large osmotic molecules and water, resulting in cerebral edema formation(14). Endothelial dysfunction further mitigates autoregulatory mechanisms and vasomotor control, additionally impairing cerebral blood distribution. Multiple studies have suggested that cerebral autoregulation is entirely absent in a significant proportion of PCBI patients. This leaves CBF mainly regulated by mean arterial pressure (MAP) in patients with variable levels of persisting cardiac dysfunction following CA(12).

Finally, hyperthermia is known to affect several pathophysiological mechanisms of PCBI. Hyperthermia further disrupts BBB function, exacerbating cerebral edema with increased intracranial pressure (ICP) causing cell death. Also, neuronal cell metabolism upregulates, generating additional ischemic stress. A raised glutamate production causes downstream intracellular influx of Ca^{2+} and cell death, referred to as excitotoxicity. Mild induced hypothermia has been the main focus to attenuate the effects of reperfusion injury with numerous positive results from experimental studies(15). The pathophysiological effects of hypothermia are more closely described under the TTM heading.

1.1.3.2 Post-cardiac arrest myocardial dysfunction

PCMD is a contributor to the poor prognosis of OHCA and the most common cause of mortality in OHCA patients within the first 3 days, while PCBI accounts for the majority of later deaths(6). An important element of the pathophysiologic process of PCMD is the cardiac no-reflow phenomena, similar to the cerebral no-reflow state previously described. As reperfusion is initiated, activation of coagulation pathways in absence of normal anticoagulant function causes microthrombi to form, simultaneously platelets and neutrophils accumulates. All of these mechanisms contribute to disturbed microcirculation of the myocardium, causing stiffness and reduced contractility, referred to as myocardial stunning. However, the notable

force from thoracic compressions during high quality CPR can sustain a moderate intermittent blood flow even during this phase, securing minimal but crucial oxygen delivery(16). Immediately after ROSC, cardiac parameters tend to vary greatly. Heart rate and blood pressure can be elevated due to endogenous or exogenous administration of catecholamines. Cardiac Index (CI) is typically initially low and reaches nadir after approximately 8 hours. However, in a majority of non-fatal cases PCMD represents a reversible condition, with CI values often normalized within 24-72 hours(17). Inotropic drugs and vasopressors serve as vital aid during this initial phase. A more protracted reduction in cardiac function has also been reported, describing continuous recovery over the course of months(18). Absence of CI improvement within 24 hours has been associated with multiple-organ failure (MOF) and death(17).

1.1.3.3 Systemic ischemia/reperfusion response

Systemic ischemia/reperfusion response accounts for the systemic effects and organ damage associated with PCAS. As for the other pathophysiological mechanisms of PCAS, its severity varies according to the severity of the CA, ranging from a mild immune response with minimal organ damage to a systemic inflammatory response syndrome (SIRS) and global organ damage. Sharing many characteristics, the systemic ischemia/reperfusion response is frequently compared to the sepsis syndrome(19).

As whole-body ischemia and reperfusion occurs a strong and immediate immune response is triggered. Activation of coagulation pathways without sufficient anticoagulatory activity leads to microthrombi formation further complicating reperfusion and amplifying tissue damage. The duration and level of ischemia well corresponds to the magnitude of the immune response and the levels of cytokines it brings with it. High levels of bacterial endotoxins in plasma is common and is thought to be mediated from translocation in areas of the gut suffering ischemia. The systemic inflammatory response often manifests with intravascular hypovolemia and dysfunctional vasoregulation, causing low oxygen delivery. It is associated with multiple organ failure and death(19, 20).

Another interesting pathophysiologic mechanism of SIRR is that circulating immune cells of various types seem to display a lowered responsiveness towards endotoxins. In vitro studies have shown that leucocyte activation from endotoxins can be suppressed when exposed to plasma from PCAS patients, suggesting that the mechanism of endotoxin tolerance is mediated by soluble factors released in conjunction with CA or reperfusion. This endotoxin tolerance might serve an important role in protecting the body from the possible severe damage of an exaggerated immune response, but might also lead to increased susceptibility to infections, a well-documented trait of PCAS patients(3, 19).

1.1.3.4 Persistent precipitating pathology

The mechanisms of injury caused by ischemia and reperfusion described under the previous three subheadings is something in common for all PCAS patients. However, the underlying pathologies leading to CA are different between individuals and may persist after resuscitation. A therapy successful in one etiology is possibly not as effective or even harmful in another etiology. For example anticoagulant therapy has a place in thromboembolic etiologies while contraindicated in hemorrhagic etiologies(5). Common persistent precipitating pathologies include ACS, pulmonary disease, sepsis, intoxications and hemorrhage(3).

1.1.4 Post resuscitation management

Depending on the severity and underlying pathology of the CA, patients will require different levels of care. Reports of the proportion of resuscitated survivors of OHCA who wake up early and are alert or responsive upon hospital admission vary greatly between studies with numbers ranging between 15-46%. The prognosis among patients who show early verbal responsiveness is dramatically better than for unresponsive survivors of OHCA(6, 21). However, most resuscitated OHCA patients will require some level of intensive care. The care given during this initial time post-resuscitation greatly influences the patient's outcome. Current recommendations from the European Resuscitation Council (ERC) and European Society of

Intensive Care suggest, if there is any doubt regarding the patients neurological function, intubation and actions according to the local OHCA treatment protocol including TTM should be initiated(6).

As both hyperoxemia and hypoxemia have been associated with worse outcome, ERC 2015 guidelines suggest titrating oxygen concentration to maintain an arterial saturation of oxygen at 94-98%. Adjusting ventilation to avoid hypocapnia is also recommended as hypocapnia causes cerebral vasoconstriction decreasing CBF and is associated with worsened outcome(6, 22).

Patients who present with ST-elevation on electrocardiogram (ECG) after ROSC should be admitted straight to a catheterization laboratory and undergo immediate coronary angiography (CAG) and percutaneous cardiac intervention (PCI) if required. Of patients not presenting with ST-elevation on ECG, ICU admission and further evaluation of potential underlying pathologies should be made. In a study of OHCA patients undergoing angiography after resuscitation from OHCA with no obvious non-cardiac pathology, a coronary occlusion was found in 48% of the patients(23). However, no trial randomising patients without ST segment-elevation to early or delayed coronary angiography has this far showed any benefit from an immediate procedure after CA(24, 25). If a respiratory or neurological pathology is suspected a computed tomography (CT) scan of the brain or thorax may be indicated(6, 26).

Echocardiography (UCG) is typically performed early to evaluate the degree of myocardial dysfunction and to identify potential regionality of the injury(27). OHCA patients in the ICU are often hemodynamically unstable and require inotropic support. As vasodilation due to the systemic inflammatory response of PCAS is usually present, administration of noradrenaline and fluids constitute an effective treatment. An arterial line for continuous blood pressure monitoring is standard care and monitoring of cardiac output by use of a pulse contour cardiac output (PiCCO) catheter provides extra guidance in treatment of hemodynamically unstable patients(6).

Seizures are common among comatose resuscitated OHCA patients and myoclonus represents a majority of the cases. Focal or generalized tonic clonic seizures or combinations represents the rest. Electroencephalogram (EEG) can be used to specify whether the seizure is epileptic or not. Myoclonus is often effectively treated with propofol, other seizures may be treated with valproate, levetiracetam, benzodiazepines, barbiturates or propofol. It is not unusual with patients presenting epileptic activity on EEG without presenting clinical symptoms of a seizure, which might be inhibited by sedation. In theory, such seizures increase metabolic activity and may exacerbate brain injury. Notwithstanding, whether identifying and treating electrographic seizures lacking detectable clinical manifestations improves outcome remains unknown(6).

When hemodynamically stable and the patient has returned to normothermia after the initial period of TTM hypothermia, an attempt to lower the sedation is usually made to assess whether sedation can be withdrawn as well as give an indication of the patient's neurological function. If the patient remains comatose after 72 hours, neurological prognostication is made to assess whether ICU care is further indicated or if withdrawal of life-sustaining therapy (WLST) and palliative measures is more appropriate. Neurological prognostication is a multimodal process including clinical examinations, neurophysiologic methods, biomarkers and brain imaging(28).

1.2 Target Temperature Management

1.2.1 Introduction

In 2002, two randomized controlled trials (RCTs) showed that therapeutic hypothermia (TH) at 32-34°C for 12-24 hours significantly improved neurological outcome and survival among comatose survivors of OHCA with an initial shockable rhythm(29, 30).

Some of the many observational studies following the wide implementation of TTM during the early 2000s questioned the reproducibility of the 2002 trials, especially among patients with initial non-shockable rhythms and in hospital cardiac arrest (IHCA) populations(31, 32).

Authors also pointed to the fact that fever was more common in the standard treatment group in one of the trials, questioning whether the treatment effect was due to hypothermia or avoidance of fever(30, 33).

The largest RCT comparing different target temperatures published thus far, "TTM1" published in 2013, compared 33°C to 36°C and found equipoise as to neurologic outcome and survival. Since the publication of "TTM1", the use of 36°C as target temperature is more widely used as standard. Also, one study showed a 16% (70,5-54,5%) reduction of TTM use in recent years(34, 35).

After the publication of "TTM1", later studies on the effectiveness of TTM at different target temperatures have been made. In 2018, a prospective study comparing target temperatures of 32°C, 33°C and 34°C did not find any different outcomes between the groups(36). However, a recent RCT comparing 33°C to normothermia among CA patients with non-shockable rhythm showed significantly better neurologic outcome in the 33°C group, albeit with no difference as to survival(37). Notwithstanding, an earlier sub-study of "TTM1" in a similar cohort failed to prove the same(38).

Today, international guidelines recommend TTM at a target temperature of 32-36°C. However also underlining that the recommendation is based on very low- or low-quality evidence and that more high-quality trials are needed(6).

1.2.2 Mechanisms of action and adverse effects of hypothermia

The most well-known physiological mechanism of TH is the associated reduced cerebral metabolism. For each degree Celsius of temperature reduction from 37°C, a decrease of 5-10% in cerebral metabolism is achieved, together with other mechanisms attenuating the cerebral reperfusion injury(15, 39). Many of the studies researching such mechanisms are animal model studies, presenting with uncertainty as to how well results can be translated into clinical practice and human injuries(15).

As previously discussed, PCAS encompasses numerous pathophysiologic mechanisms of varied importance due to individual circumstances and timing. As a result, different mechanisms of action of TH will be of different weight in individual cases and time spans after CA(3, 14, 15).

An important protective mechanism is the mitigation of apoptosis. This is accomplished through several mechanisms, e.g. inhibition of caspase activation and decreasing mitochondrial susceptibility to damage. Apoptosis is induced relatively late in PCAS, thus providing a mechanism with a wider time window where TH may be protective(40).

Hypothermia also reduces production of free radicals and restrains inflammatory response. Other mechanisms include maintaining blood-brain barrier function, decreased vasopermeability, limiting excitotoxicity and suppression of epileptical activity. Anticoagulatory effects of hypothermia constitute a theoretically protective effect due to prevention of microthrombi formation. A study documenting the anticoagulatory effects during hypothermia did not find any excessive risk of bleeding complications(41-43).

During hypothermia, an increased insulin resistance as well as a decrease in secretion of insulin is common. In order to avoid hyperglycemia, more frequent checks of the glucose level as well as higher insulin doses may be required. Hypothermia also increases fat metabolism. This can lead to elevated levels of glycerol, free fatty acids, ketonic acids and lactate, contributing to metabolic acidosis. However, in most cases these elevations are mild and without indication for treatment(15).

As immune response is restrained, an increased risk of infection is seen. Lower temperatures and longer durations of TH increase this effect. Frequent control of inflammatory parameters and consideration of antibiotic treatment should be part of the standard protocol(44).

Hypothermia decreases cardiac output, primarily due to a decrease in heart rate which correlates with the decrease in metabolic rate, keeping supply and demand within balance. Notwithstanding, an initial phase of tachycardia is usually seen as well as increased systemic

vascular resistance. This could represent an increased workload on the heart, however in most cases a systemic inflammatory response syndrome with vasodilation is present, which facilitates cardiac output. While hypothermia effects cardiac and vascular functions, studies have shown TH can be used safely among hemodynamically unstable patients following ROSC(15, 45).

In response to the heat loss following TH, shivering is frequently seen. Shivering increases heat generation through accelerated metabolic activity. It is usually treated with increased doses of sedatives such as propofol. Muscle relaxant agents can also be used(44).

Hypothermia also decreases systemic clearance of many drugs. In addition, a decrease in potency can be seen in others, thus attention to potential dose adjustments and more liberal monitoring of drug concentrations is of importance(46).

In essence, hypothermia effects every organ in the body to some extent. The effects and side effects of hypothermia are temperature dependent and the potential harmful effects must be weighed in each individual case. Widely accepted contraindications to TH include severe systemic infection and pre-existing coagulopathy (not pharmacological), however this is not applied universally(6, 44).

1.2.3 TTM clinical management

Treatment by TTM can be divided into 3 different phases, induction/maintenance (also referred to as TH phase), rewarming and normothermia. No comprehensive standard best practice on how to achieve the optimal TTM is defined by literature or international guidelines(47). Although, present TTM generally consists of an initial 24 hours of hypothermia followed by a minimum of 48 hours of controlled normothermia (sometimes referred to as fever control)(48). In the following sections, accepted quality measures of TTM are described(49).

1.2.3.1 Induction and maintenance

To cool and maintain a patient's body temperature stable at a target below 37°C, various methods and cooling devices have been developed. They include simpler solutions such as ice

packs, blankets and cold saline infusions. However, more sophisticated devices which are based on feedback loops from continuous core temperature measurements and cooling either by endovascular catheters or water circulating surface pads have proven to be more precise(50).

Trans-nasal cooling is a method where a cold highly evaporative liquid is sprayed into the nose with a combination of high flow oxygen causing global hypothermia with a regional cerebral focus(51). Recently, an RCT studying pre-hospital TH induction with trans-nasal cooling was published with an absolute 3% increase in favorable neurologic outcome in the treatment group compared to the control, although not significant(51). However, in a sub-analysis of the study, pre-hospital trans-nasal cooling initiated less than 20 minutes from CA was significantly associated with a better neurological outcome in patients with an initial shockable rhythm(52). Pre-hospital TH induction with cold saline infusions has also been studied, however without success and increased adverse effects(53).

The optimal target temperature has been a topic of scientific debate ever since the introduction of TTM following the 2002 trials(29, 30). International recommendations today suggest TTM at 32-36°C(6, 54). Consequently, the target temperature included in local standard operation protocols (SOPs) may vary within this range but with a preference for the higher temperatures(55-57).

The duration of the maintenance phase most commonly practiced and recommended as a minimum by ERC guidelines is 24 hours. However, ERC as well as other international guidelines states it is a weak recommendation of very low-quality evidence(28, 54). The optimal duration of TTM is not known. Studies comparing 24 hours to longer maintenance phases of 48-72 hours have not found any significant improvement as to neurological outcome or survival in adults(58, 59). On the other hand, 72 hours of cooling is frequently used in neonatal care of hypoxic-ischemic encephalopathy, mainly supported by pre-clinical studies of fetal sheep(60).

1.2.3.2 Rewarming

Generally, rewarming is recommended to be slow and controlled, preferably with the assistance of a device rather than passive to reduce the risk of unpredictably high rewarming rates(47). Today 0.25-0.5 °C an hour is recommended by ERC guidelines(6). Although the optimal rewarming rate remains unknown, slower rates have proven to be beneficial in both animal and human studies(61, 62).

1.2.3.3 Normothermia

The normothermia period should be at least 48 hours with strict avoidance of fever. Fever after rewarming (also known as rebound hyperthermia or rebound pyrexia) is a well-known phenomenon described in up to half of OHCA patients and associated with unfavorable neurological outcome and death(63). Treatment and avoidance of fever could be attempted by antipyretics, however in most patients rewarmed from TH additional cooling methods are required. Usually, the same devices used for the hypothermia period with continuous monitoring and feedback are of good help and will provide the most efficient protection against temperature rises(44). International post-resuscitation guidelines suggest temperatures >37.6°C should be avoided and that active cooling should be considered to achieve this(6).

1.2.4 Aspects of TTM as possible quality assurance indicators

Due to the results previously mentioned, there is a span in recommended target temperature for TTM between 32° and 36° degrees, but there are arguments that the quality of TTM is as important as the target temperature itself(47).

1.2.4.1 Time from ROSC to induction and target temperature

TTM should be initiated as soon as possible following cardiac arrest with rapid cooling reaching target temperature within a few hours(64, 65). Very short times to target temperature and even intra-arrest induction have been positively associated with favorable neurologic outcome and survival in animal models, however the results have not been easily or successfully translated

into human clinical trials(51, 53, 66, 67). Retrospective observational studies, assessing times between ROSC and target temperature have often been confounded by low initial temperatures and fast cooling among the clinically worst patients, hypothesized to have a complete loss of thermoregulatory function(6, 68, 69). However, when studying time to TH initiation, shorter times have been associated with better outcomes(65, 70). Additionally, a meta-analysis suggested better outcome among patients with shorter times to target temperature(71). The patient outcomes of studies where target temperature was reached 4 to 8 hours after ROSC were similar, however in studies where target temperature was reached within 3 hours from ROSC, a higher proportion of patients with good outcomes was seen, suggesting an important time window. Although it should be noted that the studies of such short times were limited as to sample size(71, 72). Short induction is supported by animal studies where significantly higher concentrations of neuroprotective mediators has been documented in subjects where target temperature was reached prior to 3 hours after CA(71). In the "TTM2" protocol, a goal was set that a majority of included patients should reach target temperature within 90 minutes after a 180-minute randomization window, suggesting a 4.5-hour time goal from ROSC to target temperature(73).

1.2.4.2 Temperature variability during TTM

Low temperature variability (sometimes also referred to as temperature lability or temperature fluctuation) reflects strict maintenance at target temperature(50). While this is a sought for feature, greater temperature variability has not been associated with worse clinical outcome in studies of temperature variability during TTM(74, 75). A study of shivering during cooling reported greater chance of favorable neurologic outcome among patients shivering during cooling compared to patients not. Hypothesized to be a sign of sustained thermoregulatory functions(76). Also, a meta-analysis of different cooling methods presented better outcome with devices of higher precision allowing lower variability, suggesting lower variability across an entire study population might be favorable(50). Low temperature variability is also important

for internal and external validation. In clinical practice and study protocols, low variability is a quality requirement, where deviations >0.5°C are undesirable(37, 73).

1.2.4.3 Fever

In a recent meta-analysis of post-TH fever, incidence of fever within 24-48 hours after rewarming was 30-52%(63). The largest study in the meta-analysis defined rebound fever as T>38.5°C within 36 hours after rewarming and was reported with an incidence of 52%(77). Fever defined as T>38.0°C was significantly associated with worse neurological outcome but not with mortality(63). However, fever defined as T>38.5 was associated with both worse neurological outcome and lower survival and should be avoided and actively treated according to international post-resuscitation guidelines(6, 63). Whether fever is causative or merely a surrogate of PCAS brain injury remains controversial(63).

2. Specific objectives

The specific objective of this study was to review the degree of quality achievement in the TTM treatment protocol of comatose survivors of OHCA cared for in the central ICU 96 at the Sahlgrenska University Hospital. For this assessment we used two groups of OHCA patients having been managed according to scientific study protocols during two periods; 2011-2013 and 2018-2020. Three aspects of TTM was analyzed. Timing, temperature variability and fever.

Outcome parameters of both groups was compared to detect possible management changes over time and to results in the current literature and international guidelines to assess the quality of TTM at Sahlgrenska Hospital.

3. Method

3.1 Patients

This retrospective explorative quality assessment study included 125 patients from 2 historical cohorts of OHCA patients of different treatment protocols, 2011-2013 (Study 1) and 2018-2020 (Study 2). In Study 1, 47 patients were randomized into intervention groups of TTM treatment

at target temperatures of 33°C and 36°C. In Study 2, 78 patients were randomized into intervention groups of TTM treatment at target temperatures 33°C and 37°C (strict normothermia).

3.2 Intervention

Following admission, TH patients (33°C and 36° Study groups of Study 1 and the 33°C group of Study 2) were treated with similar TTM Protocols (except for target temperature), while the

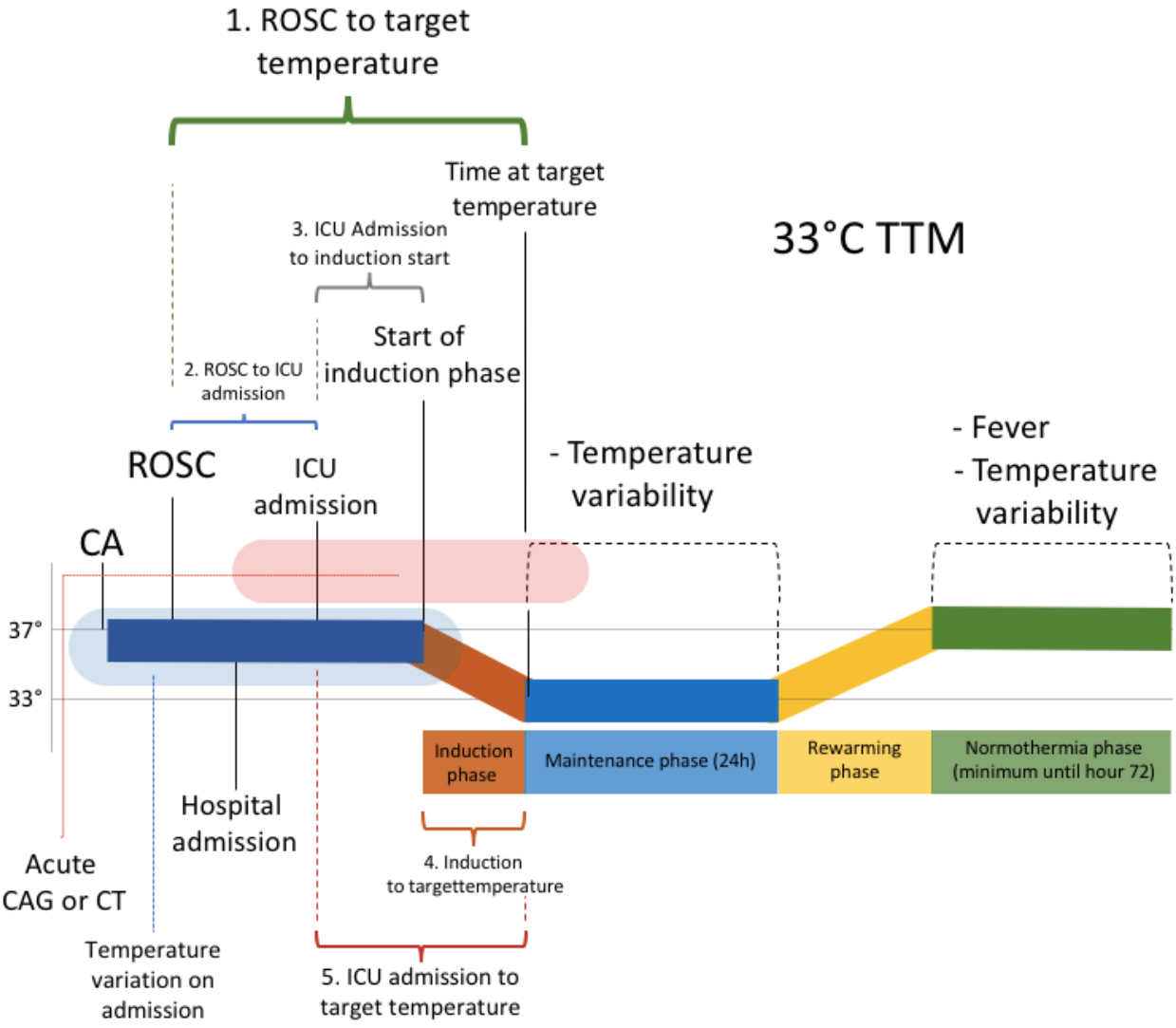

Fig. 1. The 33°C TTM procedure. Numbers 1-5 constitutes timing measures assessed in this study. Temperature variability was assessed during maintenance and normothermia phase. Occurrence of fever (T≥38.5) was assessed during normothermia phase. The induction and maintenance phase for the TH patients was 28 hours in both Study 1 and Study 2 groups (4 hours induction + 24 hours maintenance at target temperature). In Study 2, the rewarming rate was 1/3 °C/hour, leaving 12 hours for rewarming for the 33°C group. In Study 1, the rewarming rate was 1/2 °C, as such 2 hours of rewarming was left for the 36°C group, and 8 hours for the 33°C group. Normothermia phase lasted until hour 72 in all groups. Acute CAG or CT before reaching target temperature could delay time to target temperature. The figure is not drawn to scale. CA denotes cardiac arrest CAG coronary angiography, CT computed tomography scan, ICU intensive care unit, ROSC return of spontaneous circulation, TTM target temperature management.

37°C group of Study 2 were treated with a strict normothermia protocol focused on fever prevention. The normothermia phase protocol was similar for all patients. The TTM procedure for all groups can be seen in Fig. 1 (33°C) and Fig. 2 (36°C and 37°C). During the 72-hour period, exams and interventions such as CT scans, coronary angiography, PCI, EEG, MRI (magnetic resonance imaging) and SEP (somatosensory evoked potential) were carried out when indicated. The cooling device used for all groups was the same; a core temperature feedback system with surface pads of circulating water called "Arctic Sun® 5000". Hourly core temperatures were routinely measured by a bladder probe. If a patient was oliguric, study protocols specified esophageal or intra-vascular probes should be used.

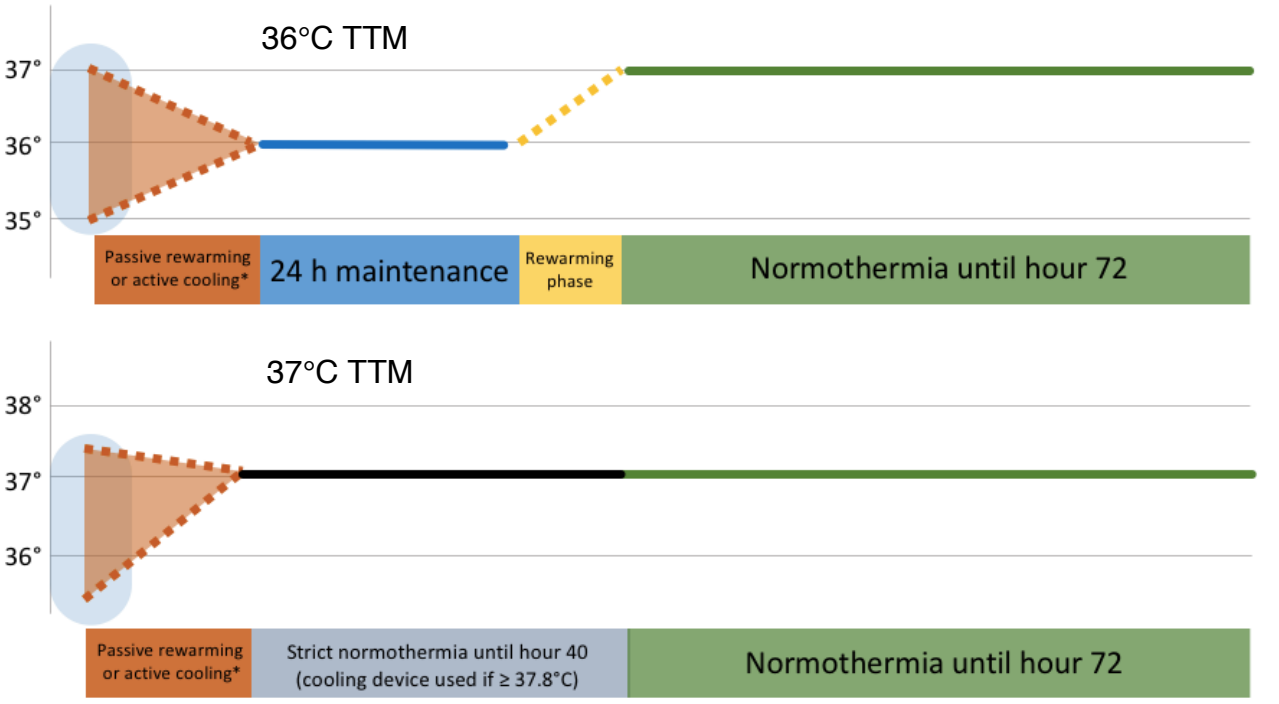

Fig. 2. The 36°C and 37°C TTM procedures. As admission temperatures is often below 36°C, 36°C and 37°C patients are commonly passively rewarmed to target temperature, this is also shown in Fig 5. In the 37°C Study 2 group, strict normothermia (36.5-37.7°C) was kept for 40 hours (mandatory use of cooling device if temperature ≥37.8°C) followed by normothermic temperature control. Normothermic temperature control at 36.5°-37.7°C (36.5-37.5°C in study 1) was kept until minimum 72 hours following admission (unless awake and extubated) in all study groups, cooling device used if needed. TTM denotes target temperature management. The figure is not drawn to scale.

3.3 Outcome parameters

The timing measures of TTM that will be analyzed are time from ROSC to target temperature, time from ROSC to ICU admission, time from ICU admission to TH initiation, time from TH initiation to target temperature, time from ICU admission to target temperature and time from ROSC to ≤ 34°C.

The time from ROSC to target temperature serves as the most important time clinically. However, to identify potential targets for improvement and when potential delays occur, the additional time measures serves an important function.

Temperature variability will be analyzed as mean absolute deviation (MAD), standard deviation (SD) and statistical variance.

Variability will be measured during both hypothermia (hour 10 to 24) and normothermia phase (hour 40 to 72). While MAD provides the main temperature variability measure in this study, SD and statistical variance will be assessed in order to compare with previously identified studies using these measures(74, 75).

Fever will primarily be assessed during the normothermia phase and measured as incidence of fever (minimum of one temperature registration ≥ 38.5°C).

CT and angiography following admission were identified as potential confounders while studying time from ROSC to target temperature. To control for this, the times for all CT and angiography procedures was collected and made into two dichotomous variables positive if the procedure occurred between ROSC and time at target temperature.

The times during the TTM procedure where measures were assessed can be seen in Fig. 1 and Fig. 2.

3.3.1 Timing of TTM

Time from ROSC to target was analyzed both as a continuous variable comparing means between study groups and as a dichotomous variable with a quality mark set to 4.5 hours, as suggested by the TTM2 study protocol. As multiple events such as ICU admission and initiation

of TH occurs between ROSC and time at target temperature, subdivisions listed above were assessed and analyzed in order to discuss where in the course of events potential delays occur and to identify potential time spans as targets for improvement. For time from initiation of TH to target temperature, a dichotomized analysis with a cut value of 90 minutes was suggested as stated by the TTM2 study protocol. However, as our moderate resolution of temperature measurements of hourly registrations, this was expanded to a ≤ 2-hour target.

In order to compare with current literature, time from ROSC to temperature ≤ 34.0°C was assessed in the most current 33°C Study 2 group.

For the 33°C groups, the time at target temperature was defined as the first temperature measurement at 33.0°C or under as in most previous studies. In the 36°C and 37°C groups, time at target temperature was defined as the time when the first temperature was registered within ≤0.5 °C from target.

3.3.2 Variability

Temperature variability was measured as mean absolute deviation (MAD) between hour 10 and 24 (as a majority of patients would be under maintenance phase during these hours) during the hypothermia phase, as well as between hour 40 and 72 during the normothermia phase. MAD is defined as the sum of all absolute deviations from the mean divided by the number of observations. High variability was defined as a MAD > 0.5°C which is the highest variability commonly accepted by study protocols(37, 73).

In order to compare high variability with a previous study(74), variability during hypothermia was also measured as SD, analyzed dichotomously with high variability defined as a SD > 1. To compare with a second previous study(75), temperature variability was measured in a third sense. Defined as the statistical variance (the average of the squared differences from the mean) of temperature registrations during the hypothermia phase.

Temperature variability was expected to be similar in both 33°C groups during hypothermia with an incidence of around 25% when defined as SD > 1°C and with a median variance in the proximity of 0.22°C^2, as reported in previous studies.

3.3.3 Fever

Fever was defined as T ≥38.5°C. Fever was assessed during the normothermia period (hour 40 to 72) as in previous literature. Fever was analyzed both as a dichotomous variable and also quantified by number of fever registrations in an ordinal variable with groups of 0, 1-4, 5-10 and >10 registrations. The occurrence of fever during normothermia was expected to be similar in all study groups with an incidence of 30-52% as reported from previous studies.

3.4 Data collection

Medical history (acute myocardial infarction [AMI], congestive heart failure [CHF], hypertension, diabetes, neurological disorder, previous PCI, coronary artery bypass graft [CABG], arrhythmia and respiratory disease), demographic data (sex, length, weight) and treatment data/outcome measures (time of hospital admission, ICU admission, length of ICU stay, hospital stay, mortality, cause of death, cerebral performance category [CPC]) were retrieved from medical records. For exact times of CA and ROSC as well as other CA characteristics (place of CA, CA to ALS, witnessed arrest, bystander CPR, use of CPR device, first presenting rhythm, defibrillations and adrenaline dose), EMS records provided supplementary information. Hourly temperatures during the initial 72 hours of ICU stay as well as time of initiation of TH was retrieved from ICU charts.

3.5 Statistical analysis

All analyses comparing the parameters of Study 1 and Study 2 included all 121 patients of the present study population. 3 patients of Study 2, 1 in the 37°C arm and 2 in the 33°C arm, were treated with 36°C TTM despite being randomized to 33°C or 37°C (36°C treatment was the

standard TTM temperature in the treating hospital before and after the study period). The data of those patients were excluded in analyses with focus comparing patients at 33°C or 37°C.

For categorical variables, a two-sided Fisher's exact test was used. For normally distributed continuous variables, student's t-test was used. For continuous variables not normally distributed, Mann-Whitney U-test was used.

All tests were 2 sided with a p-value <0.05 considered to indicate statistical significance. For all statistical analysis software IBM SPSS Statistics version 26 was used.

4. Ethical considerations

Precautions to protect the identity and integrity of the patients were taken. Each patient was given a randomization number, identification data was documented in an identification log handled with discretion for the purpose of patient anonymity and integrity. Any grouping of data or statistical analysis was undertaken without identities. The data files were stored on a secure server behind the firewalls of the hospital. Results are compilated and presented on a group level only. The retrospective nature of the study and the fact that more than half of the patients are diseased made individual consent less practical and the intrusion into patient integrity was deemed minor. Therefore, the study was classified as ethically justified by the Head of department according to the university standard procedure (dnr GU 2019/2622).

5. Results

Of the total 125 OHCA patients included, data of 4 patients were excluded from the present analysis. 2 from each study period. Two patients were excluded due to early awakening within hours after randomization, TTM was never initiated. In one patient CA was dismissed after additional information had been acquired, TTM was never initiated. The last patient excluded

Table 1. Baseline characteristics

	Study 1			Study 2			
	Total	33°C Group	36°C Group	**Total**	33°C Group	37°C Group	**P-value***
Number	**45**	23	22	**76**	35 †	38 †	
Demographics							
Age - years	**64 ± 12**	66 ± 11	62 ± 13	**68 ± 12**	67 ± 12	68 ± 12	**0.09**
Male sex - no (%)	**38 (84)**	19 (83)	19 (86)	**61 (80)**	30 (86)	29 (76)	**0.63**
BMI - mean ± SD	**27 ± 6**	27 ± 4	28 ± 5	**27 ± 6**	28 ± 5	27 ± 7	**0.92**
Medical history - no (%)							
Prevoius AMI	**12 (27)**	8 (35)	4 (18)	**12 (16)**	4 (11)	8 (21)	**0.16**
Previous CHF	**3 (7)**	2 (9)	1 (5)	**15 (20)**	8 (23)	6 (16)	**0.07**
Hypertension	**36 (47)**	13 (57)	9 (41)	**22 (49)**	18 (51)	18 (47)	**1.00**
Diabetes	**6 (13)**	5 (22)	1 (5)	**9 (12)**	6 (17)	2 (5)	**0.78**
Prevoius neurological disorder	**9 (20)**	5 (22)	4 (18)	**17 (22)**	6 (17)	10 (26)	**0.82**
Prevoius PCI	**6 (13)**	4 (17)	2 (9)	**6 (8)**	2 (6)	4 (11)	**0.36**
Previous CABG	**8 (18)**	4 (17)	4 (18)	**8 (11)**	4 (11)	4 (11)	**0.28**
Previous arythmia	**9 (20)**	4 (17)	5 (23)	**10 (13)**	5 (14)	5 (13)	**0.44**
Respiratory disease	**1 (2)**	1 (4)	0 (0)	**9 (12)**	4 (11)	4 (11)	**0.09**
CA characteristics							
Location - no (%)							**0.50**
Home	**30 (67)**	16 (70)	14 (64)	**43 (57)**	17 (49)	23 (61)	
Public place or work	**13 (29)**	6 (26)	7 (32)	**30 (39)**	16 (46)	14 (37)	
Other	**2 (4)**	1 (4)	1 (4)	**3 (5)**	2 (6)	1 (3)	
Intial rythm VF/VT - no (%)	**33 (75)`**	15 (65)	18 (86)`	**54 (74)```**	27 (79)`	25 (69)``	**1.00**
Witnessed arrest - no (%)	**41 (91)**	21 (91)	20 (91)	**68 (90)**	31 (89)	34 (90)	**1.00**
Bystander CPR - no (%)	**37 (82)**	31 (91)	27 (75)	**61 (84)**	20 (87)	17 (77)	**1.00**
Mechanical device CPR	**29 (64)**	15 (65)	14 (64)	**53 (72)**	26 (77)	25 (68)	**1.00**
Time to event - minutes							
CA to ALS - median (IQR)	**12 (9-15)**	12 (9-18)	12 (7-14)`	**10 (5-12)**	10 (5-14)	8 (6-11)	**0.02•**
CA to ROSC - median (IQR)	**29 (20-39)**	30 (24-52)	25 (18-35)	**25.5 (17-49)**	26 (17-40)	26 (16-40)	**0.18**
Admission							
Admisson temp - mean (median)	**35.2 (35.5)**	34.9 (35.4)	35.5 (35,5)	**35.5 (35.7)**	35.6 (35.7)	36.1 (35.5)	**0.16**
CT - no (%)	**11 (24)**	6 (26)	5 (23)	**27 (36)**	9 (26)	17 (45)	**0.23**
Angiography - no (%)	**21 (47)**	13 (57)	8 (36)	**39 (51)**	24 (69)	15 (40)	**0.71**
Discharge							
ICU stay (days) - median (IQR)	**3 (3-4)**	3 (2-5)	3 (3-4)	**4 (2-6)**	4 (3-6)	3 (2-5)	**0.17**
Hospital stay (days) - median (IQR)	**7 (3-12)**	5 (3-12)	8 (5-13)	**9 (4-17)**	10 (4-24)	8 (3-14)	**0.34**
ICU mortality - no (%)	**16 (36)**	12 (52)	4 (18)	**26 (34)**	11 (31)	13 (34)	**1.00**
Hospital mortality - no (%)	**28 (62)**	15 (65)	13 (59)	**42 (55)**	18 (51)	22 (58)	**0.57**
CPC at hospital discharge							**0.70**
CPC 1-2 - no (%)	**16 (36)**	7 (30)	9 (42)	**29(39)```**	14 (42)``	14 (38)`	
CPC 3-5 - no (%)	**29 (64)**	16 (70)	13 (59)	**44 (60)```**	19 (58)``	23 (62)`	

Baseline characteristics. • indicates significance. `1 missing data. ``2 missing data. ```3 missing data. † 33° group missing 2 subjects' data and 37° group missing 1 subjects' data due to treatment at 36° despite randomization to 33°/37°. * Significance level for comparisons between Study 1 and Study 2 total columns. ALS denotes advanced life support, AMI acute myocardial infarction, BMI body mass index, CA cariac arrest, CABG coronary arterial bypass graft, CHF congestive heart disease, CPC cerebral performance category, CPR cardiopulmonary resuscitation, IQR interquartile range, ICU intensive care unit, PCI percutaneous coronary intervention, SD standard deviation, VF/VT ventricular fibrillation/ventricular tachycardia

suffered CA secondary to multi-organ failure and died shortly after randomization, TTM was never initiated. As a result; 121 patients remained in a present study population. The two groups had similar baseline characteristics, shown in Table 1.

5.1 Timing of TTM

5.1.1 Time from ROSC to target temperature

The mean time from ROSC to target temperature 33°C was significantly (P<0.001) shorter in the 33° Study 2 group (mean 06:38 ± 01:41 [SD]) as compared to the 33° Study 1 group (mean 10:06 ± 04:17 [SD]). However, the proportion of patients reaching the target temperature within the 4.5-hour goal did not differ significantly (P=0.38), only 3 patients (13%) in Study 1 and 2 patients (6%) in Study 2 met this goal. The results are shown in Figure 3 and Table 2.

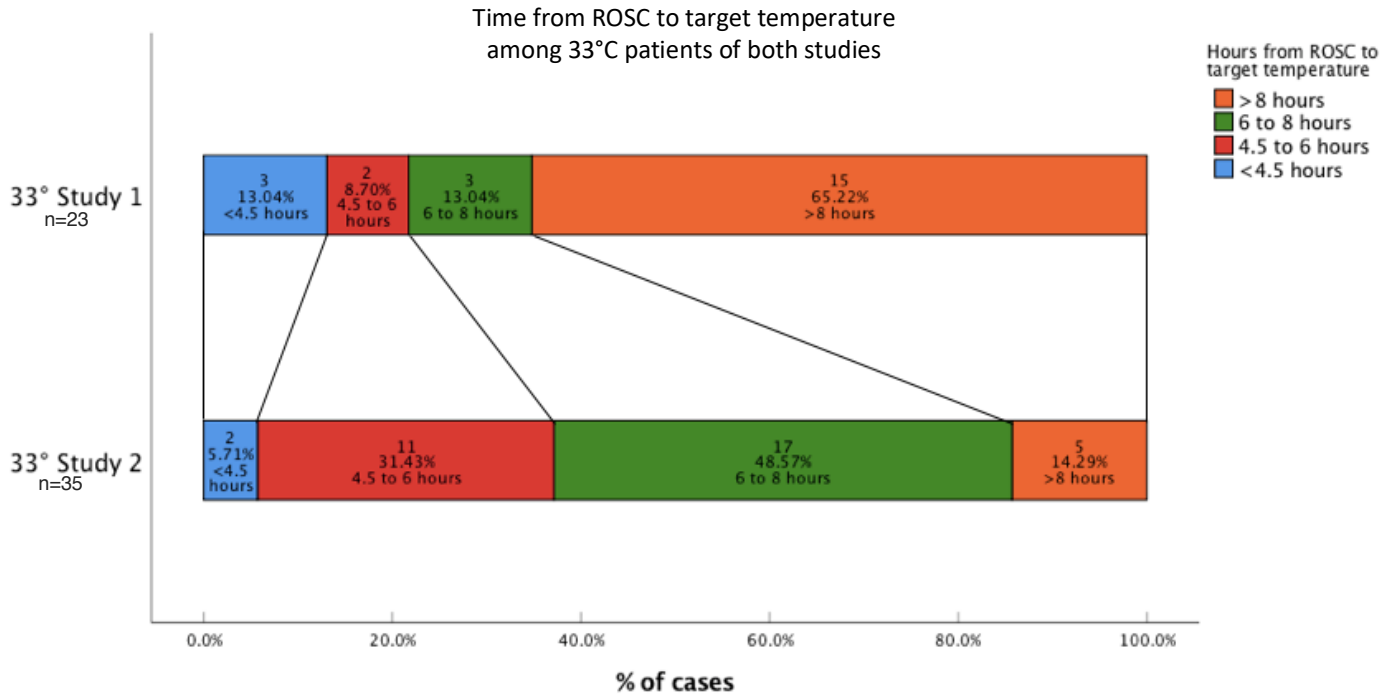

Fig 3. Time from ROSC to target temperature among 33°C groups of both studies. A majority of patients had a times >8h in Study 1, while this group only constituted a minority of cases in study 2. However, no significant difference in the proportion of patients within the 4.5-hour goal was seen. ROSC denotes return of spontaneous circulation, SD standard deviation.

Table 2. Time (hh:mm) from ROSC to target temperature

	Mean	± SD	Median
33° Study 1	10:06	04:17	09:20
36° Study 1	04:32	02:37	04:03
33° Study 2	06:38	01:41	06:26
37° Study 2	07:33	05:24	07:40

ROSC denotes return of spontaneous circulation, SD standard deviation

5.1.2 Time from ROSC to ICU admission

Time from ROSC to ICU admission did not differ significantly between the 33°C groups of both studies (P=0.82). The results are listed in Table 3.

Table 3. Time (hh:mm) from ROSC to ICU admission

	Mean	± SD	Median
33° Study 1	01:55	01:05	01:59
36° Study 1	02:00	00:51	01:57
33° Study 2	01:55	00:59	02:07
37° Study 2	01:43	00:51	01:30

33°C groups of both studies had a mean time from ROSC to ICU admission of 1h55min. ICU denotes intensive care unit, ROSC return of spontaneous circulation, SD standard deviation.

5.1.3 Time from ICU admission to TH initiation

The time from ICU admission to TH initiation did not differ significantly between the 33°C groups(P=0.10). The times and proportions of patients within 45-minute range groups are listed in Table 4 and Figure 4.

Table 4. Time (hh:mm) from ICU admission to TH initiation

	Mean	± SD	Median
33° Study 1	02:21	01:43	02:00
33° Study 2	01:35	01:05	01:20

ICU denotes intensive care unit, ROSC return of spontaneous circulation, SD standard deviation

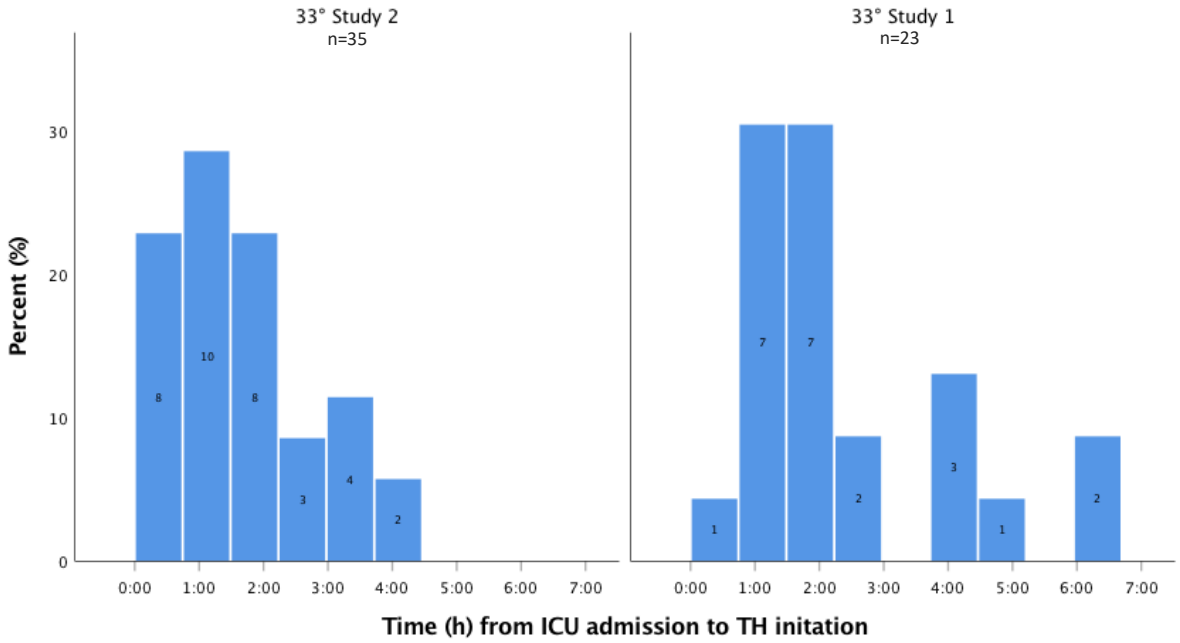

Fig 4. Time from ICU admission to TH initiation among 33°C patients of both study groups. Data labels shows number of patients in each bar and the height bars corresponds to its proportion of patients (%). Each bar spans 45 minutes. ICU denotes intensive care unit, TH therapeutic hypothermia.

5.1.4 TH initiation to target temperature

As seen in Table 5, the time from initiation to target temperature was significantly shorter in the 33° Study 2 group than in the 33° Study 1 group (P=0.004). The proportion of patients within the ≤ 2-hour target did not differ between the 33°C groups (P=0.725).

Table 5. Time (hh:mm) from TH initiation to target temperature

	Mean	± SD	Median	≤ 2 hour target
33° Study 1	05:47	03:27	06:00	3 (13%)
33° Study 2	03:07	01:36	02:30	7 (20%)

SD denotes standard deviation, TH therapeutic hypothermia

5.1.5 Time from ICU admission to target temperature

As shown in Table 6, the time from ICU admission to target temperature was significantly shorter in the 33°C Study 2 group 4:43 (± 01:53) than in the 33°C Study 1 group 08:11 (± 04:13) (P<0.001). The time from ICU admission to target temperature as well as temperature

variability and distribution during the initial 15 hours following ICU admission are visualized in Figure 5.

Table 6. Time (hh:mm) from ICU admission to target temperature

	Mean	± SD	Median
33° Study 1	08:11	04:13	08:00
36° Study 1	02:32	02:40	02:15
33° Study 2	04:43	01:53	04:30
37° Study 2	06:02	04:57	05:35

ICU denotes intensive care unit, SD standard deviation.

5.1.6 Time from ROSC to ≤ 34°C

Time from ROSC to temperature ≤ 34.0°C in the 33°C study 2 group can be seen in Table 7.

Table 7. Time (hh:mm) from ROSC to 34°C

	Mean	± SD	Median
33° Study 2	05:41	01:37	05:47

ROSC denotes return of spontaneous circulation

5.2 Variability

The mean variabilities of the different study groups are shown in Table 3. Mean temperature variability was significantly lower in the 33° Study 2 group than in the 33° Study 1 group in both TH and normothermia phase (P<0.001 and P=0.002). Variability during the first 15 hours following ICU admission is visualized by the height of the boxes in Figure 5.

Table 8. Temperature variability during TH and normothermia phase

	Hour 10 to 24 MAD		Hour 40 to 72 MAD	
	Mean	± SD	Mean	± SD
33° Study 1	0.52	0.28	0.47	0.25
36° Study 1	0.42	0.16	0.37	0.12
33° Study 2	0.23	0.15	0.29	0.15
37° Study 2	0.27	0.19	0.30	0.16
Total	0.33	0.22	0.35	0.19

Temperature variability during TH phase (hour 10 to 24) and normothermia phase (hour 40 to 72) among all study groups. Variability was significantly lower in the 33° Study 2 group than in the 33° Study 1 group in both phases (P<0.001 and P=0.002). MAD denotes mean absolute deviation, SD standard deviation, TH therapeutic hypothermia.

Initial 15h in the ICU - Temperature variation and reaching target temperature – all study groups

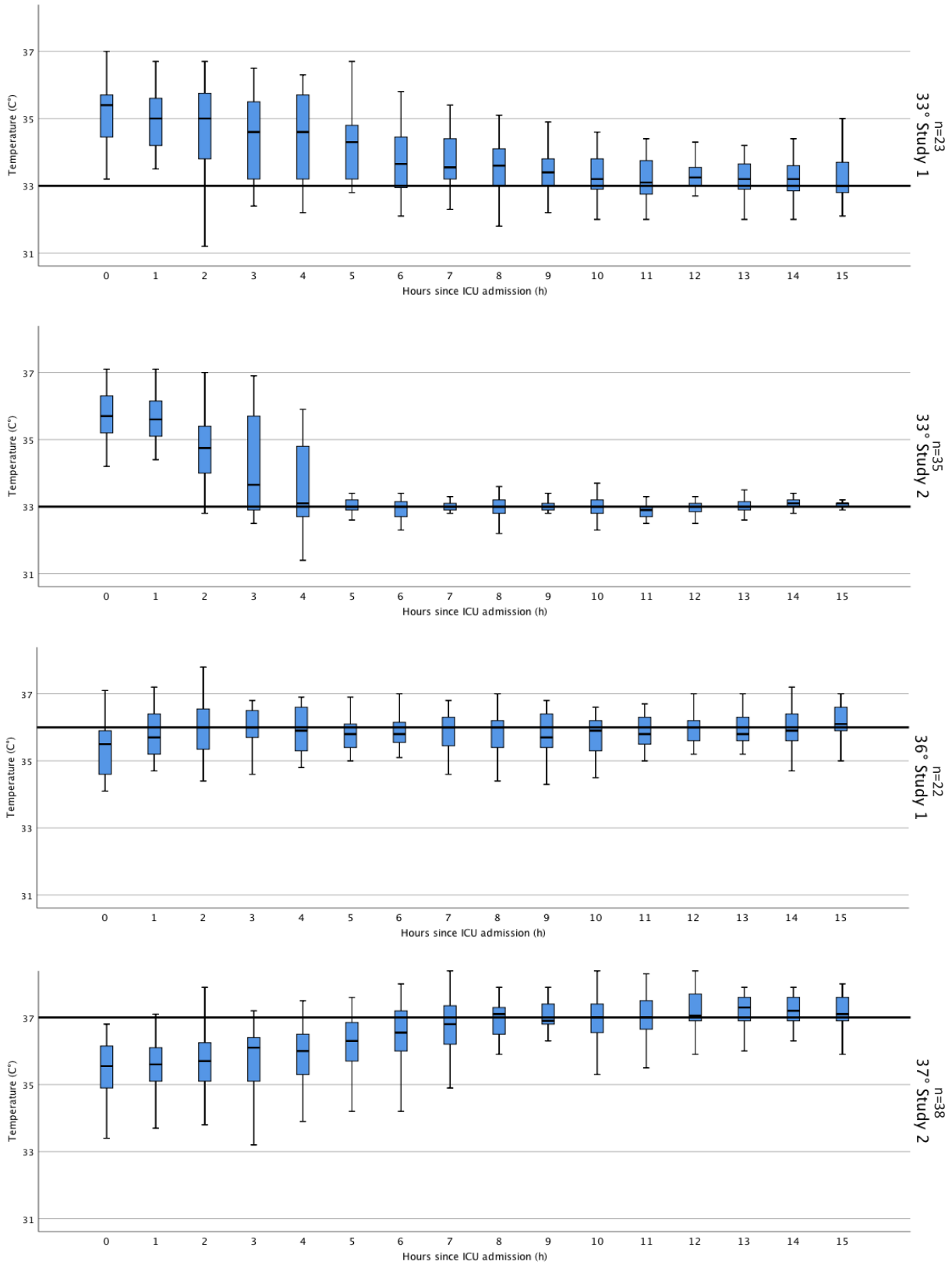

Fig. 5. Boxes represent interquartile range (IQR), the marked line is the median and the T-bars are maximum and minimum temperatures within 1,5 IQR from the box. As depicted by box plots, time from ICU admission to target temperature was shorter (P<0.001) and temperature variability was lower (P<0.001) in the 33° study 2 group compared to the 33° study 1 group. Variability corresponds to the height of the IQR box. 36° and 37° patients needed passively rewarming before reaching target temperature in a majority of cases as visualized in Fig 2. ICU denotes intensive care unit, TH therapeutic hypothermia.

Variability was also assessed dichotomously as fulfilling the MAD<0.5°C criterion or not. In the hypothermia phase, 33 (94%) of the 33° Study 2 patients had an MAD <0.5°C, while 10 patients (44%) of the 33° Study 1 met this criterion (P<0.001). In the normothermia phase, 28 (90%) of the 33° Study 2 patients met this criterion as compared with 14 (64%) of the 33° Study 1 patients (P=0.018).

Third, variability was analyzed dichotomously during hypothermia (hour 10 to 24) with high variability defined as SD of mean temperature > 1°C in order to compare results to an earlier study. One patient (3%) in the 33°C study 2 and two patients (9%) in the 33° Study 1 group had an SD > 1°C.

Fourth and last, the median temperature statistical variance during hypothermia of the 33°C Study 2 group was 0.07°C^2 (IQR 0.04-0.13).

5.3 Fever

Fever incidence and number of fever registrations among all study groups is shown in Table 9.

Table 9. Fever (T≥38.5) incidence and distribution during normothermia phase (hour 40 to 72)

	Study 1			Study 2		
Number of fever registrations	Total (n=45)	33°C Group (n=23)	36°C Group (n=22)	Total (n=76)	33°C Group (n=35)	37°C Group (n=38)
0 - no (%)	32 (71)	17 (74)	15 (68)	68 (91)	34 (97)	32 (84)
1-4 - no (%)	9 (20)	5 (22)	4 (18)	7 (8)	1 (3)	5 (13)
5-10 - no (%)	2 (4)	1 (4)	1 (5)	1 (1)	0 (0)	1 (3)
>10 - no (%)	2 (4)	0 (0)	2 (9)	0 (0)	0 (0)	0 (0)
Any fever	13 (29)	6 (26)	7 (32)	8(11)	1 (3)	6 (16)

Number of hourly temperature registrations ≥38.5°C and fever incidence (any fever) among all study groups. T denotes temperature.

5.3.1 Fever during normothermia phase (hour 40 to 72) - Study 1 and Study 2

Fever incidence during the normothermia phase was less common in Study 2 as compared to Study 1 (P=0.01). The quantity of fever registrations can be seen in Table 9 and Figure 6.

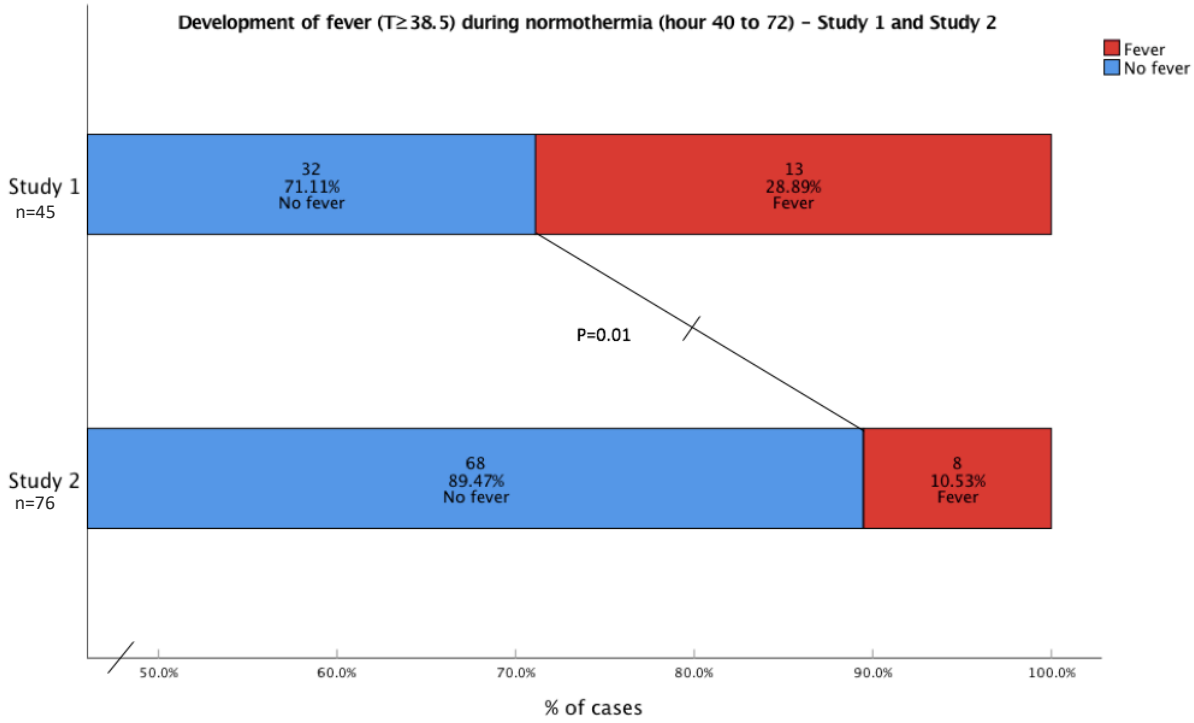

Fig. 6. Fever incidence during normothermia phase between Study 1 and Study 2. Fever incidence was significantly lower in the Study 2 group. T denotes temperature.

5.3.2 Fever during normothermia phase - 33°C study groups

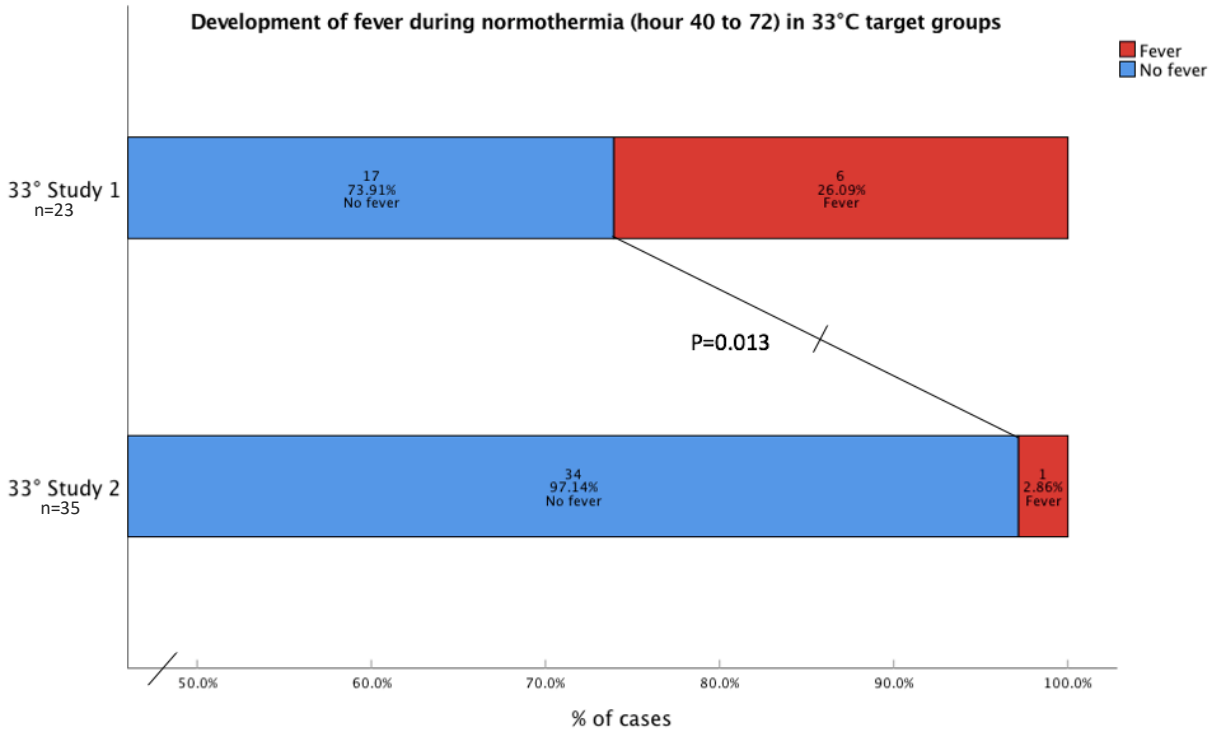

Fig. 7. Fever incidence during normothermia phase between 33°C groups of both studies. Fever incidence was significantly lower in the 33°C study 2 group as compared to the 33°C Study 1 group.

As seen in Figure 7, six patients (26%) of the 33° Study 1 group experienced any fever (T≥38.5) registration as compared to one (3%) in the 33° Study 2 group (P=0.013).

5.3.3 Fever - 33°C vs normothermia patients of Study 2

As seen in Figure 8, a higher number of patients developed fever during the normothermia phase in the 37° Study 2 group than in the 33°C Study 2 group but there was no significant difference between the groups as to the proportions of patients with fever (P=0.11).

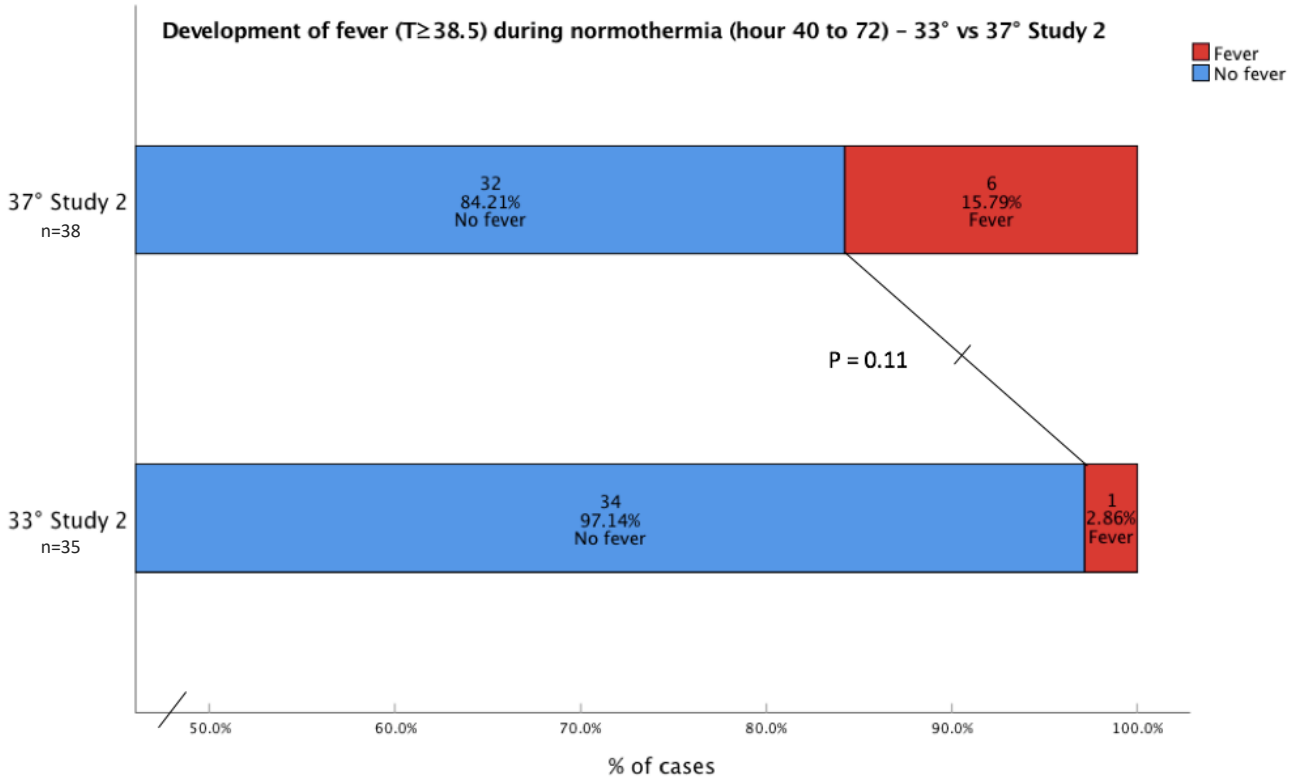

Fig. 8. Fever incidence during normothermia between 33°C and 37°C groups of Study 2 did not differ significantly. T denotes temperature.

6. Discussion

6.1 Timing of TTM

The most important finding of this analysis of two historical study cohorts was that time from ROSC to target temperature and all other subdivision timing measures but ROSC to ICU admission was shorter in the 33° Study 2 group than in the 33° Study 1 group. It could be argued that some of this difference might be attributed to the longer inclusion interval in Study 1 (240 minutes as opposed to 180). However, most difference could be seen in time from initiation to target temperature, which represents an internal intensive care process making this assumption unlikely. The "Arctic Sun® 5000" core temperature feedback surface cooling device was the same type used in both study periods with the same device settings for cooling. It should also be noted that ICU staff numbers, ICU patient numbers and CA arrest numbers did not differ between the study periods. Nor did time-consuming procedures before reaching target temperature such as CT or angiography differ significantly. While CT scans prior to reaching target temperature was documented in 26% of cases in both 33°C groups, angiography was documented in a larger proportion in the 33°C Study 2 (69%) group as compared to the 33°C Study 1 group (57%). One important factor might be increased awareness among ICU staff that shorter induction times are preferable and consequently implementation of new routines. The publications supporting early initiation and rapid cooling along with the criticism of long initiation times in earlier studies has been influential(71, 78). E.g. in the Study 2 protocol when describing the initiation phase, it is stated "rapid achievement of target temperature" while "achievement of target temperature" is stated in Study 1 protocol. Additionally, years of training and everyday practice of similar TTM protocols as well as intensified information prior to Study 2 might present other mechanisms.

Furthermore, we found that the mean ± SD time from ROSC to temperature ≤34°C was 05:41±1:37 minutes in Study 2. Of 8 clinical trials studying different aspects of TTM enrolling

a minimum of 150 patients since 2007, reported average time from ROSC to ≤34°C varied between 4.0 and 7.5 hours (overall mean 5.0 hours, median 4.7 hours)(49, 51, 60, 71, 72, 79-84).

Another recent study not included in these trials due to only reporting median time, reported a median time to 34°C of 3.0 hours. That study used an inferior vena cava cooling catheter device and was the only study which reported a time from ROSC to target temperature under 4 hours, however not reporting the same parameter (although the median was in close proximity of the mean in our data)(51). The previously mentioned study "TTM1", reported an overall average time of 4.5 hours from ROSC to ≤34°C(81). Our result at Sahlgrenska University Hospital with an average of 5 hours 41 minutes from ROSC to ≤34°C among our 33°C target patients admitted March 2018 – January 2020 is comparable to the upper-middle range of reported initiation times from the current literature. Since our study only included patients of presumed cardiac cause of arrest or unknown, it is reasonable to assume that a larger proportion of patients admitted via angiography was included, delaying initiation of TH (69% of the 33°C Study 2 participants underwent angiography on admission). While the reporting of angiography use is not standardized, a meta-analysis of studies reporting acute coronary angiographies following OHCA of mixed etiologies reported a heterogenous use with numbers ranging from 14% to 83% between studies, the overall mean being 41%(85).

Neither in our cohorts nor in the current literature, the time to target temperature among the majority of patients are close to the 3-hour goal which is suggested beneficial by animal and small sample human studies(65, 71). It should be noted that such short induction times have been achieved in very few human studies and are not part of international recommendations of TTM treatment today(6, 48). If such short times to target temperature should prove beneficial in larger materials and become part of TTM protocols, it is reasonable to assume that implementation of new strategies of early pre-hospital induction of TTM would be needed.

In summary, the time from ROSC to target temperature (or ≤34°C) at Sahlgrenska University Hospital during the 2018-2020 study period was in line with the ones reported by the largest clinical trials of TTM today. If shorter induction times were to prove beneficial in larger human clinical trials, earlier initiation of TH would represent a suitable target for improvement in our material as the mean time to initiation of TH was 3.5 hours. The specific changes in local OHCA treatment protocol needed to achieve such a goal is beyond the scope of this study and would need further investigation.

6.2 Variability

Temperature variability was lower in Study 2, both in hypothermia and in normothermia phases, suggesting improved temperature precision during TTM since the 2011-2013 Study 1 period. Only one (3%) of the patients in the most current 33°C Study 2 group had a variability during the hypothermia defined as SD > 1°C as compared to 25% of patients in a study of 229 patients conducted in Brussels using a similar cooling device(74). The temperature median statistical variance during hypothermia of 0.07°C^2 (IQR 0.04-0.13) was also low in comparison to published data(75). A prospective study of temperature variability during TTM among 242 resuscitated survivors of CA conducted in the United States and with the use of a similar cooling device, reported a median statistical variance of 0.22°C^2 (IQR 0.08-0.42)(75).

Overall, TTM precision at Sahlgrenska University Hospital as to low temperature variability have improved over time and appears to be low when compared to the sparse data published from other institutions.

6.3 Fever

Fever incidence was significantly lower during the 2018-2020 Study 2 period, both between 33°C target patients as well as for 36°C and normothermia patients. One important factor might be increased ICU staff awareness of the importance of fever mitigation and updated clinical and study protocols advocating stricter adherence to fever mitigation. For example, in the Study

2 protocol, it is specified that a cooling device should be used if needed during the normothermia period. This directive lacks in the Study 1 protocol.

Interestingly, a tendency of higher fever incidence during normothermia phase was observed in the 37°C study group (16%), compared to the 33°C study group (3%), although non-significant. The use of a cooling device to maintain normothermia in the 37°C study group was documented in 68% of patients as opposed to 100% in the 33°C group, in all cases it was documented within the first 24 hours following CA. Since cooling devices were already present and available in a larger proportion of patients in the 33°C group, they may have been used more frequently during later phases of TTM. Whether this difference in fever incidence between the 33°C and normothermia groups can be attributed to a coincidence, fever mitigating effects of 33°C TH or unidentified treatment discrepancies remains uncertain and beyond the reach of this study.

When compared to the current literature, fever incidence in our material was low. A recent meta-analysis of 6 studies enrolling a total of 950 patients treated with TTM after CA, reported incidences between 30-52%(63, 77, 82, 86-89). The two studies most similar to ours, only including OHCA patients and defining fever at 38.5°C (38°C in the remaining 4 studies) reported incidences of 30%(87) and 50%(77). Two studies reporting fever among OHCA patients not treated with TTM reported an incidence of 83% when fever was defined as ≥38.0°C(90) and 20%-53% when defined as ≥39°C(90, 91).

Overall, fever mitigation among OHCA arrest patients admitted to the ICU at Sahlgrenska University Hospital seem to have improved over time. Since fever incidence during the normothermia phase tended to be higher in the most recent normothermia group than in the 33°C group, avoidance of fever may represent a target of improvement, should strict normothermia become the main target of future TTM protocols.

7. Limitations

The Study 1 and Study 2 populations were from different time periods which may induce learning bias. Some objective recommendations differed between the protocols and may have been confounders to the results. These include an additional 60 minutes of inclusion window in Study 1 and a rewarming rate of 1/2 °C/hour instead of 1/3 °C/hour as in study 2. Despite equal length of admission periods, Study 2 admitted 78 patients while Study 1 only admitted 47.

Due to small sample size, differences between the two Study cohorts could only reach statistical significance if they were of considerable magnitude. On the other hand, this allowed findings to be of clinical importance.

A limitation of our study potentially contributing to a slight overestimation of time to target temperature was the moderate resolution of temperature registrations with 1 temperature per hour. Consequently, if a patients' target temperature was 33.1°C after 4 hours, the first registration with a temperature on or below the target of 33°C would be after 5 hours, overestimating the true time to target temperature. By trivial calculation, if target temperatures were reached evenly distributed from minute 1 to 60 every hour, this overestimation would be around 30 minutes.

There are technical limitations to the specification of temperature data to be core temperatures from urinary bladder probes. Bladder probes do not provide accurate temperatures in anuric or oliguric patients. Also, when catheters are flushed, the injected solution might alter bladder temperature. However, it was pre-specified by study protocols that temperature in oliguric patients should be measured via esophageal or intra-vascular probes.

Study periods during which strict intervention protocols are implemented do not perfectly represent everyday practice. Intensified information prior to the study period, local study leaders and staff interest might lead to increased adherence to study and treatment protocols not representative of everyday practice.

8. Conclusions

The overall precision of TTM treatment of OHCA at Sahlgrenska University Hospital as to timing, variability and fever is in line with reported data of the largest clinical trials of TTM today. In all three aspects, significant improvement between the 2011-2013 and the 2018-2020 study period was observed.

If very short induction times were to prove favorable in future clinical trials, the time from ROSC to TH initiation would provide a target for improvement in our material as this time was 3.5 hours on mean in the most recent data.

Populärvetenskaplig sammanfattning

Titel: Måluppfyllelse vid behandling med temperaturkontroll efter hjärtstopp

Examensarbete, läkarprogrammet. Författare: Axel Strålin

Hjärtstopp orsakar många dödsfall varje år runtom i världen. När en person drabbas av hjärtstopp skadas hela kroppen av den akuta syrebristen som uppstår när blodcirkulationen i kroppen upphör. Hjärnan är extra känslig för denna syrebrist och bland patienter som blir återupplivade med hjärt-lungräddning dör många i ett senare skede av sina hjärnskador. Skadorna på hjärnan och kroppen vid ett hjärtstopp kan enkelt delas upp i akuta skador och efterföljande skador. De efterföljande skadorna har att göra med inflammatoriska och kemiska reaktioner i kroppen när blodcirkulationen återfås. För att lindra de efterföljande skador som uppstår efter ett hjärtstopp använder man sig idag av kylbehandling, också kallat terapeutisk hypotermi. Endast personer som överlevt sitt hjärtstopp och fortfarande är medvetslösa behandlas med kylbehandling. Patienten skrivs in till intensivvården, där erhåller patienten kylbehandling i 24 timmar och efter detta värmer man patienten till 37°C och är extra vaksam på att patienten inte får feber, så kallad efterföljande kontrollerad normotermi.

Den här studien syftar till att utvärdera precisionen av hypotermibehandlingen över tid på Sahlgrenska och att jämföra den med publicerade data från andra studier för att se hur den står sig internationellt. För att mäta precisionen har vi studerat tid från hjärtstopp till måltemperatur, generellt tror man att kortare tid till kylning är bra och att man med för långa tider till kylning riskerar att gå miste om gynnsamma effekter. Vi har också studerat temperaturvariabilitet, som är ett mått på hur precist en patient ligger på sin måltemperatur och hur väl kylmaskinen lyckas hålla temperaturen konstant. Till sist har vi också undersökt feber efter kylningsfasen, vilket man vet påverkar prognosen negativt och därför vill undvika. Både tid till kylning, variabilitet och feber hade förbättrats över tid på Sahlgrenska och sammantaget höll behandlingen acceptabel god kvalitet som låg inom ramen för övriga publicerade data från forskningsfältet.

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