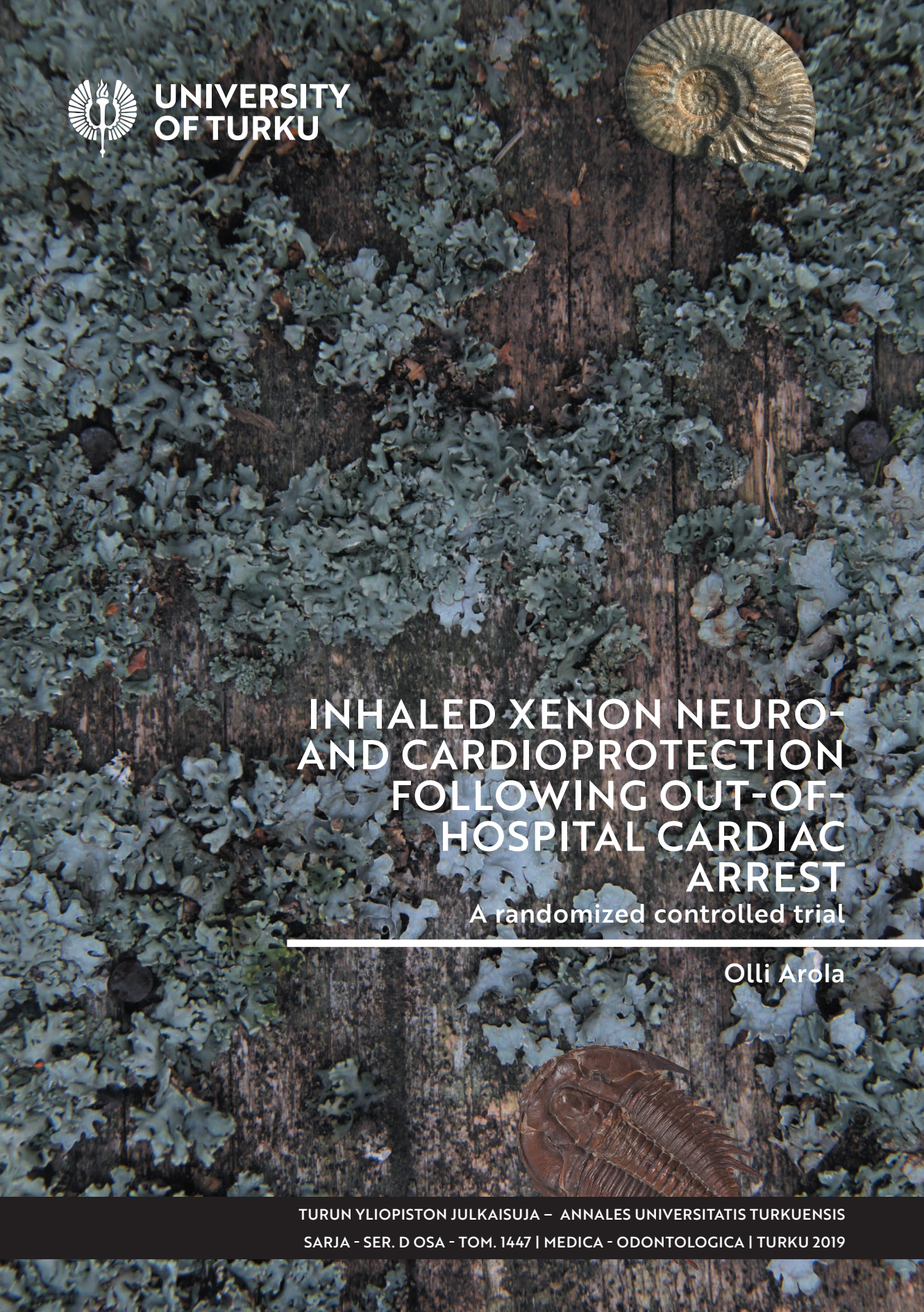


UNIVERSITY OF TURKU

INHALED XENON NEURO- AND CARDIOPROTECTION FOLLOWING OUT-OF-HOSPITAL CARDIAC ARREST

A randomized controlled trial

Olli Arola

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA - SER. D OSA - TOM. 1447 | MEDICA - ODONTOLOGICA | TURKU 2019

UNIVERSITY OF TURKU

INHALED XENON NEURO- AND CARDIOPROTECTION FOLLOWING OUT-OF-HOSPITAL CARDIAC ARREST

A randomized controlled trial

Olli Arola

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1447 | MEDICA-ODONTOLOGICA TURKU 2019

University of Turku

Faculty of Medicine
Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
Doctoral Programme in Clinical Research
Intensive Care Unit, Turku University Hospital
Heart Center, Department of Radiology, Division of Clinical Neurosciences

Supervised by

Associate Professor Timo Laitio, MD, PhD
Division of Perioperative Services, Intensive Care Medicine and Pain Management, University of Turku, Turku University Hospital
Turku, Finland

Professor Risto O. Roine, MD, PhD
Division of Clinical Neurosciences, University of Turku, Turku University Hospital
Turku, Finland

Reviewed by

Professor Christian Hassager, MD, PhD
Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Associate Professor Jesper Petersson, MD, PhD.
Department of Neurology, Rehabilitation Medicine, Memory Disorders and Geriatric Medicine.
Skåne University Hospital, Malmö, Lund University, Sweden

Opponent

Professor Matti Reinikainen, MD, PhD.
University of Eastern Finland and Kuopio University Hospital,
Kuopio, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Cover Image: Olli Arola

ISBN 978-951-29-7798-7 (PRINT)
ISBN 978-951-29-7799-4 (PDF)
ISSN 0355-9483 (Painettu/Print)
ISSN 2343-3213 (Sähköinen/Online)
Painosalama Oy, Turku, Finland 2019

To my beloved family

UNIVERSITY OF TURKU
Faculty of Medicine
Anesthesiology, Intensive Care, Emergency Care and Pain Medicine
OLLI AROLA: Inhaled xenon neuro- and cardioprotection following out-of-hospital cardiac arrest. A randomized, controlled trial
Doctoral Dissertation, 199 pp.
Doctoral Programme in Clinical Research
October 2019

ABSTRACT

Cardiac arrest leads often to death or permanent neurological damage, despite prompt advanced life support and resuscitation. Ischaemia-reperfusion injury persists, although circulation and cardiac function has been restored. The most vulnerable organs for hypoxemia and reperfusion injury are the brain and heart. The only proven intervention against ongoing ischaemia-reperfusion injury is targeted temperature management to core temperature of 33–36 °C for 24 hours after cardiac arrest. Still, at least on average third of the succesfully from ventricular fibrillation-generated cardiac arrest resuscitated patients die, particularly to hypoxic-ischaemic brain injury.

The noble gas xenon is an anaesthetic gas, which has been demonstrated in preclinical animal models to attenuate posthypoxic brain and myocardial injury. Xenon has many properties of ”an ideal anaesthetic”, but being so scarce and laborous to extract makes it expensive.

In this clinical trial, the standard-of-care after out-of-hospital cardiac arrest, targeted temperature management to 33 °C for 24 hours, was compared to hypothermia supplemented with inhaled xenon for 24 hours. Both study groups consisted of 55 cardiac arrest victims and the postarrest care was identical in both groups and in accordance with current international guidelines.

Cerebral hypoxic-ischaemic injury was assessed with brain diffusion tensor magnetic resonance imaging after rewarming. Fractional anistrophy (FA) value corresponds to the microintegrity of brain white matter tracts and is diminished after injury. Cardiac troponin-T is a marker of cardiomyocyte injury, which was serially assessed during 72 hours following resuscitation.

The main findings of this study were, that combining inhaled xenon and therapeutic hypothermia in cardiac arrest patients was safe and feasible. The combination of xenon and hypothermia significantly attenuated brain white matter injury illustrated with higher FA-values. After adjustements for age, sex, study site, primary coronary percutaneous intevention (PCI) and noradrenaline dose, Troponin-T values were lower at 72 hours post OHCA in the xenon group corresponding to an mitigating effect in myocardial injury. These results translate to significant neuro- and cardioprotection against ongoing ischaemia-reperfusion injury by xenon inhalation combined with hypothermia.

The overall mortality in this study was 30,9 %. The study was underpowered to demonstrate differences in outcome or functional neurological recovery.

KEY WORDS: Xenon, cardiac arrest, ventricular fibrillation, cardiopulmonary resuscitation, mild therapeutic hypothermia, targeted temperature management, neuroprotection, cardioprotection

Turun yliopisto
Lääketieteellinen Tiedekunta
Anestesiologia, tehohoito, ensihoito ja kivunhoito
OLLI AROLA: Hengitetty ksenon sydänpysähdystä seuraavan aivojen ja sydämen hapenpuute- ja reperfuusiovaurion muokkaajana. Satunnaistettu, kontrolloitu tutkimus
Väitöskirja, 199 s.
Turun kliininen tohtoriohjelma
Lokakuu 2019

TIIVISTELMÄ

Sydänpysähdys johtaa viiveettä aloitetusta elvytyksestä huolimatta usein potilaan kuolemaan tai vakavaan neurologiseen vammautumiseen. Hapenpuutteen ja reperfuusion aiheuttama kudosvaurio jatkuu, vaikka verenkierto ja sydämen toiminta onnistutaan elvytystoimin palauttamaan. Erityisen alttiita hapenpuutteelle ja reperfuusiovauriolle ovat aivot ja sydän. Ainoa tehokkaaksi todettu reperfuusiovaurion hoito on potilaan jäähdyttäminen 33–36 °C lämpötilaan vuorokaudeksi elvytyksen jälkeen. Hoidosta huolimatta noin kolmannes onnistuneesti kammiovärinästä elvytetyistä potilaista kuolee, tavallisimmin hapenpuuteaivovaurion seurauksiin.

Jalokaasu ksenon on anestesiakaasu, jonka on tämän lisäksi lukuisissa prekliinisissä eläintutkimuksissa todettu vähentävän hermo- ja sydänlihaskudoksen vauriota hapenpuutteen jälkeen. Ksenon-anestesialla on monia ihanteellisen anestesian piirteitä, mutta sen käytettävyyttä rajoittaa kaasun harvinaisuus ja työläs puhdistamisprosessi, minkä takia ksenon on kallista.

Tässä tutkimuksessa verrattiin vakiintunutta sydänpysähdyspotilaan jatkohoitoa teho-osastolla – vuorokauden jäähdytyshoitoa – jäähdytyshoitoon ja samanaikaiseen ksenon-kaasun hengittämiseen yhteensä 110:llä onnistuneesti kammiovärinästä elvytetyillä potilailla. Näiden kahden tutkimusryhmän potilaita (55 potilasta kummassakin ryhmässä) hoidettiin muuten samankaltaisesti noudattaen viimeisimpiä kansainvälisiä suosituksia sydänpysähdyksestä elvytettyjen jatkohoidossa.

Keskushermoston hapenpuutevauriota arvioitiin potilaan normaaliin lämpötilaan lämmittämisen jälkeen aivojen magneettitutkimuksen diffuusiotensorikuvauksen fraktioidun anisotrofia (FA) -arvon perusteella, jonka pieneneminen viittaa aivojen valkean aineen vaurioon ja mikrointegraation hajoamiseen. Sydänpysähdyksen jälkeistä sydänvauriota arvioitiin sydänlihassoluvaurion merkkiaineen troponiini-T:n muutosten perusteella.

Tutkimuksen perusteella ksenonin ja jäähdytyshoidon yhdistelmä oli turvallista ja hengitys ja verenkierto olivat hoidon aikana vakaita myös juuri elvytetyillä sydänpysähdyspotilailla, joilla valtaosalla oli merkittävä sepelvaltimotauti. Ksenon-yhdistelmähoito vähensi merkitsevästi aivojen valkean aineen vauriota magneettikuvauksen FA-arvoja verrattaessa. Myös sydänlihaksen vauriomerkkiaineen, troponiini-T:n arvot vähenivät elvytystä seuranneen 72 tunnin kuluessa merkitsevästi, sopien pienempään sydänlihasvaurioon yhdistelmähoitoa saaneessa tutkimusryhmässä. Nämä tulokset viittaavat ksenonin merkittävään neuro- ja kardioprotektiiviseen vaikutukseen käynnissä olevan hapenpuute-reperfuusiovaurion rajoittamisessa.

Tutkimuspotilaiden kuolleisuus oli 30,9 %. Hoitoryhmien koko oli liian pieni merkitsevän eron havainnointiin henkiinjäämisessä tai toiminnallisessa neurologisessa selviytymisessä.

AVAINSANAT: ksenon, sydänpysähdys, kammiovärinä, sydämen ja verenkierron elvytys, jäähdytyshoito, neuroprotektio, kardioprotektio

Table of Contents

Abbreviations

ADC	Apparent Diffusion Coefficient
AED	Automated External Defibrillator
aEEG	Amplitude Integrated Electroencephalography
AKI	Acute Kidney Injury
ALS	Advanced Life Support
AMI	Acute Myocardial infarction
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (receptor)
ATA	Atmosphere Absolute
ATP	Adenosine Triphosphatase
BLS	Basic Life Support
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CK-MB	Creatinine Kinase -MBmass
CaM K II	Ca^{2+}-calmodulin dependent protein kinase II
CmH_2O	Centimetres of Water
CPB	Cardiopulmonary Bypass
CPC	Cerebral Performance Category
CPP	Cerebral Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CT	Computed Tomography (-scanning)
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalography
ECG	Electrocardiogram
EMS	Emergency Medical Service(s)
FiO_2	Fraction of Inhaled Oxygen
FLAIR	Fluid-Attenuated Inversion Recovery
GABA	γ-Amino-Butyric Acid
GLS	Global peak systolic Longitudinal Strain
GM	(brain) Grey Matter

GOS	Glasgow Outcome Scale
GWR	(Brain) Grey matter to White matter ratio
HACA	Hypothermia After Cardiac Arrest (trial)
HIF-1α	Hypoxia Inducible Factor
HRV	Heart Rate Variability
HSP27	Heat shock protein 27
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IHCA	In-hospital Cardiac Arrest
IRI	Ischaemia Reperfusion Injury
i.v.	Intravenous
K_{ATP}	Adenosine Triphosphate-sensitive Potassium channel
LDH	Lactate Dehydrogenase
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MAC	Minimal Alveolar Concentration
MAP	Mean Arterial Pressure
MAPK	Mitogen Activated Protein Kinase
MAPKAPK-2	MAPK-activated Protein Kinase-2
MBF	Myocardial Blood Flow
MIF	Macrophage migration Inhibitory Factor
MmHg	Millimetres of Mercury
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MTH	Mild Therapeutical Hypothermia
mPTP	Mitochondrial Permeability Transition Pore
NDS	Neurologic Deficit Score
NFL	(serum) Neurofilament Light Chain
NMDA	N-methyl-D-aspartate
NO	Nitric Oxide
N_2O	Nitrous oxide
NSE	Neuron-Specific Enolase
NSTEMI	non- ST Elevation Myocardial Infarct
OHCA	Out-of-hospital Cardiac Arrest
OPCAB	Off-pump Coronary Artery Bypass
PCI	Percutaneuous Coronary Intervention
PEA	Pulseless Electrical Activity
PKC	nonselective Protein Kinase C
PKC-ε	epsilon isoform of PKC
POCD	Postoperative Cognitive Dysfunction

PONV	Postoperative Nausea and Vomiting
PPM	Parts per Million
RASS	Richmond Agitation Sedation Scale
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RISK	Reperfusion Injury Salvage Kinase
ROC	Receiver Operating Characteristic curve
ROS	Reactive Oxygen Species
ROSC	Restoration of Spontaneous Circulation
PRCS	Post Resuscitation Cardiogenic Shock
SAFE	Survivor Activating Factor Enhancement
SCD	Sudden cardiac death
SDF-1α	Stromal cell-Derived Factor-1α
SSEP	Short-latency Somatosensory Evoked Potential
STE	ST Segment Elevation
STEMI	ST Elevation Myocardial Infarct
TBSS	Tract Based Spatial Statistics
TIVA	Total Intravenous Anaesthesia
TNF-α	Tumor Necrosis Factor α
TnT	Troponin T
TREK-1	Two pore-domain potassium channel
TTM	Targeted Temperature Management
VBM	Voxel Based Morphometry
VF	Ventricular Fibrillation
VT	(pulseless) Ventricular Tachycardia
WLST	Withdrawal of Life-Sustaining Therapy
WM	(brain) White Matter
Xe	Xenon

List of original publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Olli J Arola, Ruut M Laitio, Risto O Roine, Juha Grönlund, Antti Saraste, Mikko Pietilä, Juhani Airaksinen, Juha Perttilä, Harry Scheinin, Klaus T Olkkola, Mervyn Maze, Timo T Laitio. Feasibility and cardiac safety of inhaled xenon in combination with therapeutic hypothermia following out-of-hospital cardiac arrest. Crit Care Med 2013; 41(9): 2116 – 2124

II. Ruut Laitio, Marja Hynninen, Olli Arola, Sami Virtanen, Riitta Parkkola, Jani Saunavaara, Risto O Roine, Juha Grönlund, Emmi Ylikoski, Johanna Wennervirta, Minna Bäcklund, Päivi Silvasti, Eija Nukarinen, Marjaana Tiainen, Antti Saraste, Mikko Pietilä, Juhani Airaksinen, Leena Valanne, Juha Martola, Heli Silvennoinen, Harry Scheinin, Veli-Pekka Harjola, Jussi Niiranen, Kirsi Korpi, Marjut Varpula, Outi Inkinen, Klaus T Olkkola, Mervyn Maze, Tero Vahlberg, Timo Laitio. Effect of inhaled xenon on cerebral white matter damage in comatose survivors of out-of-hospital cardiac arrest. A randomized controlled trial. JAMA 2016; 315(11): 1120 – 1128

III. Olli Arola, Antti Saraste, Ruut Laitio, Juhani Airaksinen, Marja Hynninen, Minna Bäcklund, Emmi Ylikoski, Johanna Wennervirta, Mikko Pietilä, Risto O Roine, Veli-Pekka Harjola, Jussi Niiranen, Kirsi Korpi, Marjut Varpula, Harry Scheinin, Mervyn Maze, Tero Vahlberg, Timo Laitio for the Xe-Hypotheca Study group. Inhaled xenon attenuates myocardial damage in comatose survivors of out-of-hospital cardiac arrest. The Xe-Hypotheca Trial. J Am Coll Cardiol 2017; 70(21): 2652 – 2660

1 Introduction

Cardiac arrest remains the most frequent unresolved cause of premature death in developed countries claiming annually over 3.7 million lives worldwide (Kudenchuk 2015). Out-of-hospital cardiac arrest (OHCA) is afflicting annually 275,000–500,000 persons in Europe and 420,000–500,000 in the United States (Sans 1997, Rea 2004, Atwood 2005, Daya 2015, Girotra 2015, Kudenchuk 2015, Mozaffarian 2015, Gräsner 2016), of whom emergency medical service (EMS)-assessed advanced life support is applied in 60 % of cases (Churg 2004). In an European one-month progressive registry in 27 countries any cardiopulmonary resuscitation (CPR) by a bystander or by the EMS was started in 66 % of cases (Gräsner 2016). The outcome of all-rhythm OHCA victims even with attempted resuscitation is currently still dismal; the survival 30 days post arrest is extremely low, below 10 % (Nichol 2008, Ragosta 2018) or even as low as 3.2 % (Perkins 2018). In a significant proportion of patients, sudden cardiac death (SCD) manifests with several different causes, often untreatable, without warning or a triggering mechanism (Fishman 2010).

The outcome after sudden cardiac arrest is a reflection of the critical interventions taken during resuscitation; delay to bystander or first responder EMS CPR provision, prompt defibrillation, high-performance chest compressions, assisted ventilation and early advanced cardiac life support (Cummins 1991, Sanders 2008, Daya 2015, Kudenchuk 2015). At best, in industrialised countries, 60% of patients, in whom witnessed cardiac arrest presents as ventricular fibrillation (VF) and receive bystander CPR, are “successfully” resuscitated and admitted to intensive care unit (ICU) (Nolan 2007). However, only 50 % of these (30 %) survive to hospital discharge (Kudenchuk 2015). Importantly, there is a large variation in survival after OHCA between European countries and currently, in Nordic countries, mortality after OHCA presenting with a shockable rhythm, *i.e.* VF or pulseless ventricular tachycardia (VT), is on average round 30–35 % (Holzer 2005, Sunde 2007, Bro-Jeppesen 2009, Vaahersalo 2013, Strömsöe 2015, Kirkegaard 2017).

Furthermore, if the initial rhythm is nonshockable, *i.e.* asystole or pulseless electrical activity (PEA), only 20–30% of these patients regain spontaneous

circulation. Disappointingly, after eventually successful resuscitation, only 2 to 5 % of asystole/PEA-resuscitated patients survive to hospital discharge (Cobb 2002, Kudenchuk 2015). Presenting rhythm of PEA is associated with less likelihood of witnessed cardiac arrest, less bystander CPR and longer first responder response times (Wolbinski 2016).

Taken the accumulation of remarkable insight into the importance of treatment of ischaemic heart disease, major advances in resuscitative techniques, increasing availability of defibrillators, automated external defibrillators (AED), early defibrillation programs, actions promoting out-of-hospital EMS and improvements in understanding the mechanisms of cardiac arrest in recent decades (Lopshire 2006, Daya 2015, Hasselqvist-Ax 2015), translation of this knowledge into novel strategies to affect overall outcome remain still currently unsatisfying poor (Kudenchuk 2015). Despite recent improved short-term survival from OHCA to hospital admission, the overall hospital survival rate with favourable neurocognitive outcomes has essentially remained practically unchanged during recent decades (Peberdy 2005, Bardy 2011, Mark 2014). Furthermore, fundamental understanding of the precipitating factors leading to VF/VT is incomplete, although VF is commonly associated with an acute coronary cause (Jaeger 2018).

Cardiac arrest with standstill of circulation causes global widespread ischaemia, whereas the vital organs heart and brain are most susceptible to ischaemic injury (Eastwood 2014). Ischaemia affects the brain particularly in distinct regions of tissue (hippocampus, neocortex, cerebellum and cerebral white matter), which are exquisitely sensitive to lack of oxygen, occasionally referred with *selective vulnerability hypothesis* (Schmidt-Kastner 1991, Pantoni 1996, Madl 2004, Matute 2012). Often, the consequence is death or severe permanent neurologic impairment (Angelos 2001, Neumar 2008). The cause of death in patients who achieved sustained restoration of spontaneous circulation (ROSC) but do not survive to hospital discharge is often withdrawal of intensive care based on preponderance of poor expectations of neurological recovery. However, death can occur also after recurrent cardiac arrest without ROSC, refractory haemodynamic shock, respiratory failure or multi-organ failure (Witten 2019). Furthermore, there is evidence, that the interventions applied after restoration of circulation may significantly modify the chances of survival (Nolan 2010).

Subsequent post cardiac arrest care targets are consequences of global ischaemia: posthypoxemic cerebral injury, ubiquitous myocardial dysfunction, the systemic ischaemia-reperfusion response and the persisting precipitating pathology (Neumar 2008, Girotra 2015). Coronary reperfusion with percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarcts (STEMI) improves survival in limited observational studies (Vyas 2015, Jaeger 2018). However, the reperfusion response potentially emphasizes both cardiac and cerebral injury, often

resulting in permanently incapacitating neurologic deficit and delayed death (Wolff 2009).

Since two major prospective randomized controlled studies published in 2002 illustrated the advantages of mild therapeutic hypothermia (MTH) in comatose survivors of OHCA in both survival and functional neurological outcome, this treatment became the current standard-of-care in post-resuscitation management (Bernard 2002, Holzer 2002). Induced mild hypothermia or targeted temperature management (Nielsen 2013) is to date the only in clinical trials proven therapy to improve outcome and it is recommended by international guidelines as the routine intervention for selected comatose adult survivors of witnessed OHCA (Neumar 2008, Field 2010). Although the survival rate has increased and mortality rates have declined and an improving trend in outcomes after admission to intensive care units (ICU) following cardiac arrest has been documented (Strömsöe 2015), the overall survival prospects following OHCA are still very low (Daya 2015). Complete cerebral recovery after all-rhythm OHCA is currently still a rare event (Madl 2004).

The worldwide magnitude of sudden cardiac arrest, however, is such that every intervention affecting improvement in survival translates into thousands of lives saved (Sanders 2008). Therefore, the future holds great promise, if novel therapeutic approaches can provide any improvement in individual survival and neurological recovery.

2 Review of the literature

2.1 Cardiac arrest

Sudden cardiac death (SCD) is defined usually as an abrupt and unexpected death without an obvious noncardiac cause with or without pre-existing cardiac disease and without warning of a recognized triggering mechanism. Besides witnessed SCD, unwitnessed SCD is defined as a death within 24 hours of last being observed in a person with normal health (Zipes 2006, Fishman 2010). Cardiac arrest is the leading cause of death in industrialized countries and many authorities describe SCD originating from ventricular tachycardia (VT) degenerating to ventricular fibrillation (VF) and subsequent dissolution to fatal asystole or pulseless electrical activity (PEA) (Huikuri 2001, Lopshire 2006, Skjeflo 2018). Historically, about 70% of OHCA victims were in VF at the arrival of EMS personnel, but these data originated from selected patient populations observed by EMS crew (Myerburg 1980). Previously, more patients were declared already dead on EMS arrival without indication for attempted resuscitation (Cobb 2002).

However, a major decline in the incidence of out-of-hospital VF has been observed past decades with a concomitant decline in coronary artery disease mortality, mainly originating from a marked reduction of in-hospital mortality (Kuisma 2001, Cobb 2002, Weisfeldt 2011, Karam 2019). Simultaneously, symptoms of acute myocardial infarction have lately resulted in attenuated delay in seeking care. Even though, prehospital sudden cardiac arrest, representing the very first sign of coronary artery disease, is still currently a feared complication of ST-elevation myocardial infarction (Karam 2019). The decline of VF incidence has been more pronounced in patients with unwitnessed collapse and patients collapsing at home, which apparently reflect lengthened delay, which allows VF to dissolve into asystole within minutes, probably more rapidly in patients with advanced and compromised myocardial disease (Bardy 2011, Weisfeldt 2011, Hulleman 2015). However, conversion of VF to asystole can happen also relatively slowly, as 20 minutes after collapse, 25 % of patients are still in VF (Holmberg 2000). Recent studies suggest the incidence of VF or pulseless VT as the initial rhythm in OHCA or in-hospital cardiac arrests (IHCA) to be only 16–22 % of cases (Gräsner 2016, Andersen 2017, Jabre 2018). The current annual incidence of out-

of-hospital potentially lethal VF-generated SCD in Finland has stabilized to 11,6 (95 % CI, 9,7–13,5) per 100,000 inhabitants (Väyrynen 2011). Some investigators have connected the decline of VF to increase of usage of β–blockers (Youngquist 2008).

Currently, of all resuscitations, a non-shockable rhythm is present approximately in 40–70 % of patients (asystole) whereas pulseless electrical activity (PEA) incidence is 19–46 % (Myerburg 2013, Andersen 2017, Jabre 2018). In the Finnish 6-month observational study of 1042 OHCA patients from 2010 (FINNRESUSCI), a shockable rhythm (VF or pulseless VT) was present in 31.4 % of cases (Hiltunen 2012). However, despite that the incidence of VF/VT is decreasing, the incidence of cardiac arrest with any initial rhythm is not decreasing (Herlitz 2001, Mozaffarian 2015). The true occurrence of initial VF at the time of SCD is not known, as downtime, response time and baseline characteristics between populations all affect first observed rhythm (Engdahl 2002). The evolution of pre-hospital care is likely to translate to increased hospital admissions of arrested and severely unstable patients (Olasveengen 2015).

PEA, which was earlier referred as electromechanical dissociation, is a complex presentation with multiple hypoxic/anoxic possible causes progressed to a stage where cardiac compensation is no longer possible (Parish 2003). Asystole is often considered a sign of a dying or a dead heart rather than an arrhythmia in adult patients. Despite presumed non-cardiac aetiology, there is still a chance of recovery, although usually bleak (Engdahl 2002). SCD with asystole or PEA results often from non-arrhythmic non-cardiac causes, such as drug overdose, asphyxia, exsanguination, primary respiratory failure, myocardial rupture or aortic aneurysm rupture, all of which portend a poor prognosis (McGinniss 2015, Katritsis 2016).

VF or pulseless VT in OHCA is generated by a complex interaction of a receptive anatomical or electrophysiological substrate, such as acute coronary occlusion, previous myocardial infarction scar or left ventricular hypertrophy. After a transient initiating event of functional myocardial contraction alteration caused by ischaemia, hypoxia, electrolyte imbalance, acidosis, drug toxicity or haemodynamic failure interacts with the substrate, arrhythmia with a circulatory collapse may ensue (Zipes 1998, Huikuri 2001).

Coronary artery disease is the most common cause of VF-generated SCD in developed countries, afflicting for 75 – 80 % of cases (Deo 2012). In autopsy after SCD, occlusive coronary artery disease and coronary atheromas are consistently identified as the most important responsible underlying cause (Chugh 2004). Previous myocardial infarction is apparent in 40–80 % cases (Soo 2001). Additionally, concurrent hypertension-generated left ventricular hypertrophy, which is independent of the severity of coronary disiease, is present in 75 % cases

(Perper 1975). STEMI originating from left main or left anterior descending coronary artery occlusion dominate in the patients presenting with sudden cardiac arrest (Demirel 2015).

Apart from evident ischaemia or acute coronary occlusion, myocardial scarring from a previous infarct, infiltrative or inflammatory myocardial disease may yield an explanation to ventricular tachyarrhythmias (Soo 2001). However, 6 to 14 % SCD cases generated by ventricular tachyarrhytmias occur in persons without structural heart disease (Zipes 1998, Haïssaguerre 2008). Rhythmic vulnerability involves often genetic channelopathies (e.g. long/short QT syndrome, Brugada syndrome) and other conditions that predispose to SCD, such as catecholaminergic polymorphic VT, arrhytmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, early repolarization syndrome etc., which account for only a small proportion of OHCA (Huikuri 2001, Mozaffarian 2015, Katritsis 2016). The commonest causes for non-ischaemic SCD are cardiomyopathy related to alcoholism or obesity and fibrotic cardiomyopathy (Hookana 2011). In an analysis of 206 idiopathic VF case subjects, electrocardiographic early repolarization was 6 times more frequent than in 412 matched control subjects without heart disease (Haïssaguerre 2008).

The ultimate goal of VF- or VT- generated cardiac arrest resuscitation is to rapidly restore organized electrical and contractile function and to prevent hypoxic-ischaemic brain injury (Angelos 2001, Nolan 2018).

Contemporary cardiopulmonary resuscitation (CPR) was first described in 1960, when 14 patients were salvaged from cardiac arrest by the application of closed chest cardiac massage (Kouwenhoven 1960). The absent perfusion during arrest, if no CPR is provided, is termed *no-flow* perfusion. This is a major issue, as only 20 % to 50 % of the OHCA victims receive bystander-initiated CPR – depending on the place were the collapse occurred (Loppshire 2006, Weisfeldt 2011, Mozaffarian 2015).

As advanced life support (ALS) by EMS providers is at the best only commenced several minutes after OHCA, initiation of basic life support (BLS) by first responder lay bystanders is the cornerstone to ensure a timely perfusion of the brain and optimize outcomes beyond return of spontaneous circulation (ROSC) (Field 2010). Bystander – initiated CPR increases 30-day survival more than twice as high in comparison with no CPR before EMS arrival (Hasselqvist-Ax 2015). Bystander CPR and defibrillation is additionally associated with lower risk of cerebral injury and death from any cause during 1-year follow-up (Kragholm 2017).

Defibrillation is the primary and only effective ALS intervention in pulseless ventricular tachyarrhytmias, but it is extremely time-sensitive as successful treatment of VF becomes increasingly more difficult when the VF exceeds 4

minutes (Valenzuela 1993, Angelos 2001, Nolan 2005). The success rate for defibrillation declines by approximately 10% per minute of VF (Eisenberg 1990). Good quality CPR consists of meticulous attention to the details of chest compression rate, depth, full chest recoil and minimised CPR interruptions (Kudenchuk 2015). High-performance CPR is obviously of paramount importance, although the cardiac function, cardiac output and systemic oxygen delivery achieved during adequate CPR only vaguely resembles that of a spontaneous cardiac output and is therefore termed *low-flow* perfusion (Neumar 2008, Schindler 2015). CPR –maintained circulation and perfusion is associated with a compensatory increment in general oxygen extraction, with the aftermath of oxygen debt (the difference between adumbrated oxygen consumption and actual consumption multiplied by time duration) and significantly decreased central venous oxygen saturation (Rivers 1992). Finally, the quality of bystander-initiated CPR strongly depends on experience and expertise (Rea 2010a, Koster 2015), demonstrated with a significant increase in OHCA survivors in comparison of trained responders vs. layperson bystanders (Park 2017).

Additionally, despite extended use of automated external defibrillators, public education campaigns to increase awareness and encouragement to bystander-initiated CPR, CPR is provided in less than half of victims of witnessed OHCA (Blom 2014, Mozaffarian 2015). Therefore interventions such as chest-compression-only CPR (Bobrow 2010, Svensson 2010, Rea 2010b, Nichol 2015), emergency dispatchers providing instructions to laypersons for performing CPR (Nelson 2019) and large-scale targeted public CPR training have been launched (Bobrow 2010, Olasveengen 2017).

Successful cardiac arrest resuscitation has been traditionally considered as merely achieving restoration of spontaneous circulation (ROSC). The ultimate goal of resuscitation is, however, a return to a prior quality of life and functional state of health (Field 2010). The interval to ROSC, proportion of the duration *no-flow* and *low-flow* phase and CPR quality all affect outcome after reperfusion (Angelos 2001). Fundementally, former comorbidity strongly decreases 30-day survival after eventually successful resuscitation (Hirlekar 2018).

2.1.1 Ischaemia-reperfusion injury

Unfortunately, ROSC does not indicate an end of cellular injury or cellular death (Püttgen 2007, Hoesch 2008, Varon 2012) and it merely heralds the start of reperfusion injury (Eastwood 2014). After restoration of perfusion, the patient is only technically alive (Nolan 2008). Organ injury following restored blood flow to the ischaemic tissues after cardiac arrest has three distinct mechanisms.

Firstly, at the early stage during circulation standstill and absent tissue perfusion, delivery of oxygen and removal of metabolic substrates is abruptly halted, despite still ongoing consumption of oxygen, ATP and glucose (McGinniss 2015). The brain is especially vulnerable to ischaemia, even though it constitutes less than 2 % of total body weight. However, brain devours 15–20 % of the cardiac output and consumes 20 % of resting total body oxygen (Mink 1981, Eastwood 2014). This results to that oxygen stores in the brain are depleted within 20 seconds, and ATP- generating oxidative fosforylation and sufficient glucose level maintenance are terminated within 5 minutes of complete anoxia (Siesjö 1976, Hoesch 2008, Neumar 2011, Weng 2012). This perfusion failure concludes in pervasive whole-body *no-reflow*, which was originally attributed as the "inability to reperfuse a previously ischaemic region" (Krug 1966). During *no-reflow* reduced oxygen supply is offset by lower metabolic needs, resulting in unconsciousness within 10 seconds and transient global hyperaemia with delayed, prolonged and multifocal hypoperfusion (Mongardon 2011). Initially after cardiac arrest, victims may conserve abnormal brainstem mediated gasping type of breathing, often depicted "agonal breathing", which is associated with, surprisingly, improved survival and outcome (Debaty 2017). However, contrastingly, preservation of "agonal breathing" may lead to significant delay in bystander initiation of cardiopulmonary resuscitation in witnessed arrests (Brinkrolf 2018).

Secondly, in the intermediate phase – after ROSC, reperfusion of the ischaemic tissue initiates multiple independent chemical fatal pathways, including an ischaemic destructive cytotoxic cascade and oxidative stress from the consequences of reperfusion and re-oxygenation injury (Shao 2007). This triggers several reactions, namely intracellular voltage-dependent calcium influx and diminished calcium regulation, which is associated with insufficent provision of ATP and oxygen (Mongardon 2011). Further consequences are lipid peroxidation of cell membranes, intracellular acidosis and programmed cell death (apoptosis) (Weng 2012). Mitochondrial permeability transition pore (mPTP) opens, reactive oxygen species (ROS) are generated from damaged mitochondria and bioavailability of nitric oxide (NO) is altered.

This leads to endothelial dysfunction, *"endotheliitis",* associated with impaired glucose and oxygen metabolism (Callaway 2012, McGinniss 2015). Reperfusion can paradoxically cause cell death and subsequent irreversible organ injury, termed ischaemia reperfusion injury (IRI) (Xia 2016). IRI evolves toward systemic inflammation and triggers release of circulating proinflammatory mediators including cytokines (e.g. TNFα, IL-1ra, IL-6, IL-8, IL-10), leukocyte adhesion molecules, endotoxins, complement activation and coagulopathy with platelet dysfunction (Mongardon 2011). In effect, these reactions cause accumulation of

inflammatory cells in the injured tissue, endothelial dysfunction, fibrinolysis impairment and general thrombosis (Madathill 2016). This inflammatory cascade and features of exacerbation of the inflammatory balance are similar to sepsis and the post-arrest patient after severe global hypoxemia often presents with a "sepsis-like syndrome", which is associated with poor prognosis and death (Adrie 2002). However, the alteration of the inflammatory response after cardiac arrest is not the key component and necessary for the favourable effects of post arrest interventions, such as hypothermia. This corresponds, that circulating cytokines have no specific role in post arrest neurological injury, which was demonstrated in a rodent model of asphyxial cardiac arrest (Callaway 2008).

In the brain, IRI involves abrupt release of excitatory amino acids and glutamate, activation of N-methyl-D-aspartate (NMDA) receptors, and subsequent mPTP opening results in depolarization of the membrane potential and brain matrix swelling causing rupture of the outer cell membrane and release of proteins (e.g. cytochrome C) to cytosol (Erecinska 1996, Hoesch 2008).

Thirdly, in the late phase, a pro-imflammatory state causes secondary cell injury (McGinniss 2015). The integrity of blood-brain barrier is destroyed, which further contributes to exacerbation of cerebral edema (Weng 2012). The simultaneous glutamatergic storm by excessive stimulation by neurotransmitters in glutamate receptors (NMDA, AMPA) causes excitotoxicity, which leads to influx of sodium and chloride into brain cells, causing intracellular hyperosmolarity. The high osmolarity is followed by an influx of water into the cell, resulting in intracellular oedema and neuronal death (Gonzalez-Ibarra 2011).

Acute respiratory and kidney dysfunction are common, appearing in 40 to 50 % of patients resuscitated from cardiac arrest. The digestive track IRI is often underestimated – it is associated with severe global hypoxemia facilitating bacteria translocation and major source of endotoxemia, which results in a state resembling lethal septic shock (Mongardon 2011).

2.1.2 Post cardiac arrest syndrome

Resumption of spontaneous circulation (ROSC) after prolonged global ischemia is an unnatural pathophysiological state involving multiple organs, generated by eventually successful CPR, which in the past was termed "postresuscitation disease" (Neumar 2008). Whole-body ischaemia causes global tissue and organ injury, which is exacerbated by the paradoxical injury after reperfusion. This precipitates a complex set of pathophysiological processes depicted lately as post-cardiac arrest syndrome, which has four principal components: post-cardiac arrest brain injury, post-cardiac arrest cardiac dysfunction, systemic ischaemia/ reperfusion response and persisting precipitating pathology that caused or

contributed to the cardiac arrest itself (Neumar 2008, Nolan 2010). Treating the precipitating pathology is often superimposed in the expense of the former components (Neumar 2008). In effect, it should be acknowledged, that the patient's outcome is defined by the cerebral injury rather than the myocardial damage (Ragosta 2018). Nevertheless, significant myocardial dysfunction is common after cardiac arrest but usually starts to recover by 2–3 days (Kern 1996). The severity of these disorders after ROSC varies and is strongly dependent of how rapidly resumption of perfusion was achieved (Neumar 2008).

Post-cardiac arrest brain injury is the utmost cause for mortality following successful resuscitation. Among those fortunate few resuscitated patients surviving to ICU admission but subsequently deceasing in-hospital, brain injury is the primary driver of death in two thirds of surviving patients after OHCA. The brain is vulnerable and intolerant to even short periods of ischaemia and reperfusion response (Madl 2004). The cerebral injury mechanisms involve excitotoxicity, disrupted calcium homeostasis, free oxygen radical formation and activated apoptotic pathways. Cerebral oxygen delivery is compromised also by hypotension, hypoxemia, impaired cerebrovascular autoregulation and brain oedema, which peak 24 to 72 hours after arrest (Neumar 2008). Additional factors impacting brain injury after cardiac arrest are hyperglycaemia, seizures and pyrexia, which are common during the first 48 hours post arrest. Myoclonus and seizures can occur up to 40 % in comatose survivors of cardiac arrest and portend poor neurological outcome (Dragancea 2015). Seizures are likely to be caused by, as well exacerbate, post-cardiac arrest cerebral injury (Nielsen 2011a). Clinical manifestations of post-cardiac arrest brain injury involve unresolved unconsciousness, seizures and myoclonic status epilepticus. Residual unresponsiveness reflects injury in the arousal systems in the rostral brainstem and basal ganglia associated with cognition (Stevens 2014). The general consideration is, however, that survivors of cardiac arrest regaining consciousness have a good long-term neurological outcome. Intimidately, there are still substantial neurocognitive disturbances in almost half of the population surviving (Cronberg 2009, Wachelder 2009).

2.1.3 Factors affecting resuscitation outcome

Several factors influence the outcome of OHCA victims from the very beginning of resuscitation. These include whether or not the arrest was witnessed and the promptness of resuscitation efforts, including defibrillation, were initiated (Engdahl 2002, Schulman 2006). Those patients who receive CPR from a bystander or EMS provider, and those who are found in shockable rhythms (VF/VT) and who regain ROSC in the field before hospital admission are much more likely to survive than

those who do not (Weng 2012). Other factors affecting survival are younger age, location of arrest outside home, and low adrenaline dose delivered during resuscitation (Weisfeldt 2011, Bougoin 2014). Interruptions of manual chest compressions for rescue breathing during CPR had been thought to affect blood flow and survival. However, in the comparison of groups with continuous or for rescue breathing interrupted chest compressions there were no differences in outcome (Nichol 2015).

The duration of resuscitation before regaining ROSC relates directly to extent of brain injury and to a more pronounced reperfusion injury, more severe manifestations of *low-flow* phase and metabolic consequences (Püttgen 2007). Extended time to ROSC (> 25 min) is a predictive factor for poor outcome. Long interval to ROSC has been discouraged, however, to be utilized as a sole predictor of outcome, because other factors and circumstances surrounding CPR like the quality of CPR might be equally important (Nielsen 2009, Peberdy 2010).

Those OHCA victims, who have had an abrupt period of cardiac arrest responding immediately to CPR may regain immediate normal cerebral function and do not require tracheal intubation and assisted ventilation (Nolan 2015). Spontaneous hypothermia on ICU admission has been identified as a predictor of unfavourable outcome and increased in-hospital mortality (den Hartog 2010). This associates with impaired thermoregulation, which is suggested to be an important physiologic determinant of post-resuscitation morbidity and OHCA prognosis (Benz-Woerner 2012). Curiously, on the contrary, those OHCA survivors, who are cooled sooner to target hypothermia temperature, have more favourable neurologic outcome (Wolff 2009).

Adrenaline has been recommended as an integral component of ALS already for a half of century (Pearson 1963, Safar 1964), although there is contradictory evidence of its beneficence. Adrenaline improves myocardial blood flow through constriction of arterioles, which increase aortic diastolic pressure augmenting coronary blood flow. This may promote achieving of ROSC, but potentially offset by myocardial oxygen balance, global vasoconstriction, oxidative stress and tissue hypoperfusion (Krishnamoorthy 2013, Perkins 2014). In a recent randomized, double blind trial of 8014 all-rhythm OHCA patients in the United Kingdom, adrenaline during resuscitation was compared with placebo (saline) injections. The survival rate at 30 days post OHCA was significantly higher in the adrenaline group (3.2 %) vs. placebo (2.4 %) (Unadjusted odds ratio for survival, 1.39; 95 % confidence interval 1.06 to 1.82; $p = 0.02$), but among the survivors almost twice the number in the adrenaline group had severe neurologic impairment in comparison to the placebo group. This reflects the poor prognosis in cardiac arrest patients who do not response to initial CPR and defibrillation (Perkins 2018).

During prolonged CPR, more cycles of adrenaline are required, which translates to acquired hyperglycaemia on hospital admission, which used to be considered an independent sign of poor outcome (Bellomo 2015). Antiarrhytmic drugs are utilized to treat VF and pulseless VT, in situations, where these rhythms persist after attempted shock deliveries (Soar 2018) However, none of the suggested and studied ALS drugs (adrenaline, lidocaine, vasopressin or amiodarone) has evidence that their use during resuscitation leads to improved short-termed survival, survival to discharge or improved neurological outcome (Olasveengen 2009, Olasveengen 2012, Nolan 2013, Ali 2018, Soar 2018). Moreover, in a placebo-controlled trial, neither amiodarone nor lidocaine resulted in a significantly higher rate of survival than the rate with placebo among patients with OHCA (Kudenchuk 2016). In the latest European Resuscitation Council guidelines for resuscitation, there is absent confidence to support any prophylactic antiarrhytmic agents immediately after resuscitation. A weak recommendation is given to use of amiodarone or lidocaine after five unsuccessful defibrillation attempts (Soar 2019).

2.2 Post cardiac arrest organoprotection

2.2.1 Mild therapeutic hypothermia (MTH)

Because cardiac arrest is not a predictable emergency, organoprotective actions must act, when initiated after CPR or ROSC (Rittenberger 2013). Contemporarily, the only approved cardio- and neuroprotective strategy after cardiac arrest is mild therapeutic hypothermia (MTH). MTH involves intentional controlled lowering of a patient's core temperature in an attempt to reduce ischaemia-mediated and reperfusion-mediated organ injury (Moore 2011, Girotra 2015). Lately, in 2011, five international critical care societies advocated the term MTH to be replaced with targeted temperature management (TTM) (Nunnally 2011). The beneficial effects of TTM include several mechanisms.

Firstly, hypothermia reduces the metabolic rate for oxygen by 6–10 % for every 1 °C temperature reduction (Small 1999). During hypothermia oxygen demand decreases, and as oxygen supply is interrupted or limited, cooling brings it closer to actual oxygen delivery capacity while simultaneously decreased net ATP consumption maintains acceptable high-energy ATP stores (Erecinska 2003). This was formerly considered the sole mechanism of hypothermia-based neurological protection (Polderman 2008).

Secondly, there are various other mechanisms explaining the protective effects of hypothermia: hypothermia diminishes oxygen and glucose consumption and counteracts the problems associated with reperfusion and re-oxygenation

(Polderman 2009). This contains protection of lipid membrane fluidity and inhibition of lipid peroxidation, which restores membrane integrity and prevents swelling of the post-anoxic tissue (Holzer 2005a). Nitric oxide and protein kinase C generation as well as calcium homeostasis is restored. On the other hand, proinflammatory signaling, cell destructing enzymatic processes and apoptotic pathways are inhibited. Hypothermia prevents additionally the progressive development of vascular permeability disorders and reduces postischaemic brain oedema. Moreover, therapeutic hypothermia provides cardio- and neuroprotection by increasing tissue tolerance to ischaemia and hinders the reperfusion injury - generated development of inflammatory cascade and reactive oxygen species (ROS) production (Moore 2011). However, TTM plays a dual role, as it is likely to promote infection and it impairs both usual infectious criteria and host defences (Mongardon 2011).

In regard of myocardial reperfusion injury, every 1 °C decrease in body temperature results in a 10 % reduction in myocardial infarct size, demonstrated in experimental studies in rabbits (Chien 1994).

Practically, induced hypothermia is considered a relatively simple and inexpensive intervention to deploy, which does not require substantial increase of resources (Holzer 2005b). In a meta-analysis of eleven studies exploring the impact of hypothermia following cardiac arrest, the use of TTM after OHCA was associated with improved survival and neuroprotection. This was consistent also in patients with non-shockable rhythms, more indulgent downtimes, unwitnessed arrest and/or persistent shock (Schenone 2016). However, early initiation of TTM is indisputable, as each 1-hour delay in initiation of TTM resulted in 20 % increase of mortality in a meta-analysis of human OHCA studies (Mooney 2011).

2.2.2 Historical considerations

The history of intentional manipulation of body temperature for treatment of a disease or mitigation of its symptoms is ancient, as already e.g. Hippocratic school on Cos (500 BC) recommended induced local hypothermia with cold water, ice or snow to seriously injured parts of the body to reduce blood loss or to gouty swellings, sprains, fractures, haemorrhages, tetanus or febrile convulsions (Adams 1929). However, due to the high risk of complications, the use of medical hypothermia was scarce during the following centuries and millennia.

Use of hypothermia in modern clinical medicine is only 200 years old. Russian doctors described in 1803 a surmised approach to cardiac arrest resuscitation, which consisted of covering the patient with snow in desperate hope to gain return of spontaneous circulation (Varon 2008). Contemporarily, the chief surgeon to Napoleon Bonaparte's Imperial Guard, baron Dominique-Jean Larrey, realized,

that the wounded infantrymen, who were adjacent to campfire, had greater morbidity and mortality than those, who were located remote from the warmth. Larrey utilized induced hypothermia also in (pre-anaesthesia era) amputations (Larrey 1817, Remba 2010).

Early studies on hypothermia demonstrated, that cooling exhibits a "cold narcosis" in the central nervous system, equivalent to hibernation, which was entirely reversible (Britton 1930). First clinical reports on the anaesthetic properties of therapeutic hypothermia were presented in the Third International Cancer Congress in 1939, contemplating mainly intentional human refrigeration after traumatic and infectious brain lesions and anecdotally on cancer patients in an attempt to prevent cancer cells from further multiplying at reduced temperatures (Fay 1940, Fay 1959). However, atrocious inhumane hypothermia experiments in Nazi concentration camps declined the interest in further hypothermia research for decades (Wang 2006).

Bigelow and McBirnie demonstrated in 1953, that therapeutic hypothermia reduced the myocardial and brain injury during cardiac surgery in a canine and monkey model (Bigelow 1953). In 1954, Rosomoff and Holaday showed, that in a canine model, the cerebral blood flow decreased 6,7 % per degree decline of temperature during induced hypothermia resulting in reduced brain volume and metabolic rate (Rosomoff 1954). The first clinical trial of therapeutic hypothermia in cardiac arrest patients was published in 1959. Of the 19 patients, who had cardiac arrest during surgery, 12 were cooled to 30–32 °C and hypothermia maintained for 24–72 hours. 7 of the 12 patients cooled survived without major neurological deficits compared to only 1 of 7 patients in the control group (Benson 1959). These pioneering experimental studies demonstrated the effect of long-lasting neuroprotection by cooling during and after severe hypoxemia. However, the main clinical issue was and is, how to affect hypoxemic injury after resuscitation from asphyxial or circulation standstill injuries, when the injury was in escalation (Gunn 2006). Resuscitative mild hypothermia after successful resuscitation from cardiac arrest was advocated by Peter Safar already in 1964 in his ABC of post cardiac arrest care (Safar 1964).

Since the 1950's, induced intraoperative moderate and deep hypothermia was utilized in specific surgical procedures (Dripps 1956). In 1958, extracorporeal cooling with a pump oxygenator was successfully used in open-heart surgery (Sealy 1958). This pioneering work of hypothermia for neuroprotection during cardiovascular and neurosurgical procedures was, however, again abandoned because of injurious systemic effects and significant side effects, including cardiac irritability, pneumonia and cumbersome management problems associated with deep hypothermia, which made hypothermia hazardous (De Guzman 1963). Hypothermia affects immune response and pneumonia and other infections were

incessant. Life-threatening arrhythmias were frequent in deep (below 28 °C) hypothermia (Varon 2012). Hypothermia-induced coagulopathy and electrolyte disorders were common, as well as hypothermia -induced electrolyte shifts and tubular dysfunction, leading to increased diuresis and subsequent loss of electrolytes (Wang 2006).

In the 1980's, Safar's group rekindled therapeutic hypothermia research in a canine model of cardiac arrest (Brader 1985). Hypothermia after prolonged cardiac arrest was discovered to be beneficial illustrated both as recovered brain function and mitigated histological findings. Even mild hypothermia was demonstrated to confer dramatic neuro- and cardioprotection in numerous experimental models in different sized animals; rats, gerbils, rabbits and human-sized (60–80 kg) pigs (Dae 2002). In the interim, small clinical trials in comatose patients following cardiac arrest demonstrated improved outcomes with hypothermia when compared to historical controls (Zeiner 2000).

2.2.3 Targeted temperature management (TTM)

In 2002, two prospective controlled randomized clinical trials were published in the same February issue of New England Journal of Medicine illustrating that intentional lowering of body temperature to 33 °C improved neurological outcome and salvaged lives in comatose survivors of OHCA.

Holzer and colleagues in Europe and Bernard and co-workers in Australia conducted these trials. The European trial was organized in conjunction with nine centers in five European countries. A total of 275 patients with OHCA secondary to ventricular fibrillation were enrolled, 137 randomized to mild hypothermia (bladder temperature 32–34 °C) for 24 h and 138 patients randomized to normothermic controls, which at that time allowed also uncontrolled fever. The hypothermia group was cooled with an external cooling device (circulating cold air in a cooling tent) and if needed, with external ice packs, to maintain the target core temperature. The primary outcome was favourable neurological outcome within 6 months, defined as either a Pittsburgh Cerebral Performance Category (CPC) 1 (good recovery) or 2 (moderate cerebral disability). Secondary end points were mortality at 6 months and rate of adverse effects during the first 7 days following cardiac arrest. The hypothermia group had a favourable outcome in 55 % of patients and normothermia group in 39 % ($p = 0.009$) (Holzer 2002).

The Australian therapeutic hypothermia trial was a quasi-randomized (assignment was based on the parity of the day of the month) study with four participating Melbourne emergency departments and without blinded outcomes or treatment. A total of 77 OHCA patients, all presenting an initial rhythm of ventricular fibrillation, were enrolled. 43 patients were assigned to hypothermia,

which was initiated in the ambulance and continued on hospital admission using cold packs on the head, neck, torso and limbs; the target pulmonary artery temperature was 33 °C, which was maintained for 12 h following hospital admission. To the normothermic group, 34 patients were assigned. A favourable neurological outcome was obtained nearly twice as often in the hypothermia group (49 % of patients) as opposed to the normothermia group (26 % of patients, $p = 0.046$) (Bernard 2002).

The intensive care community then very rapidly adopted mild therapeutic hypothermia (MTH) therapy in cardiac arrest survivors. In the beginning of 2003, the International Liaison Committee on Resuscitation (ILCOR) published a special report recommending that all patients who achieved ROSC following a VF-generated OHCA should be cooled as quickly as possible. Hypothermia was additionally considered beneficial in arrests from non-shockable (asystole, PEA) arrests (Nolan 2003). In Turku University Hospital, first OHCA patient was cooled in July 2003. In 2005, these recommendations were reviewed and re-endorsed by the American Heart Association (AHA class I recommendation) (ECC Committee, Subcommittees and Task Forces of the American Heart Association 2005) and European Resuscitation Council of the European Society of Cardiology (Nolan 2005a).

MTH gained widespread use and became the standard-of-care in unconscious survivors of OHCA. Nevertheless, using MTH in patients without shockable rhythms remained controversial, as the results from numerous trials remained contradictory (Testori 2011, Dumas 2011). None of the trials have, however, demonstrated any survival benefit with MTH in in-hospital cardiac arrests (IHCA). On the contrary, a recent large cohort study of 26183 IHCA patients, of whom only 6 % were treated with MTH, indicated, that MTH was associated with lower in-hospital survival and lower rates of favourable neurological survival (Chan 2016).

The seminal 2002 trials were also criticized about some major limitations: low number of enrolled patients, quasi-randomization in the Australian trial, inclusion of highly select population of patients (based on inclusion/exclusion criteria, 92 % of patients were excluded) and the care personnel were not blinded to the treatment arm. Ultimately, in both studies, failure to treat hyperthermia in the control group, or control for it did not produce uniform control group. Furthermore, both trials reported the intention-to-treat population, which resulted in study patients, who did not get hypothermic, to be also included in the hypothermia group. The Australian trial used hospital discharge destination as a proxy for neurological outcome, depicting home as a good outcome and all other options (rehabilitation or long-term care facility or death) as a poor outcome. This assumption of decision to home discharge corresponding solely functional neurological status did not consider any other sosio-economic and family factors influencing placement (Little 2014). In a

systematic review using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (Schünemann 2003) and trial sequential analysis it was demonstrated that the quality of evidence for hypothermia treatment in cardiac arrest patients to 33 °C was actually very low. In effect, it was ambiquous whether acknowledged treatment benefit was due to hypothermia or simply, to the prevention of fever (Nielsen 2011b).

To confirm or refute the existing guidelines, a new trial was designed and launched, randomizing OHCA patients to two controlled temperatures, 33 and 36 °C (Nielsen 2012). The Target Temperature Management after Out-of-hospital Cardiac Arrest trial (TTM-trial) included and randomized, in 32 study sites across Europe and Australia, 950 OHCA patients, which was more than twice the amount of patients from the previous trials combined. The principal differences in TTM trial in comparison to the 2002 trials were: firstly and most importantly, every single patient received controlled temperature management preventing fever in both study groups. Secondly, the overall care was contemporary; with attention to modern intensive care including improved pre-hospital care with high bystander CPR rate, and improved hospital care with adherence to modern post cardiac arrest care recommendations. As an example, 62–63 % of patients in both groups were subjected to an early (within 24h) coronary angiography with subsequent PCI if indicated (44 %). Additionally, in contrast to the former trials, the design, the statistical analysis plan and very importantly, the prognostication protocol for withdrawal of life-sustaining treatment were transparently published in advance (Nielsen 2012).

The study found no difference in in-hospital mortality (50 % vs. 48 %, $p = 0.51$) or survival with favourable neurological outcome at 6 months (13 % vs. 19 %, $p= 0.02$). These results reinforced the importance of controlled temperature at either of the two studied temperatures including active and simultaneous careful prevention of fever for 72 hours after OHCA without any reinforcement to dissuade hypothermia treatment *per se* (Nielsen 2013).

The intensive care community again reacted absurdly speedily: after publication of TTM-trial in December 2013, the use of MTH dropped in a US retrospective registry cohort of 45935 OHCA patients from 52.5 % (2013) to 46.0 % (2016). Concurrently, the overall risk-adjusted patient survival declined from 36.9 % to 34.3 %. This reflected a change in practice rather than a change in patient population (VF incidence declining, PEA/ASY increasing) (Bradley 2018). This alarming trend had also other explanations than allowing a more lenient temperature control after OHCA. In an Australian and New Zealand retrospective cohort study (from January 2005 to December 2016) with greater than 2 million post-OHCA ICU admissions, it was demonstrated, that after discharging MTH, also applying TTM was reduced, allowing post-OHCA patients to practically, have

hyperthermia, which was not seen in TTM-trial (Salter 2018). Hyperthermia is associated with increased mortality in OHCA patients (Zeiner 2001). This does not translate to that hyperthermia causes mortality, and conventional isolated fever treatment with e.g. scheduled administration of paracetamol has not been investigated in comparison with any cooling strategies (Bradley 2018). However, no modification in applying TTM was reported in an European survey (from May 2014 to January 2015) of 264 ICUs in 11 countries (Deye 2016). The Ilcor 2015 guidelines recommended TTM for adults with OHCA with initially shockable rhythm at constant temperature between 32 and 36 °C for at least 24 h (Donnino 2016).

2.2.4 Anaesthesia and adverse effects during targeted temperature management

Adequate sedation will reduce oxygen consumption, which is further reduced with therapeutic hypothermia. Both analgetics (opioids) and hypnotics (e.g. propofol or midazolam) are required (Elmer 2017). Sedative agents, which cause vasodilatation, such as propofol, commonly generate the need for vasoactive supportive medication, mainly noradrenaline. In haemodynamically stable patients, propofol is effective for insuring adequate sedation, and its short half-life allows eventually meaningful serial neurologic examinations, when the sedation ultimately is terminated. In patients without significant bradycardia, dexmedetomidine, which directly reduces the shivering threshold via central α-2 agonism, can alternatively be used (Callaway 2015). MTH affects cardiac conductance and induces electrocardiographic (ECG) changes, namely bradycardia and prolongation of PR- and QT_c -intervals. The risk for serious arrhythmias is still low despite the significant ECG changes (Lebiedz 2012).

Shivering is a common consequence of therapeutic hypothermia, particularly in the induction phase. It may increase the metabolic rate, oxygen consumption, work of breathing, heart rate and myocardial oxygen consumption, all unwanted factors exacerbating postischaemic injury. Shivering propagates acidosis and increases sympathetic discharge (Moore 2011, Nunnally 2011). Adequate sedation may enhance vasodilatation, which promotes heat loss and possibly suppresses the unfavourable effects of shivering and target temperature is achieved earlier (Sessler 2009). If shivering occurs despite deep sedation, neuromuscular blocking agents (as an intravenous bolus or continuous infusion) could be used. Naturally, patients require airway protection and assisted mechanical ventilation. During neuromuscular blockade convulsive activity is obscured, which can delay the diagnosis of early posthypoxic myoclonus and appropriate anticonvulsive therapy (Moore 2011, Elmer 2017).

Shivering response can be reduced also with the use of skin counter-warming, i.e. warming of the non-cooled areas of skin (Badjatia 2009). Lastly and importantly, hypothermia decreases most enzyme-based reactions prolonging half-life of drugs, such as sedatives and anaelgesic agents (e.g. bentzodiazepams, midazolam, fentanyl). At 34 °C, the clearance of sedative and paralytic agents is reduced by up to 30 % (Tortorici 2007). Additionally, some patients may have altered renal and hepatic function, which may affect drug clearance (Ben-Hamouda 2014). This should be carefully considered in prognostication, which should not take place earlier than 72 hours after rewarming and discontinuation of sedation (Elmer 2017).

Mild hypothermia increases peripheral systemic vascular resistance, which reduces cardiac output. Simultaneously, heart rate is reduced and contractility is increased, which is believed to be due to increased calcium concentration in cardiomyocytes (Nunnally 2011). However, the inotropic effect is observed only in bradycardia and not in higher heart rates. Bradycardia is an expected physiologic consequence, which is common during hypothermia. Unless associated with hypotension, a heart rate of 34 to 40 beats per minute is an acceptable goal at the target temperature (Polderman 2009). In two recent studies, bradycardia during hypothermia was independently associated with lower mortality and improved neurological outcome (Stær-Jensen 2015, Thomsen 2016). The effects of hypothermia on the myocardium and its contractility directly depend on the patient's volume status and adequacy of sedation.

During induction of hypothermia initial urine output ("cold diuresis") increases following peripheral vessel constriction and increase in venous return, resulting in changes in renal perfusion and to a failure of reabsorbtion of sodium in distal tubules, translating to constrained water wasting (Varon 2010, Moore 2011). Coexisting hypovolemia will compound haemodynamic instability. Hypothermia-induced tubular dysfunction and intracellular electrolyte shift potentially produces arrhythmia –generating electrolyte abnormalities, including hypophosphataemia, hypokalaemia, hypomagnesaemia and hypocalcaemia, in aggregate significant derangements in electrolyte and water homeostasis (Moore 2011, Nunnally 2011). However, vigorous repletion of hypokalaemia is discouraged, since serum potassium levels will predictably increase after rewarming (Elmer 2017).

Slow rewarming not faster than 0,5 °C per hour in order to prevent temperature overshoot is recommended (Bernard 2003). Most patients may develop hyperthermia after rewarming, and continuing targeted temperature management to prevent fever after rewarming has been advocated (Varon 2012).

As hypothermia can impair the immune system and suppresses the host's pro-inflammatory response, the risk for infections, particularly pneumonia is potentially increased. This is exacerbated by the concomitant use of invasive

catheters, cooling devices and assisted ventilation, which break natural barriers of intact skin and mucous membranes (Kuchena 2014). In the HACA study, pneumonia was more common in the cooled group, but this difference was not statistically significant (Holzer 2002). Neither has increased rate of pneumonia nor bacteremia during temperature management been demonstrated to impact mortality or neurological recovery (Kuchena 2014).

Post cardiac arrest circumstances result in a prothrombotic state. A marked increase in thrombin-antithrombin complexes is prevailing, which originates from exposed tissue factor after endothelial damage and *"endotheliitis"* (Callaway 2012). However, counteracting effects on platelet and clotting function by hypothermia include mild platelet dysfunction at 33–35 °C and reduction in platelet count. Clotting factors are affected at temperatures below 33 °C (Moore 2011). Bleeding related to therapeutic hypothermia has not been identified as a clinical problem (Lebiedz 2012). The bleeding risk is, however, multiplied, if coronary angiography with or without PCI was performed. This associates with the use of heparin and antithrombotic platelet inhibitors during and after invasive procedures (Nielsen 2009).

Hypothermia decreases insulin levels secondary to catecholamine release. Peripheral insulin sensitivity is reduced and insulin secretion is altered, which results in hyperglycaemia also in non-diabetic patients. This is exacerbated by the release of stress hormones, which induce insulin resistance ("critical illness hyperglycaemia") (Nunnally 2011). Additionally, deep sedation and hypothermia is linked with delayed gastric emptying and reduced gut function (Bernard 2003).

Targeted temperature management at 36 °C is closer to normal temperatures and causes less shivering and other cooling-related adverse effects. Deep sedation and neuromuscular blocking agents are not required as frequently as in lower temperatures. In the TTM-trial, the number and severity of adverse events in the two intervention arms did not differ, although there was a tendency towards less events in the 36 °C – arm ($p = 0.086$) (Nielsen 2013).

2.2.5 Percutaneous coronary intervention after cardiac arrest

Randomized trials advocate early coronary angiography and immediate, complete and sustained revascularization with PCI in STEMI and also in NSTEMI patients (Javat 2017). However, specific evidence of PCI in cardiac arrest patients has been contradictory, since many of these patients have been excluded from randomized trials of early revascularization due to limitations of post-arrest electro-cardiography-based diagnosis, unclear neurological recovery and high risk of mortality (Jobs 2017). Early coronary angiography in OHCA patients also with

NSTEMI is feasible, and associated with improved survival to hospital discharge, although the benefit is inconsistent (Hollenbeck 2014, Vyas 2015, Jobs 2017). It is likely, that early coronary angiography is selectively offered to patients with good prognosis for neurological recovery and omitted, if the outcome is prognosticated poor (Jaeger 2018). Post-arrest electrocardiogram (ECG) can be misleading: in a Norwegian study, 1 out of 7 postresuscitated survivors presenting with NSTEMI had surprisingly an acutely occluded coronary artery. Furthermore, 31 % of patients with VF/VT had an occluded coronary, but also in the patients with initial rhythm of PEA or asystole, 22 % had additionally an acute coronary occlusion (Stær-Jensen 2015).

In a recent large French registry study, early invasive strategy was independently associated with improved survival in low-risk patients and coronary angiogram after OHCA was recommended in patients with presumed favourable neurological outcome according to risk score calculations. The authors acknowledged the risk of selection bias (Bougouin 2018). In another French registry and cohort analysis of 63394 OHCA patients, both the survival and favourable neurological recovery were significantly higher in the patients, who underwent an immediate coronary angiogram after resuscitation. However, the major determinant of favourable outcome was, whether coronary revascularition with PCI was performed (Jaeger 2018). The consensus statement by European Association for Percutaneous Cardiovascular Interventions/Stent for Life groups advocated an immediate coronary angiography and subsequent revascularization in comatose OHCA patients with STEMI. In the absence of non-coronary cause, and given the high incidence of acute coronary syndrome in patients with OHCA, the committee finds it appropriate to consider immediate coronary angiography also in NSTEMI arrests (Noc 2014).

Recent study demonstrated, that an early coronary angiogram may be associated with improved short and long term survival in NSTEMI patients with initial shockable rhythm, whose CA was bystander –witnessed. These factors, however, are otherwise associated with improved outcome on their own (Elfwén 2018). Unfavourable resuscitation circumstances, which suggest refraining from early coronary angiogram, include unwitnessed arrest, non-shockable rhythm, lack of bystander CPR, extended (> 30 min) time to ROSC, ongoing CPR, end stage renal disease and severe lactic acidosis (pH < 7,2; lactate > 7 mmol/l) (Rab 2015). In a recent meta-analysis on NSTEMI patients undergoing coronary angiogram following OHCA, one third of patients presented an acute lesion necessitating emergent PCI (Millin 2016). In a prospective registry trial, early coronary angiogram (within 24 hours) following OHCA improved survival (56,2 vs. 31 %) and functional outcome, but only early PCI was associated with significant survival benefit (Jentzer 2018).

Very recently, it was demonstrated in 522 OHCA patients without STEMI, that immediate or delayed (until neurological recovery) coronary angiography resulted in comparable, nonsignificantly different overall survival at 90 days (Lemkes 2019). However, unstable and clinically significant acute coronary lesions were present in less than 20 % of the total study population and revascularizing coronary interventions were performed in less than 40 % of patients, which translates to that only minor part of the trial population was affected by the timing of coronary angiography. Intimidately, an early coronary angiography without absolute indication for performing it, can potentionally delay inception of targeted temperature management (Abella 2019, Lemkes 2019). Similarly, the potentially devastative neurologic injury leading to imminent premature death should be considered before executing excessive revascularization therapies (Ragosta 2018).

2.2.6 Subsequent post cardiac arrest care

2.2.6.1 Ventilation and tissue oxygenation

Temperature management and early coronary angiography are not the only parts of post-resuscitation care following cardiac arrest and patients need additionally intensive monitoring and advanced critical care. Firstly, optimizing ventilation, adequate arterial oxyhemoglobin provision and reversal of tissue hypoxia is addressed (Neumar 2011). During resuscitation, the fraction of inhaled oxygen is recommended to be 100 % (Spindelboeck 2013). Under-arrest hypoxemia portends lower survival, which is associated with the urge of resumption of ATP synthesis through oxidative phosphorylation (Neumar 2011, Spindelboeck 2016). However, after ROSC, post arrest hyperoxemia should be avoided because it potentially exacerbates injurious mechanisms involved in the burst of reactive oxygen species (ROS) generation. Controlled ventilation-induced hyperventilation and ensuing hypocapnia associates with cerebral vasoconstriction and worse outcome (Buunk 1996, Cokkinos 2009, Kilgannon 2010, Neumar 2011, Chu 2018, Skrifvars 2019). Metabolic lactic acidosis is common, and represents a biomarker of the CPR duration and reflects hypoperfusion originating from cardiogenic shock. Mild hypercapnia following resuscitation within the OHCA survivors may increase the likelihood of discharge from hospital (Eastwood 2014). Controlled re-oxygenation after ROSC with normoventilation and the lowest level of inspired oxygen concentration required to an arterial oxygen saturation target of 94–96 % results in better neurological outcome (Neumar 2011, Soar 2015). Cerebral autoregulation can be impaired after cardiac arrest, but the cerebrovascular reactivity to changes in arterial carbon dioxide ($PaCO_2$) is usually preserved (Neumar 2008).

2.2.6.2 Haemodynamic impairment

Secondly, after hospital admission, many cardiac arrest survivors develop systemic haemodynamic impairment, which is associated with global ischaemia-reperfusion injury leading to myocardial stunning (Laurent 2002). When compared to historical controls, a proactive therapeutical protocol with early goal-directed haemodynamic optimization improved survival in hypothermia treated OHCA victims (Gaieski 2009). Circulatory support is required to maintain adequate cardiac output, organ perfusion and systemic oxygen delivery. The optimal mean arterial pressure (MAP) for post-arrest patients has not been defined by prospective clinical trials. Management guidelines reflect early goal directed therapy, which has been studied in randomized prospective clinical trials with patients with severe sepsis (Rivers 2001). However, the optimal targets and strategies to achieve these targets potentially differ in PCAS, given the concomitant presence of post arrest cerebral injury, myocardial dysfunction and persistent precipitating arrest causes (Neumar 2008).

Cerebral perfusion pressure (CPP) is predominantly dependent of MAP, as elevated intracranial pressure (ICP) during the early post-cardiac arrest phase is uncommon (CPP = MAP – ICP). Good neurological outcomes have been reported from published studies in which the MAP target was as low as 65 to 75 mmHg (Sunde 2007). Inotropic (e.g. dobutamine) and vasoactive medication (e.g. noradrenaline) should be considered if haemodynamic goals, target blood pressure, cardiac output and systemic perfusion, are not achieved despite optimized preload.

Post cardiac arrest global myocardial dysfunction is generally reversible and responsive to inotropes. No individual drug or combination of drugs has been demonstrated to be superior in the treatment of post-cardiac arrest cardiovascular dysfunction (Neumar 2008). In a retrospective study, 168 OHCA patients undergoing MTH were analyzed in respect of mean arterial pressure (MAP), vasoactive agent requirements and outcome. Higher MAP was associated with improved outcome, but requirement of vasoactive medication was associated with mortality and poor neurological outcomes (Beylin 2013). In a Finnish trial, the effect of low-normal and high-normal MAP was compared in respect of brain injury biochemical marker (neuron specific enolase (NSE)) release at 48 hours post arrest. Targeted MAP during post-resuscitation care was feasible, but it did not affect NSE concentrations or any secondary outcomes (Jakkula 2018a). The same study group assessed also the effect of different arterial carbon dioxide and oxygen concentrations in OHCA patients. The low-normal and high-normal concentrations of arterial carbon dioxide or oxygen concentrations did not affect NSE at 48 hours (Jakkula 2018b).

2.2.6.3 Metabolic impairment

Thirdly, the post-cardiac arrest patient is likely to acquire metabolic abnormalities such as hyperglycaemia. Blood glucose concentrations need to be monitored frequently and hyperglycaemia treated with insulin infusion. Very tight glucose control is no longer advocated as the outcome benefit has not been re-established since the original trial in surgical ICU-patients (Van den Berghe 2001). In a randomized trial of 90 comatose survivors of ventricular fibrillation-generated OHCA, 2 glucose target groups were compared: a strict (4 to 6 mmol/l) glucose control group and a moderate (6 to 8 mmol/l) glucose control group. No difference in day 30 mortality was demonstrated. There were either no episodes of severe (< 2.2 mmol/l) hypoglycaemia, which in previous trials has been connected to worse outcomes (Oksanen 2007). Current recommendation for glucose target after OHCA resuscitation is below 10 mmol/l with concomitant avoidance of hypoglycaemia (Nolan 2015).

2.2.6.4 Seizures and status myoclonus

Fourthly, post cardiac arrest brain injury frequently involves seizures, myoclonus or both in 5 to 15% of patients achieving ROSC and 10 to 40 % in those who remain comatose (Cokkinos 2009, Dragancea 2015). Post cardiac arrest seizures can present particularly refractory to traditional antiepileptic therapy. However, during hypothermia, routinely administered sedatives, such as propofol, are effective to control myoclonus (Wijdicks 2002). Furthermore, clinical seizures are potentially masked and suppressed by temperature management, sedation and in particular by neuromuscular blocking agents (Hovland 2006, Bouwes 2012, Rittenberger 2012).

Prolonged, untreated seizures are detrimental in post anoxic brain injury as they inflict cerebral metabolic rate by up to 3-fold, which exacerbates the ongoing injury through excitotoxicity and enhanced metabolic stress (Ingvar 1986, Fujikawa 2005). Post arrest electroencephalography (EEG) is generally unequivocally pathologic reflecting varying extents of hypoxic ischaemic brain injury (Cloostermans 2012). It is ambiguous, whether electrographic status epilepticus is simply the electrographic expression of severe brain injury or a truly modifiable condition (Ko 2011). Epileptic activity without clinical signs and symptoms (nonconvulsive status epilepticus) is frequently described. Intimidately, no general agreement on the definition of electroencephalographic status epilepticus after cardiac arrest exists (Backman 2017).

If electroencephalographic status epilepticus is surmised, current practice includes unstandardized, moderate treatment with anticonvulsant drugs. Although widely used, this does not apparently improve patients' outcome. Currently, there

is inadequate evidence to recommend any prophylactic pharmacological strategies post arrest to prevent seizures (Ruijter 2014).

Myoclonus and electrographic seizure activity, including status epilepticus, are associated with grave clinical prognosis; in prospective case series mortality has been 90–100 % (Hofmeijer 2014). However, it is still possible, that even 10 % of individual resuscitated patients with myoclonus may survive with good functional outcome (Seder 2015).

Extended observation without premature prognostication is warranted especially after treatment of seizures with sedative agents, given the prolonged clearance of these drugs during hypothermia (Samaniego 2011). The optimum duration for anticonvulsive therapy after OHCA is unknown, but it should not be extended beyond 2 weeks, if the patient fails to awake (Rossetti 2016).

2.2.6.5 Acute Kidney Injury

Fifthly, acute kidney injury (AKI) following OHCA is common, ranging from 12 to 40 % of patients. The most used and validated consensus definition and method of classifying AKI is the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification system (Bellomo 2004). Severe AKI (RIFLE class I/F) is usually associated with post-resuscitation cardiogenic shock (PRCS). Other acknowledged independent risk factors for AKI include higher cumulative dose of noradrenaline during the first 24 hours in ICU (reflecting PRCS), previous use of blockers of renin-angiotensin-aldosterone system and higher baseline creatinine levels (Chua 2012). AKI is commonly transient and hypothermia does not increase the need for renal replacement therapy (Knafelj 2007). In another recent study, extension of hypothermia treatment at 33 °C to 48 hours did not increase renal failure when compared to hypothermia for 24 hours (Kierkegaard 2017). Usually renal function returns to normal by 28 days (Zeiner 2004).

2.3 Xenon

In 1898, British chemist Sir William Ramsay and his student Dr Morris Travers found unknown residue of evaporating components of liquid air and discovered xenon, a noble gas with the lowest concentration in air. The noble gases helium, neon, argon, krypton, xenon and radon stand at the far right in the periodic table and are colourless, tasteless and odourless monoatomic gases that are characterized by a fully occupied (complete octet, except helium) outer atomic shell of electrons, making them inert or at least less capable of interaction with other biological

compounds. At the first sight, this inertness might cause an assumption that these gases are unreactive and would not exert any biological activity (Preckel 2006).

However, the research of physiological effects under hyperbaric conditions and deep-sea diving provided evidence on the biological effects of inert gases. In 1939, US Navy captain, medical doctor Albert Behnke Jr. published observations in deep-sea divers using various breathing mixtures, including xenon, in his studies of exploring the "stupefaction" and "mental fogginess" during deep dives. He anticipated, that gases other than nitrogen could also facilitate narcosis (Behnke 1939). Nitrogen narcosis is common when diving below 30 meters seawater, corresponding to fourfold ambient pressure (4 ATA). In this environment and with breathing compressed air (21 % oxygen, 78 % nitrogen), the nitrogen partial pressure increases and can facilitate a narcosis. If the diver goes deeper, the increased nitrogen partial pressure may eventually cause loss of consciousness. To avoid nitrogen narcosis and make deeper dives possible, nitrogen was replaced with other gases in the breathing mixture (Behnke 1938). This led to the discovery that noble gases had a potential to produce anaesthesia, which was initially deduced, when Behnke and Yarbrough reported the development of progressive narcosis in divers exposed to xenon, argon or krypton in 20 % oxygen under hyperbaric conditions (Behnke 1939). Xenon was predicted to be anaesthetic at atmospheric pressures, based on its low relative solubility in fat compared to argon, krypton and nitrogen. Lawrence and co-workers corroborated the anaesthetic properties of Xenon in mice (Lawrence 1946). Eventually, Cullen and Gross reported in 1951 the first clinical xenon anaesthesias, performed on two voluntary patients undergoing orchiectomy or ligation of the fallopian tubes (Cullen 1951).

Xenon was approved for anaesthesia in Russian Federation in the year 2002, authorized in Germany in 2005 and the approval for the usage of xenon as an anaesthetic agent was extended to all Western Europe in 2007. To date, however, marketing authorization for xenon use as an anaesthetic in North America by the US Food and Drug Administration is still in progress and not yet warranted (Maze 2016).

The assumption of xenon's putative role in neuroprotection was associated with the discovery of xenon's molecular sites of anaesthetic action. Xenon was identified as an inhibitor of N-methyl-d-aspartate (NMDA) subtype of glutamate receptor (Franks 1998). NMDA receptor plays a major role in controlling synaptic plasticity and memory function (Winkler 2016). However, overexcitation of NMDA receptor is involved in various conditions of neuronal injury, which prompted the idea and investigation of xenon's use as a neuroprotective agent (Franks 1998). Overactivation of NMDA receptor appears to be crucial to the initiation of neuronal injury and cell death from various pathological conditions such as ischaemia and brain injury (Wilhelm 2002). In cultured hippocampal

neurons xenon inhibited NMDA-evoked currents by 60 % in a xenon concentration of 80 %, which is beyond sufficient to maintain anaesthesia. The inhibition was similar at micro-island cultures of glutamatergic hippocampal synapses, but in this study xenon had no effect on synaptic "non-NMDA" AMPA/kainate receptors (Franks 1998). However, recent evidence suggests, that all glutamatergic receptors, NMDA, AMPA and kainate are inhibited by xenon. NMDA and AMPA inhibition could both contribute to xenon's putative neuroprotective effect (Hasaneder 2009). The pre-synaptic effects of xenon must be minimal, consistent with the observation that several voltage-gated ion channels in cardiac tissue are unaffected by clinically relevant concentrations of xenon (Stowe 2000). Unlike most general anaesthetics (e.g. isoflurane, sevoflurane, propofol, etomidate) xenon has little or no effect on inhibitory $GABA_A$ receptors. The specifity of xenon for the NMDA-mediated component together with the lack of effect at the inhibitory GABAergic synapses imply that xenon acts postsynaptically (de Sousa 2000, Dickinson 2010).

In 2000, Preckel and co-workers provided first evidence that xenon exerts cardioprotective effects in a rabbit model of ischaemic myocardium (Preckel 2000). These protective effects by xenon in ischaemic myocardium and eventually, demonstrated also in ischaemic brain injury represent a post-conditioning effect, which is targeted to the ischaemia-reperfusion injury with a goal to restrict an ongoing injury (Smit 2015).

The evidence of synergistic organoprotection with simultaneous hypothermia and xenon inhalation was first confirmed in animal models of neonatal asphyxia and ischaemia (Ma 2005, Martin 2007, Hobbs 2008). This was corroborated in a randomized trial in a porcine model of cardiac arrest, which ostensively demonstrated the synergistic effects of these interventions as even a short exposure to xenon during induction of mild therapeutic hypothermia resulted in significant improvements in functional recovery and improved myocardial dysfunction (Fries 2012).

2.3.1 Chemical and physical characteristics

Xenon is the only noble gas, which is anaesthetic at normobaric and normothermic conditions. It is stable, non-flammable, nontoxic, non-irritant, non-explosive and does not maintain combustion. Xenon has no metabolites, active or inactive, under biologic conditions (Goto 1998). In contrast to other NMDA antagonists, such as ketamine and nitrous oxide N_2O, xenon does not produce psychotomimetic side effects (Ma 2002). The molecular weight of xenon is 131,2 Daltons, which makes it 3,2 times denser than air. The higher density makes the viscosity of xenon consequently 1,7 -fold greater than air. In effect, during xenon inhalation, airway resistance is expected to rise, especially if the airways are compromised. However,

it must be bourne in mind that the airway pressure measured at the circuit end of the tracheal tube in the breathing circuit may overestimate the airway pressure exerted within the bronchial tree (Schmidt 2009). Being chemically inert with fully occupied outer electron shell prevents covalent bonding and makes xenon molecule stable and non-reactive. However, in extreme nonbiologic conditions in laboratory environment, xenon can constitute for example oxides and halides. Interestingly, biological interactions can still occur through non-covalent van der Waals intermolecular forces. The monoatomic xenon molecule with a very large electron shell can be polarized and distorted by nearby molecules creating e.g. an induced dipole (Lynch 2000). This enables interaction with amphiphilic domains of surrounding molecules, such as human amino acids, enzymes, receptors and bilayered lipid membranes. This is the fundamental basis of xenon's biological effects (Trudell 1998). Xenon's ability to be polarized is greatest among other noble gases (Jawad 2009).

Xenon is currently produced by the same method of fractional distilling and purification of liquefied air, described by Ramsay and Travers. The majority of the produced xenon is used in space aeronautics or industry using it in car headlights and light bulbs. In medicine, the majority of consumed xenon is used up in imaging, as the radioactive isotope Xe^{133}. For anaesthesia, xenon is supplied in gas cylinders containing non-radioactive Xe^{131} (Arch 2011).

2.3.2 Xenon anaesthesia

Xenon anaesthesia is characterized by a very rapid onset and emergence (Nakata 1997). The rapidity with which patients emerge from xenon anaesthesia is remarkable compared with even propofol (Maze 2016b). The blood/gas partition coefficient, which describes the solubility of inhaled anaesthetics in blood, of xenon is lowest of all known anaesthetics (0.115), which results in a very fast induction (Goto 1998). In comparison with other current inhalational anaesthetics, the blood/gas coefficient is consistently higher than xenon, e.g. sevoflurane (0,65), desflurane (0,42) and nitrous oxide N_2O (0,47) (Steward 1973). Minimum Alveolar Concentration (MAC) is the median concentration required to produce anaesthetic effects – an inverse indicator of anaesthetic potency. The proposed original approximate of xenon MAC was 71 % (Cullen 1969). With contemporary techniques, xenon MAC is assumed to be 63 % (Nakata 2001). It should be acknowledged, that these MAC values were defined from studies in which halothane or sevoflurane was co-administered and xenon MAC was extrapolated by the lowering the MAC of the additional inhalation anaesthetic (Nakata 2001).

Furthermore, it is argued that there is a wide variability of xenon MAC between sexes, being 51 % in women and 69 % in men. In elderly patients, the

MAC value is, however, significantly even lower (Goto 2002). The implications of this high MAC include the limitation of the inhaled oxygen concentration delivered to the patient, especially in closed circuit ventilators. In some conditions it is difficult to maintain sufficient anaesthetic concentration of xenon, if it is utilized as the sole and single anaesthetic. To avoid hypoxemic gas mixtures, safe end-tidal oxygen concentration requires to be maintained over 30 %. Particularly in compromised oxygenation situations, such as pulmonary congestion or other parenchymal pulmonary disease, increased FiO_2 is required (Law 2016). Practically, xenon must be supplemented with other anaesthetic agents and techniques (Nakata 2009). When compared to other volatile anaesthetic regimens (N_2O, fluorinated alkans, hydro-chloro-fluorocarbons, alkyl ethers etc.), which are greenhouse gases with atmospheric lifetimes measured in years and involved in the depletion of ozone layer, xenon is occupationally and environmentally attractive, as it is a normal constituent of the atmosphere and not a greenhouse gas. However, xenon purification from air consumes plenty of energy, as production of one liter of xenon requires 1000 000 times more energy than for one liter of N_2O (Rossaint 2003).

2.3.2.1 Mechanism of action

Hypnotic drugs take action by activating inhibitory and/or blocking excitatory pathways (Franks 1994). To produce anaesthesia, a sufficient anaesthetic concentration has to be achieved at the site of action: the effect-site compartment (Hanne 2001). The three acknowledged anaesthetic molecular and ionic channel targets are γ–aminobuturic acid type A ($GABA_A$) receptor (etomidate, propopol, volatile agents), the glycine receptor (volatile agents) and the NMDA receptor (xenon, nitrous oxide, cyclopropane, ketamine) (Dickinson 2007).

When inhaled in concentrations exceeding 40 %, xenon causes an immediate loss of consciousness. Inhaled xenon is dissolved into blood in the alveoli and rapidly crosses the blood-brain barrier, exerting its anaesthetic effect by inhibiting excitatory glutamatergic signaling (Franks 1998, Nagele 2005).

Besides anaesthesia, xenon has been demonstrated to have anaelgesic properties, illustrated by diminished opioid expenditure during surgery (Lachmann 1990, Boomsma 1990, Nakata 1999). Xenon's antihyperaelgesic and anaelgesic potency may be related to NMDA antagonism, since other NMDA antagonists (ketamine, N_2O) have similar effects. The anaelgesic effect may be mediated by inhibition of NMDA receptors and nociceptive responsiveness in the dorsal horn of the spinal cord.

On the contrary to N_2O anaelgesia, however, xenon anaelgesia is not antagonized by naloxone, suggesting that the anaelgesic effects are not mediated by

opioid receptors (Yagi 1995). In a rodent model, xenon anaelgesia was not mediated via opioidergic or adrenergic receptor systems, which supports the assumption of a spinal mechanism of antinociception (Ohara 1997). Marx and co-workers demonstrated in a porcine model, that xenon prevented, without additional anaelgesia, haemodynamic reactions caused by nociceptive surgical stimulation. Additionally, there was a substantially lower plasma adrenaline concentration during xenon anaesthesia, not only in concentrations of about one MAC, but also at subanaesthetic concentrations of half and one-third of this amount. Their conclusion was, that xenon provides anaelgesic effects even in concentrations below its MAC (Marx 1997, Marx 1998).

2.3.2.2 Closed circuit ventilation

All noble gases exist in various concentrations within the atmosphere (ranging from 934000 ppm (0.934 %) for abundant argon to 0.0875 ppm (0.000 008 75) for very scarce xenon. For an illustrative example, a room of 50 m^3 contains 5 milliliters of xenon (Marx 2000). The purification and production cost of noble gases increases in proportion to their relative atmospheric rarity, and the laborious and costly technique of sequential cryogenic fractional distillation makes the scarcest of them expensive. In modern anaesthesia ventilators, the average amount of fresh gas required is usually 1 liter per minute. To economize the expenditure of an expensive gas, fully closed low-flow circuit ventilators are used. To simplify, the very same anaesthetic gas molecules are scavenged from exhalation and recycled within the system, which in effect reduces the gas expenditure after induction to 150 to 200 milliliters per minute. The consumption of xenon for inhalation anaesthesia induction or wash-in was demonstrated to be approximately 8 to 9 liters (Nakata 1997). The gas expenditure is highest during the first 15 minutes of anaesthesia; thereafter uptake reduces to 0.6 liters per every 15 minutes (Luttropp 1994). The major portion of total xenon consumption is the gas that remains in the anaesthesia machine after disconnection. Therefore, recycling devices have been constructed, using filters and cooling traps to remove other gases from the mixture. Marx and others have reported, that 67 % of the xenon with a purity of 89 % can be recycled and retrieved with this method (Marx 1996). In our study, the average expenditure of xenon inhalation for 24 hours was 56,3 liters, which corresponds within the average current price of 18 € per one liter of xenon to an average cost of 1013 € per single study patient xenon administration.

The fully closed-system ventilator used in our study was PhysioFlex™ (Dräger, Lübeck, Germany), where the circuit volume is about four liters (Hanne 2001). The ventilator has four membrane chambers, whose volume is constantly monitored (Baum 2005). There are no unidirectional valves in the ventilator. The anaesthetic

gas circulates within “the system” (i.e. patient airways, soluble in patient circulation and ventilator) at a rate of 70 liters per minute, driven by a blower. The volume and concentrations of oxygen, exhaled carbon dioxide (absorbed by filters) and anaesthetic gas (xenon) are continuously monitored. The concentration of oxygen is preselected as a target. Xenon anaesthesia maintaining requires

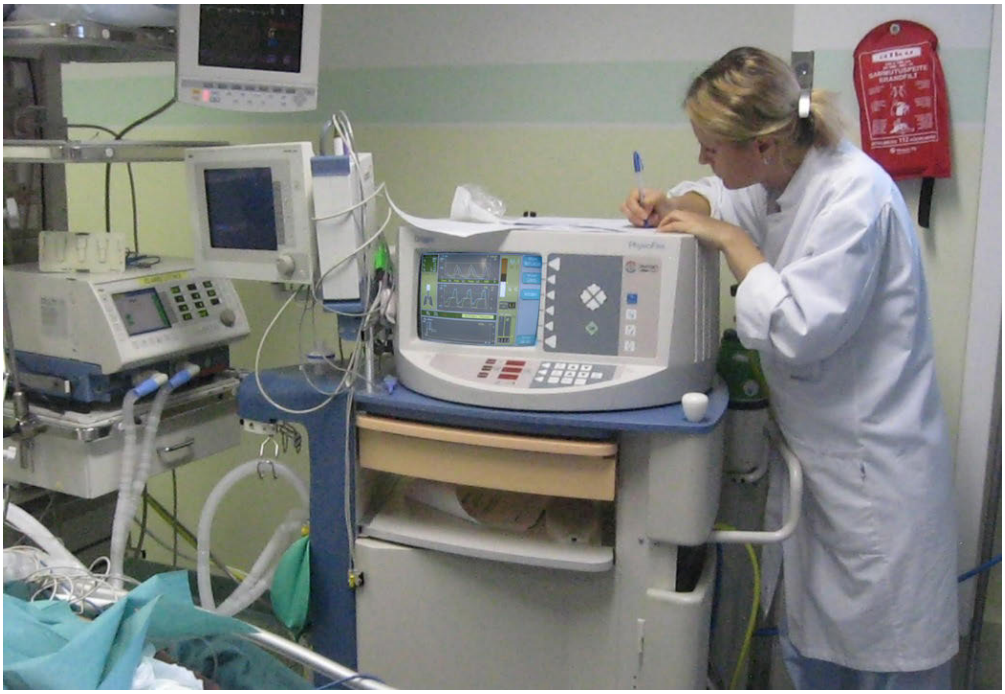


Figure 1. PhysioFlex™ (Dräger, Lübeck, Germany), fully closed circuit ventilator, used in our study. Gas cylinder containing xenon on the right. Values of volume, pressure, carbon dioxide, oxygen and xenon concentration are constantly displayed

a fraction of 50–70 % of inhaled xenon with FiO_2 25–30 %. Oxygen is delivered to the system by an electronically controlled measurement system to reach the predetermined target with the sufficient compensatory flushes of oxygen. However, the tissue nitrogen ought to be lowered in advance in order to prevent exhaled nitrogen interference and accumulation in closed circuit ventilation. Denitrogenization is achieved with 100 % oxygen inhalation for 15 to 30 minutes before starting xenon administration (Dingley 2001). Importantly, the gas circuit ought to be as closed as possible; requiring distinguished non-leaking, non-silicon, rubber plastic tubes and connectors.

2.3.2.3 Adverse effects

As opposed to other inhaled anaesthetic agents, xenon is devoid of substantial side effects. It is not associated with malignant hyperthermia (Baur 2000), coagulopathy (Sanders 2005) or reactions with absorbent (Hanne 2001). Xenon is not embryotoxic or teratogenic and does not cause allergic reactions (Natale 1998, Burov 1999). In comparison to other anaesthetic regimens, xenon anaesthesia produces the highest regional blood flow in the brain, liver, kidney and intestine (Hecker 2004). However, in a porcine model, xenon reduced portal venous flow and may compromise hepatic perfusion (Iber 2008).

One of the adverse effects related to NMDA inhibition is postoperative nausea and vomiting (PONV). These are well-known adverse effects of other NMDA-inhibitors, such as ketamine and N_2O. Xenon has this property also. In a study with healthy volunteers, inhalation of 35 % xenon induced nausea in 10 % of subjects (Bedi 2002). In another study comparing xenon and isoflurane in patients undergoing elective surgery, the incidence of xenon-associated PONV was 26 % (Rossaint 2003). Premedication with 4 mg of dexamethasone was not effective preventing nausea (Fahlenkamp 2016). In a Turku University study on anaesthesia depth monitors, 8 of the 17 healthy volunteers (47.0 %) exposed to xenon had nausea during recovery, and despite antiemetic therapy 17.6 % also vomited (Laitio 2008). In a recent meta-analysis of randomized controlled trials comparing xenon to inhaled agents or propofol anaesthesia, the incidence of PONV was higher for xenon anaesthesia (34.4 %) than volatile anaesthesia or TIVA (19.9 %), risk ratio 1.72 (CI 1.1–2.69) (Law 2016).

The laminar flow within the respiratory tract corresponds to that airway resistance depends primarily on viscosity, and if the flow is turbulent, the density of the gas is responsible of airway resistance increase (Hecker 2004). During xenon anaesthesia, the respiratory rate is decreased and tidal volume increased, which maintains constant minute volume. The airway pressure increase observed during xenon anaesthesia is attributed to its higher density and viscosity. Xenon does not affect airway diameter. Airway pressure increment during xenon anaesthesia is merely a characteristic than an adverse effect (Baumert 2002). In a retrospective study with patients mechanically ventilated with 33 % xenon/67 % oxygen and undergoing cerebral blood flow measurements by means of stable xenon-enhanced computerized tomography (CT) scanning, xenon increased the mean airway pressure from 31.6 cmH_2O to 42.7 cmH_2O. The airway pressure reversed immediately when xenon exposure was terminated (Rueckoldt 1999).

Diffusion hypoxia or “Fink effect” can theoretically occur also during emergence of xenon anesthesia. Simply, when xenon administration is discontinued, quantities of this gas cross from the blood into the alveolus (based on the concentration gradient). Accidentally, the oxygen and carbon dioxide

concentration in the alveolus are diluted by this xenon washout, which could cause the partial pressure of oxygen to decrease and could temporarily lead to hypoxia. To prevent diffusion hypoxia during anaesthesia emergence, xenon is substituted by 100 % oxygen. In a pig study comparing diffusion hypoxia after xenon and N_2O anaesthesia, the oxygen partial pressure change was three times greater after N_2O than xenon, probably due to the lower solubility of xenon (Calzia 1999).

Diffusion and storage of xenon and other inhaled anaesthetic agents to air-filled cavities, such as into the bowel has been pointed out. For example N_2O diffusion into the bowel during anaesthesia causes a progressive decrease in tissue perfusion. N_2O is traditionally contraindicated for use in paralytic ileus and relatively contraindicated for bowel surgery (Eger 1965). When xenon was compared to N_2O anaesthesia, the diffusion into obstructed bowel segments and increase of gas volume was four times higher with N_2O of that observed with xenon. Xenon did not increase intraluminal pressure, which is probably associated with the lower blood/gas partition coefficient (Marx 2000). In a porcine animal model, xenon exposure decreased superior mesenteric artery blood flow, although intestinal oxygenation was maintained. In physiological conditions, xenon does not impair intestinal or mucosal oxygenation, as other volatile anaesthetic agents have demonstrated to do (Vagts 2004).

2.3.3 The effects of Xenon in the cardiovascular system

Xenon anaesthesia is associated with cardiovascular stability. It has virtually no direct influence on myocardial blood flow and global haemodynamics in healthy and diseased hearts (Preckel 2002). Ventricular function remains unchanged during xenon anaesthesia, as assessed by transoesophageal echocardiography (Luttropp 1993, Morita 1996). Lachmann and co-workers suggested, that the haemodynamic stability during xenon anesthesia was a result of less stress-induced sympathetic stimulation, which is supported by the observation of stable or diminished plasma cortisol and catecholamine levels (Boomsma 1990, Lachmann 1990) Xenon's effects on autonomic nervous system have been compared in previous studies to those with nitrous oxide or isoflurane. Xenon reduced both parasympathetic and sympathetic activity and appeared to have a vagotonic effect (Ishiguro 2000). On the contrary to other inhaled anesthetics, xenon preserved left ventricular contractility and decreased heart rate (Wappler 2007). In a recent meta-analysis, xenon anaesthesia was compared with other inhaled agents. Xenon lowered heart rate more (mean difference -6 beats/minute (CI -10.0 to -2.3)) than other inhaled agents. In comparison with propofol, the reduction of heart rate in xenon patients was -9 beats/ minute (mean difference, CI -17.3 to -3.3), which represents a 16.2 % change. Simultaneously, administration of propofol reduced MAP by a mean of 14

mmHg (CI -29.0 to -2.5), which was a 15.0 % change (Law 2016). A crossover comparison of xenon with propofol during cardiac bypass surgery patients with normal left ventricular function found no effect on heart rate, MAP, or LVEF and none of the vasodilatory effects that were observed with propofol (Dingley 2001).

MTH influences cardiac conductance (PR-interval prolongation) and impairs cardiac repolarization, indicated by prolonged QT-interval, which can be associated with critical ventricular arrhythmias. However, in a study with healthy volunteers, inhaled xenon did not increase QT_c interval (Neukirchen 2015).

To summarize, xenon anaesthesia is associated with a high degree of preserved cardiovascular stability with no significant effects on the myocardium, atrioventricular conduction time, or coronary blood flow. Cardiac ion currents are not altered and the responsiveness of cardiac muscle to inotropic and chronotropic stimulation remains intact (Schroth 2002).

2.3.4 Xenon and postoperative neurocognitive dysfunction

Intimadately, some of the previously cognitively intact patients undergoing surgery and anaesthesia will develop symptoms of cognitive dysfunction after their operation. Commonly these involve disturbances in thinking, perception and attention (Needham 2017). Especially after cardiac surgery in the elderly (> 65 years) patients, postoperative impairment of neurocognitive function has been recognized for years as a prevalent clinical problem (Höcker 2009). Post-operative cognitive dysfunction or decline (POCD) is a controversial condition inferred from a comparison of pre-operative to post-operative cognitive function (Skvarc 2018). POCD, which is distinct of post-operative delirium, can occur in 25 % to 40 % of elderly patients at discharge (Moller 1998). The underlying pathophysiology involves neuroinflammation and oxidative stress secondary to anaesthesia and surgery (Skvarc 2018). Predisposing factors, such as previous stroke, carotid stenosis, poor functional status, atrial fibrillation, renal failure, diabetes and older age (> 62 years) increase the risk. The incidence of POCD ranges from 28 % to 100 % after cardiac surgery and from 7 % to 26 % after noncardiac surgery (Moller 1998).

Various pharmacological perioperative strategies, including xenon inhalation, have been studied to prevent or attenuate POCD (Bilotta 2013). The particular interest in xenon emerges from neuroprotective effects in cerebral ischaemia and neurologic dysfunction demonstrated in different animal models (Wilhelm 2002, Ma 2003, Schmidt 2005). However, no difference in the comparison of POCD incidence or early cognitive testing was demonstrated in the elderly patients undergoing elective surgery with desflurane or xenon anaesthesia (Coburn 2007). Similarly, in comparison with propofol, xenon-based anaesthesia did not decrease

postoperative impairment of neurocognitive function, which was observed in a substantial proportion in the elderly (65–83 years) patient population (Höcker 2009). Furthermore, in a large multicentre trial on elderly (> 75 years old) mentally functional hip fracture patients, xenon-based anaesthesia was compared to sevoflurane-based general anesthesia. In the xenon group, the incidence of postoperative delirium was non-significantly lower, but importantly, the sequential organ failure (SOFA) scores and the rate of adverse effects were significantly lower in the xenon group than in the sevoflurane group (Coburn 2018).

2.4 Xenon and neuro- and cardioprotection

Growing evidence from preclinical and clinical trials has confirmed the protective properties of xenon administered alone or in combination with hypothermia in various organs (Hobbs 2008). Very low, subanaesthetic concentrations of xenon and mild hypothermia are, however, not protective on their own, but in combination they produce synergistic organoprotection, which was demonstrated in a rodent model (Schwiebert 2010). There are great quantity of enzymes and cellular structures involved in the assumed organo-protective effects of xenon post-conditioning. These include survivor activating factor enhancement (SAFE) pathway and reperfusion injury salvage kinase (RISK) pathway (Smit 2014). The main target is the ischaemia-reperfusion injury (IRI) following an abrupt cessation and re-establishment of blood flow in vulnerable organs, most significantly heart, brain and kidney. The precise molecular targets differ between these organs.

2.4.1 Molecular targets of xenon's neuroprotective effect

Xenon was identified as a competitive NMDA receptor antagonist at glycine coagonist site (Franks 1998, Dickinson 2007, Banks 2010) through an interaction with a phenylalanine residue (Armstrong 2012). This was corroborated in a study, which demonstrated, that xenon inhibition in NMDA receptors was mitigated, if the glycine concentration was higher (Dickinson 2007). Other glutamate receptor subtypes (AMPA, kainate) (Dinse 2005) and activation of TREK-1 two-pore potassium molecular and plasmalemmal ATP-sensitive potassium channel (K_{ATP}) inducing potassium leak currents (Gruss 2004) are involved as minor and secondary targets explaining xenon's anaesthetic and neuroprotective properties.

In the brain, xenon neuroprotection is explained by its antagonism toward excitatory glutamatergic synapses, most importantly on NMDA receptor, but additionally on "non-NMDA" receptors AMPA and kainate. It is acknowledged, that xenon has a blocking effect on two-pore K^+ channels, on nicotinic acetylcholine and serotonin receptors (Dinse 2005). Importantly, ischaemic or

injured neurons release excessive amounts of glutamate, which results in depolarization and NMDA-evoked dysfunction of the plasma membrane Ca^{2+} pump. This results in intracellular influx of Ca^{2+}, disrupting mitochondrial function and increasing excitability (Franks 1994). Xenon inhibits Ca^{2+}-calmodulin dependent protein kinase II (CaM K II), which is in critical role in regulating processes such as postsynaptic plasticity following ischaemia (Petzelt 2001). Xenon blocks NMDA receptors, which reduce excitability and production of toxic cell products causing neuron necrosis (David 2003). Accumulation of toxic cell reaction products reduces cellular energy and promotes apoptosis. After ischaemic injury, cell energy stores and ATP supplies are depleted. Xenon activates opening of neuronal ATP-sensitive potassium channel (K_{ATP}) whilst decreasing the sensitivity of the channel to ATP (Bantel 2010). Xenon reduces the expression of pro-apoptotic factors as BAX, activates anti-apoptotic effectors, such as Bcl_{XL} and Bcl_2, resulting in a decline in neuroapoptosis (Ma 2007). Preventing the amount of apoptosis was demonstrated to be central mechanism in a neuron cell culture viability study, where xenon exposure doubled the number of viable cells assessed with annexin V. Necrotic cell death was not reduced with xenon exposure (Williamson 2004).

Although the activation of ATP-sensitive potassium channels (K_{ATP}) or two-pore potassium channels (TREK-1) may explain some of the neuroprotective effects of xenon, the pivotal protective pathway is limiting the overstimulation of NMDA glutamate receptors following excitotoxic stress conditions (Banks 2010, Liu 2010). Excitotoxic stress mediated by through NMDA receptors is generally associated to acute neurodegenerative conditions such as postanoxic reperfusion injury, stroke and traumatic brain injury (Lavaur 2016b). However, low-level, chronic NMDA overexcitation is involved in various neurodegenerative conditions, including amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease (Vaarmann 2013, Lewerenz 2015). An experimental model mimicking sustained, low-level NMDA excitotoxicity in cortical and basal forebrain neuronal cell cultures revealed, that xenon exposure in a concentration of 75 % reduced neuronal damage induced by a synthetic glutamate analog (L-trans-pyrrolidine-2, 4-dicarboxylic acid PDC) (Lavaur 2016a).

2.4.2 Xenon's neuroprotective effects in experimental animal studies

Xenon has been demonstrated to be neuroprotective in a variety of *in vitro* and *in vivo* models. Xenon diminishes *in vitro* acute neuronal injury in response to both exogenous administration of excitotoxins or deprivation of oxygen and glucose in cell cultures. *In vivo*, xenon mitigates the morphologic and functional

consequences of acute neuronal injury provoked by ischaemia (Wilhelm 2002). Curiously, this marked neuroprotection against hypoxemic injury has been demonstrated in well below anaesthetic concentrations, in some models as low as 10–20 % MAC (Preckel 2006).

In 2002 Nicholas Franks' study group performed *in vitro* experiments with neonatal mice mixed neuronal and glial primary cell cultures. Neuronal damage was provoked with exposure to excitatory amino acids NMDA or glutamate, or by oxygen deprivation and quantified by the predictable release of lactate dehydrogenase (LDH) into the culture medium, which was indicative for cell injury. The putative neuroprotective intervention was assessed by the cell culture exposure to xenon (at different concentrations) or nitrogen (10–75 % MAC) in gas exposure chambers. LDH concentration was significantly reduced at all xenon concentrations, relating to marked mitigation of neuronal injury (Wilhelm 2002). In the *in vivo* brain injury model of the same study, rat excitatory neuronal injury was induced with subcutaneous N-methyl-DL-aspartate (NMDA). Xenon reduced histological neuronal degeneration in the arquate nucleus of the hypothalamus in a concentration –dependent fashion (Wilhelm 2002). The results of summarized preclinical studies of xenon neuroprotection are displayed in table 1.

In a rat model of cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction, Ma and colleagues demonstrated, that 60/30 % xenon/oxygen exposure attenuated the neurocognitive consequences and improved neurological outcome (Ma 2003).

In a mouse model of transient cerebral ischemia, mice underwent 60 minutes of filament occlusion of middle cerebral artery, which is a well-established experimental model of focal ischemia. Xenon/oxygen 70/30 % exposure was compared 70/30 % N_2O/oxygen and xenon/oxygen 35/30 %. The functional performance score was better in the animals anaesthetized with 70 % xenon compared with those in the N_2O group. Both xenon groups demonstrated a significantly lower total cerebral infarct volume compared with the 70 % N_2O group (Homi 2003).

Table 1. Xenon neuroprotection in animal studies. Abbreviations: NMDA = N-methyl-D-aspartate; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; N_2O = nitrous oxide; tPA = tissue plasminogen activator; HIF-1α = Hypoxia inducible factor; VF = ventricular fibrillation; MTH = mild therapeutic hypothermia; Xe = xenon; MRI = magnetic resonance imaging

Authors	year	Model	Species	Xenon	Results
Hypoxic-ischemic injury					
Wilhelm at al	2002	Excitoxic neuronal injury by NMDA	Neonatal mice cell culture	Different concentrations in gas exposure chambers	Xenon mitigated NMDA induced neuronal injury
Ma et al	2003	Cardiopulmonary bypass -induced neurologic and neurocognitive dysfunction	Rat	60 % in CPB	Less neurological deficits, improved outcome
Ma et al	2006	Lactate dehydrogenase release after oxygen deprivation	Rat glial culture	70 % 120 min	Protective preconditioning
David et al	2008	Excitotoxic neuronal injury (NMDA injection)	Rat	50 % 4 hours	global neuroprotection, reduced neurotransmitter release
Derwall et al	2008	8 min cardiac arrest; CPR 5 min	Porcine	1 hour vs 5 hour	neurologic deficit score improvement
Experimental transient cerebral ischemia					
Homi et al	2003	Ligation of middle cerebral artery for 60 min	Mouse	70 % and 35 % compared to N_2O 70%	Attenuated infarct size, improved functional performance score
David et al	2003	Middle cerebral artery oclusion for 90 min	Rat	50 % vs N_2O 75%	Reduced cortical brain damage
Dingley et al	2006	Unilateral carotid ligation for 90 min	Rat	50 % 3 hours	Neuroprotective post injury
Limatola et al	2010	Ligation of middle cerebral artery	Mouse	70 % 2 hours 24 hours before ligation	Dose-dependent neuroprotection
David et al	2010	Thromboembolic middle cerebral artery oclusion for 90 min	Rat	37 % - 75 % after tPA-reperfusion	Postischaemic Xe supresses ischaemic brain damage
Sheng et al	2012	70 min temporary focal ischemia	Rat	Different doses for 20 hours; 30 % for 8, 20 or 44 hours	Xe preconditioning via HIF-1α
Experimental cardiac arrest					
Schmidt et al	2005	Experimental cardiac arrest; preconditioning	Porcine	75 % 15 min before cardiac arrest	Brain injury surrogate marker reduction
Fries et al	2008	Experimental VF; *no flow* 8 min; *low flow* 4 min	Porcine	70 % 1 hour or 5 hours during MTH induction	Histological and functional neuroprotection
Fries et al	2012	Experimental VF; *no flow* 10 min; *low flow* 6 min	Porcine	70 % 1 hour + during MTH induction	Neurological and cardiac functional outcome improvement
Preventing neurotoxicity					
Ma et al	2007	Exposure to different gas mixtures	Rat pup	75 % or isoflurane with 30% or 60 % Xe for 6 hours	Reduction in isoflurane-induced apoptosis
Cattano et al	2008	Isoflurane-induced neuroapoptosis	Mouse pup	70 %	Neuroprotection against isoflurane-induced apoptosis
Shu et al	2010	Neurotoxic isoflurane for 6 hours	Rat pup	70 % 2 hours	Xe pretreatment increased neuroprotection
Cattano et al	2011	Exposure to volatile anesthetics	Rat pup	75 % 120 min	Induced expression of antiapoptotic genes
Sabir et al	2013	Isoflurane-induced apoptosis	Piglet	50 % with fentanyl with MTH or not	Xe does not promote apoptosis

In another rat model of excitotoxic neuronal injury, significant *ex-vivo* and *in-vivo* postischaemic neuroprotection by xenon was demonstrated by xenon administration of 50 % up to 4 hours after intrastriatal NMDA injection and up to at least 2 hours after induction of transient brain ischaemia. Even sub-anaesthetic doses of xenon were associated with global neuroprotection with mitigated neurotransmitter release and reduced subsequent cell injury and neuronal death (David 2008).

Derwall and colleagues compared differences in xenon and isoflurane anesthesia in a porcine model after prolonged (8 min) cardiac arrest and CPR for 5 minutes. Xenon exposure was 1 or 5 hours. The neurologic deficit score (NDS) pointed a severe neurologic dysfunction in almost all untreated control animals. However, in the 1-hour xenon group, and to somewhat lesser extent in the 5-hour xenon group the NDS score was significantly reduced through postoperative follow-up on days 1–3. In comparison of xenon to isoflurane, there were no marked differencies in functional performance (Derwall 2008).

Michael Fries and co-workers studied ensuing neurohistopathologic damage and functional outcome in a porcine model of ventricular fibrillation cardiac arrest, mimicking real-life timetable and circumstances of resuscitation. Namely, after 8 minutes of cardiac arrest and 5 minutes of CPR, the successfully resuscitated pigs (32–39 kg) were randomized to receive either 70 % of xenon for 1 or 5 hours or controls receiving 70 % nitrogen. Neurocognitive and overall neurologic deficits were assessed before day 5 post-arrest, whereafter the brains were harvested for histological analysis. The main finding was, that xenon exposure post resuscitation resulted in attenuation of perivascular inflammation in the putamen and caudate nucleus. There was additionally a marked reduction in the injured neurons in the putamen. Simultaneously, the overall neurologic and neurocognitive performance was improved. In this study, the post-conditioning intervention was initiated no earlier than 1 hour after CPR, and interestingly, one-hour exposure to xenon was equally effective as 5 hours of treatment (Fries 2008). Another porcine study by the same group demonstrated, that after 10 minutes of cardiac arrest and 6 minutes of CPR, the combination of mild hypothermia (33 °C) for 16 hours and Xenon 70 % for one hour preserved cardiac output during induction of MTH significantly better than hypothermia as a sole intervention. Neuropathologically, in xenon + MTH – treated animals, hippocampal astrogliosis and microgliosis and perivascular inflammation in the putamen was mitigated. Furthermore, neurologic deficit scores over a period of 5 days follow-up time were improved in xenon + MTH -treated animals (Fries 2012).

A rat model of neonatal asphyxia demonstrated, that although delayed xenon 20 % exposure as a sole intervention was associated with relative limited neuroprotection, the combination of xenon and hypothermia for 90 minutes,

initiated 4 hours after induced hypoxia-ischemia, provided synergistic histological and functional protection up to 30 days after injury (Ma 2005). This finding was corroborated in another study of induced ischaemia and hypoxia. Right common carotid artery occlusion was followed by 90 minutes hypoxia with 8 % oxygen in rat pups. Hypothermia and xenon was administrated asynchronously, with a 1 or 5 hours interval between interventions. Significant infarct volume reduction was demonstrated even when hypothermia and xenon were administered with an intervening gap of 5 hours (Martin 2007). Similarly, other study groups have confirmed that combining mild hypothermia with delayed xenon inhalation had additional beneficial effects in neonatal rats that exceeded the individual benefit of either treatment alone (Hobbs 2008, Thoresen 2009). The plausible hypothesis is that xenon and mild hypothermia therapy converge on an anti-apoptotic pathway explaining why even asynchronous application of the interventions attenuates the injury (Kelen 2010).

2.4.3 Xenon's neuroprotective effects in human studies

Until our study, xenon inhalation was investigated in humans as an anaesthetic agent during general anaesthesia, intensive care sedation or cardiac surgery (Rossaint 2003, Bedi 2003, Coburn 2005, Lockwood 2006, Rasmussen 2006, Wappler 2007, Höcker 2009, Cremer 2011, Hofland 2017). The focus of these studies was merely the safety, feasibility and properties of the anaesthesia in terms of perioperative hemodynamics with no data provided about any neuroprotection following xenon exposure.

Xenon's putative neuroprotection effect in cardiac arrest patients is an original idea by the principal investigator of this study. Furthermore, this study was the first report about using xenon in combination with hypothermia in any group of adult patients. However, combination of hypothermia with xenon for neuroprotection after neonatal asphyxia had been utilized previously, but it will be discussed further (2.4.7).

2.4.4 Molecular targets of xenon's cardioprotective effects

Oxygen starvation damages cardiomyocytes through ATP depletion and acidosis resulting in apoptotic cardiomyocyte loss during prolonged cardiac ischaemia-reperfusion injury (Wu 2014). In postischaemic myocardium xenon affects several critical intra-cellular mechanisms. These include protein kinase c-ε (PKC-ε), protein kinase B (Akt), glycogen synthase kinase 3β (GSK- 3β), p38 mitogen-activated protein kinase (MAPK), MAPK-activated PK-2, heat-shock protein 27,

and intracellular signal-regulated kinases ½ (Weber 2005 (a), Weber 2005 (b), Preckel 2006, Weber 2006 (a), Weber 2006 (b), Mio 2009).

Moreover, xenon counteracts mitochondrial permeability transition pore (mPTP) opening, which preserves mitochondrial function, reduces generation of reactive oxygen species from damaged mitochondria and restricts ischaemia-reperfusion injury. The vascular endothelial cells are particularly vulnerable to hypoxia and reoxygenation during reperfusion. Nitric oxide (NO) production is diminished in post-ischaemic endothelial cells, which manifests as an endothelium dependent NO-mediated impaired relaxation of endothelial smooth muscle cells causing capillary malperfusion (Carden 2000). Xenon counteracts endothelial dysfunction by blocking calcium-dependent Ca^{2+} -influx into endothelial cells (Petzelt 1997). Xenon might significantly alter endothelial function, which converges to that some of the xenon's cardioprotective properties might be mediated by alterations within the endothelium (Smit 2015).

The first evidence of xenon's protective effects in ischaemic myocardium was published in 2000 (Preckel 2000). Thereafter, a growing body of experimental evidence in different sized animal models has indicated, that xenon exerts a myocardium-protective effect when applied before organ ischemia as an early or late preconditioning stimulus. This was demonstrated as reduced infarcts, restricted infarct size, improved myocardial function and mitigated release of cardiac enzymes (Table 2) (Weber 2005, Weber 2006(a+b), Baumert 2007b, Mio 2009, Li 2013).

In regard of affecting an ongoing injury in OHCA patients, postischaemic application of xenon additionally exerts a cardioprotective effect in myocardial ischaemia during reperfusion as a postconditioning stimulus (Schwiebert 2010). Most of the available knowledge about the putative signalling in xenon cardioprotection is attributed to pretreatment with bioactive molecules (PKC, calphostin C, MAPK inhibitor, etc), which abolished xenon-related effects (Pagel 2010). Experimental animal studies are summarized in table 2.

Table 2. Cardioprotective effects by xenon in experimental animal studies. Abbreviations: LAD = left anterior descending coronary artery; Xe = xenon; LV = left ventricular; RV = right ventricular; CO = cardiac output; IR = ischaemia-reperfusion; RCA = right coronary artery; MAP = mean arterial pressure; HR = heart rate; MTH = mild therapeutic hypothermia; FiO_2 = fraction of inhaled oxygen; HIF-1α = hypoxia inducible factor; VEGF = vascular endothelial growth factor

Experimental animal studies					
Authors	**Year**	**Model**	**Species**	**Xenon**	**Results**
Preckel et al	2002	prior LAD ligation 9 weeks ago; LV dysfunction	Rabbit	70 %	Xe did not compromise LV function on cardiac echo
Weber et al (b)	2006	LAD occlusion for 25 min, 120 min reperfusion	Rat	70 % 3 x 5 min	Increase in preconditioning mediators; reduction in infarct size
Baumert et al	2007	LAD occlusion for 60 min, 120 min reperfusion	Porcine	70 % anaesthesia or 3 x 10 min preconditioning	Xe anaesthesia reduced infarct size, preconditioning did not
Weber et al	2008	LAD occlusion for 25 min, 120 min reperfusion	Rat	70 % for 15 min	Reduction in infarct size
Hein et al (a)	2008	Xe anaesthesia and pulmonary artery catheter	Porcine	70 %	Systolic ventricular function intact, RV and CO reduced
Hein et al (b)	2008	IR injury by 90 min ligation of distal RCA, 120 min reperfusion	Porcine	70 % 1h before ischaemia	Infarct size and severity (inflammation) reduction
Francis et al	2008	Haemodynamic and hormonal effects during Xe anesthesia	Beagle dog	63 % + remifentanil	MAP maintained, but reduced HR, stimulation of endogenous catecholamines
Mio et al	2009	LAD occlusion for 30 min, 120 min reperfusion	Rat	70 % for 3 x 5 min	Infarct size reduction, preservation of mitochondrial function
Schwiebert et al	2010	LAD occlusion for 25 min, 120 min reperfusion	Rat	20 % + MTH 34 °C	Infarct size reduction
Chakkarapani et al	2012	Hypoxic-ischaemic insult by reduction of FiO_2	Piglet	50 % with or without MTH	Stable haemo-dynamics, inotrope-sparing effect
Goetzenich et al	2014	Induced hypoxemia in cell culture	Rat pup cardiomyo cyte culture	preconditioning 24 h prior hypoxia	Increase in preconditioning mediators HIF-1α and VEGF
Li et al	2013	1h global ischaemia, 3 h reperfusion	Rabbit pup isolated hearts	75 % pretreatment	Protection against ischaemia-reperfusion injury
Baumert et al	2016	LAD occlusion for 60 min, 120 min reperfusion	Porcine	70 % for 1 hour	Reduction in diastolic dysfunction

2.4.5 Xenon's cardioprotective effects in experimental animal studies

Hettrick and colleagues investigated the cardiovascular effects of xenon in a canine model of dilated cardiomyopathy. The dogs were chronically instrumented to facilitate continuous measurement of aortic and left ventricle (LV) pressures, aortic blood flow and LV subendocardial segment length (Hettrick 1998). Dilated cardiomyopathy was induced with rapid LV pacing, which produces similar heart disease as human idiopathic dilated cardiomyopathy (Johnson 1982). The animals were anaesthetized with 1.5 MAC isoflurane combined with four different concentrations (0 %, 30 %, 50 % and 65 %) of xenon exposure. Their conclusion was, that isoflurane and xenon in combination produced minimal haemodynamic effects – arterial and LV pressures, cardiac output and stroke volume were unchanged during administration of xenon to isoflurane-anaesthetized dogs. The findings were equal in the control group of non-cardiomyopathy animals, indicating that xenon did not affect global cardiac performance whether the animal had a heart disease or not (Hettrick 1998)

Preckels study group investigated the effects of xenon on a rabbit model of reperfusion injury after prolonged (30 minutes) coronary artery occlusion followed by a two-hour reperfusion period. Exposure to 70 %/30 % of xenon/oxygen during the first 15 minutes of reperfusion reduced myocardial infarct size in the LV area at risk from 51 $\pm$ 3 % (controls) to 39 $\pm$ 5 %. Additionally, the slope of the regression line relating infarct size to the LV area at risk was significantly reduced in the xenon-treated animals, claiming that the ratio of infact size to LV area at risk was smaller in xenon-treated rabbits (Preckel 2000). The same group demonstrated in rabbits with chronic LV dysfunction (9 weeks after coronary artery ligation), that xenon had minimal haemodynamic effects without affecting the maximal rate of increase in LV pressure (Preckel 2002).

Volatile anaesthetics (isoflurane, sevoflurane and desflurane) generally exhibit a direct depressant effect on the myocardium, which is a limiting factor in their use in patients with compromised cardiac function. However, on the contrary, xenon exposure in isolated guinea pig hearts did not alter the amplitudes of Na^+, L-type Ca^{2+} and inward –rectifier K^+ channel currents, which are acknowledged sites causing cardiac side effects. Furthermore, xenon did not affect cardiac function in isolated hearts to any degree (Stowe 2000). In another study with isolated guinea pig hearts, with extracted ventricular muscle bundles, xenon exposure did not alter myocardial contraction force or contraction time, in contrast to isoflurane, which elicited an anticipated negative inotropic effect. However, the correcting positive inotropic stimulus effect obtained with isoprotenol, calcium and increased pacing frequencies was maintained also in isoflurane group (Scroth 2002).

Grosse Hartlage and colleagues investigated in a canine model recovery from myocardial stunning, induced by 10 minutes of occlusion in left anterior descending

coronary artery. Ten dogs were chronically instrumented to provide measurement of heart rate; pressures in left atrium, aorta and left ventricle; coronary blood-flow velocity; and myocardial wall-thickening fraction. The intervention was xenon 75 % inhalation added to fentanyl-midazolam anesthesia compared to the anaesthesia alone. Global haemodynamics, blood-flow velocity and regional myocardial blood flow were similar in both groups. However, in the animals receiving xenon, a significantly better recovery of wall-thickening fraction and an attenuated plasma noradrenaline release during emergence from anaesthesia was demonstrated. This translated to that inhalational exposure to 75 % xenon improves recovery from postischaemic myocardial stunning (Grosse Hartlage 2004).

In the porcine model study of Vagts and colleagues, perioperative intestinal oxygenation was investigated, which is commonly affected by the cardiodepressive effects induced by inhalational anaesthetics. The possible consequence of intestinal hypoperfusion could contribute to sepsis and multiorgan failure. In addition to the basic i.v. anaesthesia, xenon was delivered in different concentrations (0, 20, 50 and 65 %). The authors concluded, that the mean arterial pressure (MAP) was stable during xenon exposure, although the heart rate and cardiac output decreased by 30 %. However, intestinal oxygenation was maintained, although regional macrohaemodynamic perfusion decreased without inducing hypoxic values in the intestinal mucosa (Vagts 2004).

Much of the knowledge about xenon's prosurvival signaling pathways is derived from the work of Nina C. Weber and her study group. Initially, they demonstrated in a rat myocardial infarct model, that three 5 min cycles of xenon/ oxygen 70 % /30 % inhalation intervalled with 5 minutes of NO/oxygen of 70 %/30 % before coronary occlusion protected myocardium against ischaemic injury (Weber 2005a). This preconditioning effect diminished myocardial infarct size 28 % $\pm$ 10 % of the LV area at risk compared to 51 % $\pm$ 17 % in control animals. The beneficial effects were mediated via induction of nonselective protein kinase C (PKC) and selective p38 mitogen-activated protein kinase (MAPK), as the protective effects were abolished by pretreatment with inhibitors of these pathways. Xenon caused also phosphorylation, translocation and hence activation of epsilon isoform of PKC (PKC-ε), a previously recognized sign of enzyme activation in ischaemic and anaesthetic preconditioning (Weber 2005a). These results demonstrated, that cardioprotective xenon pretreatment implicates endogenous cardioprotective signaling kinases in diminishing ischaemic injury (Pagel 2010).

Weber and colleagues further studied the downstream targets of p38 MAPK. Repetitive administration of xenon before coronary occlusion also additionally enhanced MAPK-activated protein kinase-2 (MAPKAPK-2) and small heat-shock protein 27 (Hsp 27) phosphorylation. These are acknowledged mediators of stabilization of the integrity and the actin cytoskeletal framework of the

cardiomyocyte (Weber 2005b). Additionally, Weber's group elucidated a crucial ion channel and several signaling proteins involved in xenon preconditioning. These include mitochondrial KATP channel (Weber 2006a), which maintain intracellular Ca^{2+} balance, inhibits Ca^{2+} overload and enhances oxidation-reduction rate. Further, xenon-induced cardioprotection is mediated also by activation of the reperfusion salvage kinase (RISK) pathway, which is involved during ischaemia-reperfusion injury and protects from myocardial necrosis and apoptosis. They also identified extracellular signal-regulating p44/42 MAPK (ERK ½) as a mediator of xenon preconditioning. These kinases mediate cell division, proliferation and survival (Weber 2006b). Mio and colleagues investigated the role of prosurvival kinases that target mitochondria in rat model of LAD occlusion for 30 minutes. Their conclusion was, that xenon-induced cardioprotection activates prosurvival signaling that targets mitochondria making them less vulnerable to ischaemia-reperfusion injury. Xenon preconditioning mitigates infarct size, activates Akt, glycogen synthase kinase 3β (GSK-3β) and prevents Ca^{2+} -induced opening of mPTP, which preserves mitochondrial function (Mio 2009).

In another rat infarction study, the Weber/Preckel group investigated the induced postconditioning effect on ischaemia-reperfusion by combining mild hypothermia and xenon in a subanaesthetic concentration of 20 % (Schwiebert 2010). This had already proven effective in neonatal rats when administered after hypoxic-ischemic brain injury (Ma 2005). After 25 minutes of LAD occlusion and at the onset of 120 minutes of reperfusion, the intervention groups received either 1h of mild hypothermia (34 °C), 30 minutes of xenon 20 % inhalation or the combination of xenon and hypothermia. Their conclusion was, that subanaesthetic xenon and mild hypothermia did not establish effective postconditioning stimulus if they are administered on their own. However, in combination, they act synergistically protecting myocardium from reperfusion injury. In effect, combination of 20 % xenon and hypothermia reduced the infarct size statistically significantly (Schwiebert 2010).

Roehl and colleagues investigated post-infarction myocardial remodeling 28 days after experimental perioperative myocardial infarction in a rat model. Three different anaesthetic regimes, 0,6 % isoflurane, 70 % xenon and intraperitoneal injection of s-ketamine, were compared during 60 min of LAD occlusion and 120 minutes of reperfusion. Quantification of cardiac dilatation, left ventricular function, hypertrophy, fibrosis, capillary density, apoptosis and expression of fetal genes was performed after 4 weeks. Initially, xenon and isoflurane reduced the acute effects of ischaemia-reperfusion on haemodynamics and myocardial infarct size at a comparable level. However, after 4 weeks, in xenon –treated animals, there was a lower remodeling index, better ejection fraction and reduced expression of β–myosin heavy chain and periostin, when compared to isoflurane- or ketamine-treated animals. This study demonstrated, that perioperative xenon treatment

conferred to improved recovery of contractile function after ischaemia-reperfusion injury and impeded adverse cardiac remodeling (Roehl 2013).

In the study of experimental myocardial infarction in thirty-six 30–35 kg weighing pigs, Baumert and colleagues studied the effects of ischaemic preconditioning and of xenon preconditioning and xenon anaesthesia. Myocardial ischaemia was produced by intermittent occlusion of left anterior coronary artery for one hour and followed by two hours of reperfusion. In this study, xenon preconditioning did not reduce myocardial infarct size, but xenon anaesthesia of 70 % produced mitigation of the size of myocardial infarct, myeloperoxidase activity, and plasma tumor necrosis factor α (TNF-α) and inflammatory marker interleukin 6 concentrations, which can be interpreted as a postconditioning effect on the ischaemia-reperfusion injury. The result was statistically significant, but the amount of salvaged myocardium was less than with ischaemic preconditioning (Baumert 2007b). Hein and colleagues demonstrated also in a porcine model of right ventricular ischaemia, that both 70 % xenon and 0.9 % isoflurane prevented equally haemodynamic compromise during reperfusion, in comparison to barbiturate-anaesthetized animals (Hein 2010). Previously, the Baumert group had demonstrated in pigs, that xenon combined with isoflurane compared to isoflurane alone did not have significant difference in myocardial protection (Baumert 2009). In the same porcine myocardial infarction study by Sopka and colleagues, isoflurane, xenon and thiopental were compared in a right ventricular infarction model. In this study, both xenon and isoflurane caused a similar reduction in infarct size. However, xenon induced a significant increase in apoptosis compared to isoflurane, demonstrated in higher density of apoptotic cardiomyocytes in caspase-3 staining. There was a high variability per animal, but the result was statistically significant (Sopka 2013). It has been argued before, that xenon cardioprotection might be attenuated in pigs, because the RISK pathway has a markedly less important role in this process than in smaller mammals (Pagel 2010).

The aforementioned studies indicate, based on experiments in different sized animals, that intermittent exposure to xenon before, during or after ischaemic myocardial injury attenuates the effects of ischaemia-reperfusion response and protects against irreversible ischaemic injury. Xenon exposure mitigates infarct size and enhances functional recovery of stunned myocardium and prevents adverse cardiac remodeling (Pagel 2010).

Xenon has been investigated also in human cell cultures. Hüneke and co-workers obtained human right atrium cardiomyocytes from patients undergoing heart surgery. Xenon was compared to volatile anaesthetics halothane and isoflurane, both of which are characterized with known negative inotropic and proarrhytmic side effects on the heart. Ion currents were assessed with the whole cell patch clamp technique during superfusion of cells with solutions of these gases

in concentrations corresponding to their minimum MAC. As anticipated, halothane and isoflurane exhibited inhibitory effects on voltage-gated cardiac Ca^{2+} and K^{+} currents, which adjust the duration of action potentials and repolarization and are likely to be of pathophysiologic relevance. In contrast, xenon did not affect Ca^{2+} currents and there was only slight inhibition of transient K^{+} outward currents, which in effect translates to that 70 % xenon preserved heart contractility in isolated human atrial cardiomyocytes (Hüneke 2001).

2.4.6 Xenon's cardioprotective effects in human studies

Clinical human studies displaying cardioprotective properties by xenon are summarized in table 3.

Table 3. Cardioprotection by xenon in human studies. Abbreviations: ICU = intensive care unit; Xe = xenon; HR = heart rate; MAP = mean arterial pressure; CI = contractile index; CAD = coronary artery disease; LV = left ventricular; TOE = transoesophageal echography; PET = positron emission tomography; MAC = minimal alveolar concentration; OPCAB = Off-pump coronary artery bypass; ECG = electrocardiogram; QTc = heart rate corrected ECG QT –interval; HV = healthy volunteer; CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafting; TIVA = total intravenous anesthesia

Human studies					
Authors	**year**	**Setting**	**Subjects**	**Xenon**	**Results**
Bedi et al	2003	Postoperative ICU patients	Elective surgical patients	28 ± 9 % (9–62 %) ICU sedation for 8 hours	Compared to propofol, Xe provided minimal haemo-dynamic effect and fast recovery
Rossaint et al	2003	Planned anaesthesia ≤ 2hours	Elective surgical patients	60 ± 5 % vs. isoflurane	Effective and safe anaesthesia, faster recovery
Coburn et al	2005	Anaesthesia > 60 min	Elective surgical patients	60 % vs. propofol	HR decreased, MAP maintained
Wappler et al	2007	No prior cardiac disease	Elective surgical patients	30 % vs. isoflurane	Cardiovascular stability; isoflurane decreased CI
Baumert et al	2008	Known CAD	Elective non-cardiac surgery	65 % vs. propofol	MAP higher with Xe, better LV function in TOE
Schaefer et al	2011	PET study of myocardial blood flow	Healthy volunteers	1 MAC	Minimal effects on coronary flow dynamics
Al Tmimi et al	2015	MAP > 70 mmHg, noradrenaline dose	Elective OPCAB surgery	30 % & propofol vs. propofol only	Improved haemodynamic stability, less noradrenaline
Neukirchen et al	2017	Continuous ECG monitoring, QT_c interval	HV + 35 abd & trauma patients	60 %	QT_c interval unaffected with Xe
Hofland et al	2017	Troponin I concentration 24 h post surgery	CPB CABG surgery (n = 446)	52–56 % vs. sevoflurane vs. propofol	TnI release less than with TIVA; comparable with sevoflurane

The compelling preclinical evidence establishing xenon's cardioprotective properties has been reinforced with a series of human investigations (Table 3). Most of them, however, were conducted in respect of safety and feasibility, in various surgical or intensive care patients. Bedi and co-workers investigated postoperative sedation in patients admitted to ICU following elective thoracic surgery. The duration of the sedation was 8 hours and inhaled xenon was compared to standard ICU regimen, propofol and alfentanil. Both sedative drugs exhibited similar mean Ramsay sedation scores and mean bispectral indexes, measured at 30 min intervals. Xenon sedation was feasible, well tolerated and with minimal haemodynamic effects (Bedi 2003).

In a multicenter randomized clinical trial of 224 patients, xenon 60 % was compared to isoflurane 0,5 % combined with N_2O 60 % in elective surgical patients. Supplemental sufentanil was added to the anaesthesia if indicated. Xenon in oxygen exhibited equally effective anaesthesia when compared to isoflurane-N_2O. The requirement for opioid injections was comparable in both groups. The recovery from anaesthesia was distinctly faster with xenon and it did not affect myocardial contractility, displayed by higher mean arterial pressure during anesthesia in xenon group. Data of requirements of supplemental vasoactive medication is not available (Rossaint 2003).

Goto and co-workers compared xenon 60 % to N_2O 60 % during fentanyl-midazolam anesthesia in 20 elective CABG patients. The patients were assessed with transoesophageal echocardiography and pulmonary artery catheter. After reaching the predefined end-tidal concentration of both gases, the gases were discontinued after 15 minutes of exposure. This study illustrated, that whereas xenon inhalation had minimal effects on the haemodynamic parameters, N_2O inhalation decreased mean arterial pressure, left ventricular stroke work index and the fractional area change of the left ventricle. The authors concluded, that inhaled xenon is safe also in surgical patients with heart disease (Goto 2004).

In the randomized controlled trial by Coburn and colleagues, xenon 60 % was compared to propofol anaesthesia in 160 patients undergoing elective surgery. Anaesthesia was induced with propofol and remifentanil and maintained with xenon or propofol. The main differences between groups were observed during the first 15 minutes following induction. Namely, systolic arterial pressure initially decreased, but returned to baseline values in the xenon group. The propofol group had lower systolic and diastolic pressure. Heart rate decreased significantly in the xenon group, but remained at stable values. Bispectral indexes were similar. There were no differences in hypertension or hypotension occurrence or the time to emerge from anaesthesia or recovery time in the post-anaesthetic care unit. The conclusion was, that following anaesthesia induction, xenon maintains arterial pressure and a stable low heart rate (Coburn 2005).

Bein and co-workers compared xenon and TIVA (propofol, remifentanil and rocuronium) in 39 high-risk patients undergoing aortic surgery. The patients were assessed with transoesophageal echocardiography and myocardial cell damage was illustrated with troponin T and CK-MB release. In this study, no clinically relevant differences in global myocardial performance, myocardial contractility or myocardial cell damage markers were demonstrated at any time during 72 hours of study period. Therefore, the authors found previously reported beneficial cardiovascular effects of xenon speculative (Bein 2005).

Hanss and co-workers performed an analysis on the influence of xenon 60 % on regulation of the autonomic nervous system in 44 patients undergoing major abdominal aortic surgery and at high risk of perioperative cardiac complications. Xenon was compared to propofol-remifentanil-based TIVA. During operation, heart rate, heart rate variability (HRV), arterial pressure and cardiac output were monitored. The postoperative analysis included 24 h Holter ECG, length of stay at the ICU and hospital and patient's outcome after 6 months. In HRV analysis, xenon patients exhibited lower sympathetic and higher parasympathetic activity in comparison to TIVA patients. This resulted in reduction of heart rate in xenon group, but no significant differences were observed in terms of postoperative arrhythmias, ECG changes or in markers of myocardial damage. There were no differences in short- or long-term outcome (Hanss 2006).

Rasmussen and colleagues compared xenon 50–70 % and propofol anaesthesia in 39 elderly patients undergoing knee replacement surgery. The mean age was 71 and 70 years, respectively. Besides perioperative haemodynamic parameters, cognitive function was assessed preoperatively, at discharge and at 3 months postoperatively. Perioperative blood pressure, heart rate, ventilatory frequency or end-tidal carbon dioxide concentration did not differ between groups. Xenon was well tolerated in spontaneously breathing elderly patients. A high incidence of POCD was found in both groups at discharge. The authors found no difference in cognitive function, which they speculated merely to be attributed to underpowered sample size rather than absence of a true difference (Rasmussen 2006).

Lockwood and colleagues addressed also POCD in 16 patients undergoing GABG surgery and on hypothermic cardiopulmonary bypass (CPB). This was an open-label dose-escalation study with xenon in concentrations of 0, 20, 35 and 50 % xenon in oxygen and air. Brain embolic load was assessed with transcranial middle cerebral artery Doppler and damage to vulnerable tissues was assessed for the heart with troponin I, for the brain with serum S100β and for the kidney with serum creatinine. Delivery of xenon during cardiac surgery did not produce adverse clinical consequences. No evidence of organ injury or increased embolic load was detected. There was a tendency to lower troponin I- and S100β- concentration at 24 hours in those patients receiving xenon (Lockwood 2006).

Wappler and co-workers compared xenon 60 % to isoflurane 1,2 % in 252 patients without cardiac disease undergoing elective noncardiac surgery in a randomized multicenter trial. Cardiac performance and left ventricular function was assessed with transoesophageal echocardiography. The global haemodynamic as well echocardiopraphic parameters were more stable in the xenon patients, as in the isoflurane patients. In patients receiving isoflurane, the contractile index, left ventricular end-systolic wall stress and velocity of circumferential fiber shortening decreased significantly. Xenon did not reduce contractility and the sole and only alteration from baseline was a decrease in heart rate. In comparison to isoflurane, xenon enabled favourable cardiovascular stability in patients without cardiac disease (Wappler 2007).

Autonomic cardiac control during elective noncardiac surgery was investigated in a randomized trial in 26 patients with increased cardiac risk. The authors hypothesized, that the acknowledged stable arterial pressure during xenon anaesthesia results from a lesser circulatory depression or a direct effect on vascular tone or its automatic control. They investigated beat-to-beat heart rate variability (HRV) by spectral decomposition to assess autonomic cardiovascular control. Baseline anaesthesia was achieved with etomidate and remifentanil and after 30 and 60 min propofol or xenon 60 % was added. Total spectral power of HRV was decreased with propofol, when compared to baseline etomidate anesthesia. Simultaneously, low frequency ratio, reflecting relative sympathetic contribution to HRV, was reduced with propofol. Xenon affected neither of these. With xenon, arterial pressure increased back close to awake levels, after an initial decrease from the awake state to baseline anesthesia in both groups. Blood pressure remained decreased with propofol. In conclusion, xenon exhibited better preservation of autonomic heart rate modulation when compared to propofol. This may partly be an explanation for higher arterial pressure and lower heart rate levels observed during xenon anaesthesia (Baumert 2007a).

The same group investigated further 40 coronary artery disease patients undergoing non-cardiac surgery. In comparison with propofol anaesthesia, xenon 65 % provided a higher arterial pressure level than propofol, without any signs of cardiovascular compromise. With xenon, transoesophageal echocardiographic parameters displayed better maintained left ventricle function than with propofol in these patients at cardiovascular risk (Baumert 2008).

In the positron emission tomography study by Schaefer and co-workers, myocardial blood flow (MBF) was noninvasively quantified by $H_2{}^{15}O$ in six healthy volunteers during general anaesthesia with xenon. They found only minimal effects on MBF during the anaesthesia. A nonsignificant decline in MBF was postulated to be reflecting a decrease of myocardial oxygen consumption induced by the general anaesthesia on cardiac work. Coronary artery blood flow

was unaltered, translating to minimal or no vasodilating effects by xenon. The authors concluded, that xenon renders a safe option in the care of patients at risk of perioperative myocardial ischemia (Schaefer 2011).

Feasibility and safety of xenon 45 – 50 % was compared with sevoflurane 1–1.4 % anaesthesia in 30 patients undergoing CABG surgery with cardiopulmonary bypass (CPB) and moderate hypothermia 32–34 °C. Because of the speculative potential of xenon to expand intravascular gas bubbles during CPB, xenon was applied solely pre- and post-CPB. The peak inspiratory pressures were higher in the xenon group before and after weaning from CPB, reflecting density of the gas. The primary outcome, occurrence of adverse events, and secondary outcome, feasibility criteria, did not differ between groups. However, with xenon, there was a tendency towards less acute kidney injury, as demonstrated by a trend towards lower urea and creatinine values and higher creatinine clearance during postoperative follow-up (Stoppe 2013).

Al Tmimi and colleagues investigated xenon 50–60 % in comparison with sevoflurane 1,1–1,4 % in 42 patients undergoing off-pump coronary artery bypass surgery (OPCAB; operation on a beating heart) in a non-inferiority randomized controlled trial (Al Tmimi 2012). During OPCAB, significant haemodynamic alterations occur, which entail a high risk for perioperative myocardial ischemia and haemodynamical instability. This exposes the patient to perioperative organ injury; myocardial infraction, stroke and kidney injury requiring dialysis (Lamy 2012). Primary outcome in this study was the perioperative requirement of vasoactive medication support and secondary outcome was safety and occurrence of adverse events. Xenon was demonstrated to be non-inferior to sevoflurane, and on the contrary, xenon patients required significantly less intraoperative noradrenaline to achieve the predefined haemodynamic goals. There were no differences in safety. However, significantly more sevoflurane patients developed postoperative delirium. The average arterial pressure was reduced in sevoflurane group, but no other differences were demonstrated for other haemodynamic parameters. Nor did the perioperative release of inflammatory cytokines, troponin T, serum protein S-100β and erythropoietin differ. In conclusion, xenon anaesthesia offered a significant reduction in noradrenaline administration and it was associated with a lower risk for postoperative delirium in OPCAB patients (Al Tmimi 2015).

Xenon and sevoflurane were also compared in 30 patients undergoing on-pump CABG. In this trial, perioperative inflammatory response was evaluated. In comparison with sevoflurane, xenon anaesthesia triggered pro-inflammatory (Interleukin-6) effects and suppressed the anti-inflammatory response (Interleukin-10). Both groups displayed a comparable increase of oxidative stress and an increase of the cardioprotective mediators migration inhibitory factor (MIF) and

CXCL 12/SDF-1α. MIF levels decreased in the xenon group, whereas it remained elevated in sevoflurane group (Breuer 2015)

In a large, international, multicenter randomized noninferiority trial, xenon, sevoflurane and propofol-based TIVA were compared in 492 low-risk, elective, on-pump CABG patients. The primary outcome was cardiac troponin I release 24 hours after surgery and secondary outcome was the feasibility and safety of xenon anaesthesia. The study demonstrated, that xenon was superior to propofol-based TIVA and noninferior to sevoflurane in respect of troponin release 24 hours after on-pump CABG surgery. Xenon-based anaesthesia maintenance was feasible with no concerns of safety or clinically relevant differences perioperatively or during postoperative recovery when compared to the other two regimens. This study was also confounded by the methodological necessity, that the two inhalatory anaesthetic regimens had to be interrupted with propofol-based TIVA during CPB period, which may have reduced the nevertheless significant differences in postoperative troponin I concentrations (Hofland 2017).

In conclusion, xenon anaesthesia provides equal surgical anaesthesia when compared to traditional anaesthetics. However, xenon is associated with a broad spectrum of favorable cardiovascular properties during anaesthesia.

In a preliminary report of our study, xenon with MTH (n = 17) was compared to MTH only (n = 21) in a subpopulation of patients, who had complete echocardiographic data (before MTH or Xe exposure, 20 hours after MTH commencemant, 24 hours after completing rewarming and at discharge from hospital or after 7 days) available. Left ventricular ejection fraction (LVEF) and global peak systolic longitudinal strain (GLS) were compared between groups at the different time points. LVEF was moderately reduced in both groups at ICU admission, but after 24 hours after completion of MTH and xenon therapy, both LVEF and GLS were significantly higher. This finding can be interpreted as an accelerated recovery from myocardial dysfunction after cardiac arrest in the patients whose post-arrest care with MTH was replenished with xenon inhalation (Ballo 2017).

2.4.7 Xenon and neonatal asphyxia

Perinatal asphyxial hypoxic-ischaemic encephalopathy is a major cause of acute mortality and chronic neurocognitive morbidity in infants and children worldwide (Vannucci 1997). It occurs approximately in 1–6/1000 live human full-term births at or shortly after birth with an acute mortality of 15–20 %. Severe, permanent handicapping conditions, such as cerebral palsy, blindness, deafness, epilepsy and global developmental delay are present in quarter of survivors (Vannucci 1997,

Perlman 1999, Volpe 2008), which establishes a major burden for the infant, the entire family and the community (Azzopardi 2009).

Although the underlying mechanisms differ from hypoxic-ischaemic brain injury following OHCA, neonatal asphyxial brain damage shares common features with OHCA encephalopathy. Based on neonatal animal models of hypoxic-ischemic injury, excessive and prolonged cytotoxic activation of NMDA glutamate receptors leads, at least partly, to destructive, evolving cascade of necrotic and apoptotic brain cell death (Nakajima 2000, Johnston 2001, Gill 2002). Studies involving xenon neuroprotection in experimental neonatal asphyxia models are summarized in table 4.

Table 4. Experimental animal studies of neonatal asphyxia and xenon neuroprotection. Rice - Vannucci model: After unilateral carotid ligation, the animals are exposed to hypoxemic conditions in a gas chamber with 8 % oxygen concentration. Abbreviations: MTH = mild therapeutic hypothermia, Xe = xenon

Neonatal asphyxia					
Authors	**year**	**Model**	**Species**	**Xenon**	**Results**
Ma et al	2005	Right carotid ligation + 90 min hypoxia (Vannucci model)	Rat pup	20–70 % 90 min; during, or 2 to 24 hours after hypoxia	Synergistic neuroprotection by MTH and Xe
Martin et al	2007	Right carotid ligation + 90 min hypoxia (Vannucci model)	Rat pup	20 % with asynchronous MTH 35°C	MTH + Xe increased neuroprotection
Hobbs et al	2008	Left carotid ligation + 90 min hypoxia (Vannucci model)	Rat pup	50 % 3 hour + MTH	Combination better than Xe or MTH alone
Thoresen et al	2009	Left carotid ligation + 90 min hypoxia (Vannucci model)	Rat pup	50 % 1 hour vs 3 hour immediate or delayed + MTH	Combination better than Xe or MTH alone. 3h Xe best neuroprotection
Chakkarapani et al	2010	Hypoxemia with FiO_2 5–7 %	Rat pup	50 % 18 hours with MTH	Histological, global and regional neuroprotection with the combination
Faulkner et al	2011	Transient cerebral ischemia	Piglet	50 % + MTH	Brain MRI spectroscopy injury mitigated
Sabir et al	2014	Unilateral carotid ligation for 90 min	Rat pup	0, 20, 50 % + MTH or 4 hours delayed	Simultaneous treatment neuroprotective

The first postinsult therapy proven effectively improve neurologic outcome after hypoxic-ischaemic neonatal asphyxia was mild hypothermia, as demonstrated in a neonatal asphyxia model in newborn piglets and rat pups (Bona 1998).

The combination of mild therapeutic hypothermia and inhaled xenon was then demonstrated to be neuroprotective in several animal models. Ma and co-workers

illustrated in rat pup model of neonatal asphyxia, that xenon 20 % and hypothermia administered 4 hours after hypoxic-ischaemic injury provided synergistic neuroprotection assessed by morphological criteria, by hemispheric weight and by functional neurological assessments up to 30 days after the insult. When hypothermia and xenon were administered alone, no protective effect was seen (Ma 2005). Hobbs and co-workers confirmed the same finding in rat pups: Xenon 50 % with hypothermia 32° C additively conferred greater protection after hypoxic-ischaemic injury than either treatment alone. The histopathology changes were improved in the combination of the interventions as well as the functional improvement over 10 weeks follow-up into rat adulthood was sustained (Hobbs 2008).

Dingley and co-workers compared xenon 50 % to oxygen 30 % in a rat pup model of hypoxic -ischaemic insult provided with 90 min unilateral carotid ligation. The gases were administered for 3 hours. After one week of follow-up, the brains were harvested and a significant global neuroprotection was seen in the xenon group as demonstrated with less cortical, hippocampal and basal ganglia injury (Dingley 2006).

Martin and co-workers showed in the same rat pup model (Rice-Vannucci model of neonatal asphyxia (Rice 1981)), that the combination of xenon and hypothermia increased synergistically neuroprotection, even if they were administered asynchronously (Martin 2007). In the study by Thoresen and co-workers, the authors came to equal conclusion: There was an additive long-term neuroprotection even when hypothermia and xenon inhalation was delivered immediately or delayed after neonatal rat hypoxia-ischaemia (Thoresen 2009). These results were confirmed additionally in a piglet model of neonatal asphyxia, which was induced by reducing the fraction of inhaled oxygen to 5–7 % to depress the background amplitude integrated electroencephalography (aEEG) activity for 45 minutes. 18-hour inhalation of xenon 50 % was compared in induced hypothermia (33,5 °C) or spontaneous normothermia-hyperthermia (38,5 °C). In particular, the authors evaluated requirements of inotropic support, and global haemodynamics during intervention. They concluded, that the current neonatal encephalopathy treatment by induced hypothermia could safely be complemented with inhaled xenon (Chakkarapani 2011).

Several clinical studies in human neonatal asphyxia have been conducted in respect of beneficence of cooling. Gluckman and co-workers showed in a multicentre randomized trial (CoolCap trial), that selective head cooling for 72 hours, within 6 hours of birth, in 218 full-term infants had a beneficial effect on survival in those babies, whose amplitude integrated electroencephalography (aEEG) had initially less severe changes (Gluckman 2005). The NICHD trial (National Institute of Child Health and Human Development) demonstrated, that

there was a significant reduction in death and disability with hypothermia treatment in asphyxical infants at 18 months outcome assessment (Shankaran 2005). Azzopardi and colleagues compared intensive care with cooling of the body to moderate hypothermia of 33,5 °C for 72 hours to sole intensive care in 325 infants suffering from perinatal asphyxial encephalopathy. Cooling did not affect mortality or severe disability, but resulted in improved neurologic outcome at 18 months in those infants who survived (Azzopardi 2009).

Combining xenon inhalation to moderate hypothermia after birth asphyxia was investigated in Total Body Hypothermia plus Xenon trial (TOBY-Xe). With signs of moderate to severe encephalopathy 92 infants were enrolled, with inclusion criteria of either seizures or abnormal background activity shown in aEEG, Apgar score of 5 or less 10 min after birth, sustained need for resuscitation 10 min after birth or acidosis within 1 h after birth. The standard treatment of cooling to 33.5 °C for 72 hours was compared to cooling in combination of inhaled xenon 30 % for 24 hours. The babies were assessed with magnetic resonance (MRI) spectroscopy and MRI fractional anisotropy within 15 days of birth. The authors concluded, that administration of xenon within the delayed timeframe was feasible and safe, but the combination of xenon with mild hypothermia did not enhance the neuroprotective effect of cooling after neonatal asphyxia, addressed with MRI alterations. The authors speculated the lack of efficacy in the combination of xenon and hypothermia by the suboptimal dose, and most importantly, by the significant delay in Xe administration (only 15 % of infants received xenon within 6 hours) and by the severity of asphyxic injury, which was likely to lead to minimal prospect of benefit of any intervention (Azzopardi 2016).

2.4.8 Xenon organoprotection in the kidney

The renal IRI is associated with increased reactive oxygen (ROS) species production and dysfunction of the antioxidant system, resulting in tubular cell injury and cell death (Bonventre 2011). The ensuing inflammatory process involves activation of proinflammatory cytokines and chemokines, complement activation and infiltration of neutrophils, macrophages and T cells (Bonventre 2004). The intensity of this inflammatory response in postischaemic tissue can be so great that the injury affects reperfusion in distant organs (Neary 1999). Inflammation causes acute tubular necrosis, which accounts for 75 % of AKI (Khajuria 2014).

Ma and co-workers demonstrated, that xenon preconditioning before ischemic renal injury or acute renal failure induced hypoxia inducible factor (HIF-1α), which prevented acute renal failure following IRI (Ma 2009). HIF-1α causes upregulation of cytoprotective factors such as erythropoietin and vascular

endothelial growth factor, which can interrupt apoptotic pathway and are known to be protective in several organ injury models (Ma 2009). Additionally, xenon might have a role in kidney transplantation in mitigating the kidney injury resulting from warm and cold ischaemia-reperfusion. In a rodent model of kidney transplantation, xenon exposure of graft donors or of recipients prolonged graft survival following IRI. Xenon -induced cell survival or graft functional recovery was abolished by HIF-1α and small interfering RNA (Zhao 2013).

To summarize, the desired salubrious organoprotection effect after cardiac arrest in different organs are postanoxic and post-conditioning effects. However, the protective effect is restricted and very time-dependent, requiring initiation of intervention as soon as possible, preferably within 8 hours post arrest (De Deken 2016).

Besides xenon, noble gases without anaesthetic properties, namely helium, neon and argon are hypothesized to produce organoprotection. Pagel and colleagues demonstrated in a rabbit experimental infarct model myocardial protection by these gases indepently of an anaesthetic effect. The cardioprotection was mediated by activation of prosurvival signalling kinases and prevention of mPTP opening (Pagel 2007). However, in a rodent cardiac arrest model, replacement of air in a 50/50 % air/oxygen mixture with either helium or argon for 24 hours did not affect clinical outcome or improve hippocampal neuronal damage in rats subjected to 8 min of cardiac arrest (Zuercher 2016).

2.5 Prognostication after OHCA

Prognosis is occasionally expressed as a risk for a good or poor outcome (Callaway 2018). Prognostication is essential in informing the next-of-kin about the chances of recovery and importantly, to identify those OHCA survivors with absent recovery perspectives to dissuade futile extension of life-sustaining treatment (Horn 2014, Keijzer 2018). The best predictor of favourable outcome after OHCA is awakening from coma. The longer the patients remain unresponsive, indicates greater risk of permanent brain injury (Friberg 2013). Most patients remain comatose after successful resuscitation, and the duration of unresponsiveness is prolonged with regulation of body temperature and concurrent mechanical ventilation requiring sedation and neuromuscular blocking agents (Cronberg 2018). The main objective in OHCA prognostication is primarily to identify the patients, who certainly have a poor outcome, but simultaneously, limit the degree of self-fulfilling prophecy associated with presumption of unfavourable neurologic prognosis (Horn 2014, Oddo 2017). Namely, an announcement of a humble prognosis prompts discussion of withdrawal of life-sustaining treatment (WLST), which independently impacts nurses' and physician's attitudes and eventually

patient care and ensures poor outcome (Püttgen 2007). Confounding issues, which include hypothermia-induced delayed clearance and accumulation of sedative drugs, hepatic or especially renal dysfunction, must be carefully excluded as the cause of delayed awakening (Rossetti 2016).

The first-line approach of assessing prognosis of comatose patients has generally been neurologic examination. The classical findings suggesting poor prognosis are absent motor response to pain better than extension and lack of brain stem reflexes, including corneal, papillary and oculocephalic reactivity at 72 hours (Wijdicks 2006). However, the residual effects of sedative accumulation and targeted temperature management delay motor response and additionally brain stem responses rendering sole early clinical examination inaccurate and potentially inappropriate to decisive prognostication (Ben-Hamouda 2014, Oddo 2014). Worstly, a premature prognostication based solely on neurological examination, can lead to termination of life-supporting therapy in almost 20 % of patients, who are potentially prone to neurological recovery (Perman 2012). Moreover, preserved brain stem reflexes and motor response do not translate to or predict a good outcome (Adrie 2006). Even though, assessments by clinical examination are still recommended by the American Academy of Neurology (Wijdicks 2006) and lately, in guidelines from the European Resuscitation Council and the European Society of Intensive Care Medicine, as a part of multimodal prognostication approach (Nolan 2015).

Two thirds of eventually deceasing patients admitted to ICU after OHCA die from a neurological injury. Most of the deaths are due to active WLST based on prognostication of a pessimistic and presumed poor neurological outcome, which is defined as death, persistent unresponsiveness, or the inability to undertake independent activities after 6 months (Wijdicks 2006). Accurate assessment of an uncertain neurological prognosis with correct interpretation of potential functional recovery ensures that treatment intensity is in line with patient's preferences or advance directives (Girotra 2015). A decision of limitation or withdrawal of intensive care will almost inevitably portend the death of the patient and a self-fulfilling prophecy occurs, when outcome is predicted too prematurely, e.g. during residual sedation originating from sedative and paralytic drug accumulation during hypothermia (Cronberg 2018).

In the analysis of 939 TTM-trial patients, nearly half of the trial patients had regained consciousness and 15 % of OHCA survivors died, mostly for non-neurological reasons before 72 hours after the end of TTM. At this scheduled time point for assessment, 33 % of patients remaining unconscious were subjected to neurological prognostication and three level-of-care recommendations for ICU treatment were advocated: 1) continue treatment, 2) do not escalate treatment and 3) withdraw treatment. This approach resulted in that 66 % of in-hospital deaths

occurred after WLST. Over half of the patients died during their ICU stay. The median day of WLST was day 6. Of the patients involved in neurological prognostication, 79 % had deceased within 6 Months and only 15 % had a favourable neurological outcome (Dragancea 2017). If WLST is prohibited, as in South Korea, surviving translates to almost half of the OHCA victims having a poor neurocognitive outcome at 6 months (Kim 2016).

No pre-arrest or intra-arrest parameters, including underlying morbidity, arrest duration or bystander CPR accurately predict outcome in individual patients achieving ROSC (Peberdy 2010). However, scoring systems have been developed to depict unfavourable outcome early, already at hospital admission. In the "OHCA score", outcome prediction was validated in 130 OHCA patients and initial rhythm, *no-flow* and *low-flow* intervals, blood lactate and creatinine levels were identified independently to be associated with poor outcome (Adrie 2006). Another non-neurological pretest probability of survival and recovery is the "CAHP (Cardiac Arrest Hospital Prognosis) score", which was developed in 819 OHCA patients and poor outcome was defined as CPC score 3–5 at hospital discharge. Based on independent association with poor outcome, seven variables (age, non-shockable rhythm, *no-flow* and *low-flow* intervals, location of cardiac arrest, adrenaline dose and arterial pH) were identified and the scoring presented three patient risk groups (low risk, medium risk and high-risk), which establish the fundamental basis of early risk stratification (Maupain 2016). Both scoring systems were validated statistifically significantly. However, it should be borne in mind, that any scoring may be highly reliable in population-based estimation, but consistently in clinical medicine, prediction of an individual single patient's outcome solely based on any scoring is hazardous, discouraged and potentially misleading, including inappropriate WLST (Wijdicks 2006, Püttgen 2007, Bougouin 2018).

Therefore, assessment of neurological prognosis should be delayed for at least 72 hours post rewarming (Morrison 2010) or even beyond 72 hours, which was suggested by the Swedish Resuscitation Council (Cronberg 2013). When predicting a poor outcome, the false positive rate should be zero. The contemporary prognostic tests focus almost entirely on the first few days after OHCA, although the awakening with eventual good outcome is occasionally delayed beyond the first week is some patients (Gold 2014, Oddo 2017). Especially, the 72-hour mark is not a magic deadline, where patients who have good outcomes are expected to awaken (Fugate 2015). In particular, concern has risen about the obvious existence of late awakeners and the risk of inadequate and arbitrary premature determinations of neurological outcome (Gold 2014, Cronberg 2018, Velly 2018). Potential late awakeners have been characterized e.g. by the circumstances surrounding their OHCA: initial rhythm of VF, witnessed arrest and received bystander CPR. Age was not identified to be predictive of belated aweakening (Gold 2014).

2.5.1 Biochemical markers facilitating prognostication

The rationale of blood molecular markers of resuscitated patients is that higher levels of biomarkers correspond to more pronounced neuronal injury and consequently limited chances of recovery. Additionally, blood assessments are relatively easy to sample and likely to be independent from the effects of sedative drugs (Sandroni 2015). Elevated lactate values at hospital admission and at 12 hours during follow-up were demontrated to associate with mortality at 30 days in a post-hoc analysis in 877 patients in the TTM -trial (Düring 2017).

The most utilized molecular cerebral injury marker assays include neuron-specific enolase (NSE), a cytoplasmic enzyme of neuron glycolysis, and the astroglial protein S100β, a calcium-binding soluble protein regulating neuronal differentiation and apoptosis (Snyder-Ramos 2003). High concentration of S100β is also found in some malignancies including melanoma, glioma, schwannoma and neuroblastoma (Martens 1998). Another potential confounder is the S100β release from muscle, adipocytes and chondrocytes, which may cause an initial false positive elevation after CPR circumstances, including chest compressions (Haimoto 1987, Scolletta 2012). Serum levels of S100β peak within 24 hours of cardiac arrest, and may therefore reflect systemic inflammation response and not the severity of hypoxemic cerebral injury (Tiainen 2003), although sustained S100β elevation has been demonstrated to accurately predict outcome (Rundgren 2009, Mörtberg 2011).

NSE is released from dying neurons and its concentration correlates with the magnitude of neuronal injury (Rossetti 2016). In post cardiac arrest patients, NSE values were significantly higher in patients who did not regain consciousness (Meynaar 2003). Formerly, it was believed, based on the data of a prospective randomized trial, that NSE values of more than 33 μg/l, sampled between 24 and 72 hours post arrest, were strongly predictive of poor outcome with no false positives (Zandbergen 2006). Shortly, a prospective trial, however, demonstrated, that an increment in NSE values sampled at 24 and 48 hours post OHCA was specific but only moderately sensitive indicator of 6-month outcome (Oksanen 2009). Furthermore, a retrospective data analysis illustrated, that cut-off values of S100β or NSE do represent many false positive estimates and are not sufficiently predictive of neurologic outcome (Zellner 2013). Moreover, instead of a definitive NSE cut-off point predicting poor outcome, serial NSE measurements with an increasing trend of values might be more accurate predictor of escalating neuronal injury (Tiainen 2003, Sandroni 2013, Nielsen 2013, Sandroni 2014).

We could confirm this finding in a preliminary analysis of our trial, where increment of NSE-values from 24 and 48 to 72 hours post OHCA distinguished non-survivors from survivors (Arola 2013).

In a recent analysis of 1053 in- and out-of-hospital cardiac arrest patients, again a threshold value of NSE over 90 µg/l was suggested to predict poor outcome of CPC 4–5 with almost nonexistent false positives (Streitberger 2017). However, there are still cautious reports about some individual patients with eventually good neurologic outcome, despite peaking high NSE values (Schummer 2010).

Confounders of NSE elevation include NSE- secreting tumors (i.e. parvocellular pulmonary cancer), concurrent acute brain diseases and haemolysis, which significantly distorts NSE values. Different assays may, moreover, differ as much as 40 % (Stern 2007). Presence of haemolysis should actively be considered, particularly by routine haemolysis quantification (Streitberger 2017).

A novel biomarker for post cardiac arrest prognostication is neurofilament light chain (NFL), which is elevated in cerebrospinal fluid or blood corresponding to white matter axonal injury in various neurologic conditions (De Marchis 2018). In the substudy of TTM trial, in 717 OHCA patients, it was recently demonstrated, that serum NFL concentration assay analyzed at 24, 48, and 72 hours after cardiac arrest highly predicted a long-term poor neurologic outcome (CPC 3–5) at 6-month follow-up (Moseby-Knappe 2019).

2.5.2 Neurophysiologic assessments

2.5.2.1 Electroencephalography (EEG)

Electroencephalography (EEG) is a non-invasive, relatively inexpensive and largely available assessment of cortical damage following cardiac arrest (CA). Interpretation of EEG, however, requires considerable experience and expertise (Püttgen 2007). Among expert interpretation of EEG, malignant patterns after CA are recognized in substantial agreement, but interpretation of e.g. reactivity is not as univocal (Westhall 2015). Absence of cortical activity on EEG immediately after restoration of circulation overestimates and does not accurately predict unfavourable outcome and intensivists are advised to postpone ordering of EEG at least 24 hours to avoid incorrectly disappointing interpretation (Jørgensen 1999). Intermittent two standard EEG recordings of 20–30 min (within 48 hours after OHCA) including stimulations of reactivity post OHCA has been demonstrated to be as informative as continuous EEG, with the exception of post-arrest status epilepticus, where continuous EEG approach is advocated (Alvarez 2013). Suggested time points for standard EEG assessment could be during TTM, after rewarming and cessation of sedation (Ben-Hamouda 2014). Three main EEG features need to be systematically assessed: background activity, background reactivity and epileptiform features (Rossetti 2016). Continuous EEG background activity is a robust, but strong early predictor of recovery, but residual sedation

may confound interpretation of quantitative EEG after CA (Callaway 2018). Validated and adapted criteria as well as standardized guidelines for post-cardiac arrest EEG interpretation were published by the American Clinical Neurophysiology Society (Westhall 2015). However, these definitions are still contradictory and under debate (Backman 2017).

Seizures and myoclonus are common after CA and the use of continuous EEG to monitor EEG patterns and trends as well as to detect postanoxic status epilepticus has been advocated (Hovland 2006, Cloostermans 2012). However, during MTH, generalized, tonic-clonic, focal epileptic seizures and myoclonus are likely to be suppressed by routine sedative administration (Cronberg 2013). Notably, the added value of EEG-based coma prognostication in the clinical setting still needs to be demonstrated (Friberg 2013, Duez 2019).

Clinical seizures, including myoclonus, may or may not be of epileptic origin as there are several types of myoclonus of which the majority are non-epileptic without electrographic changes. Various presentations of post-arrest motor manifestations can be misinterpreted as seizures (Legriel 2009, Benbadis 2010, Rittenberger 2012).

Nonepileptic movements can present as the appearance of almost purposeful responses to discomfort, induced by common nursing activities such as mobilization or stimulation, by repositioning or suction, all of which are highly deterrent to visiting relatives (Benbadis 2010, Bouwes 2012). Generalized periodic epileptiform discharges (GPEDs) are often depicted as malignant EEG patterns, which portend poor long-term clinical prognosis, if the OHCA victim survives (Ribeiro 2015). Further findings prognosticating death without regaining consciousness are a discontinuous EEG background before the start of electrographic status epilepticus. However, in possibly surviving patients, a continuous EEG background was present prior status epilepticus, which developed at the median time of 46 hours post arrest (Dragancea 2015).

Some quantitative EEG parameters have been identified to differentiate patients with poor or good outcomes after OHCA and TTM. These include burst-supression ratio, wavelet subband-, response- and state entropy. The value of these relatively simple quantitative values need, however, to be confirmed in larger patient populations (Wennervirta 2009). The classification of these patterns has extensive variation between studies (Rundgren 2010, Cloostermans 2012).

Myoclonus is the abrupt and involuntary twitching of a muscle group, which may have cortical or subcortical origin (Bouwes 2012). Generalized myoclonus (face, trunk and/or limbs) appearing early (< 24 hours post CA) is usually, but not always, a sign of severe cortical injury and an indicator of unfavorable outcome (Wijdicks 1994). A major development in EEG based prognostication was the understanding that there are different types of postarrest seizures, which are still

ominous conditions, but some of the victims still might have a possibility to recover (Elmer 2016). Status epilepticus (myoclonus and EEG seizures) should be distinguished from myoclonic seizures and reticular status myoclonus, which are myoclonus without EEG seizures. In reticular status myoclonus the cerebral cortex is too damaged to generate epileptiform waves. It is a sign of critical global cortical and subcortical injury and associated with premature death (Lucas 2012).

A rare consequence after cardiac arrest is Lance-Adams syndrome, an action-induced myoclonus, which is associated with good recovery, even though myoclonus symptoms are difficult to control (Rossetti 2009, Lee 2011).

Survival after post arrest seizures with good neurologic recovery has been demonstrated to be possible in several studies. The identified particular subgroups of patients have late seizures, appearing after rewarming and off sedation. Moreover, they had retained brain stem reflexes, reactive and continuous EEG background and preserved somatosensory evoked potentials (SSEP) (Rossetti 2009, Lucas 2012, Legriel 2013).

2.5.2.2 Somatosensory evoked potentials (SSEP)

Assessing short-latency SSEP involves electrical stimulation of peripheral nerve, usually the median nerve at the wrist and responses are registered over the contralateral sensory cerebral cortex, expected to appear within 20 ms (N20 potential). SSEP responses are regarded as reliable even when the patient is sedated, in contrast to EEG (Zandbergen 2006, Fugate 2010). SSEP are commonly used predictors of outcome after OHCA, especially in multimodal prognostication approaches. The bilateral absence of N20 SSEP wave assessed after rewarming, in a technically well-performed test, entails death or poor vegetative state with a specifity of 95–100 % (Zandbergen 2006, Cronberg 2013). Further treatment will be regarded futile and palliative or end-of-life care should be launched (Zandbergen 1998). However, any other isolated SSEP findings, including preserved N20 potentials, does not imply a good outcome and could be misleading and prone to the bias of self-fulfilling prophecy and premature WLST (Sandroni 2013, Karapetkova 2016). In multimodal assessment using several ancillary tests, SSEP and EEG provide complementary information and are ambiguous whenever used alone (Callaway 2018).

2.6 Imaging post cardiac arrest brain injury

Given the significant impact on survival, quantitative evaluation of post arrest hypoxic–ischaemic brain injury has a central part in prognostication and additionally when addressing the neuroprotective effect of various post arrest

interventions. The concept of intervening and mitigating an on-going ischaemic cerebral injury was introduced in 1974, when Hossmann and Zimmermann demonstrated in mammalian brains, that induced ischaemia in rhesus monkeys for up to an hour is a modifiable target and can be at least partially recovered (Hossmann 1974).

Evaluation of the efficacy of any neuroprotective intervention requires objective quantification of the neuronal injury, usually by imaging or by biochemistry. Moreover, the timing and accuracy of clinical assessments is challenging, especially during the first week after OHCA when lingering effects of sedatives, neuromuscular blocking agents and hypothermia limit accurate clinical neurological examinations (Velly 2018). Therefore, the sensitivity and specificity of performed assessments, biochemical or any imaging, should be objective, unbiased and reproducible, include a high level of certainty and identify the very patients, who have no meaningful likelihood of recovery (Wijman 2009).

2.6.1 Hypoxic-ischaemic brain injury properties

Within minutes after cardiac arrest and cerebral hypoxia and ischaemia, energy depletion results in cytotoxic edema in the areas considered most vulnerable to injury, the vascular border zone watershed areas of the cerebral grey matter hemispheres supplied by the most distal branches of the main brain arteries (Busl 2010, Okamura 2010). Hypoxia reflects reduction of oxygen supply or utilization, whereas ischaemia describes blood supply reduction and decreased oxygen delivery including limited or nonexisting removal of damaging cellular metabolites, such as lactate, protons and glutamate, which will then accumulate exacerbating brain injury (Howard 2012).). The traditionally most vulnerable and commonly injured area after prolonged ischaemia is the pyramidal neurons of the hippocampus, neocortex and cerebellum (Petito 1987, Madl 2004, Greer 2013). During the following days, increase of blood brain barrier permeability and vasogenic oedema will enhance the swelling (Järnum 2009, Okamura 2010, Sangalnamath 2016). If the patient starts to recover, primitive brain stem functions, like breathing and pupillary reflexes, reappear first, followed by the return of activities in deeper structures of the brain (Xiong 2011). Eventually, cortical activity and consciousness might recover (Jørgensen 1998). However, 30–70 % of these patients never regain consciousness (Tiainen 2007, Neumar 2008, Rossetti 2016).

Greater blood flow, synaptic activity and higher metabolic rate in grey matter are conventional explanations of grey matter ischaemic vulnerability. Most of the dendrites with postsynaptic glutamate receptors are located in the grey matter (GM) explaining the susceptibility to glutamate excitotoxicity (Arbalaez 1999,

Huang 2008, Gutierrez 2010, Kim 2013). However, there has been a marked discrepancy correlating GM lesion size and the ultimate functional outcome, which can be worse than expected by the volumetric measurement of cortical and subcortical infarction (De Vries 2001). Clinical experience also indicates, that human ischaemic brain injury is almost never restricted to GM (Goldberg 2003).

2.6.2 Hypoxic-ischaemic white matter injury

Previously, it was assumed, that cerebral white matter (WM) is less vulnerable to ischaemia than GM (Marcoux 1982, Pantoni 1996). This may be an under-appreciation and reflection of experimental animal stroke research, which could have misrepresented WM injury less important, originating from that the WM volume in rodents is only about 14 % (Zhang 2000). However, in humans, white matter comprises about 50 % of forebrain volume (Zhang 2000, Matute 2012a). Major components of cerebral WM are myelinated or unmyelinated axons, and their glial cell partners including astrocytes, oligodendrocytes and blood vasculature supporting their correct function (Goldberg 2003, Matute 2011, Matute 2012b). The metabolic rate of WM deduced from glucose consumption is, however, very comparable to GM (Harris 2012).

The vasculature for the deeper cerebral white matter consists of widespread linear arterioles with sparse anastomoses, demanding that these WM neurons are provided with a continuous supply of energy along their entire length, although they are metabolically independent of their cell bodies in respect of energy metabolism (Matute 2012b). This makes central white matter highly vulnerable to focal hypoxic ischemic injury (Busl 2010, Matute 2012b, van der Eerden 2014). Essentially, compromised blood supply originating from various reasons, results in isolated WM strokes, depicted as lacunar strokes, which in humans represent 20–25 % of all ischaemic strokes (Fisher 2011, Matute 2012b). Cerebral WM, of which the largest cellular volume component is axons, represents a significant repository of intracellular glutamate, which is released under ischaemic conditions (Doyle 2018). WM is highly susceptible to excessive excitotoxic neurotransmitter signalling, such as ischaemia-reperfusion induced excitotoxicity involving glutamate release, over-activation of glutamate receptor and ensuing cytotoxic Ca^{2+} activation, which result in WM demise (Fern 2019). Postischaemic excitotoxicity results in over-activation of oligodendrocyte functional NMDA and ultimately in non-NMDA glutamate (AMPA and kainate-preferring) receptors, which are frequently expressed in all WM cell compartments, especially in myelin (Karadottir 2005, Fern 2019). Ensuing WM injury, in effect by the primary or secondary breakdown of axons, occurs acute (Chalela 2001), subacute (Arbalaez 1999) or delayed and progressive after global ischemia (Plum 1962).

White matter attributes to cerebral regions abundant of myelinated axons, which are responsible for neural connectivity and signal transmission between various areas of the brain (Matute 2012a, Agematsu 2016). As a consequence, injury in WM leads to miscellaneous neurocognitive dysfunction, ranging from mild functional disability such as impairment of memory, visuospatial and perceptual problems to the dismal long-term disability characterized by detriment of awareness and insufficiency in arousal resulting in permanent unresponsiveness or vegetative state (Hoesch 2008, Girotra 2012, Stevens 2014, Callaway 2018, Keijzer 2018). Long-term cardiac arrest hypoxemia consequences may appear gradually and include a 10 % reduction of bilateral hippocampal volume accompanied with marked verbal memory deficits, also in patients who were discharged from hospital with a good neurological performance (Stamenova 2018).

Imaging experimental white matter injury is technically challenging in rodents that display a lower WM/GM ratio than humans. This ratio is, however, comparable and close to humans in nonhuman primates (Gladstone 2002). In the experimental stroke study in marmosets, Bihel and colleagues demonstrated in serial magnetic resonance imaging (MRI) examinations, that diffusion tensor MRI revealed pathological changes and disorganization of WM, despite absent visible ischaemic lesions in conventional MRI images at the chronic stage. The disruption of WM was strongly correlated with the chronic sensorimotor deficits (Bihel 2011).

The evaluation of brain WM injury is particularly important, when assessing OHCA survivors, who remain unresponsive after weaning from sedation. Conversely, some of these patients could have presented apparent cortical damage, displayed in initial diffusion weighted MRI. However, in patients remaining comatose, cortical changes are gradually replaced by WM changes (Greer 2011, Gerdes 2014). Deep white matter involvement is prominent as a late post ischaemic brain injury leucoencephalopathy (Howard 2012).

2.6.3 Brain computed tomography

Brain computed tomography (CT) detects abnormal features for the most part due to oedema generation, specifically sulcal effacement and widespread ischaemia with qualitative loss of margins of grey-white matter differentiation. Noncontrast CT studies do not detect pathology at the cellular level and the reliance of CT is based on gross features limiting its sensitivity (Hayman 2018).

Profound anoxic brain damage following OHCA may be present in brain imaging already at hospital admission. However, this information may not be for logistic reasons immediately available, when decisions of TTM commencement are considered (Jeon 2017). Loss of grey-white matter differentiation corresponds to poor neurological outcome, and occurs commonly, in one-third of OHCA patients

evaluated with cranial CT (Langkjær 2015). Moreover, loss of grey-white differentiation is rather coarse finding, and it identifies only the worse anoxic encephalopathies and it is subject to intra-observer variability (Hayman 2018).

In the sub-analysis of TTM-trial, findings of generalized oedema on non-contrast head CT was a reliable predictor of poor outcome (Moseby-Knappe 2017). There is also some evidence, that demonstration of a low brain grey matter to white matter ratio (GWR) obtained from a CT scan performed within 1 hour after ROSC, provides valuable information about a presumed poor outcome (Kim 2013, Scheel 2013, Gentsch 2015). GWR is measured with CT Hounsfield units in grey and white matter and calculating the ratio of both (Metter 2011). The accuracy in GWR outcome prediction increases, when it is combined with optic nerve sheath diameter measurement, which correlates to increased intracranial pressure (Chae 2016). However, the predictive performance of GWR has additionally demonstrated to be poor and useless (Lee 2015).

Even though, in respect of detecting brain white matter injury, the sensitivity of CT is low (Hayman 2017). Most importantly, CT scans performed very early after OHCA are most often normal, and thus of limited value (Yanagawa 2005). Patients with dramatic changes at CT do not pose diagnostic dilemmas (Wu 2009).

2.6.4 Brain magnetic resonance imaging

Magnetic resonance imaging (MRI), through the use of diffusion-based techniques, can provide a non-invasive insight into the living brain (Bach 2014). It provides quantitative parameters related to white matter cellular swelling, water-shifts between extra- and intracellular compartments and minor changes in tissue water content (Tournier 2011). Each MRI sequence consists of thousands of voxels of one cubic millimeter. Measurements of the MRI signal attenuation from water diffusion are calculated within each voxel. Much of the knowledge about alterations in brain white matter microstructure obtained from diffusion MRI originates from studies that compared diffusion markers between populations of interest, e.g. with and without an intervention or more commonly, between a healthy control group and a diseased population (Bach 2014).

Cellular cytotoxic oedema manifests as an increased signal on diffusion weighted imaging (DWI) and decreased signal on whole-brain apparent diffusion coefficient (ADC) imaging (Gutierrez 2010, Keijzer 2018). ADC is a scalar quantity very related to the mean diffusivity of water molecules in a voxel and it expresses the propensity of water diffusion in any direction within a voxel. Low whole brain ADC has been demonstrated to correlate with poor outcome (Wu 2009). DWI identifies early cytotoxic oedema and provides adjunct prognostic value after OHCA (Hjort 2005). However, the clinical studies involving ADC and

DWI are mostly descriptive and do not draw correlations between imaging characteristics and functional outcome (Wu 2009) with a potential to WLST (Hirsch 2016). Furthermore, ADC values are likely to be affected by temperature (Yenari 2000). Clinically, DWI is frequently used to provide an understanding of the qualitative extent of hypoxic-ischaemic damage (Greer 2012). Jeon and colleagues demonstrated, that the combination of GWR and DWI assessed shortly after hospital admission improves the sensitivity of predicting neurological outcome (Jeon 2017).

In the small prospective study in 12 patients DWI within 36 hours after global cerebral hypoxia differentiated pathological changes, which corresponded to worse clinical outcome after 6 months (Th 2004). Wijman and colleagues corroborated this in the larger prospective study, where 71 OHCA patients remaining comatose after weaning from sedation were scanned within 7 days post arrest, after they had regained normal body temperature after TTM. Functional outcome after 1, 3, and 6 months was assessed with Glasgow Outcome Scale (GOS). The final analysis constituted of 51 patients. The preliminary results demonstrated, that high quantitative ADC signals distinguished survivors and patients with low ADC signals, who died or remained in vegetative state. None of the patients with over 10 % of brain tissue with an ADC value below 650 x 10^{-6} mm^2/s to 700 x 10^{-6} mm^2/s regained consciousness during the follow-up to 3 months. This translates to that quantitative brain DWI may be a useful adjunct in the outcome prediction for post cardiac arrest patients, who prolongedly remained comatose. Additionally, it may provide information on the likelihood of long-term neurological impairment among survivors (Wijman 2009).

However, the ideal time window of DWI and ADC for prognostication is short (within 3 to 5 days after OHCA), and brain region dependent (cortex, hippocampus, putamen and corona radiata) with low sensitivity (25–30 %) for unfavourable outcome, despite high specifity (95 -100 %) (Mlynash 2010, Greer 2013).

2.6.4.1 Diffusion tensor imaging

Diffusion Tensor imaging (DTI) is a brain MRI sequence and an extension of DWI, which enables the measurement of restricted diffusion of water in tissue to produce neural tract images by characterizing the three-dimensional diffusion of water as a function of spatial location (Basser 1994). It provides specific information on the nature of brain white matter damage, besides injury localization. It addresses white matter tract connectivity and axon disruption, which takes place during ischaemia reperfusion and inflammation. DTI allows measuring of directional preference of water molecules, which facilitates to make inferences about the underlying tissue microarchitecture (Luyt 2012). This illustrates tissue microstructure, cellular

density, integrity and alterations in the directionality of the neural tract (Abe 2010). In cardiac arrest patients, prominent feature in DTI imaging is marked decrease in axial diffusivity in central brain regions and in cerebral hemispheres (van der Eerden 2014). DTI allows assessment of WM degeneration after OHCA much earlier than by traditional structural MRI, which may not demonstrate the full extent of WM injury at the early post-arrest phase (Gerdes 2014).

2.6.4.2 Tractography

In tractography, collected DTI data from specified regions of interest is processed with a mathematic three-dimensional modelling technique to visually represent nerve tracts. These two- or three-dimensional images, tractograms, generate anatomically probabilistic estimates of white matter trajectories and display the continuity, asymmetry and breakdowns of neural tracts (Alexander 2007, van Baarsen 2016). This method uses both deterministic and probabilistic algorithms and has generated tract reconstructions of major projection pathways, e.g. corticospinal tract, corona radiata, corpus callosum, cerebellum and association pathways, such as arcuate, inferior longitudinal and uncinate fasciculus (Stieltjes 2001, Mori 2002, Farquharson 2013, van Baarsen 2016). Tractography is, however, sensitive to thermal noise, physiologic fluctuations and image artifacts generated by e.g. overlapping or crossing white matter pathways. Even though, it provides plausible three-dimensional visualization of white matter trajectories in relation to brain pathology (Alexander 2007, Lerner 2014).

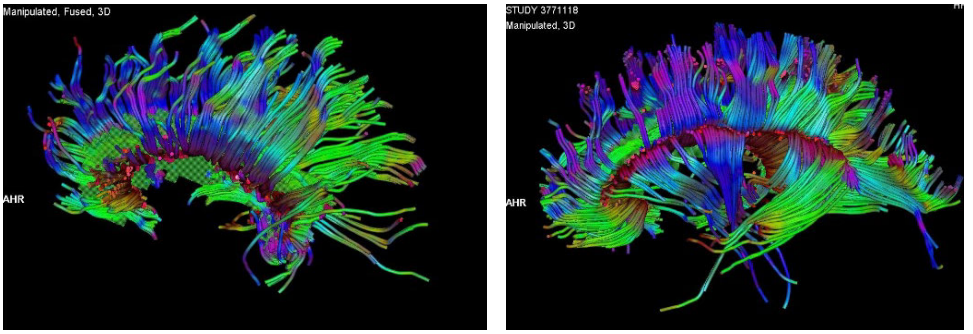


Figure 2. Tractography images from 2 subjects from the Xe-Hypotheca trial. Visual representation of white matter tract continuity and missing trajectories are displayed

2.6.4.3 Fractional anisotropy

The free water diffusion is termed isotropic diffusion, where molecular motion is equal to all directions. This may be found in the cerebrospinal fluid spaces, except

at the orifices of foramen Monro or the aqueduct of Sylvi (Mukherjee 2008). If the water diffuses in a medium with barriers, the diffusion is not uniform, which is termed and quantified as fractional anisotropy (FA) (Pierpaoli 1996). Anatomical connectivity indicates, how strongly directional local white matter tract structures are, which is quantified by FA measurement. Parallel organization of white matter fiber bundles with cell membranes, axon myelin sheaths, intracellular microtubules and various proteins hinder the diffusion of water and provides the basis for evaluation of scalar summaries of diffusion anisotropy (Alexander 2007). FA represents the standard deviation of the three diffusion eigenvalues, divided by their root-mean square (Pierpaoli 1996).

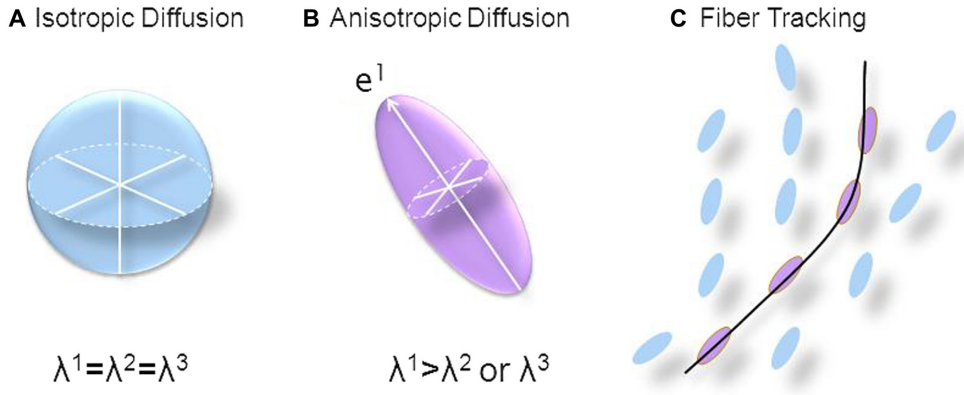


Figure 3. **A)** In isotropic diffusion, all of the eigenvalues (λ) or diffusion coefficients are equal. **B)** In anisotropic diffusion, the diffusion coefficient varies, when measured along different directions. FA is calculated from the eigenvectors (e^1) and measures the fraction of the magnitude of the diffusion tensor that is anisotropic and its directionality, represented as an ellipsoid. **C)** Fiber tracking is initiated at region of interest and tracking is propagated along adjacent ellipsoids that meet certain tresholds for FA and trajectory curvature (Lerner 2014, reproduced with permission).

FA is highest within white matter tracts (with a maximum theoretical value 1), lower in grey matter and approaches 0 in cerebrospinal fluid (Smith 2007). FA is a quantification of the directionality of water in the tissue, which corresponds to white matter organization and disorganization and it allows also quantitative comparison across subjects (Smith 2006). Low FA values correspond to brain white matter ischaemia, myelin damage, axonal degeneration and oedema, which all attenuate the water directional diffusivity in white matter tracts (Liu 2007). FA provides superior functional and anatomical information to the scalar parameters such as ADC (Luyt 2012).

In the study by Velly and colleagues, 150 OHCA victims remaining unconscious for at least 7 days after OHCA were assessed with whole brain white

matter fractional anisotropy measured with DTI. The prognostic accuracy of neurological outcome was compared to conventional MRI sequences (fluid-attenuated inversion recovery (FLAIR) and DWI). The neurological outcome was graded by Glasgow-Pittsburgh CPC at 6 months, as either favorable (CPC 1–2) or unfavorable (CPC 3–5). Prognostication performance was compared by assessing the receiver operating characteristic (ROC) curves between groups. The ROC curve was significantly higher in normalized white matter FA values than with the standard criteria for unfavorable outcome or other MRI sequences. The authors concluded, that normalized or unaltered white matter FA predicts accurately neurological outcome at 6 months. In respect of late awakeners, 12 patients were identified with eventually good outcome, even though they had signal abnormalities in the basal ganglia or cortex (Velly 2018).

2.6.4.4 Tract based spatial statistics

Comparison between multiple subjects from voxelwise analysis has been arbitrary e.g. involving the choice of spatial smoothing. In traditional morphometry, regions of interest (ROI) on brain scan images were delineated and then the volume enclosed was calculated and compared with corresponding areas in cross-subject analysis. This time consuming method was not able to detect smaller volume differences (Ashburner 2009). Voxel based morphometry (VBM) analysis, however, is fully automatic, relatively simple to elaborate and does not require prespecifying or prelocalising features or regions of interest (Smith 2006). VBM analysis involves the whole brain, highlights common features and differences across subjects in a specified population. It uses voxelwise analyses based on initial alignment of the diffusion data to a standard brain image template. Spatial smoothing and localization is then executed so that each voxel represents the average of itself and its neighboring voxels (Ashburner 2009). The voxelwise statistical analysis is then carried out to assess the in-between-group differences (Wang 2016). Although apparently objective, this method is sensitive to various artifacts, including anatomical variability, spatial smoothing, local misalignment and concerns of voxel comparison accuracy (Ashburner 2009, de Groot 2013). Tractography-based VBM approaches can overcome misalignment concerns by working in individual subject's tractography results, which do not demand presmoothing (Smith 2006).

In tract based spatial statistics (TBSS), alignment and smoothing problems are attenuated by applying an automatic whole brain analysis, which is established on multiple comparisons to an estimated group mean template. Namely, multiple subject voxelwise diffusion images are projected onto a common alignment-invariant tract representation, the mean WM FA skeleton, which represents major

WM structures. This allows group comparison of standard voxel of the same part of the same WM tract from each and every subject. The estimation of a group mean FA skeleton represents the centers of all fiber bundles, which are generally common to all subjects involved in a study. Each subject's FA data is then projected onto the mean FA skeleton in such a way that each skeleton voxel takes the FA value from the local centre, which is, in effect, the locally maximal FA value, of nearest relevant tract (Smith 2006). The thinning of the skeletonized mean FA image to exact thickness of one voxel of one cubic mm abandons the directional information captured in the diffusion data. This, however, establishes a possibility of inaccuracy especially in regions, where pathways of different structures merge, such as corpus callosum and corona radiata fiber bundles (Bach 2014). Eventually, each brain contains hundreds of thousand voxels containing one FA value within each voxel (Smith 2006). Applying permutation statistics allows millions of comparisons across voxels, across patients and between the groups, which offers a remarkable statistical power (Ludbrook 1998, Nichols 2001, Ernst 2004).

This method estimates the localized change in FA, which represents entire brain WM connectivity and injury across different subjects without having to specify in advance regions of interest or draw by hand which specific tracts to test (Smith 2007). TBSS is fully automated, observer independent and it has been demonstrated to allow comparisons of imaging studies between groups in a sensitive, objective and reproducible manner (Smith 2006). To date, TBSS has grown to be popular and widely used in neuroimaging studies involving in-between-group comparisons, also in determing the degree of global hypoxemic-ischaemic injury following cardiac arrest (Abe 2010).

Notably, the clinical role of neuroimaging studies in predicting mortality, morbidity and outcome after cardiac arrest has not yet been worldwide thoroughly defined. The implementation of group-wise data into clinical practice and to meaningful individual patient outcome prognostication has been, to date, impractical (Wijman 2009, Wu 2009, Greer 2012). Quantitave changes in MRI measurements should include practical and real-time information, to allow clinical decision-making concerning continuing or withdrawal of life-sustaining therapy.

3 Aims of the present study

The aims of the present study were:

1. To investigate the feasibility and safety of inhaled xenon in combination with mild therapeutic hypothermia in OHCA patients, who potentially are subjects to distinguished cardiac compromise
2. To determinate the effect of inhaled xenon exposure combined with mild therapeutic hypothermia on the degree of severity of the postischaemic brain white matter injury in the study treatment group as compared with the control group corresponding to neuroprotective effects of inhaled xenon exposure. This was executed with the surrogate end-point of fractional anisotrophy (FA), which corresponds to brain white injury severity (Primary end-point)
3. To explore the unestablished effect of xenon inhalation and mild therapeutic hypothermia on ongoing cardiac ischaemic reperfusion injury in OHCA patients, corresponding to cardioprotective effects of inhaled xenon exposure. This was assessed by the serial assessment of the myocardial injury surrogate, the cardiac TnT. Increment or decrement of serial TnT values reflect the amount of myocardial damage (Secondary end-point)
4. To investigate whether the neuro- and cardioprotective effects by the combination of hypothermia with xenon exposure translates to an enhanced long-term outcome and survival. Further, to study if any assessments could be identified to prognosticate mortality at 6 months follow-up (Secondary end-point)

4 Materials and methods

Xe-HYPOTHECA trial (ClinicalTrials.gov identifier: NCT00879892) was a randomized single-blind phase II clinical drug trial carried out during years 2009–2015 at two multipurpose intensive care units in Finland. The main criteria for inclusion were witnessed cardiac arrest from an initial rhythm amenable to defibrillation (ie, ventricular fibrillation or pulseless ventricular tachycardia) and return of spontaneous circulation within 45 minutes.

The ethics committee of the Hospital District of Southwest Finland and the institutional review boards of the Helsinki University Hospital and the Finnish Medicines Agency approved the study. An independent data and safety monitoring committee reviewed data after enrollment of every 4 patients and after each 6-month interval. The study was conducted according to good clinical practice and the current revision of the Declaration of Helsinki guiding clinical drug research in human subjects.

Written informed assent was obtained from the next of kin or from the legal representative of the patient within 4 hours after hospital admission. The patient's family was informed about the right to withdraw from the study at any point but the data collected until possible withdrawal could be used in the analyses as predefined in the trial protocol. Patients were informed accordingly if they regained consciousness.

4.1 Patients

Survivors of out-of-hospital cardiac arrest remaining comatose consecutively admitted to the Turku and Helsinki University hospitals were screened for eligibility. The recruitment of a comatose patient to the study required, that the attending intensivist or other physician on duty had already made the decision for commencing mild therapeutic hypothermia (MTH) treatment for the patient. The patient's eligibility to brain MRI and possible contraindications to it were carefully ruled out. The additional study inclusion criteria were:

1. Ventricular fibrillation or pulseless ventricular tachycardia as initial, presenting cardiac rhythm

2. The first attempt of resuscitation by emergency medical personnel had to appear within 15 minutes after the collapse
3. The cause for collapse should be considered primary as cardiogenic and the return of spontaneous circulation (ROSC) should have been gained in 45 minutes after the collapse
4. Patient should be still unresponsive in the emergency room
5. Age: 18–80 years
6. Consent from the next of kin or the legal representative of the patient should be obtained within 4 hours after arrival to the hospital

The study exclusion criteria were:

1. Admission hypothermia (< 30 °C core temperature)
2. Unconsciousness before cardiac arrest (reflecting to cerebral trauma, spontaneous cerebral haemorrhage, intoxication etc.)
3. Response to verbal commands after the return of spontaneous circulation and before randomization
4. Pregnancy
5. Coagulopathy
6. Terminal phase of a chronic disease
7. Systolic arterial pressure < 80 mmHg or mean arterial pressure < 60 mmHg for over 30 min period after ROSC
8. Factors making participation in follow-up unlikely
9. Enrollment in another study

Before randomization, the availability of trained nurses taking care of xenon anaesthesia maintenance was confirmed. The clinical investigators enrolled the patients and after the assent was granted within inclusion criteria time frame, randomization was performed with sealed computer -randomized envelopes followed by the assigned intervention. The patients were allocated in 1:1 ratio with random block sizes of 4, 6, and 8 to be exposed to either mild therapeutic hypothermia treatment alone for 24 hours (defined as the control group) or inhaled xenon (Xe) in combination with hypothermia for 24 hours (defined as the xenon group). Both study groups consisted of 55 patients. Due to practical and safety considerations, the personnel involved in the patient care could not be blinded.

4.2 Treatment protocol

If clinically indicated, percutaneous coronary angiography interventions (PCI) were performed already before ICU admission. Upon arrival at the emergency department, the patients underwent routine initial assessment and treatment including mechanical ventilation and correction of cardiovascular instability.

Arterial and central venous catheters were inserted in all patients. The patients were then cooled to target core temperature of 33–34 °C. Inhaled Xe was initiated simultaneously immediately after randomization through a closed-circuit ventilator (PhysioFlex™, Dräger, Lübeck, Germany). Trained study group member performed the priming of Xe ventilator and nitrogen washout (denitrogenization) of the patient still connected to conventional ICU ventilator. After switching ventilators, end-tidal Xe concentration was adjusted to at least 40 % ±10 %. Maximal allowed xenon concentration was 65 %. If the minimum Xe concentration of at least 20 % was for technical or other reason not achievable, Xe inhalation had to be terminated. The thermoconductive device on the ventilator measured Xe concentration continuously. The predefined concentration targets were adjusted by flushing the ventilation circuit with flushes of Xe, air or oxygen. Xe was delivered until start of rewarming. Adjustments to ventilation mode, tidal volume and frequency were made in accordance of standard critical care patient care. Repeated blood-gas analyses were performed at every hour during MTH and Xe exposure and later whenever clinically indicated but at least in every 4 hours. The predefined haemodynamic, chemical and arterial blood gas targets during intervention were:

	Target
Mean arterial pressure	60–90 mmHg
Systolic arterial pressure	> 100 mmHg
Central venous pressure (PEEP corrected)	6–10 mmHg
Heart rate (during MTH)	> 30 beats /min
Heart rate (after MTH)	> 40 beats/min
Blood glucose	5,0–8,0 mmol/l
Blood haemoglobin	> 70 g/l
Blood haematocrit	0,3–0,45
Partial pressure of arterial oxygen	10–18 kPa
Partial pressure of arterial carbon dioxide	4,5–5,5 kPa

The study protocol allowed liberal use of vasoactive medication (adrenaline, noradrenaline, dopamine, dobutamine, levosimendan, vasopressin, etc.) by the decision of attending physician; the medication was adjusted to meet the predefined hemodynamic targets. The entire used medication and the amount of

required crystalloids or other fluids were captured in the ICU data processing system and eventually in the case report forms (CRF).

Bradycardia (< 30 beats/min) was treated with boluses of atropine (0,01 mg/kg) and/or a raise of body target temperature (0,5 °C/h). If the safety reasons obliged core target temperature to be increased beyond 34 °C, xenon exposure and further MTH was discontinued. However, after possible study termination, the subsequent post cardiac arrest care continued according to the contemporary guidelines and treatment practices. Only the attending intensivist or physician could make decisions concerning entire medication (vasoactive, insulin etc.), core target temperature increases and study termination.

Reasons for premature withdrawal from study treatment by the investigator or the attending intensivist were:

- A failure to maintain xenon concentration $\geq$ 20 %
- A failure in ventilation and/or oxygenation of the patient with xenon delivery device (Physioflex™)
- If MTH was terminated prematurely; the decision could only be done by the attending physician
- Adverse event/serious adverse event
- Protocol violation
- If for any reason the investigator or the attending physician believed that continued participitation in the study was not in the best interest of the patient

An interim analysis was performed with 60 patients after they had undergone the 6-months follow-up.

4.3 Targeted temperature management

Cooling of the patient was executed with an invasive intravascular temperature management device (Alcius CoolGard™ 3000 thermal regulation system; Zoll Medical Corporation, Chelmsford, MA, USA). The core target temperature of 33–34 °C was then maintained for 24 hours. During hypothermia treatment and during mechanical ventilation, sedation was maintained with propofol infusion (1–5 mg/kg/h) and additional boluses if indicated. Midazolam infusion and boluses could alternatively be utilized, especially in hypotensive patients. The dose of sedative agents during MTH was adjusted to target RASS scale of - 4 – -5, which facilitated potential reduction of sedative dose during concomitant Xe anaesthesia. Anaelgesia was assured with continuous fentanyl-infusion (50–100 µg/h) and additional boluses of 25–50 µg, if indicated. Target core temperature of 33 °C was

likely to induce shivering, which was terminated by deepening the sedation and anaelgesia or with neuromuscular blocking agents (e.g. cisatracurium, rocuronium) to additionally maintain hypothermia. These drugs could be administered as a continuous infusion or boluses.

After 24 hours at target temperature, rewarming was commenced with maximum rate of 0.5 °C/h. Xe exposure was discontinued at the start of rewarming and substituted with propofol or midazolam. The invasive endovascular balloon membrane-cooling catheter (Microtherm™, Alsius Co) was preserved to purposes of preventing reactive hyperthermia after rewarming.

4.4 Assessments

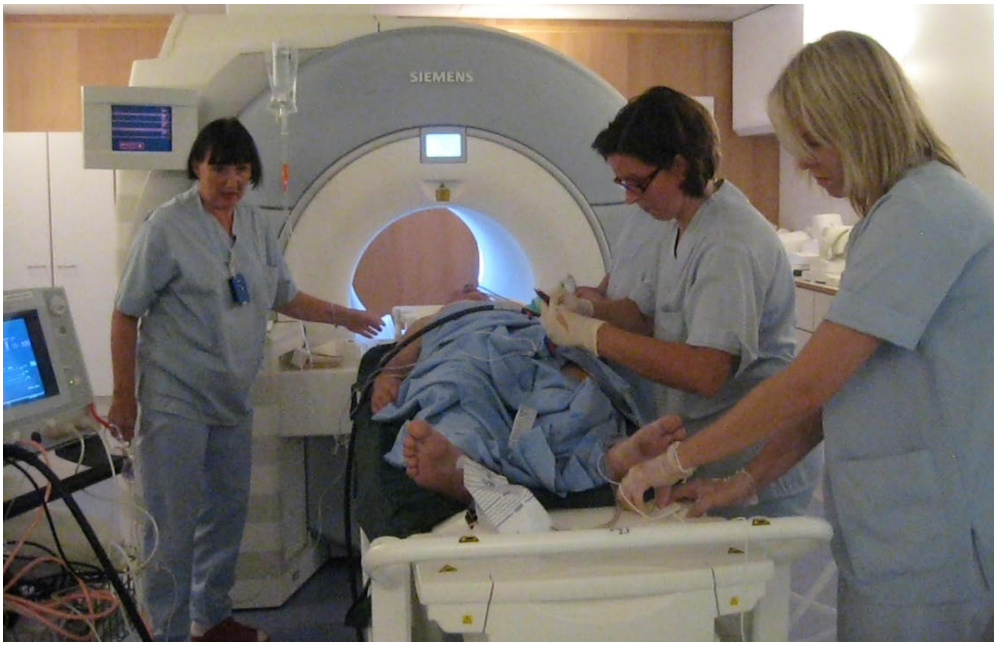
The study OHCA patients were evaluated by serial electrocardiograms (ECG) obtained at OHCA site, at hospital and ICU admissions, and 24, 48 and 72 hours after OHCA. All patients underwent a brain CT scan before ICU admission to rule out unexpected intracerebral causes of cardiac arrest and trauma to the head or neck. Routine chest x-rays were obtained according to normal ICU clinical practice. Whenever applicable (for logistic reasons), the study patients were mounted with a pulmonary artery catheter (Swan-Ganz). The ICU data processing system allowed meticulous capturing of given medication and organ function data; including fluid balance, ventilatory and haemodynamic data. All patients were equipped with an artery line for invasive haemodynamic monitoring and blood sampling. Central venous pressure was measured from a separate i.v. line.

4.4.1 Myocardial injury markers

Study blood samples of biochemical myocardial injury markers were obtained - besides whenever clinically indicated – at the ICU arrival, and 24, 48 and 72 hours after OHCA. The cardiac biomarker was plasma troponin-T (P-TnT). Until March 1st, 2012, TnT was analyzed with a limit of detection of 0.03 mg/l (Electro-chemiluminescence immunoassay, ECLIA Troponin-T Cardiac, Roche Diagnostics, Mannheim, Germany). Thereafter, a high-sensitivity cardiac TnT assay was used with a limit of detection of 5 ng/l (Electrochemiluminescence immunoassay, ECLIA Troponin T high-sensitive, Roche Diagnostics). The study latter part high-sensitivity TnT values were converted to the corresponding mg/l values with a specific formula.

4.4.2 Brain MRI

Patients underwent brain MRI within 16 hours after completion of rewarming; the acceptable range was from 36 to 52 hours after OHCA, based on logistic reasons (study scans were performed after office hours). Magnetic resonance imaging was performed with a Verio 3T scanner (Siemens Medical Solutions, Munich, Germany) at both hospitals, with identical imaging protocols. Before each scan, the safety, feasibility and obvious risks were carefully considered concerning the patient's stability, the scan, transport and limited resources outside ICU.



MRI machine is generally regarded as incompatibile with most equipment required for monitoring the patient during intensive care (Püttgen 2007). A trained team of study investigator, study nurse and additionally an ICU nurse escorted the patient during each scan and MRI compatible infusion pumps, ventilator (Servo I™, Maquet Getinge Group, Rastatt, Germany) and other equipment was used. The surviving patients underwent second MRI at 10±2 days post OHCA.

Diffusion tensor MRI data was preprocessed using DTIprep quality control software. Version 5.0 of the FSL software package (FMRIB) was used for the tract-based spatial statistical (TBSS) analysis. Fractional anisotropy (FA) and diffusivity maps were calculated for each patient and these images were projected on a mean skeleton with a voxel size of 1 x 1 x 1 mm (i.e., 119013 voxels per patient), which represents the local centers of all major white matter structures.

These skeletonized images were then used for voxelwise statistics to identify all tracts with voxels revealing statistically significant differences in diffusion parameters. Localization and labeling of the major white matter tracts were confirmed according to the Johns Hopkins University white matter tractography atlas. Other diffusion metrics (Mean-, Axial- and Radial Diffusivity) were projected in the same skeleton and analyzed in similar way.

The MRI protocol is displayed in table 5.

Table 5. Imaging protocol. FLAIR: Fluid Attenuated Inversion Recovery. MP-RAGE: Magnetization Prepared Rapid Gradient Echo. [a]Number of diffusion directions: 20, b-value s/mm^2

MRI sequence	In-plane resolution (mm)	Slice thickness (mm)	Echo time (ms)	Repetition time (ms)
T2-weighted	0.4 x 0.4	4.0	96	5210
3D FLAIR	1.0 x 1.0	1.0	395	5000
T1-weighted (3D MP-RAGE)	1.0 x 1.0	1.0	2.2	1900
Diffusion tensor imaging[a]	2.0 x 2.0	3.0	100	6100

4.4.3 EEG and neurological follow-up evaluation

Routine EEG was not a part of the study protocol, but this assessment was encouraged, whenever clinically indicated. However, during the study, continuous EEG monitoring was progressively utilized and recommended in OHCA survivors in international congresses and literature (Hovland 2006, Cloostermans 2012, Cronberg 2013, Crepeau 2014). Therefore during this study, continuous EEG was increasingly ordered in the latter part study subjects to gain knowledge and experience of its utility and use.

Best neurological response was assessed at 1, 24, 48, 72 and 96 hours after the collapse using Glascow Coma Scale (GCS). Additionally pupillary response and involuntary movements, such as seizures or myoclonus and extension reactions were reported. Recovery from coma was defined by following verbal commands. Best value of CPC and mRS were defined before hospital discharge.

Neurological long-term outcome was defined according to Pittsburgh cerebral-performance category (CPC category) and Modified Rankin Scale (mRS). The neurologist assessing the neurologic outcome at 3 months and 6 months after OHCA was unaware of the treatment assignment.

CPC categories:

- CPC 1; good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit
- CPC 2; moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment
- CPC 3; severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis
- CPC 4; coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawarness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness
- CPC 5; dead or certified brain death

The mRS scale runs from 0–6, running from perfect health without symptoms to death:

- mRS 0; no symptoms
- mRS 1; no significant disability. Able to carry out all usual activities, despite some symptoms
- mRS 2; slight disability. Able to look after own affairs without assistence, but unable to carry out all previous activities
- mRS 3; moderate disability. Requires some help, but able to walk unassisted
- mRS 4; moderate severe disability. Unable to attend to own bodily needs without assistence, and unable to walk unassisted
- mRS 5; severe disability. Requires constant nursing care and attention, bedridden, incontinent
- mRS 6; dead

Additionally, the Mini-Mental State Examination (MMSE) (score range, 0-30; ≥ 24 indicates no impairment) and the National Institutes of Health Stroke Scale (NIHSS) (score range, 0–42; higher scores indicate greater severity) were utilized to assess the 6-month neurocognitive outcome. The minimally clinically important

differences for CPC and NIHSS have not been established; changes in MMSE of 4 or more points have been interpreted as clinically significant.

4.5 Neurological prognostication consensus

Decisions to withdraw life-sustaining treatment were based on a consensus agreement on a multimodal assessment of poor neurological outcome. This was based on following principles:

- Neurological prognostication was accomplished if the patient remained unconscious 12 h after rewarming
- All sedative medication must have been discontinued 12 h previously
- In hypothermia-treated patients prognostication was performed after 72 h post resuscitation.

Neurological examination was performed by consulting neurologist; consisting:

1. Glascow Coma Scale (eye, speech and movement responses)
2. Brain stem reflexes
3. Breathing
4. Possible myoclonus

Assessments:

If the patient remained unconscious:

1. Brain CT or MRI scan was performed
2. EEG was obtained to exclude convulsive or nonconvulsive status epilepticus (NCSE).

The key EEG considerations:

- Continuity of electrical activity of the brain
- Response to external stimuli
- Spontaneous dynamics in brain electrical activity
- Presence of epileptiformic waves
- Non-convulsive status epilepticus

3. Serum neuron specific enolase (NSE) was assessed at 24 h, 48 h and 72 h after OHCA
4. Sensory evoked potential (SEP) assessment was performed if CT/MRI or EEG provided no explanation to unconsciousness

Conclusions:

Signs of poor prognosis were:

1. CT/MRI: general cerebral edema with sulcal effacement and widespread ischaemia with loss of margins of brain white and grey matter
2. EEG: generalized suppression (< 20 μV) or burst suppression, generalized epileptic activity or periodic epileptiformic discharges (PED) with background activity suppression, lack of spontaneous variation and lack of reactivity to external stimuli
3. Continuous refractory to treatments myoclonic status epilepticus with permanent unconsciousness
4. Serum NSE values: ascending trend 24 – 48 – 72 h
5. Unresponsiveness to painful stimuli or extension as the best motor response at 72 h
6. Absent brain stem reflexes at 72 h
7. Bilateral absence of thalamocortical sensory evoked potentials (SEP)
8. Generalized diminished cortical diffusion on MRI

4.6 Statistical analysis

The sample size of 110 patients was based on power analysis of the assumed fractional anisotropy (FA) values from brain magnetic resonance imaging, that is, the primary endpoint of the Xe-HYPOTHECA trial. However, no clinically relevant comparable data about the difference in the effect size was then available. Therefore, the arbitrary estimation was, that 55 patients per group would be needed to reveal an absolute median difference of 15% in FA between the groups (85% power and a two-sided α level of 0,05). This diffrenece eventually proved to be unrealistically large given that the difference in the mean FA values between those patients who survived and those who died was only 6.4% in this study.

The Shapiro-Wilk W test was used to evaluate the normality of all continuous variables. Two-sample Student's t-test and Mann- Whitney U test were used to compare continuous characteristic variables between groups. Categorical characteristic variables were analyzed with the κ^2 test or Fisher exact test. The Mann-Whitney test and the Hodges-Lehmann estimate were used for the ordinal variables of mRS and CPC to calculate median differences between the groups. Between-group differences in global FA and diffusivity values (radial, axial, and mean) were analyzed using the 2-sample t test and analysis of covariance with adjustment for age, sex and study site. Permutation-based voxel-wise statistical

analysis of FA values was performed with tract-based spatial statistics (TBSS) in conjunction with family-wise error correction for multiple comparisons across space.

The correlations between the increment in the level of troponin-T from hospital admission to 72 h and the dose of administered drugs (i.e., noradrenaline, adrenaline, dobutamine, dopamine, levosimendan, furosemide, propofol, midazolam, fentanyl, and insulin) and haemodynamic parameters (mean and systolic arterial pressure, central venous pressure, heart rate in 2-min [Turku] or 5-min [Helsinki] epochs) during the first 24 h and during 72 h after ICU admission were calculated using Spearman correlation coefficients.

The differences in changes in troponin-T values between groups were analyzed using repeated measures analysis of covariance adjusted for age, sex, study site, percutaneous coronary intervention (PCI), and cumulative noradrenaline use in the first 24 h after ICU admission. A natural logarithmic (ln) transformation was performed for troponin-T values before analyses due to their skewed distribution.

Results of troponin-T values at each time point were presented as geometric mean (95% confidence interval [CI]). The geometric means were calculated by back-transforming the means of ln-transformed troponin-T values to the original scale. An unstructured covariance matrix was used in the repeated measures model. An all-available case analysis was applied to the troponin-T. The effect of troponin-T on survival was analyzed with Cox regression adjusted for age, sex, study site, and group. Results are expressed using hazard ratios (HRs) with 95% CIs.

The follow-up time for survival analysis was calculated from the time of cardiac arrest until death or 6 months. A complete case analysis was applied to the primary end point available patients (due to missing MRI data for 6 patients in the control group and 7 patients in the Xe group). Multiple imputation was not performed due to lack of a good prognostic model to predict valid imputed values for missing data. Kaplan-Meier survival curves and a Cox proportional hazards model were used to compare mortality at 6 months between the groups in the intention to-treat population. The proportional hazards assumptions were evaluated with the log-cumulative hazard plot and martingale-based residuals; the assumptions were met. The observation was censored in the survival analysis if the patient was withdrawn from the study or was still alive at the end of the 6-month follow-up. Analyses were adjusted with the following prognostic factors: age, sex, time to ROSC, cooling rate, and study site.

Additionally, the global FA and diffusivity values were used as factors associated with 6-month mortality after adjustment for age, sex, group, and study site. Secondary end points were not adjusted for multiplicity and were therefore described as exploratory.

A two-sided p value < 0,05 was considered statistically significant. Statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute, Cary, North Carolina).

5 Results

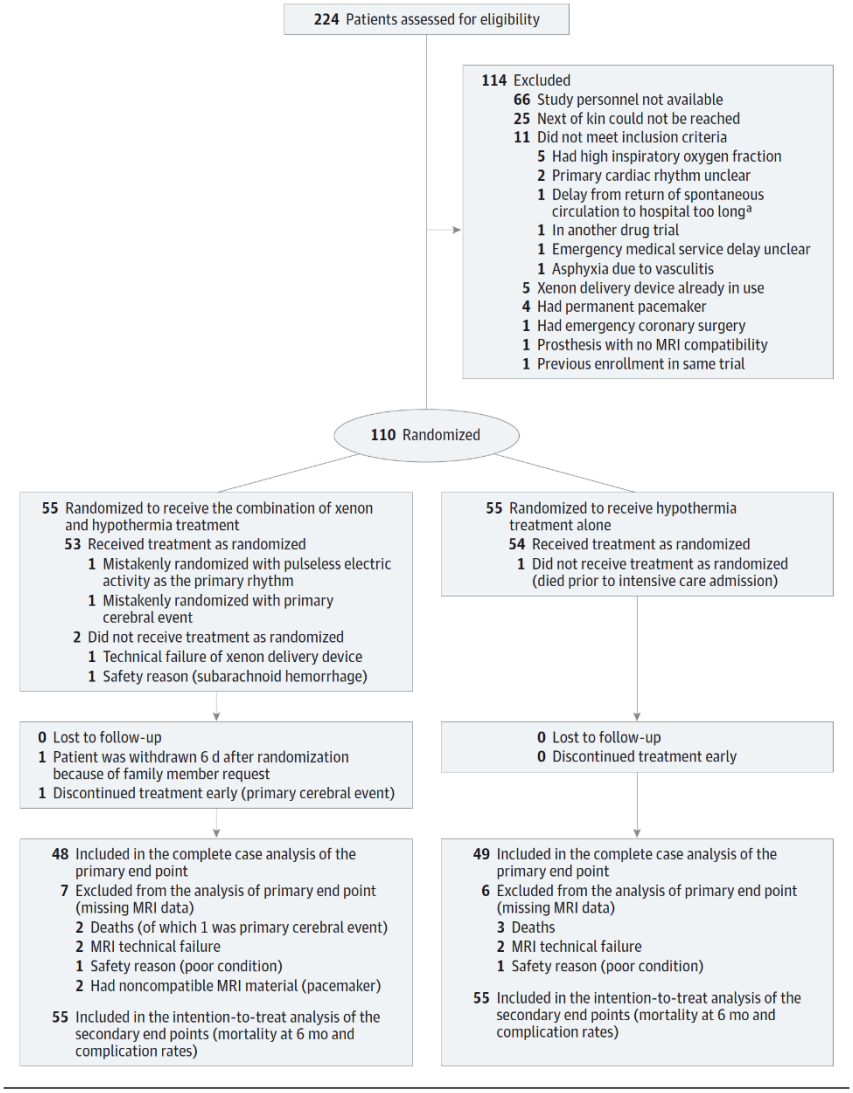


Figure 4. The flow of participants in the XE-Hypotheca trial. Reproduced by permission (II)

5.1 Patients

Turku University Hospital recruited 66 patients between August 2009 and September 2014 and Helsinki University Hospital 44 patients between October 2012 and September 2014. The first patient in Turku University Hospital was randomized on August the 5th 2009. The final 6-month neurological outcome performance assessments were completed in April 2015. A total of 224 OHCA patients were screened for eligibility and of these, 110 (aged 24 to 76 years) were enrolled and 55 randomly assigned to the xenon group and 55 to the control group (figure 4).

The main reasons for exlucion were force majeur -type situations, in which either study personnel was unavailable (66 patients, 58 %) or the next of kin could not be reached within 4 hours from the hospital admission to grant written informed assent to study participitation (25 patients, 22 %) (Figure 4).

One patient in the xenon group was withdrawn from the study 6 days after OHCA by the next of kin. One patient already randomized to the control group deceased during coronary angiography before ICU admission and received no treatment intervention. Additional reasons for patient disclosure in the final analysis in the control group were: premature death due to global perfusion failure (4 patients); and in the xenon group: two patients mistakenly randomized (basilar artery thrombosis not discovered in the initial CT scan, initial presenting rhythm of PEA, not VF/VT) and 1 technical failure of xenon delivery.

Both groups also consisted of patients, in whom MRI was not compatible due to MRI technical failure or patient condition. As a consequence, the complete case analysis for the primary end point consisted of 48 Xe group patients and 49 control group patients. The baseline characteristics in intention-to treat population are displayed in table 6.

Table 6. Baseline characteristics in the intention-to-treat population. Abbreviations: IQR: interquartile range, COPD: chronic obstructive pulmonary disease, ACEi: angiotensin convertase enzyme inhibitor, ARB: angiotensin reseptor blocking (agent). Data are expressed as No. (%) unless otherwise indicated. a) Based on ECG, patient history and angiographic findings. b) Indicates the interval from cardiac arrest to start of any chest compression by bystander or emergency medical service personnel. c) Fazekas score is a MRI system of scoring white matter hyperintensities that are often observed in elderly persons (> 65 years) and are considered small vessel disease. Score 0 indicates no lesions; 1, punctate foci; 2, beginning confluence of foci; and 3, large confluent areas.

Characteristic	Xenon (n = 55)	Control (n = 55)
Age, median (IQR); years	63 (55–70)	60 (54–67)
Male sex	41 (74.5)	39 (70.9)
Body Mass Index (BMI), median (IQR)	25.9 (23.4–27.6)	27.8 (25–31.2)
Coronary artery disease	37 (69.1)	40 (72.7)
Hypertension	22 (40.0)	26 (47.3)
Congestive heart failure	6 (10.9)	4 (7.3)
Diabetes	9 (16.4)	8 (13.0)
Asthma/COPD	6 (10.9)	9 (16.4)
Dyslipidemia	15 (27.3)	23 (41.8)
Cardiomyopathy	1 (1.9)	1 (1.9)
Chronic kidney insufficiency	1 (1.9)	3 (5.6)
Smoker	17 (30.9)	22 (40.0)
Previous medication		
ß-blocker	13 (24.1)	15 (27.8)
ACEi/ARB	15 (27.8)	20 (37.0)
Ca-channel blocker	9 (16.7)	10 (18.5)
Diuretics	5 (9.3)	6 (11.1)
Antiplatelet/Anticoagulant agents	15 (27.8)	19 (35.2)
Statin	12 (22.2)	16 (29.6)
ST-elevation myocardial infarction [a]	15 (27.3)	19 (34.5)
Resuscitation circumstances		
No-flow (min); median (IQR) [b]	0 (0–6)	0 (0–1)
Bystander resuscitation	38 (69.1)	40 (72.7)
Emergency medical service delay (min); mean (SD)	8.4 (3.4)	8.7 (3.2)
Return of spontaneous circulation (min); mean (SD)	22.6 (8.3)	21.9 (7.0)
Cumulative adrenaline dose before ROSC; mean (SD)	1.48 (1.56)	1.57 (1.65)
Blood glucose on admission; mean (SD)	11.9 (3.96)	12.7 (4.01)
Cooling		
Core temperature prior start of cooling, °C; median (IQR)	34.9 (34.3–35.8)	35.4 (34.0–36.3)
Time from OHCA to target temperature, min; median (IQR)	290 (263–338)	336 (254–395)
Time from OHCA to initiation of xenon, min; median (IQR)	247 (209–278)	-
Previous stroke	10 (18.2)	12 (21.8)
White matter degeneration score [c]		
No. of patients	48	49
Fazekas score 0–1	39 (81.3)	38 (77.6)
Fazekas score 2–3	9 (18.8)	11 (22.4)

The baseline patient characteristics did not differ between the groups. Approximately 30 % of OHCA survivors in both groups did not receive any bystander CPR. The most lengthened *no-flow* times in the study were 13 to 14 minutes, which often, but not always, were associated with poor outcome and premature death. The duration of CPR before ROSC was associated with higher cumulative doses of adrenaline, which translated to higher blood glucose values on admission (data not shown).

5.2 Anaesthesia and hypothermia

The mean sedation depth was assessed according to the Richmond Agitation Sedation Scale (RASS) every 4 hours until the end of MTH treatment. RASS score was until the end of MTH - 4,3 $\pm$ 0,6 in the control group and - 4,4 $\pm$ 0,6 in the xenon group (p = 0,17). The cumulative doses of anaelgetic (fentanyl, oxycodone) or neuromuscular blocking (cisatracurium, pancuronium or rocuronium) agents used during MTH did not differ between the groups.

Propofol was the principal sedative agent administered to all patients. Additional midazolam was given only in 4 control and 2 xenon group patients. In patients assigned to Xe inhalation, Xe anaesthesia was complemented with additional propofol, because the minimum alveolar concentration (MAC) of Xe is 63 % (Nagata 1993); whereas the mean end-tidal Xe concentration during this study was 48,2 % (SD, 3,8 %; range 41,4 % to 56,9 %). The mean duration of Xe inhalation was 25,5 hours (range 24–28 hours). The mean Xe expenditure during the intervention was 56,3 litres (SD 18,2). As anticipitated, the adequate level of sedation (RASS of at least 4) was accomplished with significantly less propofol during concomitant Xe inhalation. In contrast to the preceeding studies of Xe anaesthesia in healthy volunteers and surgical patients, postoperative (and post–anaesthesia) nausea and vomiting (PONV) was not witnessed.

The propofol consumption was statistifically significantly attenuated in the Xe group compared to control group during first 72 hours after hospital admission, but the difference observed during the 24 h intervention was not sustained during the following days after discontinuation of xenon exposure, as the propofol dose of the second (24 to 48 h post OHCA) and the third (48 to 72 h post OHCA) day after hospital arrival did not differ between the groups (p = 0,20 and p = 0,13, respectively) (Table 7). The median (IQR) interval from OHCA to the inception of Xe treatment was 250 (209–281) minutes.

All patients in both groups received hypothermia treatment for 24 hours. Initial mean core temperatures on admission to the intensive care unit were similar; 34,9 °C in the Xe group and 35,1°C in the control group. The median (IQR) interval between OHCA and attainment of target temperature was 344 (257–404) minutes in the control group and 290 (250–338) minutes in the Xe group. The mean temperature during MTH was 33,1 °C in both groups.

5.3 Intravenous medication

Vasoactive medication was adjusted to meet the predefined haemodynamic targets. Practically almost every patient was on noradrenaline infusion at least after MTH intervention. Only one patient in the Xe group did not require any vasoactive support. Dobutamine was added on top of noradrenaline in 10 patients in both groups. Only two patients in the control group received dopamine infusion. Levosimendan was used in 8 control group patients and in 9 Xe group patients, one of which had the medicine incepted during rewarming after discontinuation of Xe inhalation. Accretion of vasoactive support apparently reflected the underlying cardiac compromise. Moreover, the significant difference in propofol consumption between groups caused a trend of inotrope-sparing effect in the Xe group, in which cumulative doses of noradrenaline were smaller. However, this trend was not statistically significant. None of the other intravenous medications administered during the first 72 h differed significantly between the groups (Table 7).

Table 7. Selected intravenous medication during the first 24 and 72 hours after ICU admission. Median (IQR). Number of patients receiving the medication during the first 72 hours: Propofol: 54 control patients and 54 xenon patients; Noradrenaline: 54 control patients and 53 xenon patients; Dobutamine: 10 control and 10 xenon patients; Dopamine: 2 control and 0 xenon patients; Levosimendane: 8 control and 9 xenon patients; Adrenaline: 7 control and 7 xenon patients; Insulin: 38 control and 40 xenon patients

	First 24 hours after ICU admission			First 72 hours after ICU admission		
	Xenon (N = 54)	Control (N = 54)	P-value	Xenon (N = 54)	Control (N = 54)	P-value
Medication						
Propofol, mg	2325 (1700–2980)	6605 (5071–7880)	< 0.0001	11019 (6585–14599)	16010 (12060–20846)	<0.0001
Noradrenaline, mg	5.0 (1.1–14.4)	8.3 (3.9–12.7)	0.10	12.1 (5.6–34.2)	22.3 (10.8–41.0)	0.07
Dobutamine, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.87	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.71
Dopamin, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.33	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.16
Levosimendan, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.96	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.84
Adrenaline, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.64	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.97
Insulin, IU	9.6 (0.0–28.1)	8.0 (0.0–30.4)	0.90	14.0 (0.0–62.9)	25.7 (0.0–63.1)	0.88
Furosemide, mg	20.0 (0.0–10.0)	2.5 (0.0–15.0)	0.58	30.0 (10.0–55.0)	30.0 (10.0–75.0)	0.62
Fentanyl, mg	2.1 (1.5–2.3)	2.1 (1.4–2.4)	0.80	3.1 (2.3–4.0)	3.4 (2.2–4.7)	0.80
Midazolam, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.19	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.64

5.4 Haemodynamic and laboratory parameters

The median (IQR) heart rate was significantly lower in the Xe group during Xe inhalation than in the control group during MTH treatment. Also after rewarming during the first 72 h after ICU admission, the median (IQR) heart rate was significantly lower in the Xe group than in the control group. The other pre-defined haemodynamic parameters did not differ between the groups during the first 24 to 72 h (Table 8).

Table 8. Abbreviations: MAP = Mean arterial pressure; SAP = Systolic arterial pressure; CVP = Central venous pressure. Values are median (IQR) or means (SD). The haemodynamic parameters were recorded in 2 minute epochs in Turku and in 5 minute epochs in Helsinki.

	First 24 hours after ICU admission			First 72 hours after ICU admission		
	Xenon (N = 54)	Control (N = 54)	P-value	Xenon (N = 54)	Control (N = 54)	P-value
Haemodynamics						
Heart rate, beats/min	46.0 (40.5–54.9)	52.9 (43.6–58.5)	0.02	61.6 (56.8–69.4)	68.8 (59.8–75.9)	0.03
MAP, mmHg	79.3 (6.3)	78.8 (6.7)	0.68	80.3 (7.9)	78.7 (6.3)	0.27
SAP, mmHg	110.6 (103.2–116.3)	109.0 (105.2–117.0)	0.91	119.3 (109.5–127.0)	115.3 (110.8–123.8)	0.29
CVP, mmHg	10.0 (8.3–13.0)	10.8 (8.7–12.9)	0.67	10.5 (8.6–13.5)	11.6 (9.6–13.1)	0.20

The blood pH, lactate, and glucose did not differ between the groups during ICU stay. There were no differences in other routine laboratory tests between the study groups. Assays of TnT are discussed separately. The preliminary results of NSE kinetics were described in chapter 2.5.1

The impact of underlying or acquired kidney disease was assessed by RIFLE classification (Bellomo 2004, Chua 2012) of the study patients (table 9).

Table 9. Acute kidney injury and plasma creatinine values according to RIFLE classification. Values are number (%) of patients or median (IQR). Baseline value was 1) the most recent serum creatinine value within 2 years prior to OHCA, or 2) lowest value during 1 week prior to hospital discharge, or 3) lowest value anytime during current admission. Diagnosis of acute kidney injury was based on an increase in serum creatinine level from a baseline value to the peak value within 6 days after ICU admission. RIFLE classifications: Risk = plasma creatinine increase by more than 1.5-fold from the baseline value to the peak value; Injury = plasma creatinine increase by two- to three-fold, Failure = plasma creatinine increase by more than three-fold.

	Xenon group (n=54)	Control group (n=54)	P-value
Plasma creatinine, µmol/l			
Baseline	67.0 (60.0 – 81.0)	72.0 (61.0 – 86.0)	0.32
Peak value during the first 6 days	92.0 (78.0 – 108.0)	93 (74 – 138.0)	0.67
Acute kidney injury	18 (33.3)	19 (35.2)	1.00
RIFLE – Risk	14 (25.9)	10 (18.5)	0.49
RIFLE – Injury	2 (3.7)	6 (11.1)	0.27
RIFLE – Failure	2 (3.7)	3 (5.6)	1.00

5.5 Myocardial infarct

When assessing the precipitating pathology leading to cardiac arrest, ST-elevation myocardial infarct (STEMI) was present in 36 (32,7 %) patients, non-ST-elevation myocardial infarct (NSTEMI) in 64 (58,2 %) patients and an arrhythmogenic heart disease in 7 (6,4 %) patients. Two patients mistakenly randomized had a primary cerebral event (basilar artery thrombosis, subarachnoidal haemorhage) undiscovered at hospital admission. Primary percutaneous coronary intervention (PCI) was performed on admission in 14 of the 16 Xe group STEMI patients, in 16 of the 19 control group STEMI patients and in NSTEMI patients, 1 in the Xe group and 2 in control group. Coronary angiography with an eventual PCI was performed during the entire hospital stay in 44 (81,5 %) of Xe group patients and in 47 (87,0 %) of control group patients. Regarding occlusive coronary artery disease, there were no significant differences in between the study groups. Details of coronary heart disease are displayed in table 10.

Table 10. Coronary heart disease characteristics. Values are n (%). The diagnosis of acute myocardial STEMI infarction was based ECG findings. * The data is based on the 44 patients in the xenon group and for 47 patients in the control group, of which angiography was performed

	Xenon (N = 54)	Control (N = 54)	P-value
STEMI	17 (31,5)	19 (35,2)	0.68
Anterior	17 (31,5)	11 (20,4)	0.19
Inferior	0 (0,0)	5 (9,3)	0.06
Lateral	0 (0,0)	3 (5,6)	0.24
Right side	0 (0,0)	0 (0,0)	1.00
NSTEMI	32 (59,3)	32 (59,3)	1.00
Primary PCI on admission	15 (27,8)	18 (33,3)	0.53
Coranary angiography during hospital stay	44 (81,5)	47 (87,0)	0.43
Angiography findings *			
Nonocclusive coronary artery disease	12 (27,3)	11 (23,4)	
Left main disease	3 (6,8)	8 (17,0)	
1-vessel disease	15 (34,1)	14 (29,8)	
2-vessel disease	10 (22,7)	9 (19,1)	
3-vessel disease	7 (15,9)	13 (27,7)	

In the deceased patients, the exact determination of the coronary artery disease was impossible in 7 xenon patients and in 4 of the control patients because neither coronary angiography nor autopsy was performed on these patients.

5.6 Adverse effects

Adverse effects were recorded as defined in the study protocol. Serious adverse events included complications during seven days after cardiac arrest. Some patients had more than one adverse event. There were no diffrences in adverse events in between the study groups. Serious adverse events in the intention to treat population are represented in the table 11.

Table 11. Serious adverse events in the intention-to-treat population

Serious adverse event	Xenon (n = 48/55)	Control (n = 50/55)	P value
Status epilepticus	15	17	0.67
Acute kidney injury			
Risk	14	10	0.36
Injury	2	6	0.27
Failure	2	3	1.00
Pulmonary oedema	4	4	1.00
Ventricular fibrillation	6	3	0.49
Ventricular tachycardia	5	8	0.38
Atrial fibrillation (new onset)	8	4	0.22
Coronary stent thrombosis	1	1	1.00
Sepsis	1	2	1.00
Pneumonia	33	36	0.55
Multi-organ failure	1	2	1.00
Adult respiratory distress syndrome	1	1	1.00
Bradycardia requiring pacemaker	1	0	1.00
3rd degree atrioventricular block	0	1	1.00
Subarachnoid hemorrhage	1	1	1.00
Carotid dissection	0	1	1.00
Carotid thrombosis	0	1	1.00
Serious bleeding			
Intracranial	0	1	1.00
Gastrointestinal	1	0	1.00
Total	96	102	0.81

5.7 Neuroprotection by xenon inhalation (primary end point)

The effect of xe inhalation on the ongoing cerebral injury was quantified by the loss of directionality in the diffusion of water molecules in cerebral white matter tracts. Fractional anistrophy (FA) values, which quantify water directionality, is low, when diffusion is less organized, corresponding to more pronounced white matter injury. Localization and labeling of the tracts were confirmed and identified with Johns Hopkins University white-matter tractography atlas.

Diffusion tensor MRI data for the TBSS analysis were obtained from 48 patients in the Xe group and 49 patients in the control group. The interval from OHCA to MRI scan was 53 hours (median; IQR 47– 64 hours). For safety reasons, some of the MRI scans were postponed, until the patient and haemodynamic

condition was more stable. The reasons for missing MRI data are displayed in Figure 4. In brief, some patients deceased before or were too unstable before the scan. There were also some MRI technical failures and two xe- patients were excluded because of MRI contraindication (required pacemaker post arrest).

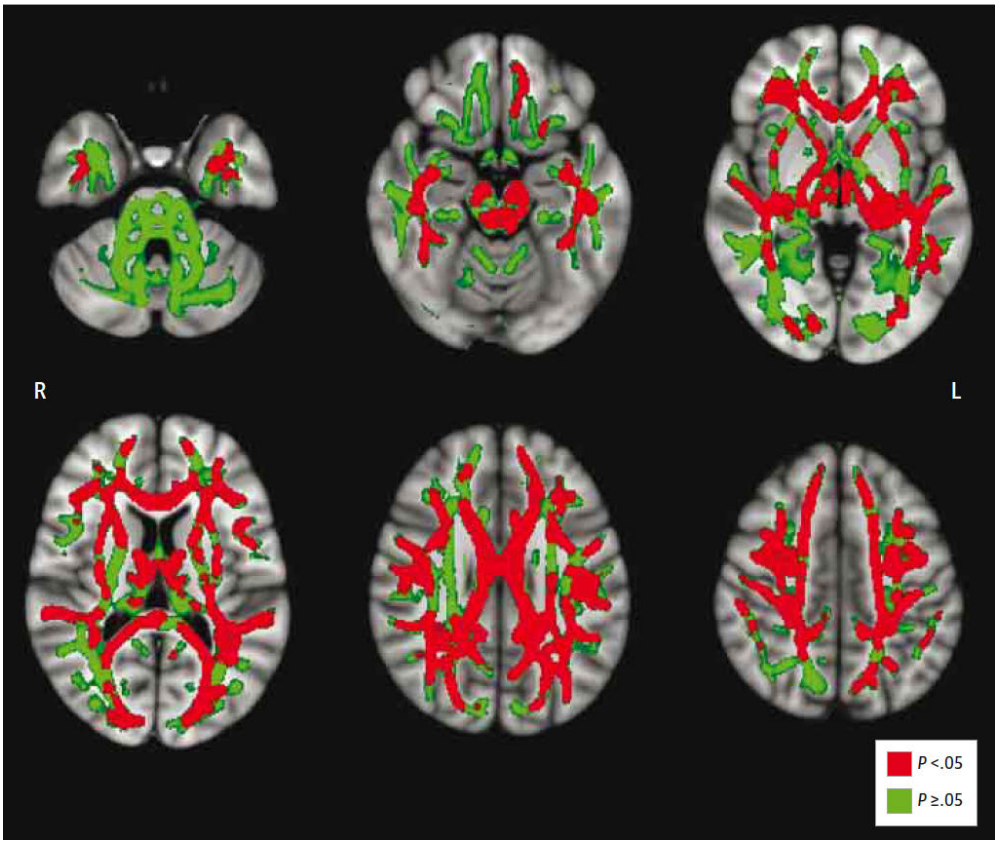


Figure 5. TBSS analysis of voxel-wise statistical analysis of FA values between the Xe and control group. Voxels with significantly lower FA values in the control group are displayed in red in statistical visualization. Voxels without significant difference between FA values between the groups are displayed green. The main differences were in cingulated gyrus, hippocampal region, forceps minor and major, superior and inferior longitudinal fasciculus, anterior thalamic radiation, inferior fronto-occipital fasiculus and corpus callosum. Reproduced by permission (II)

Using TBSS analysis, the statistical parametric map containing 119 013 voxels was created to visualize the spatial distribution of areas with significantly lower FA in the control group (Figure 5, reproduced by permission II).

The FA value was significantly lower in 41.7 % of the voxels in the control group than in the xenon group (i.e. 58,3 % of the voxels did not differ between the

groups). The tract-wise distribution is displayed in Figure 5. None of the voxels had significantly lower FA values in the xenon group.

The mean global FA values of all voxels presented in Figure 5 were 0,433 (SD, 0,028) in the Xe group and 0,419 (SD, 0,033) in the control group (P = 0,03; Table 12). The age-, sex-, and study site-adjusted mean global FA value was 3,8 % higher (95 % CI, 1,1 % to 6,4 %) in the Xe group (adjusted mean difference, 0,016 [95 %CI, 0,005 to 0,027], P = 0,006). The mean radial diffusivity value was 0,598 (SD, 0,051) for the xenon group and 0,619 (SD, 0,062) for the control group. The adjusted radial diffusivity value was 3,9 % lower (95 % CI, 0,5 %-7,4 %) in the Xe group than in the control group (adjusted mean difference, -0,024 [95 % CI, -0,046 to -0,003], P = 0,03; Table 12).

Table 12. Results of diffusion tensor MRI imaging in the complete case population. [a]Data are adjusted for age, sex and study site.

	Unadjusted mean (SD)		Mean difference (95 % CI)		P value	
Global values	**Xenon group (n = 48)**	**Control group (n = 49)**	**Unadjusted**	**Adjusted[a]**	**Unadjusted**	**Adjusted[a]**
Fractional anisotrophy	0.433 (0.028)	0.419 (0.033)	0.014 (0.002–0.026)	0.016 (0.005–0.027)	0.03	0.006
Type of diffusivity, 10^{-3} mm^2/s						
Axial	1.190 (0.052)	1.199 (0.051)	-0.009 (-0.030–0.012)	-0.011 (-0.031–0.010)	0.40	0.30
Radial	0.598 (0.051)	0.619 (0.062)	-0.021 (-0.043–0.002)	-0.024 (-0.046–0.003)	0.08	0.03
Mean	0.795 (0.050)	0.812 (0.056)	-0.017 (-0.038–0.005)	-0.020 (-0.040–0.0007)	0.13	0.06

Taken together, these various quantitative differences in diffusion tensor MRI values indicated that the loss of connectivity, demyelinisation and disruption of brain white matter was more pronounced in the control group.

5.8 Cardioprotection by xenon inhalation (secondary end-point)

5.8.1 Troponin-T release

The effect of xenon inhalation and mild therapeutic hypothermia following cardiac arrest was assessed by quantification of myocardial injury with absolute values of TnT at hospital arrival, and at 24, 48, and 72 h in both groups (represented in figure

6). The intention-to-treat population consisted of 54 patients in both groups. Absent TnT assays were explained by death before ICU admission (1 control patient) and mistaken randomization after primary subarachnoidal haemorrhage (1 Xe patient).

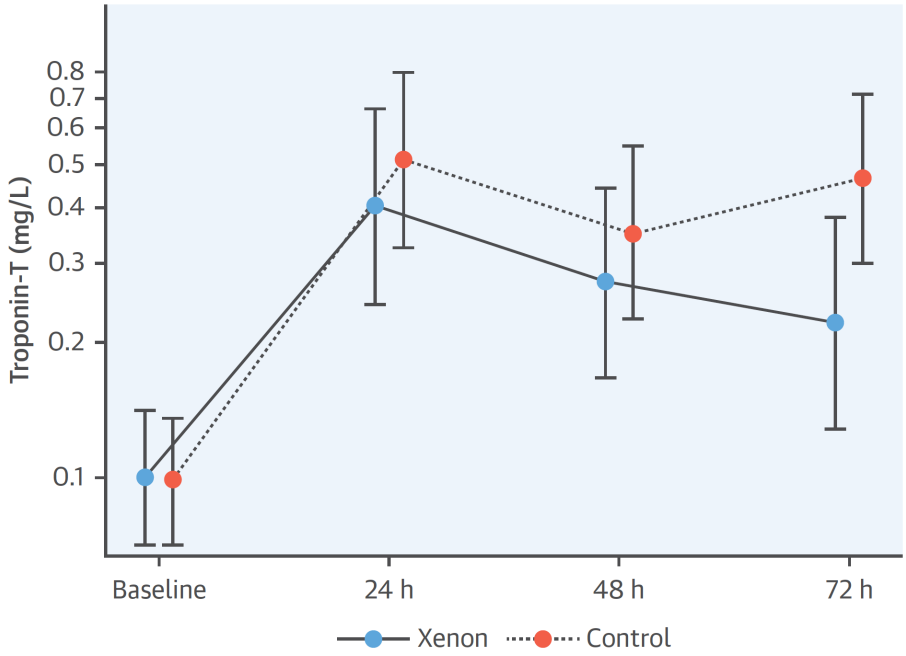


Figure 6. Troponin-T levels in the xenon and control groups after OHCA at hospital admission (baseline) and 24, 48, 72 h post cardiac arrest. Values are presented in geometric means (95 % confidence intervals) on a logarithmic scale (Reproduced by permission III)

The baseline values at hospital arrival did not differ between the Xe and control groups (geometric mean [95 % CI] 0,100 mg/l [0,070 to 0,141 mg/l] vs. 0,098 mg/l [0,071 to 0,135 mg/l], respectively). At 72 h after OHCA, the geometric mean troponin-T was 111 % higher in the control group than in the Xe group (geometric mean [95 % CI] 0,464 mg/l [0,300 to 0,716 mg/l] vs. 0,220 mg/l [0,128 to 0,380 mg/l], respectively) as illustrated in the figure 6 and in table 13. Adjusted geometric means of troponin-T peaked at 24 h in both groups with a significant increase at 72 h from the baseline values ($p < 0,0001$). The decline of troponin-T from the peak to 72 h differed significantly between the groups ($p = 0,0008$) with a significant decline of 44,8 % ($p < 0,0001$) in the xenon group and a nonsignificant decline of 11,3 % ($p = 0,56$) in the control group.

Table 13. Adjusted geometric mean values of troponin-T. *P < 0,0001 difference between 24 and 72 hours. †P = 0,56 difference between 24 hours and 72 hours. P < 0,0008 decline of troponin-T from 24 hours to 72 hours; difference between the groups. P = 0,27, difference of area under curve between the groups including baseline and all single time points. ǂ Data are for 52 patients due to missing values of troponin-T of two patients at 72 hours. § Data are for 53 patients due to missing values of troponin-T of one patient at 72 hours. Values are adjusted for age, gender, study site, percutaneous coronary intervention and dose of noradrenalin during the first 24 hours after intensive care admission.

	Xenon group n = 54	**Control group n = 54**
	Troponin-T; Adjusted geometric mean (95 % CI)	
Baseline	0.10 (0.06–0.16)	0.09 (0.06–0.14)
24 hours	0.39 (0.24–0.65)	0.46 (0.28–0.75)
48 hours	0.27 (0.16–0.44)	0.32 (0.20–0.51)
72 hours	0.22 (0.13–0.37)*ǂ	0.41 (0.24–0.69)†§
AUC	21.6 (13.1–35.4)ǂ	31.0 (20.3–47.1)§

In NSTEMI patients, the decline from peak to 72 h was significantly different between the groups (p = 0,0004): a significant decline of 48,6 % within the xenon group (p < 0,0001), but a nonsignificant increase of 0,9 % within the control group (p = 0,93). In STEMI patients, the difference of troponin-T decline between the groups was nonsignificant (p = 0,61); the decline from peak to 72 h was significant within the xenon group (p = 0,01), but nonsignificant within the control group (p = 0,053) (table 14)

Table 14. TnT Values in STEMI and NSTEMI patients. P = 0,0004 difference between the groups in NSTEMI. P = 0,61 difference between the groups in STEMI. *Data are for 31 patients due to death before 72 hours. †Data are for 31 patients due to death before 72 hours. ǂ Values are adjusted for age, gender, study site and dose of noradrenaline during the first 24 hours after ICU admission. § P = 0,01 for the TnT difference within group from the peak concentration at 24 hours to 72 hours. || P = 0,053 for the TnT difference within group from the peak concentration at 24 hours to 72 hours. # P < 0,0001 for the TnT difference within group from the peak concentration at 24 hours to 72 hours. ** P = 0,94 for the TnT difference within group from the peak concentration at 24 hours to 72 hours.

	Xenon Group	Control Group	Xenon Group	Control Group
	Absolute values (µg/L), Median (IQR)		Adjusted‡ Geometric Mean (95 % CI)	
STEMI patients	n = 17	n = 19	n = 17	n = 19
Baseline (hospital admission)	0.17 (0.08–0.52)	0.08 (0.05–0.23)	0.14 (0.07–0.28)	0.07 (0.04–0.14)
24 hours after OHCA	1.16 (0.58–4.07)	1.57 (0.50–3.69)	1.16 (0.55–2.43)	0.91 (0.44–1.89)
48 hours after OHCA	0.72 (0.33–3.20)	1.48 (0.29–2.92)	0.78 (0.38–1.58)	0.61 (0.30–1.23)
72 hours after OHCA	0.64 (0.30–2.49)	1.51 (0.27–2.46)	0.74 (0.34–1.60)§	0.66 (0.31–1.40)||
NSTEMI patients	n = 32	n = 32	n = 32	n = 32
Baseline (hospital admission)	0.07 (0.03–0.25)	0.10 (0.04–0.25)	0.09 (0.06–0.17)	0.09 (0.05–0.14)
24 hours after OHCA	0.30 (0.12–0.55)	0.36 (0.15–1.11)	0.33 (0.19–0.60)	0.30 (0.18–0.51)
48 hours after OHCA	0.18 (0.07–0.39)	0.32 (0.10–0.63)	0.22 (0.13–0.40)	0.20 (0.12–0.34)
72 hours after OHCA	0.12 (0.04–0.28)*	0.34 (0.14–0.77)†	0.17 (0.09–0.32)*#	0.30 (0.17–0.53)†**

Geometric mean (95 % CI) of TnT was significantly higher in STEMI than in NSTEMI at each time point after baseline (table 15).

Table 15. Comparison of TnT values between STEMI and NSTEMI patients during 72 hours after OHCA. Abbreviations: STEMI = ST Elevation Myocardial Infarct; NSTEMI = Non ST Elevation Myocardial Infarct; OHCA = Out-of-Hospital Cardiac Arrest; CI = Confidence Interval; TnT = Troponin-T

	STEMI (n = 36)	NSTEMI (n = 64)	P - value
Adjusted* Geometric Mean (95% CI), µg/l			
TnT at Baseline	0.10 (0.06–0.17)	0.09 (0.0.6–0.13)	0.668
TnT 24 hours	1.03 (0.597–1.7)	0.32 (0.21–0.47)	0.0003
TnT 48 hours	0.69 (0.410–1.16)	0.21 (0.15–0.31)	0.0002
TnT 72 hours	0.70 (0.40–1.22)	0.23 (0.15–0.35)†	0.001

* Values adjusted for age, gender, study site, group and dose of noradrenaline during the first 24 hours after ICU admission. † Missing data for two patients at 72 hours

The change over time of the levels of TnT differed between the Xe and the control groups (time by group interaction p = 0,003); after adjustment for age, sex, study site, PCI, and noradrenaline, the increase of troponin-T values from hospital admission to 72 h was significantly less in the Xe group than in the control group (adjusted mean difference of ln-transformed values: -0,66; 95 % CI: -1,16 to -0,16; ratio of adjusted geometric means: 0,52; 95 % CI: 0,31 to 0,85; p = 0,01) (table 16).

Table 16. TnT increment from baseline to 72 h after OHCA. Values are median (IQR) or mean ± SD, unless otherwise indicated. Natural logarithmic transformation for TnT values was used in the statistical analysis due to skewness of the data. *Data is for 52 patients due to missing data of 2 patients at 72 hours. †Data is for 53 patients due to missing data of one patient at 72 hours. ǂData are adjusted for age, gender, study site, percutaneous coronary intervention and dose of noradrenalin during the first 24 hours after ICU admission. Abbreviations: TnT = Troponin-T, values are in µg/l, Ln = natural logarithm, Δ = Change from the baseline, CI = confidence interval, OHCA = out-of-hospital cardiac arrest.

	Xenon group (n = 54)	Control group (n = 54)	Mean difference (95 % CI)		P value	
			Unadjusted	Adjustedǂ	Unadjusted	Adjustedǂ
Absolute values, µg/l						
Baseline (admission)	0.09 (0.03–0.30)	0.08 (0.04–0.23)				
24 h after OHCA	0.38 (0.15–1.27)	0.47 (0.12–1.74)				
48 h after OHCA	0.25 (0.09–0.85)	0.41 (0.10–1.48)				
72 h after OHCA	0.22 (0.05–0.69)*	0.40 (0.14–1.87)†				
Ln-transformed change from baseline						
Ln ΔTnT 24h	1.40 ± 1.39	1.65 ± 1.38	-0.26 (-0.79–0.27)	-0.16 (-0.62–0.30)	0.33	0.49
Ln ΔTnT 48h	1.00 ± 1.37	1.28 ± 1.38	-0.28 (-0.80–0.25)	-0.18 (-0.63–0.27)	0.29	0.43
Ln ΔTnT 72h	0.79 ± 1.54*	1.56 ± 1.38†	-0.76 (-1.33– -0.20)	-0.66 (-1.16– -0.16)	0.009	0.01

The effect of Xe on the change in the TnT values did not differ in patients with or without PCI or in those with a diagnosis of STEMI (PCI or STEMI by group by time interaction effect; p = 0,72 and p = 0,29, respectively).

As propofol consumption was reduced in the Xe group, consequenting in an inotrope-sparing effect in noradrenaline-requirement in maintaining predefined

haemodynamic goals, these correlations were assessed in relation to TnT increment. In the Xe group, the increment of TnT values from hospital admission to 72 h correlated significantly with noradrenaline (r = 0,51; p = 0,0001) and dobutamine (r = 0,27; p = 0,049) doses during the first 72 h after ICU admission. However, the increment of TnT from hospital admission up to 72 h did not correlate with administered drugs, propofol or any of the vasoactive drugs or hemodynamic parameters in the two groups or within the whole population (tables 7 and 16).

5.9 Mortality and mode of death

The total mortality in this study was 30,9 %. Most of the deaths were due to severe hypoxic-ischaemic brain injury, which was assessed by the multimodal approach described in chapter 4.5. Neurological mode of death included permanent unconsciousness, which involved treatment refractory status epilepticus in 49 % of the deceased patients. The overall incidence of status epilepticus was 29,1 % (32 patients). Five patients with status epilepticus eventually regained consciousness. All of the deceased patients had STEMI or NSTEMI, and two patients from both groups died after severe cardiac failure (table 17).

Table 17. Death, mode of death and withdrawal of life-sustaining therapy in the intention-to-treat population. Values are mean (SD) or median (IQR) depending on the distribution of the data. Neurological mode of death corresponded to findings of severe hypoxic-ischemic brain injury. Withdrawal of life-sustaining treatments was executed by the principles described in the neurological prognostication consensus (chapter 4.5). *One patient did not receive Xe treatment due to technical failure of the Xe delivery device and one patient had a primary cerebral event but was mistakenly randomized. †One patient died in the angiolaboratory before ICU arrival

	Xenon group (n = 55)	Control group (n = 55)
Deceased	15*	19†
Mode of death		
Neurological	13	16
Cardiac	2	2
Multi-organ	0	1
STEMI or NSTEMI in non-survivors	15	18
Withdrawal of life support	14	15
Mortality in withdrawals	14	15
Time from cardiac arrest to withdrawal, days	6.5 (4.0–11)	5.0 (4.0–8.0)

Life-sustaining therapy was withdrawn after multimodal consensus agreement in pessimistic, hopeless situations 5–6,5 days after cardiac arrest. It is not possible to reliably distinguish between a cardiac and a noncardiac cause of death because all patients with severe ischaemic cerebral injury had also myocardial damage due to global, as well as occlusive, ischaemia. Of the deceased patients, 85 % did not regain consciousness due to a severe ischaemic encephalopathy, and the deaths were eventually classified as neurological mode of death.

5.10 Outcome (secondary end-point)

At 6 months, 75 patients (68.2 %) were alive and able to provide data for follow-up. In the intention-to-treat population, the Kaplan-Meier mortality estimate after 6-month follow-up was 27,3 % (15/55) in the xenon group and 34,5 % (19/55) in the control group (adjusted hazard ratio, 0,49 [95 % CI, 0,23-1,01], P = 0,053) (figure 7).

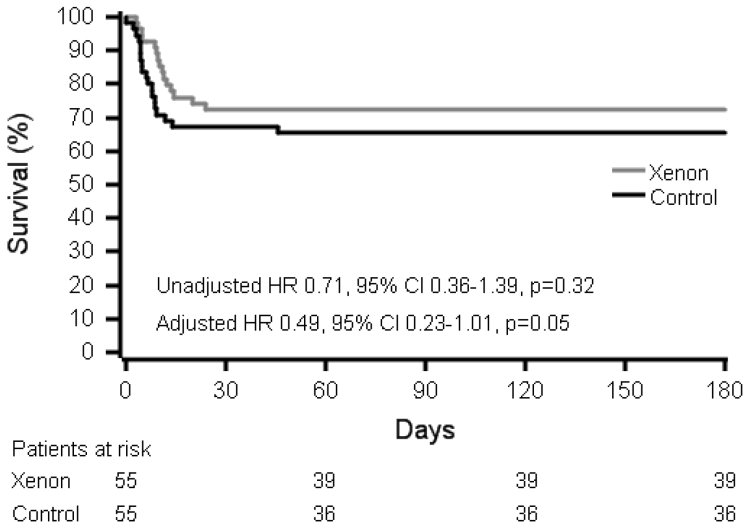


Figure 7. Probability of survival through the end of the 6-month follow-up in the intention-to-treat population. Values were adjusted with age, sex, time to ROSC, cooling rate and study site. Time point 0 indicates the time of OHCA. HR = hazard ratio, CI = confidence interval. Reproduced by permission (II)

At 6 months, functional neurological outcome was not significantly different between the groups as assessed with the CPC (median score of 1 [IQR, 1-5] for the xenon group and 1 [IQR, 1-5] for the control group; median difference, 0 [95 %CI, 0–0], P = 0,93) or the mRS (median score of 1 [IQR, 0–6] for the xenon group and

1 [IQR, 0-6] for the control group (table 18); median difference, 0 [95 % CI, 0–0], P = 0,68).

Similarly, the rates of serious adverse events were not significantly different between the groups at 6 months. In addition, there was not any difference in neurocognitive outcome measures of MMSE (median of 29 [IQR, 27–30] for the xenon group and median of 29 [IQR, 28–30] for the control group) and NIHSS (median of 0 [IQR, 0–0] for the xenon and control groups).

Table 18. Neurological outcome in the complete case population. [a]Data are expressed as number (%). There was no significant difference between groups in CPC score (p = 0,93) mRS score (p = 0,68). [b]One patient was withdrawn from the study 6 days after index event by the next of kin. [c]Prior the index event, 1 patient had a CPC score of 3 (due to mental retardation) and a mRS score of 4.

	Description of category	Xenon group[a] (n = 54)[b]	Control roup[a] (n = 55)
Cerebral Performance category score			
1	Good cerebral performance: conscious, alert, able to work, might have mild cognitive deficit	30 (55.6)	32 (58.2)
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent daily life	7 (13.0)	4 (7.3)
3	Severe cerebral disability: conscious, dependent on others for daily support; ranges from ambulatory state to severe dementia	2 (3.7)[c]	0
4	Coma or vegetative state	0	0
5	Death	15 (27.8)	19 (34.5)
Modified Rankin scale score			
0	No symptoms	23 (42.6)	22 (40.0)
1	No significant disability: able to carry out usual activities, despite some symptoms	7 (13.0)	8 (14.5)
2	Slight disability: able to look after own affairs without assistance, but unable to carry out all previous activities	6 (11.1)	5 (9.1)
3	Moderate disability: requires some help, but able to walk unassisted	1 (1.9)	1 (1.8)
4	Moderate severe disability: unable to attend to own bodily needs without assistance	2 (3.7)[c]	0
5	Severe disability: requires constant nursing care and attention	0	0
6	Death	15 (27.8)	19 (34.5)

Factors affecting mortality during the 6-month follow-up period were evaluated from MRI measures. In this study of all the diffusion tensor MRI variables, global FA exhibited the best independent predictive value for mortality (mean [SD] of 0,433 [0,026] in the surviving patients *vs* 0,407 [0,035] in those who died). The

hazard ratio per 0,01- unit increase in FA was 0,81 (95% CI, 0,69–0,94; P = 0,006; adjusted by age, sex, study group and study site). The mean global FA was 6,4 % higher (95 % CI, 3,3–9,5 %) in the surviving patients than in those who died (table 19).

Table 19. Hazard ratio (HR) was estimated for 0,01 unit increase for the fractional anisotrophy and for the diffusivity values. *Values were adjusted for age, gender, study group and study site.

	Surviving patients (n = 68)	**Non-surviving patients (n = 29)**	**Unadjusted HR (95 % CI)**	**Adjusted* HR (95 % CI)**	**Unadjusted p value**	**Adjusted * p value**
Global values	*Unadjusted mean (SD)*					
Fractional anisotrophy	0.433 (0.026)	0.407 (0.035)	0.77 (0.68–0.87)	0.81 (0.69–0.94	< 0.0001	0.006
Axial diffusivity, $10^{-3}mm^2/s$	1.193 (0.037)	1.199 (0.076)	1.02 (0.93–1.12)	0.98 (0.89–1.08	0.68	0.70
Radial diffusivity, $10^{-3}mm^2/s$	0.598 (0.044)	0.633 (0.076)	1.12 (1.04–1.20)	1.07 (0.98–1.17)	0.002	0.12
Mean diffusivity, $10^{-3}mm^2/s$	0.796 (0.040)	0.821 (0.074)	1.11 (1.02–1.20)	1.05 (0.95–1.16)	0.02	0.31

The predictive value of elevated TnT for both short- and long-term morbidity and mortality in cardiac arrest patients is renowned. Moreover, regardless of the underlying disease, TnT is predictive for mortality in all intensive care patients, which was declared in the latest consensus statement of the Joint Task Force and recent trials (Thygesen 2012, Babuin 2008, Gilje 2016, Thygesen 2018). In this study, all-cause mortality at all the time points of TnT besides the baseline within the groups and in the whole population had a predictive value for all-cause mortality at 6 months after OHCA (table 20).

Table 20. TnT values in survivors and non-survivors (all-cause mortality) during 72 hours after OHCA. Abbreviations: TNT = Troponin-T, values are in µg/l, ln = natural logarithm, Δ = change from the baseline, *Data are for 74 patients due to missing data of one patient at 72 hours; †Data are for 31 patients due to missing data of two patients at 72 hours; ǂ Values are adjusted for age, gender, study site and group. § One surviving patient was mistakenly randomized with a primary cerebral event and not included in the analysis. One patient died in the angiolaboratory before ICU admission. Natural logarithmic transformation for TnT values was used in the statistical analysis due to skewness of the data.

	Survivors (n = 75§)	non-Survivors (n = 34§)		
Absolute values, Median (IQR)				
TnT at Baseline	0.07 (0.21)	0.11 (0.22)		
TnT 24 hours	0.34 (1.01)	1.16 (1.55)		
TnT 48 hours	0.23 (0.82)	0.55 (1.28)		
TnT 72 hours	0.25 (0.70)*	0.64 (2.40)†		
ln transformed values, Mean (SD)			**Adjustedǂ Hazard ratio (95% CI)**	**P-value**
ln TnT at Baseline	-2.40 (1.24)	-2.13 (1.20)	1.23 (0.92–1.65)	0.155
ln TnT 24 hours	-1.09 (1.68)	-0.13 (1.71)	1.34 (1.08–1.65)	0.007
ln TnT 48 hours	-1.46 (1.67)	-0.54 (1.60)	1.37 (1.09–1.72)	0.006
ln TnT 72 hours	-1.45 (1.80)*	-0.39 (1.60)†	1.31 (1.06–1.60)	0.011
Change from the baseline, Mean (SD)				
ln ΔTnT 24 hours	1.32 (1.24)	1.99 (1.59)	1.30 (1.02–1.66)	0.033
ln ΔTnT 48 hours	0.94 (1.25)	1.59 (1.57)	1.31 (1.02–1.69)	0.034
ln ΔTnT 72 hours	0.94 (1.39)*	1.75 (1.61)†	1.29 (1.01–1.64)	0.040

However, the association of TnT release on survival did not differ between groups, as the interaction by TnT in the group for all time points was non-significant (p > 0,10).

6 Discussion

This study was to our best knowledge the first investigation, where combined inhaled xenon and mild therapeutic hypothermia treatment was applied to adult cardiac arrest survivors.

The key findings in this prospective, randomized and controlled clinical trial were, that combining xenon inhalation for 24 hours to mild therapeutic hypothermia in comatose ventricular fibrillation-generated OHCA patients conferred to attenuated cerebral and myocardial injury, adressed with surrogate endpoints of cerebral WM injury by FA and in the heart, with altered Troponin T value kinetics. This represents the ongoing ischemia-reperfusion injury as a modifiable and viable therapeutic target for neuroprotection and cardioprotection.

This evidence indicates, that the extent of ongoing hypoxemic injury can be affected resulting that the outcome of cardiac arrest survivors might be improved. However, albeit these results represented a significant treatment effect in surrogate endpoints, no significant effect could be demonstrated in survival or neurological outcome, possibly originating from the underpowered sample size.

Difficulties in translating established preclinical evidence in neuro- and cardioprotection to marked clinical benefit is a renowned phenomen in clinical medicine, particularly in experimental stroke, traumatic brain injury and myocardial infarction research. These difficulties are associated with the time frame of the therapeutic intervention, heterogeneity of the study population in comparison to animal models, sample size and dosing/concentration differences in comparison to experimental animal models and clinical situations (Hoyte 2004, Menon 2009, Sutherland 2012, Xu 2013, Rossello 2016, Hausenloy 2017).

6.1 Neuroprotective effect by xenon inhalation following OHCA

6.1.1 Methodological aspects of fractional anisotrophy in various cerebral injuries

Diffusion tensor MRI provides an observer-independent, fully automated and quantitative assessment of injury in cerebral white matter tracts, which has been validated in studies in various cerebral injuries. Previously, recent studies have indicated, that quantitative diffusion tensor MRI with low fractional anisotrophy values predict outcome in severe traumatic brain injury, subarachnoidal haemorrhage as well as after OHCA (Yeo 2012, Sener 2016, Fragata 2017, Velly 2018, Fragata 2019). Cerebral white matter injury following these insults is explained by the location of WM NMDA receptors, which are expressed in WM myelin oligodendrocytes (Káradóttir 2005).

Nonsurviving patients could be identified also in this study by the global low FA values. However, generalized outcome prediction requires comparisons and estimations of normal FA values in different healthy age groups, which are not available. For example, in elderly patients, general white matter degeneration involved in ageing lowers FA values.

6.1.2 Neuroprotection by xenon in OHCA survivors

Xenon's neuroprotective properties in this study were demonstrated as an enhanced preservation of white matter tracts, which was displayed with higher fractional anisotrophy values. These reflect an attenuation of the ongoing disruption of white matter microintegrity as compared to the control group. In this study observed increased radial (but unchanged axial) diffusion has been correlated to mitigation of demyelination in previous studies (Song 2002).

In this study the lower radial diffusivity in the Xe group reflected less demyelination of white matter tracts and preserved intact axons. The mean global FA value was significantly higher among surviving Xe-patients, when compared to those who died or those in the control group. In particular, of all diffusion tensor measures, lower FA and degree of white matter injury was the strongest predictor of mortality at 6 months. Each of the other diffusivity values (axial, radial and mean) was lower in the xenon group, but only radial diffusivity differed statistically significantly (table 12). Despite higher unadjusted radial and mean diffusivity values were independent predictors of mortality during the 6-month follow-up, the adjusted diffusivity values were not capable to discriminate between surviving or not surviving patients (table 19).

The statistically significant difference (p = 0.006) in adjusted global mean FA values between survivors and nonsurvivors seems at the first sight to be trifling; 0.443 vs 0.407 – corresponds to only 6.4 % difference. However, this still represents the diffrence between life and death. These data emphasizes, that the equally highly significant difference (p = 0.006) in adjusted global mean FA values between Xe- and control group; 0.443 vs 0.419 – which is only 3.8 % difference (adjusted mean difference 0.016), represents a more than 50 % treatment effect of Xe on global FA, when associated with the values of surviving or nonsurviving patients (table 19).

On average 50 % of the total brain volume consists of white matter, which is extremely vulnerable to even short periods of focal ischemia (Pantoni 1996). The observed widespread white matter injury in voxelwise TBSS visualization (figure 4), which corresponded to lower FA values in the control group, demonstrated, that on average 41.7 % of white matter tracts were significantly more injured in the control group. The control group's higher radial diffusivity, which corresponds to more pronounced demyelination, is presumably responsible for the lower FA values. The location (based on Johns Hopkins University white-matter tractography atlas) of low FA values in control group were: cingulum (cingulate gyrus) (54.6%), cingulum (hippocampal region) (1.4%), forceps minor (49.4%) and major (35.5%), superior longitudinal fasciculus (49.3%), inferior longitudinal fasciculus (34.8%), anterior thalamic radiation (45.1%), inferior fronto-occipital fasciculus (41.0%), corticospinal tract (28.7%), uncinate fasciculus (36.4%), and the body of corpus callosum (72.3%). These tracts are involved in multiple neurocognitive functions, e.g. attention, memory, language, emotions, auditory, visual and executive processing and motor functions of the body.

Despite a significant demonstrated difference in white matter injury between the groups, there was neither significant difference in the (exploratory) analysis of neurological (CPC or mRS score; table 18) or cognitive outcomes (NHISS or MMSE score). These assays are tools for somewhat coarse analysis of mainly functional, motor and memory performance. However, they are important estimates of neurological performance allowing comparisons between studies. Generally, as also in this study, about 90 % OHCA victims, who were alive at the 6-month follow-up, had a favourable neurological outcome (CPC 1 or 2), and patients with severe neurological impairment were likely to die during convalescent care. However, these scales provide an important framework, which allows comparison between trials.

Functional neurocognitive deficiency assessment requires more sensitive methods. The study was underpowered to detect a statistically significant difference in clinical outcome.

6.2 Cardioprotective effects by xenon inhalation following OHCA

6.2.1 Methodological aspects of TnT assay on quantification of myocardial damage and influence in overall survival

Troponin T (TnT) is the validated and fundamental basis of assessment of an acute myocardial infarct and injury by the latest definitions and recommendations (Thygesen 2012, Thygesen 2018). TnT is routinely used whenever a ST-segment elevation (STEMI) or non-ST-segment elevation myocardial infarct (NSTEMI) are evaluated or defined and TnT levels correspond and quantify the myocardial infarct size (Stone 2016). The contemporary myocardial infarction definition guidelines describe and differentiate even minor changes in TnT values over hours to facilitate confirmation or rejection of the diagnosis of acute myocardial damage, which eventually and most importantly guide intensity of further treatment actions (Thygesen 2018). This translates to, that troponin assays are considered highly reliable assessments in quantification of myocardial injury and simultaneously, a reliable indicator of any action, which may have influenced or even mitigated myocardial injury following an insult.

Moreover, TnT has been identified as an independent predictive marker of all-cause morbidity and mortality due to a cardiovascular cause or multi-organ failure (Gilje 2016, Morrison 2017). Increment of Tnt at hospital admission also correlates significantly to short- and long-term mortality in general intensive care patients, regardless of the underlying disease (Babuin 2008).

6.2.2 Attenuatuation of myocardial injury by xenon inhalation after OHCA

A predefined secondary objective of the trial was to assess Xenon's cardioprotective effect with the extent of myocardial injury and the surrogate endpoint of difference in TnT increment post OHCA between groups of Xe inhalation and hypothermia and hypothermia only. In previous models of ischaemic myocardial injury in different sized animals, xenon exposure has been demonstrated to reduce experimental myocardial infarct size (Weber 2006b, Baumert 2007, Weber 2008, Mio 2009, Schwiebert 2010) and TnT release (Hein 2008b). The main finding of this study was that among comatose survivors of VF-generated OHCA, inhaled xenon combined with MTH attenuated TnT release profile corresponding to restricted myocardial injury when compared with that achieved by hypothermia only. This was demonstrated by the significantly lower

release of TnT at 72 h after OHCA in the Xe group. The TnT increment corresponded also to higher mortality at 6 months.

These results indicated significantly lower TnT release in the xenon group than in the control group at 72 h, but not at 24 and 48 h, explaining why the area under the curve remained nonsignificant. The high sensitive assay of TnT peaks on average 12 hours after injury (Solecki 2015). Duration of CPR chest compressions or the amount of defibrillations required does not affect TnT release (Müllner 1998), although it has been postulated, that the elevation of serum biomarkers post arrest could also be attributed to the resuscitation circumstances (Morrison 2017). In both study groups, the highest TnT values were at 24 h, which represents the initial myocardial injury leading to cardiac arrest and resuscitation.

However, if a cardioprotective strategy is applied with a goal of ongoing myocardial injury restriction, the release profiles of TnT from baseline should decline. This was demonstrated in this study, as there was a significant difference in first 72 h TnT release profile with a significant decline of 44.8% in the Xe group and a nonsignificant decline of 11.3% in the control group from the peak at 24 h to 72 h. The difference was even more distinct between the groups in patients with NSTEMI, with a significant decline in the Xe group as compared with a nonsignificant increment in the control group from the peak to 72 h. Although the decline was significant only in the xenon group, the release profile of the current control group was very similar to a recently published population of 699 OHCA patients, with a TnT decline of 10.8% (Gilje 2016).

Occlusive coronary artery disease resulting in STEMI naturally causes higher TnT release than NSTEMI, consisting additionally of “TnT washout” following possible revascularization. The infarct mass in STEMI is likewise extended, which has previously been demonstrated to significantly correlate with all single-point measures of TnT at 24, 48, and 72 h (and also at 96 h) (Giannitsis 2008). STEMI patients had significantly higher TnT release than NSTEMI patients also in the current study. Consequently, the single-point values of TnT, rather than the area under the curve, were considered to be reliable estimates of the ongoing ischemia-reperfusion injury. The demonstrated difference between the groups reflects a significant cardioprotective treatment effect by MTH and Xe inhalation, which was observed over the first 72 h.

In the statistical analysis, the attenuation of myocardial injury in the Xe group was independent of age, sex, study site, dose of noradrenaline, and performed PCI. The effect of Xe on the TnT release was similar in patients with or without PCI or with a diagnosis of STEMI, as well as in both survivors and nonsurvivors. The severity of coronary artery disease in the study patients was evaluated by patient history, coronary angiography, and autopsy report (when available). The extent of coronary artery disease was comparable in the study groups, suggesting that the

effect of Xe was not likely to be modified by the severity of ischemic cardiac disease burden (table 10).

6.2.3 Confounding factors of TnT release

The accuracy of cardiac injury markers has been questionable after OHCA and resuscitation (Kruse 2014). There are distinct confounding factors, which could affect TnT release. Firstly, patients with chronic kidney disease (CKD) have a high prevalence of elevated troponin levels (Jacobs 2009, Unger 2016), which reduces the diagnostic accuracy of TnT in acute myocardial infarction in patients with CKD (Stacy 2014, Parikh 2015). Whether this reflects reduced TnT clearance in the kidneys or is a genuine representation of non-ischaemic myocardial stress or chronic structural heart disease, is still controversial (Diris 2004, Stacy 2014, Parikh 2015, Fridén 2017). In the current study, the influence of acute (or chronic) kidney injury was carefully ruled out by comparison of alterations in kidney function and RIFLE score during the first 7 days after OHCA. There were no statistifically significant differences, which could have inflicted the interpretation of TnT analysis (table 9).

Secondly, haemodynamic parameters and requirements of vasoactive medication during TnT release observation over the first 72 h may influence TnT release. Because of the predefined haemodynamic targets, there were no differences in blood pressure between the study groups during intervention or follow-up. However, heart rate was significantly lower in Xe group than in the control group during MTH, with this effect lasting at least up to 72 hours after OHCA (table 8). Xenon's heart rate–decreasing properties have been well documented previously (Dingley 2001, Coburn 2005, Wappler 2007, Al Tmimi 2015). Coincidentaly, a recent trial demonstrated that marked sinus bradycardia during MTH following OHCA is an early marker of improved outcome, and it was suggested to represent an independent marker of favorable neurocognitive outcome (Thomsen 2016). Therefore, one could anticipate, that xenon's ability to reduce heart rate may have some beneficial clinical value in cardiac arrest patients. However, this was not supported by the current results because no correlation could be detected between heart rate and attenuated myocardial injury, deducted from lower TnT release at 72 hours post OHCA.

Thirdly, in the current trial with over 24 h of Xe inhalation, the dose of propofol was significantly lower during MTH and extending cumulatively to the follow-up over 72 h, although the propofol doses after Xe discontinuation were comparable. Less propofol was accompanied with a reflectory, clear, but nonsignificant trend of inotrope-sparing effect in Xe group. Of vasoactive medication, doses of noradrenaline and dobutamine showed a significant positive

correlation with troponin-T release only in the Xe group. Otherwise, there was not significant difference between the groups. Consequently, vasoactive medication was unlikely to have been responsible for the extended TnT release connected to more severe myocardial injury in the control group.

Forthly, in preclinical animal studies and especially in cardiac surgery, propofol in comparison to sevoflurane has been recocnized as an anaesthetic with cardioprotective properties in patients with severe coronary ischemia, cardiovascular instability or undergoing urgent surgery. Besides antioxidant effects, propofol has been connected to reduction of oxidative stress and cardiac protection against ischaemia-reperfusion injury (Jakobsen 2007). This is illustrated as mitigated TnT release after CABG surgery (Javadov 2000, Xia 2006). Consequently, one could expect a reduction of propofol cardioprotection in the Xe group, as the dose of propofol was significantly lower than in the control group. Despite the possible cardioprotective properties of propofol, there was no correlation between the administered dose and the troponin-T release within the groups in this study. Therefore, it is unlikely that the administration or dose of propofol had any significant impact on the current results.

Taken together, none of these major confounding variables included in the study model either differed between the groups or exhibited any correlation with the release of TnT. Hence, Xe combined with MTH was a significant independent factor attenuating the severity of the myocardial injury after OHCA addressed with TnT release profile. In this study, the effect on the TnT release was likely due to a post-conditioning effect, because xenon inhalation was initiated with a mean delay of 4 h after OHCA. Speculatively, earlier Xe inhalation initiation might have improved the cardioprotective effects by Xe, but during this study, the major factor delaying the treatment was waiting the written informed assent by the next of kin within the protocol time frame, i.e. within 4 hours from the hospital admission.

6.3 Status epilepticus after hypoxic-ischaemic brain injury

The incidence of status epilepticus did not differ between study groups. If epilepsy was encountered, antiepileptic drugs were started and adjusted in co-operation with the consulting neurologist. As propofol is an antiepileptic drug, one could argue, that the reduction in propofol dose during Xe inhalation could have facilitated more epilepsy. This was, however, not the case.

Postanoxic status epilepticus bears a notorious reputation with high likeliness of severe brain injury and permanent unconsciousness. In this study, epilepsy was associated also with poor prognosis. However, this was not always, which has been demonstrated also by others (Hofmeijer 2014, Seder 2015), as 5 patients in this

study with post cardiac arrest epilepsy regained consciousness with eventually satisfactory outcome. Pessimisticly, it is very hard to to distinguish these surviving patients from those whose antiepileptic treatment eventually translates to be futile.

6.4 Survival

In this study two major variables were identified to predict all-cause mortality at 6 months after OHCA. Firstly, low FA value (mean [SD] of 0.433 [0.026] in the surviving patients *vs* 0.407 [0.035] in those who died) distinguished the patients who survived or deceased after hypoxic-ischaemic brain injury (table 19). Secondly, TnT increment at all the time points of TnT besides the baseline within the groups and in the whole population had a predictive value for all-cause mortality at 6 months after OHCA (table 20). However, this study was not sufficiently powered to address Xe's long-term effect on either cardiac or all-cause mortality.

6.5 Study limitations

Due to the small study group, this study was underpowered to identify differences in survival (mortality) or neurological cognitive outcome. This might also reflect, that these promising results in surrogate endpoints, i.e. reduced brain WM FA descent and cardiac TnT release mitigation, are not the sole affectors translating to clinical success in outcome.

Brain grey matter injury was not investigated in this study and therefore, this study provides no information on the role of grey matter injury following OHCA.

Furthermore, the effect of the beneficial intervention was demonstrated with the combination of xenon inhalation and targeted temperature management at 33 °C. It is impossible to deduce, whether complementary xenon inhalation would have a neuroprotective effect in other normothermic or hypothermic temperatures. This question will be adressed in the already ongoing phase III trial. In the current study, however, all patients were treated with induced hypothermia in both study groups. In previous preclinical studies, xenon has been demonstrated to have neuroprotective properties with and without simultaneous hypothermia (Wilhelm 2002, Banks 2010, Thoresen 2009, Chakkarapani 2010, Hobbs 2008 and Table 1). Because the standard intervention, hypothermia, was constant, differences between groups represent a genuine and independent treatment effect by xenon inhalation in OHCA survivors.

6.6 Clinical implications and future considerations of xenon use in cardiac arrest patients

A phase III clinical trial in 1436 OHCA patients (Xenon for Neuroprotection During Post-Cardiac Arrest Syndrome in Comatose Survivors of an Out Of Hospital Cardiac Arrest (XePOHCAS – NCT3176186)) is already launched, which will provide further evidence, whether these observations translate to a clinical benefit and improved outcome in post cardiac arrest syndrome patients (Maze 2018).

The noble gas Xe is scarce and therefore costly, which makes its use unlikely in routine perioperative settings. Utilizing recirculating ventilators diminishes Xe consumption during anaesthesia but it is still high-priced when compared to the cheaper alternatives. Furthermore, closed-circuit ventilation is technically somewhat more challenging, which propably might cause prejudices and the availability of these ventilators has this far been limited. Xenon has, however, many attractive properties and an anaesthesia performance resembling “an ideal anaesthetic”, which could promote its use particularly in intensive care medicine, where the patients are potentially haemodynamically unstable, very exposed to unwanted pharmacological interactions and suspectible to secondary injurous cascades of cell damage.

Hypoxic ischaemic cerebral, myocardial reperfusion injury and the multi-organ post cardiac arrest syndrome following successful cardiac arrest resuscitation are examples of these conditions, where despite all current treatment practices – including targeted temperature management – the modest results in outcome and low survival are still unresolved.

This study provides the first evidence since mild therapeutic hypothermia treatment adaptation, that ischaemia reperfusion injury is modifiable and the extent of injury can be diminished with simultaneous combination of MTH and Xe inhalation in subanaesthetic doses. The putative organoprotective effect by xenon in e.g. kidney evokes possibilities of further post cardiac arrest syndrome burden attenuation, especially if the delay to xenon exposure after collapse and ischaemia-reperfusion injury initiation is narrowed by almost immediate xenon administration.

Curiously, at cardiac arrest site commenced xenon inhalation would allow extremely rapid evaluation of post arrest neuro- and cardioprotective treatment imperatives, as xenon anaesthesia involves emergence from sedation within a couple of minutes, which facilites immediate evaluation of consciousness. Lack of responsiveness after xenon discontinuation would instantly uncover the organoprotective goals of further treatment in unresponsive cardiac arrest survivors.

7 Summary and conclusions

Main results and conclusions according to the aims of the study were:

1. Combining mild therapeutic hypothermia with xenon inhalation for 24 hours in ventricular fibrillation-generated out-of hospital cardiac arrest victims remaining comatose is safe and feasible. Xenon inhalation is associated with stable hemodynamics, mitigation of the dose of hypnotics required during induced hypothermia resulting in an inotrope-sparing effect during cooling. Bradycardia during MTH was emphazised, which is suggested to be an independent marker of more favorable neurological outcome in recent studies. The density of Xe is higher than air, which causes a temporary increase in airway pressure during Xe inhalation.
2. The combination of Xe inhalation and MTH attenuated the ischaemia reperfusion induced cerebral white matter injury, which was demonstrated with the surrogate endpoint of diffusion tensor magnetic resonance imaging fractional anisotrophy, which was higher, corresponding to enhanced preservation of white matter tracts in the Xe group in comparison to the MTH only control group. Similarly, DTI MRI radial diffusivity values were lower in the Xe group than in the control group. High radial diffusivity values correspond to demyelination of white matter axons, which was attenuated in the Xe group. These findings correspond to a significant neuroprotective effect by Xe + MTH compared to MTH only.
3. Ischaemia-reperfusion injury in the myocardium was assessed with the release of cardiac intracellular protein troponin-T, which corresponds to cardiomyocyte disruption after ischaemic insult. In the Xe group, the profile of TnT release over the first 72 hours after OHCA had a significant decline in comparison to the control group. This finding illustrated a cardioprotective effect in ongoing cardiomyocyte ischaemia-reperfusion injury in the Xe group when compared to MTH only.
4. Although this study was underpowered to any estimations of functional recovery or outcome, two factors affecting survival at 6 months were

identified. A low initial brain DTI MRI value of FA was associated with mortality during follow-up. Furthermore, high TnT values during ICU follow-up were associted with all-cause-mortality at 6 months.

Acknowledgements

This study was carried out during years 2009–2015 in Turku University Hospital and during years 2012–2015 in Helsinki University Hospital. The study was funded by the Academy of Finland and clinical research funding (EVO grants) provided by the Hospital District of South-Western Finland. The study was investigator-originated, i.e. the funders had no role in the study.

My warmest gratitude is expressed to the study patients – the OHCA victims and their next of kin, who allowed the patients to participate in this clinical research. The decision of participating in a randomized, blinded, prognostic clinical trial after sudden death experience is a serious issue. The study group could, however, guarantee, that the best-known contemporary care was provided for the OHCA survivors in both groups. Inhaled xenon was considered safe based on preclinical and clinical studies, but no cardiac arrest patients had previously been exposed to it.

I am most grateful to professor Klaus Olkkola, who was during the study head of the Division of Perioperative Services, Intensive Care Medicine and Pain Management at Turku University Hospital and the professor of Anaesthesiology at Turku University. Adjunct professor Juha Perttilä, who tragically deceased in a boating accident in December 2012, was the head of Turku Intensive Care Unit during major study time. He is most warmly acknowledged - besides being a wonderful person and leader – for being the principal character and mentor affecting the start and course of my intensivist career. Juha had a remarkable ability to pick the suitable colleagues and make them feel, that the chosen person was the most appropriate for the provided task. His successors, adjunct professors Minna Tallgren and Mika Valtonen are warmly acknowledged for maintaining the good spirits and encouraging scientific environment in the, sometimes very hectic, ICU work. Mika is sincerely appreciated for realizing, that the preparation of this thesis required lots of out-of-office hours and time.

Adjunct professor Tuula Manner, who is presently the head of the Division of Perioperative Services, Intensive Care Medicine and Pain Management at Turku University Hospital is warmly acknowledged for creating an encouraging atmosphere in the clinic in scientific work and everyday work.

It was a huge privilege for me to be invited as a PhD student into the study group. Prognostic, randomized clinical trials in ICU environment of this magnitude are, after all, extremely rare in Finland. The major driving force of the study was the inventor of the study concept, associate professor, the principal investigator Timo Laitio, who meticulously was *the supervisor* and thoroughly involved in all parts of the study. Timo reviewed and rewrote countless of manuscripts, governed the correspondence, managed the collaboration between the study sites, statistical co-operation and had without interruption a crystal clear vision of study goals and the means how to reach them. Timo's impact in this study is incomparable, boundless and he is deeply acknowledged for his expertise, patience and perseverance.

The study was designed by a group of distinguished professionals; from the department of anaesthesiology: adjunct professor Ruut Laitio, professor Harry Scheinin and associate professor Timo Laitio; from the department of Cardiology / Heart Center: professor Antti Saraste; from the department of Radiology: professor Riitta Parkkola; from the department of Neurology / Division of Clinical Neurosciences: professor Risto O Roine; and finally, scientific and intellectual collaboration in the study group was granted by the presence of distinguished professor of anaesthesiology Mervyn Maze, from University of California, San Francisco. It is truly an honour to participate in a group like this, which is most humbly acknowledged. A fascinating feature in this clinical investigation was, that whatever result followed after the intervention, it was anyway novel information and very publishable.

I express my gratitude to my former chiefs, emerita/emeritus professors Auli Toivanen and Jorma Viikari, from the department of Medicine, for providing a solid model for how to be a University Hospital clinician. Professor Viikari is especially acknowledged for introducing me to medical writing. Adjunct professor Liisa-Maria Voipio-Pulkki is acknowledged for being my very first ICU work mentor and introducing me to scientific work and scientific writing.

Professor Christian Hassager and associate professor Jesper Petersson are warmly thanked for excellent and constructive review of this thesis.

Much of the logistics and practical issues of this study were on the shoulders of study nurse Keijo Leivo, who was always available, usually in very inconvenient working hours and especially without hesitation extracting countless sets of information from the ICU data processing system. A striking feature in our collaboration was the continuous casualty in everything, whether preparing the Xenon ventilator in the wee wee hours or escorting unstable patients to MRI at out-of-office hours. My gratitude to Keijo is immense – this study would not have taken place without his assistance. Study nurse Tuukka Tikka, who is additionally acknowledged, accomplished similar work in Helsinki University Hospital.

The heart and soul of this study was however, the research team caring about the patients during study intervention and ICU stay. Non-interrupted recruitment over 5 study years on a 24 hour / 7 days -basis required lots of collaboration. The team of intensivists Timo and Ruut Laitio, Juha Grönlund, Outi Inkinen and Emmi Ylikoski in Turku and intensivists Marja Hynninen, Minna Bäcklund, Eija Nukarinen, Päivi Silvasti, Emmi Ylikoski (continued in Helsinki after moving to Helsinki) and Johanna Wennervirta in Helsinki are acknowledged for recruitment and care of the study OHCA survivors. Intensivist Ruut Laitio had the profoundest experience of xenon use and is warmly thanked for sharing this expertise with the rest of the group. Besides a scientist, Ruut is a skillful clinician and after all these years, I would still choose her to be the number one partner in demanding and "tight spot" ICU patient care situations. Intensivist Outi Inkinen is warmly acknowledged for being such an experienced, broad-spectrum clinician and person, not forgetting for being such a long time good friend who also acts as a true support in unofficial work counseling. Generally, the ICU staff - junior and senior intensivists and nurses form a casual working community, which is always welcoming despite of the laborious nature of the work. I am proud to be a part of this community.

The "xenon nurses", Keijo Leivo, Anna Ali-Keskikylä, Juhapekka Haaranen, Tellervo Joutsalainen, Nina Kallio, Jutta Kotamäki, Esa Mäkimaa, Sanna Nerjanto, Kaj Nyman, Leena Paarnio-Saarela and Jukka Perus are especially acknowledged. They were the ones ready to come to take care of the xenon anesthesia maintenance especially at nighttime without being on call for this. The nurses were compensated for their collaboration.

The cardiologist team, in Turku Juhani Airaksinen, Antti Saraste and Mikko Pietilä; and in Helsinki Veli-Pekka Harjola, Kirsi Korpi, Jussi Niiranen and Marjut Varpula are greatly acknowledged for their collaboration in performing cardiac ultrasound assessments, confirming ECG analyses as well analyzing and quantifying coronary angiogram findings.

The Turku neurologist team consisted of professor Risto O Roine, who was also the second supervisor of this thesis. He is one of the fundamental European pioneers of induced hypothermia research. He was also essential in the initial study funding. The Helsinki neurologist was Marjaana Tiainen, an experienced colleague in post cardiac arrest syndrome research. I express both my warm gratitude for collaboration, e.g. performing the blinded 3 and 6 month follow-up examinations for the surviving study patients.

The radiologist team is acknowledged for precise and laborious work in somewhat challenging study patient population. They are separately cheered for applying a totally novel technique (e.g. TBSS) when the study was already ongoing. The responsible radiology team in Turku was professor Riitta Parkkola,

radiologist Sami Virtanen and medical physicist Jani Saunavaara. In Helsinki, the radiologists were adjunct professor Leena Valanne, Juha Martola and Heli Silvennoinen. They are all warmly acknowledged. Lastly, but not leastly, I express my warmest gratitude for the radiographers, who performed the MRI investigations generally after working hours and also during weekends, if indicated.

The professional statistifical collaboration by MSc Tero Vahlberg, from the Department of Biostatics, University of Turku is warmly acknowledged for perseverance and compassionateness.

My mother and late father, siblings, friends and colleagues are acknowledged for continuous support and cheerful encouragement during these years.

Finally, and most importantly, I express my deepest gratitude to my family; Aila for being such a devoted, ever-loving, supporting and flexible wife; my marvelous children Helmi, Ilkka and Tytti with their spouses, who grew during this study from young adulthood to parenthood and professionalism, providing lots of fascinating and interesting activities outside the hospital, for example four charming grandchildren. I am looking forward to enhance my presence in your lives, which was more restricted during this study and especially during the preparation of this thesis.

October 2019
Olli Arola

List of references

Abe O, Takao H, Gonoi W, Sasaki H, Murakami M, Kabasawa H, Kawaguchi H, Goto M, Yamada H, Yamasue H, Kasai K, Aoki S, Ohtomo K. Voxel-based analysis of the diffusion tensor. Neuroradiology 2010; 52: 699 – 710

Abella BS, Gaieski DF. Coronary angiography after cardiac arrest – the right timing or the right patients? N Engl J Med 2019; 380: 1474 – 1475

Adams F. The genuine works of Hippocrates. William Wood, New York 1929; pp 741 - 742

Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Ding-Xuan T, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002; 106: 562 – 568

Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, Rhaoui A, Thuong M, Monchi M. Predicting survival with good neurological recovery at hospital admission after succesful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006; 27: 2840 – 2845

Agematsu K, Korotcova L, Morton PD, Gallo V, Jonas RA, Ishibashi N. Hypoxia diminishes the protective function of white-matter astrocytes in the developing brain. J Thorac Cardiovasc Surg 2016; 151: 265 – 272

Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007; 4: 316 – 329

Ali MU, Fitzpatrick-Lewis D, Kenny M, Raina P, Atkins DL, Soar J, Nolan J, Ristagno G, Sherrifali D. Effectiviness of antiarrhythmic drugs for shockable cardiac arrest: a systematic review. Resuscitation 2018; 132: 63 – 72

Alkadri ME, Peters MN, Katz MJ, White CJ. State-of-the-Art Paper: Therapeutic Hypothermia in Out of Hospital Cardiac Arrest Survivors. Cath and Cardiovasc Intervent. 2013; 82: E482 –E490

Al tmimi L, Van Hemelrijck J, Van de Velde M, Sergeant P, Meyns B, Missant C, Jochmans I, Poesen K, Coburn M, Rex S. Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial. Br J Anaesth 2015; 115: 550-59

Alvarez V, Sierra-Marcos A, Oddo M, Rossetti AO. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. Crit Care Med 2013; 17: R190 – R195

Alzaga AG, Cerdan M, Varon J. Therapeutic hypothermia. Resuscitation 2006; 70: 369 – 380

Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, Kurth T, Donnino MW for the American Heart Associations's Get With The Guidelines-Resuscitation Investigators. JAMA 2017; 317: 494 – 506

Angelos MG, Menegazzi JJ, Callaway CW. Bench to bedside: Resuscitation from Prolonged Ventricular Fibrillation. Acad Emerg Med 2001; 8: 909 – 924

Arbalaez A, Castillo M, Mukherji SK. Diffusion-weighted MR imaging of global cerebral anoxia. Am J Neuroradiol 1999; 20: 999 – 1007

Arch AM, Harper NJN. Xenon: An element of protection. Trends in Anaesth and Crit Care 2011; 1: 238 – 242

Armstrong SP, Banks PJ, McKitrick TJ, Geldart CH, Edge CJ, Babla R, Similis C, Franks NP, Dickinson R. Identification of two mutations (F758W and F758Y) in the N-methyl-D-aspartate receptor glycine-binding site that selectively prevent competitive inhibition by xenon without affecting glycine binding. Anesthesiology 2012; 117: 38 – 47

Arola O, Virtanen S, Laitio R, Parkkola R, Roine RO, Tiainen M, Silvennoinen H, Martola J, Valanne L, Airaksinen J, Saraste A, Pietilä M, Saunavaara J, Olkkola K, Hynninen M, Wennervirta J, Bäcklund M, Ylikoski E, Scheinin H, Inkinen O, Grönlund J, Harjola VP, Niiranen J, Korpi K, Varpula M, Leivo K, Vahlberg T, Laitio T, for the Xe-HYPOTHECA Study Group. Brain white matter damage predicts poor short-term outcome after out-of-hospital cardiac arrest. Intens Care Med 2013; 39: S338

Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for Neuroprotection in adults after cardiopulmonary resuscitation (Review). Cochrane Database of Systematic Reviews 2016; 15: CD004128

Ashburner J. Computational anatomy with the SPM software. Magn Reson Imaging 2009; 27: 1163 – 1174

Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-trated out-of-hospital cardiac arrest in Europe. Resuscitation 2005; 67: 75 – 80

Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P for the TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009; 361: 1349 – 1358

Azzopardi D, Robertson NJ, Bainbridge A, Cady E, Charles-Edwards G, Deierl A, Fagiolo G, Franks NP, Griffiths J, Hajnal J, Juszczak E, Kapetanakis B, Linsell L, Maze M, Omar O, Strohm B, Tusor N, Edwards AD. Moderate hypothermia within 6h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomized controlled trial. Lancet Neurol 2016; 15: 145 – 153

Babuin L, Vasile VC, Rio Perez JA, Alegria JR, Chai HS, Afessa B, Jaffe AS. Elevated cardiac troponin is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. Crit Care Med 2008; 36: 759 – 765

Bach M, Laun FB, Leemans A, Tax CMW, Biessels GJ, Stieltjes B, Maier-Hein KH. Methodological considerations on tract-based spatial statistics (TBSS). Neuroimage 2014; 100: 358 – 369

Backman S, Westhall E, Dragancea I, Friberg H, Rundgren M, Ullén S, Cronberg T. Electroencephalographic characteristics of status epilepticus after cardiac arrest. Clin Neurophysiol 2017; 128: 681 – 688

Badjatia N, Strongilis E, Prescutti M, Fernandez L, Fernandez A, Buitrago M, Schmidt JM, Mayer SA. Metabolic benefits of surface counter warming during therapeutic temperature modulation. Crit Care Med 2009; 37: 1893 – 1897

Ballo H, Saraste A, Laitio R, Arola O, Airaksinen J, Pietilä M, Harjola VP, Niiranen J, Korpi K, Varpula M, Laitio T. Echocardiographic analysis of effect of the inhaled xenon in combination with therapeutic hypothermia on ischemic myocardial injury associated with cardiac arrest. Eur Heart J Cardiovasc Imaging Abstracts 2017; 18(suppl 3): iii192 – iii193

Banks P, Franks NP, Dickinson R. Competitive inhibiition at the glycine site of the N-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia-ischemia. Anesthesiology 2010;112: 614 – 622

Bantel C, Maze M, Trapp S. Noble gas xenon is a novel adenosine triphosphate-sensitive potassium channel opener. Anesthesiology 2010; 112: 623 – 630

Bassand J-P, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non- ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Eur Heart J 2007; 28: 1598 – 1660

Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J 1994; 66: 259 – 267

Baumert JH, Reyle-Hahn M, Hecker K, Tenbrick R, Kuhlen R, Rossaint R. Increased airway resistance during xenon anaesthesia in pigs is attributed to physical properties of the gas. Br J Anaesth 2002; 88: 540 – 545

Baumert JH (Baumert 2007a), Hein M, Hecker KE, Satlow S, Schnoor J, Rossaint R. Autonomic cardiac control with xenon anaesthesia in patients at cardiovascular risk. Br J Anaesth 2007; 98: 722 - 727

Baumert JH (Baumert 2007b), Hein M, Gerets C, Baltus T, Hecker KE, Roissant R. The effect of xenon anesthesia on the size of experimental myocardial infarction. Anaesth Analg 2007; 105: 1200 – 1206

Baumert JH, Hein M, Hecker KE, Satlow S, Neef P, Rossaint R. Xenon or propofol anaesthesia for patients at cardiovascular risk in non-cardiac surgery. Br J Anaesth 2008; 100: 605 – 611

Baumert JH, Hein M, Gerets C, Baltus T, Hecker KE, Rossaint R. The effect of xenon on isoflurane protection against experimental myocardial infarction. J Cardiothorac Vasc Anesth 2009; 23: 614 – 618

Baumert JH, Roehl AB, Funcke S, Hein M. Xenon protects left ventricular diastolic function during acute ischemia, less than ischemic preconditioning. Med Gas Res 2016; 6: 130 – 137

Baur CP, Klingler W, Jurkat-Rott K, Froeba G, Schoch E, Marx T, Georgieff M, Lehmann-Horn F. Xenon does not induce contracture in human malignant hyperthermia muscle. Br J Anaesth 2000; 85: 712 – 716

Bedi A, Murray JM, Dingley J, Stevenson MA, Fee JP. Use of xenon as a sedative for patients receiving critical care. Crit Care Med 2003; 31:2470 – 2477

Behnke A, Yarbrough O. Physiologic studies of helium. US Navy Med Bull 1938; 36: 542 – 558

Behnke AR, Yarbrough OD. Respiratory resistance, oil-water solubility, and mental effects of argon, compared with helium and nitrogen. Am J Physiol 1939; 121: 409 – 415

Behringer W, Arrich J, Holzer M, Sterz F. Out-of-hospital therapeutic hypothermia in cardiac arrest victims. Scand J Trauma, Resusc Emerg Med 2009; 17: 52 – 58

Bein B, Turowski P, Renner J, Hanss R, Steinfath M, Scholz J, Tonner PH. Comparison of xenon-based anaesthesia compared with total intravenous anaesthesia in high risk surgical patients. Anaesthesia 2005; 60: 960 – 967

Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, for the Acute Dialysis Quality Initiative workgroup. Acute renal failure — definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:R204 – R212

Bellomo R, Märtensson J, Eastwood GM. Metabolic and electrolyte disturbance after cardiac arrest: How to deal with it. Best Pract Res Clin Anaesthesiol. 2015; 29: 471 – 484

Benbadis SR, Chen S, Melo M. What's shaking in the ICU? The differential diagnosis of seizures in the intensive care setting. Epilepsia 2010; 51: 2338 – 2340

Ben-Hamouda N, Taccone FS, Rossetti AO, Oddo M. Contemporary approach to neurologic prognostication of coma after cardiac arrest. Chest 2014; 146: 1375 – 1386

Benson DW, Williams GR, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anaesth Analg 1959; 38(6): 423 – 428

Benz-Woerner J, Delodder F, Benz R, Cueni-Villoz N, Feihl F, Rossetti AO, Liaudet L, Oddo M. Body temperature regulation after cardiac arrest and therapeutic hypothermia. Resuscitation 2012; 83: 338 – 342

Berdowski J, Berg RA, Tijssen JGP, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation 2010; 81: 1479 – 1487

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of the out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346: 557 – 563

Bernard SA, Buist M. Induced hypothermia in critical care medicine: a review. Crit Care Med 2003; 31: 2041 – 2051

Beylin ME, Perman SM, Abella BS, Leary M, Shofer FS, Grossestreuer AV, Gaieski DF. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Int Care Med 2013; 39: 1981 – 1988

Bihel E, Roussel S, Toutain J, Bernaudin M, Touzani O. Diffusion tensor MRI reveals chronic alterations in white matter despite the absence of a visible ischemic lesion on conventional MRI. A nonhuman primate study. Stroke 2011; 42: 1412 – 1419

Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP, Rosa G. Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. Br J Anaesth 2013; 110 suppl 1: i113 – i120

Blom MT, Beesens SG, Homma PCM, Zijlstra JA, Hulleman M, van Hoijen DA, Bardai A, Tijssen JGP, Tan HL, Koster RW. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. Circulation 2014; 130: 1868 – 1875

Bobrow BJ, Spaite DW, Berg RA, Stolz U, Sanders AB, Kern KB, Vadeboncoeur TF, Clark LL, Gallagher JV, Stapczynski JS, LoVecchio F, Mullins TJ, Humble WO, Ewy GA. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. JAMA 2010; 304: 1447 – 1454

Bona E, Hagberg H, Løberg EM, Bågenholm R, Thoresen M. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short – and long-term outcome. Pediatr Res 1998; 43: 738 – 745

Bonventre JV, Zuk A. Ischemic acute renal failure: an inflammatory disease? Kidn Intern 2004; 66: 480 - 485

Boomsma F, Ruprecht J, Man in ‘t Veld AJ, de Jong FH, Dzoljic M, Lachmann M. Hemodynamic and neurohumoral effects of xenon anesthesia. A comparison with nitrous oxide. Anesthesia 1990; 45: 273 – 278

Bougoin W, Lmahaut L, Marijon E, Jost D, Dumas F, Deye N, Beganton F, Empana JP, Chazelle E, Cariou A, Jouven X. Characteristics and prognosis of sudden cardiac death in greater Paris. Population-based approach from the Paris sudden death expertise center (Paris – SDEC). Int Care Med 2014; 40: 846 – 854

Bouwes A, van Poppelen D, Koehlman JH, Kuiper MA, Zandstra DF, Weinstein HC, Tromp SC, Zandbergen EG, Tijssen MA, Horn J. Acute posthypoxic myoclonus after cardiopulmonary resuscitation. BMC Neurol 2012; 12: 63 doi: 10.1186/1471-2377-12-63.

Brader E, Jehle D, Safar P. Protective head cooling during cardiac arrest in dogs. Ann Emerg Med 1985; 14: 510

Bradley SM, Liu W, McNally B, Vellano K, Henry TD, Mooney MR, Burke NM, Brilakis ES, Grunwald GK, Adhaduk M, Donnino M, Girotra S, for the Cardiac Arrest Registry to Enhance Surcical (CARES) Surveillance Group. Temporal trends in the use of therapeutic hypothermia for out-of-hospital cardiac arrest. JAMA Netw Open 2018; 1: e184511

Breuer T, Emontzpohl C, Coburn M, Benstoem C, Rossaint R, Marx G, Schälte G, Bernhagen J, Bruells CS, Goetzenich A, Stoppe C. Xenon triggers pro-inflammatory effects and suppresses the anti-inflammatory response compared to sevoflurane in patients undergoing cardiac surgery. Crit Care 2015; 19: 365 – 379

Brinkrolf P, Metelmann B, Scharte C, Zarbock A, Hahnenkamp K, Bohn A. Bystander-witnessed cardiac arrest is associated with reported agonal breathing and leads to less frequent bystander CPR. Resuscitation 2018; 127: 114 – 118

Britton SW. Extreme hypothermia in various animals and in man: with notes on the detection of life and the possibility of recovery in cases of apparent death from exposure to cold. Can Med Assoc J 1930; 22: 257 – 261

Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, LaRoche SM, Riviello Jr JJ, Shutter L, Sperling MR, Treiman DM, Vespa PM for the Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012; 17: 3 – 23

Burov NE, Kornienko LI, Makeev GN, Potapov VN. Clinical and experimental study of xenon anaesthesia. Anesteziol Reanimatol 1999; 56 -60

Busl KM, Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. NeuroRehab 2010; 26: 5 – 13

Buunk G, van der Hoeven JG, Frölich M, Meinders AE. Cerebral vasoconstriction in comatose patients resuscitated from cardiac arrest? Intensive Care Med 1996; 22: 1191 – 1196

Callaway CW, Rittenberger JC, Logue ES, McMichael MJ. Hypothermia after cardiac arrest does not alter serum inflammatory markers. Crit Care Med 2008; 36: 2607 – 2612

Callaway CW. Endothelial damage after cardiac arrest – "Endotheliitis" . Resuscitation 2012; 83: 667 – 668

Callaway CW, Elmer J, Guyette FX, Molyneaux BJ, Andersson KB, Empey PE, Gerstel SJ, Holquist K, Repine MJ, Rittenberger JC. Dexmedetomidine reduces shivering during mild hypothermia in waking subjects. PLoS ONE 2015; 10: e0129709

Callaway CW. Neuroprognostication postcardiac arrest: translating probabilities to individuals. Curr Opin Crit Care 2018; 24: 158 – 164

Calzia E, Stahl W, Handschuh T, Marx T, Froba G, Georgieff M, Rademacher B. Continuous arterial pO_2 and pCO_2 measurements in swine during nitrous oxide and xenon elimination: prevention of diffusion hypoxia. Anesthesiology 1999; 90:829 – 834

Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. J Pathol 2000; 190: 255 – 266

Cattano D, Williamson P, Fukui K, Avidan M, Evers AS, Olney JW, Young C. Potential of xenon to induce or to protect against neuroapoptosis in the developing mouse brain. Can J Anesth 2008; 55: 429 – 436

Cattano D, Valleggi S, Cavazzana AO, Patel CB, Ma D, Giunta F. Xenon exposure in the neonatal rat brain: effects on genes that regulate apoptosis. Minerva Anesthesiol 2011; 77: 571 – 578

Chae MK, Ko E, Lee JH, Lee TR, Yoon H, Hwang SY, Cha WC, Shin TG, Sim MS, Jo IJ, Song KJ, Rhee JE, Jeong YK. Better prognostic value with combined optic nerve sheath diameter and grey-to-white matter ratio on initial brain computed tomography in post-cardiac arrest patients. Resuscitation 2016; 104: 40 – 45

Chakkarapani E, Dingley J, Liu X, Hogue N, Aquilina K, Porter H, Thoresen M. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. Ann Neurol 2010; 68:330–341

Chakkarapani E, Thoresen M, Liu X, Walloe L, Dingley J. Xenon offers stable haemodynamics independent of induced hypothermia after hypoxia-ischaemia in newborn pigs. Intensive Care Med 2012; 38: 316 – 323

Chalela JA, Wolf RL, Maldjian JA, Kasner SE. MRI identification of early white matter injury in anoxic-ischemic encephalopathy. Neurology 2001, 56: 481 – 485

Chan PS, MvNally B, Tang F, Kellermann A, for the CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 2014; 130: 1876 – 1882

Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA for the American Heart Association's Get with the Guidelines-Resuscitation Investigators. Association between therapeutic hypothermia and survival after in-hospital cardiac arrest. JAMA 2016; 316: 1375 – 1382

Chien GL, Wolff RA, Davis RF, Van Winkle DM. “Normothermic range” temperature affects myocardial infarct size. Cardiovasc Res 1994; 28: 1014 – 1017

Choi DW, Koh JY, Peters S. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. J Neurosci 1988; 8: 185 – 196

Chu DK, Kim LHY, Young PJ, Zamiri N, Almenawer SA, Jaesche R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in cautely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018; 391: 1693 – 1705

Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogre V, Daya M, Kron J, Zheng ZJ, Mensah G; Mc Anulty J. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004; 44: 1268 – 1275

Chua HR, Glassford N, Bellomo R. Acute kidney injury after cardiac arrest. Resuscitation 2012; 83:721 –727

Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJAM. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med 2012; 40: 2867 – 2875

Cobb LA, Fahrenbusch CE, Olsufka M, Copass MK. Changing incidence of Out-of-Hospital ventricular fibrillation, 1980 – 2000. JAMA 2002; 288: 3008 – 3013

Coburn M, Kunitz O, Baumert JH, Hecker K, Haaf S, Zühlsdorff A, Becker T, Rossaint R. Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. Br J Anaesth 2005, 94: 198 – 202

Coburn M, Baumert JH, Roertgen D, Thiel V, Fries M, Hein M, Kunitz O, Fimm B, Rossaint R. Emergence and ealy cognitive function in the elderly after xenon or desflurane anaesthesia: a double-blinded randomized controlled trial. Br J Anaesth 2007; 98: 756 – 762

Coburn M, Sanders RD, Maze M, Nguyên-Pascal ML, Rex S, Garrigues B, Carbonell JA, Garcia-Perez ML, Stevanovic A, Kienbaum P, Neukirchen M, Schaefer MS, Borghi B, van Oven H, Tognù A, Al Tmimi L, Langeron O, Capdevila X, Arnold GM, Schaller M, Rossaint R: HIPELD Study Investigators. The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial. Br J Anaesth 2018; 120: 127 – 137

Cokkinos P. Post-resuscitation care: current therapeutic concepts. Acute Cardiac Care 2009; 11: 131 – 137

Cremer J, Stoppe C, Fahlenkamp AV, Schälte G, Rex S, Rossaint R, Coburn M. Early cognitive function, recovery and well-being after sevoflurane and xenon anaesthesia in the elderly: a double-blinded randomized controlled trial. Med Gas Res 2011; 1: 9 – 19

Crepeau AZ, Fugate JE, Mandrekar J, White RD, Wijdicks EF, Rabinstein AA, Britton JW. Value analysis of continuous EEG in patients during therapeutic hypothermia after cardiac arrest. Resuscitation 2014; 85: 785 – 789

Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 2009; 80: 527 – 522

Cronberg T, Brizzi M, Liedholm LJ, Rosén I, Rubertsson S, Rylander C, Friberg H. Neurological prognostication after cardiac arrest – recommendations from the Swedish Resuscitation Council. Resuscitation 2013; 84: 867 – 872

Cronberg T. White matter is what matters after cardiac arrest. Lancet Neurol 2018; 17: 291 – 292

Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science 1951; 113: 580 – 582

Cullen SC, Eger EL, Cullen BF, Gregory P. Observations on the anesthetic effect of the combination of xenon and halothane. Anesthesiology 1969; 31: 305 – 309

Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U. Vascular pathophysiology in response to increased heart rate. J Am Coll Cardiol 2010; 56:1973–1983

Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol Heart Circ Physiol 2002; 282: H1584 – 1591

David HN, Leveille F, Chazalviel L, MacKenzie ET, Buisson A, Lemaire M, Abraini JH. Reduction of ischemic brain damage by nitrous oxide and xenon. J Cereb Blood Flow Metab 2003; 23: 1168 – 1173

David HN, Haelewyn B, Rouillon C, Lecoq M, Chazalviel L, Apiou G, Risso JJ, Lemaire M, Abraini JH. Neuroprotective effects of xenon: a therapeutic window of opportunity in rats subjected to transient cerebral ischemia. FASEB J 2008; 22: 1275 – 1286

David HN, Haelewyn B, Risso JJ, Colloc'h N, Abraini JH. Xenon is an inhibitor of tissue-plasminogen activator: adverse and beneficial effects in a rat model of thromboembolic stroke. J Cereb Blood Flow Metab 2010; 30: 718 – 728

Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, Brooks S, Christenson J, MacPhee R, Craig A, Rittenberger JC, Davis DP, May S, Wigginton J, Wang H, for the Resuscitation Outcome Consortium Investigators. Resuscitation 2015; 91: 108 – 115

De Deken J, Rex S, Monbaliu D, Pirenne J, Jochmans I. The efficacy of noble gases in the attenuation of ischemia reperfusion injury: a systematic review and meta-analysis. Crit Care Med 2016; 44: e886 – e896

De Groot M, Vernooij MW, Klein S, Ikram MA, Vos FM, Smith SM, Niessen WJ, Andersson JLR. Improving alignment in tract-based spatial statistics: evaluationand optimization of image registration. NeuroImage 2013; 76: 400 – 411

De Marchis GM, Katan M, Barro C, Fladt J, Traenka C, Seiffge DJ, Hert L, Gensicke H, Disanto G, Sutter R, Peters N, Sarikaya H, Goeggel-Simonetti B, El-Koussy M, Engelter S, Lyrer PA, Christ-Crain M, Arnold M, Kuhle J, Bonati LH. Serum neurofilament light chain in patients with acute cerebrovascular events. Eur J Neurol 2018; 25: 562 – 568

Debaty G, Labarere J, Frascone RJ, Wayne MA, Swor RA, Mahoney BD, Domeier RM, Olinger ML, O'Neill BJ, Yannopoulos D, Aufderheide TP, Lurie KG. Long-term prognostic value of gasping during out-of-hospital cardiac arrest. J Am Coll Cardiol 2017; 70: 1467 – 1476

De Guzman VC. Hypothermia: its effects upon hematologic clearance in experimentally induced staphylococcal bacteremia. Surgery 1963; 52: 643 – 647

Demirel F, Rasoul S, Elvan A, Ottervanger JP, Dambrink JHE, Gosselink ATM, Hoorntje JCA, Ramdat Misier AR, van't Hof AWJ. Impact of out-of-hospital cardiac arrest due to ventricular fibrillation in patients with ST-elkevation myocardial infarction admitted for primary percutaneous coronary intervention: Impact of ventricular fibrillation in STEMI patients. Eur Heart J Acute Cardiovasc Care 2015; 4: 16 – 23

Den Hartog AW, De Point AC, Robillard LBM, Binnikade JM, Schultz MJ, Horn J. Spontaneous hypothermia on intensive care unit admission is a predictor of unfavourable neurological outcome in patients after resusscitaion: an observational cohort study. Critical Care 2010; 14: R121 – R125

Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012; 125: 620 – 637

Derwall M, Timper A, Kottmann K, Rossaint R, Fries M. Neuroprotective effects of the inhalational anesthetics isoflurane and xenon after cardiac arrest in pigs. Crit Care Med 2008; 36(suppl): S492 – S495

De Sousa SLM, Dickinson R, Lieb WR, Franks NP. Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. Anesthesiology 2000; 92: 1055 – 1066

De Vries AC, Nelson RJ, Traystman RJ, Hurn PD. Cognitive and behavioral assessment in experimental stroke research: will it prove useful? Neurosci Biobehav Rev 2001; 25: 325 – 342

Deye N, Vincent F, Michel P, Ehrmann S, da Silva D, Piagnerelli M, Kimmoun A, Hamzaoui O, Lacherade JC, de Jonghe B, Brouard F, Audoin C, Monnet X, Laterre PF, for the SRLF trial

group. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. Ann Intensive Care 2016; 6: 4

Dickinson R, Peterson BK, Banks P, Similis C, Martin JCS, Valenzuela CA, Maze M, Franks NP. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modelling and electrophysiology. Anesthesiology 2007; 107: 756 - 767

Dickinson R, Franks NP. Bench-to-bedside review: molecular pharmacology and clinical use of inert gases in anesthesia and neuroprotection. Critical Care 2010; 14: 229 – 241

Dingley J, King R, Hughes L, Terblanche C, Mahon S, Hepp M, Youhana A, Watkins A. Exploration of xenon as a potential cardiostable sedative: a comparison with propofol after cardiac surgery. Anaesthesia 2001; 56:829 – 835

Dingley J, Tooley J, Porter H, Thoresen M. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. Stroke 2006; 37:501–506

Dinse A, Fohr KJ, Georgieff M, Beyer C, Bulling A, Weight HU. Xenon reduces glutamate-, AMPA-, and kainate-induced membrane currents in cortical neurons. Br J Anaesth 2005; 94: 479 – 485

Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004; 109: 23 – 25

Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, Lang E, Cocchi MN, Xanthos T, Callaway CW, Soar J. ILCOR ALS Task Force. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2016; 98: 97 – 104

Doyle S, Hansen DB, Vella J, Bond P, Harper G, Zammit C, Valentino M, fern R. Vesicular glutamate release from central axons contributes to myelin damage. Nat Commun 2018; 9: 1032

Dragancea I, Backman S, Westhall E, Rundgren M, Friberg H, Cronberg T. Outcome following postanoxic status epilepticus in patients with targeted temperature management after cardiac arrest. Epilepsy Behav 2015; 49: 173 – 177

Dragancea I, Wise M, Al-Subaie N, Cranshaw J, Friberg H, Glover G, Pellis T, Rylance R, Walden A, Nielsen N, Cronberg T, the TTM trial investigators. Protocol-driven neurological prognostication and withdrawal of life-sustaining therapy after cardiac arrest and targeted temperature management. Resuscitation 2017; 117: 50 – 57

Dripps RD, ed. The physiology of induced hypothermia: Proceedings of a symposium, 28 – 29 October 1955. Washington, D.C. National Academy of Sciences 1956

Duez CHV, Johnsen B, Ebbesen MQ, Kvaløy MB, Grejs AM, Jeppesen AN, Søreide E, Nielsen JF, Kirkegaard H. Post resuscitation prognostication by EEG in 24 vs 48 h of targeted temperature management. Resuscitation 2019; 135: 145 – 152

Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, Vivien B, Varenne O, Carli P, Jouven X, Empana JP, Cariou A. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. Circulation 2011; 123:877 – 886

Düring J, Dankiewicz J, Cronberg T, Hassager C, Hovdenes J, Kjrærgaard J, Kuiper M, Nielsen N, Pellsi T, Stammet P, Vulto J, Wanscher M, Wise M, Åneman A, Friberg H. Lactate, lactate clearance and outcome after cardiac arrest: a post-hoc analysis of the TTM trial. Acta Anaestheiol Scand 2018; 62: 1436 – 1442

Eastwood GM, Young PJ, Bellomo R. The impact of oxygen and carbon dioxide management on outcome after cardiac arrest. Curr Opin Crit Care 2014; 20: 266 – 272

ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2005; 112 (24 suppl): IV1 – IV203

Eger EI, Saidman LJ. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 1965; 26: 61 – 66

Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Haertle R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. Ann Emerg Med 1990; 19: 179 – 186

Elfwén L, Lagedal R, James S, Jonsson M, Jensen U, Ringh M, Claesson A, Oldgren J, Herlitz J, Rubertsson S, Nordberg P. Coronary angiography in out-of-hospital cardiac arrest without ST elevation on ECG – short – and long-term survival. Am Heart J 2018; 200: 90 – 95

Elmer J, Rittenberger JC, Faro J, Molyneaux BJ, Popescu A, Callaway CW, Baldwin M for the Pittsburgh Post-Cardiac Arrest Service. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. Ann Neurol 2016; 80: 175 – 184

Elmer J, Polderman KH. Emergency neurological life support: resuscitation following cardiac arrest. Neurocrit Care 2017; 27: S134 – S143

Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital 'sudden' cardiac arrest. Resuscitation 2002; 52: 235 – 245

Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab 2003; 23: 513 – 530

Ernst MD. Permutation methods: a basis for exact inference. Statist Sci 2004; 19: 676 – 685

Fahlenkamp AV, Stoppe C, Cremer J, Biener IA, Peters D, Leuchter R, Eisert A, Apfel CC, Rossaint R, Coburn M. Nausea and vomiting following balanced xenon anesthesia compared to sevoflurane: a post-hoc explorative analysis of a randomized controlled trial. PLoS ONE 2016; 11: e0153807

Farquharson S, Tournier JD, Calamante F, Fabinyi G, Schneider-Kolsky M, Jackson GD, Connelly A. White matter fiber tractography: why we need to move beyond DTI. J Neurosurg 2013; 118: 1367 – 1377

Fay T. Observations on prolonged human refrigeration. NY State J Med 1940; 40: 1351 – 1354

Fay T. Early experiences with local and generalized refrigeration of the human brain. J Neurosurg 1959; 16: 239 – 260

Fern R, Matute C. Glutamate receptors and white matter stroke. Neurosci Lett 2019; 694. 86 – 92

Field JM, Hazinski MF, Sayre MR, Chameides L, Schexnayder SM, Hemphill R, Samson RA, Kattwinkel J, Berg RA, Bhanji F, Cave DM, Jauch EC, Kudenchuk PJ, Neumar RW, Peberdy MA, Perlman JM, Sinz E, Travers AH, Berg MD, Billi JE, Eigel B, Hickey RW, Kleinman ME, Link MS, Morrison LJ, O'Connor RE, Shuster M, Callaway CW, Cucchiara B, Ferguson JD, Rea TD, Vanden Hoek TL. Part 1: Exexutive summary. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122(suppl 3): S640 – S656

Fisher CM. Lacunes: small, deep cerebral infarcts. Neurology 2011; 77: 2104

Fishman GI, Chugh SS, DiMarco JP, Albert CM, Anderson ME, Bonow RO, Buxton AE, Chen PS, Estes M, Jouven X, Kwong R, Lathrop DA, Mascette AM, Nerbonne JM, O'Rourke B, Page RL, Roden DM, Rosenbaum DS, Sotoodehnia N, Trayanova NA, Zheng ZJ. Sudden cardiac arrest prediction and prevention. Report from a national heart, lung, and blood institute and heart rhythm society workshop. Circulation 2010; 122: 2335 – 2348

Francis RCE, Reyle-Hahn MS, Höhne C, Klein A, Theruvath I, Donaubauer B, Busch T, Boemke W. The haemodynamic and catecholamine response to xenon/remifentanil anaesthesia in beagle dogs. Lab Anim 2008; 42: 338 – 349

Fragata I, Alves M, Papoila AL, Nunes AP, Ferreira P, Canto-Moreira N, Canhao P. Early prediction of delayed ischemia and functional outcome in acute subarachnoid hemorrage. Stroke 2017; 48: 2091 – 2097

Fragata I, Alves M, Papoila AL, Ferreira P, Nunes AP, Moreira NC, Canhao P. Prediction of clinical outcome in subacute subaracnoid hemorrage using diffusion tensor imaging. J Neurosurgery 2019; 130: 337 – 346

Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. Nature 1994; 367: 607 – 614

Franks JJ, Horn JL, Janicki PK, Singh G. Halothane, isoflurane, xenon and nitrous oxide inhibit calcium ATPase pump activity in rat brain synaptic plasma membranes. Anesthesiology 1995; 82: 108 - 117

Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia? Nature 1998; 396:324

Friberg H, Cronberg T. Prognostication after cardiac arrest. Best Pract Res Clin Anaesthesiol 2013; 27: 359 – 372

Fries M, Nolte KW, Coburn M, Rex S, Timper A, Kottmann K, Siepmann K, Häusler M, Weis J, Rossaint R. Xenon reduces neurohistopathological damage and improves the early neurological deficit after cardiac arrest in pigs. Crit Care Med 2008; 36: 2420 – 2426

Fries M, Brücken A, Çizen A, Westerkamp M, Löwer C, Deike-Glindemann J, Schnorrenberger NK, Rex S, Coburn M, Nolte KW, Weis J, Rossaint R, Derwall M. Combining xenon and mild therapeutic hypothermia preserves neurological function after prolonged cardiac arrest in pigs. Crit Care Med 2012; 40: 1297–1303

Fridén V, Starnberg K, Muslimovic A, Ricksten SE, Bjurman C, Forsgard N, Wickman A, Hammarsten O. Clearance of cardiac troponin T with and without kidney function. Clin Biochem 2017; 50: 468 – 474

Fugate JE, Wijdicks EF, Mandrekar J, Claassen DO, Manno EM, White RD, Bell MR, Rabinstein AA. Predictors of Neurologic Outcome in Hypothermia after Cardiac Arrest. Ann Neurol 2010; 68: 907 – 914

Fugate JE, Rabinstein AA, Wijdicks EFM. Neurologic Assessment of comatose survivors of cardiac arrest: the details matter. Crit Care Med 2015; 43: e120 - e121

Fujikawa DG. Prolonged seizures and cellular injury: understanding the connection. Epilepsy Behav 2005; 7(suppl 3): S3 – S11

Gaieski DF, Band RA, Abella BS. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation 2009; 80: 418 – 424

Gentsch A, Storm C, Leithner C, Schroeder T, Ploner CJ, Hamm B, Wiener E, Scheel M. Outcome prediction in patients after cardiac arrest: a simplified method for determination of gray-white matter ratio in cranial computed tomography. Clin Neuroradiol 2015; 25: 49 – 54

Gerdes JS, Walther EU, Jaganjac S, Makrigeorgi-Butera M, Meuth SG, Deppe M. Early detection of widespread progressive brain injury after cardiac arrest: a single case DTI and post-mortem histology study. PLoS One 2014; 14: e92103

Giannitsis E, Steen H, Kurz K, Ivandic B, Simon AC, Futterer S, Schild C, Isfort P, Jaffe AS, Katus HA. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol 2008; 51: 307 – 314

Gilje P, Koul S, Thomsen JH, Devaux Y, Friberg H, Kuiper M, Horn J, Nielsen N, Pellis T, Stammet R, Wise MP, Kjaergaard J, Hassager C, Erlingee D. High-sensitivity troponin-T as a prognostic marker after out-of-hospital cardiac arrest – A targeted temperature management (TTM) trial substudy. Resuscitation 2016; 207: 156 – 161

Gill R, Soriano M, Blomgren K, Hagberg H, Wybrecht R, Miss MT, Hoefer S, Adam G, Niederhauser O, Kemp JA, Loetscher H. Role of caspase-3 activation in cerebral ischemia-induced neurodegeneration in adult and neonatal brain. J Cereb Blood Flow Metab 2002; 22: 420 - 430

Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012; 367: 1912 – 1920

Girotra S, Chan PS, Bradley SM. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. Heart 2015; 0: 1 – 7

Gladstone DJ, Black SE, Hakim AM. Toward wisdom from failure: lessons from neuroprotective stroke trials and new therapeutic directions. Stroke 2002; 33: 2123 – 2136

Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005; 365: 663 – 670

Goetzenich A, Hatam N, Preuss S, Moza A, Bleilevens C, Roehl AB, Autschbach R, Bernhagen J, Stoppe C. The role of hypoxia-inducible factor-1α and vascular endothelial growth factor in late-phase preconditioning with xenon, isoflurane and levosimendan in rat cardiomyocytes. Interact Cardiovasc Thorac Surg 2014; 18: 321 – 328

Gold B, Puertas L, Davis SP, Metzger A, Yannopoulos D, Oakes DA, Lick CJ, Gillquist DL, Osaki Holm SY, Olsen JD, Jain S, Lurie KG. Awakening after cardiac arrest and post resuscitation hypothermia: are we pulling the plug too early? Resuscitation 2014; 85: 211 – 214

Goldberg MP, Ransom BR. New light on white matter. Stroke 2003; 34: 330 – 332

Gonzalez-Ibarra FP, Varon J, Lopez-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. Frontier Neurology 2011; 2: 4

Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S. The blood-gas partition coefficient of xenon may be lower than generally accepted. Br J Anaesth 1998; 80: 255 – 256

Goto T, Nakata Y, Morita S. The minimum alveolar concentration of xenon in the elderly is sex-dependent. Anesthesiology 2002; 97: 1129 – 1132

Goto T, Hanne P, Ishiguro Y, Ichinose F, Niimi Y, Morita S. Cardiovascular effects of xenon and nitrous oxide in patients during fentanyl-midazolam anaesthesia. Anesthesia 2004; 59: 1178 - 1183

Greer D, Scripko P, Bartscher J, Sims J, Camargo E, Singhal A, Parides M, Furie K. Clinical MRI interpretation for outcome prediction an cardiac arrest. Neurocrit Care 2012; 17: 240 – 244

Greer DM, Scripko PD, Wu O, Edlow BL, Bartscher J, Sims JR, Camargo EE, Singhal AB, Furie KL. Hippocampal magnetic resonance imaging abnormalities in cardiac arrest are associated with poor outcome. J Stroke Cerebrovasc Dis 2013; 22: 899 - 905

Grosse Hartlage MA, Berendes E, Van Aken H, Fobker M, Theisen M, Weber TP. Xenon improves recovery from myocardial stunning in chronically instrumented dogs. Anesth Analg 2004; 99: 655 – 64

Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Mol Pharmacol 2004; 65: 443 – 452

Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IBM, Ortiz FR, Maurer H, Baubin M, Mols P, Hadzibegovic I, Ionnides M, Skulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdottir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Strömsöe A, Burkart R, Perkins GD, Bossaert LL, on behalf of EuReCa ONE Collaborators. EuReCa ONE - 27 nations, one Europe, one registry. A prospective one month analysis of out-of-hospital cariac arrest outcomes in 27 countries in Europe. Resuscitation 2016; 105: 188 – 195

Gutierrez LG, Rovira A, Portela LA, Leite Cda C, Lucato LT. CT and MR in non-neonatal hypoxic-ischemic encephalopathy: radiological findings with pathophysiological correlations. Neuroradiology 2010; 52: 949 – 976

Haimoto H, Hosoda S, Kato K. Differential distribution of immunoreactive S100-alpha and S100-beta proteins in normal nonnervous human tissues. Lab Invest 1987; 57: 489 – 498

Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mäyry S, de Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O´Neill M, Hocini M, Lin KT, Knecht S, Veehuyzen GD, Bordachar P, Chaucin M,

Jais P, Coureau P, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008; 358: 2016 – 2023

Hanne P, Marx T, Musati S, Santo M, Suwa K, Morita S. Xenon: Uptake and Costs. Int Anesthesiol Clin 2001; 39: 43 – 61

Hanss R, Bein B, Turowski P, Cavus E, Bauer M, Andretzke M, Steinfath M, Scholz J, Tonner PH. The influence of xenon on regulation of the autonomic nervous system in patients at high risk of perioperative cardiac complications. Br J Anaesth 2006; 96: 427 – 436

Harris JJ, Attwell D. The energetics of CNS white matter. J Neurosci 2012; 32: 356 – 371

Hasaneder R, Kratzer S, Kochs E, Mattusch C, Eder M, Rammes G. Xenon attenuates excitatory synaptic transmission in the rodent prefrontal cortex and spinal cord dorsal horn. Anesthesiology 2009; 111: 1297 – 1307

Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, Ringh M, Jonsson M, Axelssson C, Lindqvist J, Karlsson T, Svenson L. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. N Engl J Med 2015; 372: 2307 – 2315

Hausenloy DJ, Garcia-Dorado D, Bøtker HE, Davidson SM, Downey J, Engel FB, Jennings R, Lecour S, Leor J, Madonna R, Ovize M, Perrino C, Prunier F, Schulz R, Sluijter JPG, Van Laake LW, Vinten-Johansen J, Yellon DM, Ytrehus K, Heusch G, Ferdinandy P. Novel targets and future strategies for acute cardioprotection: position paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. Cardiovasc Res 2017; 113: 564 – 585

Hayman EG, Patel AP, Kimberly WT, Sheth KN, Simard JM. Cerebral edema after cardiopulmonary resuscitation: a therapeutic target following cardiac arrest? Neurocrit Care 2018; 28:276 – 287

Hecker K, Baumert JH, Horn N, Rossaint R. Xenon, a modern anaesthesia gas. Minerva Anestesiol 2004; 70: 255 – 260

Hein M (Hein 2008 a), Baumert JH, Roehl AB, Pasch L, Schnoor J, Coburn M, Rossaint R. Xenon alters right ventricular function. Acta Anesth Scand 2008; 52: 1056 – 1063

Hein M (Hein 2008 b), Roehl AB, Baumert JH, Bantes B, Bleilevens C, Bernstein N, Steendijk P, Rossaint R. Establishment of a porcine right ventricular infarction model for cardioprotective actions of xenon and isoflurane. Acta Anesth Scand 2008; 52: 1194 – 1203

Hein M, Roehl AB, Baumert JH, Bleilevens C, Fischer S, Steendijk P, Rossaint R. Xenon and isoflurane improved biventricular function during right ventricular ischemia and reperfusion. Acta Anesth Scand 2010; 54: 470 - 478

Herlitz J, Bahr J, Fischer M, Kuisma M, Lexow K, Thorgeirsson G. Resuscitation in Europe: a tale of five European regions. Resuscitation 1999; 41: 121 -131

Herlitz J, Andersson E, Bång A, Engdahl J, Holmberg M, Lindqvist J, Karlson BW, Waagstein L. Experiences from treatment of out-of-hospital cardiac arrest during 17 years in Göteborg. Eur Heart J 2000; 21: 1251 – 1258

Hirlekar G, Jonsson M, Karlsson T, Hollenberg J, Albertsson P, Herlitz J. Comorbidity and survival in out-of-hospital cardiac arrest. Resuscitation 2018; 133: 118 – 123

Hirsch KG, Mlynash M, Eyngorn I, Pirsaheli R, Okada A, Komshian S, Chen C, Mayer SA, Mescia JF, Bernstein RA, Wu O, Greer DM, Wijman CA, Albers GW. Multi-center study of diffusion-weighted imaging in coma after cardiac arrest. Neurocrit care 2016; 24: 82 - 89

Hjort N, Christensen S, Sølling C, Ashkanian M, Wu O, Røhl L, Gyldensted C, Andersen G, Østergaard L. Ischemic injury detected by diffusion imaging 11 minutes after stroke. Ann Neurol 2005; 58: 462 - 465

Hobbs C, Thoresen M, Tucker A, Aquilina K, Chakkarapani E, Dingley J. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. Stroke 2008; 39:1307–1313

Hoesch RE, Koenig MA, Geocadin RG. Coma after global brain injury: pathophysiology and emerging therapies. Crit Care Clin 2008; 24: 25 – 44

Hofland J, Ouattara A, Fellahi JL, Gruenewald M, Hazebroucq J, Ecoffey C, Joseph P, Heringlake M, Steib A, Coburn M, Amour J, Rozec B, de Liefde I, Meybohm P, Preckel B, Hanouz JL,

Tritapepe L, Tonner P, Benhaoua H, Roesner JP, Bein B, for the Xenon-CABG study group. Effect of xenon anesthesia compared to sevoflurane and total intravenous anesthesia for coronary artery bypass graft surgery on postoperative cardiac troponin release: an international, multicenter, phase 3, single-blinded, randomized noninferiority trial. Anesthesiology 2017; 127: 918 – 933

Hofmeijer J, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, van Putten MJAM. Unstandardized treatment of electroencephalographic status epilepticus does not improve outcome of comatose patients after cardiac arrest. Front Neurol 2014; 5: 39 – 48

Hollenbeck RD, McPherson JA, Mooney MR, Unger BT, Patel NC, McMullan PW. Hsu CH, Seder DB, Kern KB. Early cardiac catheterization is associated with improved survival in comatose survivors of cardiac arrest without STEMI. Resuscitation 2014; 85: 88 – 95

Holmberg M, Holmberg S, Herlitz J. Incidence, duration and survival from ventricular fibrillation in out-of-hospital cardiac arrest in Sweden. Resuscitation 2000; 44: 7 – 17

Holzer M, Cerchiari E, Martens P, et al for the Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002; 346: 549 – 556

Holzer M (Holzer 2005a). Therapeutic hypothermia after cardiac arrest. Curr Opin Anesthesiol 2005; 18: 163 – 168

Holzer M (Holzer 2005b), Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Müllner M on behalf of the Collaborative Group of Induced Hypothermia for Neuroprotection After Cardiac Arrest. Crit Care Med 2005; 33: 414 – 418

Homi HM, Yokoo N, Ma D, Warner DS, Franks NP, Maze M, Grocott HP. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology 2003; 99:876 – 881

Hookana E, Junttila MJ, Puurunen VP, Tikkanen JT, Kaikkonen KS, Kortelainen ML, Myerburg RJ, Huikuri HV. Causes of nonischemic sudden cardiac death in the current era. Heart Rhythm 2011; 8: 1570 – 1575

Horn J, Cronberg T, Taccone F. Prognostication after cardiac arrest. Curr Opin Crit Care 2014; 20: 280 – 286

Hovland A, Waage Nielsen E, Klüver J, Salvesen R. EEG should be performed during induced hypothermia. Resuscitation 2006; 68: 143 – 146

Howard RS, Holmes PA, Siddiqui A, Treacher D, Tsiropoulos I, Koutroumanidis M. Hypoxic-ischaemic brain injury: imaging and neurophysiology abnormalities related to outcome. Q J Med 2012; 105: 551 – 561

Hoyte L, Kaur J, Buchan AM. Lost in translation: taking neuroprotection from animal models to clinical trials. Exp Neurol 2004; 188: 200 – 204

Huang BY, Castillo M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. RadioGraphics 2008; 28: 417 – 439

Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001; 345: 1473 – 1482

Hulleman M, Zijlstar JA, Beesems SG, Blom MT, van Hoeijen DA, Waalewijn RA, Tan HL, Tijssen JGP, Koster RW. Causes of the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation 2015; 96: 23 – 29

Hüneke R, Jüngling E, Skasa M, Rossaint R, Lückhoff A. Effects of anesthetic gases xenon, halothane, and isoflurane on calcium and potassium currents in human atrial cardiomyocytes. Anesthesiology 2001; 95: 999 – 1006

Höcker J, Stapelfeldt C, Leiendecker J, Meybohm P, Hanss R, Scholz J, Bein B. Postoperative neurocognitive dysfunction in elderly patients after xenon versus propofol anesthesia for major noncardiac surgery. Anesthesiology 2009; 110: 1068 – 1076

Ingvar M. Cerebral blood flow and metabolic rate during seizures: relationship to epileptic brain damage. Ann N Y Acad Sci 1986; 462: 194 – 206

Ishiguro Y, Goto T, Nakata Y, terui K, Niimi Y, Morita S. Effect of xenon on autonomic cardiovascular control – comparison with isoflurane and nitrous oxide. J Clin Anesth 2000; 12: 196 – 201

Jabre P, Penaloza A, Pinero D, Duchateau FX, Borron SW, Javaudin F, Richard O, de Longueville D, Bouilleau G, Devaud ML, Heidet M, Lejeune C, Fauroux S, Greingor JL, Manara A, Hubert JC, Guihard B, Vermylen O, Lievens P, Auffret Y, Maisondieu C, Huet S, Claessens B, Lapostolle F, Javaud N, Reuter PG, Baker E, Vicaut E, Adnet F. Effect of bag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest. A randomized clinical trial. JAMA 2018; 319: 779 – 787

Jacobs LH, van der Kerkhof J, Mingels AM, Kleijnen VW, van der Sande FM, Wodzig WK, Kooman JP, van Dieijen-Visser MP. Haemodialysis patients longitudinally assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and cardiac troponin I assays. Ann Clin Biochem 2009; 46: 283 – 290

Jacobshagen C, Pelster T, Pax A, Horn W, Schmidt-Schweda S, Unsöd BW, Seidler T, Wagner S, Hasenfuss G, Maier LS. Effects of mild hypothermia in cardiac arrest survivors and isolated failing human myocardium. Clin Res Cardiol 2010; 99: 267 – 276

Jaeger D, Dumas F, Escutnaire J, Sadoune S, Lauvray A, Elkhoury C, Bassand A, Girerd N, Gueugniaud PY, Tazarorte K, Hubert H, Cariou A, Chouihed T, the RéAC Group. Benefit of immediate coronary angiography after out-of-hospital cardiac arrest in France: A nationwide propensity score analysis from the RéAC Registry. Resuscitation 2018; 126: 90 97

Jakkula P (Jakkula 2018a), Pettilä V, Skrifvars M, Hästbacka J, Loisa P, Tiainen M, Wilkman E, Toppila J, Koskue T, Bendel S, Birkelund T, Laru-Sompa R, Valkonen M, Reinikainen M, and COMACARE study group. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomized pilot trial. Int Care Med 2018; 44: 2091 – 2101

Jakkula P (Jakkula 2018b), Reinikainen M, Hästbacka J, Loisa P, Tiainen M, Pettilä V, Toppila J, Lähde M, Bäcklund M, Okkonen M, Bendel S, Birkelund T, Pulkkinen A, Heinonen J, Tikka T, Skrifvars MB, and COMACARE study group. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomized pilot trial. Int Care Med 2018; 44: 2112 – 2121

Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. The influence of propofol versus sevoflurane anesthesia on outcome in 10535 cardiac surgical procedures. J Cardiothorac Vasc Anesth 2007; 21: 664 – 671

Javadov SA, Lim KHH, Kerr PM, Suleiman MS, Angelini GD, Halestap AP. Protection of hearts from reperfusion injury by propofol is associated with inhibition of the mitochondrial permeability transition. Cardiovasc Res 2000; 45: 360 – 369

Jawad N, Rizvi M, Gu J, Adeyi O, Tao G, Maze M, Ma D. Neuroprotection (and lack of neuroprotection) afforded by a series of noble gases in an in vitro model of neuronal injury. Neurosci Lett 2009; 460: 232 – 236

Javat D, Heal C, Buchholz S, Zhang Z. Early versus delayed invasive strategies in high-risk non-ST elevation acute coronary syndrome patients – a systematic literature review and meta-analysis of randomized controlled trials. Heart Lung Circ 2017; 26: 1142 – 1159

Jentzer JC, Scutella M, Pike F, Fitzgibbon J, Krehel NM, Kowalski L, Callaway CW, Rittenberger JC, Reynolds JC, Barsness GW, Dezfulian C. Early coronary angiography and percutaneous coronary intervention are associated with improved outcomes after out of hospital cardiac arrest. Resuscitation 2018; 123: 15 – 21

Jeon CH, Park JS, Lee JH, Kim H, Kim SC, Park KH, Yi KS, Kim SM, Youn CS, Kim YM, Lee BK. Comparison of brain computed tomography and diffusion-weighted magnetic resonance imaging to predict early neurologic outcome before target temperature management comatose cardiac arrest survivors. Resuscitation 2017; 118: 21 – 26

Jobs A, Mehta SR, Montalescot G, Vicaut E, van't Hof AW, Badings EA, Neuman FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A. Stankovic G, Milasinovic D, Vonthein R,

Desch S, Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. Lancet 2017; 390: 737 – 746

Johnson RA, Palacios I. Dilated cardiomyopathies of the adult. N Engl J Med 1982; 307: 1051 – 1058

Johnston MV. Excitotoxicity in neonatal hypoxia. Ment Retard Dev Disabil Res Rev 2001; 7: 229 – 234

Jørgensen EO, Holm S. The natural course of neurological recovery following cardiopulmonary resuscitation. Resuscitation 1998; 36: 111 – 122

Jørgensen EO, Holm S. Prediction of neurological outcome after cardiopulmonary resuscitation. Resuscitation 1999; 41: 145 – 152

Järnum H, Knutsson L, Rundgren M, Siemund R, Englund E, Friberg H, Larsson EM. Diffusion and perfusion MRI of the brain in comatose patients treated with mild hypothermia after cardiac arrest: A prospective observational study. Resuscitation 2009; 80: 425 – 430

Káradóttir R, Cavelier P, Bergersen LH, Attwell D. NMDA receptors are expressed in oligodendrocytes and activated in ischemia. Nature 2005; 438: 1162 – 1166

Karam N, Bataille S, Marijon E, Tafflet M, Benamer H, Caussin C, Garot P, Juliard JM, Pires V, Boche T, Dupas F, le Bail G, Lamhaut L, Simon B, Allonneau A, Mapouata M, Loyeau A, Empana JP, Lapostolle F, Spaulding C, Jouven X, Lambert Y, for the e-MUST study Investigators. Incidence, Mortality, and outcome-predictors of sudden cardiac arrest complicating myocardial infarction prior to hospital admission. Circ Cardiovasc Interv 2019; 12: e007081 – e007089

Karapetkova M, Koenig MA, Jia X. Early prognostication markers in cardiac arrest patients treated with hypothermia. Eur J Neurol 2016; 23: 476 – 488

Katritsis DG, Gersh BJ, Camm AJ. A Clinical Perspective on Sudden Cardiac Death. Arrhytmia & Electrophysiol Rev 2016; 5: 177 – 182

Keijzer HM, Hoedemaekers CWE, Meijer FJA, Tonino BAR, Klijn CJM. Brain imaging in comatose survivors of cardiac arrest: pathophysiological correlates and prognostic properties. Resuscitation 2018; 133: 124 – 136

Kelen D, Robertson NJ. Experimental treatments for hypoxic ischaemic encephalopathy. Early Hum Dev 2010; 86: 369 - 377

Kelly FE, Nolan JP. The effects of mild induced hypothermia on the myocardium: a systematic review. Anaesthesia 2010; 65: 505 – 515

Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol 1996; 28: 232 – 240

Khajuria A, Tay C, Shi J, Zhao H, Ma D. Anesthetics attenuate ischemia-reperfusion induced renal injury: effects and mechanisms. Acta Anaesthesiol Taiwanica 2014; 52: 176 – 184

Kilgannon H, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S, for the Emergency Medicine Shock Research Network (EMShockNet) Investigators. JAMA 2010; 303: 2165 – 2171

Kim SH, Choi SP, Park KN, Youn CS, Oh SH, Choi SM. Early brain computed tomography findings are associated with outcome in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Scand J trauma Resusc Emerg Med 2013; 21: 57 – 64

Kim YJ, Ahn S, Sohn CH, Seo DW, Lee JH. Long-term neurological outcomes in patients after out-of-hospital cardiac arrest. Resuscitation 2016; 101: 1 – 5

Kirkegaard H, Søreide E, de Haas I, Pettilä V, Taccone FS, Arus U, Storm C, Hassager C, Nielsen JF, Sørensen CA, Ilkjær S, Jeppesen AN, Grejs AM, Duez CHV, Hjort J, Larsen AI, Toome V, Tiainen M, Hästbacka J, Laitio T, Skrifvars MB. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest. A randomized clinical trial. JAMA 2017; 318: 341 – 350

Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneuous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation 2007; 74: 227 – 234

Ko SH, Yu CW, Lee SK, Choe H, Chung MJ, Kwak YG, Chae SW, Song HS. Propofol attenuates ischemia-reperfusion injury in the isolated rat heart. Anesth Analg 1997; 85: 719 – 724

Ko SB, Ortega-Gutierrez S, Choi HA, Claassen J, Presciutti M, Schmidt M, Badjatia N, Lee K, Mayer SA. Status-epilepticus- induced hyperemia and brain tissue hypoxia after cardiac arrest. Arch Neurol 2011; 68: 1323 – 1326

Kokita N, Hara A, Abiko Y, Arakawa J, Hashizume H, Namiki A. Propofol improves functional and metabolic recovery in ischemic reperfused isolated rat hearts. Anesth Analg 1998; 86: 252 – 58

Koster RW. Continuous or interrupted chest compressions for cardiac arrest. N Engl J Med 2015; 373: 2278 – 2279

Kouwenhoven W, Jude J, Knickerbocker C. Closed-chest cardiac massage. JAMA 1960; 173: 1064 – 1067

Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Hansen CM, Thosteinsson K, Rajan S, Lippert F, Folke F, Gislason G, Køber L, Fonager K, Jensen SE, Gerds TA, Torp-Pedresen C, Rasmussen BS. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. N Engl J Med 2017; 376: 1737 – 1747

Krishnamoorty V, Vavila MS, Fettiplace MR, Weinberg G. Epinephrine for cardiac arrest. Are we doing more harm than good? Anesthesiology 2013; 120: 792 – 794

Krug A, Du Mesnil de Rochemont R, Korb G. Blood supply of the myocardium after temporary coronary occlusion. Circ Res 1966; 19: 57 – 62

Kruse JM, Enghard P, Schröder T, Hasper D, Kühnle Y, Storm C. Weak diagnostic performance of troponin, creatinine kinase and creatine kinase-MB to diagnose or exclude myocardial infarction after successful resuscitation. Int J Cardiol 2014; 173: 216 – 221

Kuchena A, Merkel MJ, Hutchens MP. Postcardiac arrest temperature management: infectious risks. Curr Opin Crit Care 2014; 20: 507 – 515

Kudenchuk PJ, Sandroni C, Drinhaus HR, Böttiger BW, Cariou A, Sunde K, Dworschak M, Taccone FS, Deye N, Friberg H, Lauryes S, Ledoux D, Oddo M, Legriel S, Hantson P, Diehl JL, Laterre PF. Breakthrough in cardiac arrest: reports from the 4th Paris international conference. Ann Intensive care 2015; 5: 22 – 46

Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison B, Leroux C, Vaillancourt C, Wittwer L, Callaway CW, Christenson J, Egan D, Ornato JP, Weisfeldt ML, Stiell IG, Idris AH, Aufderheide TP, Dunford JV, Colella MR, Vilke GM, Brienza AM, Desvigne-Nicjens P, Gray PC, Gray R, Seals N, Straight R, Dorian P for the Resuscitation Outcomes Consortium Investigators. Amiodarone, Lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016; 374: 1711 – 1722

Kuisma M, Repo J, Alaspää A. The incidence of out-of-hospital ventricular fibrillation in Helsinki, Finland from 1994 to 1999. Lancet 2001; 358: 473 – 474

Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, Van Daal GJ, Kusuma A, Erdmann W. Safety and efficacy of xenon in routine use as an inhalational anaesthetic. Lancet 1990; 335: 1413 – 1415

Lai CS, Hostler D, D'Cruz BJ, Callaway CW. Prevalence of troponin-T elevation during out-of-hospital cardiac arrest. Am J Cardiol 2004; 93:754 – 756

Laitio RM, Kaskinoro K, Särkelä MOK, Kaisti KK, Salmi E, Maksimow A, Långsjö JW, Aantaa R, Kangas K, Jääskeläinen S, Scheinin H. Bispectral index, entropy, and quantitative electroencephalogram during single-agent xenon anesthesia. Anesthesiology 2008; 108: 63 – 70

Langhelle A, Nolan J, Herlitz J, Castren M, Wenzel V, Soreide E, Engdahl J, Steen PA; 2003 Utstein Consensus Symposium. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. Resuscitation 2005; 66:271 – 283

Lampe JW, Becker LB. State of the art in therapeutic hypothermia. Annu Rev Med 2011; 62: 79 – 93

Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavivus S,

Yusuf S for CORONARY investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012; 366: 1489 - 1497

Langkjær S, Hassager C, Kjærgaard J, Salam I, Thomsen JH, Lippert FK, Wanscher M, Køber L, Nielsen N, Søholm H. Prognostic value of reduced discrimination and oedema on cerebral computed tomography in daily clinical cohort of out-of-hospital cardiac arrest patients. Resuscitation 2015; 92: 141 - 147

Larrey DJ. Mémoires de chirurgie militaire, et compagnes. Paris: J. Smith; 1812 – 1817, Vol I – IV

Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, Dhainaut JF. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002; 40: 2110 – 2116

Lavaur J (Lavaur 2016a), Lemaire M, Pype J, Le Nogue D, Hirsch EC, Michel PP. Xenon-mediated neuroprotection in response to sustained, low-level excitotoxic stress. Cell Death Discov 2016; 2: 16018

Lavaur J (Lavaur 2016b), Lemaire M, Pype J, Le Nogue D, Hirsch EC, Michel PP. Neuroprotective and neurorestorative potential of xenon. Cell Death Dis 2016; 7: e2182 – e2183

Law LSC, Lo EAG, Gan TJ. Xenon anesthesia: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2016; 122: 678 – 697

Laver S, Farrow C, Turner D, Nolan J: Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004; 30:2126 - 2128

Lawrence JH, Loomis WF, Tobias CA, Turpin FH. Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. J Physiol 1946; 105: 197 – 204

Lebidz P, Meiners J, Samol A, Wasmer K, Reinecke H, Waltenverger J, Eckardt L. Electrocardiographical changes during therapeutic hypothermia. Resuscitation 2012; 83: 602 – 606

Lee HL, Lee JK. Lance-Adams syndrome. Ann Rehabil Med 2011; 35: 939 – 943

Lee BK, Jeung KW, Song KH, Jung YH, Choi WJ, Kim SH, Youn CS, Cho IS, Lee DG, for the Korean Hypothermia Network Investigators. Resuscitation 2015; 96: 46 – 52

Legriel S, Bruneel F, Sediri H, Hilly J, Abbosh N, Lagarrigue MH, Troche G, Guezennac P, Pico F, Bedos JP. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care 2009; 11: 338 – 344

Legriel S, Hilly-Ginoux J, Resche-Rigon M, Merceron S, Pinoteau J, Henry-Lagarrigue M, Bruneel F, Nguyen A, Guezennec P, Troché G, Richard O, Pico F, Bédos JP. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac arrest survivors in the therapeutic hypothermia era. Resuscitation 2013; 84: 343 – 350

Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van den Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van der Bogaard B, Heestermans TACM, de Ruijter W, Delnoij TSR, Crijns HJGM, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van der Ven PM, Oudemans-van Straaten HM, van Royen N. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med 2019; 380: 1397 – 1407

Lerner A, Mogensen MA, Kim PE, Shiroishi MS, Hwang DH, Law M. Clinical applications of diffusion tensor imaging. World Neurosurg 2014; 82: 96 – 109

Li Q, Lian C, Zhou R, Li T, Xiang X, Liu B. Pretreatment with xenon protected immature rabbit heart from ischemia/reperfusion injury by opening the mitoK_{ATP} channel. Heart Lung Circ 2013; 22: 276 – 283

Little NE, Feldman EL. Therapeutic hypothermia after cardiac arrest without return of consciousness. Skating on thin ice. JAMA neurology 2014; 71: 823 – 824

Liu Y, D'Arceuil HE, Westmoreland S, He J, Duggan M, Gonzalez RG, Pryor J, de Crespigny AJ. Serial diffusion tensor MRI after transient and permanent cerebral ischemia in nonhuman prmates. Stroke 2007; 38: 138 - 145

Lockwood GG, Franks NP, Downie NA, Taylor KM, Maze M: Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: phase I study. Anesthesiology 2006; 104:458–465

Lopshire JC, Zipes DP. Sudden cardiac death. Better understanding of risks, mechanisms, and treatment. Circulation 2006; 114: 1134 – 1136

Lucas JM, Cocchi MN, Salciccioli J, Stanbridge JA, Geocadin RG, Herman ST, Donnino MW. Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus. Resuscitation 2012; 83: 265 – 269

Ludbrook J, Dudley H. Why permutation tests are superior to t and F tests in biomedical research. Am Stat 1998; 52: 127 – 132

Luttropp HH, Romner B, Perhag L, Eskilsson J, Fredriksen S, Werner O. Left ventricular performance and cerebral haemodynamics during xenon anaesthesia. A transoesophgeal echocardiography and transcranial Doppler sonography study. Anaesthesia 1993; 48: 1045 – 1049

Luttropp HH, Thomasson R, Dahm S, Persson J, Werner O. Clinical experience with minimal flow xenon anesthesia. Acta Anaesthesiol Scand 1994; 38: 121 – 125

Luyt CE, Galanaud D, Perlbang V, Vanhaudenluyse A, Stevenes RD, Gupta R, Besancerot H, Krainik A, Audibert G, Combes A, Chastre J, Benali H, Laureus S, Puybasset L, for the neuro Imaging for coma emergence and recovery consortium. Diffusion tensor imaging to predict long-term outcome after cardiac arrest: a bicentric pilot study. Anesthesiology 2012; 117: 1311 – 1321

Lynch III C, Baum J, Tenbrinck R. Xenon anesthesia. Anesthesiology 2000; 92: 865 – 868

Ma D, Wilhelm S, Maze M, Franks NP. Neuroprotective and neurotoxic properties of the inert gas xenon. Br J Anaesth 2002; 89: 739 - 746

Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP: Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. Anesthesiology 2003; 98: 690–698

Ma D, Hossain M, Chow A, Arshad M, Battson RM, Sanders RD, Mehmet H, Edwards AD, Franks NP, Maze M. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. Ann Neurol 2005; 58:182–193

Ma D, Williamson P, Januszewski A, Nogaro MC, Hossain M, Ong LP, Franks NP, Maze M. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. Anesthesiology 2007; 106: 746 – 753

Ma D, Lim T, Xu J, Tang H, Wan Y, Zhao H, Hossain M, Maxwell PH, Maze M. Xenon preconditioning protects against renal ischemic-reperfusion injury via HIF-1alpha activation. J Am Soc Nephrol 2009; 20: 713 – 720

Madathill RJ, Hira RS, Stoeckl M, Sterz F, Elrod JB, Nichol G. Ischemia reperfusion injury as a modifiable target for Cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. Resuscitation 2016; 105: 85 – 91

Madl C, Holzer M. Brain function after resuscitation from cardiac arrest. Curr Opin Crit Care 2004; 10: 213 – 217

Marcoux FW, Morawtz RB, Crowell RM, DeGirolami U, Halsey JH jr. Differential regional vulnerability in transient focal cerebral ischemia. Stroke 1982; 13: 339 – 346

Mark DG, Vinson DR, Hung YY, Anderson ES, Escobar GJ, Carr BG, Abella BS, Ballard DW. Lack of improved outcomes with increased use of targeted temperature management following out-of-hospital cardiac arrest: a multicenter retrospective cohort study. Resuscitation 2014; 85: 1549 – 1556

Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke 1998; 29: 2363 – 2366

Marx T, Froeba G, Wagner D. Retrieval and purification of xenon in anaesthesia. Acta Anaesthesiol Scand 1996; 40: 217

Marx T, Froeba G, Wagner D, Baeder S, Goertz A, Georgieff M. Effects on haemodynamics and catecholamine release of xenon anaesthesia compared with total i.v. anaesthesia in the pig. Br J Anaesth 1997; 78: 326 – 327

Marx T, Wagner D, Baeder S, Goertz A, Georgieff M, Froeba G. Hemodynamics and catecholamines in anaesthesia with different concentrations of xenon. Appl Cardiopulm Pathophysiol 1998; 7: 215 – 221

Marx T, Schmidt M, Schirmer U, Reinelt H. Xenon anaesthesia. J R Soc Med 2000; 93: 513 – 517

Margey R, Browne L, Murphy E, O'Reilly M, Mahon N, Blake G, McCann H, Sugrue D, Galvin J. The Dublin cardiac arrest registry: temporal improvement in survival from out-of-hospital cardiac arrest reflects improved pre-hospital emergency care. Europace 2011; 13: 1157 – 1165

Martin JL, Ma D, Hossain M, Xu J, Sanders RD, Franks NP, Maze M. Asynchronous administration of xenon and hypothermia significantly reduces brain infarction in the neonatal rat. Br J Anaesth 2007; 98: 236 – 240

Mathur S, Farhangkhgoee P, Karmazyn M. Cardioprotective effects of propofol and sevoflurane in ischemic and reperfused rat hearts. Role of K_{ATP} channels and interaction with the sodium-hydrogen exchange inhibitor HOE 642 (cariporide). Anesthesiology 1999; 91: 1349 – 1360

Matute C. Glutamate and ATP signaling in white matter pathology. J Anat 2011; 219: 53 – 64

Matute C (Matute 2012a), Ransom BR. Roles of white matter in central nervous system pathophysiologies. ASN Neuro 2012; 4: 89 – 101

Matute C (Matute 2012b), Domercq M, Pérez-Samartín A, Ransom BR. Protecting white matter from stroke injury. Stroke 2013; 44: 1204 – 1211

Maupain C, Bougouin W, Lamhaut L, Deye N, Diehl JL, Geri G, Perier MC, Beganton F, Marijon E, Jouven X, Cariou A, Dumas F. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J 2016; 37: 3222 – 3228

Maze M (Maze 2016a). Preclinical neuroprotective actions of xenon and possible implications for human therapeutics: a narrative review. Can J Anesth 2016; 63: 212 – 226

Maze M (Maze 2016b), Pirracchio R. Will xenon be a valuable addition in perioperative and critical care settings? Anesth Analg 2016; 122: 593 – 596

Maze M, Laitio T. Xenon limits brain damage following cardiac arrest. Xenon and brain injury. ICU management Pract 2018; 18: 192 – 195

McGinniss J, Marshall P, Honiden S. Novel Uses of Targeted Temperature Management. Clin Chest Med 2015; 36: 385 – 400

Menon DK. Unique challenges in clinical trial in traumatic brain injury. Crit Care Med 2009; 37(suppl): S129 – S135

Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011; 82: 1180 – 1185

Meybohm P, Gruenewald M, Zacharowski KD, Albrecht M, Lucius R, Fösel N, Hensler J, Zitta K, Bein B. Mild hypothermia alone or in combination with anesthetic post-conditioning reduces expression of inflammatory cytokines in the cerebral cortex of pigs after cardiopulmonary resuscitation. Critical Care 2010; 14: R21

Meynaar IA, Oudemans-van Straaten HM, van den Wetering J, Verlooy P, Slaats EH, Bosman RJ, van der Spoel JI, Zandstra DF. Serum neuron-specific enolase predicts outcome in post-anoxic coma: a prospective cohort study. Intensive Care Med 2003; 29:189 – 195

Millin MG, Comer AC, Nable JV, Johnston PV, Lawner BJ, Woltman N, Levy MJ, Seaman KG, Hirshon JM. Patients without ST elevation after return of spontaneous circulation may benefit from emergent percutaneous intervention: a systematic review and meta-analysis. Resuscitation 2016; 108: 54 – 60

Mink JW, Blumenschine RJ, Adams DB. Ratio of central nervous system to body metabolism in vertebrates: its constancy and functioinal basis. Am J Physiol 1981; 241: R203 – R212

Mio Y, Shim YH, Richards E, Bosnjak ZJ, Pagel PS, Bienengraeber M. Xenon preconditioning: the role of prosurvival signalling, mitochondrial permeability transition and bioenergetics in rats. Anesth Analg 2009; 108: 858 – 866

Mlynash M, Campbell DM, Leproust EM, Fischbein NJ, Bammer R, Eyngorn I, Hsia AW, Moseley M, Wijman CA. Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. Stroke 2010; 41: 1665 – 1672

Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998; 351: 861 – 861

Mongardon N, Dumas F, Ricome S, Grimaldi D, Hissem T, Pène F, Cariou A. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care 2011; 1: 45 – 56

Mooney MR, Unger BT, Boland LL, Burke MN, Kebed KY, Graham KJ, Henry TD, Katsiyiannis WT, Satterlee PA, Sendelbach S, Hodges JS, Parham WM. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation 2011; 124: 206 – 214

Moore EM, Nichol AD, Bernard SA, Bellomo R. Therapeutic hypothermia: Benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury. Injury 2011; 42: 843 – 854

Mori S, Kaufmann WE, Davatzikos, Stieltjes B, Amodei L, Fredericksen K, Pearlson GD, Melhem ER, Solaiyappan M, Raymond GV, Moser HW, van Zijl PC. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. Magn Reson Med 2002; 47: 215 – 223

Morita S, Goto T, Niimi Y, Ichinose F, Saito H. Xenon produces minimal cardiac depression in patients under fentanyl-midazolam anesthesia. Anesthesiology 1996; 85: A362

Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, Parr M, Shuster M, Sunde K, Peberdy MA, Tang W, Hoek TL, Böttiger BW, Drajer S, Lim SH, Nolan JP, for the Advanced Life Support Chapter Collaborators. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation 2010; 122(Suppl 2): S345 – S421

Moseby-Knappe M, Pellis T, Dragancea I, Friberg H, Nielsen N, Horn J, Kuiper M, Roncrati A, Siemund R, Undén J, Cronberg T, for the TTM-trial investigators. Head computed tomography for prognostication of poor outcome in comatose patients after cardiac arrest and targeted temperature management. Resuscitation 2017; 119: 89 – 94

Moseby-Knappe M, Mattsson N, Nielsen N, Zetterberg H, Blennow K, Dankiewics J, Dragancea I, Friberg H, Lilja G, Insel PS, Rylander C, Westhall E, Kjaergaard J, Wise MP, Hassager C, Kuiper MA, Stammet P, Jaeger Wanscher J, Wetterslev J, Erlinge D, Horn J, Pellis T, Cronberg T. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. JAMA Neurol 2019; 76: 64 – 71

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howrd VJ, Huffman MD, Judd SJ, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics – 2015 Update. A report from the American Heart Association. Circulation 2015; 131: e29 – e322

Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. Diffusion tensor MR Imaging and fiber tractography: theoretic underpinnings. Am J Neuroradiol 2008; 29: 632 – 641

Müller D, Agrawal R, Arntz HR. How sudden is sudden cardiac death? Circulation 2006; 114: 1146 – 1150

Müllner M, Oschatz E, Sterz F, Pirich C, Exner M, Schörkhuber W, Laggner AN, Hirschl MM. The influence of chest compressions and external defibrillation on the release of creatine kinase-MB and cardiac troponin T in patients resuscitated from out-of-hospital cardiac arrest. Resuscitation 1998; 38: 99 – 105

Mörtberg E, Zetterberg H, Nordmark J, Blennow K, Rosengren L, Rubertsson S. S- S100β is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. Resuscitation 2011; 82: 26 – 31

Nakajima W, Ishida A, Lange MS, Gabrielson KL, Wilson MA, Martin LJ, Blue ME, Johnston MV. Apoptosis has a prolonged role in the neurodegeneration after hypoxic ischemia in the newborn rat. J Neurosci 2000; 20: 7994 – 8004

Nakata Y, Goto T, Morita S. Effects of xenon on hemodynamic responses to skin incisions in humans. Anesthesiology 1999; 90: 406 – 410

Nakata Y, Goto T, Ishiguro Y, Terui K, Kawakami H, Santo M, Niimi Y, Morita S. Minimum alveolar concentration (MAC) of xenon with sevoflurane in humans. Anesthesiology 2001; 94:611–614

Neary P, Redmond HP. Ischaemia-reperfusion injury and the systemic inflammatory response syndrome. In Ischaemia-Reperfusion Injury, Blackwell Science: London 1999; pp 123 – 136

Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. Br J Anaesth 2017; 119 (suppl); i115 – i125

Nelson TMH, Joseph WWE, Daniel PCYN, Clement KRH, Jonas HRY, Hong KJ, Benjamin LSH, Junxiong P, Jeff HYF. The use of dispatcher assistance in improving the quality of cardiopulmonary resuscitation: a randomized controlled trial. Resuscitation 2019; 138: 153 – 159

Neukirchen M, Schaefer MS, Kern C, Brett S, Werdehausen R, Rellecke P, Reyle-Han M, Kienbaum P. Xenon does not increase heart rate-corrected cardiac QT interval in volunteers and in patients free of cardiovascular disease. Anesthesiology 2015; 123: 542 – 547

Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT Jr, Merchant RM, Morley P, Morrison LJ, Nadkami V, Peberdy MA, Rivers EP, Rodriguez-Nunes A, Sellke FW, Spaulding C, Sunde K, Vanden Hoek T. Post cardiac arrest syndrome: Epidemiology, Pathophysiology, Treatment, and Prognostication. A Consensus Statement from the International Liaison Committee on Resuscitation. Circulation. 2008; 118: 2452 – 2483

Neumar RW. Optimal oxygenation during and after cardiopulmonary resuscitation. Curr Opin Crit Care 2011; 17: 236 – 240

Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008; 300: 1423 – 1431

Nichol G, Leroux B, Wang H, Callaway C, Sopko G, Weisfeldt M, Stiell I, Morrison LJ, Aufderheide TP, Cheskes S, Christenson J, Kudenchuk P, Vaillancourt C, Rea TD, Idris AH, Colella R, Isaacs M, Straight R, Stephens S, Richardsson J, Condle J, Schmicker RH, Egan D, May S, Ornato JP, for the ROC Investigators. Trial of continuous or interrupted chest compressions during CPR. N Engl J Med 2015; 373: 2203 – 2214

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2001; 15: 1 – 25

Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, Valsson F, Wanscher M, Friberg H. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009; 53: 926 – 934

Nielsen N (Nielsen 2011a), Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, Nilsson F, Friberg H, for the Hypothermia Network. Adverse events and their relation to mortality in out-of-

hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011; 39: 57 – 64

Nielsen N (Nielsen 2011b), Friberg H, Gluud C, Herlitz J, Wetterslav J. Hypothermia after cardiac arrest should be further evaluated: a systematic review of randomized trials with meta-analysis and trial sequential analysis. Int J Cardiol 2011; 151: 333 – 341

Nielsen N, Wetterslev J, al-Subaie N, Andersson B, Bro-Jeppesen J, Bishop G, Brunetti I, Cranshaw J, Cronberg T, Edqvist K, Erlinge D, Gasche Y, Glover G, Hassager C, Horn J, Hovdened J, Johnsson J, Kjærgaard J, Kuiper M, Langørgen J, Macken L, Martinell L, Martner P, Pellis T, Pelosi P, Petersen P, Persson S, Rundgren M, Saxena M, Svensson R, Stammet P, Thorén A, Undén J, Walden A, Wallskog J, Wanscher M, Wise MP, Wyon N, Aneman A, Friberg H. Target temperature management after out-of-hospital cardiac arrest – a randomized, parallel group, assessor-blinded clinical trial – rationale and design. Am Heart J 2012; 163:541–548

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjærgaard J, Kuiper M, Pellis T, Pelosi P, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie M, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, for the TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369: 2197 – 2206

Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI) / Stent for Life (SFL) groups. Eurointervention 2014; 10: 31 – 37

Nolan J, Morley P, Vanden Hoek T, Hickey RW, Kloeck WG, Billi J, Böttiger BW, Morley PT, Nolan JP, Okada K, Reyes C, Shuster M, Steen PA, Weil MH, Wenzel V, Hickey RW, Carli P, Atkins D, for the International Liaison Committee on Resuscitation. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 2003; 108: 118 – 121

Nolan J (Nolan 2005a), European Resuscitation Council. European Resuscitation Council for resuscitation 2005, Section 1. Introduction. Resuscitation 2005; 67 (Suppl 1): S3 - S6

Nolan JP (Nolan 2005b), Deakin CD, Soar J, Bottiger BW, Smith G. European resuscitation council guideline for resuscitation 2005 section 4: adult advanced life support. Resuscitation 2005; 67 (Suppl 1): S39 – S86

Nolan JP, Laver SR, Welch CA, Harrison DA, Gupta V, Rowan K. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC case mix programme database. Anaesthesia 2007; 62: 1207 – 1216

Nolan JP, Soar J. Postresuscitation care: entering a new era. Curr Opin Crit Care 2010; 16: 216 – 222

Nolan JP, Perkins GD. Is there a role for adrenaline during cardiopulmonary resuscitation? Curr Opin Crit Care 2013; 19: 169 – 174

Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Böttiger BW, Friberg H, Sunde K, Sandroni C, European Resuscitation Council, European Society of Intensive Care Medicine. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 2015; 41: 2039 – 2056

Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Böttiger BW, Friberg H, Sunde K, Sandroni C. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015; 95: 202 – 222

Nunnally ME, Jaeschke R, Bellingan GJ, Lacroix J, Mourvillier B, Rodriguez-Vega GM, Rubertsson S, Vassilakopoulos T, Weinert C, Zanotti-Cavazzoni S, Buchman TG. Targeted temperature management in critical care: a report and recommendations from five professional societies. Crit Care Med 2011; 39: 1113 – 1125

Oddo M, Rossettil AO. Early multimodal prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014; 42: 1340 – 1347

Oddo M, Friberg H. Neuroprognostication after cardiac arrest in the light of targeted temperature management. Curr Opin Crit Care 2017; 23: 244 – 250

Ohara A, Mashimo T, Zhang P, Inagaki Y, Shibuta S, Yoshiya I. A comparative study of the antinociceptive action of xenon and nitrous oxide in rats. Anesth Analg 1997; 85: 931 – 936

Okamura T, Ishibashi N, Kumar TS, Zurakowski D, Iwata Y, Lidov HG, Jonas RA. Hypothermic circulatory arrest increases permeability of the blood brain barrier in watershed areas. Ann Thorac Surg 2010; 90: 2001 – 2008

Oksanen T, Skrifvars MB, Varpula T, Kuitunen A, Pettilä V, Nurmi J, Castrén M. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med 2007; 33: 2093 – 2100

Oksanen T, Tiainen M, Skrifvars MB, Varpula T, Kuitunen A, Castrén M, Pettilä V. Predictive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. Resuscitation 2009; 80: 165 – 170

Olasveeengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest. A randomized trial. JAMA 2009; 302: 2222 – 2229

Olasveengen TM. Can drugs ever improve outcome after cardiac arrest? Resuscitation 2012; 83: 663 – 664

Olasveengen Tm, Kramer-Johansen J. Insight to the black hole currently characterizing the initial post arrest phase. Resuscitation 2015; 87: A3 – A4

Olasveengen TM, de Caen AR, Mancini ME, Macnochie IK, Aickin R, Atkins DL, Berg RA, Bingham RM, Brooks SC, Castrén M, Chung SP, Considine J, Couto TB, Escalante R, Gazmuri RJ, Guerguerian AM, Hatanaka T, Koster RW, Kudenchuk PJ, Lang E, Lim SH, Løfgren B, Meaney PA, Montgomery WH, Morley PT, Morrison LJ, Nation KJ, Kee-Chong NG, Nadkarni VM, Nishiyama C, Nuthall G, Ong GYK, Perkins GD, Reis AG, Ristagno G, Sakamoto T, Sayre MR, Schexnayder SM, Sierra AF, Singletary EM, Shimizu N, Smyth MA, Stanton D, Tijssen JA, Traves A, Vaillancourt C, Vande Voorde P, Hazinski MF, Nolan JP, on behalf of the ILCOR collaborators. 2017 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations summary. Circulation 2017; 136: e424 – e440

Pagel PS, Krolikowski JG, Shim YH, Venkatapuram S, Kersten JR, Weihrauch D, Warltier DC, Pratt PF Jr. Noble gases without anesthetic properties protect myocardium against infarction by activating prosurvival signalling kinases and inhibiting mitochondrial transition in vivo. Anesth Analg 2007; 105: 562 – 569

Pagel PS. Cardioprotection by noble gases. J Cardiothorac Vasc Anesth 2010; 24: 143 – 163

Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. Stroke 1996; 27: 1641 – 1646

Parikh RH, Seliger SL, deFilippi CR. Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction. Clin Biochem 2015; 48: 247 – 253

Parish DC, Chandra KMD, Dane FC. Success changes the problem: why ventricular fibrillation is declining, why pulseless electrical activity is merging, and what to do about it. Resuscitation 2003; 58: 31 – 35

Park YM, Shin SD, Lee YJ, Song KJ, Ro YS, Ahn KO. Cardiopulmonary resuscitation by trained responders versus lay persons and outcomes of out-of-hospital cardiac arrest: a community observational study. Resuscitation 2017; 118: 55 – 62

Pearson JW, Redding JS. The role of epinephrine in cardiac resuscitation. Anesth Analg 1963; 42: 599 – 606

Peberdy MA, Ornato JP. Post-resuscitation care: is it the missing link in the chain of survival? Resuscitation 2005; 64: 135 – 137

Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Vanden Hoek TL, Kronick SL. Part 9: Post-Cardiac Arrest Care. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122(suppl): S768 – S786

Perkins GD, Cottrell P, Gates S. Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest? BMJ 2014; 348: g2435

Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R, for the PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018; 379: 711 – 721

Perlman JM. Markers of asphyxia and neonatal brain injury. N Engl J Med 1999; 341: 364 – 365

Perman SM, Kirkpatrick JN, Reitsma AM, Gaieski DF, Lau B, Smith TM, Leary M, Fuchs BD, Levine JM, Abella BS, Becker LB, Merchant RM. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. Crit Care Med 2012; 40: 719 – 724

Perper J, Kuller L, Cooper M. Arteriosclerosis of coronary arteries in sudden, unexpected deaths. Circulation 1975; 52(suppl): 27 – 33

Petito CK, Feldmann E, Pulsinelli WA, Plum F. Delayed hippocampal damage in humans following cardiorespiratory arrest. Neurology 1987; 37: 1281 – 1286

Petzelt C, Osés-Prieto J, Klett FF, Schmehl W, Kox WJ. Effects of xenon on intracellular Ca^{2+} release in human endothelial cells. Exp Biol Online 1997; 2: 3 -9

Petzelt CP, Kodirov S, Taschenberger G, Kox WJ. Participation of the –calmodulin-activated kinase II in the control of metaphase-anaphase transition in human cells-Cell Biol Int 2001; 25: 403 – 409

Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 1996; 36: 893 – 906

Plum F, Posner JB, Hain RF. Delayed neurological deterioration after anoxia. Arch Intern Med 1962; 110: 18 – 25

Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008; 371: 1955 – 1969

Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009; 37(suppl): S186 – S202

Preckel B, Müllenheim J, Moloschavij A, Thãmer V, Schlack W. Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart in vivo. Anesth Analg 2000; 91: 1327 – 1332

Preckel B, Schlack W, Heibel T, Rütten H. Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function. Br J Anaesth 2002; 88: 264 – 269

Preckel B, Weber NC, Sanders RD, Maze M, Schlack W. Molecular mechanisms transducing the anesthetic, analgesic and organ-protective actions of xenon. Anesthesiology 2006; 105: 187 – 197

Püttgen HA, Geocadin R. Predicting neurological outcome following cardiac arrest. J Neurol Sci 2007; 261: 108 – 117

Rab T, Kern KB, Tamis-Holland JE, Henry TD, McDaniel M, Dickert NW, Cigarroa JE, Keadey M, Ramee S, on behalf of the Interventional Council, American College of Cardiology. J Am Coll Cardiol 2015; 66: 62 – 73

Ragosta M. The heart or the brain? Which takes priority after cardiac arrest and can we identify patients in whom aggressive cardiac care is futile? JACC Cardiovasc Interv 2018; 11: 257 – 259

Rasmussen LS, Schmehl W, Jakobsson J. Comparison of xenon with propofol for supplementary general anaesthesia for knee replacement: a randomized study. Br J Anaesth 2006; 97: 154 – 159

Rasmussen JH, Mosfeldt M, Pott FC, Belhage B. Xenon for induction of anaesthesia. Acta Anaesthesiol Scand 2009; 53: 549 – 550

Rea TD, Eisenberg MS, Sinibaldi G, White RD. Incidence of EMS-treated out-of-hospital cardiac arrest in the United States. Resuscitation 2004; 63: 17 – 24

Rea TD (Rea 2010a), Stickney RE, Doherty A, Lank P. Perormance of chest compressions by laypersons during the public access defibrillation trial. Resuscitation 2010; 81: 293 – 296

Rea TD (Rea 2010b), Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, Bloomingdale M, Subido C, Romines S, Eisenberg MS. CPR with chest compression alone or with rescue breathing. N Engl J Med 2010; 363: 423 – 433

Remba SJ, Varon J, Rivera A, Sternbach GL. Dominique-Jean Larrey: The effects of therapeutic hypothermia and the first ambulance. Resuscitation 2010; 81: 268 – 271

Ribeiro A, Singh R, Brunnhuber F. Clinical outcome of generalized periodic epileptiform discharges on first EEG in patients with hypoxic encephalopathy postcardiac arrest. Epilepsy Behav 2015; 49: 268 – 272

Rice 3rd JE, Vannucci RC, Brierley JB. The influence of immaturity on hypoxic-ischemic brain damage the rat. Ann Neurol 1981; 9: 131 – 141

Rittenberger JC, Popescu A, Brenner A, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose postcardiac arrest subjects treated with hypothermia. Neurocrit Care 2012; 16: 114 – 122

Rittenberger JC, Callaway CW. Temperature management and modern post-cardiac arrest care. N Engl J Med 2013; 369: 2262 – 2263

Rivers EP, Martin GB, Smithline H, Rady MY, Schultz CH, Goetting MG, Appleton TJ, Novak RM. The clinical implications of continuous central venous oxygen saturation during human CPR. Ann Emerg Med 1992; 21: 1094 – 1101

Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich G, Peterson E, Tomlanovich M, for the Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368 – 1377

Roehl AB, Funcke S, Becker MM, Goetzenich A, Bleilevens C, Rossaint R, Steendijk P, Hein M. Xenon and Isoflurane reduce left ventricular remodeling after myocardial infarction in the rat. Anesthesiology 2013; 118: 1385 – 1394

Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, Giunta F, Del Turco M, Erdmann W, Tenbrinck R, Hammerle AF, Nagele P for the Xenon Study Group. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology 2003; 98:6 – 13

Rossello X, Yellon DM. A critical review on the translational journey of cardioprotective therapies. Int J cariol 2016; 220: 176 – 184

Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009; 72: 744 – 749

Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol 2016; 15: 597 – 609

Rueckoldt H, Vangerow B, Marx G, Haubitz B, Meyer MC, Piepenbrock S, Leuwer M. Xenon inhalation increases airway pressure in ventilated patients. Acta Anaesthesiol Scand 1999; 43: 1060 – 1064

Ruijter BJ, van Putten MJAM, Horn J, Blans MJ, Beishuizen A, van Rootselaar AF, Hofmeijer J, on behalf of the TELSTAR study group. Treatment of electroencephalographic satus epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials 2014; 15: 433 – 440

Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and s-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation 2009; 80: 784 - 789

Rundgren M, Westhall E, Cronberg T, Rosén I, Friberg H. Continuous amplitude integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med 2010; 38:1838 – 1844

Sabir H, Bishop S, Cohen N, Maes E, Liu X, Dingley J, Thoresen M. Neither xenon nor fentanyl induces neuroapoptosis in the newborn pig brain. Anesthesiology 2013; 119: 345 – 357

Safar P. Community-wide cardiopulmonary resuscitation. (The CPCR system). J Iowa Med Soc 1964; 54: 629

Salter R, Bailey M, Bellomo R, Eastwood G, Goodwin A, Nielsen N, Pilcher D, Nichol A, Saxena M, Shehabi Y, Young P on behalf of the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE). Changes in temperature management of cardiac arrest patients following publication of the target temperature management trial. Crit Care Med 2018; 46: 1722 – 1730

Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation counfounds outcome prediction in cardiac arrest survivors treated with hypothermia. Neurocrit Care 2011; 15: 113 – 119

Sanders RD, Franks NP, Maze M. Xenon: no stranger to anaesthesia. Br J Anaesth 2003; 91: 709 – 717

Sandroni C, Cavallaro F, Callaway CW, D'Arrigo S, Sanna T, Kuiper MA, Biancone M, Della Marca G, Farcomeni A, Nolan JP. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: patients treated with therapeutic hypothermia. Resuscitation 2013; 84: 1324 - 1338

Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO, Soar J. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitaton Council and the European Society of Intensive Care Medicine. Intensive Care Med 2014; 40: 1816 – 1831

Sandroni C, Geocadin RG. Neurological prognostication after cardiac arrest. Curr Opin Crit Care 2015; 21: 209 – 214

Sanganalmath SK, Gopal P, Parker JR, Downs RK, Parker Jr JC, Dawn B. Global cerebral ischemia due to circulatory arrest: insights into cellular pathophysiology and diagnostic modalities. Mol Cell Biochem 2016; 426: 111 – 127

Schaefer W, Meyer PT, Roissant R, Baumert JH, Coburn M, Fries M, Rex S. Myocardial Blood Flow during General Anesthesia with Xenon in humans. A Positron Emission Tomography Study. Anesthesiology 2011; 114: 1373 – 1379

Sans S, Kesteloot H, Kromhaut D. The burden of cardiovascular diseases mortality in Europe. Task Force of European Society of Cardiology on cardiovascular mortality and morbidity statistics in Europe. Eur Heart J 1997; 18: 1231 – 1248

Scheel M, Storm C, Gentsch A, Nee J, Luckenbach F, Ploner CJ, Leitner C. The prognostic value of gray-white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma Resusc Emerg Med 2013; 21: 23 – 29

Schenone AL, Cohen A, Patarroyo G, Harper L, Wang XF, Shishehbor MH, Menon V, Duggal A. Therapeutic hypothermia after cardiac arrest: a systematic review/meta-analysis exploring the impact of extended criteria and targeted temperature. Resuscitation 2016; 108: 102 – 110

Schindler O, Gemes G, Spindelboeck W. Oxygen and cardiac arrest: the timepoint matters. Intensive Care Med 2015; 41: 952

Schmidt M, Marx T, Glöggl E, Reinelt H, Schirmer U. Xenon attenuates cerebral damage after ischemia in pigs. Anesthesiology 2005; 102:929 – 936

Schmidt M, Marx T, Papp-Jambor C, Reinelt H, Schirmer U. Airway pressures during xenon anaesthesia. Apll Cardiopulm Pathophysiol 2009; 13: 208 – 211

Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience 1991; 40: 599 – 636

Scolletta S, Donadello K, Santonocito C, Franchi F, Taccone FS. Biomarkers as predictors of outcome after cardiac arrest. Expert Rev Clin Pharmacol 2012; 5: 687 – 699

Schulman SP, Hartmann TK, Geocadin RG. Intensive care after resuscitation from cardiac arrest: a focus on heart and brain injury. Neurol Clin 2006; 24: 41 – 59

Schummer W, Schummer C, Wiegand J. High levels of neuron-spesific enolase after CPR and good clinical outcome. Resuscitation 2010; 81: 365

Schünemann HJ, Best D, Vist G, Oxman AD, for the GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. CMAJ 2003; 169: 677 – 680

Scroth SC, Schotten U, Alkanoglu O, Reyle-Hahn MS, Hanrath P, Rossaint R. Xenon does not impair the responsiveness of cardiac muscle bundles to positive inotropic and chronotropic stimulation. Anestesiology 2002; 96: 433 -427

Schwiebert C, Huhn R, Heinen A, Weber NC, Hollmann MW, Schlack W, Preckel B. Postconditioning by xenon and hypothermia in the rat heart in vivo. Eur J Anaesthesiol 2010; 27: 734 – 739

Sealy WC, Brown IW Jr, Young WG Jr. A report on the use of both extracorporeal circulation and hypothermia for open-heart surgery. Ann Surg 1958; 147: 603 – 613

Seder DB, Sunde K, Rubertsson S, Mooney M, Stammet P, Riker RR, Kern KB, Unger B, Cronberg T, Dziodzio J, Nielsen N, for the International Cardiac Arrest Registry. Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. Crit Care Med 2015; 43: 965 – 972

Sener S, Van Hecke W, Feyen BFE, van der Steen G, Pullens P, Van de Hauwe L, Menovsky T, Parizel PM, Jorens PG, Maas AIR. Diffusion tensor imaging: a possible biomarker in severe traumatic brain injury and aneurysmal subarachnoid hemorrhage? Neurosurgery 2016; 76: 786 – 793

Sessler DI. Thermoregulatory defense mechanisms. Crit Care Med 2009: 37: S203 – S210

Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole K, Wright LL, Higgins RD, Finer NN, Carlo WA for the National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005; 353: 1574 – 1584

Sheng SP, Lei B, James ML, Lascola CD, Venkatraman TN, Jung JY, Maze M, Franks NP, Pearlstein RD, Sheng H, Warner DS. Xenon neuroprotection in experimental stroke: interactions with hypothermia and intracerebral hemorrhage. Anesthesiology 2012; 117:1262 – 1275

Shu Y, Patel SM, Pac-Soo C, Fidalgo AR, Wan Y, Maze M, Ma D. Xenon pretreatment attenuates anesthetic-induced apoptosis in the developing brain in comparison with nitrous oxide and hypoxia. Anesthesiology 2010; 113: 360 – 368

Siesjö BK, Carlsson C, Hägerdal M, Nordström CH. Brain metabolism in the critically ill. Crit Care Med 1976; 4: 283 – 294

Skjeflo GW, Nordseth T, Loennechen JP, Bergum D, Skogvoll E. ECG changes during resuscitation of patients with initial pulseless electrical activity are associated with return of spontaneous circulation. Resuscitation 2018; 127: 31 – 36

Skrifvars MB, Olasveengen TM, Ristagno G. Oxygen and carbon dioxide targets during and after resuscitation of cardiac arrest patients. Intensive Care Med 2019; 45: 284 – 286

Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, Marriott A, Moore EM, Morris G, Page RS, Gray L. Post-operative cognitive dysfunction: an exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev 2018; 84: 116 – 133

Small DL, Morley P, Buchan AM. Biology of ischemic cerebral cell death. Prog Cardiovasc Dis 1999; 42: 185 – 207

Smit KF, Weber NC, Hollmann MW, Preckel B. Noble gases as cardioprotectants – translatability and mechanism. Br J Pharmacol 2015; 172: 2062 – 2073

Smith SM, Jenkinson M, Johansen-Berg, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Zaheer Cader M, Matthews PM, Behrens TEJ. Tract- based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 2006; 31: 1487 – 1505

Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, Robson MD, Jones DK, Klein JC, Bartsch AJ, Behrens TEJ. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. Nat Protoc 2007; 2: 499 – 503

Snyder-Ramos SA, Böttiger BW. Molecular markers of brain damage – clinical and ethical implications with particular focus on cardiac arrest. Restor Neurol Neurosci 2003; 21: 113 – 139

Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, Pellis T, sandroni C, Skrifvars MB, Smith GB, Sunde K, Deakin CD, for the adult advanced life support section C. European resuscitation council guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation 2015; 95: 100 – 147

Soar J, Donnino MW, Maconochie I, Aickin R, Atkins DL, Andersen LW, Berg KM, Bingham R, Böttiger BW, Callaway CW, Couper K, Couto TB, de Caen AR, Deakin CD, Drennan IR, Guerguerian AM, Lavonas EJ, Meaney PA, Nadkarni VM, Neumar RW, Ng KC, Nicholson TC, Nuthall GA, Ohshimo S, O'Neill BJ, Ong GYK, Paiva EF, Parr MJ, Reis AG, Reynolds JC, Ristagno G, Sandroni C, Schexnayder SM, Scholefield BR, Shimizu N, Tijssen JA, Van der Voorde P, Wang TL, Welsford M, Hazinski MF, Nolan JP, Morley PT, on behalf of the ILCOR Collaborators. 2018 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations summary. Resuscitation 2018; 133: 194 – 206

Soar J, Perkins GD, Maconochie I, Böttiger BW, Deakin CD, Sandroni C, Olasveengen TM, Wyllie J, Greif R, Lockey A, Semerano F, Van de Voorde P, Lott C, Bossaert L, Monsieurs KG, Nolan JP, on behalf of the European Resuscitation Council. European resuscitation Council Guidelines for resuscitation: 2018 Update – antiarrhythmic drugs for cardiac arrest. Resuscitation 2019; 134: 99 – 103

Solecki K, Dupuy AM, Kuster N, Leclercq F, Gervasoni R, Macia JC, Cung TT, Lattuca B, Cransac F, Cade S, Pasquié JL, Cristol JP, Roubille F. Kinetics of high-sensitivity cardiac troponin T or troponin I compared to creatinine kinase in patients with revascularized acute myocardial infarction. Clin Chem Lab Med 2015; 53: 707 – 714

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchained axial) diffusion of water. Neuroimage 2002; 17: 1429 - 1436

Soo LH, Gray D, Hampton JR. Pathological features of witnessed out-of-hospital cardiac arrest presenting with ventricular fibrillation. Resuscitation 2001; 51: 257 – 264

Sopka S, Mertens C, Roehl AB, Schiffl K, Rossaint R, Classen-Linke I. Effects of xenon and isoflurane on apoptosis and inflammation in a porcine myocardial infarction model. Ann Anat 2013; 195: 166 – 174

Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, Michos ED. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. Ann Intern Med 2014; 1616: 502 – 512

Stamenova V, Nicola R, Aharon-Peretz J, Goldsher D, Kapeliovich M, Gilboa A. Long-term effects of brief hypoxia due to cardiac arrest: hippocampal reductions and memory deficits. Resuscitation 2018; 126: 65 – 71

Stær-Jensen H, Sunde K, Olasveengen TM, Jacobsen D, Drægni T, Nakstad ER, Eritsland J, Andersen GØ. Bradycardia during therapeutic hypothermia is associated with good neurologic outcome in comatose survivors of out-of-hospital cardiac arrest. Crit Care Med 2014; 42: 2401 – 2408

Stær-Jensen H; Nakstad ER, Fossum E, Mangschau A, Eritsland J, Drægni T, Jacobsen D, Sunde K, Anderson GØ. Post-resuscitation ECG for selection of patients for immediate coronary

angiography in out-of-hospital cardiac arrest. Circ Cardiovasc Interv 2015; 8: e002784 – e0027811

Stern P, Bartos V, Uhrova J, Bezdickova D, Vanickova Z, Tichy V, Pelinkova K, Prusa R, Zima T. Performance characteristics of seven neuron-specific enolase assays. Tumour Biol 2007; 28: 84 – 92

Stevens RD, Hannawi Y, Puybasset L. MRI for coma emergency and recovery. Curr Opin Crit Care 2014; 20: 168 – 173

Steward A, Allott PR, Cowes AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil, and biological media. Br J Anaesth 1973; 45: 282 – 293

Stieltjes B, Kaufmann WE, van Zijl PC, Fredericksen K, Pearlson GD, Solaiyappan M, Mori S. Diffusion tensor imaging and axonal tracking in the human brainstem. Neuroimage 2001; 14: 723 – 735

Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016; 67: 1674 – 1683

Stoppe C, Fahlenkamp AV, Rex S, Veeck NC, Gozdowsky SC, Schälte G, Autschbach R, Rossaint R, Coburn M. Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study. Br J Anaesth 2013; 111: 406 – 416

Storm C, Hasper D, Nee J, Joerres A, Schefold JC, Kaufmann J, Roser M. Severe QTc prolongation under mild hypothermia treatment and incidence of arrhythmias after cardiac arrest – a prospective study in 34 survivors with continuous Holter ECG. Resuscitation 2011; 82: 859 – 862

Stowe DF, Rehmert GC, Kwok WM, Weigt HU, Gerogieff M, Bosnjak ZJ: Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes. Anesthesiology 2000; 92: 516 –522

Streitberger KJ, Leithner C, Wattenberg M, Tonner PH, Hasslacher J, Joannidis M, Pellis T, Di Luca E, Födisch M, Krannich A, Ploner CJ, Storm C. Neuron-specific enolase predicts poor outcome after cardiac arrest and targeted temperature management: a multicenter study on 1,053 patients. Crit Care Med 2017; 45: 1145 – 1151

Strömsöe A, Svensson L, Axelsson ÅB, Claesson A, Göransson KE, Nordberg P, Herlitz J. Improved outcome in Sweden after out-of-hospital cardiac arrest and possible association with improvements in every link in the chain of survival. Eur Heart J 2015; 36: 863 – 871

Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardized treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007; 73: 29 – 39

Sutherland BA, Minnerup J, Balami JS, Arba F, Buchan AM, Kleinschnitz C. Neuroprotection for ischaemic stroke: translation from the bench to the bedside. Int J Stroke 2012; 7: 407 – 418

Svensson L, Bohm K, Castrèn M, Pettersson H, Engerström L, Herlitz J, Rosenqvist M. Compression-only CPR or standard CPR in out-of-hospital cardiac arrest. N Engl J Med 2010; 363: 434 – 442

Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, Janata A, Arrich J, Holzer M, Losert H. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. Resuscitation 2011; 82: 1162 – 1167

Th E, Kassubek J, Kubalek R, Klisch J. Diffusion-weighted MRI during early global cerebral hypoxia: a predictor for clinical outcome? Acta Neurol Scand 2004; 110: 361 -367

Thomsen JH, Nielsen N, Hassager C, Wanscher M, Pehrson S, Køber L, Bro-Jeppesen J, Søholm H, Winther-Jensen M, Pellis T, Kuiper M, Erlinge D, Friberg H, Kjærgaard J. Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients. Crit Care Med 2016: 44: 308 – 318

Thoresen M, Hobbs CE, Wood T, Chakkarapani E, Dingley J. Cooling combined with immediate or delayed xenon inhalation provides equivalent long-term neuroprotection after neonatal hypoxia-ischemia. J Cereb Blood Flow Metab 2009; 29:707–714

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD for the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Eur Heart J 2012; 33: 2551 – 2567

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, for the Executive Group on behalf of the Joint European Society of Cardiology/ American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infraction. Fourth universal definition of myocardial infarction (2018). Circulation 2018; 138: e618 – e651

Tiainen M, Roine RO, Pettilä V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003; 34: 2881 – 2885

Tiainen M, Poutiainen E, Kovala T, Takkunen O, Häppölä O, Roine RO. Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. Stroke 2007; 38: 2303 – 2308

Tortorici MA, Kochanek PM, Polyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007; 35: 2196 – 2204

Tournier JD, Mori S, Leemans A. Diffusion tensor imaging and beyond. Magn Reson Med 2011; 65: 1532 – 1556

Trudell J, Koblin D, Eger EI 2nd. A molecular description of how noble gases and nitrogen bind to a model site of anesthetic action. Anesth Analg 1998; 87: 239 – 241

Unger ED, Dubin RF, Deo R, Daruwalla V, Friedman JL, Medina C, Beussink L, Freed BH, Shah SJ. Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2016; 18: 103 – 112

Vagts DA, Hecker K, Iber T, Roesner JP, Spee A, Otto B, Rossaint R, Nöldge-Schomburg GFE. Effects of xenon anaesthesia on intestinal oxygenation in acutely instrumented pigs. Br J Anaesth 2004; 93: 833 – 841

Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation 1997; 96: 3308 – 3313

Van Baarsen KM, Kleinnijenhuis M, Jbabdi S, Sotiropuolos SN, Grotenhuis JA, van Cappellen van Walsum AM. A probabilistic atlas of the cerebellar white matter. Neuroimage 2016; 124: 724 – 732

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill Patients. N Engl J Med 2001; 345: 1359 – 1367

Van der Eerden AW, Khalilzadeh O, Perlbarg V, Dinkel J, Sanchez P, Vos PE, Luyt CE, Stevens RD, de Campfleur NM, Delmaire C, Tollard E, Gupta R, Dormont D, Laureys S, Benali H, Vanhaudenhuyse A, Galanaud D, Puybasset L, for the NICER (Neuro Imaging for Coma Emergence and Recovery) Consortium. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: comparative diffusion-tensor imaging study. Radiology 2014; 270: 506 – 516

Vannucci RC, Perlman JM. Interventions for perinatal hypoxic-ischemic encephalopathy. Pediatrics 1997; 100: 1004 – 1014

Varon J, Acosta P. Therapeutic hypothermia: past, present and future. Chest 2008; 133: 1267 – 1274

Varon J, Marik PE, Einav S. Therapeutic hypothermia: a state-of-the-art emergency medicine perspective. Am J Emerg Med 2012; 30: 800 – 810

Velly L, Perlbarg V, Boulier T, Adam N, Delphine S, Luyt CE, Battisti V, Torkomian G, Arbelot C, Chabanne R, Jean B, Di Perri C, Laureys S, Citerio G, Vargiolu A, Rohaut B, Bruder N, Girard

N, Silva S, Cottenceau V, Tourdias T, Coulon O, Riou B, Naccache L, Gupta R, Benali H, Galanaud D, Puybasset L, for the MRI-COMA Investigators. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. Lancet Neurol 2018; 17: 317 - 326

Voicu S, Sideris G, Deye N, Dillinger JG, Logeart D, Broche C, Vivien B, Brun PY, Capan DD, Manzo-Silberman S, Megarbane B, Baud FJ, Henry P. Role of cardiac troponin in the diagnosis of acute myocardial infarction in comatose patients resuscitated from out-of-hospital cardiac arrest. Resuscitation 2012; 83: 452 – 458.

Volpe JJ (ed). Neurology of the newborn. Philadelphia: Saunders Elsevier 2008

Von Vopelius-Feldt J, Coulter A, Benger J. The impact of pre-hospital critical care team on survival from out-of-hospital cardiac arrest. Resuscitation 2015; 96: 290 – 295

Vyas A, Chan PS, Cram P, Nallamothu BK, McNally B, Girotra S. Early Coronary Angiography and Survival After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Interv 2015; 8: e002321 – e002327

Väyrynen T, Boyd J, Sorsa M, Määttä T, Kuisma M. Long-term changes in the incidence of out-of-hospital ventricular fibrillation. Resuscitation 2011; 82: 825 – 829

Wachelder EM, Moulaert VR, van Heugten C, Verbunt JA, Bekkers SC, Wade DT. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation 2009; 80: 517 – 522

Wang D, Luo Y, Mok VCT, Chu WCW, Shi L. Tractography atlas-based spatial statistics: statistical analysis of diffusion tensor image along fiber pathways. NeuroImage 2016; 125: 301 – 310

Wang H, Olivero W, Wang D, Lanzino G. History of neurosurgery. Cold as a therapeutic agent. Acta neurochir (Wien) 2006; 148: 565 – 570

Wappler F, Rossaint R, Baumert J, Scholz J, Tonner PH, van Aken H, Berendes E, Klein J, Gommers D, Hammerle A, Franke A, Hofmann T, Schulte Esch J, for the Xenon Multicenter Study Rearch Group. Multicenter randomized comparison of xenon and isoflurane on left ventricular function in patients undergoing elective surgery. Anaesthesiology 2007; 106: 463 – 471

Weber NC (Weber 2005a), Toma O, Wolter JI, Obal D, Müllenheim J, Preckel B, Schlack W. (2005a). The noble gas xenon induces pharmacological preconditioning in the rat heart *in vivo* via induction of PKC-epsilon and p38 MAPK. Br J Pharmacol 2005; 144: 123–32

Weber NC (Weber 2005b), Toma O, Wolter JI, Wirthle NM, Schlack W, Preckel B. Mechanisms of xenon- and isoflurane-induced preconditioning. A potential link to the cytoskeleton via the MAPKAPK-2/HSP27-pathway. Br J Pharmacol 2005; 146: 445 - 455

Weber NC (Weber 2006a), Toma O, Damla H, Wolter JI, Schlack W, Preckel B. Upstream signaling of protein kinase C-epsilon in xenon-induced pharmacological preconditioning. Implication of mitochondrial adenosine triphosphate dependent potassium channels and phosphatidylinositol-dependent kinase-1. Eur J Pharmacol 2006; 539: 1 - 9

Weber NC (Weber 2006b), Stursberg J, Whirtle NM, Toma O, Schlack W, Preckel B. Xenon preconditioning differently regulates p44/42 MAPK (ERK ½) and p46/54 MAPK (JNK ½ and 3) in vivo. Br J Anaesth 2006; 97, 298 – 306

Weber NC, Frässdorf J, Ratajczak C, Grueber Y, Schlack W, Hollmann MW, Preckel B. Xenon induces late cardiac preconditioning in vivo: a role for cyclooxygenase 2? Anesth Analg 2008; 107: 1807 – 1813

Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, Bigham B, Brooks SC, Foerster C, Gray R, Ornato JP, Powell J, Kudenchuk PJ, Morrison LJ, for the Resuscitation Outcomes Consortium (ROC) Investigators. Ventricular tachyarrhytmias after cardiac arrest in public versus at home. N Engl J Med 2011; 364: 313 – 321

Weng Y, Sun S. Therapeutic Hypotermia After Cardiac Arrest in Adults: Mechanism of Neuroprotection, Phase of Hypothermia, and Methods of Cooling. Crit Care Clin 2012; 28: 231 – 243

Wennervirta JE, Ermes MJ, Tiainen M, Salmi TK, Hynninen MS, Särkelä MOK, Hynynen MJ, Stenman UH, Viertiö-Oja HE, Saastamoinen KP, Pettilä VY, Vakkuri AP. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Crit Care Med 2009; 37: 2427 – 2435

Westhall E, Rosén I, Rossetti AO, van Rootselaar AF, Wesenberg K, Friberg H, Horn J, Nielsen N, Ullén S, Cronberg T. Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol 2015; 126: 2397 – 2404

Wijdicks EF, Young GB. Myoclonus status in comatose patients after cardiac arrest. Lancet 1994; 343: 1642 – 1643

Wijdicks EF. Propofol in myoclonus status epilepticus in comatose patients following cardiac resuscitation. J Neurol Neurosurg Psychiatry 2002; 73: 94 – 95

Wijdicks EF. Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 67: 203 – 210

Wijman CAC, Mlynash M, Caulfield AF, Hsia AW, Eyngorn I, Bammer R, Fischbein N, Albers GW, Moseley M. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. Ann Neurol 2009; 65: 394 - 402

Wilhelm S, Ma D, Maze M, Franks NP. Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology 2002; 96:1485–1491

Williamson PB, Ma D, Hossain M, Franks NP, Maze M. Xenon does not cause apoptotic neurodegeneration in the neonatal rat, and protects against isoflurane-induced apoptosis (abstract). Anesthesiology 2004; 101 (suppl): A-864

Winkler DA, Thornton A, Farjot G, Katz I. The diverse biological properties of the chemically inert noble gases. Pharmacol Ther 2016; 160: 44 – 64

Witten L, Gardner R, Holmberg MJ, Wiberg S, Moskowitz A, Mehta S, Grossestreuer AV, Yankama T, Donnino MW, Berg KM. Reasons dor death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. Resuscitation 2019; 136: 93 – 99

Wolbinski M, Swain AH, Harding SA, Larsen PD. Out-of-hospital cardiac arrest patient characteristics: comparing ventricular arrhytmia and pulseless electrical activity. Heart Lung Circ 2016; 25: 639 – 644

Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol 2009; 133: 223 – 228

Wu O, Sorensen AG, Benner T, Singhal AB, Furie KL, Greer DM. Comatose patients with cardiac arrest: predicting clinical outcome with diffusion-weighted MR imaging. Radiology 2009; 252: 173 – 181

Yagi M, Mashimo T, Kawaguchi T, Yoshiya I. Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. Br J Anaesth 1995; 74: 670 – 673

Yanagawa Y, Un-no Y, Sakamoto T, Okada Y. Cerebral density on CT immediately after a successful resuscitation of cardiopulmonary arrest correlates with outcome. Resuscitation 2005; 64: 97 – 101

Yenari MA, Onley D, Hedehus M, deCrespigny A, Sun GH, Moseley ME, Steinberg GK. Diffusion- and perfusion-weighted magnetic resonance imaging of focal cerebral ischemia and cortical spreding depression under conditions of mild hypothermia. Brain Res 2000; 885: 208 – 219

Yeo SS, Choi BY, Chang CH, Kim SH, Jung YJ, Jang SH. Evidence of corticospinal tract injury at midbrain in patients with subarcachnoid hemorrahge. Stroke 2012; 43: 2239 – 2241

Young GB. The EEG in coma. J Clin Neurophysiol 2000; 17: 473 – 485

Youngquist ST, Kaji AH, Niemann JT. Beta-blocker use and the changing epidemiology of out-of-hospital cardiac arrest rhythms. Resuscitation 2008; 76: 376 – 380

Zhang K, Sejnowski TJ. A universal scaling law between gray matter and white matter of cerebral cortex. Procl Natl Acad Sci U.S.A. 2000; 97: 5621 – 5626

Xia Z, Huang Z, Ansley DM. Large-dose propofol during cardiopulmonary bypass decreases biochemical markers of myocardial injury in coronary surgery patients: A comparison with isoflurane. Anesth Analg 2006; 103: 527 – 532

Xiong W, Hoesch RE, Geocadin RG. Post-cardiac arrest encephalopathy. Semin Neurol 2011; 31: 216 – 225

Xu SY, Pan SY. The failure of animal models of neuroprotection in acute ischemic stroke to translate to clinical efficacy. Med Sci Monit Basic Res 2013; 19: 37 – 45

Zandbergen EGJ, de Haan R, Stoutenbeek CP, Koelman JHTM, Hijdra A. Systemic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998; 352: 1808 – 1812

Zandbergen EGJ, Hijdra A, Koelman HTM, Hart AAM, Vos PE, Verbeek MM, de Haan RJ for the PROPAC Study Group. Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology 2006; 66: 62 – 68

Zeiner A, Holzer M, Sterz F, Behringer W, Schörkhuber W, Müllner M, Frass M, Siostrzonek P, Ratheiser K, Kaff A, Laggner AN, for the hypothermia after cardiac arrest (HACA) study group. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Stroke 2000; 31: 86 – 94

Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, Kliegel A, Laggner AN. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001; 161, 2007 – 2012

Zeiner A, Sunder-Plassmann G, Sterz F, Holzer M, Losert H, Laggner AN, Müllner M. The effect of mild hypothermia on renal function after cardiopulmonary resuscitation in men. Resuscitation 2004; 60: 253 – 261

Zellner T, Gärtner R, Schopohl J, Angstwurm M. NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest. Resucitation 2013; 84: 1382 – 1386

Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation 1998; 98: 2334 – 2351

Zipes DP, Rubart M. Neural modulation of cardiac arrhytmias and sudden death. Heart Rhythm 2006; 3: 108 – 113

Zuercher P, Springe D, Grandgirard D, Leib SL, Grossholz M, Jakob S, Takala J, Haenggi M. A randomized trial of the effects of the noble gases helium and argon on neuroprotection in a rodent cardiac arrest model. BMC Neurology 2016; 16: 43 – 53

Sydänpysähdys aiheuttaa nopeasti hapenpuutevaurion etenkin aivoissa ja sydänlihaksessa. Onnistuneen elvytyksen jälkeisestä verenkierron palautumisesta huolimatta aivojen ja sydämen hapenpuutevaurio jatkuu (reperfuusiovaurio), jota voidaan jonkin verran rajoittaa lämpötilanhallinnalla pitämällä potilaan lämpötila 33 – 36 °C välillä ja estämällä kuumeen aiheuttama vaurion paheneminen.

Jalokaasu ksenon on anestesiakaasu, jonka on aiemmin osoitettu eri eläinmalleissa vähentävän hapenpuutteen aiheuttamaa vauriota aivoissa ja sydänlihaksessa yksin ja jäähdytyshoitoon yhdistettynä.

Tässä tutkimuksessa verrattiin ksenonin ja jäähdytyshoidon (33 °C) yhdistelmää pelkän jäähdytyshoidon vaikutukseen 110:llä kammiovärinästä elvytetyllä sydänpysähdyspotilaalla. Yhdistelmähoito vähensi sekä aivojen valkean aineen vauriota että sydänlihasvauriota enemmän kuin jäähdytyshoito yksin.

UNIVERSITY OF TURKU

Painosalama Oy, Turku, Finland 2019

ISBN 978-951-29-7798-7 (PRINT)
ISBN 978-951-29-7799-4 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)