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With special reference to post-cardiac arrest care

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DOI:
10.21996/86b3-jf22

Publication date:
2023

Document version:
Final published version

Citation for pulished version (APA):
Mølstrøm, S. (2023). *Bedside Assessment of Global Cerebral Energy Metabolism utilizing Intravenous Microdialysis: With special reference to post-cardiac arrest care*. [Ph.D. thesis, SDU]. Syddansk Universitet. Det Sundhedsvidenskabelige Fakultet. https://doi.org/10.21996/86b3-jf22

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Bedside Assessment of Global Cerebral Energy Metabolism utilizing Intravenous Microdialysis:

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PhD Thesis

Simon Mølstrøm, MD

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Indholdsfortegnelse

PREFACE AND ACKNOWLEDGEMENTS

Open the Black Box of the Brain

The human brain is the most complex biological structure on Earth. It has about 100 billion neurons, each having thousands of connections to other neurons. Because the brain is so complex and dynamic, it is still akin to a locked black box. Brain injury processes after cardiac arrest remain highly complex and involve numerous pathophysiological pathways. Indeed, our understanding of brain injury remains rudimentary compared to our knowledge of other organs.

This thesis represents an attempt to open the black box and discuss the complex changes in brain energy metabolism during post-resuscitation care. Understanding even the most minor neuroscientific aspects of the brain in a clinical setting may translate to more advanced therapies, improving patient outcomes.

Since 2017 I have been fortunate to be part of an outstanding group of clinical researchers within post-resuscitation care after out-of-hospital cardiac arrest (OHCA), cerebral metabolism, and microdialysis led by the following supervisors: Professor Palle Toft, Doctor Troels Halfeld Nielsen, Doctor Carl H. Nordström and Doctor Henrik Schmidt. I am incredibly grateful for your invaluable advice, continuous support, and patience during my Ph.D. study. Their immense knowledge and great experience have encouraged me in my academic research. Thank you all; it has been a pleasure working together. During my fellowship in Anesthesiology at Odense University Hospital, I was allowed to focus on brain metabolism during cardiac surgery. Since I have focused my time on neuroscientific research in a Ph.D.-project concerning brain energy metabolism in comatose cardiac arrest survivors. Financially, the fulfillment of this Ph.D. grade would not have been possible without the support of the Anesthesiology department chair at Odense University Hospital. For this, I feel very fortunate and grateful.

This thesis was based on several ideas explored from the earlier work of my college Rasmus Jacobsen, co-supervisor Troels Halfeld Nielsen, and their collaboration with professor emeritus of Lund University Carl-Henrik Nordström. I owe them much for presenting me with their understanding of the field, the methods, the interpretations, constructive criticism, and moral support. A special thanks to Doctor Jesper Kjaergaard, Professor Jacob Eifer Moller, and Professor Christian Hassager at Rigshospitalet, for whom the main study would not have been possible to conduct since the trial was a sub-study in the Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial (BOX). Further, I would like to thank Professor Christian Hassager for the thoughtful comments and recommendations on this dissertation.

Also, I owe much gratitude to Johannes Grand, who has been running the BOX trial in Copenhagen and have been a fantastic colleague. Finally, I have enjoyed working and sparring with colleagues and friends Axel Forsse, Jimmy Holm, and Rasmus Jacobsen, especially in professional discussions.
This thesis would not have been possible without the cardiac intensive care unit staff, VITA, OUH. I am grateful that you have continued to assist me despite working in a busy and sometime resource-deficient clinical setting.

Finally, I would like to express my gratitude to my parents, friends, and children. Without their tremendous understanding and encouragement over the past few years, it would be impossible for me to complete my study.

Simon Mølstrøm, Odense, 10/06-2022

ORIGINAL ARTICLES

The current thesis is based on the following research articles:

Paper I[1]

Bedside monitoring of cerebral energy state during cardiac surgery - A novel approach utilizing intravenous microdialysis.

Molstrom S, Nielsen TH, Andersen C, Nordstrom CH, Toft P.

J Cardiothorac Vasc Anesth 31: 1166-1173. 2017.

Paper II[2]

Design paper of the "Blood pressure targets in post-resuscitation care and bedside monitoring of cerebral energy state: a randomized clinical trial".

Molstrom S, Nielsen TH, Nordstrom CH, Hassager C, Moller JE, Kjaergaard J, Moller S, Schmidt H, Toft P.

Trials 20: 344. 2019.

Paper III[3]

Bedside microdialysis for detection of early brain injury after out-of-hospital cardiac arrest.

Molstrom S, Nielsen TH, Nordstrom CH, Forsse A, Moller S, Veno S, Mamaev D, Tencer T, Schmidt H, Toft P.

Sci Rep 11: 15871. 2021.

Paper IV

A randomized, double-blind trial comparing the effect of two blood pressure targets on global brain metabolism after out-of-hospital cardiac arrest

Molstrom S, Nielsen TH, Nordstrom CH, Forsse A, Moller S, Veno S, Mamaev D, Tencer T, Theódórsdóttir A, Kroigard T, Moller J, Hassager C, Kjaergaard J, Schmidt H, Toft P.

Submitted

Throughout this thesis, the papers are referred to as Papers I, Paper II, Paper III, and Paper IV.

Related studies conducted during PhD-study, not formally included in the thesis

Moderately prolonged permissive hypotension results in reversible metabolic perturbation evaluated by intracerebral microdialysis - an experimental animal study[4].
Jakobsen RP, Nielsen TH, Molstrom S, Nordstrom CH, Granfeldt A, Toft P
Intensive Care Med Exp 7: 67. 2019.

A Prospective Observational Feasibility Study of Jugular Bulb Microdialysis in Subarachnoid Hemorrhage[5].
Forsse A, Nielsen TH, Molstrom S, Hjelmborg J, Nielsen KS, Nygaard KH, Yilmaz S, Nordstrom CH, Poulsen FR.
Neurocrit Care 33: 241-255. 2020.

Cerebral venous blood is not drained via the internal jugular vein in the pig[6].
Nordstrom CH, Jakobsen R, Molstrom S, Nielsen TH.
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Cerebral microdialysis after cardiac arrest - misinterpretations based on a misconception[7].
Nordstrom CH, Rasmus RJ, Molstrom S, Nielsen TH.
Resuscitation. 2021.

Hemodynamic evaluation by serial right heart catheterizations after cardiac arrest; protocol of a sub-study from the Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial (BOX)[8]
Grand, J, Hassager, C, Schmidt, H, Moller, J. E, Molstrom, S, Nyholm, B, Kjaergaard.
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Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest[9]

Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Lindholm MG, Frydland M, Meyer MAS, Winther-Jensen M, Frikke-Schmidt R, Wiberg S, Boesgaard S, Madsen SA, Jørgensen VL, Hassager C.

N Engl J Med. 2022 Oct 20;387(16):1456-1466. doi: 10.1056/NEJMoa2208687. Epub 2022 Aug 27.

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FUNDING

Department of Clinical Research, Faculty Stipend

Region of Southern Denmark´s Ph.D. fund

Department of Anesthesiology and Intensive Care, Odense

A.P. Moeller Foundation for the Advancement of Medical Science

Intensive Symposium Hindsgavl

Danish Society of Anesthesiology & Intensive Care Medicine

The Board of Physicians' Legacy Committee, Odense University Hospital

LIST OF ABBREVIATIONS

ADP	adenosine diphosphate
ATP	adenosine triphosphate
AQP-4	aquaporin-4
CA	cardiac arrest
CABG	coronary artery bypass graft
CBF	cerebral blood flow
CPB	cardiopulmonary bypass
CPR	cardiopulmonary resuscitation
CT	computed tomography
GLUT	glucose transporter
F-18-FDG	positron emission tomography (PET) 18-Fluor deoxyglucose
ICU	intensive care unit
IL-1β	Interleukin-1 beta
IQR	interquartile range
JBM	jugular bulb microdialysis
LDH	lactate dehydrogenase
LPR	lactate to pyruvate ratio
MAP	mean arterial pressure
MCT	monocarboxylate transporter
MD	microdialysis
MMSE	mini-mental state exam
NADH	nicotinamide adenine dinucleotide
NIRS	near-infrared spectroscopy
OHCA	out-of-hospital cardiac arrest
OPEN	odense patient data explorative network
$PbtO_2$	parenchymal brain tissue oxygen tension
PCABI	post-cardiac arrest brain injury
PRC	post-resuscitation care
RBC	red blood cells
ROSC	return of spontaneous circulation
RSO_2	cerebral oxygen saturation
TCA	citric acid cycle
TNF-α	tumor necrosis factor alpha
TTM	targeted temperature management
WBC	white blood cells

SUMMARY

Resuscitated out-of-hospital cardiac arrest (OHCA) is associated with a high risk of brain injury and mortality. Post-cardiac arrest care focuses on minimizing secondary brain injury and optimizing the chances of recovery. Brain-directed therapies, including e.g., hemodynamic support to optimize cerebral perfusion and oxygen delivery, remain an essential factor. Blood pressure derangements may attenuate secondary brain injury, but the optimal blood pressure target during post-resuscitation care is currently unknown. Bedside monitoring of cerebral metabolism can potentially ensure optimal clinical care in comatose patients due to post-cardiac arrest brain injury. However, until recently, no routine technique has been available for bedside assessment of cerebral energy metabolism after cardiac arrest. For more individualized post-resuscitation care and target-driven therapy to improve patient outcomes, markers measuring global cerebral energy metabolism and reflecting metabolic variations after resuscitation are required.

This thesis´ overall objectives were assessment of optimal blood pressure and characterizing changes in global cerebral energy metabolism using novel bedside microdialysis application in comatose patients resuscitated from OHCA. Therefore, this thesis aimed to assess I) whether the post-resuscitated brain exhibits persistent perturbations of energy metabolism monitored with jugular bulb microdialysis (JBM) and II) the effect of different blood pressure levels on global cerebral energy metabolism in comatose patients resuscitated from OHCA and III) biochemical patterns including brain ischemia between patients with unfavorable and favorable neurological outcome.

Paper I compared the effect of two mean arterial blood pressure (MAP) levels on global cerebral energy metabolism during cardiac surgery. The study showed that placing a microdialysis catheter in the jugular bulb was feasible for monitoring transient perturbations of variables reflecting intracerebral energy metabolism. Targeting a higher MAP during cardiopulmonary bypass did not significantly improve cerebral energy metabolism or oxygenation. Furthermore, the study established reference values for “normal” microdialysate values in human jugular venous blood in anesthetized patients without cerebral pathophysiology.

Paper II, a clinical trial protocol, described how Paper IV was conducted (rationale, objectives, design, methods, analysis plan) and ensured the safety of the trial subjects and integrity of the data collected.

Paper III was designed to investigate whether JBM might be used to monitor secondary deterioration of cerebral energy metabolism after OHCA. The study indicated that JBM was feasible and safe. Variables reflecting cerebral energy metabolism could be distinguished from systemic variables obtained from intraarterial microdialysis in patients with poor clinical outcome. Biochemical signs of

ischemia and mitochondrial dysfunction were frequent and long-lasting after the return of spontaneous circulation (ROSC) and more pronounced in patients with unfavorable outcome.

Paper IV aimed at assessing the effect of different blood pressure levels on global cerebral energy metabolism in comatose patients resuscitated from OHCA. In this double-blinded trial, 60 comatose OHCA patients were randomly assigned to low (63 mmHg) or high (77 mmHg) MAP. Targeting a higher MAP 180 min after ROSC did not significantly improve cerebral energy metabolism or oxygenation within 96 hours of post-resuscitation care. We could predict poor neurological outcome based on specific metabolic patterns obtained by JBM.

Overall, the studies described in this thesis have given new insights into pathophysiological mechanisms following transient global cerebral ischemia after cardiac arrest. Microdialysis of cerebral venous blood in the jugular bulb have shown promise to give important information of cerebral energy metabolism. Main findings indicated persistent compromised cerebral oxidative metabolism in the majority of resuscitated comatose patients, and that mitochondrial oxidative energy metabolism can be evaluated online by performing microdialysis of the draining venous blood. However, detection of isolated cerebral metabolic perturbations in cardiac arrest patients were dependent on a certain degree of brain injury. Patients with a poor clinical outcome exhibited significantly worse biochemical patterns, illustrating that insufficient tissue reperfusion and oxygenation during the initial hours after ROSC were essential factors determining neurological outcome.

Future efforts to improve outcomes after OHCA may focus on treatment that augments cerebral energy metabolism during early post-resuscitation care.

DANSK RESUMÉ

Hvert år får ca. 5.000 personer pludseligt hjertestop uden for hospital i Danmark. Heraf overlever kun ca. 13% mere end 30 dage. Den høje dødelighed på intensiv skyldes hovedsageligt hjerneskade, men de patofysiologiske mekanismer bag er meget komplekse og sparsomt belyst. Aktuelt findes der ikke et klinisk instrument, der kan overvåge hjernens energimetabolisme og monitorere eventuel pågående iskæmi (manglende blodforsyning) hos komatøse hjertestops-overlevere. Der er et behov for at identificere de patienter, der har pågående reversibel hjerneskade, og dermed har et behov for yderligere beskyttende behandling på intensiv. Potentielt vil dette instrument kunne individualisere patientbehandlingen og forbedre overlevelsen.

Samtidigt er nogle patienter hæmodynamisk ustabile som en del af post-hjertestop syndromet, hvor behandling med vasopressor og inotropika er nødvendigt for, at sikre et tilstrækkeligt perfusionstryk og blodtilførsel til hjernen.

Denne afhandling har til formål at undersøge følgende kliniske problemstillinger: I) undersøge de mekanismer, der forårsager sekundær hjerneskade hos bevidstløse hjertestop-overlevere indlagt på intensiv II) afprøve hypotesen om, at forstyrrelser i hjernens samlede energimetabolisme kan spores i den venøse drænage målt i halsvenen (vena jugularis) ved anvendelse af en ny, innovativ biosensor-metode III) evaluere effekten af to forskellige blodtryksniveauer på hjernens energimetabolisme hos bevidstløse hjertestops-overlevere på intensiv. Afhandlingen er baseret på resultater fra kliniske patientstudier af hjernens energimetabolisme efter transient iskæmi og reperfusion, som er centrale patofysiologiske mekanismer i hjernen ved hjertestop.

I et prospektivt klinisk pilotstudie (studie I) ønskede vi at evaluere effekten af to forskellige blodtryksniveauer på hjernens energimetabolisme under hjertekirurgi og anvendelse af hjerte-lungemaskine. Et yderligere formål var at teste effekten og pålideligheden af den innovative biosensor-metode. Metoden benytter et mikrodialyse-kateter, som kontinuerligt opsamler stofskiftemolekyler (metabolitter) i det venøse blod fra hjernen. Ideen var, at man gennem en minimal invasiv procedure kunne opnå en kontinuerlig monitorering afspejlende hjernens samlede tilstand. Resultaterne viste, at et højere blodtryk ikke signifikant forbedrede hjernens energimetabolisme under hjertekirurgi. Biosensor-metoden var sikker og pålidelig, og kunne detektere mindre forstyrrelser i hjernens samlede energimetabolisme, og dermed implementeres i de efterfølgende kliniske studier.

Forudsætningen for det kliniske randomiserede studie (IV) var studie II, en forsøgs-protokol, som beskrev rationale, mål, design, metoder, analyseplan, og sikrede forsøgspersonernes sikkerhed og integriteten af de indsamlede data.

I de to kliniske studier (III og IV) undersøgte vi, om lavt arterielt blodtryk under målrettet temperaturstyring efter hjertestop uden for hospitalet var forbundet med øget hjerneskade. Studie III (pilotstudie) var designet til at undersøge, om biosensor-metoden kunne bruges til at overvåge sekundær forværring af hjernens energimetabolisme efter hjertestop. Undersøgelsen viste, at teknikken igen var sikker, anvendelig og pålidelig. Biokemiske tegn på iskæmi var hyppige og langvarige efter tilbagevenden af spontan cirkulation og mere udtalt hos patienter, som ikke overlevede. Studie IV havde til formål at vurdere effekten af forskellige blodtryksniveauer på hjernens energimetabolisme hos komatøse patienter genoplivet fra hjertestop. I dette dobbeltblindede forsøg blev 60 komatøse patienter tilfældigt behandlet med enten lavt (63 mmHg) eller højt (77 mmHg) middel-blodtryk. Et højere blodtryk forbedrede ikke signifikant hjernens energimetabolisme og iltning på intensiv.

Samlet set har studierne givet en ny indsigt i de metaboliske effekter af transient global iskæmi, ny viden om de patofysiologiske mekanismer, der forårsager hjerneskade efter hjertestop, samt øget vores forståelse af de metoder, som anvendes til at monitorere disse effekter. De vigtigste resultater var at patienter med et dårligt klinisk outcome udviste signifikant værre biokemiske mønstre, hvilket viste, at utilstrækkelig vævsreperfusion og iltning i løbet af de første timer efter genoplivning var væsentlige faktorer for det neurologiske udfald.

Desuden har vi kunne dokumentere afgørende karakteristika ved mikrodialyse af hjernens venøse drænage, tekniske detaljer og kliniske perspektiver. Fremtidige bestræbelser på at forbedre resultater efter hjertestop bør fokusere på behandling, der forbedrer hjernens energimetabolisme.

INTRODUCTION

OHCA is a frequent cause of death or morbidity in Denmark, with approximately 5,000 persons suffering an out-of-hospital cardiac arrest (OHCA) each year [10]. About 40% of all OHCAs are resuscitated successfully for intensive care unit (ICU) admission [11]. In general, comatose patients resuscitated from OHCA are admitted to the ICU, spend on average 3-5 days and represent up to 10% of ICU admissions [12]. Despite extensive research in post-resuscitation care (PRC), survival rates remain around 50% for comatose patients treated in the ICU [13-15]. International registry data indicate that, on average, 19% of survivors to hospital discharge have moderate to severe neurological impairments, preventing a return to work and activities of daily living [16].

ICU mortality and long-term disability are mainly caused by post-cardiac arrest brain injury (PCABI) [17, 18]. Managing post-cardiac arrest patients is complex, and brain-directed therapies, including, e.g., hemodynamic support to optimize cerebral perfusion and oxygen delivery, remain an essential factor with the potential for improving neurological recovery and survival after OHCA. Blood pressure derangements may attenuate PCABI, but the optimal blood pressure target during PRC is currently unknown. In comatose patients due to PCABI, bedside monitoring of cerebral metabolism has the potential to ensure optimal clinical care. Until recently, no routine technique has been available for bedside assessment of biochemical variables reflecting compromised cerebral energy metabolism after cardiac arrest (CA). For more tailored post-resuscitation treatment and target-driven therapy to improve patient outcomes, markers measuring global cerebral energy metabolism and reflecting metabolic alterations after resuscitation are needed. Therefore, we introduced the concept of characterizing changes in global cerebral energy metabolism using jugular bulb microdialysis (JBM) application in comatose patients resuscitated from OHCA. To our knowledge, this method has never been tested in cardiac arrest patients. Assessment of optimal blood pressure and bedside monitoring of brain metabolism may be two essential factors in post-resuscitation care and will be the focus of this thesis.

BACKGROUND

Post-cardiac arrest brain injury

PCABI is caused by complex pathophysiological mechanisms triggered by ischemia and secondary reperfusion. The severity and duration of initial global ischemia is the main determinant of the primary brain injury (no flow), followed by secondary damage during cardiopulmonary resuscitation (CPR) (low flow) and after ROSC (reperfusion). The physiology and metabolic consequences associated with brain injury after CA will be described in the following. First, a description of the time-dependent

pathophysiology mechanisms related to PCABI, followed by a basic introduction to cerebral energy metabolism and glycolysis, focusing on ischemia and mitochondrial dysfunction.

Primary injury

Cardiac arrest results in primary global ischemia due to cardiac output and oxygen delivery cessation. This no-flow phase begins with the onset of cardiac arrest and continues until partial reperfusion is achieved by cardiopulmonary resuscitation (CPR). The brain is devoid of nutrient stores, and normal aerobic brain metabolism depends highly on a stable supply of oxygen and mainly glucose. Cellular damage starts momentarily in the absence of CBF, with loss of consciousness within seconds. Cerebral ischemia results in cessation of aerobic metabolism and subsequent oxygen, glucose, and high-energy substrate adenosine triphosphate (ATP) depletion [19]. This results in dysfunctional energy-dependent Na^+/K^+ ion-exchange pump action, leading to a massive sodium and water influx and intracellular cytotoxic edema [20-22]. Neurotransmitter-release, glutamate-induced excitotoxicity further drives the opening of voltage-sensitive Ca^{++}-channels and intracellular Ca^{++}-influx activating pathological proteases resulting in irreversible brain damage [23]. Unfortunately, ROSC induced reperfusion and restoration of oxygen oxidative phosphorylation and mitochondrial membrane potential contributes to free radical generation, damaging DNA, proteins, and lipids [22]. Reactive oxygen species trigger the opening of the mitochondrial permeability transition pore, further escalating the injury cascade [24]. Intracellular calcium accumulation results in mitochondrial dysfunction, swelling, and diminished ATP production, and the inability to sustain cellular respiration leads to cell death and apoptosis.

Secondary injury

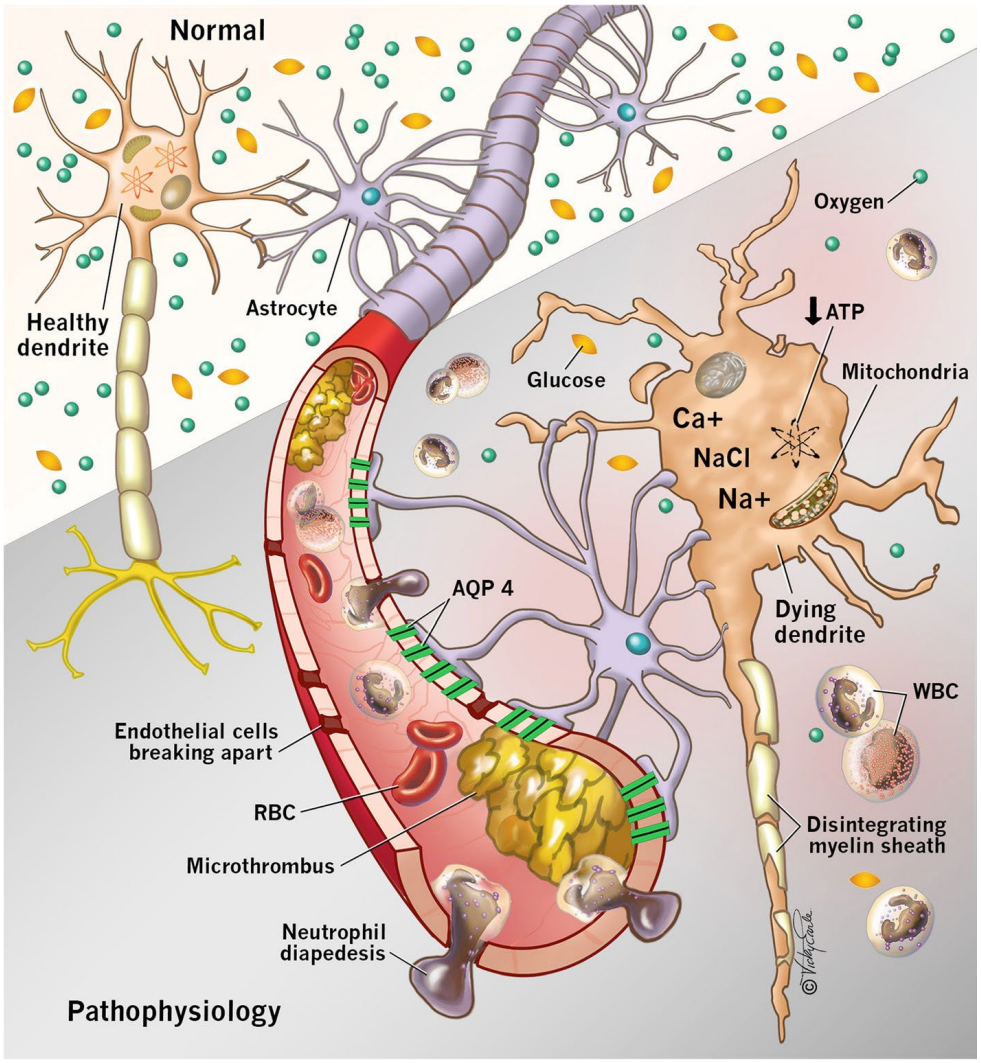
Secondary brain injury processes remain complex and involve a variety of pathophysiological pathways that substantially impact neurologic outcome during the post-resuscitation period. Following partial (CPR with low flow) or complete restoration of blood flow (ROSC), persistent or intermittent inadequate brain oxygen delivery can cause secondary brain injury. CBF is only partially restored during CPR but remains suboptimal to sustain neuronal integrity since CPR generates approximately 25% of normal CBF, significantly less than the 40-50% of normal CBF required to avoid additional ischemic injury [25].

Additional contributing factors include hypoxemia, ischemia-reperfusion, delayed cerebral hypoperfusion, mitochondrial dysfunction, diffusion limitations of oxygen and disrupted cerebral autoregulation [17, 19, 21, 26-29]. Furthermore, seizures, hyperglycemia, and hyperthermia increase brain metabolic demand, causing secondary brain injury [22]. After cardiac arrest, the systemic inflammatory response triggers a complex inflammatory cascade in the brain that is likely to be detrimental to neuronal survival. Cerebral edema after ischemia (reperfusion) results primarily from cellular swelling over the first days after ischemia as water shifts intracellularly because disruption of the blood-brain

barrier is brief and transient [30]. However, edema can develop quickly, raise intracranial pressure, and compromise local and global cerebral perfusion. Figure 1 illustrates the various microvascular and cellular pathophysiologic effects occurring during primary and secondary injury after cardiac arrest.

Two-thirds of in-hospital deaths after OHCA are due to severe brain injury, and the leading cause of disability is neurological sequalae related to anoxic brain injury [31, 32]. However, our knowledge regarding the multiple pathophysiological pathways and biochemical events during post-resuscitation care is limited. The novel use of jugular bulb microdialysis, described in this thesis, has the clinical potential to provide novel insights into the dynamic pathogenic metabolic patterns associated with secondary brain injury.

Figure 1



Text figure 1. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. M. Sekhon, P. Ainslie, D. Griesdale. Published 13 April 2017. AQP 4 Aquaporin-4, RBC Red blood cells, WBC White blood cells. Permission granted.

Brain perfusion changes in PCABI

No-reflow

In experimental models, reperfusion of the brain after transient global ischemia is incomplete, termed no-reflow, and manifests as multiple perfusion defects in brain tissue [33]. Furthermore, the severity of these perfusion defects increases with the duration of global ischemia [34].

Delayed hypoperfusion

In animal models, ROSC is followed by a transient (15-30 min) increase in global CBF (global hyperemia), followed by delayed hypoperfusion [35]. CBF may fall by more than 50% in patients with PCABI during this phase [25]. Hypoperfusion can persist for hours or even days with multiple mechanisms implicated, including endothelial cell lesions, unbalance of local vasodilators/vasoconstrictors, impaired autoregulation, reduced metabolism, and anesthesia [36].

Blood pressure targets and neuroprotective treatment after cardiac arrest

Circulatory restoration and adequate mean arterial blood pressure (MAP) is vital to maintain cerebral blood flow (CBF) at a level sufficient for preserving oxidative energy metabolism. Cerebral autoregulation is impaired or right-shifted in approximately 30–50% of patients following cardiac arrest [26, 27, 37]. Consequently, hypotension subsequent to cardiac arrest may result in cerebral hypoperfusion, aggravating PCABI. Several studies have found an association between low blood pressure after OHCA and poor outcome [38-40].

However, the optimal arterial blood pressure target after cardiac arrest to prevent PCABI secondary to ischemic injury is unknown. Randomized controlled trials studying specific MAP targets (65 mmHg vs. 80-100 mmHg) in post-resuscitation care have failed to show any signs of benefit on surrogate outcomes, nor in the rates of good neurological outcome at six months [41, 42]. These pilot trials were limited by a lack of blinding and a sample size too small to assess clinically relevant endpoints.

Further, no clinical interventional studies have prospectively evaluated whether a bedside autoregulation-driven MAP target may influence neurological outcome using, *e.g.*, transcranial Doppler, cerebral oxygenation index (Cox), and pressure reactivity index (PRx) [26, 43, 44].

The current guidelines on post-resuscitation care do not advocate any specific blood pressure target but recommend avoiding hypotension (MAP <65 mmHg) and targeting MAP to achieve adequate urine output (>0.5 ml/kg/h) and normal or decreasing lactate [45].

Post-ischemic neuronal death occurs in the hours and days after ROSC, which may open a therapeutic window to improve cognitive outcomes. Unfortunately, there is no real-time clinical monitoring method for cerebral “energy failure” during post-resuscitation care. Therefore, we introduced the concept of jugular bulb microdialysis application in comatose patients resuscitated from OHCA (see

the section below). Using this novel monitoring method, main Paper IV was designed to compare the effect of two levels of MAP on global cerebral energy metabolism testing the hypothesis that higher MAP improves cerebral oxygenation and cerebral oxidative metabolism during post-resuscitation care compared with lower MAP.

Microdialysis for monitoring global cerebral energy metabolism

The following describes the basic concepts of cerebral energy metabolism, standard clinical cerebral microdialysis typically used in neurointensive care, and the novel application of jugular bulb microdialysis for global monitoring of global cerebral metabolism after OHCA. The section focuses specifically on derangements of cerebral energy metabolism after transient ischemia and related biochemical patterns of microdialysis from a clinical perspective.

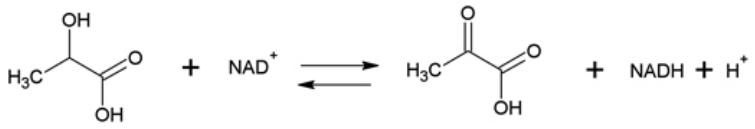
Variables reflecting cerebral energy metabolism

Despite comprising only 2% of body weight, the brain consumes between 15-20% of total cardiac output in order to maintain tissue homeostasis [25]. This section focuses on the variables directly associated with cerebral energy metabolism, primarily glucose, pyruvate, and lactate. These variables also seem to have the strongest correlation between intracerebral and jugular measurements in the clinic without no relevant delay [46].

The brain is nearly exclusively dependent on glucose for fueling metabolic processes. Glucose is transported across the blood-brain barrier into the brain's cells down the concentration gradient via facilitated transport by different isoforms of carrier protein GLUT. The most significant part of glucose-derived energy is consumed through neuron-specific action potentials and synaptic signaling, which are highly dependent on astrocyte support [47, 48].

In the cytosol, glucose is degraded to pyruvate (glycolysis), yielding two ATP per glucose molecule. Cerebral energy metabolism is strictly aerobic, and the majority of pyruvate enters the citric acid cycle (TCA) in the mitochondria and is entirely degraded to CO_2 and H_2O with a net yield of another 36 ATP due to oxidative phosphorylation [49]. Depending on the cytoplasmatic redox balance, part of the pyruvate is reduced to lactate, catalyzed by the enzyme lactate dehydrogenase (LDH). A small amount of ATP is produced in this process, and reduced nicotinamide adenine dinucleotide (NADH) is oxidized to NAD^+ needed to uphold glycolysis.

The lactate to pyruvate (LP) ratio reflects the cytoplasmatic redox-state, which can be expressed in terms of the lactate dehydrogenase equilibrium (K_{LDH}: equilibrium constant) [50]:



Lactic Acid Pyruvic Acid

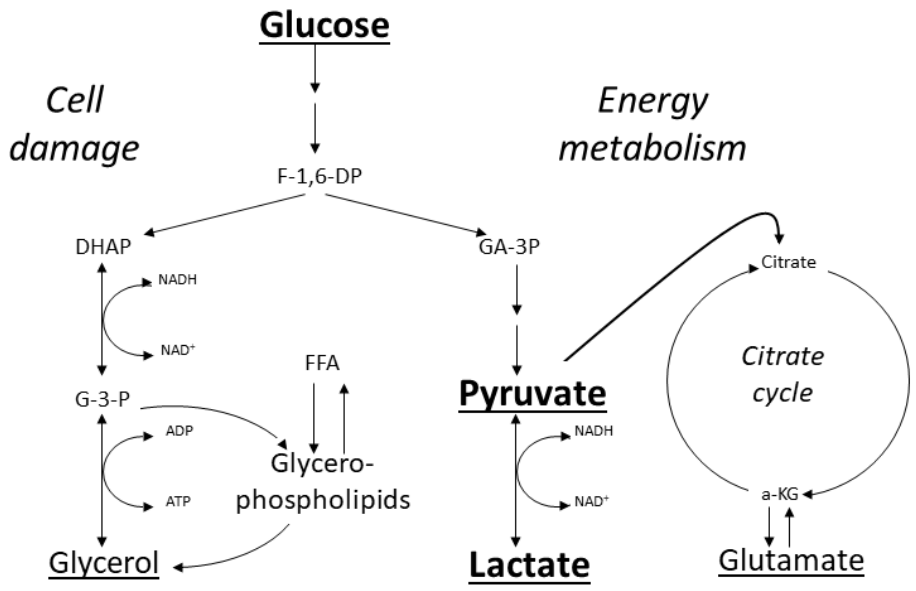
$$\frac{[NADH]\ [H^+]}{[NAD^+]} = \frac{[Lactate]}{[Pyruvate]} \times K_{LDH}$$

The LP ratio indicates the efficiency of cerebral oxidative energy metabolism. The ratio increases mainly during deficient oxygen delivery (ischemia, hypoxia) and mitochondrial dysfunction [51-55]. Lactate and pyruvate are water-soluble and rapidly equilibrate across cellular membranes due to monocarboxylate transporters (MCTs). The driving forces for the transport of the monocarboxylates are obtained from facilitated diffusion [56]. Due to MCTs, lactate and pyruvate levels in cerebral interstitial fluid can be used as a measure of their cytoplasmatic levels.

Besides cellular respiration and ATP production, the TCA is closely linked to several non-energy-related functions such as glutamatergic metabolism and the synthesis of additional important amino-acid precursors, nucleotides, and fatty acids [57].

Figure 2 depicts a simplified illustration of the intermediate metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids, and the citric acid.

Figure 2



Normal level	**Glucose** mmol /L	**Lactate** mmol/L	**Pyruvate** µmol/L	**LP ratio**	Glutamate µmol/L	Glycerol µmol/L
Human brain	1.7±0.9	2.9±0.9	166±47	23±4	16±16	80±40
Jugular bulb	5.0±1.0	1.0±0.2	82±11	12±3	80±37	105±75

Text figure 2. Schematic diagram of cerebral metabolism. A simplified illustration of cerebral intermediary metabolism is shown with a focus on the glycolytic pathway and its relation to glycerol, glycerophospholipids, and the citric acid cycle. F-1,6-DP, fructose-1,6-diphosphate; DHAP, dihydroxyacetone phosphate; GA-3P, glyceraldehyde-3-phosphate; G-3-P, glycerol-3-phosphate; NADH, reduced nicotinamide adenine dinucleotide; NAD^+, oxidized nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; ADP, adenosine diphosphate; FFA, free fatty acids; a-KG, a-ketoglutarate. Underlined metabolites are currently being measured at the bedside with enzymatic techniques. Reference values of glucose, lactate, pyruvate, glycerol, glutamate, and the LP ratio in the normal awake human brain during neurosurgery (perfusion rate 0.3 µl/min and 10 mm MD membrane) [58]. Reference values obtained in cerebral venous blood measured at the level of the jugular bulb obtained in anesthetized patients undergoing elective cardiac bypass surgery (perfusion rate 0.3 µl/min and 10 mm MD membrane) [1].

Ischemia and cerebral metabolism

Cerebral ischemia is commonly defined as inadequate organ perfusion regardless of the cause relative to metabolic demand. Limited glucose and oxygen delivery or cerebral hypoxia lead to brain tissue death if not CBF is restored. CA results in global ischemia due to cessation of cardiac output and oxygen delivery and encompasses wide areas of brain tissue, potentially resulting in hypoxic-ischemic encephalopathy. A gradual decrease in CBF will lead to insufficient cerebral tissue oxygenation before substrate/glucose delivery is compromised [50, 59].

A sudden, total cessation of CBF is immediately reflected by a change in cytoplasmic redox state and a marked increase in cerebral LP ratio [51]. Within a few minutes, variables reflecting cerebral energy state (glucose and pyruvate) are entirely depleted, and lactate levels have reached their maximum [51]. A protraction of complete ischemia will not result in a further rise in lactate once the substrate has been consumed. An increase in the LP ratio in the presence of low pyruvate (and low oxygen pressure) indicates ischemia. Reperfusion after 30 minutes of global cerebral ischemia results in nearly complete normalization of cerebral LP ratio within 90 minutes if CBF is adequately restored [60]. However, the lactate level remains high and is paralleled by a marked increase in pyruvate [60]. Transient cerebral ischemia is known to cause mitochondrial dysfunction, and persistently altered mitochondrial function has been observed in experimental cardiac arrest after apparently successful resuscitation [61-63].

Increased levels of glutamate and glycerol indicate hypoxia/ischemia and have been defined as indicators of excitotoxicity and cell membrane breakdown, respectively [64].

The fundamentals of microdialysis

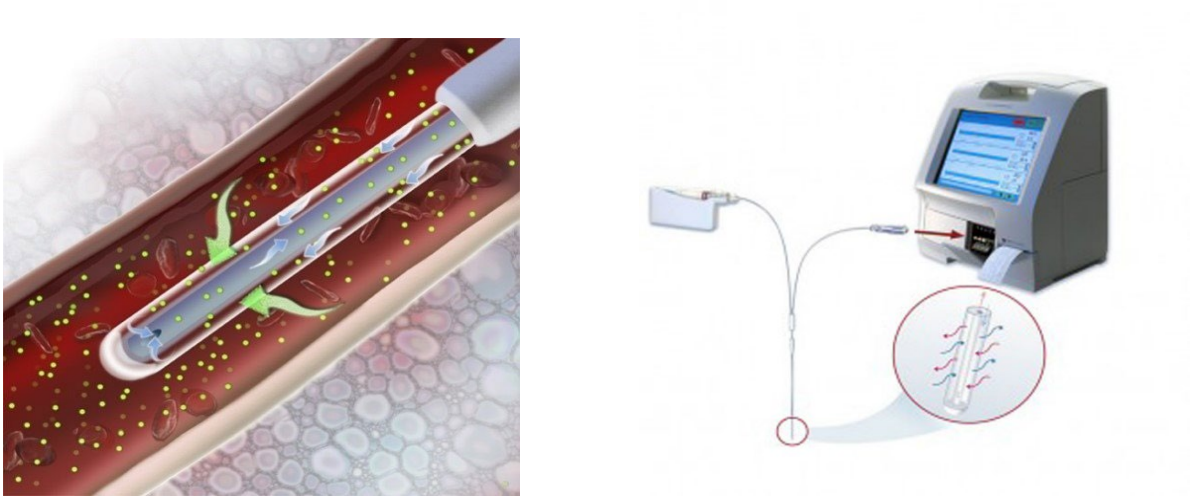
Microdialysis is an established technique for monitoring regional cerebral energy metabolism during neurocritical care, detecting early ischemia, mitochondrial dysfunction, glucose utilization, cellular membrane degradation, and excitotoxicity [64].

MD is an invasive sampling method developed to continuously study biochemical variables of the extracellular interstitial fluid and provides information on substrate supply and metabolism at the cellular level in the brain. Cerebral microdialysis uses a fine double-lumen probe lined with a semipermeable dialysis membrane. The MD catheter mimics a “blood capillary,” which allows energy metabolites (lactate, pyruvate, glutamate, glucose, and glycerol) to diffuse down the concentration gradient moving across the semipermeable membrane, enabling sample collection (Fig. 3). Using an MD pump, chemical substances are carried out of the catheter by a perfusion fluid flow to a microvial. Membrane pore size (cut-off), length, and perfusion flow rate determine the extent of uptake and recovery (equilibration over the membrane). Due to incomplete relative recovery, sample data, e.g., glucose, pyruvate, lactate, glutamate, and glycerol, do not show their actual interstitial levels. With a perfusion rate of 0.3 µl/min, the relative recovery in cerebral tissue was shown to be about 70% for the variables studied [65]. When placed in arterial or venous blood, the relative recovery is expected to

be considerably higher. A time-delay factor inherent in the microdialysis technique should be noted: the concentrations of the measured variables represent the average since the previous microdialysis sample – usually obtained 60 minutes earlier.

A bedside analyzer utilizing enzymatic photometric techniques can measure energy metabolites and enables early detection of ischemia in patients at risk, e.g., comatose patients resuscitated from OHCA (Fig. 3).

Figure 3



Text figure 3. MD catheter placed in a blood vessel mimicking a "blood capillary". Bedside analyzer utilizing enzymatic photometric techniques. Images and permission from https://www.mdialysis.com/images.

Specific cerebral biochemical patterns of intracerebral microdialysis

The pattern of intracerebral microdialysis values during cerebral ischemia and correlations to functional outcomes in humans have been extensively described in the literature [64, 66-68]. Conventionally, the LP ratio is a marker of cellular redox status, and increased levels are associated with unfavorable outcome in neurocritical care [58, 64, 69, 70]. In traumatic brain injury, the pathological threshold for the LP ratio of the human brain has been defined as >25 and >40 [58, 64].

Despite comprehensive research, uncertain pathological thresholds for intracerebral MD variables remain. Biochemical variables measured during routine intracerebral microdialysis and their reference values in a normal human brain are illustrated in figure 2 [58]. At present, no established reference values for MD variables in cerebral venous blood measured at the level of the jugular bulb exist. For clarity, a preview of reference values obtained in cerebral venous blood measured at the level of the jugular bulb obtained in anesthetized patients undergoing elective cardiac bypass surgery is described in figure 2 (Paper I, established technique with perfusion rate 0.3 µl/min and 10 mm MD membrane) [1].

However, it is widely accepted that dynamic trends outweigh deviations from normal values [64]. Furthermore, The LP ratio is a quantitative measure independent of relative recovery.

Experimental and clinical studies support several different biochemical patterns observed during and after transient ischemia (e.g., cardiac arrest). The LP ratio increases instantaneously during insufficient aerobic energy metabolism, and cerebral ischemia is characterized by a significant increase in intracerebral LP ratio at simultaneous decreases in pyruvate, glucose, and CBF levels. In addition, transient cerebral ischemia is known to cause mitochondrial dysfunction, defined as moderately increased LP ratio (normal or elevated CBF) at a marked increase in cerebral lactate with normal or high pyruvate levels [64, 71]. This biochemical pattern has also been described after mitochondrial dysfunction induced by intracerebral infusion of cyanide in the pig [55].

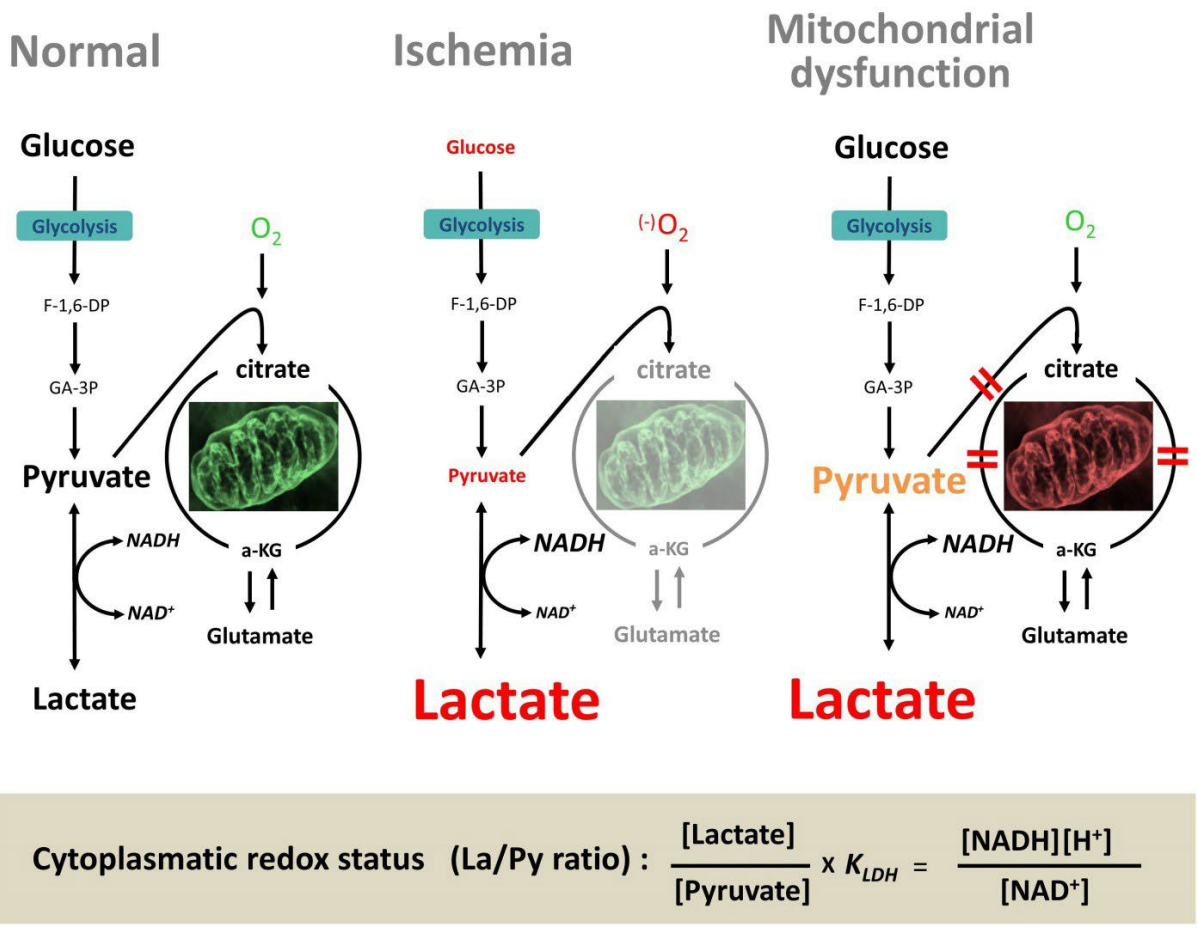
Differentiating between these metabolic patterns is essential for interpretations in transient cerebral ischemia, mitochondrial dysfunction and potentially related clinical therapy.

Figure 4 describes the relations of cerebral energy metabolites in three different metabolic states and associated intracellular pathways in redox metabolism, observed by conventional clinical microdialysis in normal brain, ischemia, and mitochondrial dysfunction (normal substrate supply).

However, the biochemical pattern interpreted as mitochondrial dysfunction does not necessarily indicate malfunctioning mitochondria. For example, a similar metabolic pattern is observed during hypoxic hypoxia (selective decrease in arterial oxygen supply) and when cerebral energy requirements surpass mitochondrial capacity for oxidative metabolism (e.g., severe epileptic seizures; myoclonic seizures) [54, 72, 54, 73, 74].

This thesis's biochemical definitions of ischemia and mitochondrial dysfunction are based on principles obtained from intracerebral microdialysis [75].

Figure 4



Text figure 4. Relations of cerebral energy metabolites in three different metabolic states and associated intracellular pathways in redox metabolism. Elevated lactate to pyruvate ratio is seen in ischemia and mitochondrial dysfunction. In ischemia, pyruvate is low due to substrate deficiency, whereas pyruvate levels are normal or elevated in mitochondrial dysfunction. Font size and color indicate relative abundance and critical values (red). Permission from Forsse A et al. Cerebral monitoring of neurocritical patients. *Ugeskr. Laeger* **180**, V01180025 (2018).

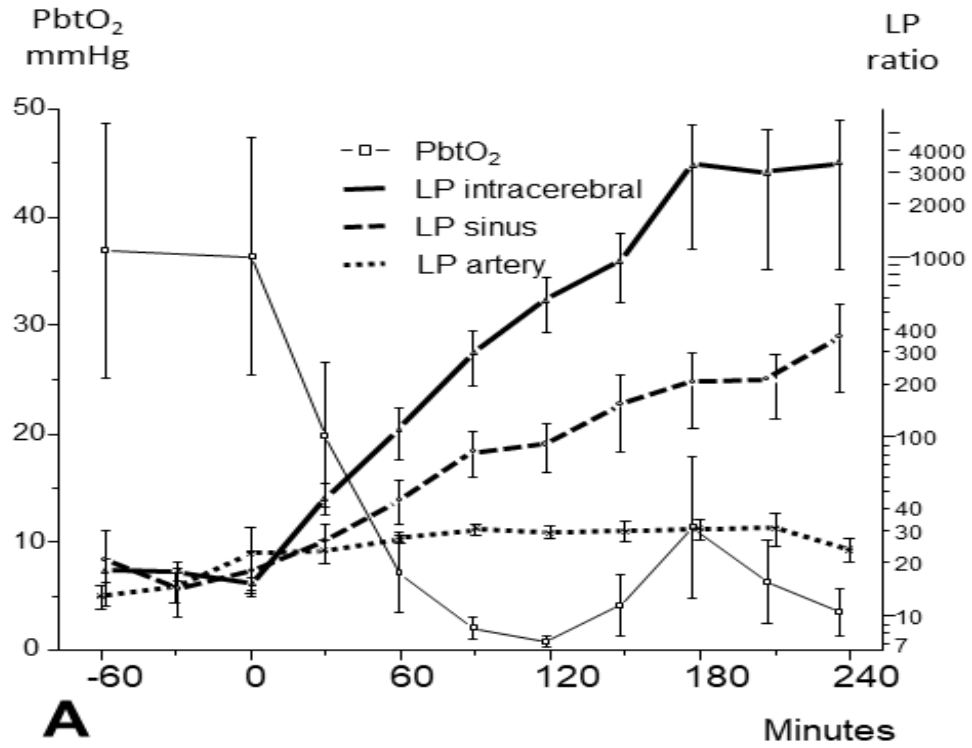
Microdialysis of cerebral venous blood

Microdialysis is an established technique for monitoring regional cerebral energy metabolism during neurocritical care [64]. However, after cardiac arrest it is problematic to insert an intracerebral catheter and only a limited number of patients have been studied following resuscitation after cardiac arrest [76-78].

In a previous experimental animal study, our group has shown that during severe global brain ischemia due to hemorrhagic shock, information on cerebral energy state could be obtained from microdialysis of the draining cerebral venous blood, reflected in an increased LP ratio (Fig. 5) [79]. However, the internal jugular vein is the dominant outflow vein from the human brain (Fig. 6) [80]. To avoid extracranial contamination and ensure accurate monitoring of cerebral blood metabolites, the MD catheter tip must be positioned in the jugular bulb above the inlet of the common facial vein [81, 82]. Additionally, ultrasound provides valuable information regarding the dominant cerebral venous drainage without the need for a CT scan [83].

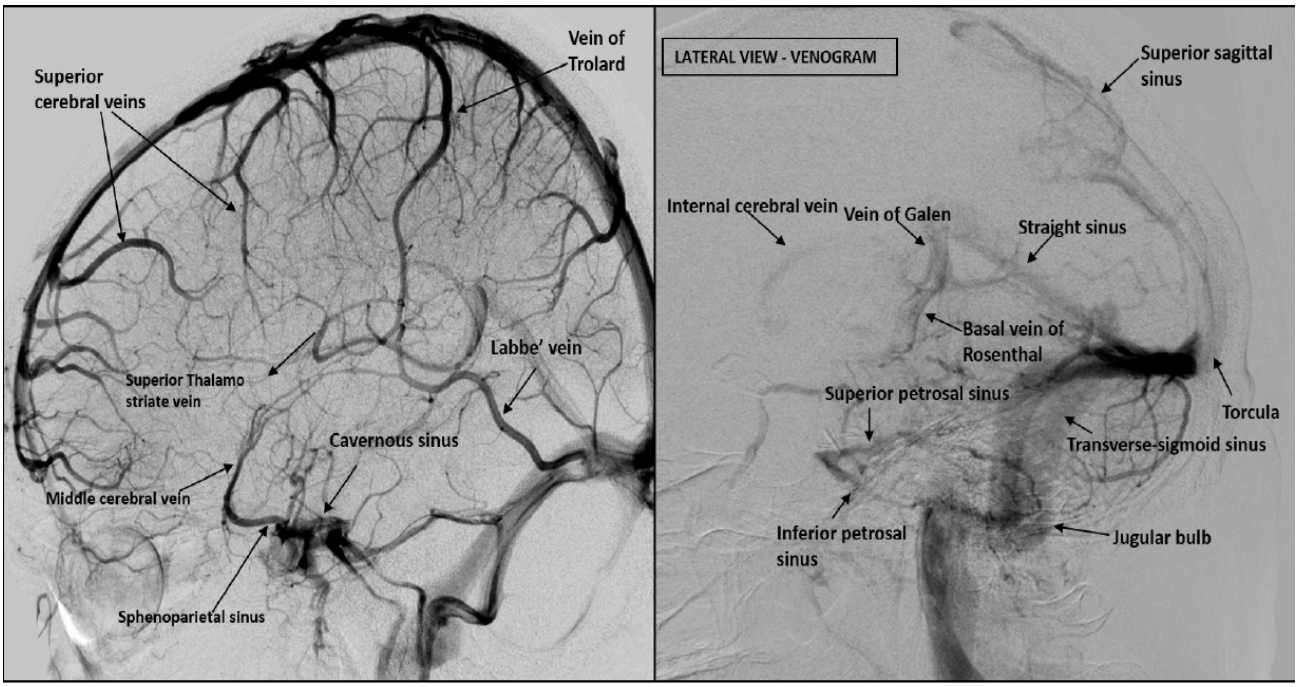
In this context, the thesis attempts to characterize dynamic changes in global cerebral energy metabolism using jugular bulb microdialysis application in comatose patients resuscitated from OHCA. This method has, to our knowledge, never been studied in cardiac arrest patients.

Figure 5



Text figure 5. The figure illustrates the simultaneous changes in LP ratio in the intracerebral compartment and in venous (superior sagittal sinus) and arterial (femoral artery) blood. During severe global brain ischemia (hemorrhagic shock), microdialysis of the venous drainage gave qualitative information on cerebral energy metabolism that could be separated from the perturbation of energy metabolism in the rest of the body. Brain tissue oxygenation ($PbtO_2$). Permission from Jakobsen R et Al. Intensive Care Med Exp 2016.

Figure 6



Text figure 6. Venogram depicting superficial and deep venous drainage of the human brain. Venous drainage of the superficial and deep cerebral venous system is via the transverse sinuses to the sigmoid sinuses, which then drain into the jugular bulb. Permission from https://radiopaedia.org.

OBJECTIVES

The overall objective of this thesis was to characterize changes in global cerebral energy metabolism using novel bedside microdialysis application in comatose patients resuscitated from OHCA. Paper I-II created the research groundwork for the clinical feasibility study (paper III). Finally, the main trial (paper IV) compared the effect of two MAP levels on global cerebral energy metabolism in comatose patients resuscitated from OHCA. The hypothesis was that higher MAP improves cerebral oxidative metabolism and oxygenation during post-resuscitation care compared with lower MAP.

Specific thesis aims

1. Test the hypothesis that a higher CPB-MAP improves cerebral oxidative metabolism and cerebral oxygenation during cardiac surgery compared with lower CPB-MAP (Paper I).
    a. Is it technically feasible to place a microdialysis catheter in the jugular bulb and monitor biochemical variables related to cerebral energy metabolism during cardiac surgery?
    b. Establish reference values for "normal" microdialysate values (lactate, pyruvate, glucose, glycerol, glutamate, LP ratio) in human jugular venous blood in anesthetized patients (pre-CPB) without cerebral pathophysiology.

2. Test the hypothesis whether the LP ratio monitored in the cerebral venous outflow changes over time, reflecting cerebral metabolism after cardiac arrest, and hence is different from the corresponding LP ratio observed in arterial blood (Paper III).
    a. Is bedside microdialysis monitoring of the cerebral drainage in the jugular bulb feasible and safe during post-resuscitation care?
    b. Can the JBM technique be used for real-time brain injury detection in comatose patients resuscitated from OHCA?

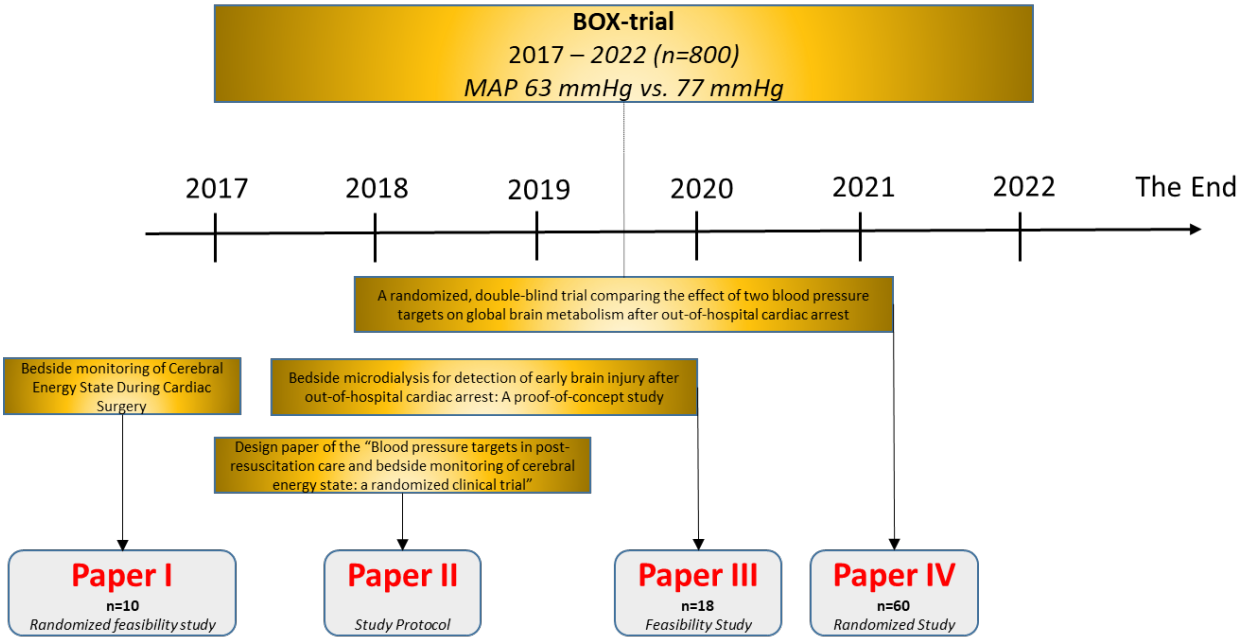
3. Test the hypothesis that a higher MAP improves cerebral oxygenation and cerebral oxidative metabolism by lowering the LP ratio, during post-resuscitation care compared with lower MAP (Paper II and IV).
    a. Are we able to differentiate neuro-metabolic patterns between patients with unfavorable and favorable neurological outcome?

METHODS

Clinical studies

Figure 7 illustrates the different studies (Paper I-IV) over time. The trials, including study designs, interventions, and patient characteristics, are described in detail in the attached papers at the end of this thesis. For clarity, Paper IV The trial was a sub-study in the Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial (BOX) [9, 84, 85]. The design of this double-blinded, randomized, superiority clinical trial and the statistical analysis plan have been published previously [84].

Figure 7



Text figure 7. Chart of included study papers, interactions, and related timeline.

Novel neuromonitoring of brain injury

Microdialysis of cerebral venous blood

Papers I, III, and IV introduced the concept of characterizing changes in global cerebral energy metabolism using jugular bulb microdialysis (JBM) application during cardiac surgery and in comatose patients resuscitated from OHCA. The MD technique used in all papers was the same except for paper IV, which solely used intravenous microdialysis.

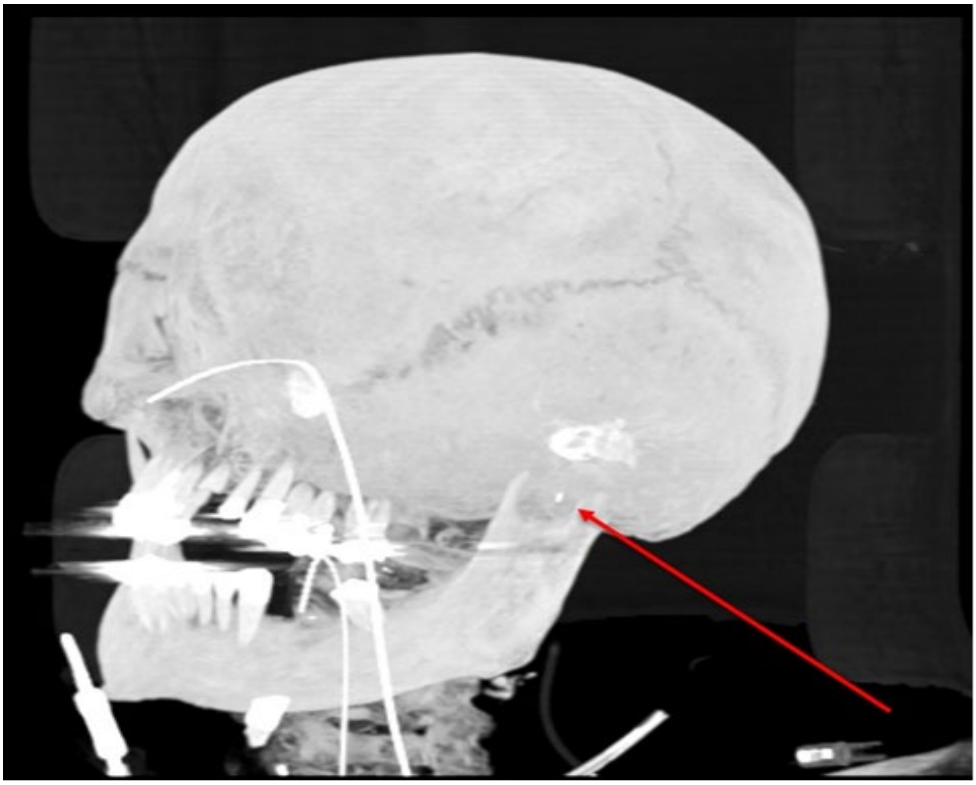
20 kDa cutoff intravenous MD catheters (CMA 67 IV, MDialysis AB, Stockholm, Sweden) were inserted in one jugular vein (shaft length 130 mm, membrane 10 mm) and one peripheral artery (shaft length

46 mm, membrane 10 mm). The dominant jugular vein was accessed by retrograde insertion of an MD catheter (130 mm) through a 16 G intravenous catheter, with the tip placed in the jugular bulb under ultrasound guidance. The optimal positioning of the MD catheter tip corresponds to the anatomical landmark at the level of the mastoid. The accurate positioning of the jugular bulb catheter tip was verified on cranial computed tomography (CT) scan (see figure 8A). The microdialysis monitoring setup is illustrated in figure 8B.

The catheters were perfused from an MD pump (CMA 106, MDialysis AB, Stockholm, Sweden) MD at a flow rate of 0.3 µL/min with Ringers Acetate and the anticoagulant Dalteparin sodium (25 IU/mL). The Ringer solution was used as perfusate since it is a physiological and nearly isotonic solution. Samples of energy-related metabolites (lactate, pyruvate, glucose, glutamate, glycerol) were collected in microvials and analyzed using enzymatic photometric techniques (Iscus, MDialysis AB, Stockholm, Sweden).

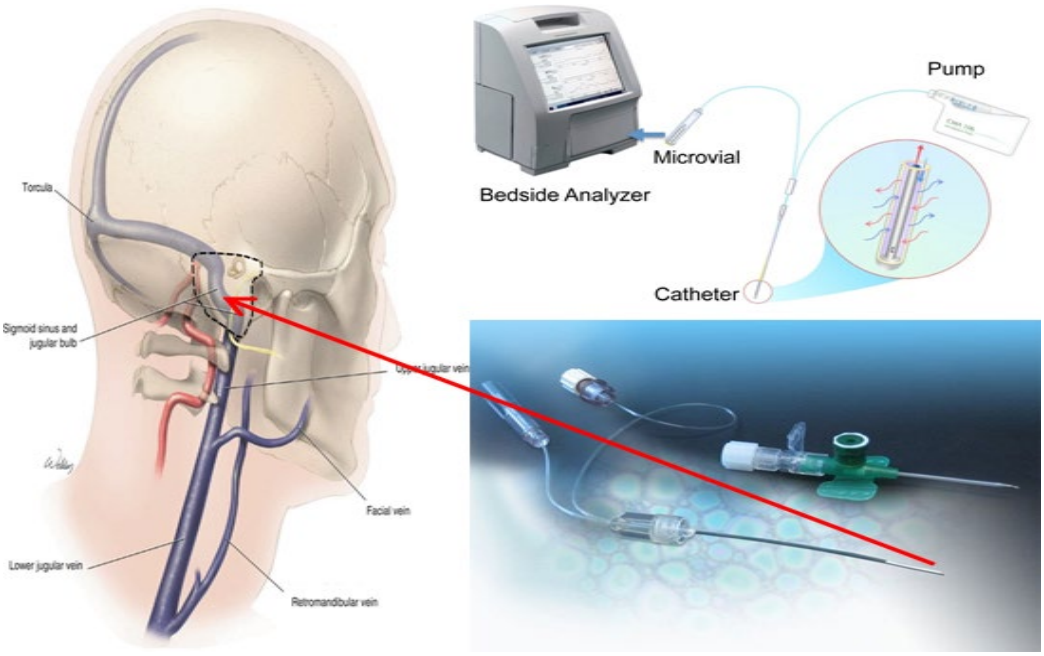
The clinicians did not change clinical practice based on bedside JBM monitoring.

Figure 8A



Text figure 8A. CT scan with 3D reconstruction documented a correct positioning of the jugular bulb catheter tip (red arrow). The image has been downloaded from the GE Web Pacs database with permission to use in the article.

Figure 8B



Text figure 8B. The microdialysis monitoring setup. The illustration was published with the permission of https://www.mdialysis.com, Sweden.

JBM reference values and classification of ischemia and mitochondrial dysfunction

Normal levels of the studied variables (lactate, pyruvate, glucose, glycerol, glutamate, LP ratio) in human jugular venous blood were defined using JBM reference values obtained in anesthetized patients undergoing elective cardiac bypass surgery (Paper I) [1]. Preoperative metabolite concentrations may approximate normal values relevant for an OHCA population. Pathological thresholds for each JBM variable at a perfusion rate of 0.3 µl/min (mean ± 2SD) (Fig. 2) are indicated as the shaded area in the following graphs.

The biochemical patterns for cerebral ischemia and mitochondrial dysfunction were based on principles obtained from intracerebral microdialysis [55, 75]. In the present study, LP ratio >16 at pyruvate <70 µM was categorized as indicative of ischemia, and a pattern with LP ratio >16 at pyruvate >70 µM was classified as indicating mitochondrial dysfunction.

Cerebral oxygenation

Cerebral near-infrared spectroscopy (NIRS) is a non-invasive, continuous monitoring technique used to assess cerebral oxygenation in various clinical settings [86]. Bilateral cerebral oxygenation saturation (rSO_2) (Somanetics INVOS Cerebral Oximeter system) was monitored continuously with a pre-defined desaturation threshold of 50% (Paper I, III, and IV) [87]. The rSO_2 values of the left and right frontal sensors were averaged and used in the analysis. The clinicians did not change routine clinical practice based on bedside rSO_2.

Paper I

Design of Paper I

This randomized feasibility study was designed to determine the yield of bedside monitoring of cerebral energy state during cardiac surgery utilizing JBM. Ten patients aged >60 years, who were scheduled to undergo elective CABG on CPB, were enrolled in the study. The patients were randomized blindly to a low MAP (40-60 mmHg, n=5) or a high MAP (60-80 mmHg, n=5) group during CPB. JBM, intraarterial MD, and cerebral oxygenation were monitored continuously intraoperatively and for two hours postoperatively.

Outcome measures of Paper I

The primary objective was to compare microdialysis parameters of the jugular venous and the arterial blood during cardiac surgery. The main secondary outcome was to compare the difference between MD parameters between MAP groups. Furthermore, the association between MAP, MD data, cerebral desaturation, and postoperative cognitive function (mini-mental state examination, MMSE) was assessed. MMSE score <24 indicated cognitive impairment [88].

Paper II

Design of paper II

Paper IV was based on this trial protocol, describing the details of the study rationale, objectives, methods, intervention, statistical analysis, organization, conduct, and ethical considerations. In addition, the protocol included the SPIRIT 2013 statement for RCT studies and the schedule for enrolment, intervention, and assessment.

Paper III

Design of paper III

This single-center prospective feasibility study enrolled patients at Odense University Hospital, Denmark, from May 2018 to October 2019. This study investigated whether bedside JBM reflects secondary brain injury after OHCA. Patients with sustained return of spontaneous circulation (ROSC) after OHCA were eligible for inclusion if complying with the following criteria: age ≥ 18 years, OHCA of presumed cardiac cause, and score ≤8 on the Glasgow Coma Scale (GCS).

Post-resuscitation procedure

Eighteen unconscious patients with sustained ROSC were admitted to the cardiac intensive care unit following OHCA. Microdialysis and near-infrared spectroscopy monitoring were the sole modifications from international clinical treatment guidelines for comatose OHCA patients [45]. To document that the biochemical variables measured in cerebral venous blood after ROSC reflected their intracerebral levels, MD catheters were placed in a peripheral artery for systemic reference and the jugular bulb.

JBM was initiated after ICU admission and continued for 96 hours or until arousal. Targeted temperature management (TTM) was commenced at the time of ICU admission targeting 36.0°C for 24 h, followed by rewarming at a rate of 0.5°C/h. Sedation, primarily with the use of propofol and fentanyl, was mandated in both groups during the TTM period. A mean arterial pressure (MAP) >65 mmHg was targeted. Norepinephrine was the first-line vasopressor agent, and dopamine was used secondarily. Milrinone was initiated in case of low cardiac output syndrome. Mechanical ventilation was adjusted to achieve normocapnia ($PaCO_2$ of 4.5 – 6.0 kPa), and oxygenation was maintained in the range of 13-14 kPa. The blood glucose level was strictly maintained between 6 and 10 mmol/l.

Neurologic prognostication

Active treatment continued until 72 hours after TTM, except for patients with status myoclonus, brain death, or refractory shock with multiple organ failure. Patients who remained comatose despite cessation of sedation were evaluated by combining neurologic examination, EEG, somatosensory-evoked potential (SSEP), biomarkers (NSE) and brain CT. As previously described, EEGs were classified as highly malignant, malignant, or benign [89]. Assessment of neurological outcome was performed by a multidisciplinary team in accordance with guidelines (Supplementary Methods) [45]. The clinicians performing the neurological prognostication were blinded to microdialysis variables.

Outcome measures of paper III

The primary objective was to compare time-averaged means of microdialysis parameters (intervals of 12 hours) of the jugular venous and the arterial blood during post-resuscitation care. Secondary objectives of clinical interest were to compare (i) neuro-metabolic patterns between patients with unfavorable and favorable neurological outcome and (ii) total duration of cerebral desaturation and clinical outcome. Neurological outcome was assessed at hospital discharge according to the Cerebral Performance Category (CPC) scale [90, 91]: CPC 1-2 are considered 'favorable' outcomes and a CPC 3-5 'unfavorable' outcomes.

Paper IV

Design of paper IV

The trial was a double-blinded, randomized, superiority clinical trial recruiting patients in a single intensive care unit at Odense University Hospital, Denmark, from September 2017 to May 2020. The trial was a sub-study in the Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial (BOX) [9, 84, 85]. The design of the trial and the statistical analysis plan is described in paper II [2]. Patients aged ≥18 years with OHCA of presumed cardiac cause, sustained return of spontaneous circulation and score ≤8 on the Glasgow Coma Scale (GCS) were enrolled. The main exclusion criteria

were an interval from ROSC to randomisation >240 minutes, and unwitnessed asystole. For this substudy only patients randomized to liberal oxygen targeting PaO2 13-14 kpa were enrolled [85].

Summarily, 64 comatose patients were admitted to the intensive care unit following OHCA and randomly assigned in a 1:1 ratio to low (63 mmHg) or high (77 mmHg) MAP. JBM, continuous cardiac output, and near-infrared spectroscopy monitoring were the sole modifications from regional clinical treatment guidelines for comatose OHCA patients. Global cerebral energy metabolism was continuously monitored bedside with jugular bulb microdialysis during 96 hours of post-resuscitation care utilizing identical techniques as Paper III.

Similar post-resuscitation care and neurological prognostication procedure were performed as in Paper III, except for intraarterial MD monitoring and supplemental prognostic biomarker at 48h (neuron-specific enolase (NSE)). The biomarker of neurological damage, plasma NSE level at 48h, was measured by electrochemiluminescence and by a COBAS analyzer system (Roche Diagnostics) [92].

As the pilot study (Paper III) showed a strong correlation between systemic blood lactate and MD arterial lactate, the former was used as a reference to replace arterial MD in the present study.

Intervention

The MAP intervention was double-blinded and commenced at randomization, and continued for as long as the patients needed invasive blood pressure measurements during ICU stay. Patients were randomized to receive monitoring with a module (Phillips M1006B) offset to –10% or a module offset to +10%. Targeting a MAP of 70 mmHg during treatment in both groups caused a blinded comparison of approximately 63 and 77 mmHg, a 20% separation. A randomized, controlled clinical study has validated the method for double-blinded comparison of MAP targets in the ICU setting [93].

A mean arterial blood pressure of 70 mmHg was achieved in a three-stage approach: volume resuscitation to a central venous pressure of 10 mmHg, norepinephrine infusion, and the addition of a dopamine infusion for a maximal dose of 10 µg per kilogram of body weight per minute, if needed.

Outcome measures of paper IV

The primary outcome was the difference between time-averaged means of microdialysis parameters and LP ratio (intervals of 12 hours) between low vs high MAP group within 96 hours of post-resuscitation care. Secondary outcomes of clinical interest were to compare (i) variables reflecting cerebral energy metabolism and patterns of ischemia and mitochondrial dysfunction in patients with unfavourable and favourable neurological outcome [94], (ii) cerebral oxygenation (rSO_2) between MAP groups, (iii) biochemical variables in relation to critical clinical episodes such as EEG-verified seizures and hypotension and (iv) neurological outcome at hospital discharge and 90 days after OHCA. Additional secondary outcomes were association between JBM markers, neurological outcome and

brain injury defined by NSE levels at 48h. As the study was planned and powered for the primary outcome, the secondary outcomes should be considered exploratory and interpreted with caution.

Neurological outcome was assessed at hospital discharge and 90 days after OHCA according to the Cerebral Performance Category (CPC) scale [90, 91]: CPC scores of 1-2 are considered 'favourable' outcomes, and a CPC 3-5 'unfavourable' outcomes.

The adverse events included in this report are bleeding, infection, arrhythmia, and seizures as well as complications related to the MD technique.

Data management

Demographics, clinical, laboratory, radiological characteristics, treatment, and outcomes data were obtained from the cardiac ICU and operating theater electronic journal systems. Study data were collected and managed using REDCap electronic data capture tools hosted at Odense Patient Data Explorative Network (OPEN) [95]. Microdialysis data was transferred manually from the ISCUSflex analyzer to OPEN. The prehospital study dataset complied with the Utstein definitions [96].

Statistical methods

Statistical analysis was performed using Stata V.16 (Stata Corporation, College Station, Texas, USA). For patient characteristics, results were expressed as counts and proportions, median with IQR or mean ± SD, as appropriate. Unpaired t-tests or Mann–Whitney U-tests were applied for unpaired comparisons of numerical variables. Chi-square or Fischer's exact test examined differences between categorical variables. A p-value <0.05 was considered statistically significant.

For Paper I, one-way analysis of variance (ANOVA) was corrected for multiple comparisons using the Bonferroni test ($\alpha = 0.006$) and was used to compare the means of three or more groups. Repeated-measures ANOVA was used to assess the statistical significance of differences between the repeated recording times for MD-cerebral venous outflow, MD-arterial, MAP, NIRS, and MMSE data

In Paper III and IV, dynamic changes of MD variables were analyzed by longitudinal data analysis using linear mixed models. The mixed model fitting procedure handled missing values, assumed to be missing completely at random. Missing MD data rates were less than 5% and imputation where not used. Missing measurements were taken into account by the maximum likelihood estimation of the mixed models.

Associations between MD variables, episodes of hypotension, EEG-verified seizures, ischemic periods, duration of cerebral desaturation, NSE levels and neurological outcome were assessed with chi-square-test and logistic regression. In addition, statistical comparison of secondary episodes of ischemia and cerebral desaturation between outcome groups was performed by utilizing the non-parametric Mann-

Whitney U-test, and associations between peak values of MD variables and outcome groups were investigated by applying a t-test.

In Paper IV, we estimated that a sample of 46 patients would provide 90% power to detect an absolute LP ratio reduction of 30% in the high MAP group, as compared with the low MAP group, using a patient-to-patient variation with standard deviation (SD) of 15 [1, 2]. To allow for possible higher patient-to-patient variation and deviations from normality, a sample size of 60 was chosen. The mean between-group difference in blood pressure during the intervention period was calculated by mixed effects linear regression. Dynamic changes of MD variables were compared between treatment groups by linear mixed effects linear regression. Time-averaged means of MD parameters in intervals of 12 hours ensured statistical robustness in contrast to point values. Note that all hourly measurements were included in the mixed models, and only aggregated in the parametrization of the model, not in the measurements themselves.

Research ethics and legal requirements

The Danish Regional Committee on Health and Research Ethics and Danish Data Protection Agency approved Paper I (trial registration: S-20130166). Following national requirements and the principles of the Declaration of Helsinki, informed consent was obtained from each patient before surgery (trial register: ClinicalTrials.gov NCT02846818).

Performing clinical research in unconscious and incapacitated patients is ethically challenging. According to the Helsinki statement of ethical principles, clinical research must only be conducted after obtaining informed consent. However, for research in acute situations not involving pharmaceuticals, Danish legislation allows for randomization and subsequent proxy consent involving, e.g., comatose OHCA patients, as soon as possible. Informed consent in Paper III and IV was permitted in proxy consent by the patients' closest relatives.

According to national requirements and the principles of the Declaration of Helsinki, informed consent was obtained from next of kin and one independent medical doctor not involved with the trials. In addition, informed consent was obtained from patients who regained appropriate neurological function for independent decision-making.

For Paper III and IV, The Danish Regional Committee on Health and Research Ethics and Danish Data Protection Agency approved the studies (S-20130166) and (S-20150173 HLP), respectively.

RESULTS

The results of the four papers are presented in detail in the attached manuscripts. In this section, the main results are listed.

Microdialysis during cardiopulmonary bypass

Paper I

All ten patients completed the study protocol and were included in the analyses. Calculated laminar flow during CPB was identical in the two MAP groups. The difference in mean arterial pressure between groups was statistically significant (low MAP 44 (41-49) mmHg vs. high MAP 65 (60-76) mmHg) (Fig. 10). NIRS detected no cerebral desaturations (decrease in rSO_2 <20% from baseline) in either group. The MAP intervention had no significant impact on cognitive function postoperatively, although 50% of the patients in each group showed a significant cognitive decline (MMSE 3 points).

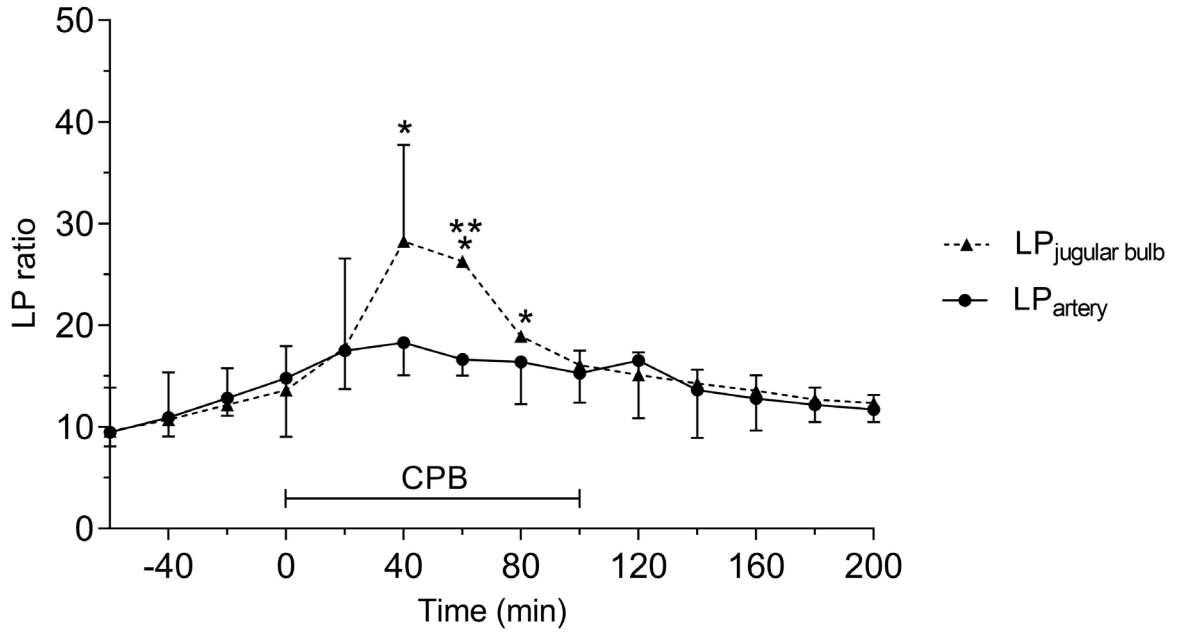
Outcomes

Microdialysis

The LP ratio measured simultaneously in the jugular bulb and intraarterial microdialysis is illustrated in figure 9. During CPB, the pooled peak LP ratio was significantly higher in JBM.

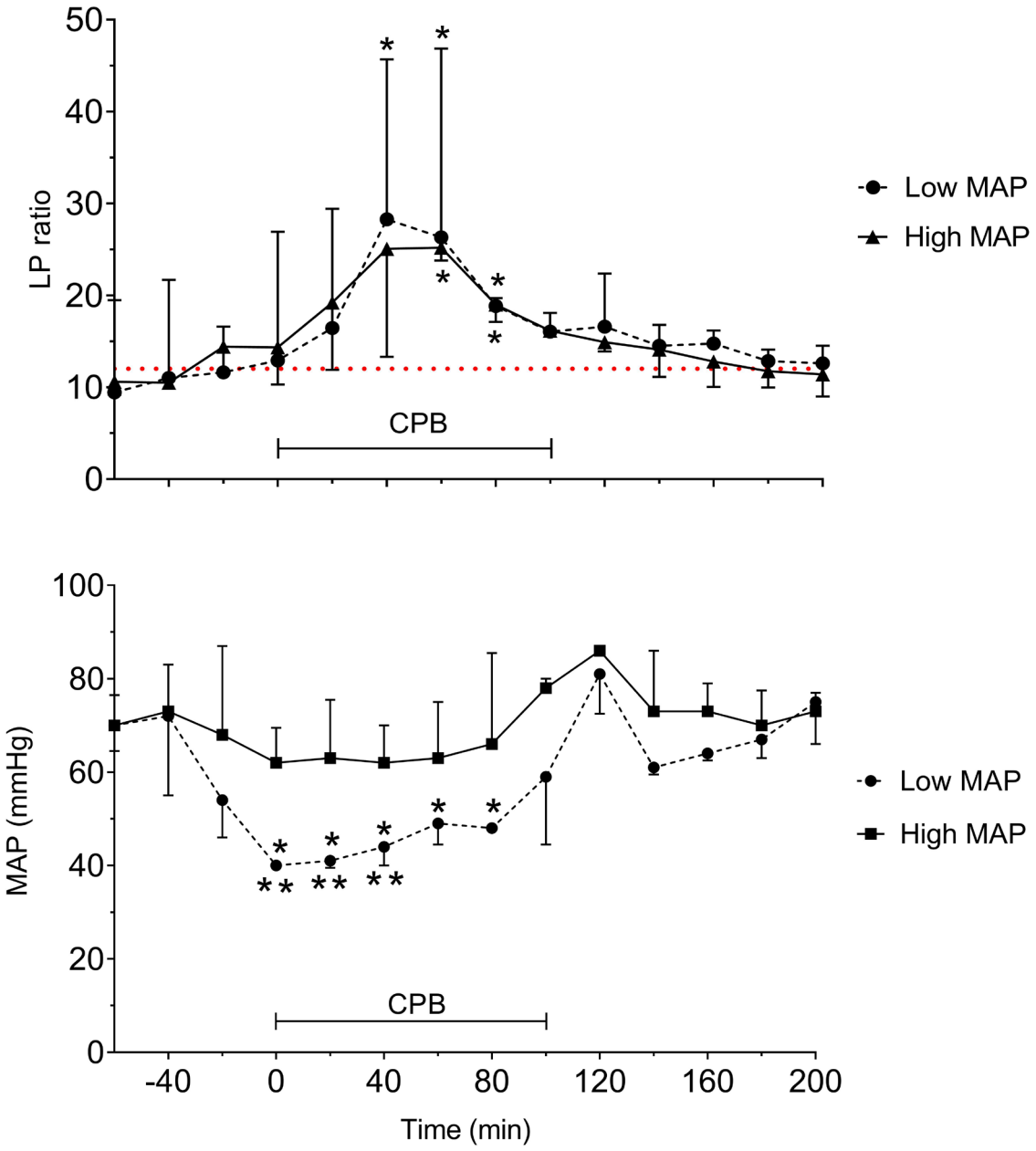
The LP ratios obtained from JBM in both MAP groups are shown in figure 10. The mean LP ratio increased significantly by 160% (low MAP) and 130% (high MAP) following initiation of CPB. In both groups, the average peak LP ratio also increased significantly. Despite the fact that low MAP patients tended to have higher LP ratios, the difference remained not statistically significant. After CPB, the LP ratio returned to baseline in both groups. Despite massive anticoagulation during cardiac surgery, no adverse events related to microdialysis monitoring were observed. The definition of normal microdialysate values (lactate, pyruvate, LP ratio, glucose, glycerol, and glutamate) in human jugular venous blood was based on pre-CPB data from this study (Fig. 2).

Figure 9



Text figure 9. During cardiac surgery and cardiopulmonary bypass (CPB), the LP ratios were monitored simultaneously from the jugular bulb and intraarterial microdialysis. The pooled (low and high MAP) peak LP ratio during CPB was significantly higher in JBM. * Significant difference from baseline. ** Significant difference between corresponding data points by one-way analysis of variance. Values are median and error with interquartile range (n = 10).

Figure 10



Text figure 10. The LP ratios obtained from JBM in the two MAP groups are shown in the upper panel. The difference between groups was statistically non-significant. The dotted red line indicates the upper normal reference value for the LP ratio obtained in the jugular bulb. The difference in MAP between the two groups was significant (lower panel). * Significant difference from baseline. ** Significant difference between corresponding data points by one-way analysis of variance. Values are median and error with interquartile range (n = 10).

Summary of Paper I

- It was feasible and safe to place a microdialysis catheter in the jugular bulb during cardiac surgery and CPB.
- During CPB, peak LP ratio was significantly higher in JBM compared to systemic LP ratio.
- Targeting a higher MAP during cardiopulmonary bypass did not significantly improve cerebral energy metabolism or cerebral oxygenation.
- The study established reference values for "normal" microdialysate concentrations in the jugular vein blood of anesthetized patients without cerebral pathophysiology.

Microdialysis after out-of-hospital cardiac arrest

Paper III

This feasibility study included eighteen comatose patients with sustained return of spontaneous circulation after OHCA of presumed cardiac cause. During ICU stay, main regulators of CBF remained stable and within normal therapeutic range with no differences in MAP, CI, PaO_2, and $PaCO_2$ at any time points between outcome groups. The two outcome groups had similar baseline characteristics. A favorable outcome was observed at hospital discharge in 28% of patients, while 72% had an unfavorable outcome (CPC 5 85%). Overall mortality during hospital stay was 61% due to primarily severe anoxic brain injury and life-sustaining therapy withdrawal.

Outcomes

Microdialysis monitoring

The median time from return of spontaneous circulation to microdialysis monitoring in the trial was 300 minutes. Median monitoring times were 40h (IQR 36-41) for CPC 1-2 and 72h (IQR 49-91) for CPC 3-5. CT scans documented a correct positioning of JBM catheters in all patients, without no adverse events related to the MD technique, see figure 8.

Differences between systemic and cerebral energy metabolism

Figure 11A compared the changes over time in arterial and jugular blood lactate and pyruvate and the calculated LP ratio for patients in the poor outcome (CPC 3–5) group. During the periods depicted in the figure, the difference between the time-averaged means of LP ratio, lactate, and pyruvate was statistically significant ($p < 0.02$). In the first 50 hours after ROSC, JBM measured significantly elevated glycerol levels compared to systemic MD.

Association between cerebral energy metabolism and neurological outcome

Except for glycerol, differences between time-averaged mean JBM variables and corresponding systemic values were not statistically significant in patients with favorable outcome (CPC 1-2). The LP ratio in jugular blood remained elevated (>16) during the first 20 h in both outcome groups (Fig. 11B). After 20h, almost complete normalization of the LP ratio was observed. However, the cerebral lactate level remained high in the CPC 3–5 group (mean level >2.7 mM) and was paralleled by a marked increase in pyruvate. The latter correlated significantly to unfavorable outcome ($p=0.02$). According to the biochemical definitions described previously, six patients with unfavorable outcomes exhibited ongoing secondary ischemia during 20% of the first 24h of MD monitoring. In the favorable group, three patients exhibited ischemia for a total of 13 hours (13%). Biochemical signs interpreted as caused

by mitochondrial dysfunction were noticed in 46% and 38% of the time in patients with unfavorable outcomes (n = 13) and favorable outcomes (n = 5).

Regional cerebral desaturation

Only a few patients in each CPC group showed minimal transient signs of cerebral desaturation (1.0% (CPC 1-2) and 0.6% (CPC 3-5) of the total INVOS monitoring period). In addition, no differences in rSO_2 between outcome groups were observed at any time point (Fig. 12), without a correlation between JBM-verified ischemic periods and cerebral desaturation.

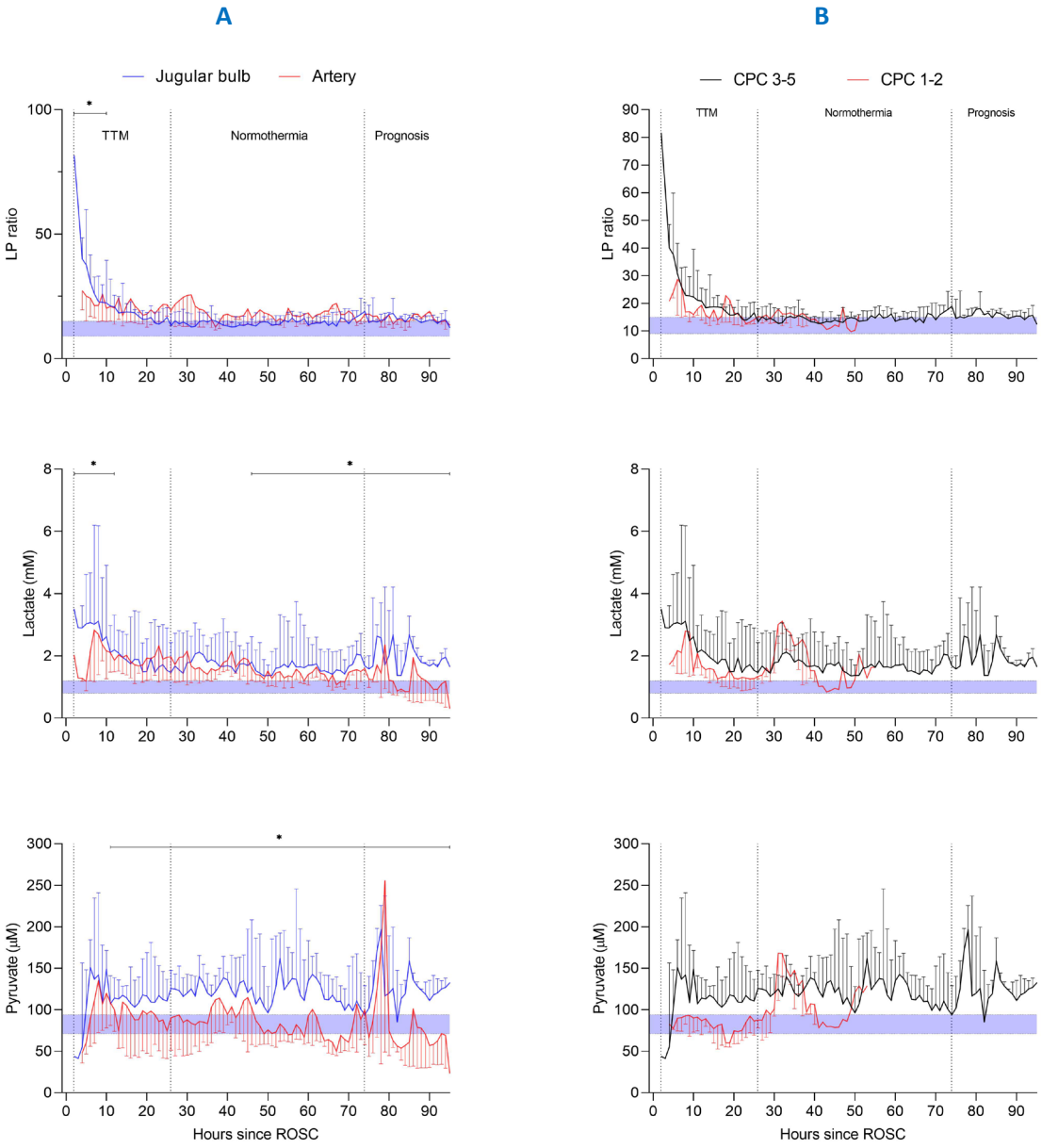
JBM variables in relation to critical clinical episodes

In patients with poor outcomes, regression analysis revealed a significant negative correlation between MAP and corresponding jugular bulb lactate. For a one-unit increase in MAP (mmHg), cerebral lactate changed by –0.011 mM (p=0.005). Nonetheless, no extreme JBM variables were observed during periods of hypotension.

Accuracy of the MD catheter

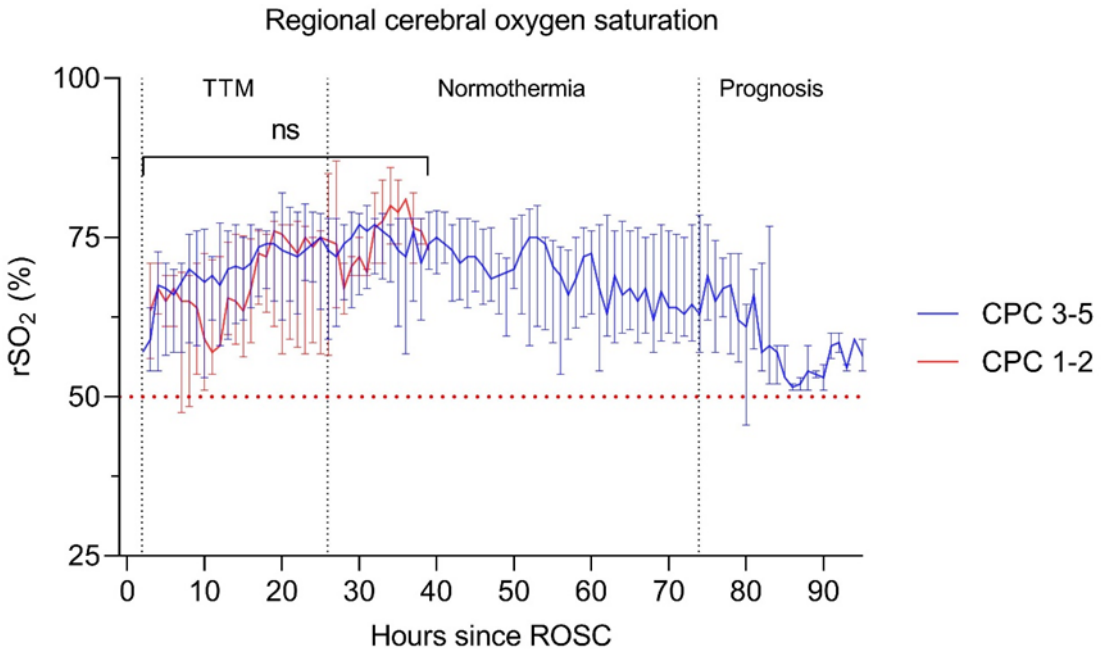
The accuracy of the MD catheter was evaluated by exploring the correlation and agreement between systemic blood lactate (Lac_{sys}) and MD arterial lactate ($Lac_{MD\text{-}Art}$). A highly significant correlation with r=0.73 and coefficient at 0.82 [0.75-0.89] ($p<0.0001$) was obtained. Bland-Altman statistics showed an average bias for Lac_{sys} of 0.18 mM higher than $Lac_{MD\text{-}Art,}$ with the 95 % limits of agreement ranging from −0.75 to 1.11.

Figure 11



Text figure 11. Figure 11A illustrates microdialysis parameters of the jugular venous and arterial blood during post-resuscitation care in patients with unfavorable outcome (n=13). The difference between time-averaged means (in intervals of 12 hours) of LP ratio, lactate, and pyruvate of the jugular venous and the arterial blood was significant during post-resuscitation care (*, p <0.02) when using mixed effects models. Figure 11B shows jugular bulb microdialysis parameters during post-resuscitation care in patients with unfavorable outcome (CPC 3-5, n=13) compared to patients with favorable outcome (CPC 1-2, n=5). The difference between time-averaged means (intervals of 12 hours) of LP ratio, lactate, and pyruvate between outcome groups, was not significant during post-resuscitation care when using mixed effects models. Normal reference values are displayed (shaded area) in the graphs for each JBM variable. Median (IQR).

Figure 12



Text figure 12. Median (IQR). Regional cerebral oxygen saturation (rSO2) during post-resuscitation care in patients with favorable (CPC 1-2) and unfavorable (CPC 3-5) outcome. No significant (ns) differences between outcome groups were observed. The dotted red line indicates cerebral desaturation threshold rSO_2 <50%.

Summary of Paper III

- The study indicated that JBM was feasible and safe in cardiac arrest patients.
- All JBM catheters were positioned correctly according to CT scans performed in all patients.
- Variables reflecting cerebral energy metabolism (LP ratio, lactate, pyruvate) could be distinguished from systemic variables obtained from intraarterial microdialysis in patients with poor clinical outcome.
- The LP ratio in jugular blood remained elevated (>16) during the first 20 h in both outcome groups with almost complete normalization of the LP ratio after 20h.
- During post-resuscitation care, biochemical signs of ischemia and mitochondrial dysfunction were frequent and long-lasting and more pronounced in patients with unfavorable outcome.
- No differences in rSO_2 between outcome groups were observed.

Paper II and IV

Sixty unconscious patients with sustained ROSC admitted to the intensive care unit following OHCA completed the trial and were included in the analysis. A consort flowchart of patient enrollment and group allocation is presented in figure 13. The two MAP groups had similar baseline characteristics (Table 1). The median time from ROSC to randomization in the trial was 180 [120-210] minutes. There was a clear separation in MAP between the groups (mean difference: 15 mmHg ([CI], 13.1 to 17.3), p <0.0001) (Fig. 14). In the low MAP group, the norepinephrine dose and Vasoactive-Inotropic Score (VIS) was significantly higher (p=0.0001) during the first 24 h after admission (Table 2).

During ICU stay, there was no significant difference in cardiac output, mixed venous saturations, and systemic lactate (Table 2). Reduced global metabolic demand (TTM and analog-sedation) during the first ICU days was illustrated by high and stable levels of mixed venous saturations associated with low cardiac output.

Additional regulators of cerebral blood flow remained within therapeutic range with no difference in PaO_2 and $PaCO_2$ at any time points between MAP groups (Table 2).

Outcomes

Association between cerebral energy metabolism and MAP

The median time from ROSC to microdialysis monitoring was 260 minutes in low and high MAP group with monitoring durations of 65 [47-91] and 63 [45-89] hours, respectively. Except for glycerol in the early post-resuscitation phase (12-36 h, p<0.001), no significant difference in microdialysis values was observed between the two MAP groups (Fig. 15 and Table 3). The LP ratio remained high (>16) in both groups during the first 30 h.

Irrespective of MAP allocation, 75% of patients exhibited pronounced secondary ischemia during 22% of total MD monitoring. In almost all patients, biochemical signs of mitochondrial dysfunction were detected 31% and 35% of the time in low MAP and high MAP groups, respectively (Table 3).

Association between cerebral energy metabolism and neurological outcome

Figure 16 compares changes in biochemical variables for outcome groups CPC 1-2 and CPC 3-5. During the first 24 hours, JBM lactate was significantly higher in the CPC 3-5 group (mean level >2.3 mM and peak level >16 mM). During the first 36 hours, JBM pyruvate was significantly higher in the CPC 3-5 group, and LP ratio was significantly higher during the first six hours. Significantly increased glycerol levels were observed during the period 12-36 h after start of JBM (CPC 3-5). Patients with unfavorable outcomes exhibited a significant difference between jugular bulb lactate and systemic lactate within

the first 36 hours. There was no significant difference between CPC groups in terms of the severity of cerebral ischemia and mitochondrial dysfunction.

During the first 24 hours, cerebral lactate >2.5 mM, pyruvate levels >110 µM, LP ratio >30, and glycerol >260 µM predicted death with AUC 0.80.

At 48h, the median NSE (n=39) level was significant lower in the CPC 1-2 group compared to the CPC 3-5 group (11 [7-13] µg per liter vs 22 [11-40] µg per liter, p=0.006). In patients with poor outcome a relative high correlation for cerebral lactate and NSE levels (n=25) was observed, R=0.73.

Regional cerebral oxygen saturation

During MAP intervention, no significant differences in rSO_2 between MAP groups were observed at any time point (Fig. 17). The median (IQR) rSO_2 during the first 48h was 69.5% (62.0–75.0%) in the low MAP group and 69.0% (61.3–75.5%) in the high MAP group, p = 0.16. Irrespective of chronic hypertension, no significant differences in rSO_2 between MAP groups were observed at any time point using mixed effects models. Data were not stratified for neurological outcome since similar non-significant differences between outcome groups were observed (Fig. 18). No correlations between JBM-verified ischemic periods and cerebral desaturation were observed.

Neurological outcome between MAP groups

At hospital discharge 22 of 30 patients (73%) in the low MAP group and 15/30 (50%) in the high MAP group had a poor functional outcome CPC 3-5 (relative risk with low MAP, 1.46; 95% confidence interval [CI], 0.97 to 2.23; p=0.06). At 90 days, 12 of 30 patients (40%) in the low MAP group and 8 of 30 patients (27%) in the high MAP group had died (relative risk with low MAP, 1.5; 95% confidence interval [CI], 0.72 to 3.14; p=0.27). Overall mortality during hospital stay was 33% due primarily to severe anoxic brain injury and withdrawal of life-sustaining therapy. At 48h, the median NSE level was 15 µg per liter in the low MAP group and 12 µg per liter in the high MAP group, p=0.92. Detailed results for outcomes are given in Table 3.

JBM variables in relation to critical episodes

JBM levels in patients with EEG-verified epileptiform activity were not significantly different from other patients, except for significantly higher pyruvate levels during the first 48 hours (p=0.001). Among patients (n=14) with malignant and highly malignant EEG patterns, no differences in JBM levels were observed.

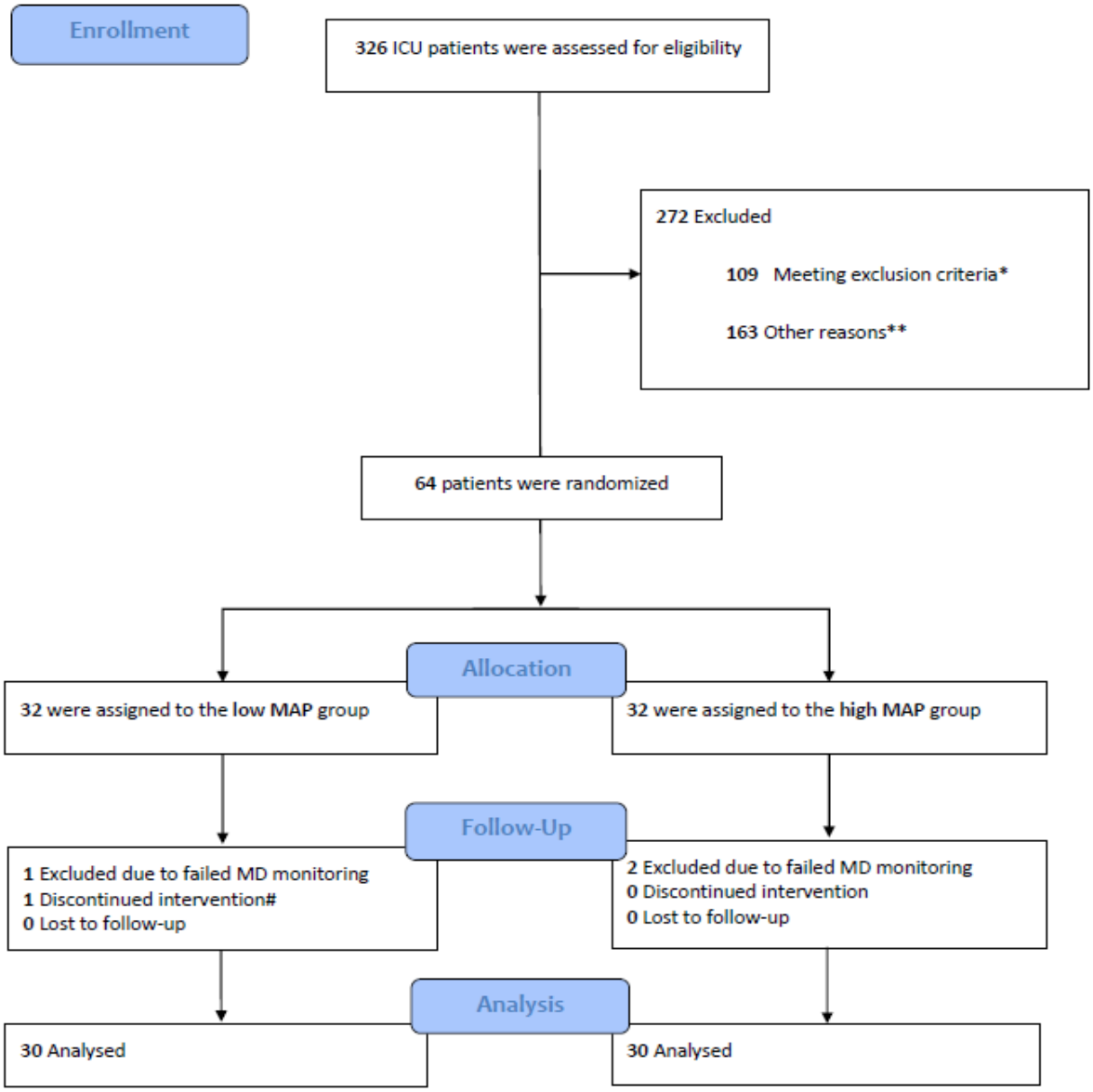
Jugular bulb lactate, LP ratio, and glycerol correlated negatively to the corresponding MAP in all patients. For each one-unit increase in MAP (mmHg), cerebral lactate changed by –0.010 mM (95% CI -0.014; -0.006, p<0.001), LP ratio -0.16 (95% CI -0.28; -0.04, p=0.01) and glycerol by -1.5 µM (95% CI -1.81; -1.17, p<0.001). Patients with preexisting hypertension responded even better for every unit increase in MAP; lactate -0.014 mM, (95% CI -0.019; - 0.009, p<0.001), LP -0.34 (95% CI -0.51; -0.18, p< 0.001).

Few patients in outcome groups showed minimal transient signs of cerebral desaturation with rSO_2 <50% in <2% of the total INVOS monitoring period. No correlations between JBM-verified ischemic periods and cerebral desaturation were observed.

Serious Adverse Events

No significant differences were found in the percentage of patients with serious adverse events between MAP groups (Table 3). In addition, complications related to the MD technique were not observed, e.g., carotid artery puncture, pneumothorax, venous hematoma, catheter-related thrombosis, or infection.

Figure 13



Text Figure 13. Screened, excluded, and included patients in the study. * Exclusion criteria were: OHCA with presumed non cardiac cause (asphyxia, trauma, massive bleeding, aortic dissection) (n=26), conscious patients (GCS ≥ 8) (n=25), suspected or confirmed acute intracranial bleeding (n=5), > 240 minutes from ROSC to randomization (n=6), refractory shock (n=12), unwitnessed asystole (n=13), known pre-arrest cerebral performance category (CPC) score of 3 or 4 (n=5), in-hospital cardiac arrest (n=17). ** Other reasons: participating in other studies (n=131), logistics (n=26), trial staffs was not informed about the patient (n=6). # Hemodynamic instability and mechanical assist device (Impella). Abbreviations: ICU, intensive care unit; MAP, mean arterial pressure; MD, microdialysis.

Table 1. Baseline characteristics according to MAP intervention

Characteristic	Low MAP N = 30	High MAP N = 30
Demographic characteristics		
Age – years	69±12	63±14
Male sex – no. (%)	28 (93)	24 (80)
Medical history – no. (%)		
Chronic heart failure	8 (27)	3 (10)
Ischemic heart disease	11 (37)	7 (23)
Arterial hypertension	20 (67)	14 (47)
Previous stroke	3 (10)	0 (0)
Diabetes mellitus	7 (23)	4 (13)
Previous percutaneous coronary intervention	6 (20)	5 (17)
Neurological function before cardiac arrest		
Normal, CPC score 1*	26 (87)	29 (97)
Some disability, CPC score 2	4 (13)	1 (3)
Characteristics of the cardiac arrest		
Witnessed cardiac arrest – no. (%)	27 (90)	26 (87)
Bystander performed CPR – no. (%)	26 (87)	29 (97)
First monitored rhythm – no. (%)		
Shockable rhythm	22 (73)	22 (73)
Time from cardiac arrest to event – min		
Start of basic life support, median (IQR)	2 [1-5]	1 [1-3]
Start of advanced life support, median (IQR)	8 [5-10]	10 [6-16]
Return of spontaneous circulation, median (IQR)	16 [10-23]	20 [12-32]
Clinical characteristics on admission		
First measured body temperature – °C	35.5±1.0	35.1±1.3
Glascow Coma Scale score §, median (IQR)	3 [3-3]	3 [3-3]
Pupillary reflex present – no. (%)	17 (57)	19 (63)
Serum pH	7.26±0.12	7.23±0.15
Serum lactate – mmol/liter	5.1±4.1	5.2±4.3
Shock – no. (%) ¶	10 (33)	8 (26)
ST-segment elevation myocardial infarction – no. (%)	8 (27)	18 (60)

Text Table 1. Plus-minus values are means ± SD. Abbreviations: CPC, Cerebral Performance Category; AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; IQR, interquartile range. * CPC score: 1, alert, able to work and lead a normal life; 2, moderate cerebral disability and sufficient cerebral function for part-time work; severe cerebral disability, dependent on others, and impaired brain function; 4, coma and vegetative state; 5, dead or certified brain dead. § Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness. ¶ Shock was defined as a systolic blood pressure of less than 90 mmHg for more than 30 min or end-organ hypoperfusion (cool extremities, urine output <0.5 ml/kg per hour, lactate >2.5 mmol/l).

Table 2. Post-resuscitation care data

ICU monitoring	Low MAP (n = 30)	High MAP (n = 30)
Hemodynamics		
MAP – mmHg		
Day 1	64±6	**80±9**
Day 2	67±8	**86±12**
Day 3	68±9	**90±13**
Day 4	70±8	**91±15**
CI – l/min/m^2		
Day 1	2.4±0.9	2.2±0.5
Day 2	3.1±0.8	2.8±0.8
Day 3	3.1±0.7	3.1±0.9
Day 4	3.3±0.7	3.1±0.9
SvO_2 – %		
Day 1	73±8	70±7
Day 2	72±7	71±6
Day 3	70±7	71±7
Day 4	71±8	72±9
Average serum lactate - mmol/liter		
Day 1	1.9±1.4	1.7±1.9
Day 2	1.6±0.8	1.4±0.8
Day 3	1.4±0.7	1.3±0.5
Day 4	1.1±0.4	1.2±0.3
Average NE infusion (µg/kg/min), median (IQR)		
Day 1	**0.17 [0.09-0.27]**	0.09 [0.05-0.14]
Day 2	0.12 [0.05-0.18]	0.07 [0.03-0.12]
Day 3	0.06 [0.04-0.09]	0.04 [0.02-0.10]
Day 4	0.07 [0.05-0.15]	0.03 [0.02-0.05]
Average VIS, median (IQR)		
Day 1	**18 [11-28]**	8 [4-14]
Day 2	9 [3-18]	6 [3-12]
Day 3	6 [4-11]	6 [2-10]
Day 4	7 [3-13]	4 [2-6]
PaO_2 – kPa		
Day 1	14.4±3.1	14.0±3.0
Day 2	13.8±2.8	13.5±2.4
Day 3	13.5±2.8	13.2±2.9
Day 4	14.2±2.5	13.1±2.5
$PaCo_2$ – kPa		
Day 1	5.5±0.8	5.3±0.8
Day 2	5.6±0.7	5.5±0.7
Day 3	5.4±0.8	5.4±0.7
Day 4	5.5±0.8	5.6±0.5

Text Table 2. Plus-minus values are means ± SD. Bold text indicates a statistically significant difference with a p-value less than 0.05. n = number of patients. Abbreviations: MAP, Mean arterial pressure; CI, Cardiac index; SvO_2, mixed venous saturations; NE, norepinephrine; VIS, Vasoactive-Inotropic Score. P<0.05 is highlighted in bold.

Table 3. Outcomes and Adverse Events

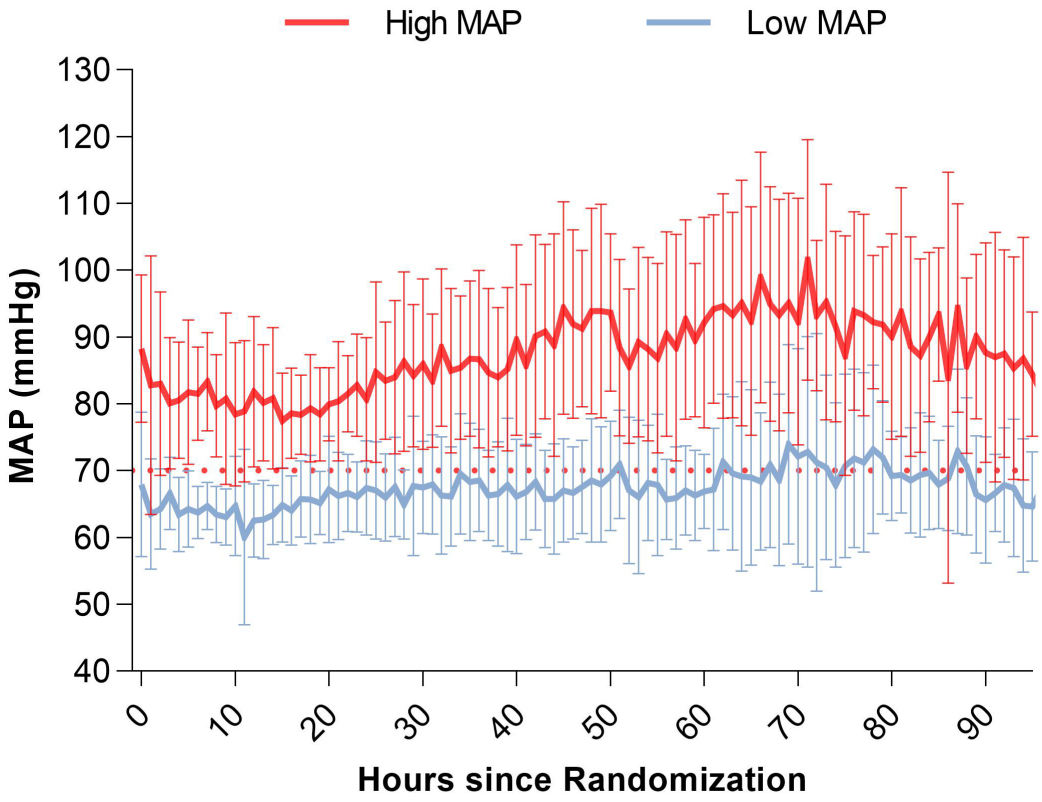
Outcomes or Events	Low MAP (n = 30)	High MAP (n = 30)
Primary outcome:		
LP ratio within the first 24 hours – median (IQR)		
Day 1	19 [16-31]	23 [16-33]
Day 2	15 [12-20]	16 [13-21]
Day 3	15 [13-21]	15 [12-20]
Day 4	14 [12-18]	17 [12-24]
Secondary outcomes:		
Jugular bulb microdialysis – median (IQR)		
Time from ROSC to MD analysis (min)	255 [236-300]	268 [202-345]
Microdialysis time (hours)	65 [47-91]	63 [45-89]
Metabolic pattern		
Ischemia*	21.4% (375 h), n=23	22.3% (357 h), n=22
Mitochondrial dysfunction**	31.2% (547 h), n=28	34.8% (557 h), n=29
INVOS - (rSO_2 %) - median (IQR)		
Day 1	69 [62-74]	68 [60-74]
Day 2	72 [64-77]	72 [64-78]
Day 3	68 [63-80]	70 [63-75]
Day 4	64 [60-70]	73 [69-76]
Cerebral desaturation - % of total INVOS monitoring***	1.3% (18 h), n=4	1.5% (18 h), n=6
Median NSE at 48 h (IQR) — µg/liter ****	15 [10-27]	12 [9-28]
Mortality 90 days after OHCA - no./total no. (%)	12/30 (40%)	8/30 (27%)
Time to death (days) – median (IQR)	6 [4-9]	6 [3-8]
Location of death		
ICU	5/12 (42%)	4/8 (50%)
Ward	7/12 (58%)	4/8 (50%)
Cause of death		
Cerebral	10/12 (84%)	6/8 (75%)
Hemodynamic	2/12 (16%)	2/8 (25%)
Neurologic function at hospital discharge no./total no. (%)		
Good, CPC score 1-2	8/30 (27%)	15/30 (50%)
CPC Category[#]		
1	2/30 (7%)	5/30 (17%)
2	6/30 (20%)	10/30 (33%)
3	10/30 (33%)	6/30 (20%)
4	-	1/30 (3%)
5	12/30 (40%)	8/30 (27%)
Serious Adverse Events[¤] – no./total no. (%)		
Bleeding	0/0 (0%)	0/0 (0%)
Sepsis	1/30 (3%)	2/30 (6%)
Arrhythmia	4/30 (13%)	3/30 (10%)
Microdialysis catheter complications	0/0 (0%)	0/0 (0%)

Text Table 3. Median (IQR). Bold text indicates a statistically significant difference with a p-value <0.05. N = number of patients. Abbreviations: MD, microdialysis; ICU, intensive care unit; INVOS, In-Vivo Optical Spectroscopy (regional oxygen saturation); NSE, neuron-specific enolase; OHCA, out-of-

hospital cardiac arrest; CPC, Cerebral Performance Category. *Microdialysis verified ischemia defined as LPR >16 and pyruvate <70 µmol/l. Percentage (%) of total MD monitoring during ICU stay. **Microdialysis verified mitochondrial dysfunction defined as LPR >16 and pyruvate >70 µmol/l. Percentage (%) of total MD monitoring time during ICU stay. ***Cerebral desaturation defined as rSO2 <50%. **** Reference values for neuron-specific enolase range from 0 to 16.3 µg per liter. Levels at 48 hours were available for 39 patients (20 in the low MAP group and 19 in the high MAP group).

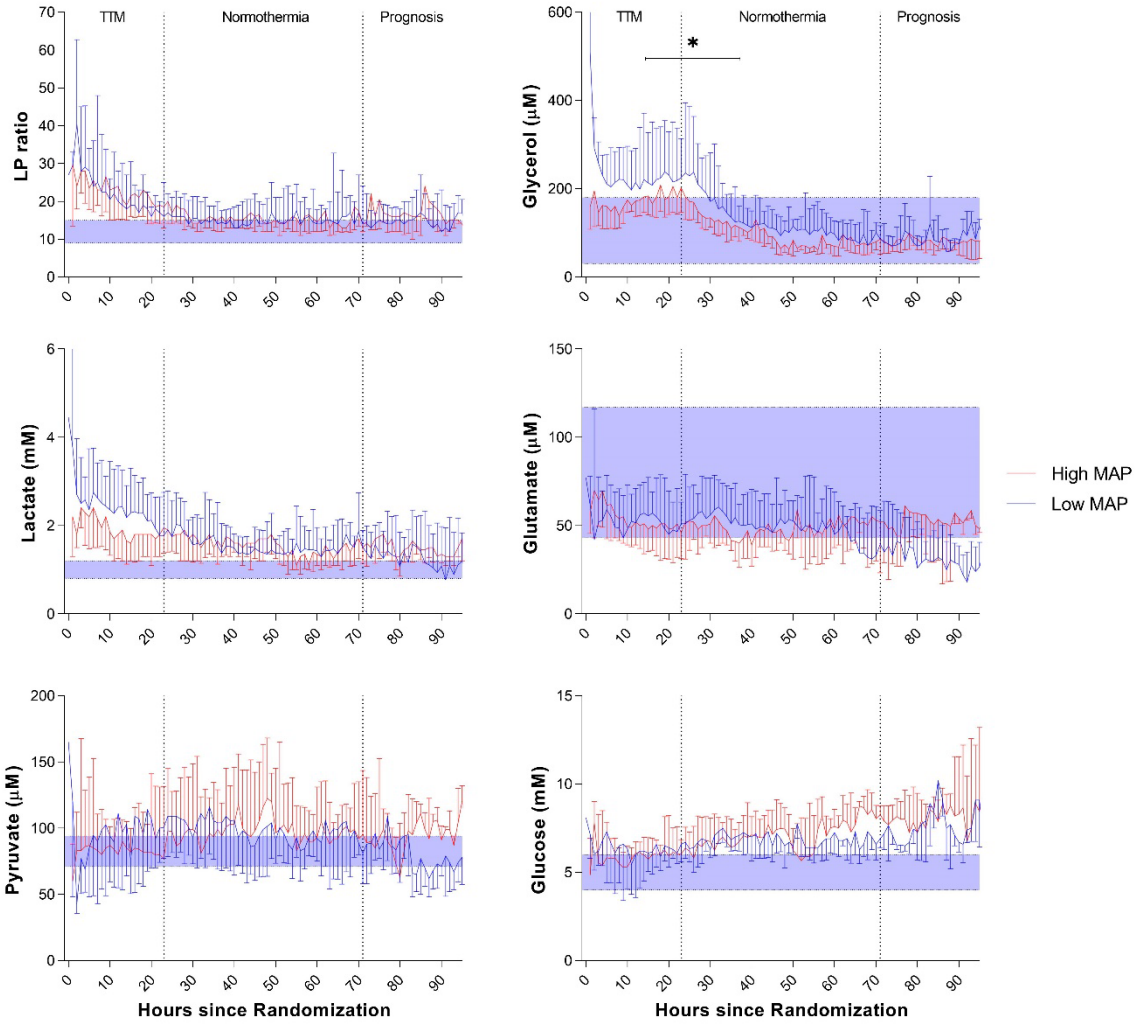
#CPC score: 1, alert, able to work and lead a normal life; 2, moderate cerebral disability and sufficient cerebral function for part-time work; 3, severe cerebral disability, dependent on others, and impaired brain function; 4, coma and vegetative state; 5, dead or certified brain dead. ¤Uncontrolled bleeding (>1 unit of blood/10 kg/1h), bleeding causing fatality, intracerebral bleeding, septic shock, and arrhythmia resulting in hemodynamic compromise. Microdialysis catheter complications; carotid artery puncture, pneumothorax, venous hematoma, catheter-related thrombosis, or infection. No significant differences between groups were observed.

Figure 14



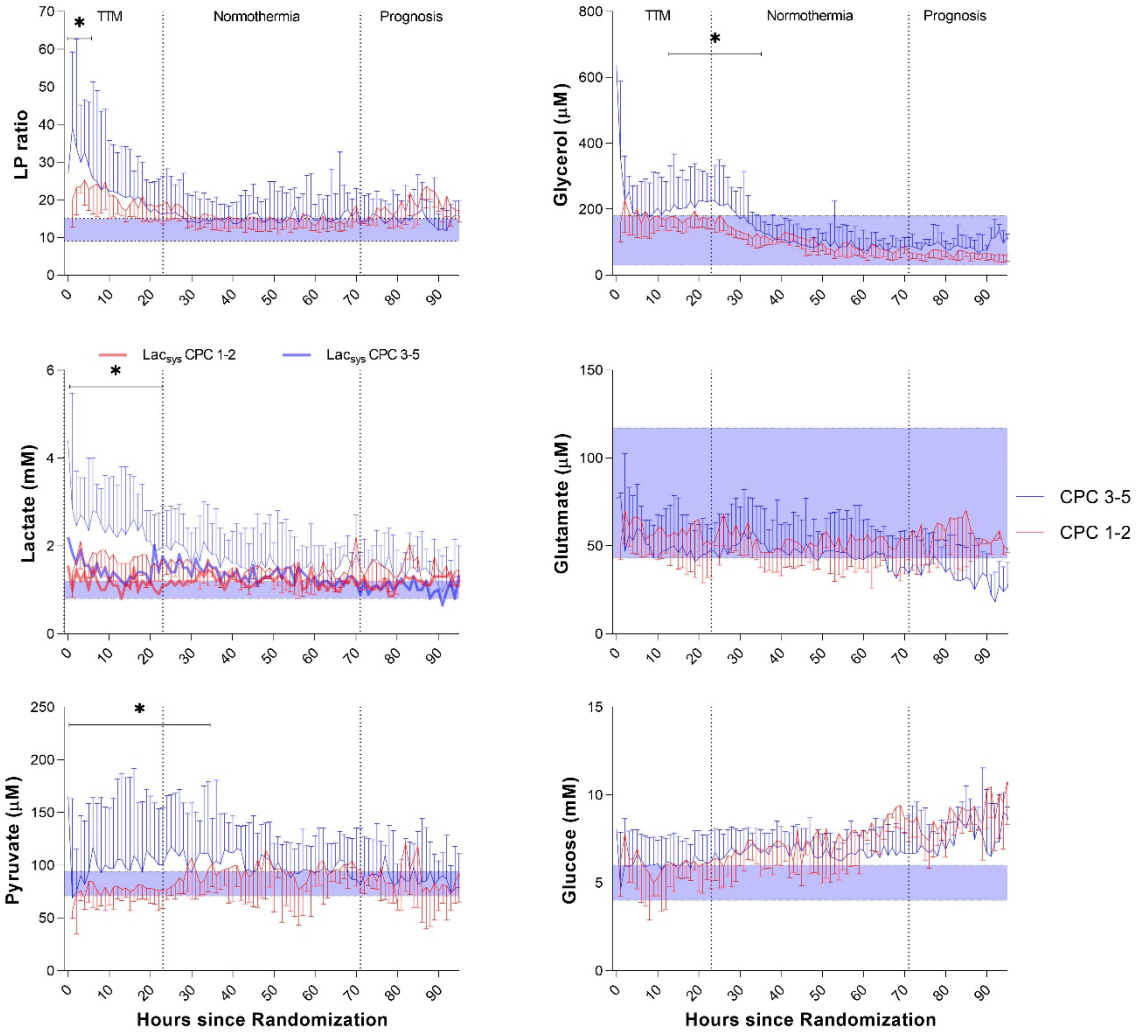
Text Figure 14. Mean arterial pressure during the intervention period. The MAP curves show the means, and the bars indicate ±2 SD (95% of the observations are within the error bars). A clear separation in MAP between the groups (mean difference: 15 mmHg, p <0.0001) was observed. The dotted red line indicates the target MAP of 70 mmHg. The median time from return of spontaneous circulation to randomization in the trial was 180 minutes.

Figure 15



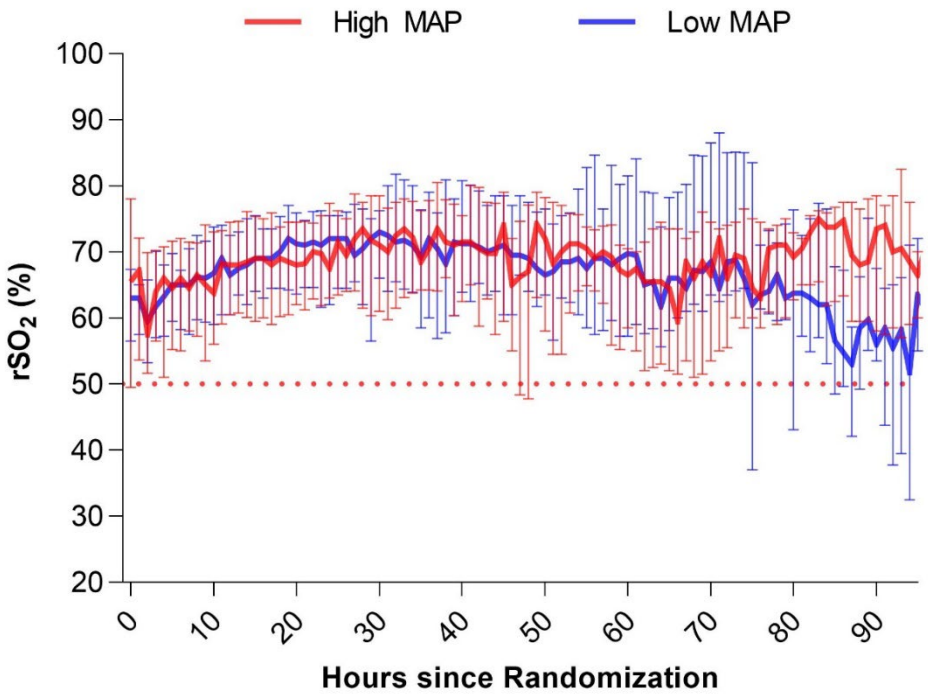
Text Figure 15. Data are expressed as median (interquartile range). LP ratio: lactate/pyruvate ratio. Jugular bulb microdialysis variables in the study groups (n=60) during MAP intervention. The median time from return of spontaneous circulation to microdialysis monitoring in the trial was 260 minutes. * The difference between time-averaged means (in intervals of 12 hours) of the variables was insignificant during post-resuscitation care except for glycerol when using mixed effects models. The graphs display normal reference values (shaded area) for each JBM variable: LP ratio (12±3); Lactate (1.0±0.2 mM); Pyruvate (82±11 µM); Glycerol (105±75 µM); Glutamate (80±37 µM); Glucose (5.0±1.0 mM) [1].

Figure 16



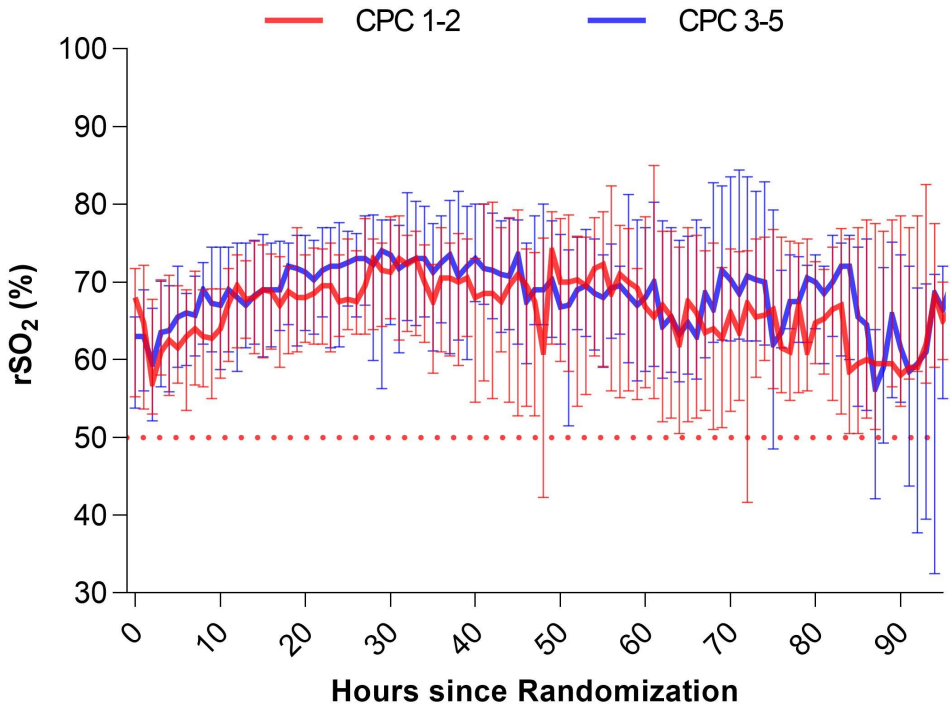
Text Figure 16. Median (IQR). Jugular bulb microdialysis parameters during the intervention period in patients discharged with unfavourable outcome (black line) (CPC 3-5, n=37) compared to patients with favourable outcome (red line) (CPC 1-2, n=23). The median time from return of spontaneous circulation to microdialysis monitoring in the trial was 257 minutes. * The difference between time-averaged means of LP ratio (interval of 6 hours) and lactate, pyruvate, and glycerol (intervals of 12 hours), was significant during post-resuscitation care when using mixed effects models. JBM variables were not stratified for MAP group. In patients with unfavourable outcome, a significant difference between jugular bulb lactate and systemic lactate (Lac_{sys}) was observed for the entire period. During the first 24 hours, systemic lactate was significantly higher in the CPC 3-5 group compared to CPC 1-2 group. The graphs display normal reference values (shaded area) for each JBM variable: LP ratio (12±3); Lactate (1.0±0.2 mM); Pyruvate (82±11 µM); Glycerol (105±75 µM); Glutamate (80±37 µM); Glucose (5.0±1.0 mM) [1].

Figure 17



Text Figure 17. Median (IQR). Regional cerebral oxygen saturation (rSO_2) during MAP intervention in the study groups (n=60). No significant differences between MAP groups were observed. Data not stratified for neurological outcome. The dotted red line indicates cerebral desaturation threshold rSO_2 <50 %.

Figure 18



Text Figure 18. Median (IQR). Regional cerebral oxygen saturation (rSO_2) during post-resuscitation care in patients with favorable (CPC 1-2, n=23) and unfavorable (CPC 3-5, n=37) outcome. No significant differences between outcome groups were observed. Data not stratified for MAP intervention. The dotted red line indicates cerebral desaturation threshold rSO_2 <50 %.

Summary of Paper IV

- 60 comatose OHCA patients were randomly assigned to low (63 mmHg) or high (77 mmHg) MAP. Overall mortality during hospital stay was 33% due mainly to severe anoxic brain injury.
- There was a clear separation in MAP between the groups (mean difference: 15 mmHg).
- The median time from ROSC to microdialysis monitoring was 260 minutes in both MAP groups.
- Targeting a higher MAP 180 min after ROSC did not significantly improve cerebral energy metabolism or oxygenation within 96 hours of post-resuscitation care. The LP ratio remained high (>16) in both groups during the first 30h.
- JBM discriminated specific subgroups (preexisting hypertension), benefiting more from an augmented MAP on cerebral metabolism.
- During the first 24 hours, cerebral lactate >2.5 mM, pyruvate levels >110 µM, LP ratio >30, and glycerol >260 µM predicted death with AUC 0.80.
- At 48h, the median NSE level was significant lower in the CPC 1-2 group compared to the CPC 3-5 group (11 [7-13] µg per liter vs 22 [11-40] µg per liter, p=0.006).
- In patients with poor outcome a relative high correlation for cerebral lactate and NSE levels was observed, R=0.73.
- No significant differences were found in the percentages of patients with serious adverse events. Complications related to the MD technique were not observed.

Discussion

Hypoxic/ischemic brain injury is the leading cause of mortality and long-term neurologic disability in cardiac arrest survivors. Understanding the pathophysiological mechanisms of the ongoing injury cascade is clinically relevant for these patients.

The potential advantages of jugular bulb microdialysis of the cerebral venous drainage in intensive care management of comatose patients resuscitated from cardiac arrest may include real-time monitoring of global cerebral "energy failure", detection of impending global cerebral ischemia, and monitoring the effects of impact of different therapeutic interventions on cerebral energy metabolism. To our knowledge, JBM monitoring has never been tested in cardiac arrest patients. Assessment of optimal blood pressure and bedside monitoring of global brain metabolism may be two essential factors in post-resuscitation care and was the main focus of this thesis.

Microdialysis of the draining venous blood represents the first attempt to open the brain's black box and discuss the complex changes in brain energy metabolism during post-resuscitation care.

Microdialysis of cerebral venous blood

Intracerebral microdialysis is an established technique for monitoring regional cerebral energy metabolism during neurocritical care. However, some problematic factors concerning monitoring regional energy metabolism in cardiac arrest patients include focal measure, selective brain tissue vulnerability, uncertain pathological thresholds, and invasiveness. Furthermore, patients suffering from cardiac arrest experience global transient cerebral ischemia followed by complex regional changes in vascular tone, cerebral blood flow, and cerebral metabolic activity [97].

Several potential complications are associated with invasive intracerebral monitoring, including infection, technical failure, and intracranial hemorrhage. In addition, it is especially problematic to insert an intracerebral catheter in patients resuscitated from CA, with a limited number of patients studied due to anticoagulation [76-78].

Measuring surrogate markers of cerebral function in the jugular bulb during post-resuscitation care is not new. Still, previously tested methods, e.g., jugular bulb saturation and arterio-venous difference of lactate and glucose, have not gained wide recognition in the clinic [75, 98-100].

At present, there is no real-time clinical monitoring method for global cerebral "energy failure" during cardiac surgery and post-resuscitation care. In these clinical settings, JBM might offer a new possibility.

Does microdialysis of the draining venous blood reflect intracerebral energy metabolism?

Bedside monitoring of global cerebral energy metabolism is a novel technique. There is currently no established gold standard method for evaluating global cerebral energy state. Therefore, it was not possible to compare jugular bulb microdialysis with a clinically proven established method.

The hypothesis of the clinical studies (Paper I, III-IV) were primarily based on experimental studies in pigs showing that microdialysis of the draining venous cerebral blood gives semi-quantitative information of cerebral interstitial levels of lactate, pyruvate and LP ratio at cerebral ischemia (figure 5) [4, 79].

Systemic derangements will influence measurements from the jugular bulb, e.g. systemic lactate production versus cerebral lactate production, since systemic blood flow will also perfuse the brain. As the energy metabolites lactate and pyruvate quickly equilibrate over cell membranes and readily pass the blood brain barrier, there is a solid theoretical basis to hypothesize that jugular bulb microdialysis may yield a surrogate marker of global cerebral redox metabolism relevant for monitoring purposes in cardiac arrest patients.

Moreover, experimental intracerebral microdialysis data collected during resuscitation are essential for interpreting biochemical changes observed during clinical microdialysis [66]. Translating experimental study findings into novel clinical trials is challenging, and interpretations of changes in clinical JBM of cerebral metabolites after cardiac arrest, are based on previous experimental studies of transient global cerebral ischemia evaluated from whole brain tissue homogenates as well as intracerebral microdialysis [75]. These studies were summarized in a recent review [94].

It is unclear whether jugular bulb microdialysis potentially reflects the same biochemical patterns as measured by intracerebral MD in acute brain injury. In this thesis, however, biochemical definitions of ischemia and mitochondrial dysfunction were based on intracerebral microdialysis principles. Furthermore, intravascular microdialysis has yielded reliable values in numerous studies of peripheral and central blood vessels [101, 102].

The JBM technique requires that brain ischemia and the perturbation of energy metabolism can be assumed to be global and was evaluated in explorative clinical studies during cardio-pulmonary bypass in open heart surgery and after OHCA [1, 3].

Paper I showed that biochemical variables measured in cerebral venous blood reflected their intracerebral levels compared to systemic references. Even though the transient cerebral energy crisis was only mild during CPB, the peak LP ratio was significantly higher in JBM compared to the arterial LP ratio. The brain is exclusively dependent on oxidative metabolism, and the significant increase in the

jugular LP ratio indicates impaired cerebral energy metabolism, validating the novel MD technique. NIRS-based monitoring of cerebral oxygenation did not reveal a corresponding decrease in cerebral oxygenation. As patients demonstrated diminished cognitive functions following CPB, an increase in jugular venous LP ratio may be a sensitive indicator of impending cerebral damage.

In summary, Paper I documented that it was feasible and safe to place a microdialysis catheter in the jugular bulb during cardiac surgery.

However, post-cardiac arrest patients with anoxic brain injury and completely different hemodynamics, such as pulsatile flow, low cardiac output, and vasoplegia, constitute an entirely separate patient population. Therefore, these JBM data cannot necessarily be extrapolated from cardiac surgery to OHCA.

Paper III aimed to investigate whether JBM might be used to monitor secondary deterioration of cerebral energy metabolism after OHCA. More specifically, we tested whether the LP ratio monitored in the cerebral venous outflow changed over time, reflecting cerebral metabolism, and therefore was different from corresponding arterial LP ratio.

The study showed that bedside JBM was feasible and safe during post-resuscitation care. All JBM catheters were positioned correctly according to CT scans performed in all 18 patients. The results of microdialysis showed that cerebral metabolic parameters could be distinguished from systemic parameters in patients with poor outcomes, and may be used to assess global cerebral energy metabolism in comatose OHCA patients. Especially, during the majority of the study period, the concentrations of glycerol, lactate, and pyruvate were significantly higher in jugular blood than in arterial blood in patients with unfavorable outcomes. The significant increase in glycerol in jugular venous blood may reflect a degradation of cerebral cellular membranes related to an increase in BBB permeability.

Furthermore, a significant difference between jugular bulb lactate and systemic lactate in patients with unfavorable outcomes was observed during the first 36 hours in Paper IV.

In conclusion, the technique has been assessed by performing jugular bulb microdialysis in explorative clinical studies during cardio-pulmonary bypass in open heart surgery and after OHCA. Mitochondrial oxidative energy metabolism can be evaluated online by performing microdialysis of the draining venous blood, but detection of isolated cerebral metabolic perturbations in cardiac arrest patients were dependent on a certain degree of brain injury.

The JBM-method might be used for real-time brain injury detection and early treatment titration following ROSC to improve patient outcomes. However, the clinical significance needed evaluation in

a larger study, why we conducted a randomized controlled trial examining the effect of higher MAP on global cerebral metabolism in 60 OHCA-resuscitated comatose patients (Paper IV).

Effects of MAP therapy on cerebral metabolism

MAP intervention - microdialysis during cardiopulmonary bypass

Despite significant advances in surgical CPB and anesthetic techniques, brain damage continues to be a major complication of cardiac surgery. [103, 104]. It has been hypothesized that a higher MAP-target during cardiac surgery is preferable and might reduce neurologic complications. Despite the fact that MAP targets as high as 80 mmHg have been investigated in clinical studies, it has not been possible to demonstrate a benefit of higher blood pressure targets [105]. Intraoperative cerebral monitoring may offers a possibility to individualize and optimize hemodynamics during cardiac surgery, and microdialysis may provides the most direct means to monitor cerebral "energy failure" in real time.

In Paper I we introduced the concept of characterizing dynamic changes in global cerebral energy metabolism using jugular bulb microdialysis application during cardiac surgery. Paper I compared the effect of two mean arterial blood pressure (MAP) levels on global cerebral energy metabolism during cardiac surgery. The study showed that placing a microdialysis catheter in the jugular bulb was feasible for monitoring transient perturbations of variables reflecting intracerebral energy metabolism. During CPB, the LP ratio of cerebral venous blood increased significantly, indicating impaired cerebral oxidative metabolism due to a decrease in CBF when MAP was below the normal pressure autoregulation range (60-160 mmHg) [106]. However, LP ratio rapidly returned to normal after CPB, indicating that the insult to cerebral energy metabolism was mild and transient.

Targeting a higher MAP during cardiopulmonary bypass did not significantly improve cerebral energy metabolism indicating a sufficient CPB flow between MAP groups. The results agrees with a prospective, randomized trial showing that targeting a higher MAP range (70-80 versus 40-50 mmHg) among 200 patients undergoing on-pump cardiac surgery did not affect the volume or number of new cerebral infarcts [107].

However, it should be noted that the observed cognitive decline was paralleled by a significant increase in jugular venous LP ratio while no significant decline in rSO_2 was obtained by NIRS. The observation indicates that a larger study including high risk patients might be indicated and an increase in jugular venous LP ratio may be a sensitive indicator of impending cerebral damage.

Furthermore, Paper I established reference values for “normal” microdialysate values (lactate, pyruvate, glucose, glycerol, glutamate, LP ratio) in human jugular venous blood in anesthetized

patients without cerebral pathophysiology (Fig. 1). These preoperative reference values were used to define the pathological thresholds for each variable indicated in Paper III-IV.

MAP intervention - microdialysis after cardiac arrest

Maintaining cerebral blood flow at a sufficient level for preserving oxidative energy metabolism requires an adequate mean arterial blood pressure. Secondary brain injury seems to occur in the early period after OHCA and is driven by complex pathophysiological mechanisms such as reperfusion injury with mitochondrial dysfunction, impaired autoregulation and delayed hypoperfusion [27, 37, 108, 109]. Especially, cerebral autoregulation is impaired or right-shifted in approximately 30–50% of patients following cardiac arrest [26, 27, 37]. Consequently, hypotension after cardiac arrest may result in cerebral hypoperfusion and oxygenation, worsening brain injury.

However, randomised controlled trials studying specific MAP targets in post-resuscitation care have failed to show any signs of benefit on surrogate outcomes [41, 42].

Paper IV compared two blood pressure targets in comatose patients resuscitated from OHCA. Targeting a higher MAP (77 vs 63 mmHg) did not significantly improve cerebral energy metabolism or cerebral oxygenation within 96 hours of post-resuscitation care.

Despite a clinically significant separation between MAP groups of approximately 15 mmHg in the present study, we found no significant between-group differences in the levels of lactate, pyruvate, or the LP ratio during the 96 h study period. Moreover, there was no significant difference between MAP groups in terms of the severity of cerebral ischemia and mitochondrial dysfunction.

Glycerol was significantly increased in the low MAP group during a prolonged period. The increase in glycerol in the low MAP group and the tendencies toward higher lactate and lower pyruvate during the first 20 hours of JBM may suggest that low MAP influences cerebral energy metabolism also 3-4 h after ROSC. However, lipolytic activity in adipose tissue is enhanced by adrenergic mechanisms mediated via beta-adrenoreceptors [110-112]. Accordingly, the noted increase in glycerol may be influenced by the higher VIS score in the low MAP group.

Furthermore, a higher MAP did not decrease NSE levels at 48h, indicating an insignificant therapeutic effect and/or difference in brain injury/hypoxia between MAP groups. The results agree with the main BOX trial (MAP difference 10.7 mmHg), showing no significantly different percentages of patients dying, having severe disability (CPC 3-4) or biomarkers of neurologic brain injury [9]. Furthermore, other prospective, multi-center, randomized trials showed that targeting a specific MAP range (170 min after ROSC) after transfer to the ICU did not affect surrogate outcomes [41, 42].

These non-significant findings between MAP groups could be explained by several factors.
Delayed hypoperfusion can persist for hours or even days with multiple mechanisms implicated, including endothelial cell lesions, unbalance of local vasodilators/vasoconstrictors, impaired autoregulation, reduced metabolism, and anesthesia [36]. However, the clinical role of delayed hypoperfusion related to PCABI is uncertain. Studies in comatose resuscitated patients have demonstrated a similar decrease in the cerebral metabolic rate of oxygen and cerebral oxygen extraction fraction that occurs 24-72h after cardiac arrest, suggesting a maintained coupling between CBF and oxygen demand [113, 114]. Patients who died from PCABI had considerably lower oxygen extraction rates. It is unclear whether this was caused by decreased oxygen utilization due to mitochondrial dysfunction, irreversible brain injury, or reduced oxygen delivery to the brain. Recent clinical research confirmed that almost half of comatose patients with PCABI 13–40 h post-arrest experienced brain tissue hypoxia and simultaneously released biomarkers of neuronal injury [29, 115].

Compromised cerebral metabolism and brain hypoxia probably depend on numerous factors. Despite optimized MAP and oxygen delivery, diffusion limitations of oxygen [29], mitochondrial dysfunction and blood-brain barrier breakdown with secondary oedema or cell death may exacerbate secondary injury [116]. A sub-set of patients with hypoxic/ischemic brain injury are perfusion dependent with intact oxygen diffusion, which may benefit from an augmented and individualized MAP. Targeting a higher mean arterial pressure in the post-resuscitation period may be warranted in patients with preexisting hypertension [37]. Nevertheless, subgroup analysis of the primary outcome in the BOX trial suggested no benefit of a higher blood-pressure target in patients with known hypertension.
Interestingly, JBM revealed that jugular bulb lactate, LP ratio, and glycerol correlated negatively to the corresponding MAP in all patients. Nonetheless, no extreme JBM variables were observed during periods of hypotension (MAP <60 mmHg). Moreover, we were able to discriminate specific subgroups (preexisting hypertension), benefiting more from an augmented MAP on cerebral metabolism.

Microdialysis after cardiac arrest - a prognostic marker in the ICU?

Cerebral reperfusion after OHCA is complex, and data regarding the first hours after ROSC are lacking. In both Paper III and IV, a majority of patients exhibited severe disturbance in cerebral energy metabolism with markedly increased LP ratio up to 20-30 h after the start of JBM. A similar long-lasting perturbation was described using intracerebral MD after CA [77].

In experimental studies, animals exposed to 30 minutes of total cerebral ischemia achieve near-normalization of the LP ratio 60 to 120 minutes after recirculation [60, 117]. Mitochondrial aerobic activity

will be almost normalised within this time limit, provided adequate cerebral blood flow is obtained immediately with recirculation [61]. A porcine cardiac arrest model also described normalised LP ratio 30-60 minutes after ROSC [118]. The discrepancy between previous experimental data and our clinical findings supports the hypothesis that initial cerebral reperfusion in most patients is insufficient to restore cytoplasmic redox state.

Despite JBM did not start until about 260-300 min after ROSC, significant differences were obtained between outcome groups (Paper IV) for variables related to oxidative energy metabolism (lactate, pyruvate, LP ratio). During the first 12 hours of JBM, the significant increase in LP ratio in the CPC 3-5 group indicates that tissue oxygenation and recirculation were worse in this group than in the CPC 1-2 group. Lactate and pyruvate levels in the CPC 3-5 group remained elevated for up to 60 hours, indicating mitochondrial dysfunction due to a more severe initial ischemic insult.

The same metabolic pattern was observed between outcome groups in Paper III, with elevated lactate and pyruvate levels throughout the entire monitoring period in the CPC 3-5 group. A study by Zhang et al. describing significant increases in [18F]-FDG uptake in the brain of post-CA animals provides support for the interpretation of mitochondrial dysfunction [119]. In addition, mitochondrial oxidative phosphorylation capacity was reduced in out-of-hospital cardiac arrest patients undergoing TTM compared to healthy controls [109]. This supports the pathophysiological mechanism that ischemia-reperfusion injury in post-cardiac arrest patients is caused, in part, by persistent mitochondrial dysfunction. The discrepancy between outcome groups indicates that energy metabolism was initially more compromised in CPC group 3-5 in both Papers.

Very interestingly, cerebral lactate >2.5 mM, pyruvate levels >110 µM, LP ratio >30, and glycerol >260 µM was highly predictive for poor neurological outcome and death with AUC 0.80 during the first 24 hours (Paper IV). Furthermore, NSE levels were significantly higher in the CPC 3-5 group, and a relative high correlation for cerebral lactate and NSE levels was observed.

In conclusion we were able to differentiate neuro-metabolic patterns between patients with unfavorable and favorable neurological outcome in post-cardiac arrest patients. Moreover, we were able to predict poor neurological outcome based on specific metabolic patterns obtained by JBM.

Identifying patients bedside suffering from severe mitochondrial dysfunction using JBM, might optimize prognostication and individualize (improving oxygen utilization) the treatment of post-cardiac arrest patients and improve outcome.

Cerebral oxygenation after cardiac arrest

In Paper IV, there was no difference in rSO_2 between the MAP or outcome groups, demonstrating that JBM may provide more detailed information not obtained by other techniques in the clinic. These findings are not novel and the COMACARE trial showed similar findings with regards to no differences in cerebral oxygenation between high vs low MAP [42]. The NEUROPROTECT trial targeted a higher MAP in post-CA patients with improved cerebral oxygenation but did not improve the extent of anoxic brain damage or neurological outcome [41].

NIRS has numerous limitations and may be an inaccurate reflector of tissue oxygenation, and the results underscore the limitations of rSO_2-monitoring as a surrogate for cerebral blood flow [42, 43, 120]. Moreover, studies have shown that INVOS has poor agreement of direct tissue measurements of brain oxygenation in post arrest patients and correlates poorly with direct measures of cerebral autoregulation and blood flow [26, 121, 122].

On the other side the non-significant difference between MAP groups could reflect an intact cerebral autoregulation. However, irrespective of chronic hypertension, no significant differences in rSO_2 between MAP groups were observed at any time point, indicating that disturbed autoregulation is probably not a major issue.

Limitations

The studies had several limitations.

The sample size of paper I as a feasibility and explorative study was limited, and no sample size calculation was performed. Definitions of normal microdialysate values in human jugular venous blood, and pathological thresholds for biochemical patterns, were based on JBM reference values obtained in only 10 anesthetized patients undergoing elective cardiac bypass surgery [1]. Nevertheless, preoperative metabolite concentrations may approximate normal values pertinent to the OHCA population. MMSE is a global screening tool used to assess cognitive mental status, and may have limited value in identifying patients with mild cognitive impairment post-cardiac surgery [123].

The number of patients in Paper III-IV was limited, and larger studies are required to evaluate the clinical value of the technique. Patients included in Paper III-IV consisted of OHCA patients exclusively with presumed cardiac cause and were relatively hemodynamic stable, thus limiting external validity.

The assumption for the main study (BOX) 2×2 factorial design was that the effects of the MAP and Oxygen interventions were independent (no interaction) in relation to the primary outcome (death or CPC 3-4). However, central factors influencing cerebral metabolism are mainly e.g., MAP, carbon dioxide and oxygen levels. These main regulators of cerebral metabolism have the potential of important interaction, which justified the exclusion of the "restrictive" oxygen group in Paper IV. Numerous patients were excluded from the main Paper IV due to their participation in other studies (restrictive oxygen group), posing a risk of selection bias.

The blinded MAP intervention was limited to a 20% separation, because the module manufacturer did not support a larger modification without changing the module software. Based on the main BOX trial, we expected significantly higher vasopressor-doses in the high MAP group [9]. Still, the opposite was observed during the first 24 h caused by a higher percentage of shock and organ hypoperfusion in the low MAP group.

The normal range of the measured JBM variables and classification of neuro-metabolic patterns are based on minor patient samples (Paper I) and experiences from intracerebral microdialysis. Further investigations regarding the relationship between global brain 18-FDG-PET (cerebral metabolic rate of glucose) and levels of biochemical variables in cerebral tissue and the draining venous blood are warranted. However, variables reflecting cerebral energy metabolism could be distinguished from systemic variables obtained from intraarterial microdialysis in patients with poor clinical outcome (Paper III-IV).

We did not measure CBF during the study periods to demonstrate coherent findings in cerebral blood flow and JBM.

The study is mainly limited by the fact that, due to established clinical routines, it was impossible to start JBM until about 3-4 h after ROSC. The clinical impact of the JBM technique should be re-evaluated when the JBM catheter is positioned within 60 minutes after ROSC.

Regional saturation of oxygenation using near infrared spectroscopy as a measure of "brain oxygenation" was used in post-cardiac arrest patients. Physiologic data has demonstrated that near infrared spectroscopy has poor agreement of direct tissue measurements of brain oxygenation in post arrest patients, does not present a relationship when plotted against mean arterial pressure and agrees poorly with direct measures of cerebral autoregulation and blood flow [26, 121, 122]. Given the known limitations of INVOS monitoring to estimate meaningful cerebrovascular physiology, it is uncertain whether a higher MAP improved brain oxygenation.

Summary of the hypothesis

1. Paper I compared the effect of two mean arterial blood pressure (MAP) levels on global cerebral energy metabolism during cardiac surgery. The study showed that placing a microdialysis catheter in the jugular bulb was feasible for monitoring transient perturbations of variables reflecting intracerebral energy metabolism. Targeting a higher MAP during cardiopulmonary bypass did not significantly improve cerebral energy metabolism or cerebral oxygenation. Furthermore, the study established reference values for "normal" microdialysate values in human jugular venous blood in anesthetized patients (pre-CPB) without cerebral pathophysiology.

2. Paper III investigated whether JBM might be used to monitor secondary deterioration of cerebral energy metabolism after OHCA. This feasibility study included eighteen comatose patients with a high mortality rate of 61% due primarily to severe anoxic brain injury during hospitalization.

   JBM was feasible and safe. Variables reflecting cerebral energy metabolism could be distinguished from systemic variables obtained from intraarterial microdialysis in patients with poor clinical outcome. Persistent compromised cerebral oxidative metabolism was observed during the first 20h in both outcome groups. Biochemical signs of ischemia and mitochondrial dysfunction were frequent and long-lasting after the return of spontaneous circulation and more pronounced in patients with unfavorable outcome. No difference in cerebral oxygenation saturation between outcome groups were observed.

3. Paper IV aimed at assessing the effect of different blood pressure levels on global cerebral energy metabolism and cerebral oxygen saturation in comatose patients resuscitated from OHCA. In this double-blinded trial, 60 comatose OHCA patients were randomly assigned to low (63 mmHg) or high (77 mmHg) MAP. Aiming for a higher MAP 180 minutes after ROSC did not improve cerebral energy metabolism or oxygenation during post-resuscitation care. No secondary outcomes, including cerebral oxygenation (rSO_2), NSE levels, metabolic patterns of ischemia, or neurological outcome, were significantly affected by higher MAP. During the first 24 hours, cerebral lactate >2.5 mM, pyruvate levels >110 µM, LP ratio >30, and glycerol >260 µM was highly predictive for poor neurological outcome and death. Patients with a poor clinical outcome exhibited significantly worse biochemical patterns, indicating that inadequate tissue reperfusion and oxygenation in the first few hours after ROSC were crucial factors determining neurological outcome.

Conclusion

The studies described in this thesis have given new insights into pathophysiological mechanisms following transient global cerebral ischemia after cardiac arrest. Microdialysis of cerebral venous blood in the jugular bulb have shown promise to give important information of cerebral energy metabolism. Mitochondrial oxidative energy metabolism can be evaluated online by performing microdialysis of the draining venous blood, but detection of isolated cerebral metabolic perturbations in cardiac arrest patients were dependent on a certain degree of brain injury. Main findings indicated persistent compromised cerebral oxidative metabolism in the majority of resuscitated comatose patients. Biochemical signs of ischemia and mitochondrial dysfunction were frequent and long-lasting after the return of spontaneous circulation and more pronounced in patients with unfavorable outcome. Targeting a higher MAP 180 min after ROSC did not significantly improve cerebral energy metabolism or oxygenation within 96 hours of post-resuscitation care. Patients with a poor clinical outcome exhibited significantly worse biochemical patterns, illustrating that insufficient tissue reperfusion and oxygenation during the initial hours after ROSC were essential factors determining neurological outcome.

Future perspectives

The possible clinical value of the JBM technique used in cardiac surgery should be evaluated in larger studies. Future research should define normal variations in the LP ratio of cerebral venous blood and investigate the relationship between an increase in the LP ratio and the onset of permanent cognitive decline and neurologic lesions after cardiac surgery.

Our current microdialysis results reflect the complex pathophysiologic mechanisms underpinning secondary brain injury, and combined JBM, CBF measurements (e.g., brain ^{15}O-H_2O-PET CT, Xenon-enhanced CT), and monitoring of mitochondrial function (^{18}F-BCPP-EF PET-CT) might provide additional future insights into the dynamics of pathogenic mechanisms [124]. Currently, we are recruiting patients in an exploratory trial: Combined Microdialysis and FDG-PET Study for Detection of Brain Injury After Cardiac Arrest (COMA-PROTECT), ClinicalTrials.gov Identifier: NCT04774055.

Differentiating between these metabolic patterns are of particular importance for interpretations in transient cerebral ischemia and adjusting clinical therapy. Furthermore, mitochondrial dysfunction is considered a potential target of neuroprotective treatment with implications for individualized post-resuscitation care improving patient outcome. Multimodal monitoring including JBM may also be beneficial for confirming mechanisms of new drug targets.

There are no guidelines on how to integrate multimodal monitoring data in patients with CA to improve management. JBM monitoring showed the ability to discriminate specific subgroups (preexisting hypertension), benefiting more from an augmented MAP on cerebral metabolism. Future efforts to improve outcomes after OHCA may focus on individualized treatment that augments cerebral perfusion and energy metabolism assessed by JBM, during early post-resuscitation care. Individualized brain resuscitation strategies that prevent secondary brain injury may include, e.g. increasing blood pressure, optimizing cardiac output and modifying PaO_2 and $PaCO_2$.
If JBM is initiated within the first hour after ROSC, it may be possible to identify patients with inadequate cerebral reperfusion prior to irreversible cell damage.

Furthermore, generalized periodic discharges may result in metabolic crisis for one patient, but may not be clinically relevant in another; in this case, markers of metabolic stress, such as JBM may be useful.

In the future, this multimodal approach might optimize brain metabolism and individualize the treatment of post-cardiac arrest patients suffering from secondary ischemia, mitochondrial dysfunction and potentially improve outcomes. Time to drop 'one-size-fits-all' hemodynamic targets?

Final remarks

"It must be recognized that no monitor, in the end, will change outcome. Instead, it is how that information is interpreted and integrated into clinical decision-making and then how the patient is treated that will influence outcome. Monitoring can be valuable in learning about pathophysiology after acute brain injury and potentially help identify new therapies." [125].

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Appendix

Paper I

Bedside monitoring of cerebral energy state during cardiac surgery - A novel approach utilizing intravenous microdialysis.

Paper II

Design paper of the "Blood pressure targets in post-resuscitation care and bedside monitoring of cerebral energy state: a randomized clinical trial".

Paper III

Bedside microdialysis for detection of early brain injury after out-of-hospital cardiac arrest.

Paper IV

A randomized, double-blind trial comparing the effect of two blood pressure targets on global brain metabolism after out-of-hospital cardiac arrest.

Paper I

Paper II

Paper III

Paper IV