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Prolonged Cardiopulmonary Resuscitation in Accidental Hypothermia:

Physiological and pathophysiological effects of cardiopulmonary resuscitation (CPR) in hypothermia regarding hemodynamics, oxygen transport and regional blood flow.

Sergei Valkov

A dissertation for the degree of Philosophie Doctor, July 2023

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1 Acknowledgements

This study was performed at the Anesthesia and Critical Care research group at the UiT, the Arctic University of Norway. It was gratefully funded by The Research Council of Norway and Barents 2020. My Ph.D. journey started in 2013 as a young medical doctor, inexperienced in research, and a newbie husband and father who had just moved from abroad. The years passed are a separate chapter in my life. They were spent learning how to conduct the research and building a whole new reality with all its ups and downs. Without endless support and mentorship, professionalism, patience, love, and care of all of you people surrounding me during this time, it would never be possible to achieve this goal.

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2 Abstract

Main objectives of this study were to examine the physiological and pathophysiological effects of 3 hours continuous cardiopulmonary resuscitation (CPR) at 27°C with respect to hemodynamics, O_2 transport, and regional blood flow. We aimed to explore mechanisms responsible for successful resuscitation of accidental hypothermia victims in hypothermic (27°C) cardiac arrest (HCA) and evaluate their value during prolonged mechanical CPR as part of pre-hospital interventions. We performed three randomized controlled studies using an intact porcine model to answer different parts of the question:

The first paper is a descriptive report of changes in hemodynamic function, O_2 transport, and organ blood flow during 3-hours deep stable hypothermia (27°C) with maintained spontaneous circulation and rewarming using the thoracic lavage method. The results indicated that despite a hypothermia-induced substantial reduction in cardiac output (CO) and mean arterial pressure (MAP), physiological compensatory responses could provide adequate O_2 delivery and blood flow distribution to essential organs after rewarming from 3-hours deep hypothermia (27°C)

The second paper describes the effects of CPR using an automated mechanical device to replace spontaneous CO during 3 hours at 27°C vs. 45 min at normothermia by determining hemodynamics, O_2 transport, and organ blood flow. We found that the level to which CPR could replace CO and MAP does not change with hypothermia. Moreover, CPR at 27°C could provide marginal but sufficient global O_2 delivery to sustain aerobic metabolism throughout 3 hours. In contrast, normothermic CPR for 45 min showed impaired hemodynamics, O_2 transport and organ blood flow.

The third paper aimed to investigate autoregulation of cerebral blood flow and cerebral O_2 transport during 3-hours hypothermic (27°C) CPR compared to during spontaneous circulation at the same temperature. Potent physiological compensatory responses during 3-hours CPR provided unaltered cerebral O_2 delivery as during spontaneous circulation, and maintained aerobic metabolism and autoregulation of cerebral blood flow during the first 2 of 3 hours of CPR at 27°C.

Results from Paper I-III support using early and continuous CPR in accidental hypothermia patients in HCA under rescue and transport to hospitals capable of introducing specific rewarming techniques.

3 List of papers

Studies included in the current thesis were carried out at the Anesthesia and Critical care Research Group, Department of Clinical Medicine at UiT, the Arctic University of Norway. Papers included in this thesis are listed below and will further be mentioned according to their numerals.

Paper I

Valkov S, Mohyuddin R, Nilsen J.H, Schanche T, Kondratiev TV, Sieck GC, Tveita T. Organ blood flow and O_2 transport during hypothermia (27°C) and rewarming in a pig model. Exp Physiol. 2019; 104: 50–60. https://doi.org/10.1113/EP087205.

Paper II

Nilsen JH, Valkov S, Mohyuddin R, Schanche T, Kondratiev TV, Naesheim T, Sieck GC, Tveita T. Study of the Effects of 3 h of Continuous Cardiopulmonary Resuscitation at 27°C on Global Oxygen Transport and Organ Blood Flow. Front Physiol. 2020 Apr 16;11:213. https://doi:10.3389/fphys.2020.00213.

Paper III

Valkov S, Nilsen JH, Mohyuddin R, Schanche T, Kondratiev T, Sieck GC, Tveita T. Autoregulation of Cerebral Blood Flow During 3-h Continuous Cardiopulmonary Resuscitation at 27°C. Front Physiol. 2022 Jun 9;13:925292. https://doi:10.3389/fphys.2022.925292.

4 Abbreviations

ACD CPR – active compression/decompression CPR

ACLS – advanced cardiac life support

AED – automated external defibrillator

AHA – American Heart Association

BLS – basic life support

CA – cardiac arrest

CBF – cerebral blood flow

CBV – circulating blood volume

CPB – cardiopulmonary bypass

CO – cardiac output

CPP – cerebral perfusion pressure

CPR – cardiopulmonary resuscitation

CVP – central venous pressure

CVR – cerebrovascular resistance

DO_2 – global oxygen delivery

ECC – extracorporeal circuit (rewarming)

ECLS – extracorporeal life support

ECMO – extracorporeal membrane oxygenation

ERC – European resuscitation council

HCA – hypothermic cardiac arrest

HR – heart rate

ICP – intracranial pressure

IHCA – in-hospital cardiac arrest

ILCOR – International Liaison Committee on Resuscitation

LVSP – left ventricular systolic pressure

MAP – mean arterial pressure

O_2ER – oxygen extraction ratio

ERcrit – critical extraction ratio

OHCA – out-of-hospital cardiac arrest

PAP – pulmonary artery pressure

PVC – polyvinylchloride

RCT – randomized control study

ROSC – return of spontaneous circulation

sARI – static autoregulation index

SV – stroke volume

SvO_2 – mixed venous oxygen saturation

TPR – total peripheral resistance

VF – ventricular fibrillation

VO_2 – global oxygen consumption

5 Introduction

5.1 Hypothermia. Definition, classification, and ranges of severity

Hypothermia is defined as intentional or accidental reduction of core temperature to a level lower than 35°C in a state when a cold stressor engulfs the body's temperature regulation mechanisms [1-3].

This definition distinguishes two major types of hypothermia – *intentional* and *unintentional (accidental)*. Intentional or therapeutic hypothermia is used as a measure of organ protection during cardiovascular surgery, and for cerebral protection in unconscious survivors after resuscitation from cardiac arrest. Unintentional or accidental hypothermia is the consequence of environmental exposure and can be either *primary* or *secondary*. Primary accidental hypothermia occurs when a healthy, unprotected person is exposed to low ambient temperature, as mimicked in the current thesis. Secondary hypothermia is related to an underlying medical illness.

One can differentiate between three basic types of accidental hypothermia depending on the speed of entry. *Acute type (e.g., immersion)* occurs when an extensive cold stressor chills the human body before it loses all energy reserves, outpacing heat production. The duration of exposure is usually a maximum of a few hours. *Subacute type (e.g., exhaustion)* arises when cooling occurs after depletion of the energy reserves in the body. The duration of exposure is several hours. *Subchronic/chronic type (e.g., urban)* occurs after exposure to a mild or moderate cold environment for days or weeks [4].

Over the years authors have proposed different staging of the hypothermia severity. In 1974, Popovic defined core temperature above 32°C as mild hypothermia, between 22°C and 32°C as moderate hypothermia, between 8°C and 22°C as deep hypothermia, and lower than 8°C as profound hypothermia [5]. In 1983, Wong defined mild hypothermia as 32-35°C, moderate as 26-31°C, and deep as 20-25°C [6]. Then, in 1986, Moss classified mild hypothermia as 32-35°C, moderate as 28-32°C, and severe below 28°C. This classification is used in the European Resuscitation Council (ERC) guidelines [7]. However, the American Heart Association (AHA) recommends to classify mild hypothermia as core temperature above 34°C, moderate as 30-34°C, and severe below 30°C [8, 9]. Its focus falls on the clinically relevant border of 30°C, below which the risk of life-threatening arrhythmias and CA is greatly enhanced.

There is, however, still another classification of hypothermia severity [10]. A clinical staging scheme by the International Commission for Mountain Emergency Medicine described the following grading system: mild (HT I) – normal mental status with shivering, estimated core temperature is 32-35°C; moderate (HT II) – altered mental status without shivering, estimated core temperature is 28-32°C; severe (HT III) – unconscious, estimated core temperature is 24-28°C; severe (HT IV) – apparent death, core temperature 13.7 to 24°C. At the latter stage, resuscitation may still be possible. The last stage (V) is characterized by death due to irreversible hypothermia with a core temperature < 9-13.7°C where resuscitation is not possible [10]. This system was first intended to help medical personnel estimate the severity of hypothermia by the clinical presentation during the rescue of accidental hypothermia victims [3]. It is, however, well known that hypothermic physiological response may vary significantly from patient to patient; hence the stages can overlap, making it difficult to assess the objective status.

5.2 Accidental hypothermia, its place in human history

5.2.1 In peacetime

Even though death from cold was first described more than a thousand years ago by Hippocrates (460-370 BC), hypothermia as a clinical term was not used until the middle of the 20th century [11]. The main reason for that was the need for an appropriate tool for recognizing and grading this condition. The clinical thermometer was invented by Sir Thomas Clifford Allbutt in 1866, and became routinely used in the early 1900's [12]. First in the 1930s and 1940s did researchers start more detailed physiological experiments inspired by the potential effects of therapeutic hypothermia to cure malignant diseases and to prevent organ ischemia during cardiac surgery.

It is remarkable that in the reports from the Antarctic expeditions (1895-1922), there was no mention of hypothermia as a term, especially regarding the fact that five men from Robert Scott's expedition to the South Pole were lost due to freezing, including Scott himself. Only short journal descriptions stated that core temperatures of the adventurers were "subnormal" and that the "clinical thermometer was not marked low enough" to measure their temperatures. It was stated, however, that such temperature lowering could be deadly [13].

Very little data are available regarding the hypothermia experience of Nansen's and Amundsen's expeditions to the North and South Poles. In Nansen's memoirs, it is, however, mentioned that Johansen saved his life with the expert use of passive rewarming after Nansen attempted saving lost kayaks in the arctic water [14].

Well-documented deaths from accidental hypothermia during peacetime are mainly related to large accidents. The first documented incident occurred with the "unsinkable"

steam liner “Titanic” in the northern Atlantic on the night of April 14, 1912, on its maiden journey from Southampton to New York City. Between 1490 and 1635 dead victims were reported. Many of them perished due to severe hypothermia, immersed in the ice-cold water. The interesting fact is that the dead victims, floating in life jackets on calm water, were declared dead due to drowning. Recently, in his letter to Lancet in 2003, Shetty declared that the death cause was due to the accidental hypothermia [15]. If a similar accident had happened today, many casualties could have been avoided with the application of the current knowledge of transportation and specific rewarming techniques. This was somehow demonstrated in the 2011 Danish Præstø fjord dragon boat incident, where 15 healthy individuals, primarily children, became severely hypothermic from immersion in ice-cold salty water. Seven of them experienced circulatory arrest. Due to timely transportation with early cardiopulmonary resuscitation (CPR), application of in-hospital extracorporeal membrane oxygenation (ECMO) rewarming, and intensive neurorehabilitation, all victims survived the accident with good neurologic outcomes [16].

5.2.2 At war. «General Frost»

As opposed to the historical reports at peacetime, much documentation has been collected from numerous war campaigns. In 492 BC, the Persian general Mardonios sailed against the Greeks and lost about 300 ships and 20,000 men in a cold stormy sea. In the chronicles by Herodotus, it was written: “… some were seized by these [sea monsters] and so perished, while others were dashed against the rocks; and some of them did not know how to swim and perished for that cause, others again by reason of cold” [17]. While crossing the Alps in 218 BC in his campaign against the Romans, Hannibal lost 20,000 men because his army of men and elephants was unprepared for harsh weather conditions [11]. Many war

chronicles from ancient times up to the 16th and 17th centuries describe suffering from cold. However, most of them do not differentiate frostbite from hypothermia.

In more recent history, several European armies underestimated harsh weather conditions. Possibly the best example was the retreat of the Great Napoleon army in the winter of 1812. The notes of his surgeon Larrey were later interpreted by Moricheau-Beaupré, another famous French surgeon: “They were seen walking insensible and ignorant where they went. …In a word, when no longer able to continue walking, having neither power nor will, they fell on their knees. The muscles of the trunk were the last to lose the power of contraction. Many of those unfortunates remained some time in that posture contending against death. Once fallen, it was impossible for them with their utmost efforts to rise again…” [18].

While preparing the “Barbarossa,” a “blitzkrieg” plan of defeating the Soviets, Adolf Hitler did not consider the weather conditions as he expected to be done with the eastern front before the winter of 1941. The “Center army group” struggled to capture first Moscow and then, a year after, Stalingrad before winter, becoming acquainted with a new enemy – cold Russian winter.

The “General Frost” or “Le général Hiver,” as it was posted on a front-page illustration of the French periodical Le Petit Journal in 1916 during the First World War, is the most used cliché describing the main reason for the abovementioned losses.

5.3 Epidemiology of accidental hypothermia

The annual incidence of accidental hypothermia varies greatly between different studies, due to the vast diversity of study cohorts, differing by number, type of accidental

hypothermia, statistical methods, and population. A cohort study from the USA showed an annual incidence of hypothermia and other cold-related morbidity emergency room visits to 0.56 per 100000 inhabitants [19]. Accidental hypothermia incidence in the European countries range from 3.4 to 5.4 per 100000 [20, 21]. In comparison, a study from New Zealand denotes incidence at 6.9 per 100000 inhabitants [22]. The absence of reliable data sources can be a reason for the scarcity of data. The newly established International Hypothermia Registry in Geneva hopefully will improve data collection in the future [23].

Accidental hypothermia, if compared to other deadly conditions, is not a frequent cause of death. The epidemiologic studies from different countries provide similar mortality rates, seemingly dependent on geographical position, the number of inhabitants, and the development of emergency services for treating accidental hypothermia. For example, in Norway, mortality rates are estimated as 0.5 deaths per 100000 inhabitants per year [24], in France 0.13 [25], in the USA 0.3 [26], and in Great Britain 1.8-2.2 per 100000 inhabitants per year [27].

Overall case-fatality rate from accidental hypothermia described in several retrospective studies varies significantly within the time they were published. The older studies show a case-fatality rate of 52 to 80% depending on the method of rewarming [28]. Weyman et al. (1974) in their retrospective study, reported case-fatality rate at the level of 75% [29]. With the introduction of new guidelines, rewarming protocols, and extracorporeal life support, overall case-fatality rate from accidental hypothermia started to decrease. Survival rates depend greatly on prognostic factors such as age >75 years, hemodynamic instability, elevated serum lactate level and hyperkalemia, asystole, and witnessed/unwitnessed CA at presentation. Almost all hemodynamically stable, otherwise

healthy patients survive neurologically intact [30, 31]. In a recent study using data from the International Hypothermia Registry, including hypothermia victims due to outdoor activities, the survival rate of those without CA was reported at 95% [32]. Those patients who developed CA due to accidental hypothermia had poorer survival chances. Survival rates in this group varied whether they had witnessed (73%) [33] or unwitnessed (27%) [34] CA at presentation.

5.4 Pathophysiology of accidental hypothermia

In patients subjected to therapeutic hypothermia, body temperature is intentionally decreased in controlled conditions, complemented by suppressing the homeostatic thermoregulatory defense mechanisms to cooling by administering anesthetics [35]. On the other hand, in accidental hypothermia, one would often meet hypothermic insult in clear consciousness, leading to the activation of the sympathetic nervous system as a response to cold stress [36]. The activation of such sympathetic response will result in an increase in respiration, blood pressure, heart rate (HR), and CO [6], as well as intense muscle shivering, leading to increased oxygen consumption (VO_2) and blood flow centralization by vasoconstriction to maintain body temperature [36]. Eventually, it would lead to the depletion of body energy reserves and O_2, making a treatment of accidental hypothermia patient more challenging from one in therapeutic hypothermia.

After reaching a core temperature of 32°C, one would need exogenous heat to rewarm as the thermoregulation mechanisms are impaired at this point. The sympathetic response disappears with further cooling and reaching 30°C body temperature, accompanied by bradycardia and decreasing CO and MAP [37]. The risk of fatal arrhythmias leading to CA –

the primary factor reducing survival in accidental hypothermia – increases at temperatures below 28°C [37].

5.4.1 Hypothermia-induced cardiovascular failure

Hypothermia deteriorates cardiovascular function both during hypothermia and after rewarming. The depth and length of hypothermia exposure would determine deterioration severity [38-40], clinically ranging from compensated systolic dysfunction [41] to severe reduction of CO and MAP, known as a "rewarming shock" [38, 42, 43]. Experimental studies have shown that hypothermia exposure results in cardiac failure of non-ischemic origin associated with the reduction of circulating blood volume (CBV) [42, 44, 45], increased blood viscosity and total peripheral resistance (TPR) [42, 46], and several changes on the cellular level, resulting in impaired contractility of the heart [47-49].

CBV reduction occurs mainly due to the trapping of whole blood and plasma in certain vascular beds [50], resulting in increased blood viscosity and hematocrit [44, 51, 52]. Hypothermia also alters erythrocyte morphology [53, 54], leading to enhanced erythrocyte aggregation in microcirculation and compromising flow [55]. Increased blood viscosity during hypothermia is suggested to be a reason for an increased TPR [46, 56]. Blood viscosity appears normalizing during rewarming [57], but TPR remains increased both during and after rewarming [42, 46, 58], worsening the hypothermia-induced cardiovascular failure.

On the cellular level, the mechanisms leading to reduced contractility as a part of hypothermia-induced cardiovascular dysfunction are still scarcely studied. Experimental studies have shown increased accumulation of reactive oxygen species [58, 59], alterations in high energy phosphates metabolism [43, 60], and disturbances in intracellular ion balance,

characterized mainly by intracellular Ca^{2+} overload [47, 48, 60-62] and decreased Ca^{2+} sensitivity [49].

5.4.2 Rewarming shock

Rewarming shock, or rewarming collapse is a clinical term that refers to a sudden failure of hemodynamic function during and/or after rewarming a hypothermic patient [43], first described by Maclean and Emslie-Smith in 1977 [28]. The main finding would be sudden low arterial pressure and failure to increase CO to compensate for the low arterial pressure. Despite the rewarming collapse being a well-known complication during rewarming, the whole cascade of pathophysiologic events in rewarming shock is not yet described. However, extensive research on this issue has been performed in the past decades. Findings from several studies reproducing rewarming shock indicate that the main component is Ca^{2+} overload in cardiac cells [47, 48, 60-62]. It is also documented that hypothermia leads to increased phosphorylation of cardiac troponin I which will reduce Ca^{2+} sensitivity of troponin C and lead to reduced cardiac contractility [49, 63]. Hypothermia-induced reduction of circulating blood volume and peripheral vasodilation resulting in the release of cold and stagnant blood into circulation are also recognized as contributors to rewarming shock development [64]. There is a consensus on using warm fluids infusion during rewarming from hypothermia to avoid hypovolemia [3, 28, 65]. At the same time, inotropic support could be used at temperatures above 30°C to compensate for the reduced cardiac output (CO) due to hypothermia-induced cardiac dysfunction if a patient is refractory to the volume treatment [66, 67].

5.4.3 O_2 transport during hypothermia. The concept of critical O_2 delivery

Hypothermia slows metabolic rate, which results in a gradual decrease in both O_2 consumption (VO_2) and O_2 delivery (DO_2) along with the hemodynamic variables such as CO and MAP. The rate of lowering obeys Vant Hoff's Arrhenius rule and can be expressed in the Q_{10} coefficient. It defines the factor by which the metabolic rate increases/decreases for every 10°C change in temperature. For most biological systems the Q_{10} factor varies between 2 and 3 [68]. This notion, and the fact that O_2 transport is maintained during cooling, stable hypothermia, and under rewarming, has been documented in numerous animal studies [39, 41, 69, 70]. Other experimental studies [41, 71] also have reported that the rate of VO_2 decline, in response to lowering of temperature, is more prominent than the decline in DO_2, which is explained by hypothermia-induced reduction in O_2 extraction, increase in vascular resistance and reduced O_2 demand due to slowing of metabolic rate. This phenomenon would favor tissue oxygenation despite impaired DO_2 caused by hypothermia-induced cardiovascular failure.

DO_2 usually abundantly exceeds VO_2, set by tissue metabolic activity. Thus, VO_2 is constantly independent of O_2 delivery, even with modest alterations in DO_2 [72]. Continuous reduction of DO_2 will increase O_2 extraction, whereas VO_2 remains constant. It is demonstrated in the O_2 extraction ratio ($VO_2/DO_2 = O_2ER$) changes. The O_2ER will rise until DO_2 falls below critical levels. When critical DO_2 is reached, VO_2 will become delivery dependent. Any increase in VO_2 or any further decrease in DO_2 will eventually lead to tissue hypoxia and anaerobic metabolism [73]. Thus, measuring mixed venous blood saturation and plasma lactate can help assess the adequacy of oxygen delivery. Critical O_2ER (ER_{crit}) is experimentally defined and varies from 0.6 to 0.7 in most healthy tissues [72]. In

hypothermia, it is determined at 0.65, reflecting that mechanisms for O_2 extraction and O_2 demand are largely unaltered with a lowering in core temperature [74]. In other critical conditions, such as sepsis, the slope of O_2ER flattens, representing a decreased ability of tissues to extract O_2. Moreover, the O_2ER would not plateau (i.e reach ER_{crit}) since VO_2 continues to increase when compensating for decreased DO_2, indicating hidden O_2 debt [73].

5.4.4 Cerebral autoregulation

The brain is highly vulnerable to reduced O_2 delivery. Impaired cardiovascular function due to accidental hypothermia or/and HCA leads to inadequate blood perfusion and tissue O_2 delivery, increasing the risk of hypoxic brain injury, and reducing chances for neurologically intact survival after hypothermic insult. *Cerebral autoregulation* is a homeostatic mechanism that sustains stable cerebral blood flow (CBF) in a wide range of compromised cerebral perfusion pressures (a difference between MAP and intracranial pressure (ICP)) [75]. Stable CBF is achieved through changes in the diameter of cerebral vessels, which in turn causes changes in cerebrovascular resistance (CVR), obeying the Hagen-Poiseuille law of laminar flow [76].

The exact mechanisms underlying cerebral autoregulation is unknown, but it is believed that a complex interaction of four following processes play a major role: 1) *Myogenic tone* via contraction/relaxation of arterioles and small arteries to changes in pressure; 2) *Neurogenic response* via secretion of neurotransmitters from neurons, astrocytes, and glial cells affecting small and medium-sized vessels; 3) *Metabolic mechanism* via changes in vasomotor responses of small vessels mainly due to changes in CO_2 partial pressure; and 4) *Endothelial mechanism* via vasodilating action of nitric oxide and vasoconstricting effect of thromboxane A2 and endothelin-1 [77].

Cerebral autoregulation can be determined by use of two different methods:

1) Static method reveals a steady-state relationship between changes in CBF, in response to alterations in cerebral perfusion pressure (CPP), without considering the dynamics of these changes in time. Static autoregulatory index – sARI (sARI = % ΔCVR / % ΔCPP), demonstrates the degree of autoregulation from 0 to 1. Zero means absent, and 1 indicates perfect autoregulation [75, 78].

2) Dynamic method reveals how fast changes in CPP will lead to changes in CBF and how long it will take for CBF to return to its primary value. Various methods can be applied to achieve this, such as the thigh-cuff method [79], the method of studying CBF changes in response to fluctuations in MAP caused by breathing, head-tilting, or periodic thigh-cuff inflation [80], and some other methods [81].

There are a solid number of pre-clinical [78, 82, 83] and human studies [84, 85] investigating the implications of hypothermic CA on cerebral autoregulation in the post-resuscitation phase or after cardiac surgery, demonstrating that autoregulation is not impaired. However, little is known about autoregulation during prolonged CPR in hypothermia. During normothermic CPR, autoregulation functions only during the first 200 seconds of resuscitative efforts [86].

5.5 Management of accidental hypothermia

The main goals in managing accidental hypothermia are to support free airways, breathing, and circulation; avoiding more heat loss during resuscitation; using appropriate rewarming techniques, and handling the complications [87-89]. Functioning guidelines for acute treatment of accidental hypothermia are essential for the successful treatment of these

patients. The ICAR MEDCOM (International Commission for Mountain Emergency Medicine) algorithm is one of the most used and included in ERC guidelines for cardiopulmonary resuscitation [90]. The University Hospital of Northern Norway has its own algorithm [91]. The North Norwegian algorithm has always been more liberal concerning triage points for core temperature and K^+ levels in avalanche-buried victims of accidental hypothermia, and advised extracorporeal circulation (ECC) rewarming in all patients whose body temperature is < 32°C and K^+ level~~s~~ is up to 12 mmol/l [92]. The newest update of the ICAR MEDCOM algorithm from 2022 [90] removed traditional triage with serum K^+ and core temperature (K^+ >7 mmol/l and T > 30°C) as less reliable. The current recommendation is to transport all avalanche victims to a hospital with extracorporeal life support (ECLS) and further assess them using the HOPE score (Hypothermia outcome prediction after ECLS) as a tool for in-hospital prognostication to determine the benefit of ECLS. HOPE was constructed based on the analysis of outcomes in 286 patients from 18 studies and obtained from hospital data in search for a better triage of patients suffering from hypothermic CA. Scoring is based on analyzing such variables as age, sex, core temperature at admission, serum K^+, mechanism of cooling, and duration of CPR [93]. It showed superior prediction value of ECLS benefit compared to triage based on serum K^+ alone [93]. The findings were later validated externally [94].

5.5.1 Cardiovascular drugs

Temperature reduction may alter the pharmacodynamic effects of cardiovascular drugs. The documentation of cardiovascular drugs' effects on hemodynamic function and ventricular arrhythmias at temperatures below 30°C is mainly gained from pre-clinical animal studies. At reduced temperatures, drug metabolism is depressed, and indiscriminate use may

lead to the accumulation of toxic plasma levels [90]. The latest ERC guidelines advocate using adrenaline and other CPR drugs in core temperatures over 30°C with doubled intervals when the patient is also eligible for cardioversion. Once normothermia is reached (>35°C), standard protocols can be used [7].

Over the past two decades, our research group has studied effects of catecholamines, phosphodiesterase 3 (PDE-3) inhibitors, and Ca^{2+} sensitizers in animal models of accidental hypothermia both during hypothermia and rewarming.

In a series of experiments utilizing a rat model, the central hemodynamic effects of adrenaline were suppressed during cooling and hypothermia. In temperatures below 34°C, it failed to restore CO and was associated with increased TPR due to higher α than β receptor response [95-97]. At the same time, low-dose adrenaline in the same model had better inotropic effect in both hypothermia [96] and after rewarming [98]. In contrast, in pigs cooled to 32°C, administration of adrenaline in both low and high doses exerted positive inotropic effects and reduced TPR, supporting its use in hypothermic patients at temperatures >32°C [99].

A recent review article [97] concluded that noradrenaline and isoprenaline depress cardiac function in hypothermia and during rewarming. Dopamine studies also show its inability to elevate CO in core temperatures down to 32°C [100] and 25°C [101]. Nevertheless, dopamine restores its vasopressor function during rewarming, despite four-fold accumulation in plasma [101]. North Norwegian guidelines for accidental hypothermia [92] and UpToDate [3] advocate the use of dopamine to support cardiac function during rewarming from accidental hypothermia.

The PDE-3 inhibitors and Ca^{2+} sensitizers milrinone and levosimendan showed better effects in supporting cardiovascular function during rewarming in a rat model of accidental hypothermia. It was therefore suggested that preventing cAMP breakdown and increasing Ca^{2+} sensitivity might be a better strategy for ameliorating hypothermia-induced cardiac dysfunction [102, 103]. Nevertheless, human trials evaluating their effects are missing; thus, these pre-clinical results should be interpreted cautiously.

5.5.2 Rewarming

Rewarming of accidental hypothermia patients should start as soon as possible using an adequate method, depending on the degree of hypothermia [1, 2]. Techniques include:

Passive external rewarming. The method is applicable for mild hypothermia. It includes removing of wet clothes, use of insulation, and maintaining room temperature > 28°C. The main goal is to prevent further heat loss since patients still have intrinsic heat production. The method is ineffective if a patient presents with comorbid conditions, such as sepsis or hypovolemia. It is not recommended for the elderly because they may present with metabolic and cardiovascular dysfunction [3].

Active external rewarming. Sources of warmth, such as heating pads, baths, or forced warm air are applied directly to the skin [3]. This method is helpful in mildly hypothermic patients lacking physiologic reserves to rewarm passively or as an initial measure for a hemodynamically stable patient suffering from moderate or severe hypothermia. To avoid an after-drop phenomenon, the trunk should be rewarmed before the extremities. The latter occurs when acidemic cold blood returns to the central circulation due to peripheral vasodilation. This may result in acidosis and further drop in core temperature. At the same time, one can

experience deterioration of the existing reduction in circulating blood volume (CBV), resulting in further worsening of hypotension, disturbances in coronary blood flow, and ventricular fibrillation (VF) [104].

Active core rewarming. It is a method of choice in severe hypothermic patients without cardiac arrest who do not require ECLS, or if ECLS is not feasible. One can divide it into two sub-methods:

- *Endovascular rewarming* using endovascular temperature control catheters is a less invasive method of rewarming than ECC rewarming [105, 106]. The catheter with temperature-controlled circulating water is introduced into the femoral vein and warms the blood in the vessel while it passes the catheter tip. Temperature is controlled via feedback from the temperature probe in the esophagus. The same devices may be used in therapeutic hypothermia. This method is not giving a faster rewarming rate than other active core rewarming methods but is considered safe and feasible [107].

- *Peritoneal or pleural lavage*. Peritoneal irrigation involves infusing 10-20 ml/kg of warm (42°C) isotonic saline into the peritoneal cavity. The fluid is left for 20 min before being drained and replaced. This method gives a rewarming rate of 2-4°C/h, but in situations with CA, it does not transfer heat directly to the myocardium [108], postponing probability to successful defibrillation. In contrast, pleural lavage has this advantage and is not dependent on intact circulation [109] and is accomplished by placing two thoracostomy tubes in the pleural cavity, allowing anterior infusion and posterior drainage of warm (42°C) saline [110] or tap water. The method can be

effectively used with good neurologic outcomes in patients with severe hypothermia presenting both with [111, 112] and without cardiac arrest [110].

- *ECLS (extracorporeal life support) rewarming.* This term unites different rewarming strategies when blood is being rewarmed extracorporeally. It includes continuous veno-venous rewarming (CVVR), continuous arterio-venous rewarming (CAVR), cardiopulmonary bypass (CPB), and extracorporeal membrane oxygenation (ECMO)[3]. The method is preferred in severe hypothermic patients with cardiovascular instability or CA [1]. CPB and preferably ECMO, if available, give the best rewarming speed (up to 9.5°C/h) [113] in severe accidental hypothermia patients and are recommended by ERC guidelines [7]. The ECMO is superior to CPB because it can simultaneously treat noncardiogenic pulmonary edema, commonly present as a complication of severe accidental hypothermia for days after rewarming, and consequently improve survival [114]. In a recent systematic review and meta-analysis of 23 observational studies including 464 patients, survival rate was significantly higher (41%) in patients rewarmed by ECMO compared to CPB. Nevertheless, survivors subjected to ECMO, had a lower probability of a good neurological outcome (75% versus 87%) [115].

5.5.3 Hypothermic cardiac arrest

The risk of life-threatening arrhythmias leading to HCA is highly increasing at core temperatures below 32°C [116]. The reason for HCA due to hypothermia lies in the cascade of pathophysiological changes leading to reduced tissue oxygenation. These changes include depressed myocardial contractility, worsened oxygen availability due to shifts in the oxygen dissociation curve, vasoconstriction, ventilation-perfusion mismatch, and increased blood

viscosity [117]. Eventually, the asystole may develop with further cooling, prolonged respiratory arrest, and hypoxia. Since it is hard to mitigate pathophysiological changes in heart muscle while the body is hypothermic, arrhythmias are usually hard to treat, and cardioversion is hardly feasible before the patient is rewarmed [1, 4, 88].

Even though hypothermia seem to reduce the extent of ischemia-reperfusion injury, the HCA is a major cause of the fatal outcome from accidental hypothermia, according to the recent retrospective study on the data in the international accidental hypothermia registry, established in Geneva in 2010 [32]. In 201 patients included in the registry, the overall survival rate in those who had preserved circulation was 95%, and 36% in patients with CA [32]. These findings are in concert with data from two different university hospitals in Norway, where 74% of accidentally hypothermic patients with CA on admission died during treatment [118, 119]. Another retrospective cohort study from the Netherlands shows a survival rate of 99,3% among patients rewarmed with ECC having perfusion rhythm on admission [120].

Indeed, successful rewarming with ECC is more likely if a patient initially has a perfusion rhythm. However, high survival rates in hypothermic patients with perfusing rhythm on admission can be explained by selection bias, like a large number of young and healthy individuals [32] or low inclusion of patients with asphyxia-related causes of accidental hypothermia [30]. It is also relevant for patients admitted with HCA. In the cohort of patients who suffered from HCA prior to asphyxia, the survival rate was 46.7% [119]. These findings support the knowledge of a higher potential for resuscitation with good neurologic outcomes in patients with HCA who become hypothermic before hypoxic.

Cardiomyocytes can tolerate ischemic episodes for up to 15 minutes in normothermia [121, 122]. Later, a spectrum of changes develops due to significant ischemia-reperfusion injury, including myocardial stunning, microvascular and endothelial injury, and irreversible myocardial necrosis [123, 124], resulting in poor clinical outcomes in normothermic CA patients if ROSC is not reached within 20-30 minutes [125, 126]. On the other hand, there is a large body of case reports describing successful resuscitation for HCA for many hours [1, 16, 118, 127, 128] due to hypothermia-induced reduction in metabolism, oxygen demand, and prolonged survival of essential organs during ischemia [118, 128].

The ERC guidelines recommend early and continuous CPR in accidentally hypothermic patients in HCA, even with very low temperatures and prolonged downtime, if nonsurvivable traumas are present [7]. The statement "Nobody is dead until warm and dead," coyly pronounced at the end of the 80s, became a strong credo nowadays among intensive care specialists worldwide [118]. Nevertheless, CPR itself is quite a young term. The first CPR guidelines will celebrate its 60th anniversary in 2026 since the Ad hoc Committee on Cardiopulmonary Resuscitation of the American Medical Association first published them in 1966 [129].

5.6 History of CPR

In 1956, Dr. Peter Safar and his colleague James Elam began their research on what is now called CPR [130]. Safar and Elam performed a series of experiments on paralyzed human volunteers and demonstrated successfully that tilting the head back and thrusting the jaw forward effectively frees airways. They also showed that exhaled mouth-to-mouth air could sustain satisfactory O_2 levels in the blood of non-breathing patients [131]. Their experiments have rediscovered the first two components of CPR – "A, airway," and "B,

breathing." By combining their research with the research of Safar´s contemporary William B. Kouwenhoven, who validated the third component – "C, circulation" [132], they wrote the book "ABC of resuscitation" in 1957. This A-B-C paradigm was later used for training of public and was implemented by resuscitation organizations worldwide. Defibrillation as a step in basic life support (BLS) was first added after automated external defibrillators (AED) came into use in the 1990s. In 1992 several of the most prominent resuscitation organizations of the world created the International Liaison Committee on Resuscitation (ILCOR). Its goal was to produce and review resuscitation guidelines [133].

The components of modern CPR were studied separately at different times, long before the middle of the 20th century, when they were combined into one system. The first lines about *airway* management were mentioned already in 1540 by Vesalius in his pattern-breaking "De humani corporis fabrica": *"... life may . . . be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put*" [134-136]. However, it was not taken seriously, and scientific society forgot it for two centuries. The pioneers of the Dutch Humane Society, founded in 1768, were the first who tried to respond to sudden death in humans, mostly drowned. Most of their methods for stimulating the human body, such as bloodletting or anal fumigation of tobacco smoke, seem ridiculous now. However, some of them, namely cleaning the airways, applying manual pressure to the abdomen, or mouth-to-mouth respirations, are in use today [137].

The first reference to the attempt to replace natural *breathing* dates back to the book of Kings in the Old Testament, where one of the prophets, named Elisha, restored breathing in a boy with a method resembling the mouth-to-mouth technique [138, 139]. The first who described this technique in more recent history was already mentioned Napoleon's chief

battlefield surgeon Dr. D.J. Larrey [137]. Unfortunately, at that time, it was not further studied and popularized because of the discovery of oxygen by Scheele [140]. Lavoisier found it relevant for respiration [141], defacing the exhaled air usefulness since rescuer's lungs already used it. Researchers therefore attempted to achieve artificial respiration by rotating the patients and lifting their extremities [142]. These methods were used up to the revolutionary 1950s and Safar's experiments with mouth-to-mouth breathing [143].

It was evident that *circulation* is bound to breathing and that the cessation of breathing will cause a cardiac arrest [134, 144]. Schiff's first report and introduction of the term "cardiac massage" dates back to 1874 [145]. He noticed carotid pulsation after manually squeezing the canine heart. Then, in 1901, Kristian Igelsrud achieved the first successful human resuscitation by open-chest cardiac massage on a patient with anesthesia-induced cardiac arrest at Tromsø Amtsykehus [146]. Since that time, this fatal condition could be successfully treated, but only in a hospital setting. The revolutionary discovery of closed-chest cardiac massage in 1958, known today as chest compressions, belongs to William Bennett Kouwenhoven, Guy Knickerbocker, and James Jude. They accidentally noticed a rise in arterial pressure while pressing the electrodes firmly to the chest while studying defibrillation in dogs [132]. Already in 1960, they published a report on 20 cases of in-hospital CA. Fourteen patients were saved by their novel method [132].

Unlike "A," "B," and "C" for resuscitation, the last but not the least "D" for defibrillation could not be found in historical references before the 18th century, as Galvani's experimentation discovered the electricity only in the mid-1700 [138, 147, 148]. By the end of the eighteenth century, he proved, using a recently invented Leyden jar, that electricity could induce contractions of the dead frog's muscles [148]. However, the possible role of

electricity in human resuscitation was not studied for almost a hundred years. Dr. John McWilliam published the first systematic study on the effects of electricity on mammalian hearts only in 1889, stating that «the death is not due to immediate CA but due to fibrillations» [149]. Several studies on the open chest have revealed the effect of electric shock on defibrillating the heart [150, 151]. Hooker and Kouwenhoven were the first to demonstrate that defibrillation can be possible on the closed chest without direct contact with the heart [152]. At this time, Dr. Claude Beck perceived that cardiac arrest often occurs in young and otherwise healthy people, announcing the credo “Hearts too good to die.” Later in 1947, he was the first who successfully performed human open-chest defibrillation on a fourteen-year-old boy [153]. Inspired by Beck’s achievement, Paul Zoll invented and described the successful use of an external defibrillator in 1955 [154]. Later in 1961, Bernard Lawn, after a series of dog experiments, proved that DC is superior to AC in defibrillation [155].

5.7 Modern principles of CPR

The first guidelines for CPR were published more than 50 years ago [129]. Since that time, every component of classic CPR has been refined, and ILCOR reviews their recommendations annually. Based on these recommendations, the world’s most prominent resuscitation organizations update their own guidelines. Guidelines underline the strong order of the CPR sequence to achieve a successful resuscitation. It is defined as a “Chain of Survival” and includes early recognition of CA, early access, early CPR, early defibrillation, early advanced cardiac life support (ACLS), and early recovery [156]. According to the Ontario Prehospital Advanced Life Support Study Group, the odds ratios for improved survival were 4.4, 3.7, and 3.4, respectively, when the first three steps were present [157]. A

study by Daya et al. (2015) has shown that links in the “Chain of Survival”, carried out in an effective way, increase the chances for survival, approaching 50% in patients after witnessed out-of-hospital VF arrest [158]

Nevertheless, despite sound improvements in CPR science in past decades, the survival rate from normothermic CA remains low (1-20% for out-of-hospital cardiac arrest (OHCA) and < 40% for in-hospital cardiac arrest (IHCA)) [159]. From 10 to 50% of survivors suffer impaired neurological function. The rates have not changed dramatically since conventional CPR was described and implemented [159].

5.7.1 Search for the improvements

Normothermic CPR can provide up to 30% of CO obtained by spontaneous circulation [160-162]. To reach even that level, one should strictly stick to the CPR recommendations provided by resuscitation organizations. They define high-quality CPR as a rate of 100-120, duty cycle 50%, depth 5 cm, and positive pressure ventilation ratio 30:2 for BLS [163], or asynchronous ventilation once after every 10^{th} compression for ACLS [88]. Too frequent compressions and failure to allow full chest recoil will lead to reduced heart filling, low-pressure generation, and high ICP, resulting in poor coronary and cerebral blood flow [164]. Too ardent ventilation would also result in decreased venous return, high ICP, and low coronary perfusion pressure [165]. The latter is essential for return of spontaneous circulation (ROSC). A recent study showed 70% reduction in absolute survival when pigs were hyperventilated during 4 minutes of CPR [166], and further, the absence of intermittent positive pressure ventilation would lead to pulmonary collapse, decreased cerebral perfusion, and a poorer outcome of CA [167].

As a result of more than 50 years of research, there is a consensus that blood flow during CPR is mediated by two main mechanisms, the “cardiac pump” and the “thoracic pump.” The cardiac pump was a pioneering theory proposed in 1960 [132]. It states that direct compression of both ventricles between the sternum and spine generates a pressure gradient between the ventricle and either aorta or pulmonary artery. This theory requires the closure of the atrioventricular valves during the decompression phase of CPR [132]. It was validated in human and animal echocardiographic studies [168, 169]. Other studies showed that the mitral valve is often open during CPR [170, 171], with preserved forward mitral flow and venous return, therefore proposing the existence of the “left atrial pump,” a theory that suggested the left atrium as a compression point [171]. Optimal hand positioning due to age and variations in thoracic anatomy [172], amount of cardiac adipose tissue [173], and vascular compliance [174] are limiting factors to cardiac pump efficacy.

The thoracic pump [175] postulates that blood flows during CPR from the thoracic to the systemic circulation due to increased intrathoracic pressure and to an arterio-venous pressure gradient across the heart. According to that theory, atrioventricular valves are open during compression, while retrograde flow to the systemic veins is blocked by venous valves [176, 177]. Forward blood flow is therefore possible even if the heart is not directly squeezed as in the cardiac pump theory. There is a consensus that both mechanisms are essential during CPR [178, 179]. Their role is highly dependent on the quality and modifications of CPR [179].

Several improvements were proposed to alleviate both mechanisms during CPR and improve the outcomes of CA. Among them are intrathoracic pressure regulation therapy utilizing active compression-decompression (ACD) CPR, impedance threshold device (ITD), and intrathoracic pressure regulator device [159]. They are meant to create negative

intrathoracic pressure during CPR and augment venous return, favoring cerebral and coronary blood flow generated by CPR [159]. Despite promising results in animal studies, none of them alone or in combination showed a significant difference in neurologically favorable survival in CA compared to standard CPR in large human trials, including 2470 OHCA patients [180] and 27380 patients with non-traumatic CA [181]. Their use is therefore not recommended in routine practice since 2015 [182].

Increasing interest and debate related to head-up CPR emerged in the past decade. During CPR in a conventional supine position, chest compressions elevates both arterial and venous pressures to the brain, which, by opposing each other will lead to reduced cerebral blood flow [159]. Tilting the head up enhances venous return from the brain to the heart, consequently filling the heart during decompression. Simultaneously it leads to lower ICP during compressions and recoil, enabling better CBF [159]. Head-up CPR in combination with ACD and ITD showed significant improvements of cerebral [183], coronary [184] and systemic blood flow [185], as well as improvement in neurological survival [186] in animal studies. So far, only one human observational study on 1835 OHCA patients using head-up CPR has been performed. It showed an increased rate of ROSC when using head-up CPR in combination with a mechanical resuscitation device with ITD [187]. However, ILCOR does not recommend its routine use in their latest report due to weak evidence for late outcomes but encourages future clinical trials [188].

5.7.2 Automated mechanical CPR devices

High-quality CPR is essential for favorable outcomes after CA [189, 190]. Nevertheless, certain factors, such as rescuer fatigue [191, 192], lack of physical strength to overcome the stiffness of the patient's thorax [193], and special circumstances related to the

resuscitation conditions [194] may limit the quality of CPR. Physical and mental status of the rescuer also affect the quality of CPR, probably making it less efficient [194]. Sugerman et al. (2009) reported that compression depth is reduced after 90 seconds of high-quality CPR in real CA situations [191]. A study on mannequins showed signs of rescuer fatigue after three minutes of compression-only CPR [192]. Analysis of 9136 OHCA patients' data revealed that only 45% of them had high-quality CPR with appropriate compression depth [195].

In the early 2000's, several automated mechanical CPR devices were invented and gradually introduced into practice to provide high-quality chest compressions. They are built using two techniques: 1) a piston device that can provide ACD CPR, consisting of a backplate and a piston mechanism with a suction cup, which are connected and surrounds the patient [196], or 2) a load-distributing band, bearing in mind the thoracic pump mechanism; it is a circumferential chest compression device consisting of an electrically or pneumatically constricting band and a rigid backboard [197].

Over the last two decades, several RCTs, metanalyses, and systematic reviews were performed to study the efficacy of mechanical CPR in CA. Most of the latest data suggest that mechanical CPR does not improve outcomes compared to standard CPR [198-201]. One systematic review of IHCA patients reports evidence that the use of mechanical chest compressions improves outcomes in this patient group [202]. The latest systematic review and meta-analysis on OHCA patients reports that mechanical CPR improves the probability of ROSC and survival on admission but not survival to discharge with favorable neurologic outcomes [203]. ILCOR and major resuscitation organizations still advise using mechanical CPR only when high-quality standard CPR is not feasible. Such situations include evacuation and transport as a bridge to extracorporeal CPR, during percutaneous coronary interventions,

or in cases with unsuccessful resuscitation before organ donation [88]. Hypothermic cardiac arrest often involves prolonged CPR, which can provide survival even after 6 h and 30 min of resuscitation [204]. ERC advocates using mechanical CPR in accidental hypothermia if prolonged transport is required [7].

6 Aims of the study

Even with significant improvements in critical care for OHCA over the past decades, few patients still survive the condition, and survival rates have stagnated since 2012 [205]. In 2015, among 350000 adults in the USA who experienced non-traumatic OHCA, only 10.4% survived their hospitalization, and only 8.2% had good neurological outcomes [206]. Patients suffering from hypothermic OHCA have similarly poor outcomes. A recent report from Northern Norway reveals that despite sound improvement of rewarming techniques such as CPB and ECMO, there has been no change in survival rate over the last 30 years [119]. Even though survival from OHCA due to severe accidental hypothermia remains low, several successful resuscitations have been reported over the past decades. Reducing metabolism and, hence, demand for O_2 at low body temperatures provided resuscitation and further neurologically intact survival even at very low temperatures [128] and prolonged downtime [207]. The recommendation to use prolonged CPR in hypothermic patients with CA is now included in most recent guidelines and particular protocols for resuscitation. However, a lack of detailed insight in background pathophysiological mechanisms for successful resuscitation remains. In order to gain some new insight, we studied the effects of hypothermia and prolonged CPR on hemodynamics, global O_2 transport, and regional blood flow. We used an intact porcine model of severe hypothermia developed by our research group.

The specific aims of the papers included in the thesis are as follows:

Paper I

Before studying the effects of CPR in severe hypothermia, we assessed the effects of cooling on hemodynamics, O_2 transport, and organ blood flow in a porcine model with

preserved spontaneous circulation. Animals were immersion cooled to 27°C, maintained for 3 h at this temperature, before being rewarmed with pleural lavage to 38°C. In this paper, we simulated the representative duration for evacuation and transport of a hypothermic patient (3 h), and 27°C core temperature was chosen because this is close to the lower limit of ability to maintain spontaneous circulation in humans. We also wanted to evaluate pleural lavage as a rewarming technique since it is an efficient method of active core rewarming that is feasible in remote areas where ECLS is not available.

Paper II

Paper II aimed to assess the value of CPR by means of an automated mechanical chest-compression device as part of prehospital interventions for hypothermic patients with CA. We hypothesized that the level to which CPR can replace CO is unaffected by temperature. Thus, it can eventually match the physiological reduction in CO created by lowering core temperature during spontaneous circulation. We used the hypothermic porcine model of induced CA during prolonged (3 h) hypothermia (27°C). We compared the hemodynamic effects of CPR to those in spontaneous circulation during three hours at 27°C vs. 45 min at normothermia by determining global hemodynamics, oxygen delivery (DO_2), consumption (VO_2), and organ blood flow.

Paper III

Paper III aimed to assess whether cerebral blood flow autoregulation is preserved during prolonged hypothermic CPR by calculating static autoregulatory index during CPR for 3 h vs. spontaneous circulation at 27°C. We hypothesized that it could be feasible due to reduced O_2 demand during hypothermia and the presence of a stable CO during prolonged CPR. We utilized the same animal model as in Paper II.

7 Methodological considerations

7.1 Ethical considerations, choice of species and approval

The appropriateness of animal research has gone a long way through history and stems from the initial confrontation between two basal philosophical camps – empirics and Cartesians [208]. Cartesians, following Descartes' idea, "I think therefore I am," could not agree with Aristotle's philosophy follower's axiom that every living creature has consciousness and can feel pain [208]. The scales tipped radically to different sides before the first legislation in laboratory animal science came into effect in 1978. It was based on the conception of the "3 R" (replacement, reduction, refinement), proposed by Russell and Burch in 1959 [209].

Based on the "3 R principle," we have made the following ethical considerations:

Replacement:

The animal model is the only possible way to study complex pathophysiological changes and interactions in the living organism taking place during hypothermia and cardiac arrest. Knowledge of these mechanisms would help provide better treatment and save many human lives. Therefore, we could not *replace* the animal model with other research types.

To study different aspects of accidental hypothermia, our research group usually used rats and dogs as research animals. Indeed, sound hemodynamic stability and viability against dramatically low temperatures in rats make them a good candidate as a model for hypothermia research [210]. Nevertheless, we have not initially considered the rat a suitable animal for our research since its small size, high heart rate, and unavailability of an appropriate CPR device make it impossible to conduct CPR.

Even though dogs have been extensively used as research animals to study basic physiology throughout history, nowadays, their use is limited to toxicology studies [211] and comprised only 0.3% of all animal research conducted in 2018 [212]. In addition, the physiological vascular responses to hypothermia in dogs and rodents may vary from those in humans, especially during rewarming. For example, it was shown that rats increase their stroke volume (SV) while they are severely hypothermic [60, 98].

The pig is like humans in many aspects of physiology and morphology. Thus, one can assume that their response to hypothermia would be more appropriate for translational research [213, 214]. The pig is also suitable for CPR research as it responds to CPR measures, defibrillation, and cardiovascular drugs [215]. Considering that the subject of the investigation is CPR's beneficial effects during hypothermia, this study may have a large translational potential.

Reduction:

A similar hypothermia protocol in the porcine model was established and used by our research group previously [41]. It has shown good stability and sound results. We performed a power analysis of existing data to calculate a minimum sample size of animals. According to the previous study, 6-8 animals per group give good statistical reliability.

Refinement:

The animals included in study received humane care in approved animal facilities at UiT the Arctic University of Norway. They had minimum stress, allowing rest for 2-5 days before the experiments. They had continuous access to water and received food two times a day. During experiments, they were in deep general anesthesia. Its level was controlled several

times during the experiments. After termination of the experiment, bolus doses of pentobarbital and potassium chloride euthanized the animals painlessly.

In Paper II and III, we refined the model for using mechanical CPR. The current studies used juvenile piglets aged 2-3 months and weighing 20-29 kg from NOROC stock. The NARA (Norwegian Animal Research Authority) approved the experimental protocols (Ref.nr 14/56323). Experiments were conducted in accordance with the rules and guidelines of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 18.03.1986).

7.2 Study design and experimental protocols

The studies were performed at UiT the Arctic University of Norway in an animal research laboratory operation room as acute, prospective, controlled experimental studies. The animals were randomized into control or intervention groups in Paper I and II. Paper III had only one group of animals serving as their own controls. All animals received the same anesthetic and respiratory support in all studies. The animals in Paper I were additionally instrumented with polyvinylchloride (PVC) tubes for pleural lavage rewarming.

Paper I. Sixteen pigs were divided into two experimental groups. Ten animals were immersion cooled to a core temperature of 27°C, maintained at this temperature for 3 h, and then rewarmed utilizing pleural lavage. Six animals served as normothermic time-matched controls and underwent the same instrumentation with subsequent 6.5 h of observation using a pleural lavage procedure starting at 4.5 h timepoint and lasting for 2 h.

Hemodynamic measurements/calculations, assessment of global and cerebral O_2 transport, and injection of microspheres for measurement of regional blood flow were

performed at baseline conditions (38°C), during cooling at 32°C and 27°C, hourly during stable hypothermia (27°C), and at 32°C and 37°C during rewarming in the hypothermic group. In normothermic controls, time points were time matched to 45 min, 1.5 h, 2.5 h, 3.5 h, 4.5 h, 5.5 h, and 6.5 h.

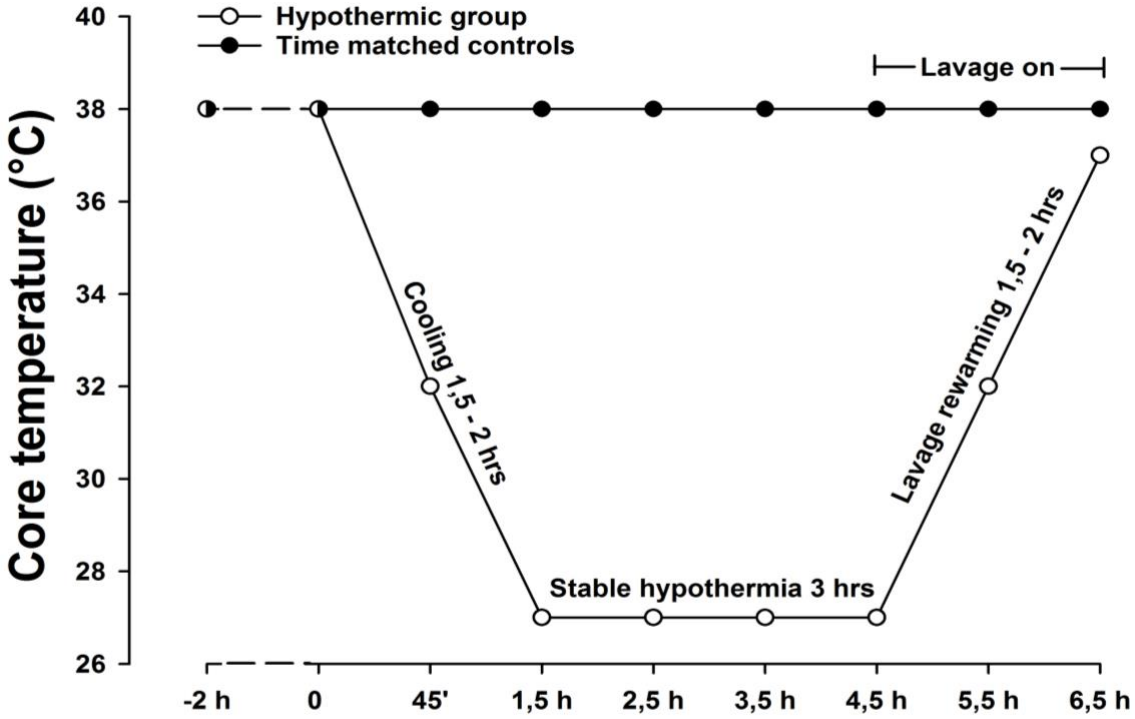

Figure 1: Experimental protocol, paper I.

Paper II. Eleven pigs were assigned into two groups. Seven pigs in the hypothermia group were cooled to 27°C and subjected to 3 h of CPR after induced cardiac arrest. Four pigs served as normothermic controls and underwent CPR for 45 min in normothermia (38°C).

Hemodynamic measurements/calculations, assessment of global O_2 transport and injection of microspheres for measurement of regional blood flow were performed at baseline (38°C); during cooling at 32°C and 27°C; 15 min after start of CPR, and hourly during

hypothermic CPR. In normothermic controls, the hemodynamic variables were recorded after instrumentation at baseline (38°C), and after 15 and 45 minutes of CPR before the termination of the experiment**.**

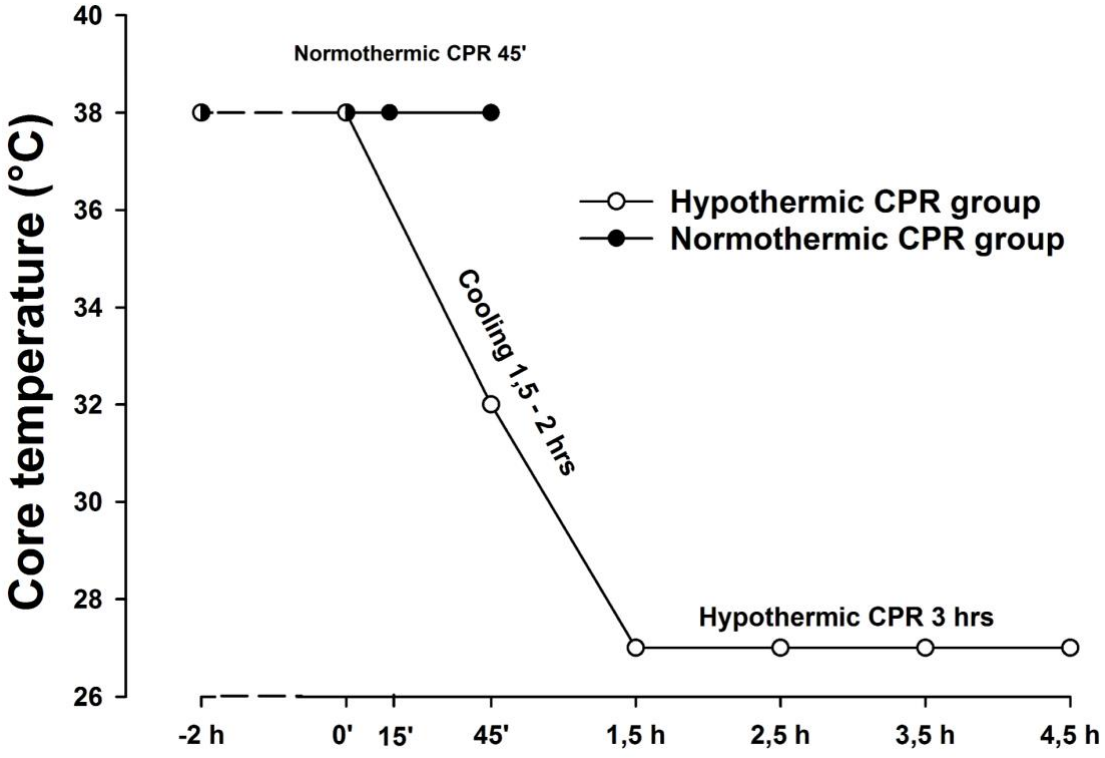

Figure 2: Experimental protocol, paper II.

Paper III. Eight pigs were cooled to 27°C. After cooling, CA was induced, and CPR started and lasted for 3 h in the same manner as in Paper II.

Hemodynamic measurements/calculations, assessment of global O_2 transport and injection of microspheres for measurement of regional blood flow were performed at baseline (38°C), during cooling at 32°C and 27°C, 15 min after start of CPR, and hourly during hypothermic CPR.

Measurement of regional blood flow (paper I, II, III): After termination of the experiment, tissue samples were taken from the brain (paper I, II, III), heart, kidneys, liver, stomach, and small intestine (paper I, II). The material was further sent to BioPal for determination of regional blood flow.

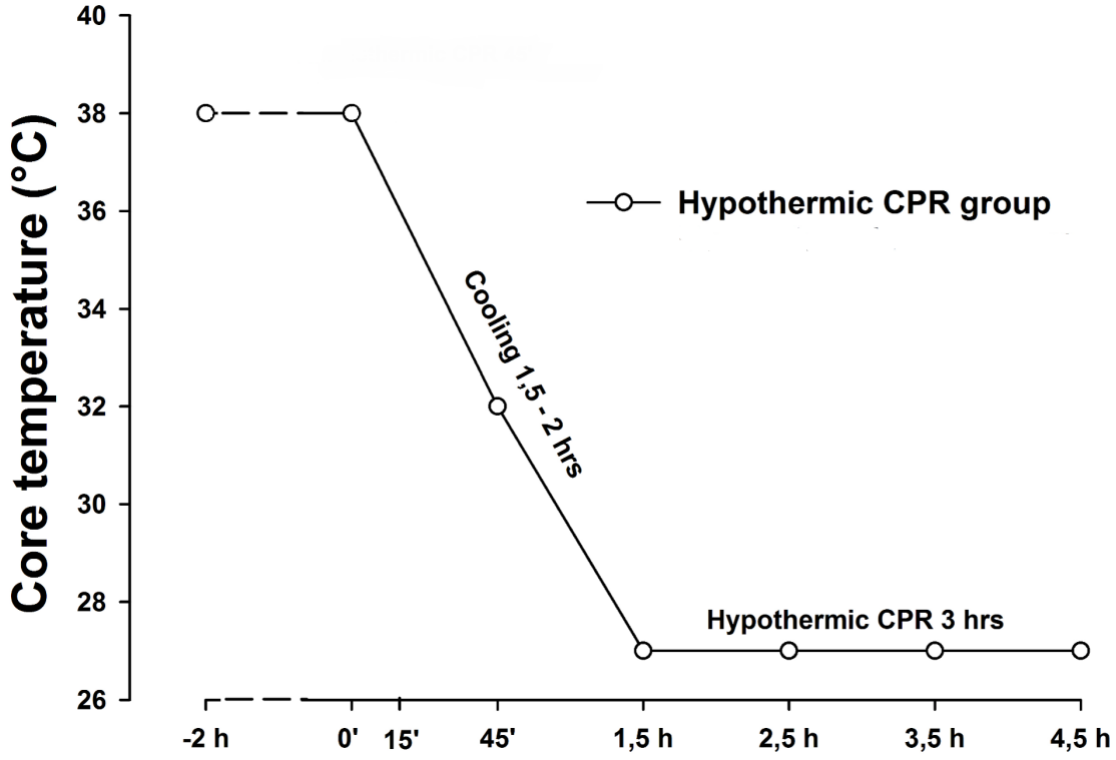

Figure 3: Experimental protocol, paper III.

7.3 Anesthesia and respiratory support (paper I, II, III)

General anesthesia was administered at the animal department facilities by an intramuscular bolus of ketamine hydrochloride 20 mg*kg^{-1} (Ketalar, Pfizer Norge AS, Oslo, Norway), midazolam 30 mg (B. Braun Melsungen AG, Germany) and atropine 1.0 mg (Takeda AS, Asker, Norway) before transferring the animal to the laboratory. Later, in the operation room, an ear vein catheter was inserted and a bolus injection of fentanyl 10 µg*kg^{-1} (Fentanyl-

Hameln, Hameln Pharma plus Gmbh, Hameln, Germany) and pentobarbital-sodium 10 $mg*kg^{-1}$ (Ås produksjonslab, Ås, Norway) was given. After tracheostomy, inserting a nr 7 endotracheal tube, a continuous infusion of fentanyl 20 $\mu g*kg^{-1}*h^{-1}$, midazolam 0,3 $\mu g*kg^{-1}*h^{-1}$, pentobarbital-sodium 4 $mg*kg^{-1}*h^{-1}$ and Ringer's acetate 9 ml/kg/h in the right external jugular vein was started and maintained throughout the experiment.

During experiments, both in normothermic and hypothermic animals, the level of surgical anesthesia was assessed frequently by applying a pinching stimulus to the septum of the nose. Animals were ventilated without positive end-expiratory pressure (Siemens Servo 900D, Solna, Sweden). The fraction of inspired O_2 was adjusted to maintain arterial P_{O2}>10 kPa, and alveolar ventilation was adjusted to keep arterial P_{CO2} between 4.5 and 6 kPa uncorrected for temperature. Arterial blood gases were analyzed (ABL800 FLEX; Radiometer Medical, Copenhagen, Denmark) to confirm adequate ventilation. After termination of the experiment, animals were killed by an i.v. lethal dose of pentobarbital and 20 ml potassium chloride, 1 mmol ml^{-1}. Neuromuscular blockers were not used during the experiments.

7.4 Instrumentation (paper I, II, III)

A summary of instrumentation is presented on the figure 4. A 6F fluid filled pigtail catheter was placed (Cordis Corporation, Miami, USA) in the right common carotid artery through a 10F Super Arrowflex (Arrow international Inc., Reading, USA) introducer for microspheres injections and recordings of left ventricular pressure. A 7.5F Swan - Ganz thermodilution catheter (Edwards lifesciences LLC, Irvine, USA) was introduced via an 8F Super Arrowflex in the right external jugular vein to enable measuring pulmonary artery pressure (PAP), central venous pressure (CVP), core temperature measurements, and for determination of mixed venous and venous blood gases. A 7.5F Swan - Ganz thermodilution

catheter was positioned in the aortic arch via the left femoral artery for arterial blood gas analysis, MAP recordings, and collection of reference blood samples for using the microsphere technique. An 18-gauge central venous catheter (Arrow international Inc., Reading, USA) was inserted cranially into the left internal jugular vein and advanced to the jugular bulb for sampling of cerebral venous blood. A 14F urinary bladder catheter was introduced via a lower abdominal incision for continuous monitoring of urinary output. A 3.5F pressure catheter (DPR-524, Millar instruments Inc., Houston, TX, USA) was placed into the left hemisphere through a burr hole in the skull for measuring ICP at given timepoints. 3000 IU of heparin was given as a single dose after placement of a thermodilution catheters.

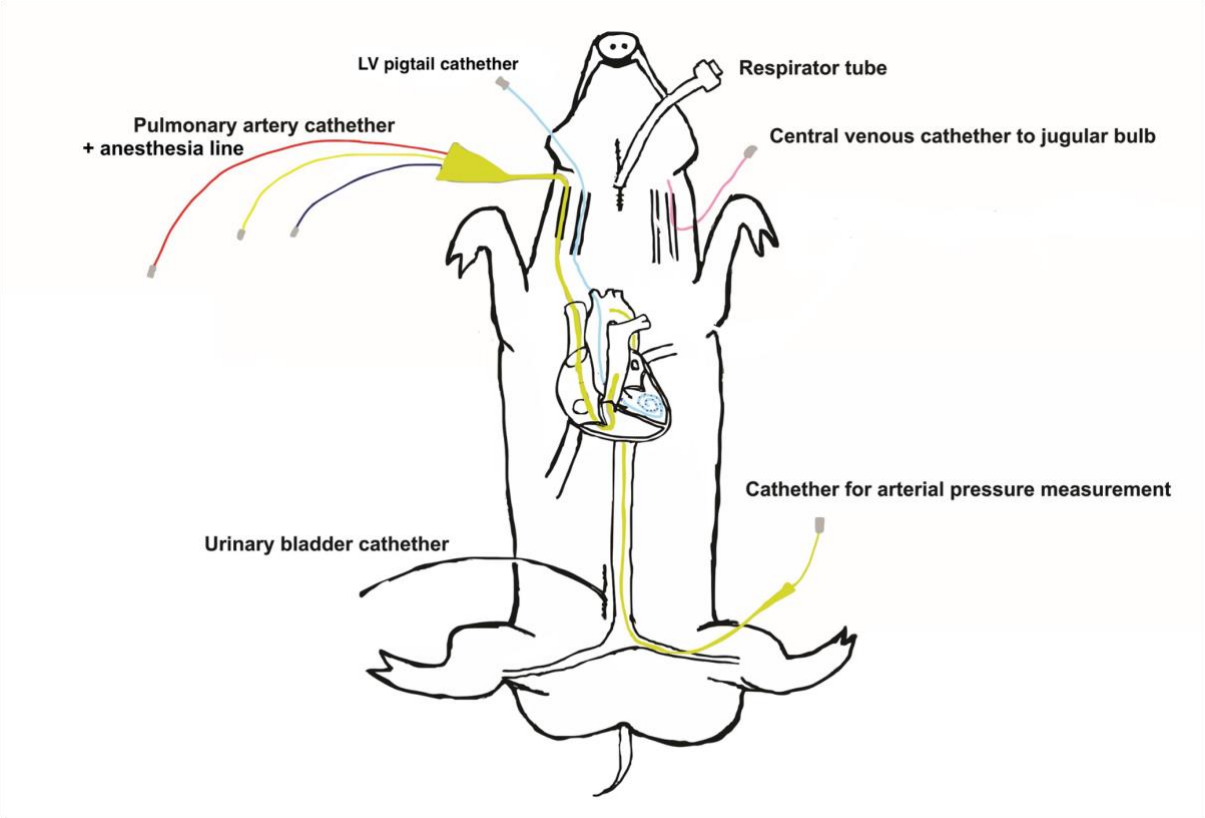

Figure 4: Instrumentation, paper I, II, III.

7.5 Core cooling (intervention groups in paper I, II, III)

Animals were immersion cooled in a waterproof tub, mounted on the top of the operating table, in cold water (5°C) with ice slush, and two-thirds of the animal not immersed in the water. The head was isolated from cold water and ice slush by being placed on a cushion. Blood core temperature was monitored using a temperature sensor in a pulmonary artery catheter. After the core temperature reduction to 28°C, the immersion was terminated by draining the tub, after which the core temperature subsequently dropped to 27°C. We placed the operation lamps as close as possible to the animal to prevent further decrease in core temperature. The same cooling technique was routinely used in previous studies by our research group [24, 41].

7.6 Induction of cardiac arrest and mechanical CPR (paper II, III)

After cooling to 27°C, animals were immobilized in a vacuum mattress. CA was induced by stimulating the epicardial surface using an alternating current (5-20 mA, 6Hz, and 30 V), conducted via a 15 cm needle electrode placed through the epigastric area and directed to the apex of the heart. CA was defined as VF on the electrocardiogram with no fluctuations in arterial pressure. Following 90 seconds of CA, active compression-decompression CPR (duty cycle of 50 ± 5% at a rate of 100 ± 5 compressions/min, depth 4-5 cm) by means of an automated mechanical CPR device (LUCAS chest compression system, Physio-Control inc., Lund, Sweden) was started and lasted for 3 h in hypothermic groups of Paper II, III and for 45 min in the normothermic group of Paper II. The animals were then euthanized.

7.7 Pleural lavage rewarming (paper I)

Active internal rewarming is often the method of choice in severe hypothermic patients presenting with spontaneous circulation, while ECLS is reserved for patients in cardiac arrest [90, 110]. We chose pleural lavage in our Paper I, with spontaneously circulated animals, as it gives one of the fastest rewarming rates among active rewarming techniques. This technique transfers heat directly to the heart and allows effective heat exchange in the well-circulated pleural cavity [111]. Additionally, it may reduce the increasing mismatch between reduced CO and fall in TPR (one of the main components of the "rewarming shock" pathophysiology) as the heart and lungs are rewarmed prior to skin, fat, and muscles [216]. It may as well protect from ventricular fibrillations during rewarming due to the same reason [217]. It is feasible in any local hospital and for most medical professionals [111, 216].

We used a method described by Barr et al. (1988) [217]: Two PVC tubes were placed in the left pleural space, one (16 F) in the mid-clavicular line in the second intercostal space and the other (24 F) in the mid-axillar line in the sixth intercostal space. Via tubing, the upper (inlet) pleural tube was connected to a roller pump circulating water at 40–42°C from the reservoir, whereas drainage was obtained via the outlet tube by gravity. Care was taken to keep the flow rate < 500 ml min^{-1} to avoid potential tension hydrothorax, as described by Barr, Halvorsen, and Donovan [217]. A close attention was given to the water temperature and level in the reservoir. Time-matched normothermia control animals were kept immersed in warm water (38–40°C) to maintain core body temperature at 38°C for 6.5 h. Pleural lavage was performed during the last 2 h in the same manner as in the hypothermia group.

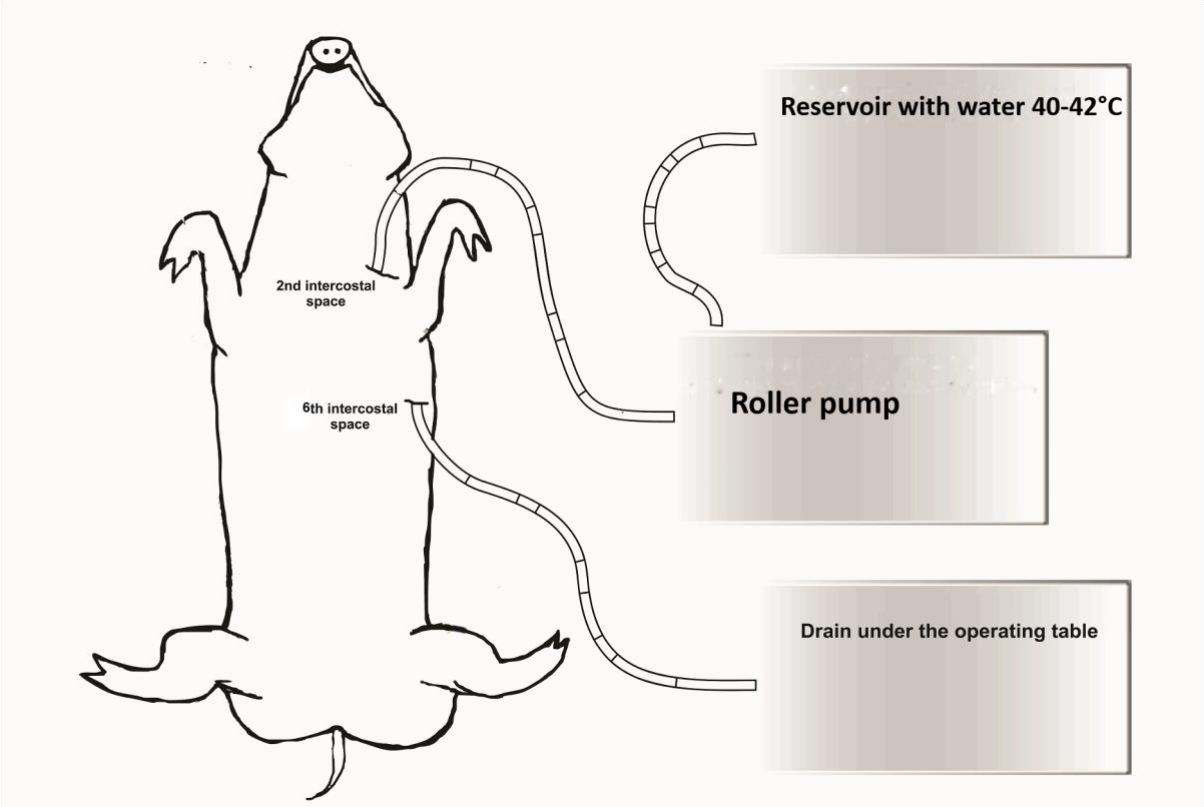

Figure 5: Pleural lavage set-up, paper I.

7.8 Measurements/calculations (paper I, II, III)

MAP, heart rate (HR), CVP, PAP, ICP, left ventricular systolic pressure (LVSP) and urinary output was measured and monitored continuously during experiments using LabChart software (powerLAB 16/35, ADInstruments, Dunedin, New Zealand).

7.8.1 Cardiac output

CO in Paper I and III was measured according to the following formula as in Hales et al. (1973) [218]:

CO (in liters per minute) = Qref × TotCPM/RefCPM/1000, where Qref is the reference flow rate in milliliters per minute, TotCPM is the total activity of injected microspheres, and

RefCPM is the activity of the microspheres in the reference blood sample in counts per minute [218].

The decision to use the microsphere method to measure CO in Paper I and III, rather than thermodilution, was made since we had already used microspheres in current studies to measure regional blood flow. It allowed us to measure CO at precisely the same time points as tissue blood flow. The microsphere method is accurate, as it directly measures CO and blood flow based on the number of microspheres injected [218, 219]. In contrast, thermodilution relies on the temperature change in a bolus of cold injectate and only provides an average CO measurement.

Nevertheless, thermodilution is acknowledged as a practical "gold standard" for measuring CO during CPR in the clinical setting [220]. Therefore, in Paper II, accordingly to the paper's goals, mimicking the clinical scenario of hypothermic cardiac arrest, we measured CO in triplets using the thermodilution method by means of a Swan-Ganz pulmonary artery catheter. Both methods showed comparable results in the same experimental model.

7.8.2 Calculation of other hemodynamic variables

Stroke volume (SV) (paper I) was calculated as follows: SV (in milliliters) = CO/HR × 1000. Total peripheral resistance (TPR) (paper I) was calculated as follows: TPR (in dynes seconds per centimeter raised to the fifth power) = (MAP − CVP) × 80/CO. Mean CBF (paper III) from different areas of the brain at the given timepoint was used as mean cerebral blood flow (CBF). Cerebral vascular resistance (CVR) was calculated as (MAP – ICP)/CBF (paper III). Cerebral perfusion pressure (CPP) was calculated as MAP – ICP as ICP was higher than CVP in all animals (paper III)

7.8.3 Blood gases, global (paper I, II), cerebral (paper I, III) oxygen transport and O_2 extraction ratio (paper I, II, III)

Blood gases from aortic arch arterial blood (paper I, II, III), mixed-venous blood from the pulmonary artery (paper I, II), and venous blood from the jugular bulb (paper III), were sampled and analyzed at 37°C using an ABL800 (FLEX, Radiometer Medical, Copenhagen, Denmark) blood gas analyzer. In accordance with the alpha-stat strategy blood gas values were not temperature corrected.

Blood O_2 content was calculated using the following formula: (Sat O_2 × Hb × 1.34) + (0.0031 × PO2). Global DO_2 (paper I, II) was calculated as the product of CO and arterial O_2 content. Global VO_2 (paper I, II) was calculated as the product of CO and the difference in O_2 content between arterial and mixed venous blood. Cerebral DO_2 (paper I, III) was calculated as the product of mean CBF and arterial O_2 content. Cerebral VO_2 (paper I, III) was calculated as the product of mean CBF and arterio-venous difference in arterial and jugular bulb venous blood O_2 content. The O_2 extraction ratio (O_2ER) was calculated as the ratio of VO_2 to DO_2, either cerebral or global.

7.8.4 Regional blood flow (paper I, II, III)

Stable isotope-labeled microspheres were used for determining regional organ blood flow (BioPAL Inc., Worchester, MA, USA). In the validation study, stable isotope-labeled microspheres showed a wide detection range during neutron activation analysis, comparable to values obtained from radioactive microspheres and thus superior to other non-radioactive microsphere techniques. They do not emit ionizing radiation, making them easier and safer to

use. In contrast, radioactive microspheres produce low-level radioactive waste and require special handling and storage [219].

An injection of approximately 10 million microspheres marked with different stable isotopes was used at all data sampling points through a fluid-filled pigtail catheter placed in the left ventricle. Simultaneously, a reference blood sample was drawn from the aortic arch using a 20 ml syringe and a withdrawal pump (New Era Pump Systems, Inc, Farmingdale, USA) at a known suction rate (5 ml min^{-1} for 2 minutes). Each reference blood sample containing a specific type of microspheres (in accordance with the data collection point) was placed in a 20 ml sample vial. The syringe was rinsed with "sansSaLine" medium (BioPhysics Assay Laboratory (BioPAL), Inc., Worcester, USA) to remove debris of microspheres attached to its walls. To secure the removal of the sodium, chloride, supernatant, and microspheres attached to the vial wall and to improve the signal-to-noise ratio, the reference blood sample was centrifuged twice with 'sansSaLine'. At the end of the experiment, animals were euthanized, and organ tissue samples to determine regional blood flow were taken from the same locations (heart, brain, kidneys, liver, stomach, and small intestine) in all animals and rinsed with 'sansSaLine' to remove surface blood and other potential contaminants. Reference blood and organ tissue samples were then dried in an oven (70°C overnight). After processing, they were analyzed at the BioPAL laboratory to determine specific activity.

Calculation of regional blood flow (expressed in milliliters per minute per gram) by microsphere activity was calculated using the following equation $Q = (Tis_{CPM} \times Q_{ref})/(Ref_{CPM} \times g)$ where Q is blood flow in milliliters per minute, Tis_{CPM} is the number of radioactive counts in the tissue sample in counts per minute, Q_{ref} is the reference flow rate in milliliters per

minute, Ref_{CPM} is the number of radioactive counts in the reference blood sample in counts per minute, and *g* is weight of the tissue sample in grams.

7.9 Assessment of cerebral autoregulation (paper III)

Since our experimental model did not allow continuous cerebral blood flow measurements, a static method to assess cerebral autoregulation was used, as described in Armstead et al. (2016) [75]. Cerebral autoregulation was evaluated after 15 min and each hour during 3-h hypothermic CPR as compared to spontaneous circulation at 27°C by measuring the steady-state response to the initiation of cardiac arrest, and thereby CPP challenge. To determine the effectiveness of cerebral autoregulation, we calculated the static autoregulation index (sARI) using the following formula: $sARI = \% \Delta CVR / \% \Delta CPP = ((CVR_{CPR} - CVR_{spontaneous\ circ.\ 27°C}) / CVR_{spontaneous\ circ.\ 27°C}) / ((CPP_{CPR} - CPP_{spontaneous\ circ.\ 27°C}) / CPP_{spontaneous\ circ.\ 27°C})$. This index reflects the reactivity of the brain vessels to adjust to a reduced CPP. Cerebral autoregulation is functioning when sARI is between 0,4 - 1 [78].

In addition, we used the ratio CBF/cerebral VO_2 to estimate the relationship between changes in CBF and cerebral O_2 uptake, as described by Mezrow et al. (1992) [82].

7.10 Statistics

Statistical analyses in all papers were performed using SigmaPlot statistical software version 14 (Systat Software Inc., Richmond, CA, USA). The results are presented as means ± standard deviations (SD). The level of significance was set at $p < 0.05$ in all papers. Within - groups changes in hemodynamic variables, values for global and cerebral O_2 transport, regional blood flow (paper I, II, III), and determinants of cerebral autoregulation (paper III) were compared using One-way repeated measures ANOVA if the data were normally

distributed (Shapiro-Wilk test). Otherwise, Friedman repeated measure ANOVA on ranks was used. If significant differences were found, Dunnet's post hoc test was used to compare intragroup values vs. baseline values. In Paper II, comparisons between data in the intervention and the control group, and intragroup comparisons at 38°C baseline, 15 min, and 45/60 min CPR were performed using two-way repeated measures ANOVA. If significant differences were found, all multiple pairwise comparisons were made by using the Holm-Sidak test.

8 Summary of the results

8.1 Paper I

In Paper I, we assessed the physiological effects of 3 h severe hypothermia (27°C) with preserved spontaneous circulation and rewarming with pleural lavage on hemodynamics, global and cerebral O_2 transport, and regional organ blood flow.

Normothermic controls

All hemodynamic variables remained unchanged during the first 4.5 h. After start of the lavage procedure (4.5 h), and until the end of the protocol (6.5 h), a significant decrease in SV and CO, and a significant increase in CVP were observed compared to 0 h baseline. At the end of the experiment (6.5 h), SV and CO were significantly reduced by 43% and 25%, respectively, despite the compensatory increase in HR, MAP, and TPR. However, when compared to 4.5 h, before the start of the lavage procedure, only a decrease in SV and an increase in HR were significant at 6.5 h.

Changes in global and cerebral oxygen transport, plasma lactate, and mixed venous O_2 saturation (SvO_2) were insignificant as compared to baseline at 0 h. Both global and cerebral O_2ER were significantly increased, touching the upper critical limit (0.7) during the 2 h of lavage procedure (4.5 h - 6.5 h).

No significant changes in organ blood flow were found during the experiment in any organs except for both kidneys where flow was significantly reduced during the lavage procedure (4.5 h - 6.5 h).

Cooling to 27°C, 3 h stable hypothermia and rewarming

Hemodynamics. CO, HR, SV, CVP, MAP, and LVSP decreased significantly in response to progressive cooling to 27°C. All variables remained at these reduced levels during stable hypothermia for 3 h, except CVP which returned to normothermic baseline after 1 h, and remained unchanged during the rest of the experiment. Compared to baseline a linear increase in TPR was observed during cooling and stable hypothermia and was significantly increased after 2 h at 27°C. During rewarming, CO and SV remained significantly reduced and after rewarming they both were reduced by 40% when compared to their baseline control values. However, MAP, LVSP, CVP, and HR returned to within their pre-hypothermic baseline values. TPR remained significantly increased when compared to the normothermic baseline value.

Global and cerebral O_2 transport, O_2 ER, SvO_2 and plasma lactate. Both global and cerebral DO_2 and VO_2 were significantly decreased during cooling to 27°C and remained at these reduced levels during 3 h of stable hypothermia. After rewarming, global VO_2 returned to its pre-hypothermic value, while global DO_2 failed to restore in parallel with CO and was significantly reduced compared to the normothermic baseline. Both cerebral DO_2 and cerebral VO_2 were significantly reduced during 3 h hypothermia but were fully restored after rewarming. Global O_2ER never exceeded its critical value (0.6-0.7) during hypothermia and rewarming. However, it was significantly increased after 2 h stable hypothermia and after rewarming as compared to baseline values. Its significant increase after rewarming to 37°C was in concert with a significant reduction in SvO_2. Cerebral O_2ER and plasma lactate levels remained unchanged during the experiment.

Regional blood flow. After being reduced during cooling and 3 h stable hypothermia, blood flow in heart, brain, and small intestine was fully restored after rewarming. Blood flow in other organs remained significantly reduced.

8.2 Paper II

In Paper II, we evaluated if the fraction of CO generated by CPR for hypothermic CA is independent of core temperature and, thus, able to replace spontaneous CO at 27°C and fully support metabolic demands, O_2 transport, and organ blood flow during 3 h CPR. We also compared the effects of hypothermic (27°C) CPR for 1 h vs. normothermic CPR for 45 min.

Normothermic 45 min CPR vs hypothermic 60 min CPR. CPR initiated in the normothermic, and the hypothermic group provided a similar significant reduction in CO after 15 min (71% and 74% respectively) and 45/60 min (80% and 74% respectively) as compared to spontaneous circulation at 38°C, without significant differences between groups. However, MAP after 45 min in the normothermia group was significantly lower than MAP after 60 min in the hypothermia group. In the hypothermia group, MAP remained at the same reduced level after 15 min of CPR. After 45/60 min of CPR in both groups, global VO_2 was significantly lower in the hypothermia group than in the normothermia group, while there were no differences in global DO_2. At the same time, the hypothermia group had a higher SvO_2, a lower increase in serum lactate (2.81 vs. 7.38 mmol/l), and lower O_2ER indicating better O_2 transport. In the normothermia group, regional blood flow was significantly lower in all organs after 15 min of CPR compared to during spontaneous circulation, and blood flow was not detectable after 45 min of CPR. In the hypothermia group, a similar reduction in organ blood flow as in the normothermia group occurred after 15 min but, in contrast to the

normothermia group, organ blood flow remained at the same reduced levels throughout 60 min of CPR.

Effects of hypothermic (27°C) CPR for CA during 3 h. After 15 min of CPR, CO and MAP remained unchanged throughout the 3 h period of continuous CPR, whereas DO_2 continued to decrease and was significantly lowered after 2 h of CPR. VO_2 remained at the same reduced level throughout the experiment. O_2ER approached O_2ER_{crit} after 1 h of CPR and remained at this level for the next 2 h of CPR. SvO_2 reached its nadir after 1 h CPR (27 %) and remained at this reduced level for the rest of the CPR period. Serum lactate was significantly elevated after 1 h of CPR and increased linearly during the experiment, ending at 5.56 mmol/l after 3 h. Compared to after 15 min of CPR, blood flow in the heart was significantly reduced after 3 h CPR, but blood flow in both the right and left brain - hemispheres remained at the same reduced level throughout the CPR period. Blood flow to the kidneys was significantly reduced after 1 h, to the small intestine after 2 h, and to the stomach and liver after 3 h CPR.

8.3 Paper III

In Paper III, we studied if CPR for 3 h in severe hypothermia (27°C) would provide sufficient O_2 transport to preserve autoregulation of cerebral blood flow. For these purposes, we analyzed cerebral blood flow in 5 different brain areas and calculated sARI and CBF/cerebral VO_2 ratio.

Cooling to 27°C with spontaneous circulation. An apparent liner reduction in CO and MAP emerged during cooling to 27°C, but without statistical significance. ICP, CVP, and CVR remained unchanged, while CPP was significantly reduced, all compared to their

normothermic baseline values. Cerebral DO_2, VO_2, and O_2ER were significantly reduced by the end of cooling, while jugular bulb SvO_2 significantly increased. Mean CBF was significantly reduced by the end of cooling when compared to spontaneous circulation at 38°C. Regional CBF was significantly reduced only in the left cerebellum and hippocampus.

3 h CPR at 27°C. CO, MAP, and CPP were significantly reduced 15 min after the start of CPR as compared to spontaneous circulation at 27°C and remained at these reduced levels throughout the 3 h CPR period. CVR returned to within the pre-hypothermic values and remained unchanged throughout 3 h CPR. A modest yet significant increase in CVP was observed 15 min after start of CPR (from 6 to 13 mmHg). CVP remained increased following 3 h of CPR. Cerebral DO_2 remained at the same level during the first 2 h of CPR as during spontaneous circulation at 27°C but became significantly reduced after 3 h of CPR. Cerebral VO_2 remained statistically unchanged during 3 h of CPR compared to spontaneous circulation at 27°C. Cerebral O_2ER after the first 15 min and subsequent 2 h of CPR returned to the levels of normothermic baseline but increased significantly after 3 h of CPR, yet still being below Ercrit (0.6-0.7). During the first 2 h of CPR jugular bulb SvO_2 remained unchanged from the pre-hypothermic baseline value. During the third CPR hour, a statistically significant decrease in SvO_2 occurred. Mean and regional CBF in all brain areas evaluated remained unchanged during the first 2 h of CPR when compared to spontaneous circulation at 27°C. CBF in the left and right temporal lobes and mean CBF significantly decreased after 3 h of CPR.

Cerebral autoregulation. sARI remained above the lower limit for functioning cerebral autoregulation (>0.4) during the first 2 h of CPR. After 3 h it was reduced to 0.1 in parallel with reduced mean CBF, indicating impaired autoregulation. CBF/Cerebral VO_2 ratio was

significantly increased during cooling to 27°C with spontaneous circulation but returned to the same level as calculated at baseline 38°C during the ensuing 3 h of CPR.

9 General discussion

Studies included in the current thesis show that despite the deterioration of hemodynamic function caused by long-term (3 h) severe hypothermia (27°C) with spontaneous circulation or in combination with CPR for hypothermic CA, the maintenance of adequate O_2 transport to support cardiovascular homeostasis and blood flow to essential organs was feasible. We attribute our findings to the hypothermia-induced reduction in metabolic demands and thus maintained compensatory responses to a reduced CO, such as cerebral autoregulation. Moreover, we showed that both global and cerebral O_2 transport and organ blood flow in essential organs (brain and heart) are also preserved after rewarming for 3 h severe hypothermia with spontaneous circulation, despite hypothermia-induced cardiovascular dysfunction and negative effects of thoracic lavage procedure.

9.1 Cardiopulmonary resuscitation for hypothermic vs normothermic cardiac arrest

Typically, the first minutes of high-quality normothermic CPR can provide up to 25 - 40% of pre-arrest CO [221-225]. However, its efficacy quickly deteriorates due to ensuing ischemia-reperfusion injury, leading to persistent neurologic damage [226] and cessation of blood flow to the brain and heart [227, 228]. AHA and ERC guidelines state that normothermic CPR for OHCA should last at least 20 minutes before the decision on its cessation could be considered. One should consider termination of resuscitation efforts if CA is not witnessed, no shocks with AED is provided and no ROSC registered [88, 229]. However, recommendations are ambiguous since the maximum duration of CPR for normothermic CA with favorable outcomes remains undetermined [230]. Nevertheless, due to the neuroprotective effects of

hypothermia, there is consensus that CPR for hypothermic CA should be started immediately and last continuously during evacuation and transport unless there are signs of evident fatal injury or the body is chilled to the level where chest compressions are not possible [188].

Hypothermia directly inhibits neural activity and reduces tissue metabolism [3]. Lowering of metabolism obeys Vant-Hoffs Arrhenius rule, and one can expect a 50-75% reduction of metabolism and a corresponding fall in CO following a decrease in core temperature to 27°C [64].

We showed a similar linear reduction in HR, CO, SV, and MAP in all three papers during cooling. These findings correspond with findings in our previous studies using the porcine model [41, 101, 231]. In both hypothermic and normothermic animals in Paper II and III, we obtained comparable CO values during the first 15 min of CPR, which otherwise correspond with CO measured during the first minutes of high-quality CPR. Thereby, we verified our working hypothesis that the level of CO obtainable by CPR is unaffected by reduction in core temperature to 27°C. However, in the normothermic CPR Paper II, CO and MAP continued to fall and were almost absent after 45 minutes of CPR. The latter was in concert with the findings of Carretero et al. (2010) [220], who found a similar CO reduction to 83% (vs. 80% in paper II) after 45 min of mechanical CPR utilizing LUCAS in his pig model. Gervais et al. (1997) [227] found a similar decrease in MAP after 30 min of CPR to 87% (vs. 80% in paper II), accompanied by almost undetectable cerebral and myocardial blood flow. Few investigators have studied normothermic CPR this long, as it is less clinically relevant [232]. Nevertheless, our findings of MAP and CO after 15 min were like other studies utilizing the porcine model of CPR with the same or comparable duration [196, 220].

Further, we found that reduced CO, generated after 15 min of CPR in hypothermia groups of Paper II and III, was persistently sustained and able to generate the same level of MAP for the next 2 h of CPR. However, after the third hour of CPR, all hemodynamic variables showed a significant reduction, but not as prominent as in normothermic animals after 45 min of CPR (paper II).

Hypothermia induces a cascade of favorable physiological changes that may help to sustain organism's viability in CA. Among them is lowering of metabolism, and hence, excess oxygen available for delivery during compromised circulation due to CA [82]. In Paper II and III, the latter resulted in avoidance of tissue hypoxia during the first 2 h and hence less pronounced acidosis after 3 h of hypothermic CPR. It was reflected in a modest yet significant increase in lactate levels (from 1.9 after 1 h, to 3.9 after 2 h and 5.7 after 3 h of CPR). In contrast, normothermic animals of Paper II showed prominent elevation in lactate levels shortly after the start of CPR (3.7 after 15 min and 7.38 after 45 min), resulting in severe lactic acidosis.

Acidosis precipitates a decrease in vascular tone and results in arterial vasodilation [233, 234]. However, it is usually partly compensated by the endogenous release of catecholamines due to acidemia [235]. On the contrary, the venous system reacts to acidosis with venoconstriction [236]. It would be further enhanced by the abovementioned catecholamines release [237]. The latter, enhanced by hypoxic pulmonary vasoconstriction and failing cardiac pump function during CPR, leads to the elevation of CVP [238]. Stable CVP, within the physiological levels, is crucial for venous return to the heart [238], further determining the CO and global hemodynamics. We have reported an increase in CVP from 7 to 43 mmHg in normothermic animals in Paper II, in concert with the dramatic decrease in CO and almost

complete cessation of organ blood flow. In contrast, CVP increased from 6 to only 14 mmHg after 3 h of hypothermic CPR in hypothermic animals in Paper II and III, suggesting the absence of venous congestion, adequate venous return to the heart, and antegrade flow. The finding of unchanged, stable CVP in animals with spontaneous circulation in Paper I during 3 h of severe hypothermia suggests preserved cardiac pump function.

9.1.1 Global and cerebral O_2 transport

One can expect a two- to threefold reduction in metabolism with cooling to 27°C [68]. Linear reduction of DO_2 and VO_2 to cooling was previously demonstrated experimentally [39, 41, 69]. We, as well, showed it uniformly in all three studies. Consequently, we hypothesized that the already discussed sustained CO and MAP generated by CPR for CA at this temperature could provide a greater DO_2 to the body's metabolic needs (VO_2) than CPR in normothermia. We utilized the concept of oxygen extraction ratio (O_2ER) [72] to demonstrate the relationship between oxygen delivery and consumption in Paper I, II, and III. When oxygen delivery is limited, the ratio approaches its critical level of 0.6-0.7 (ER_{crit}), and oxygen consumption starts to depend on oxygen supply. In hypothermia, the range is narrowed to approximately 0.65, possibly due to the reduced effectiveness of O_2 extraction and increased vascular resistance, which impedes the arteriole's response to changes in metabolism and blood flow distribution [74].

At the end of cooling, both global (paper I and II) and cerebral (paper I and III) O_2ER reduced by 50%, indicating an excess of oxygen delivery during spontaneous circulation at 27°C, mainly due to reduced VO_2 and following hypothermia induced reduction in metabolism. The common finding of Paper II and III is that hypothermic CPR could sustain

stable reduced (due to 74% reduction in CO) levels of global DO_2 and unaltered, as compared to spontaneous circulation at 27°C, cerebral DO_2 during the first two hours of CPR. Beyond these two hours, both global and cerebral DO_2 fell, but was compensated by increased O_2 extraction, expressed in the decreased SvO_2 (27%) in both Paper II and III. Based on these findings, together with sustained values of global and cerebral O_2ER, never exceeding ER_{crit}, and the fact that both global and cerebral VO_2 remained unchanged throughout 3 h of CPR, we concluded that 3 h hypothermic CPR provided marginal but sufficient global O_2 transport (paper II) and cerebral O_2 transport within the physiological levels (paper III). It is in essential contrast to normothermic CPR, where we showed parallel continuous lowering of global DO_2 and VO_2 during 45 min of CPR. O_2ER crossed ER_{crit} already after 15 min of CPR with immediate signs of severe lactic acidosis (7.38 mmol/l after 45 min), indicating delivery dependent VO_2 and anaerobic metabolism.

In spontaneously circulated animals (paper I), we also showed more prominently reduced DO_2 than VO_2, indicating limited oxygen supply during severe hypothermia. Nevertheless, global VO_2, decreased due to the lowering of metabolism in hypothermia, returned to its pre-hypothermic levels after rewarming, indicating that physiologic mechanisms for O_2 extraction to tissues are functioning in severe hypothermia, as it was previously shown in other studies [39, 64]. O_2ER never exceeded ER_{crit}, and first approached it only at 38°C after rewarming, when both CO and SV were reduced by 40% due to hypothermia-induced cardiovascular dysfunction. These findings, together with unaltered lactate and SvO_2 within physiological levels during cooling-hypothermia-rewarming, also indicate preserved delivery-independent VO_2.

9.1.2 Global and cerebral regional blood flow. Cerebral autoregulation

Stable CO, MAP, and maintained delivery independent VO_2 during hypothermic CPR indicated that compensatory mechanisms for autoregulation of blood flow were preserved. The expected compensatory response to CO reduction in critical conditions focuses on maintaining cerebral and coronary blood flow. For example, such a response was described after thermal injury and during hemorrhagic shock [239, 240] . Voorhes et al. (1980) found that the brain and heart receive 90% and 35% of blood flow, respectively, during the first minutes of CPR to normothermic CA in dogs, compared to sinus rhythm [224]. Studying the blood flow distribution during 30 min of severe hypothermia (21°C) exposure in spontaneously circulated dogs, Anzai et al. (1978) showed that both myocardial and brain stem blood flow remained at 40% of normothermic control values, despite the hypothermia-induced reduction of CO to 20%. At the same time, other organs demonstrated less than 20% of the basal flow [241]. In pigs subjected to 20 minutes of mechanical CPR at 22°C, Maningas et al. (1986) found that cerebral blood flow was at 13% and myocardial blood flow was at 8%, while hepatic and kidneys blood flow reduced to 5% of prearrest baseline values [242]. Blood flow distribution, prioritizing cerebral blood flow in the abovementioned studies, correlated with the patterns we demonstrated during hypothermic CPR (paper II and III) and hypothermic animals with spontaneous circulation (paper I). However, organ blood flow reduction was not that prominent in our CPR studies, likely because of the difference in depth and length of hypothermia exposure. In animals subjected to normothermic CPR (paper II), similar patterns were followed during the first 15 minutes of CPR. However, after 45 minutes, organ blood flow was almost undetectable, in parallel with the findings of Gervais et al. (1997) [227].

Maintaining cerebral blood flow during hypothermic CPR is essential to achieve favorable neurologic outcomes in victims of accidental hypothermia with CA. Cerebral autoregulation is a homeostatic mechanism aimed at implementing this goal in a wide range of CPP [75]. CPP is one of the main determinants of CBF [243]. It is known that changes in CPP between 50 mmHg and 130 mmHg cause no alteration in CBF during spontaneous circulation in normothermia [243-246]. When autoregulation malfunctions, the CBF is governed by factual changes in CPP. Hence, malfunctioning autoregulation will eventually lead to cerebral hypoperfusion or hyperemia [84]. Cerebral hyperemia usually manifests in increased ICP levels [247], while hypoperfusion logically results in reduced CBF. In a normothermic CA situation, the brain quickly develops ischemic injury associated with impaired autoregulation. Sundgreen et al. (2001) showed impaired autoregulation in 13 out of 18 OHCA patients with 8 minutes median time to ROSC [248]. Another study reported absent or impaired autoregulation after resuscitation of 8 patients, stating that the level of impairment is directly associated with the degree of ischemic injury [249].

However, the data on the impact of hypothermia on autoregulation are conflicting. Evidence from pre-clinical CPB studies [78, 82, 83], and data from cardiac surgery patients advocate that mild hypothermia in post-CA states may have protective effects on cerebral autoregulation [84, 85]. In contrast, human CPB studies suggest that hypothermia during CPB is associated with impaired autoregulation [250-253]. A recent porcine study, however, questioned whether impaired autoregulation during CPB was due to hypothermia and not hypotension [254]. The authors found that static autoregulation was preserved during 155 min of severe hypothermia at 20°C in spontaneously circulated animals. They have also found an unaltered lower pressure limit sustaining autoregulation compared to normothermic controls. These findings were later validated in human CPB patients [255]. A study in pigs mimicking

accidental hypothermia (28°C) scenario with rapid induction of hypothermia (160 min) showed preservation of cerebral autoregulation in temperatures down to 30°C but further cooling, however, indicated impaired autoregulation [256]. In a pig study of hypoxic-asphyxic CA with the application of therapeutic hypothermia (34°C), cerebral autoregulation was preserved to both hypo- and hypertension during 20 h and only to hypotension after rapid rewarming to normothermia [257].

In Paper III, we showed maintained CBF and its uniform distribution in 5 different brain areas during the first 2 h of hypothermic CPR on the background of preserved delivery independent VO_2. Static autoregulation index indicated maintained cerebral autoregulation during this period. The actual findings of stable CBF, despite reduced MAP and CPP, together with preserved ICP and CVP within the physiological levels, indicate the absence of either cerebral hypoperfusion or cerebral hyperemia. This finding further supports the notion of preserved autoregulation during CPR in hypothermia. It is similar to findings in Paper I and II, suggesting preserved autoregulation, even though indexes of autoregulation were not measured in these papers.

9.2 Rewarming followed by 3 h severe hypothermia with preserved spontaneous circulation

In their pioneering works, Popovic and Kent demonstrated that maintaining stable hemodynamics is feasible for up to 3-4 h of severe hypothermia exposure [38, 40]. However, hypothermia is well known to deteriorate hemodynamic function, leading to reduced CO and MAP due to increased blood viscosity, reduced circulating blood volume and increased vascular tone [27, 44, 48, 49, 51]. These changes could result in cardiac mechanical dysfunction during rewarming, as described in previous studies [38, 39, 41-43, 48, 60].

In Paper I, after 3 h of stable hypothermia and rewarming, we showed that despite restoring MAP to pre-hypothermic baseline values, both CO and SV remained significantly decreased without signs of compensating increase in HR. These findings indicate the presence of decompensated mechanical dysfunction due to exposure to hypothermia. It is in contrast to a previous study by Filseth et al. (2010) using this animal model, where after 1 h of hypothermia at 25°C, isolated LV systolic cardiac dysfunction was compensated by reduced TPR and increased HR [41]. However, despite a 40% reduction in CO and SV after rewarming, we demonstrated delivery-independent global and cerebral VO_2 and restored myocardial and brain blood flow. Therefore, we conclude that adequate compensatory autoregulative responses were preserved after 3 h hypothermia and rewarming. Contrarily, in rats exposed to 5 h hypothermia at 15°C [64], blood flow in essential organs remained significantly reduced after rewarming, suggesting that maintenance of these compensatory responses appears to be dependent on depth and length of hypothermia exposure.

9.2.1 Pleural lavage as the method of rewarming from severe hypothermia

Different modifications of controlled rewarming using the extracorporeal circuit as ECMO or CPB, remain the most efficient and safe methods in accidental hypothermic victims with cardiac arrest [90]. However, the successful application of these methods is impossible without a dedicated team of professionals using complex and expensive equipment available only in large centers. Therefore, other methods of rewarming should be considered when transport of accidentally hypothermic patients to such centers is practically impossible. A few accepted methods of active external and internal rewarming from severe hypothermia can provide comparable efficacy in patients without hemodynamic instability [3]. In a previous study utilizing a similar animal model, full-body immersion in warm water was used [41].

However, using this method in a clinical setting is controversial and not recommended by a recent expert review as it may result in an after-drop phenomenon and the risk of cardiovascular collapse [87]. We utilized pleural lavage since it is recommended as a rewarming method by international guidelines and accidental hypothermia reviews as an alternative to ACLS rewarming when the latter is not available [1, 133]. It is also advocated in local guidelines for accidental hypothermia when evacuation is complicated [92]. The method's efficacy was shown in severe hypothermic patients presenting with both spontaneous circulation and cardiac arrest [110, 111].

We used the procedure described in previous studies [216, 217, 258], carefully preventing flow from causing tension hydrothorax in a closed circuit whereby the increase in intrathoracic pressure will compromise hemodynamic function [259-261]. Unexpectedly, we experienced significant reduction in CO and SV during the 2 h lavage procedure in normothermic control animals compared to baseline measurements. Only Otto et al. (1988) reported CO measurements among studies describing the technique, and our findings (40% reduction in CO) in the hypothermia group were like those in his study. They can be associated with hypothermia-induced mechanical dysfunction [258], but since the current animal model has previously shown hemodynamic stability, without the use of thoracic lavage, we suspect the actual reduction in CO and SV in normothermic was a consequence of the thoracic lavage procedure.

Thoracic lavage was introduced in human clinical practice a few years after describing its successful use in a case report [262]. Even though the method showed its safety and efficacy when applied by trained specialists in subsequent series of case reports [110-112, 263], the

evidence base for its safety to consider it as an alternative to ACLS rewarming is lacking [264]. Based on our results, the use of this method should be considered with awareness.

10 Limitations of the study

In our CPR experiments, we used an automated mechanical CPR device (LUCAS chest compression system, Physio-Control inc., Lund, Sweden) (paper II and III). It was designed and refined several times during the past two decades for clinical use in humans [265]. Its use, however, was validated using a porcine model, focusing on similarities between pigs and humans with respect to anatomy (the size, but not the shape), metabolic and cardiovascular function [196]. Nevertheless, it was stated that because of anatomical peculiarities, the pigs heart is not being compressed between the sternum and spine, suggesting the thoracic pump circulation mechanism is dominant during CPR in pigs [196]. Since then, many CPR studies have been performed using automated CPR in porcine models, with reproducible results in humans [266].

To our knowledge, no comparable data are available on the use of automated CPR in a porcine model with respect to duration. The shape of a rib cage in pigs is different from that of a human and can be compared to an egg standing on its end in contrast to lying on its side as would be the case in humans [267]. It is, therefore, difficult to position the animal inside the compression device to achieve adequate compression quality during prolonged CPR (3 h in our studies) without repositioning the animal or device. During our pilot studies, some animals died after repositioning. We hypothesize that it was due to bleeding from intrathoracic vessels caused by rib and sternal fractures, which otherwise is a common complication to CPR [268]. To avoid complications described in the pilot studies we used a vacuum mattress to immobilize the animals, and this intervention helped to avoid repositioning the device during experiments.

Nevertheless, the finding of multiple costal (all animals) and sternal fractures (6 of 8 animals) was observed in Paper II and III. Interestingly, other animal studies do not share our experiences using the LUCAS device in pigs, reporting only skin wounds, episodic rib fractures, and lung contusion as common complications [266, 267, 269]. Human studies also report such complications to a lesser extent. LINC study reports 7 serious events using LUCAS on 1300 patients [270]. Koster et al. (2017) found a similar incidence of severe life-threatening injuries during CPR using LUCAS (1-7%) and manual CPR (0-6%) [271]. In a prospective multicenter study of 222 patients with unsuccessful CPR after OHCA, it was found that mechanical CPR with LUCAS more frequently led to rib fractures compared to manual CPR. However, the frequency of sternal fractures was similar, and no injury was proclaimed a cause of death [272]. Therefore, we suggest that our findings in pilot studies were due to the use of a device initially designed for humans.

11 Translational value

The duration of the experiments in the papers included in the thesis simulated the expected duration of evacuation and transport of severe accidental hypothermic patients in areas such as ours, as described in reports of successful neurological resuscitations in our catchment area [128, 207]. University Hospital of Northern Norway covers vast area from Finnmark to Nordland counties, and total evacuation and transport time can be even longer.

Results of Paper I show that successful rewarming is feasible after 3 h of hypothermia with spontaneous circulation, despite hypothermia-induced cardiovascular dysfunction. These results give a vital insight into physiological compensatory responses during hypothermia/rewarming that might be useful when applying an in-hospital complex treatment of accidental hypothermia victims both with and without cardiac arrest.

The results of Paper II show that prolonged mechanical CPR for 3 h for hypothermic CA can provide adequate hemodynamics, O_2 transport, and organ blood flow. These results support the current ERC recommendation for using mechanical CPR when prolonged transport is needed [7]. Ambulance airplanes and helicopters in our catchment area are equipped with automated chest compression devices, and their utilization is crucial for successful resuscitation of accidental hypothermia victims with CA.

Finally, the results of Paper III show preserved autoregulation of cerebral blood flow and adequate cerebral O_2 transport during 2 h CPR at 27°C. They give essential information on the background mechanism for successful resuscitations without neurologic sequelae in hypothermic CA patients treated with continuous CPR during evacuation and transport, further supporting recommendations of ERC [7].

12 Conclusions and future research

The main objective of the current thesis was to describe pathophysiologic changes and physiological compensatory responses during severe hypothermia and rewarming with and without CA. We have assessed the value of CPR as part of pre-hospital interventions and discovered possible mechanisms that might give an essential insight into the successful resuscitation of accidental hypothermic patients with CA subjected to long-term CPR. For these reasons, we have studied hemodynamics and pressure generation, global and regional oxygen transport, and regional blood flow during 3 h stable hypothermia and rewarming using a closed chest thoracic lavage procedure. Further, we evaluated the effects of 3 h automated CPR for CA at the same temperature employing an automated mechanical CPR device. Based on the results from our experiments, we draw the following conclusions:

- The presence of hypothermia-induced myocardial mechanical dysfunction, and negative effects of thoracic lavage procedure result in significantly reduced CO and SV after rewarming for 3 h severe hypothermia (27°C) with maintained spontaneous circulation. However, maintained physiological compensatory responses provided adequate oxygen transport and restoration of blood flow in essential organs after rewarming.

- The fraction of CO provided by CPR for CA in severe hypothermia (27°C) employing an automated mechanical CPR device is unaffected by temperature. This fraction favors end organ survival when given at 27°C compared to at 38°C. Further, due to functioning peripheral circulation in hypothermia, CPR could sustain stable MAP and

global DO_2 to support marginal but sufficient delivery independent global VO_2 along with the maintained regional blood flow in essential organs throughout 3 h.

- Static cerebral autoregulation was maintained during 2 h of CPR for hypothermic (27°C) CA, whereby optimal O_2 balance and cerebral O_2 transport on a delivery-independent level was provided. Thus, CBF remained unchanged in 5 different areas of the brain during CPR at 27°C, like in animals with spontaneous circulation at this temperature, despite dramatically decrease in CO, CPP, and MAP.

These conclusions support the recommendation for using early and continuous mechanical CPR in severely hypothermic patients during rescue and evacuation and the present experimental results give new insight into mechanisms for its success after controlled rewarming in a hospital setting. Nevertheless, still little is known about the consequences and long - term effects of prolonged, continuous CPR on the thoracic skeleton and vital organs. Thus, more studies are needed to elaborate newer and refined guidelines when giving a complex in-hospital treatment for accidental hypothermia patients.

13 References

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