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CEREBRAL PROTECTION IN AORTIC ARCH SURGERY WITH A SPECIAL REFERENCE TO ACUTE TYPE A AORTIC DISSECTION

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Abstract

Acute Stanford Type A Aortic Dissection (ATAAD) is one of the most life-threatening acute pathologies in the human body; without treatment mortality nears 100%. One third of ATAAD patients suffer from cerebral malperfusion, and permanent ischaemic brain injury occurs in approximately 10% of patients. ATAAD is treated with open aortic arch surgery that involves cardiopulmonary bypass (CPB) and deep or profound (18–24 °C) hypothermic circulatory arrest (HCA); they can provide sufficient cerebral protection for up to 20–30 minutes by lowering the glucose and oxygen consumption of the brain. However, additional strategies on cerebral protection are still needed.

ATAAD patients often present with shock, cardiac tamponade, malperfusion, or they could be still resuscitated while they are brought to the operation room. The rapid institution of antegrade cerebral blood flow through the CPB circuit is particularly vital for these patients and a new aortic cannulation strategy of direct true lumen cannulation after venous exsanguination (DTLC) was developed accordingly. However, associated normothermic circulatory arrest carries an inherent risk for neurologic sequalae.

Our research group has studied the field of cerebral protection in aortic arch surgery extensively for the last 20 years through the use of a porcine model that closely simulates the clinical situation. One of the most promising neuroprotective strategies that has emerged from this research has been remote ischaemic preconditioning (RIPC), which is based on the notion that applying short ischaemia-reperfusion periods to a skeletal muscle increases ischaemic tolerance in other organs including the brain. Therefore, the present thesis studied whether DTLC with a 5-minute normothermic circulatory arrest was safe in terms of cerebral ischaemia (I), if RIPC would prolong the permissible period of HCA (II), and if it would improve the neurologic outcome combined with moderate hypothermia (III).

The first study suggested that DTLC would not impair the neurologic outcome, even with a prolonged cannulation process. The second study proposed that RIPC would prolong the permissible period of HCA to up to nine minutes at 18 °C. The third study suggested that RIPC at 24 °C would provide five additional minutes of permissible HCA as compared to HCA alone at 18 °C. It also proposed that moderate HCA at 24 °C combined with RIPC would provide a superior neurologic outcome as compared to deep HCA alone at 18 °C.

Keywords: aortic arch surgery, aortic cannulation, aortic dissection, cardiopulmonary bypass, ischaemic brain injury, remote ischaemic preconditioning

Mustonen, Caius, Aivojen suojaus aortan kaaren kirurgiassa, erityisenä huomiona tyypin A aortan akuutti dissekoituma.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu;
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Tiivistelmä

Tyypin A akuutti aortan dissekoituma (ATAAD) on edelleen yksi ihmiskehon hengenvaarallisimmista akuuteista sairaustiloista. Kolmanneksella potilaista aivojen verenkierto häiriintyy ja noin 10 prosenttia potilaista saa pysyvän aivovaurion joko itse sairaustilasta tai operaatiosta johtuen. ATAAD hoidetaan sydän-keuhkokoneen avulla syvässä (18–24°C) hypotermiassa eli alilämpöisyydessä tapahtuvan verenkierron seisautuksen (HCA) aikana. HCA vähentää sekä aivojen sokeriaineenvaihduntaa että hapen käyttöä, jolloin saadaan aikaa 20–30 minuuttia kirurgiselle toimenpiteelle riippuen lämpötilasta.

ATAAD-potilaat ovat usein kriittisessä tilassa saapuessaan leikkaussaliin. Heillä voi olla verenkiertoshokki, verenkierto pääte-elimiin voi olla estynyt, tai heitä voidaan elvyttää. Erityisesti näiden potilaiden kohdalla on tärkeää edetä nopeasti kehonulkoiseen verenkiertoon sydän-keuhkokoneen avulla. Tätä varten kehitettiin uusi nousevan aortan kanylaatiomenetelmä. Potilaan verenkierto pysäytetään valuttamalla veri sydän-keuhkokoneeseen, nouseva aortta avataan ja aorttakanyyli asetetaan aorttaan näkökontrollissa (DTLC). Normaalissa kehon lämpötilassa tapahtuva verenkierron seisautus kuitenkin altistaa nopeasti neurologisille vaurioille.

Tutkimusryhmämme on tutkinut aivojen suojaamista aortan kaaren kirurgian aikana jo 20 vuoden ajan kliinisesti merkittävän kokeellisen porsasmallin avulla. Etäinen iskeeminen esialtistus (RIPC) on osoittautunut lupaavaksi aivojen suojausmenetelmäksi. Siinä raajan lihaskudokseen kohdistetaan lyhyitä verenkierron pysäytyksiä ja palautuksia tavallisella verenpainemansetilla, minkä on osoitettu lisäävän aivojen sietokykyä hapenpuutteelta.

Tässä väitöskirjassa tutkittiin, onko DTLC-kanylointimenetelmä aivojen kannalta turvallista, jos oletetaan sen kestävän viisi minuuttia (I). Lisäksi tutkimme, pidentääkö RIPC turvallista HCA:n kestoa (II) ja parantaako RIPC maltilliseen (24 °C) hypotermiaan yhdistettynä neurologista toipumista (III). Ensimmäinen tutkimus näytti, että DTLC ei vaikuta huonontavan neurologista lopputulosta. Toisen tutkimuksen perusteella RIPC pidentää turvallista HCA:n kestoa yhdeksällä minuutilla 18 asteen lämpötilassa. Kolmannen tutkimuksen mukaan RIPC pidentää turvallista HCA:n kestoa kymmenellä minuutilla 24 asteen lämpötilassa ja RIPC yhdessä maltillisen hypotermian kanssa parantaa neurologista lopputulosta.

Asiasanat: aortan dissekoituma, aortan kaaren kirurgia, aortan kanylaatio, etäinen iskeeminen esialtistus, iskeeminen aivovaurio, sydän-keuhkokone

What mankind can dream research and technology can achieve.

C. Walton Lillehei (1918-1999)

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Oulu, February 2021 Caius Mustonen

Abbreviations

A1R	Adenosine A1 receptor
AAD	Acute aortic dissection
ADP	Adenosine diphosphate
AKI	Acute kidney injury
Akt	Protein kinase B
AMP	Adenosine monophosphate
ATAAD	Acute Type A Aortic Dissection
ATP	Adenosine triphosphate
B1R	Bradykinin receptor 1
B2R	Bradykinin receptor 2
BBB	Blood-brain barrier
BDNF	Brain derived neurotrophic factor
CABG	Coronary artery bypass grafting
CBF	Cerebral blood flow
$CMRO_2$	Cerebral metabolic rate for oxygen
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
CGRP	Calcitonin gene related peptide
CPB	Cardiopulmonary bypass
CT	Computed tomography
CTD	Connective tissue disease
DTLC	Direct true lumen cannulation
eNOS	Endothelial nitric oxide synthase
EPO	Erythropoietin
ER	Endoplasmic reticulum
ERK	Extracellular-signal-regulated kinase
ETC	Electron transport chain
FET	Frozen elephant trunk
FL	False lumen
HIF-1	Hypoxia-inducible factor 1
HIF-P4Hs	Hypoxia-inducible factor prolyl-4-hydroxylases
HCA	Hypothermic circulatory arrest
I/R	Ischaemia-reperfusion
IL	Interleukin

iNOS	Inducible nitric oxide synthase
IPC	Ischaemia preconditioning
JAK/STAT	Janus kinase/signal transducers and activators of transcription
KATP	ATP-sensitive potassium
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
MI	Myocardial infarction
MMP	Matrix metalloproteinase
NADH	Reduced nicotinamide adenine dinucleotide
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NIRS	Near-infrared spectroscopy
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2-related factor 2
PaCO2	Partial pressure of carbon dioxide
PaO2	Partial pressure of oxygen
PCI	Percutaneous coronary intervention
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PET	Primary entry tear
PND	Permanent neurological deficit
Q10	Temperature coefficient
RCP	Retrograde cerebral perfusion
RIPC	Remote ischaemic preconditioning
RISK	Reperfusion injury salvage kinase
ROS	Reactive oxygen species
SA	Segmental artery
SAFE	Survivor activating factor enhancement
SCP	Selective cerebral perfusion
TND	Temporary neurological dysfunction
TNFα	Tumour necrosis factor
TL	True lumen
VEGF	Vascular endothelial growth factor

List of original publications

This thesis is based on the following publications, which are referred to their Roman numerals throughout the text by:

I Mustonen C, Honkanen HP, Lehtonen S, Tuominen H, Mäkelä T, Kaakinen T, Yannopoulos F, Anttila V, Juvonen T. (2019) Safety of direct true lumen cannulation after venous exsanguination: a study in a surviving porcine model. Eur J Cardiothorac Surg. Sep 1;56(3):451-457. doi: 10.1093/ejcts/ezz047.

II Mustonen C, Honkanen HP, Anttila T, Herajärvi J, Yannopoulos F, Mäkelä T, Kaakinen T, Anttila V, Juvonen T. (2019) Remote ischaemic preconditioning may prolong permissible period of hypothermic circulatory arrest in a porcine model. Scand Cardiovasc J. Aug;53(4):192-196. doi: 10.1080/14017431.2019.1629005.

III Mustonen C, Honkanen HP, Lehtonen S, Tuominen H, Mäkelä T, Kaakinen T, Kiviluoma K, Anttila V, Juvonen T. (2020) Moderate hypothermia with remote ischaemic preconditioning improves cerebral protection compared to deep hypothermia: a study using a surviving porcine model. Eur J Cardiothorac Surg. Aug 1;58(2):269-276. doi: 10.1093/ejcts/ezaa065.

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1 Introduction

The brain is the most vulnerable organ to ischaemia because of its high glucose metabolism and oxygen demand; it requires continuous blood flow to function properly. Even a short period of circulatory arrest in normal temperatures results in the initiation of an ischaemic cascade, which ultimately leads to cell death. However, recovery of blood flow after a serious ischaemic incident often makes matters worse through the infliction of an ischaemia-reperfusion (I/R) injury (Ankarcrona et al., 1995; Carden & Granger, 2000).

Aortic arch surgery is used to treat pathologies involving the proximal aorta, such as Stanford acute type A aortic dissection (ATAAD) and aortic arch aneurysms. Both the underlying aortic pathology and the surgical procedure compromise the cerebral blood flow (CBF). Shock, cardiac tamponade, and arch vessel obstruction are related to ATAAD itself while cerebral ischaemia results also from the cessation or alteration of CBF that is often needed for the subsequent repair (Easo et al., 2012; Krüger et al., 2012; Krüger et al., 2011).

Hypothermia has been the primary cerebral protection strategy since the progression of aortic arch surgery in the 1960s and 1970s as it was noted that it decreased cellular metabolic activity and increased neurons' tolerance to ischaemia (Griepp, Stinson, Hollingsworth, & Buehler, 1975). Hypothermia is achieved through the use of a cardiopulmonary bypass (CPB) circuit with a heat exchanger. When CPB was first introduced in the 1950s, it revolutionised cardiac surgery, and ultimately enabled the invention of aortic arch surgery (Gibbon, Miller, Dobell, Engell, & Voigt, 1954). In the 1970s, Griepp et al. became the first to implement hypothermic circulatory arrest (HCA) during aortic arch surgery on a larger scale. HCA was initiated by lowering patients' core temperatures to a profound hypothermia of 12-18 °C. The circulation was then interrupted in order to create a clear, bloodless operating field. After the repair, blood flow was restored and the patient was warmed to normothermia (Griepp et al., 1975).

Soon afterwards, it was noted that even deep and profound HCA is not completely safe as risk for neurologic sequalae seemed to increase after 30-35 minutes of HCA (Ergin, O'Connor, Guinto, & Griepp, 1982). McCullough et al. demonstrated the permissible periods of HCA for each temperature and found that the safe period of arrest was only 31 minutes at 15 °C (McCullough et al., 1999). These findings led to an understanding that hypothermia alone may not offer sufficient cerebral protection, especially in mild to moderate temperatures. Selective cerebral perfusion (SCP) was therefore introduced into aortic arch

surgery in the 1990s. It provided antegrade blood flow to the brain during all phases of the surgery, even when the aorta was opened (Bachet et al., 1991; Guilmet et al., 1986; Kazui, 1986). However, SCP has been shown to have its own pitfalls; it requires an additional cannulation site, clamping of the fragile arch vessels, and its use might lead to increased cerebral oedema and embolic load, especially in inexperienced hands or fragile aortas during ATAAD surgery.

Another challenge in ATAAD surgery is the arterial cannulation site; the aortas are fragile and situations emerge as the patients experience shock, tamponade, or malperfusion, or upon resuscitation in the operating room. Traditional cannulation strategies, namely axillary and femoral artery cannulation, are often used, but they are associated with certain weaknesses that might prove detrimental for ATAAD patients. These include the additional incision, graft suturing, and possibility of de novo dissection or propagation with axillary cannulation (Fleck et al., 2006; Imanaka et al., 2000; Schachner, Nagiller, Zimmer, Laufer, & Bonatti, 2005) as well as retrograde embolization, aggravation of malperfusion, and inadequate proximal aortic flow with femoral artery cannulation (Conzelmann et al., 2016; Immer et al., 2008; Kamiya et al., 2009). Therefore, a bailout cannulation strategy was introduced. It is performed by exsanguinating the patient into the venous reservoir, transecting the ascending aorta, and inserting the aortic cannula using vision control (Conzelmann et al., 2009; Jakob et al., 2007). This is referred to as direct true lumen cannulation after venous exsanguination (DTLC) and it has been shown to be a feasible strategy, even in extremely unstable patients. It carries an inherent risk for ischaemic brain injury due to causing normothermic circulatory arrest, but studies have proven its non-inferiority regarding cerebral events as compared to other cannulation methods (El Beyrouti et al., 2020; Kitamura et al., 2018).

In the 1980s, Murry et al. found out that applying cycles of brief periods of ischaemia and reperfusion to the myocardium provided protection from a later-occurring, more severe ischaemia in that same area; this technique is called ischaemic preconditioning (IPC) (Murry, Jennings, & Reimer, 1986). It was soon determined that preconditioning a different part of the myocardium would provide protection from a later-occurring, severe ischaemia in other parts of the myocardium (Przyklenk, Bauer, Ovize, Kloner, & Whittaker, 1993). This paved the way for remote ischaemic preconditioning (RIPC), as it was found that applying cyclic ischaemia-reperfusion to a skeletal muscle would provide protection for the heart, the brain, and the kidneys (Dave, Saul, Prado, Busto, & Perez-Pinzon, 2006; Kharbanda et al., 2002).

The first clinical studies regarding RIPC in cardiac protection were promising. However, large, randomized, controlled multi-centre cardiac surgery trials did not find positive effects in terms of myocardial or kidney protection (Hausenloy et al., 2015; Meybohm et al., 2015). It is important to note, however, that these trials had some issues, as the studied patients had significant co-morbidities and anaesthesia protocols interfered with the results. The optimal patient population in terms of benefitting from RIPC is still unknown and clinical studies regarding cerebral protection in cardiac and aortic surgery have not yet been published. Results from previous large animal studies have postulated that RIPC would preserve cerebral oxygen tension, improve cerebral recovery, and protect the brain from an ischaemic insult after HCA (Jensen et al., 2011; Yannopoulos et al., 2012; Yannopoulos et al., 2010). Improvements in respiratory chain function, brain metabolism, immune response, and antioxidant response were also noted (Herajärvi et al., 2017; Yannopoulos et al., 2014).

The present thesis sought to study cannulation and cerebral protection strategies specifically in terms of ATAAD surgery with a special reference to unstable patients that undergo surgery in low-volume centres. As the use of SCP has gained superiority over HCA in longer, elective aortic arch operations, the use of HCA is now mainly limited to hemiarch replacement in emergent ATAAD patients, as it is simple to apply and can be performed in less than 30 minutes. The first study (I) aimed to prove that DTLC would be a safe cannulation method in terms of both cerebral and global ischaemia, even when the circumstances were so scarce that it would take five minutes of normothermic ischaemia to complete it. The second study (II) investigated whether RIPC could significantly extend the permissible period of HCA. The third study (III) was based on the results of the second, which showed that moderate hypothermia with RIPC would provide equal cerebral protection as deep hypothermia control group. Therefore, a comparison of the neurological outcomes of those groups was conducted in study III. The cellular mechanisms of RIPC were not studied but the basic principles are presented in the literature review.

2 Review of literature

2.1 The human brain

The central nervous system (CNS) is divided into two components, the brain and the spinal cord. The brain is then anatomically divided into three different sections, the cerebrum, the cerebellum, and the brain stem. The cerebrum consists of two hemispheres that are further divided into frontal, parietal, occipital, and temporal lobes. The pons, the medulla oblongata, and the midbrain form the brain stem.

2.1.1 Anatomy

The brain consists of neurons and neuroglial cells that form grey and white matter. The grey matter consists of neuronal somas as well as myelinated and non-myelinated axons. Neuroglial cells in the grey matter include astrocytes, oligodendrocytes, and microglial cells. In contrast, the white matter includes all the above, except for the neuronal somas.

The body of a neuron is called the soma; it contains the nucleus and the perikaryon. Multiple extensions, called dendrites, connect the soma to other neurons. Each neuron has only one axon, which transmits the neural impulse forward to the next neuron. This axon can be myelinated or non-myelinated. In the CNS, myelin is produced by oligodendrocytes.

Oligodendrocytes are abundant in the brain. They are located near the perikaryon in the grey matter but near the myelinated axons in the white matter. Oligodendrocytes can take part in the myelinisation of several axons, unlike the Schwann cells in the peripheral neural system. They have the most active cellular metabolism in the CNS and therefore are the most susceptible cells to ischaemia (Connor & Menzies, 1996; McTigue & Tripathi, 2008).

Astrocytes are neuroglial cells that have multiple branches in perivascular contact with the endothelial cells, making them part of the blood-brain barrier (BBB). They also participate in ion, neurotransmitter, and metabolism product homeostasis (Chen & Swanson, 2003; Parpura et al., 2012; Zonta et al., 2003). They make up most of the brains mass and offer mechanical support to the neurons. There are two types of astrocytes, protoplasmic and fibrous; the former is in the grey matter while the latter is in the white.

Microglial cells act as macrophages of the CNS. They are activated by cellular damage, pathogens, and proinflammatory cytokines. In the event of activation, they can rapidly proliferate and migrate to prevent further damage from happening. However, ischaemic cellular injury can also lead to the overactivation of microglial cells, exacerbating the injury (Brown & Vilalta, 2015; Yenari, Kauppinen, & Swanson, 2010).

One form of neuroglial cell is the ependymal cell, which is a neuroepithelial cell. These cells do not have basement membrane; they are connected to astrocytes, which provide mechanical support, and cover the inside of cerebral ventricles.

2.1.2 Blood flow

Blood is directed to the brain by four vessels, the left and right internal carotid arteries and the left and right vertebral arteries. Approximately 70% of the CBF comes from internal carotid arteries (Willie, Tzeng, Fisher, & Ainslie, 2014).

The brain is the most vulnerable organ to ischaemia; it requires 50ml/100g of blood flow every minute. Therefore, approximately 20% of the cardiac output (CO) must be directed to the brain to ensure that it functions properly (Willie et al., 2014). The same cerebral blood flow must be achieved in various hemodynamical circumstances to avoid excessive or insufficient blood flow, which can cause oedema, hypoxia, or ischaemia, respectively. Thus, explicit regulation systems, also called autoregulation, have formed. This autoregulation ensures that the CBF remains the same with mean arterial pressures (MAP) of 60-170 mmHg (Iadecola & Nedergaard, 2007).

CBF is equal to cerebral perfusion pressure (CPP) times cerebral vascular resistance, which is inflicted by arteriole and capillary vasoconstriction or vasodilation due to metabolic factors such as partial pressures of carbon dioxide (PaCO2), oxygen (PaO2), and pH (Gottesman et al., 2012; Kety & Schmidt, 1948; Mandell et al., 2008; Mardimae et al., 2012; Metry et al., 1999). Cerebral perfusion pressure, however, is defined as the difference between MAP and intracranial pressure. In summary, CBF is regulated by metabolic and myogenic factors. Autoregulation is systemically present in the vasomotor nervous system through arteries and arterioles, but is also present locally, in capillaries.

The aorta

The aorta is the largest artery in the human body. It emerges from the heart and extends all the way up to lumbar level, giving rise to two common iliac arteries. It consists of intimal, medial, and adventitial layers. Circulation within the aorta is distributed from the vasa vasorum in the adventitial layer; inflammation or stenosis in these vessels damages the connective tissue in the aortic wall, often leading to dilatation, thinning, and sclerosis (Borges et al., 2010; de Figueiredo Borges et al., 2008; Erbel et al., 2001). Other risk factors for these effects are fluoroquinolone use (Carino, Zafar, Singh, Ziganshin, & Elefteriades, 2019) and connective tissue disorders (CTD) such as Marfan syndrome (Wisler et al., 2015), Loyes-Dietz syndrome (Loeys et al., 2005), Ehlers-Danlos syndrome (Regalado et al., 2011), and Turner syndrome (Matura, Ho, Rosing, & Bondy, 2007). A bicuspid aortic valve and a family history of aortic dissection or dilatation are also known risk factors (Cury, Zeidan, & Lobato, 2013; Faggion Vinholo et al., 2019; Saeyeldin, Ziganshin, Zafar, & Elefteriades, 2019).

The aorta is anatomically divided into different sections, the ascending aorta, the aortic arch, and the descending aorta. The ascending aorta consists of Valsalva sinuses that include coronary ostia, the sinotubular junction, and the tubular part of the ascending aorta, which ends at the level of the brachiocephalic trunk. The aortic arch is located between the ascending and descending aortas and consists of the lesser and greater curvatures. The greater curvature gives rise to the brachiocephalic trunk, which, in turn, divides into the right subclavian and the right common carotid arteries. The left common carotid artery and the left subclavian artery originate from the greater curvature. The descending aorta begins after the left subclavian artery; it has both thoracic and abdominal sections and is divided by the diaphragm. The thoracic section gives rise to segmental arteries (SA) and the abdominal part to the visceral vessels. The thoracic aorta is divided into zones 0-4, which describe the extent of dissection or the surgical procedure. A graphical illustration of thoracic aortic zones and vessels is presented in Figure 1.

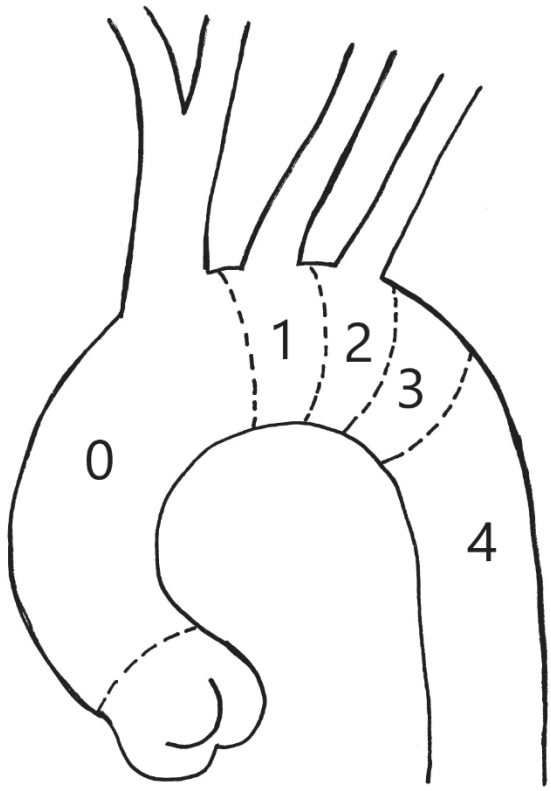

Fig. 1. The human aortic arch and the zones therein.

2.1.3 Oxygen metabolism

Neurons and neuroglial cells have a high metabolic rate and therefore are in continuous need of glucose and oxygen; their metabolism is optimal in aerobic conditions, they cannot produce glucose themselves, and the storing capacity of glucose in glycogen is limited in the brain (Falkowska et al., 2015). The primary mode of energy on the cellular level is adenosine triphosphate (ATP), which is produced from adenosine diphosphate (ADP) and a phosphate ion (Pi) through either glycolysis or oxidative phosphorylation (Berg, Tymoczko, & Stryer, 2002; Lodish et al., 2000). The most effective way to produce ATP is the electron transport chain (ETC) in the mitochondria, but this requires glucose and oxygen (Berg et al., 2002; Lodish et al., 2000).

Glycolysis is a chemical reaction that does not need oxygen. In glycolysis, glucose is converted into pyruvate by a chain of enzymes and two molecules of ATP are released in the process. In aerobic conditions, the reaction will continue down a tricarboxylic acid chain as pyruvate is converted to acetyl coenzyme A. In this tricarboxylic acid chain, three molecules of nicotinamide adenine dinucleotide (NADH), one molecule of flavin adenine dinucleotide, and one molecule of guanosine triphosphate are produced from acetyl coenzyme A and oxygen while CO2 is released as a waste product. NADH and flavin adenine dinucleotide are then oxidized through oxidative phosphorylation, producing 36 molecules of ATP (Berg et al., 2002; Lodish et al., 2000).

2.1.4 Differences in the porcine brain

The porcine brain has an unequivocally better resemblance to the human brain than the traditional model, the rat brain. The porcine brain has gyrii and the topography of the brain cortex is quite similar to that of the human brain (Lind et al., 2007). The porcine brain is also approximately 50 times larger than the rat brain (Lind et al., 2007). In addition, its vascular and histopathological anatomy is close to that of humans; its white/grey matter ratio is also similar (Zhang, K. & Sejnowski, 2000). However, the porcine aortic arch gives rise to only two arch vessels as compared to the human aortic arch's three, the bi-carotid brachiocephalic trunk and the left subclavian artery.

2.2 Ischaemic damage to the brain

Ischaemic damage to the brain results from inadequate blood flow. Ischaemia can be anoxic if oxygen is not present at all or hypoxic if the oxygen level is decreased to such a level that it cannot meet oxygen consumption needs. Hypoxic injuries begin to accumulate when CBF decreases below 20ml/100g/min (Obrenovitch et al., 1988). The resulting ischaemic brain injury can be global, as in cardiac arrest or in HCA, or focal, as in atrial fibrillation, induced thromboembolism, or plaque-induced thrombosis in cerebral vessels (Howard, R. S., Holmes, & Koutroumanidis, 2011; Janardhan & Qureshi, 2004). The former manifestation of cerebral ischaemia is examined in these studies.

Recent stroke studies have revealed that a restriction of blood flow to below 12ml/100g/min in the grey matter leads to critical ischaemia and, therefore, the occurrence of irreversible ischaemic damage over the next few hours. However, if

blood flow to the grey matter is between 12-18ml/100g/min, the ischaemic damage can be reversed through early thrombectomy, thrombolysis, or systemic vasopressors (Donnan, Baron, Ma, & Davis, 2009).

2.2.1 Pathogenesis of the ischaemic brain injury

The ischaemic cascade commences after only one to three minutes of cerebral ischaemia, eventually leading to neuronal death if blood flow is not rapidly restored to an adequate level. As previously mentioned, CBF of 20ml/100g/min is the threshold, after which point oxidative phosphorylation is compromised, leading to the accumulation of lactate, acidosis, and lack of ATP production (Obrenovitch et al., 1988). As a result, the ATP-dependant Na^+/K^+-ATPase loses its function, which leads to alterations in the resting potential of the cell membrane, anoxic depolarisation, and accumulation of intracellular Na^+ and excess fluid due to the iso-osmotic gain of H_2O. The Na^+/Ca^{2+} exchanger pumps Na^+ out of the cell in order to reverse this, resulting in excess intracellular Ca^{2+}. This then leads to an even more depolarized cell membrane as glutamate spillage from neurons is increased (Taxin, Neymotin, Mohan, Lipton, & Lytton, 2014; Wroge, Hogins, Eisenman, & Mennerick, 2012). Meanwhile, the lack of ATP has led to the accumulation of lactate and H^+ in the cell; transportation of these molecules is impaired due to ionic pump dysfunction. Acidosis adds insult to injury by promoting reactive oxygen species (ROS) production, enhancing glutamate excitotoxicity, and impairing the effect of antioxidants (Lewerenz, Dargusch, & Maher, 2010; Siesjö, Katsura, Kristián, Li, & Siesjö, 1996). A summary of the ischaemic cascade is presented in Figure 2 and discussed in more detail below.

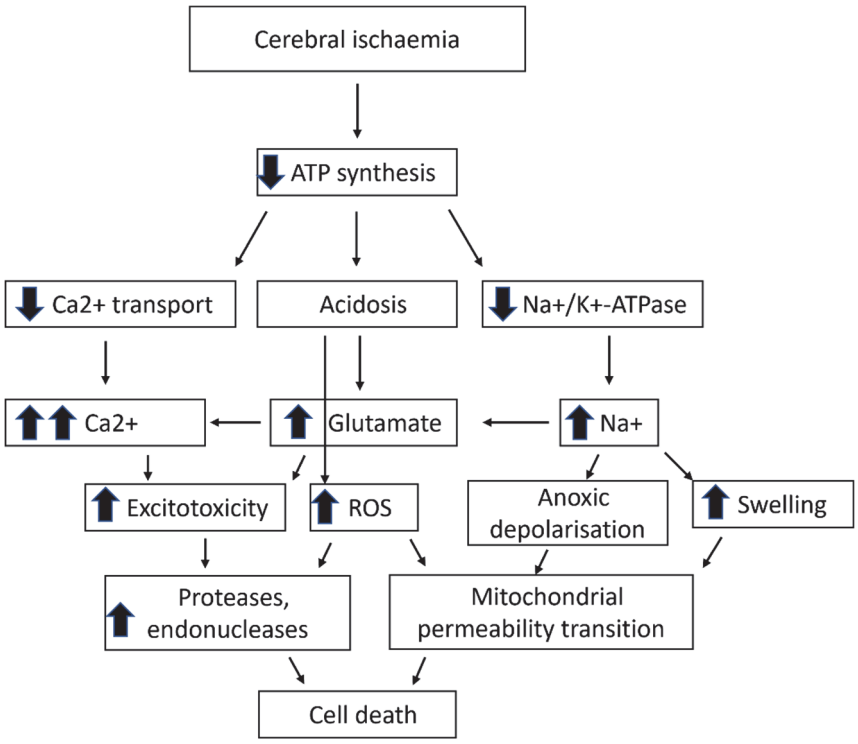

Fig. 2. Simplified illustration of the ischaemic cascade in the brain. ROS = Reactive oxygen species.

Glutamate

Furthermore, intracellular Ca^{2+} increases due to glutamate-specific receptors like the N-methyl-D-aspartate (NMDA) receptor, which is highly permeable to Ca^{2+}. The extrasynaptic glutamate overstimulates the NMDA receptor; the Na^{+}/Ca^{2+} exchanger remains activated due to anoxic depolarisation occurring simultaneously, leading to excess intracellular Ca^{2+} (Brittain et al., 2012; White, R. J. & Reynolds, 1996). As the Na^{+}/K^{+}-ATPase loses its function, extracellular K^{+} increases. This leads to decreased reuptake of glutamate and increased efflux of glutamate in the neuronal synapses, increasing cytosolic Ca^{2+} (Longuemare et al., 1999; Zhang, L.N., Sun, Wang, & Gao, 2016).

There have been attempts to inactivate the NMDA receptor by using NMDA-receptor antagonists to prevent Ca^{2+}-induced brain injury, but the complexity of the

Ca^{2+} influx has rendered these trials ineffective (Davis, Albers, Diener, Lees, & Norris, 1997; Davis et al., 2000; Rimpiläinen et al., 2001).

Calcium

Optimal intracellular concentration of Ca^{2+} is crucial for the proper function of neurons, and so its release and uptake are carefully regulated. Storing of Ca^{2+} occurs mainly in mitochondria, lysosomes, and the endoplasmic reticulum (ER) (Burgoyne & Haynes, 2015).

During anoxic depolarisation, excess intracellular Ca^{2+} is primarily influxed via the aforementioned routes, the Na^{+}/Ca^{2+} exchanger, and the NMDA receptor (Pignataro et al., 2004; Sattler, Charlton, Hafner, & Tymianski, 1998). In addition, the increased Ca^{2+} influx activates Phospholipase-C signalling pathways, leading to the release of intracellular stores of Ca^{2+} from the mitochondria and ER (Kim, J. K. et al., 2011; Paschen & Doutheil, 1999; Schinder, Olson, Spitzer, & Montal, 1996)

The excess Ca^{2+} contributes to ischaemic brain injury by increasing neuronal oxygen consumption and further impairing homeostasis in already nutrition depleted circumstances (Gleichmann, Collis, Smith, & Mattson, 2009; Wang, G. J., Randall, & Thayer, 1994). Furthermore, increased intracellular Ca^{2+} has been shown to promote the production of ROS and therefore induce mitochondrial dysfunction (Carriedo, Yin, Sensi, & Weiss, 1998; Lipton, 2006). This causes mitochondrial swelling, alterations in membrane potential, and leakage of pro-apoptotic factor resulting from the mitochondrial permeability transition (Liu, Kim, Yang, Jemmerson, & Wang, 1996; Zoratti & Szabò, 1995). Increased intracellular Ca^{2+} has also been shown to independently induce cell death by activating secondary pathways (Hamilton, Kolodziejczyk, Kougioumtzidou, & Attwell, 2016; Schanne, Kane, Young, & Farber, 1979). Additionally, Ca2+ has been shown to activate pathways related to calpain, caspase, phospholipase, and nitric oxide (NO) production (Higuchi et al., 2005; Lai, Zhang, & Wang, 2014; Orrenius, Zhivotovsky, & Nicotera, 2003; Peters-Golden, Song, Marshall, & Brock, 1996).

Mitochondrial dysfunction

Mitochondria are essential to the survival of neurons; their failure leads to neuron cell death almost uniformly. The ischaemic cascades that have been initiated in the

cytosol, in the cell membranes, or in the neuronal synapses reach their final effect in the mitochondria (Budd & Nicholls, 1998).

The excess Ca^{2+} in the cytoplasm enters the mitochondria through an uniport because of the negative membrane potential (White, R. J. & Reynolds, 1997). The positive ion current resulting from excess Ca^{2+} in the mitochondria inhibits oxidative phosphorylation, leading to lower production of ATP and the inhibition of Ca^{2+} efflux pumps (White, R. J. & Reynolds, 1996). The increased concentration of Ca^{2+} in the mitochondria leads to the disruption of membrane potential, which then leads to a transition in mitochondrial permeability, pore opening, and the interruption of ETC. Concurrently, pro-apoptotic factors and apoptosis inducing factor are leaked through mitochondrial permeability transition pores while antioxidants like glutathione leak out of the mitochondria (Kroemer & Reed, 2000; Schild & Reiser, 2005; Starkov, Chinopoulos, & Fiskum, 2004). The interruption of ETC simultaneously results in free electron radicals, leading to ROS and NO production (Rego, Santos, & Oliveira, 2000).

Calpains

Calpains are cysteine proteases that are present in the cytoplasm. They are calcium regulated and calpastatin binds reversibly to calpains in physiologic conditions, preventing them from functioning. Their main function is to regulate the cell cycle and apoptosis (Jánossy et al., 2004). During anoxic depolarisation, increases in Ca^{2+} concentration leads to the inactivation of calpastatin and therefore the activation of calpains (Zadran, Bi, & Baudry, 2010). As they are activated, they degrade the cytoskeleton and neurofilaments, ultimately leading to either cell apoptosis or necrosis, depending on the situation (D'Orsi et al., 2012).

Reactive oxygen species and nitric oxide

Oxygen is impartially reduced as the mitochondrial ETC chain deteriorates. This results in the production of oxidizing molecules, such as hydrogen peroxide, superoxide anion, and NO (Boveris & Chance, 1973). These molecules are known as ROS. They are also produced under normal conditions but endogenous antioxidants such as superoxide dismutase 2 and nuclear factor erythroid 2-related factor 2 (Nrf2) can outweigh the oxidative stress (Itoh et al., 1999; Keller et al., 1998; Niizuma, Endo, & Chan, 2009; Niizuma et al., 2009). However, in unsteady circumstances, such as during ischaemia and excess Ca^{2+} accumulation, the

antioxidative defence mechanisms can fail to outweigh the excess ROS formation. This leads to lipid peroxidation, protein oxidation, and DNA oxidation, ultimately resulting in cell injury and death (Chan, 1994; Chan, 2001).

NO is an essential mediator in neurotransmission and a key regulator of cerebral perfusion (Iadecola, 1997). It is produced by the endothelial nitric oxide synthase (eNOS) in the blood vessels, inducible nitric oxide synthase (iNOS) in the immune system (macrophages), and neuronal nitric oxide synthase (nNOS) in the neurons (Bredt & Snyder, 1990; Bredt, 1999; Lamas, Marsden, Li, Tempst, & Michel, 1992; Xie et al., 1992). However, the effects of NO rely on its concentration. In low levels, it acts as a neuroprotective agent that promotes cell survival, but higher concentrations can lead to apoptosis or necrosis (Kim, Y. M., Talanian, & Billiar, 1997; Thomas et al., 2008). NO itself has an ability to form reactive nitrogen species with ROS, potentially inducing oxidative stress and promoting cell apoptosis (Bian, Gao, Weisbrodt, & Murad, 2003).

The nNOS is activated by excess Ca^{2+} in the cytoplasm, causing NO to accumulate in the neurons (Lipton et al., 1993). The high concentration of NO also exacerbates the Ca^{2+} influx by releasing the ER supplies; this causes ER stress and leads to apoptosis via the ER stress pathway (Oyadomari et al., 2001). It has also been shown that high concentrations of NO inhibit mitochondrial ETC and promote glutamate release, creating a vicious cycle that leads to neuronal death (Brown, 2010).

Neuronal apoptosis and necrosis

Depending on the severity of the ischaemic insult and the level of Ca^{2+} and glutamate exposure, the neurons can undergo cell death through either apoptosis or necrosis (Ankarcrona et al., 1995). The former occurs in normal tissue development as redundant and defective neurons undergo a systematic process of cell shrinkage, DNA fragmentation, and preservation of the cellular components in the apoptotic bodies, which can then be phagocytosed. The process is active, controlled, and requires ATP to be completed (Kerr, Wyllie, & Currie, 1972; Leist, Single, Castoldi, Kühnle, & Nicotera, 1997). Necrosis, on the other hand, is an uncontrolled event resulting from membrane lysis, swelling, and the leakage of proteolytic enzymes and excitatory amino acids. There is a significant difference in the immune response to these two forms of cell death; apoptosis elicits minor changes (Savill, 1997) while necrosis leads to neutrophil activation and the release of pro-inflammatory cytokines. As apoptosis and necrosis are often present concurrently

in the neuronal cultures after an ischaemic insult, it has been hypothesized that ischaemic excitotoxic brain injury is more of a continuum and coexistence of these two rather than an either/or situation (Shimizu, S. et al., 1996; Wang, Y. & Qin, 2010; Yamashima & Oikawa, 2009).

2.2.2 Ischaemia-reperfusion injury in the brain

As previously discussed, ischaemia triggers pathways that lead to neuronal death or necrosis, depending on the severity of the ischaemic insult in terms of duration, temperature, and level of CBF (Ankarcrona et al., 1995). Therefore, limiting the duration of the ischaemic insult is the key to cerebral protection in clinical situations. However, other harmful processes are initiated when the CBF is restored. Restoration of blood flow accelerates the necrosis that began during the ischaemic insult (Jennings, Sommers, Smyth, Flack, & Linn, 1960). As the mitochondrial membranes, the integrity of the ETC chain, and permeability pumps are compromised, reperfusion leads to excessive amounts of ROS production, which, in turn, adds to the oxidative stress burden (Granger, Rutili, & McCord, 1981; Seet et al., 2011). The addition of reperfusion to the ischemic injury makes it an I/R injury (Pundik, Xu, & Sundararajan, 2012). Necrosis is exacerbated by the reperfusion injury and so the inflammatory response increases significantly, leading to an entirely different pathway (Kvietys & Granger, 2012).

Cells and mediators of cerebral innate immune response

The rapidly acting part of human immune system is called innate immunity. The main cells responsible for the innate immune response in the brain are microglial cells, perivascular macrophages, mast cells, blood monocytes, and neutrophils (Iadecola & Anrather, 2011). The microglial cells reside in the brain parenchyma. Excess purine in the intercellular space activates microglial cells to differentiate toward the pro-inflammatory M1 phenotype that produces both pro-inflammatory cytokines and ROS (Davalos et al., 2005; Nimmerjahn, Kirchhoff, & Helmchen, 2005). However, the M2 phenotype produces anti-inflammatory cytokines, vascular endothelial growth factor (VEGF), brain-derived neurotropic factor (BDNF), platelet-derived growth factor, and progranulin, suppressing the inflammatory response and promoting regeneration (Hanisch & Kettenmann, 2007; Kanazawa, Ninomiya, Hatakeyama, Takahashi, & Shimohata, 2017; Lo, 2010). Perivascular macrophages are located between the brain vasculature and the

parenchyma (Bechmann et al., 2001). They have the same M1-M2 phenotyping as microglial cells but a slightly wider range of secreted substances. Macrophage signalling is thought to be the main force driving inflammatory cells to the post-ischemic area (Konsman, Drukarch, & Van Dam, 2007). Mast cells are responsible for the early vasodilatation, neutrophil accumulation, and BBB disruption that takes place after I/R by secreting histamine, cytokines, heparin, and proteases (Lindsberg, Strbian, & Karjalainen-Lindsberg, 2010; Strbian, Karjalainen-Lindsberg, Tatlisumak, & Lindsberg, 2006). Neutrophils reside in the circulation and the vascular bed but transmigrate rapidly to the ischaemic area via adhering and cytokine signalling. They are capable of both secreting substances from their granules and vesicles and phagocytosis. They elicit a strong inflammatory response by secreting iNOS, NADPH oxidase, myeloperoxidase, matrix metalloproteinase 8 (MMP8), MMP9, elastase, and cathepsins (Borregaard, 2010; Yilmaz & Granger, 2010).

Cytokines are small glycoproteins that participate in the inflammatory response. They can be either pro-inflammatory or anti-inflammatory depending on their activation pathway. The most important pro-inflammatory cytokines are tumour necrosis factor α (TNFα), interleukine-1β (IL-1β), IL-12, and IL-23 while IL-6, IL-10, and tumour growth factor β (TGFβ) are the most important anti-inflammatory examples (Iadecola & Anrather, 2011). Chemokines, such as the chemokine (C-X-C motif) and chemokine (C-C motif) ligand families, are responsible for attracting blood-borne inflammatory cells to the injury site (Iadecola & Anrather, 2011; Kim, J. S. et al., 1995). The final activation and migration to the nervous tissue of blood-borne inflammatory cells is done by cellular adhesion molecules in the endothelium. There are three main types: selectins, integrins, and the immunoglobulin gene superfamily. These substances, along with the previously mentioned proteases, enzymes, and growth factors, form the mediators of the post-ischemic inflammatory response (Rallidis et al., 2009; Zhang, R., Chopp, Zhang, Jiang, & Powers, 1998).

Innate immune response to cerebral ischaemia-reperfusion injury

Necrotic neurons leak proteolytic enzymes, ROS, and purine nucleotides to the intercellular space. These substances then trigger an innate immune response similar to the reaction to invading pathogens such as bacteria (Kvietys & Granger, 2012).The microglial cells are the first to respond to excess amounts of ROS, glutamate, and purine nucleotides. The M1 microglial cells release TNFα, IL-1β,

and ROS (Iadecola & Anrather, 2011). These factors attract perivascular M1 macrophages that begin to produce IL-1β, IL-12, IL-23, TNFα, chemokines, ROS, and NO (Konsman et al., 2007). I/R injury to cerebral vasculature can simultaneously lead to blood clotting, platelet aggregation, and cytokine release (Carden & Granger, 2000; del Zoppo, Schmid-Schönbein, Mori, Copeland, & Chang, 1991; Eltzschig & Carmeliet, 2011). This results in excess E- and P-selectin in the endothelial surface (Yilmaz & Granger, 2010), which, along with local vasoconstriction, creates an optimal adhesion and transmigration platform for neutrophils (Engelhardt & Sorokin, 2009; Ishikawa, Zhang, Nanda, & Granger, 2004; Yemisci et al., 2009). Neutrophils release MMPs, ROS, and NO, which, together with mast cell secretion, disrupt the BBB, leading to oedema, neutrophil invasion, and increased release of pro-inflammatory cytokines and chemokines into the bloodstream and brain parenchyma. This eventually creates a vicious cycle, which exacerbates the ischaemic brain injury by adding the proteolytic and oxidative burden (Iadecola & Anrather, 2011; Konsman et al., 2007; Lindsberg et al., 2010).

2.2.3 Innate neuroprotective response to ischaemia

Several protective mechanisms have evolved to assist with adaptation into different conditions and balancing out the negative effects of cerebral hypoxia and ischaemia. The same factors that initiated the cascade of ischaemic injury induce the production of protective proteins and activate cellular defence mechanisms against oxidative stress, innate inflammatory response, and oxygen and glucose depletion (Sprick, Mallet, Przyklenk, & Rickards, 2019). Graphical illustration of these factors is presented in Figure 3 and discussed below.

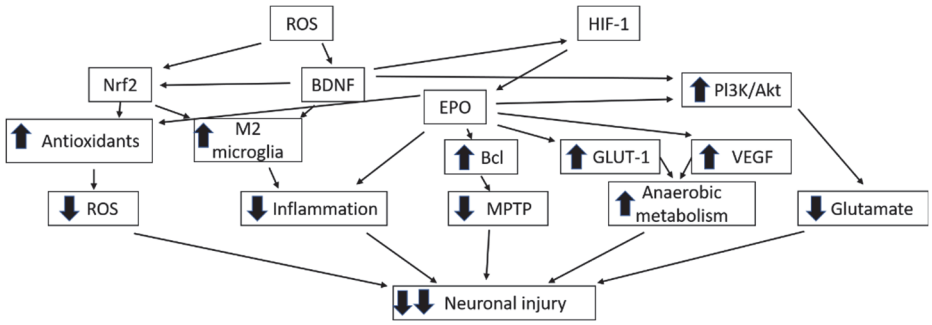

Fig. 3. Simplified overview of the innate neuroprotective response to ischaemia. Akt = protein kinase B, Bcl = B-cell lymphoma associated peptides, BDNF = brain derived neurotrophic factor, EPO = erythropoietin, GLUT-1 = glucose transporter 1, HIF-1 = hypoxia inducible factor 1, MPTP = mitochondrial permeability transition pore, Nrf2 = nuclear factor erythroid 2-related factor 2, PI3k = phosphoinositide 3-kinase, ROS = reactive oxygen species, VEGF = vascular endothelial growth factor.

Nitric oxide, phosphatidylinositol 3-kinase-Akt, and pro- and anti-apoptotic proteins

As discussed earlier, NO is vital but can also be harmful to neurons depending on its source and quantity (Kim, Y. M. et al., 1997; Thomas et al., 2008). Studies have revealed that moderate NO formation is beneficial during cerebral ischaemia but only when it is produced from eNOS. Harmful effects were noted when NO was primarily produced from nNOS and iNOS (Gidday et al., 1999; Malyshev et al., 1999). Phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) mediate NO-induced neuronal protection in the astrocytes by initiating the synthesis of glutamate-transporter-1 (Li, L. B. et al., 2006). Glutamate transporter-1 acts as a Na^+-glutamate symport that prevents glutamate excitotoxity by clearing the glutamate out of the synapses. Studies have suggested that glutamate transporter-1 is conserved in hypoxia and that it could be an important factor in attenuating ischaemic cerebral injury (Gao et al., 2008; Geng et al., 2008; Gong et al., 2016). B-cell lymphoma proteins play an important role in modulating apoptosis and controlling mitochondrial membrane pores. Moderate hypoxia has been shown to increase the expression of B-cell lymphoma proteins and to protect against neuronal apoptosis (Rybnikova, Sitnik, Gluschenko, Tjulkova, & Samoilov, 2006; Wu, Yu, Ma, & Liu, 2015).

Hypoxia-inducible factor-1 (HIF-1)

In normal circumstances, hypoxia-inducible factor-1 (HIF-1) is deactivated with the degradation of HIF-1's α subunit by HIF prolyl-4-hydroxylases (HIF-P4Hs). However, the function of HIF-P4Hs is inhibited in hypoxic and ischaemic conditions, which leads to the stabilization of HIF-1α and a functional HIF-1 heterodimer (Myllyharju, 2008; Wang, G. L., Jiang, Rue, & Semenza, 1995; Zhang, L. et al., 2009). Neuronal resistance to oxidative stress and ischaemia is markedly improved in this case, as stabilization of HIF-1 leads to increased expression of the GLUT1 glucose transporter, augmentation of glycolytic enzymes, VEGF, and erythropoietin (EPO). These factors promote anaerobic metabolism, angiogenesis, neurogenesis, and cytoprotection (Brix, Mesters, Pellerin, & Jöhren, 2012; Lim, D. C. et al., 2016; Ran, Xu, Lu, Bernaudin, & Sharp, 2005; Zhu et al., 2014).

Erythropoietin

EPO is also released by hypoxic astrocytes, along with the HIF-1 pathway (Marti et al., 1996). EPO has numerous positive effects on the neurons as it attenuates excitotoxic and ischaemic injury (Costa et al., 2013; Wang, R. et al., 2017). EPO activates the B-cell lymphoma-pathway (Wen et al., 2002), enhances anti-inflammatory and antioxidant protein production (Genc, Egrilmez, & Genc, 2010), and increases eNOS production (Buckley, Li, & Whorton, 2008; Genc et al., 2010) and VEGF formation (Li, Y., Lu, Keogh, Yu, & Wei, 2007). It also induces neurogenesis (Zhang, Y. et al., 2009), blocks glutamate excitotoxicity and excitotoxic-induced production of ROS (Costa et al., 2013; Garzón et al., 2018), and activates the PI3K/Akt signalling chain, leading to the stabilization of Ca^{2+} (Malhotra, Savitz, Ocava, & Rosenbaum, 2006).

Nuclear factor erythroid 2-related factor 2 (Nrf2), Brain derived neurotrophic factor (BDNF), and microglial polarity

One important innate neuroprotective protein, Nrf2, was discovered quite recently (Bouvier et al., 2017; Zhang, M. et al., 2013). Its regulation process is quite intricate and still under investigation; studies indicate increased ROS-activated binding points in the Nrf2 protein that aid its nuclear transportation. Concurrently, Nrf2 activates a complex that accommodates the release of its gene program (Zhang, M. et al., 2013). The main neuroprotective function of Nrf2 involves enhancing the

production of antioxidants, such as thioredoxins, peroxiredoxins, and sulfiredoxins (Zhang, M. et al., 2013). It also assists in the production of the vital antioxidant glutathione, generates NADPH (Esteras, Dinkova-Kostova, & Abramov, 2016; Yamazaki, Tanji, Wakabayashi, Matsuura, & Itoh, 2015), and increases IL-10 (Piantadosi et al., 2011). BDNF is also activated by ROS (Rahimi et al., 2018; Wang, H., Ward, Boswell, & Katz, 2006) and acts as an important activator of PI3K/Akt, signalling cascade (Numakawa et al., 2010) and a HIF-1 pathway (Nakamura et al., 2006). Interestingly, there seems to be a feed-forward mechanism between Nrf2 and BDNF, as these factors activate each other (Bouvier et al., 2017; Sakata et al., 2012). Studies have proposed that both Nrf2 and BDNF prevent the M2-M1 shift in the microglial cells, which attenuates the pro-inflammatory cascade after I/R injury in the brain (Wang, Y. et al., 2018; Xia et al., 2016).

2.3 Cerebral protection in aortic arch surgery

The brain is the organ that is most susceptible to ischaemia. Aortic arch surgery requires alterations to the cerebral perfusion or even the cessation of CBF in order to achieve a bloodless operating field, therefore exposing the brain to iatrogenic ischaemic brain injury. The aortic pathologies that require surgical interventions are aortic arch aneurysms as well as ATAAD.

2.3.1 Type A aortic dissection

Acute aortic syndrome involves acute aortic dissection (AAD), an intramural aortic hematoma, a penetrating aortic ulcer, and aortic trauma. However, the latter three occur more frequently in the descending aorta, which does typically not require aortic arch surgery. Additionally, the intramural haematoma and the penetrating aortic ulcer are slightly more confined pathologies than AAD but still can lead to hazardous outcome, for example, through aortic rupture (Tsai, Nienaber, & Eagle, 2005).

Incidence, predisposing factors, presentation, and diagnosis

The incidence of ATAADs is 2.0-3.5/100,000 people per year (Czerny et al., 2011; Hagan et al., 2000; Hiratzka et al., 2010; Howard, Sideso, Handa, & Rothwell, 2014; Krüger et al., 2012; LeMaire & Russell, 2011; Mészáros et al., 2000; Tsai et al., 2005). It is defined as acute if the symptoms have lasted less than two weeks

(Hiratzka et al., 2010). Factors that predispose ATAAD include CTD; additionally, patients can often have hypertension, a history of smoking, aortic inflammation, and a family history of thoracic aortic diseases without a CTD. Surprisingly, patients with diabetes mellitus and hypercholesterolemia are quite rare in the AAD population, making this population different from those undergoing other cardiac surgical operations (Czerny et al., 2011; Hagan et al., 2000; Hiratzka et al., 2010; Howard et al., 2014; Krüger et al., 2012; LeMaire & Russell, 2011; Mészáros et al., 2000; Tsai et al., 2005).

A primary intimal entry tear (PET) in the aortic wall gives rise to AAD. Blood is then discharged into the medial layer of the aortic wall, creating a false lumen (FL) between the intima-media and media-adventitial layers. FL often advances distally in the aortic wall and can create multiple re-entries back to the true lumen (TL) of the aorta. The most applicable classification method in clinical settings is the Stanford classification, types A and B (Czerny et al., 2011; Hagan et al., 2000; Hiratzka et al., 2010; Howard et al., 2014; Krüger et al., 2012; LeMaire & Russell, 2011; Mészáros et al., 2000; Tsai et al., 2005). ATAAD involves the ascending aorta, however, in type B cases the ascending aorta is preserved of dissection. The DeBakey classification uses the site of the PET and distal extent of FL. In type I AAD, the PET is located in the ascending aorta and the FL extends all the way into the descending aorta. Type II AAD, however, involves only the ascending aorta, as both the PET and false lumen are present in the ascending aorta and both the aortic arch and the descending aorta are left unharmed. The AAD is defined as type III if the PET is in the descending aorta. As the subject of this thesis is cerebral protection in aortic arch surgery, only ATAAD is examined thoroughly in the text (Czerny et al., 2011; Hagan et al., 2000; Hiratzka et al., 2010; Howard et al., 2014; Krüger et al., 2012; LeMaire & Russell, 2011; Mészáros et al., 2000; Tsai et al., 2005). A graphical illustration of the AAD classifications is presented in Figure 4.

The presentation of ATAAD is often emergent; approximately 90% of ATAAD patients experience severe chest/back pain that can extend into the abdomen and extremities depending on the extent of FL. 20-30% of patients experience pulse losses, which can be alternating (Hagan et al., 2000; Hiratzka et al., 2010). The patients can also experience the symptoms of stroke, spinal cord injury, acute bowel necrosis, limb ischaemia, and acute kidney injury due to malperfusion, depending on the extent of ATAAD (Bonser et al., 2011; Hagan et al., 2000; Krüger et al., 2012). 10-15% of patients experience shock due to pericardial tamponade, aortic free rupture, ostial coronary occlusion, and severe aortic valve insufficiency (Hagan et al., 2000). Approximately 5% of the ATAAD patients present with

cardiac arrest prior the surgery (Pan et al., 2019). Pericardial tamponade is present in 5-10% of cases while a right coronary artery dependent acute myocardial infarction (MI) is present in 1-7% (Bonser et al., 2011). A new aortic insufficiency is present in almost half of cases as the aortic valve commissures stretch and sufficient coaptation of the leaflets is compromised (Hagan et al., 2000). AAD might also involve a syncope and low blood pressure, which could indicate either an underlying aortic rupture that has temporarily limited itself or a transient neurological deficit (TND) due to from arch vessel involvement (Hiratzka et al., 2010). It should be noted that these numbers come from patients that have had contact with an emergency department or emergency medical services; some 40% of ATAAD patients die immediately due to aortic rupture, pericardial tamponade, massive MI, or stroke (Bonser et al., 2011; Czerny et al., 2011; Krüger et al., 2012; Van Arsdell, David, & Butany, 1998).

The primary diagnosis of ATAAD is a clinical one that takes all of the previously mentioned predisposing factors and the clinical presentation into account. If the suspicion is strong or moderate and the differential diagnoses do not match well, the patient should be imaged with aortic computed tomography (CT) with contrast enhancement and then transferred to the nearest cardiothoracic centre (Bonser et al., 2011; Rengier et al., 2013). Additional imaging can be done with transoesophageal echocardiography to determine left ventricular and aortic valve function (American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists Task Force on Transoesophageal Echocardiography, 2010).

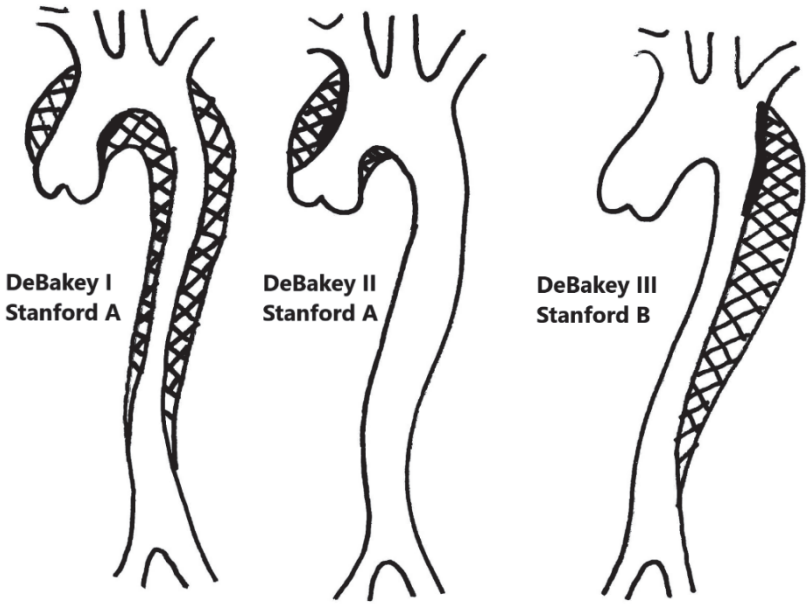

Fig. 4. Classifications of ATAAD.

Treatment of ATAAD

40-50% of the ATAAD patients die instantly or prior to reaching the hospital (Howard et al., 2013). Mortality after this is 1-2% every hour during the first 48 hours. Without treatment, 90% patients die of ATAAD (Hagan et al., 2000). Even with aggressive blood pressure treatment, the in-hospital mortality rate is still as high as 60%. 30-day mortality after surgical treatment is 13-20%, depending on the centre and the patient population (Conzelmann et al., 2016; Geirsson et al., 2019 Jormalainen et al., 2020a; Weigang, Conzelmann, Kallenbach, Dapunt, & Karck, 2010). A mortality rate of 40% was found even in patients aged over 80, therefore justifying surgical treatment in almost all patients (Bonser et al., 2011; Czerny et al., 2011; Krüger et al., 2012). Neurological deficits, acute disorientation, or resuscitation before coming to the OR have not been shown to be contraindications for surgery (Chemtob et al., 2020; Pan et al., 2019); Deep dementia, and extensive metastatic cancer would qualify as contraindications to surgical intervention (Bonser et al., 2011; Hiratzka et al., 2010; Krüger et al., 2012). Large bowel necrosis is a devastating complication of ATAAD and aortic surgery should not be

done before it and the associated lactatemia and circulatory collapse have been resolved with interventional radiology, even when the process could lead to aortic rupture (Leshnower, Keeling, Duwayri, Jordan, & Chen, 2019). Other malperfusion problems, such as kidney and limb ischaemia, usually resolve during the surgical treatment because TL flow is ensured, though additional interventions are sometimes needed (Norton, Khaja, Williams, & Yang, 2019).

The surgical treatment of ATAAD is still open-heart surgery, even though there has been some experimentation with endovascular grafts, even up to aortic zone 0 (Czerny et al., 2012; Preventza, Tan, Orozco-Sevilla, Euhus, & Coselli, 2018; Srivastava & Bhan, 2019). The most important surgical principles in ATAAD surgery are the resection of the primary entry tear, the stabilization of the aortic wall, and ensuring the integrity of cerebral vessels, and if necessary, reversing malperfusion by excluding the FL flow (Czerny et al., 2011; Czerny et al., 2018; Hiratzka et al., 2010; Krüger et al., 2012). The operation is surgically demanding; it the takes place in emergent situations and the aortic wall is faint and fragile. Secondary principles of the operation include preparing the landing zone for possible endovascular operations in the future and preventing late aortic events by compressing the false lumen in the descending aorta (Czerny et al., 2011; Czerny et al., 2018; Hiratzka et al., 2010; Krüger et al., 2012). However, the individual surgeon's experience and the patient's long-term survival probability should be factored in before a more extensive procedure is performed.

The aorta has to be opened in order for the surgical procedure to be completed. Therefore, extracorporeal circulation is needed to ensure perfusion of the brain, the heart, the kidneys, and the viscera. A total circulatory arrest is often needed as well. These characteristics make aortic arch surgery a unique surgical and anaesthesiologic challenge, which is discussed further below.

2.3.2 Cardiopulmonary bypass

As cardiac surgery began to be performed on a larger scale during and soon after the Second World War, it quickly became evident that the heart had to stop in order to ensure safe and efficient procedures. Surgeons like C. Walton Lillehei, John H. Gibbon, Jr., and F. John Lewis revolutionized open-heart surgery with cross-circulation experiments and different versions of the heart-lung-machine, which paved the way for the glory days of cardiac surgery (Gibbon et al., 1954; Gott, 1990; Lewis, 1956; Niazi & Lewis, 1957). Gibbon's version of the heart-lung machine

was the basis of the modern CPB circuits, as it had a roller pump and an oxygenator (Gibbon et al., 1954).

CPB's function is to temporarily replace the heart and lungs by bypassing circulation. Blood is directed from a venous cannula in the right atrium or venae cavae through silicone rubber or heparin-coated PVC tubing to a venous reservoir. Blood is then pumped from the reservoir with either a roller or centrifugal pump through a membrane oxygenator. The pump is responsible for circulation and the flow rate can be modified accordingly. The membrane oxygenator is flushed with O_2, which diffuses into the blood through the membranes as CO_2 simultaneously diffuses in the other direction. From the oxygenator, blood is pumped back to the patient, usually to the ascending aorta, through an aortic cannula. Other cannulation options are discussed later on in this section. The CPB circuit usually contains additional sucking devices and vent cannulas to clear the operating field. Additional pumps are also used to facilitate the flow of cardioplegia solutions and to achieve separate cerebral and lower body perfusions. A heat exchanger is used to modify and maintain adequate core temperature (Sarkar & Prabhu, 2017).

2.3.3 Hypothermic circulatory arrest

The first successful use of hypothermic circulatory arrest (HCA) in open-heart surgery dates back to 1952, when F. John Lewis corrected an atrial septal defect in a five-year-old girl with a temperature of 28 °C and without the use of CPB (Lewis, 1956). Prior to this, Dr. Bigelow had conducted numerous experiments on hypothermia with both humans and animals; he should therefore be credited regarding the use of hypothermia in cardiac surgery (Bigelow, Lindsay, & Greenwood, 1950). The first reports on aortic arch surgery date back to the 1950s when the legends of cardiac surgery, Michael E. DeBakey, E. Stanley Crawford, and Denton A. Cooley, operated on arch aneurysms and ATAAD (Crawford, Bellizzi, De Bakey, & Cooley, 1960; De Bakey, Crawford, Cooley, & Morris, 1957). Borst et al. completed the first open-heart surgery using CPB and HCA in the 1960s (Borst, Schaudig, & Rudolph, 1964). The first reports of the successful use of HCA in aortic arch surgery date back to the 1970s (Griepp et al., 1975). Griepp et al. used a CPB circuit, a heat exchanger, and topical cooling to lower patients' core temperature down to 12-18 °C. The pump was then stopped and total body HCA was initiated to achieve a bloodless operating field. At the time, the mortality rate of those operations was approximately 30% (Ergin, O'Connor, Guinto, & Griepp, 1982). Since then, the mortality rate has dropped to 2-25%, depending on the

treated pathology and the situation (Gega et al., 2007). Another significant complication of aortic arch surgery and HCA is neurological dysfunction. Neurological dysfunction can be divided into two forms, strokes and temporary neurological dysfunction (TND). TND is defined as a functional manifestation of subtle and transient brain injury. Stroke and seizure rates are relatively low (3-5%) (Gega et al., 2007) while TND rates can be high (12-63%) depending on the definition, reporting, and length of HCA (Ergin et al., 1999).

Acid-base management and hypothermia

When the blood temperature is altered, the solubility of the gases increases but partial gas pressures decrease according to the laws of physics. Therefore, two main acid-base management strategies in the use of hypothermic CPB have emerged, which are called the alpha stat and pH stat strategies. The latter relies on the patient's actual temperature; additional CO_2 is added to the membrane oxygenator to keep the pH at 7.40 and the partial pressure of CO_2 at 40 mmHg (5.33 kPa). The alpha stat strategy, in turn, relies on keeping the ionisation state of the imidazole of histidine constant by keeping the CO_2 content equal in different temperatures. Therefore, the partial pressures of CO_2 are not corrected for temperature and CO_2 is not added to the circuit. This results in an alkalotic pH and low partial pressure of CO_2 in hypothermic temperatures in the uncorrected values. This method is thought to mitigate intracellular acidosis and aid optimal protein function, even in hypothermic conditions. However, the pH stat strategy leads to relative acidosis, which can impair protein function (Halstead et al., 2005), though the increased CO_2 aids autoregulatory vasodilatation in the cerebral vessels, enabling uniform cooling and distribution of nutrients and O_2 (Broderick, Damberg, Ziganshin, & Elefteriades, 2018; Dahlbacka et al., 2005; Nauphal et al., 2007; Piccioni, Leirner, & Auler, 2004; Pokela et al., 2003).

In the alpha stat strategy, cerebral autoregulation is preserved, even until 22-24 °C (Duebener et al., 2002; Ehrlich et al., 2002; Halstead et al., 2005). Therefore, the pump flow rate will not directly affect CBF and small increases or decreases in MAP will not result in excess CBF. However, the pH stat strategy uncouples the relationship between CBF and cerebral metabolism for the aforementioned reasons, thereby eliminating cerebral autoregulation (Duebener et al., 2002). This has been shown to be beneficial in children undergoing operations that require HCA because it leads to increased CBF, reduced O_2 consumption, and increased O_2 availability (du Plessis et al., 1997; Jonas, 2018). However, in adults, the pH stat strategy has

proven to be potentially harmful, as it nearly doubles the CBF, therefore leading to an increased risk of embolic load to the brain or cerebral oedema. The alpha stat strategy has therefore emerged as the standard acid-base management method in adults (Broderick et al., 2018; Chau, Friedman, Tranquilli, & Elefteriades, 2013; Damberg et al., 2017; Gega et al., 2007; Percy, Widman, Rizzo, Tranquilli, & Elefteriades, 2009; Ziganshin & Elefteriades, 2013). It must also be noted that standardized pump flow rates or MAPs should not be used, as they can lead to hypo- or hyperperfusion. Minimal flow rates for each temperature have been determined and should be followed (Anttila et al., 2005). However, an individualized perfusion strategy according to O_2, CO_2, and lactate levels from serial arterial and venous blood samples should also be applied (Abdul Aziz & Meduoye, 2010).

Robust temperature changes during cooling and warming with CPB have been shown to have detrimental effects. A cooling temperature gradient of more than 10 °C between arterial inflow and venous outflow was shown to induce the formation of microemboli (Geissler et al., 1997). The rewarming phase must also be conducted cautiously as temperature gradients of over 10 °C can lead to rapid evaporation of the dissolved gases (Engelman et al., 2015). Interestingly, a cold 10-minute perfusion period after HCA but before starting the rewarming period was shown to attenuate neurologic outcomes (Di Mauro et al., 2013). If the cerebral temperature is not measured, it can be extrapolated from rectal and bladder temperatures, which are 2-3 °C lower than cerebral temperature during the rewarming phase (Nussmeier et al., 2006). The avoidance of cerebral hyperthermia after HCA is a key factor in achieving a good neurologic outcome as even mild cerebral hyperthermia has been shown to impair it (Nussmeier, 2005). Therefore, the warming phase should target a cerebral temperature of 35-35.5 °C and the end of the warming phase should be slow; it should max out at 0.5 °C/min (Engelman et al., 2015).

The permissible period of hypothermic circulatory arrest

Ever since the advent of aortic arch surgery, hypothermia has been the primary neuroprotective measure. Its protective function is based on the fact that it decreases neuronal metabolism by 5-7% with every 1 °C drop in core temperature (Erecinska, Thoresen, & Silver, 2003). The particular mechanisms involve decreased release of excitatory neurotransmitters, such as glutamate, which then leads to reduced Ca^{2+} influx and diminished activation of the ischaemic cascades

(Okuda, Saito, Miyazaki, & Kuriyama, 1986; Zhao et al., 2007). Hypothermia also prevents almost all factors that account for caspase-independent apoptosis or necrosis. In addition, hypothermia mitigates ROS production and tempers the associated inflammatory response (Horiguchi et al., 2003; Xiong, Yang, Chen, & Zhou, 2009).

The classification of the degree of hypothermia has been a source of conflict since the early days; different definitions are still being used today. The most used classifications of hypothermia seem to be mild (35–33 °C), moderate (32–28 °C), deep (27–21 °C), and profound (<20 °C). Some would argue that 25 °C would still qualify as moderate hypothermia, and 18 °C would be deep hypothermia; unified definitions are certainly needed to compare surgical results accordingly (Etz, Mohr, Luehr, & Bachet, 2013).

The permissible period of HCA has interested of aortic surgeons since its implementation. The first modern experiment on pigs in the 1990s indicated that the cerebral metabolism decreases 5% per every °C at the beginning of the cooling, and evens out to 2-3% later in the cooling process, indicating that the relationship between cerebral metabolism and cerebral temperature is not linear (Laptook, Corbett, Sterett, Garcia, & Tollefsbol, 1995). This finding was repeated by Ehrlich et al., who found that the relationship was best described with a natural logarithm. They found out that cerebral metabolism can be reduced by over 50% of the baseline values at 28 °C, by over 80% at 18 °C, and by almost 90% at 8 °C, respectively (Ehrlich et al., 2002).

These experiments paved the way for the human study conducted by McCullough et al., which aimed to define the permissible periods of HCA for each temperature by examining both the jugular bulb and arterial blood samples and the carotid artery blood flow at various temperatures in 37 patients undergoing aortic arch surgery with HCA. The estimation was based on the fact that hypothermia is the only contributing factor to decreased cerebral metabolism and the idea that the brain could safely tolerate 5 minutes of ischaemia at normal temperatures. Therefore, the permissible periods of HCA for different temperatures were as follows: 9 min at 30 °C, 14 min at 25 °C, 21 min at 20 °C, 31 min at 15 °C, and 45 min at 10 °C. These results proved to be surprising, as higher temperatures and longer durations were often applied during aortic arch surgery (McCullough et al., 1999).

The current evidence from large patient registries has proved these results to be relevant in clinical settings as well. A large German database on ATAAD patients (GERAADA) revealed that the incidence of neurological sequalae increases

rapidly after the cut-off point of 30 minutes of HCA, impairing the neurologic outcome (Kruger et al., 2011). Mortality has been shown to increase after the cut-off point of 40 minutes of HCA, but these durations are rarely used and could indicate that the repair had to be more extensive than was anticipated or that there were significant problems with the procedure itself (Conzelmann et al., 2016b.

2.3.4 Arterial cannulation options

The traditional arterial cannulation method for CPB is a simple, straight-tip cannula into the ascending aorta (Khaladj et al., 2008). However, ATAAD presents a unique challenge as the true lumen might be compressed and the aorta is fragile. The traditional cannulation methods in the ATAAD cases are the right axillary or the right subclavian arteries and the femoral artery (Bonser et al., 2011; Conzelmann et al., 2016; De Paulis et al., 2015). The right axillary or the right subclavian route produces antegrade flow but it is more time-consuming to complete as another incision under the clavicula is required and a perfusion graft must be stitched in an end-to-side fashion to avoid propagation or dissection of the artery (Budde, Serna, Osborne, Steele, & Chen, 2006; Immer et al., 2008; Schachner et al., 2005). The femoral route also requires an additional incision to the groin area, though it is easily accessible from that point and the vessel calibre is optimal. However, it produces retrograde flow into the dissected aorta, which can lead to false lumen perfusion, aggravated malperfusion, retrograde particle embolization, and insufficient coronary and cerebral blood flow (Robicsek & Thubrikar, 1994; Yavuz, 2008). Therefore, some centres have begun to utilize traditional ascending aortic cannulation in ATAAD patients as well, with great results (Jormalainen et al., 2020a; Khaladj et al., 2008). Nevertheless, additional tools are still used to ensure TL cannulation. These aids include the use of an epiaortic ultrasound to detect the TL, and the Seldinger technique (Kamiya et al., 2009; Khoynezhad & Plestis, 2006). However, these methods can also prove to be ineffective or too time-consuming in the most emergent situations, and so a bail-out cannulation method is needed to ensure sufficient outcome.

Direct true lumen cannulation after venous exsanguination, or Samurai cannulation of the aorta, has been introduced to aid the arterial cannulation of ATAAD patients in a critical state (Conzelmann et al., 2009; Jakob et al., 2007; Kitamura, Nie, Horai, & Miyaji, 2017; Kitamura et al., 2018). It is executed by exsanguinating the patients into the venous reservoir, transecting the ascending aorta, and then inserting the aortic cannula into the TL with vision control. After

this, the aorta is tightly snared over the cannula and CPB is initiated. It is performed with prior 100% oxygen ventilation; the cannulation-related normothermic circulatory arrest typically lasts less than two minutes (Conzelmann, Weigang, Mehlhorn, & Vahl, 2012; Jakob et al., 2007; Kitamura et al., 2017). Taking into account the assumption of a safe circulatory arrest of less than 5 minutes at normothermia, DTLC might provide a non-lethal ischaemic response, possibly leading to ischaemic preconditioning. However, if the 5-minute time limit is challenged, it could also lead to permanent neurological deficits (PND).

The early clinical results of DTLC have been promising. Retrospective studies have shown that, though TNDs and PNDs were found in 21-25% of patients, not a single patient has died. These reports involved 37 patients combined and no controls, making it difficult to compare the efficiency of this method to others (Conzelmann et al., 2009; Jakob et al., 2007). One recent retrospective cohort presented comparisons between DTLC (N=61) and other cannulation options (N=39) in patients with ATAAD. The TL cannulation success rate in the DTLC group was 100%. However, three complications related to the cannulation procedure were noticed with the traditional methods. The 30-day mortality rates did not differ vastly between the groups (5% DTLC, 8% control). Major strokes were observed in 7% of the patients with DTLC and in 10% of the patients in the control group (Kitamura et al., 2018).

A recent retrospective study from Germany presented the largest number of patients yet in DTLC studies; there were 528 patients, 52.4% of which received DTLC. The choice of the cannulation method was left to the operator, but analyses showed that DTLC was employed significantly more with patients in critical states that demonstrated shock, tamponade, hypoperfusion, cerebral malperfusion, or were resuscitated. New TNDs or PNDs were observed in 8% of the patients in both groups. Despite a worse clinical status before the operation, the patients in the DTLC group showed promising signs of a faster neurological recovery as compared to the control group. This difference, however, did not reach statistical significance. There were no differences in overall survival during the maximum follow-up period of 10 years at each time point (El Beyrouti et al., 2020).

None of these studies showed differences that reached statistical significance, but the results suggest the non-inferiority of DTLC to traditional cannulation methods. The results also suggest that DTLC might be beneficial for patients in a critical state, though further studies are needed to confirm this result.

2.3.5 Surgical strategies

As it became evident that even deep or profound HCA would only provide sufficient cerebral protection for a maximum of 30 minutes, other modes of cerebral protection were introduced to ensure the safety of more time-consuming arch procedures.

In the early 1990s, retrograde cerebral perfusion (RCP) was considered an excellent neuroprotective measure because its use did not interfere with the surgery. It was performed by introducing a cannula into the upper vena cava and snaring it tightly. Retrograde perfusion through the cerebral venous was then initiated while the lower body was in total HCA. Unfortunately, later studies proved that RCP was in fact quite ineffective in neuroprotection, as it did not deliver O_2 or nutrients into cerebral microcirculation (Ehrlich et al., 2001). However, there have been studies with contradictory results, and some centres still use RCP as an adjunct to HCA to achieve permissible periods of 40-50 minutes (Gaudino et al., 2018; Ueda, 2013). Nowadays, RCP is rarely used; its main function is to keep the brain cold and to flush debris back to the aorta (De Paulis et al., 2015).

Selective cerebral perfusion (SCP) or selective antegrade cerebral perfusion was introduced to aortic surgery in the late 1980s by Guilmet, Bachet, and Kazui. This new method could provide antegrade CBF during aortic arch procedures, as the flow could be directed toward the brain from the previously mentioned right subclavian or axillary artery by clamping the other cerebral vessels. Balloon-tip cannulas were used to perfuse the brain bilaterally through the opened aorta. The early results were promising, as longer operating times could be safely tolerated at higher core temperatures (Bachet et al., 1991; Guilmet et al., 1986; Kazui, 1986; Kazui et al., 2001). Since the early days of SCP, the method has been fine-tuned in terms of blood pressure, flow rate, haematocrit, temperature, and the amounts of vessels perfused to ensure an optimal CBF to all parts of the brain and avoid both hypo- and hyperperfusion. The optimal MAP during SCP seems to be 50 mmHg, as higher pressures lead to increased intracranial pressure and cerebral oedema (Halstead et al., 2008). An excess flow rate has also shown to be deleterious, which favours the use of alpha-stat pH management, and the minimal flow rate needed seems to be as low as 6ml/kg/min (Haldenwang et al., 2010; Halstead et al., 2005; Halstead et al., 2008; Jonsson et al., 2011). The avoidance of haemodilution seems to prevent these issues as well, and so haematocrit levels of around 30 are preferred (Halstead, Wurm et al., 2007). As the cerebral autoregulation is uncoupled somewhere between 22-25 °C, it was suggested that the perfusate temperature

should stay above that range. However, one study suggested otherwise, indicating that SCP temperatures ranging from 10-15 °C led to a better neurologic outcome than temperatures of 20-25 °C (Strauch et al., 2005). The question of unilateral versus bilateral SCP has been present since SCP's implementation. The current consensus is as follows: 40-59% of humans have been shown to have an incomplete circle of Willis, suggesting that unilateral SCP would not provide sufficient perfusion to the other side for them (Merkkola et al., 2006). Additionally, some patients have anomalies, cerebral vessel stenoses, or previous strokes complicating unilateral perfusion. However, additional studies have indicated that haemodynamically significant alterations preventing unilateral perfusion only occur in 14-17% patients (Papantchev et al., 2007). In addition, it has been shown that SCP durations of over 40 minutes lead to worse neurologic outcomes with unilateral SCP as compared to bilateral SCP (Krähenbühl et al., 2010; Malvindi, Scrascia, & Vitale, 2008).

Therefore, in the light of the aforementioned studies, an evidence-based method for utilizing SCP for optimal cerebral protection can be formed. The flow rate should be adjusted to achieve a proximal MAP of 50 mmHg and the pump flow rate cannot be under 6ml/min/kg. Haematocrit is to be kept near 30 and the perfusate temperature should be 10-15 °C. Unilateral perfusion can be initiated if there are no known significant alterations in cerebral vessels and the expected SCP duration is under 40 minutes. Additionally, a near-infrared spectroscopy (NIRS) sensor can be used to detect differences in brain oxygenation between the hemispheres in real time (Urbanski, Babin-Ebell, Fröhner, & Diegeler, 2012). However, it does not work as a definitive sensor of brain oxygenation as it functions mostly as real-time monitor of central venous saturation (Kytta, Ohman, Tanskanen, & Randell, 1999; Rao, Nigro, & Karamlou, 2017; Urbanski et al., 2013). Nevertheless, it is useful in detecting differences between hemispheres and in guiding the shift to bilateral perfusion. Nowadays, SCP and core temperatures have steadily risen, removing the tolerance of the spinal cord and the visceral organs to ischaemia. Ischaemic tolerance of the spinal cord at 28 °C is only 60-75 minutes and exceeding that can lead to a hazardous outcome (Etz et al., 2009; Kamiya et al., 2007).

The choice between operative strategies

The simplest procedure in ATAAD patients is applying a supra-coronary interposition graft to replace the dissected part of the ascending aorta, though this

procedure is only sufficient in rare cases, such as iatrogenic spontaneously limited ATAADs and small DeBakey type II ATAADs. The application of circulatory arrest is not necessary, though it has been shown that, if distal anastomosis is done with a clamp-on technique, it could lead to a worse long-term outcome because possible intimal tears in the aortic arch might be missed (Geirsson et al., 2019). Additionally, more dissected aorta will be left unresected and the clamp could cause intimal damage, exacerbating the dissection (Bonser et al., 2011; Easo et al., 2012; Krüger et al., 2011).

The fate of the aortic root after ATAAD depends on the extent of the dissection, the condition of the aortic leaflets, the presence of CTD, life expectancy, the presence of root dilatation, and the experience of the surgeon. If the commissures and leaflets are intact and the root is relatively intact, a simple supra-coronary interposition graft and resuspension will be sufficient (Bonser et al., 2011; Krüger, et al., 2012; Pan et al., 2018; Rylski et al., 2014; Tanaka et al., 2018). If the coronary ostia are involved or the valve or aortic root is severely damaged, a Bentall-DeBono procedure will have to be done with either a mechanical or biological prosthesis, depending on the age and comorbidities of the patient. In rare (CTD) cases and in experienced hands, a valve sparing root replacement procedure might be performed, preferably according to David et al. Aggressive aortic root surgery during the initial ATAAD repair adds complexity and duration to the operation, possibly hampering the short-term outcome, but incidence of late aortic root surgery after a root sparing operation in the acute phase ranges from 8-28% (Bonser et al., 2011; Krüger et al., 2012; Pan et al., 2018; Rylski et al., 2014; Tanaka et al., 2018). However, long-term outcome and freedom from future root operations remain similar in patients both with and without aortic root surgery. Therefore, careful consideration must be made during the operation before determining the optimal operative strategy for an individual patient.

The aortic arch has been shown to be dissected in 80% of ATAAD patients, which is essentially the proportion of DeBakey type I ATAADs. The PET, however, is usually located in the ascending aorta (Conzelmann et al., 2016). This situation can be dealt with by using either a hemiarch replacement and extending the interposition graft into the end of the lesser curvature of the aortic arch or by replacing the whole aortic arch with a specified graft (Conzelmann et al., 2016; Czerny et al., 2018; Easo et al., 2012; Rylski et al., 2014). The aortic arch replacement adds complexity to the operation, and it has been shown to increase the incidence of neurological sequalae, but not in-hospital mortality. The aortic arch replacement has also been shown to aid false lumen thrombosis, therefore

potentially preventing late aortic events and operations (Easo et al., 2012). If significant re-entries or the PET are present in the aortic arch, the only acceptable method is aortic arch replacement (Czerny et al., 2018).

If life-expectancy is long and the PET is in the proximal descending aorta, the aortic arch replacement can also be supplemented with either an elephant trunk prosthesis extending freely 5-10cm into the descending aorta, aiding landing zone for possible future endovascular therapies (Borst, 1999) or with a frozen elephant trunk (FET) prosthesis that extends 15cm in the descending aorta and expands against the aortic wall, blocking the SAs (Fleck et al., 2002). FET has been shown to induce false lumen thrombosis in the descending aorta but has also been shown to increase the incidence of spinal cord injuries.

The aortic arch replacement, whether with or without FET, is thought to prevent late events and operations after primary surgery (Shrestha, Haverich, & Martens, 2017; Uchida et al., 2009). However, some studies have shown poorer short-term outcomes and no differences in late events or operations (Shrestha et al., 2015). Hemiarch replacement, however, is a simpler operation that most cardiothoracic surgeons are able to complete in emergent settings with acceptable operation durations. Hemiarch replacements have been shown to produce an excellent short-term outcome and an acceptable long-term outcome, even in a small cardiac centre with a single surgeon operating on 0-2 cases per year (Jormalainen et al., 2020b; Jormalainen et al., 2020a).

Finally, there is a choice between different temperatures and neuroprotective strategies. The opponents of the use of deep HCA argue that it leads to an increased incidence of coagulation disorders and therefore bleeding complications (Haverich & Hagl, 2003). There are some studies that back up this argument, but current evidence points out that moderate hypothermia causes the same reoperation rate for bleeding as deep hypothermia (Harrington, Fragomeni, & Bonser, 2007; Milewski et al., 2010). Increased bleeding seems to be more closely associated with longer CPB durations, which are, in fact, required for deep HCA, as well as the aortic disease itself (Harrington, Lilley, Rooney, & Bonser, 2004; Salis et al., 2008). The proponents of HCA, however, argue that the associated bleeding can easily be reversed with blood products and coagulation factors (Straub et al., 2007). Some also argue that the prolonged warm visceral ischaemia during SCP causes coagulopathies, multiorgan injury, and spinal cord injuries (Etz et al., 2009; Kamiya et al., 2007). The longer whole body CBP duration associated with deep HCA is certainly a factor to be noted, as prolonged perfusion can lead to permeability dysfunction, oedema formation, and organ dysfunction despite the protective effect

of hypothermia (Haverich & Hagl, 2003). In addition, deep or profound hypothermic temperatures exceed the limit of cerebral autoregulation, which can lead to excess perfusion of the brain (Ehrlich et al., 2002).

The choice between HCA only and SCP is decided by the surgeon or by the institution. Deep HCA and SCP have been shown to produce equal results in aortic arch surgery when the HCA duration is under 30 minutes (Krüger et al., 2011). This, however, might not be sufficient for complex procedures on the aortic arch, which would favour the use of SCP. Nevertheless, ATAAD presents a different challenge to cerebral perfusion as the arch vessels might be dissected or be prone to dissection, propagation, or thrombus formation, which could worsen the neurologic outcome (Fleck et al., 2006; Imanaka et al., 2000; Schachner et al., 2005). Moreover, in patients in a critical state, right axillary/subclavian cannulation might not be possible, as previously discussed. In addition, balloon-tip catheters can always be utilized for selective SCP during deep HCA if the safe time limit is challenged and neurologic outcome does not seem to be impaired from the initial HCA period (Halstead et al., 2007). There are centres that have adopted deep HCA as their sole method of cerebral protection, even in elective settings without ATAAD. The Yale group, for example, led by Professor Elefteriades, has published numerous studies with excellent results, even with HCA durations exceeding 30 minutes (Broderick et al., 2018; Chau et al., 2013; Damberg et al., 2017; Percy et al., 2009; Yan, Ji, & Lou, 2018; Ziganshin & Elefteriades, 2013; Ziganshin et al., 2014). They argue that SCP could easily lead to overperfusion, increased embolic load, and oedema formation, especially in unexperienced hands, ultimately impairing the neurologic outcome (Elefteriades & Ziganshin, 2020). On the other hand, most high-volume centres only use SCP and their results are equally as good (De Paulis et al., 2015; O'Hara et al., 2020). It seems that the results are somewhat associated with the experience of the institution or the single surgeon with certain operative strategies (Andersen et al., 2014). However, other simple aids for cerebral protection are being sought out to improve neurologic outcome after aortic arch surgery.

2.4 Remote Ischaemic preconditioning in cerebral protection

The concept of ischaemic preconditioning was first named by Murry et al. in the 1980s, who noted that myocardium tolerates long ischaemic periods much better if it is first preconditioned by shorter periods of myocardial ischaemia (Murry et al., 1986). The first cerebral IPC studies were done a few years later with a short occlusion of both carotid arteries before a subsequent longer occlusion (Kitagawa

et al., 1990). Encouraged by these results of that study, Przyklenk et al. hypothesized that preconditioning to a different part of the myocardium would provide protection from ischaemic insult in the other parts of the myocardium as well (Przyklenk et al., 1993). This positive result led to the invention of remote ischaemic preconditioning (Gho, Schoemaker, van den Doel, Duncker, & Verdouw, 1996). Shortly after, it was noted that the same protective effects could be achieved by exposing the skeletal muscle in the extremities to short ischaemia reperfusion periods (Kharbanda et al., 2002). This finding yielded numerous studies on cerebral (Dave et al., 2006; Vlasov, Korzhevskii, & Polyakova, 2005), cardiac (Kharbanda et al., 2002), and renal protection (Ren, Gao, Steinberg, & Zhao, 2008) from ischaemic injury; the results were almost uniformly positive and encouraging. However, unveiling the mechanistic network of RIPC and translating these positive effects into clinical situations has been challenging (Sprick et al., 2019).

2.4.1 Application and mechanisms

The most popular way of completing RIPC was established in the 2000s, the most active study period. It involves three to four cycles of 5-minute ischaemia and 5-minute reperfusion periods in the upper or lower extremities. Occlusion of blood flow is achieved with a blood pressure cuff that is filled with supraphysiological (200-300mmHg) pressures (Jensen et al., 2011). Most animal studies have applied RIPC to the lower extremities, but clinical studies have used both upper and lower extremities. This might be one explanation for the different result patterns between species (Johnsen et al., 2016). There are two time-windows that have been shown to be protected after RIPC: an instant preconditioning from 1 to 3 hours after RIPC and a second window of between 24 to 72 hours (Bhuiyan & Kim, 2010).

The mechanism of RIPC has been under thorough investigation for a couple of decades. Most studies have concerned mechanisms in cardiac protection. There is significant interest in finding crucial genes and proteins that could be affected by new, specifically tailored pharmacological agents, which would change the treatment of ischaemic pathologies. However, extensive research has proved that the effects of RIPC are mediated by a complex network that includes humoral and neuronal factors and immunomodulatory mechanisms (Sprick et al., 2019). The exact mediator through which the target tissue receives the RIPC's message is still unknown. A summary of its most important mechanisms is shown in Figure 5.

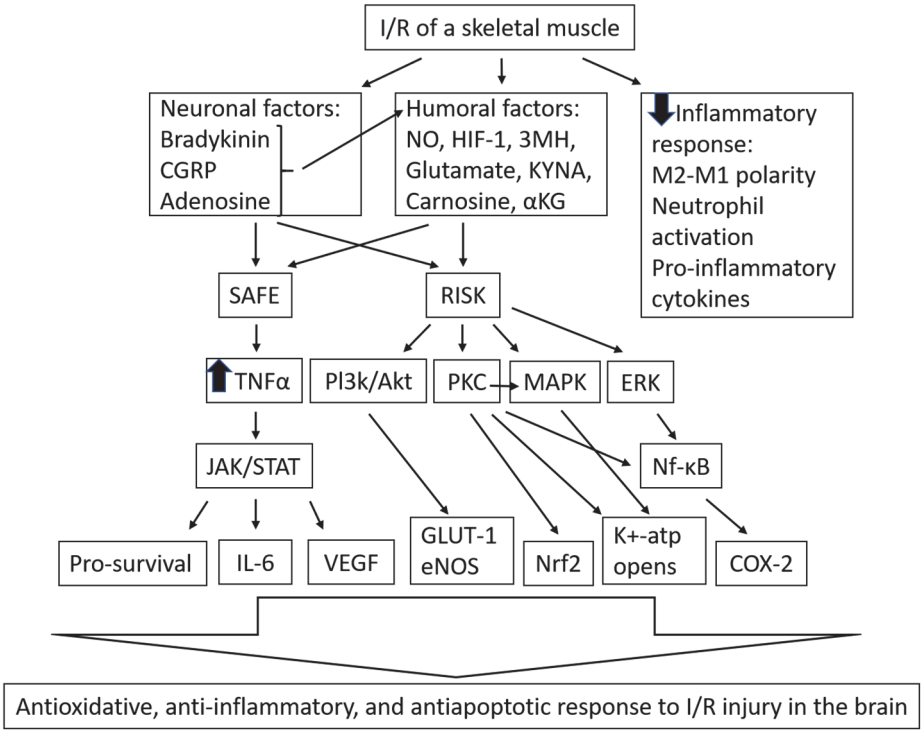

Fig. 5. Simplified summary of the most important mechanisms in RIPC. 3MH = 3-methyhistidine, αKG = α-ketoglutarate, AKT = protein kinase B, CGRP = calcitonin gene-related peptide, COX-2 = cyclo-oxygenase 2, eNOS = endothelial nitric oxide synthase, ERK = extracellular signal-regulated kinases, GLUT-1 = glucose transporter 1, HIF-1 = hypoxia inducible factor 1, I/R = ischaemia-reperfusion, IL-6 = interleukin 6, JAK/STAT = janus kinases/signal transducers and activators of transcription, K+-atp = ATP-sensitive potassium channel, KYNA = kynurenic acid, MAPK = mitogen activated protein kinases, Nf-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, NO = nitric oxide, Nrf2 = nuclear factor erythroid 2-related factor 2, Pl3k = phosphoinositide 3-kinase, PKC = protein kinase C, RISK = reperfusion injury salvage kinase, SAFE = surviving factor enhancement, TNFα = tumour necrosis factor α, VEGF = vascular endothelial growth factor.

2.4.2 Humoral factors

As previously discussed, ischaemic and hypoxic cells undergo a cascade of events that lead to secretion and leakage of proteins into the bloodstream (Ankarcrona et al., 1995; Pundik et al., 2012). However, reperfusion of the ischaemic tissue is

essential in spreading these factors to other tissues and inducing RIPC in the target organ. Evidence of the humoral mechanisms of RIPC has also been shown in experimental studies that have transferred plasma from a RIPC-treated animal to a non-preconditioned animal, resulting in observations of the same protective effects (Dickson et al., 1999; Gedik et al., 2017). There have been abundant proposals regarding potential humoral factors that could mediate the effect of RIPC. The most important factors at this moment include eNOS-produced NO (Hepponstall et al., 2012), stabilized HIF-1 (Cai, Luo, Zhan, & Semenza, 2013; Martin-Puig, Tello, & Aragones, 2015), 3-methyl histidine, glutamate, carnosine (Chao de la Barca et al., 2016), α-ketoglutarate, kynurenic acid (Olenchock et al., 2016), adenosine (Takaoka et al., 1999), bradykinin (Schoemaker & van Heijningen, 2000), calcitonin gene-related peptide (CGRP) (Wolfrum et al., 2005), and endocannabinoids (Hausenloy & Yellon, 2008). However, small, hydrophobic factors that are yet unknown have been found in the plasma of RIPC-treated humans and animals; these could be proteins or micro-RNA carrying particles (Breivik, Helgeland, Aarnes, Mrdalj, & Jonassen, 2011; Shimizu M et al., 2009; Sprick et al., 2019).

2.4.3 Neuronal factors

A neuronal pathway was discovered in an animal study in which the cardioprotective effect of RIPC could be abolished by a ganglion antagonist hexamethonium (Gho et al., 1996). The neuronal pathway was also present in a study with humans, as ganglion antagonist trimetaphan blocked the endothelial effects of RIPC (Loukogeorgakis et al., 2005); this includes the spinal cord and both the autonomous and somatosensory nervous systems. The complexity of the mechanisms of RIPC has been noted in numerous studies as bradykinin, CGRP, and adenosine, among others, can also act as neuronal factors by stimulating afferent nerve fibres, which distribute the effect throughout the nervous system and toward the target tissue (Hausenloy & Yellon, 2008).
Neuronal effects have been noted when the transection of a peripheral nerve and sensory nerve blocker eliminated the effect of RIPC. However, other studies have shown that blocking the neuronal pathway abolishes only a certain part of the effect, but not all of it. The neuronal pathway of RIPC on cerebral protection was proved in animal studies in which interfering with sensory nerves reduced the protective effect of RIPC (Basalay et al., 2012; Lim, S. Y., Yellon, & Hausenloy, 2010; Malhotra, Naggar, Stewart, & Rosenbaum, 2011)

2.4.4 Immune response

The effects of RIPC via innate immune response rely on tempering the inflammatory response to attenuate the I/R injury. RIPC has been shown to decrease the expression of adhesion molecules ICAM-1 and selectin-P (Peralta et al., 2001). This decreases neutrophil activation, extravasation, and chemotaxis. The landmark paper by Konstantinov et al. on the inflammatory factors of RIPC suggested that RIPC suppresses pro-inflammatory signalling and modifies leukocytes (Konstantinov et al., 2004). These leukocyte modifications decrease their activation, adhesion, and intercellular signalling to mast cells and macrophages (Hu et al., 2012; Liang et al., 2011; Shimizu, M. et al., 2010). Interestingly, the role of TNFα seems to be reciprocal during RIPC; it functions as a negative autoregulator on the production of pro-inflammatory cytokines. It also regulates the expression of transporters and enzymes in the brain related to pro-inflammatory cascades (Zhang, M. et al., 2013). The microglial M2-M1 polarity shift is also mitigated by ischaemic preconditioning. All these effects suppress the inflammatory response and inhibit the exacerbation of the I/R injury (Wang, R. et al., 2017; Wang, Y. et al., 2018).

2.4.5 Target tissue response to RIPC

The pathways of RIPC create a similar activation pattern on humoral, neuronal, and immunological factors and endogenous protective mechanisms as in ischaemic or hypoxic neurons, but the final effect is different. As previously discussed, the same cells, cytokines, and pathways can either act as neuroprotective or lead to permanent cell death (Sprick et al., 2019). RIPC is thought to elicit a response primarily to the neuroprotective side of the ischaemic cascade, balancing out the situation. Most studies have focused on the cardioprotective mechanisms of RIPC, but mechanistic information regarding RIPC on cerebral protection is still quite vague. As the present thesis focuses on cerebral protection strategies, neuroprotective pathways will be discussed in further detail.

Pro-survival signalling pathways

The previously discussed neuro-humoral factors, like NO, EPO, endocannabinoids, adenosine, and bradykinin, that reach the target tissue have been shown to activate pro-survival signalling pathways, namely the reperfusion injury salvage kinases

(RISK) pathway (Hausenloy & Yellon, 2007) and the survivor activating factor enhancement (SAFE) pathway (Hausenloy, Tsang, Mocanu, & Yellon, 2005).

The RISK pathway leads to the activation of pro-survival factors Akt, extracellular-signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), and PI3K (Hausenloy et al., 2005). Akt and PI3K have been shown to induce the expression of glucose transporter 1 and eNOS (Gao et al., 2008; Geng et al., 2008; Gidday et al., 1999; Gong et al., 2016; Li, L. B. et al., 2006), therefore reducing glutamate excitotoxicity and promoting neuroprotective NO-formation during ischaemia. The PKC mediator pathway is present in both cardiac and cerebral protection (Pérez-Pinzón & Born, 1999; Wolfrum et al., 2002). PKC plays an important role in activating the mitochondrial K_{ATP} channels that will be discussed in more detail later in this section (Wang, Y., Takashi, Xu, Ayub, & Ashraf, 2001). PKC also activates MAPK, which opens the same mitochondrial channel (Baines et al., 1999; Baines et al., 2002). Activation and phosphorylation of Nrf2 are functions of PKC as well (Huang, Nguyen, & Pickett, 2000). Nuclear factor-κB (NF-κB) is a key regulator of protein synthesis and it produces cyclo-oxygenase-2, which is an important mediator of the proinflammatory response and ischaemic tolerance of the brain (Gendron, Brunette, Tauskela, & Morley, 2005). NF-κB is dependent on PKC and ERK activation and so it belongs to the same survival signalling pathway (Kim, E. J., Raval, Hirsch, & Perez-Pinzon, 2010).

Activation of the SAFE pathway leads to moderate TNFα production, which binds to the TNF receptors of the target cells. This activates the Janus kinase (JAK/STAT) pathway inside the cell and leads to modifications in response to different cytokines and growth factors, like IL-6 and VEGF. This pathway promotes cell survival and anti-inflammatory response (Harrison, 2012).

Adenosine, endocannabinoids, bradykinin, and ROS

Adenosine is produced and released from the hypoxic and ischaemic cells as ATP, ADP, and AMP are depleted to adenosine (Barletta, Ley, & Mehrad, 2012). Adenosine A_1 receptor (A1R) is abundant in the brain and heart and has been shown to mediate opioid-induced cardiac protection as well as cerebral protection through IPC (Heurteaux, Lauritzen, Widmann, & Lazdunski, 1995; Hu et al., 2012; Reshef, Sperling, & Zoref-Shani, 2000; Yao, Wong, Xia, & Irwin, 2011; Yoshida, Nakakimura, Cui, Matsumoto, & Sakabe, 2004). Mediating these processes involves the activation of mitochondrial K_{ATP} channels (Heurteaux et al., 1995;

Reshef et al., 2000; Yoshida et al., 2004). In addition, the previously mentioned MAPK and PKC pathways are also activated by adenosine, leading to cerebral protection (Reshef et al., 2000). Endocannabinoids have been linked to improved spinal cord protection by RIPC through endocannabinoid 1 receptors with possible elevations in CGRP and prostaglandins. However, studies have not yet been conducted regarding cerebral protection (Rehni, Singh, & Jaggi, 2007; Su, B. et al., 2009).

Bradykinins are proinflammatory in nature and are released into the bloodstream during ischaemia and cellular damage. They are both humoral and neuronal factors, as their effect can be blocked with both nerve blocking and receptor antagonists (Austinat et al., 2009). Their two main receptors, B1R and B2R, are abundant in the CNS. B1R antagonists have been shown to be neuroprotective but the role of B2R is unclear, as both activation and inactivation led to neuroprotective effects (Austinat et al., 2009; Lumenta et al., 2006; Su, J., Tang, Zhou, Liu, & Dong, 2012). However, there is also evidence that bradykinin is not an important factor for RIPC as its inhibition did not block the effects of RIPC in humans (Pedersen et al., 2011).

As is clearly evidenced by the earlier discussion, excess ROS formation is detrimental to cell survival (Sprick et al., 2019). However, moderate ROS production elicits an innate antioxidant defence mechanism (Ambrosio, Tritto, & Chiariello, 1995). ROS activates Nrf2, which, in turn, induces the transcription of numerous antioxidants (Bell, Fowler, Al-Mubarak, Horsburgh, & Hardingham, 2011; de Vries et al., 2008; Esteras et al., 2016; Perez-Pinzon, Stetler, & Fiskum, 2012; Zhang, M. et al., 2013). Mild oxidative stress produced by RIPC and IPC has been shown to prepare neurons for a more severe ischaemic insult, mainly through mitochondrial K_{ATP} opening and antioxidant upregulation (Bell et al., 2011; Thompson, Narayanan, & Perez-Pinzon, 2012).

Studies utilizing IPC for cerebral protection have noted that it has numerous protective mitochondrial effects, including preservation of membrane integrity and oxidative phosphorylation (Sisalli, Annunziato, & Scorziello, 2015; Thompson et al., 2015). Additionally, our group demonstrated that RIPC attenuates a respiratory chain redox state in the brain after global brain ischaemia (Yannopoulos et al., 2014). As was previously discussed, excess Ca^{2+} in the mitochondria has detrimental effects, and so the role of Na^{+}- Ca^{2+} exchangers have been studied in neuroprotection. They seem to be abundant in the mitochondrial membra after preconditioning stimulus and aid in cerebral protection. Na^{+}- Ca^{2+} exchangers

interplay with the ER, which also plays a crucial role in storing and releasing Ca^{2+} (Sisalli et al., 2015).

Mitochondrial K_{ATP} channels

Mitochondrial inner membrane K_{ATP} channels seem to be the endpoint of most protective pathways of RIPC (O'Rourke, Cortassa, & Aon, 2005; Pérez-Pinzón & Born, 1999; Reshef et al., 2000; Thompson et al., 2015). This channel is thought to be the deciding factor between life and death of the cell (O'Rourke et al., 2005). They are abundant in mitochondria of every cell, but neurons express K_{ATP} channels seven times more than cells in the liver or the heart (Bajgar, Seetharaman, Kowaltowski, Garlid, & Paucek, 2001). The K_{ATP} channels are activated by excess adenosine through A1R during hypoxia and ischaemia (Heurteaux et al., 1995; Reshef, Sperling, & Zoref-Shani, 2000; Yoshida et al., 2004). Activation of PKC and the PIK3/Akt pathway can also lead to K_{ATP}-channel induction (Wang, Y. et al., 2001). The activation of K_{ATP} opens the channel, resulting in decreased synaptic transmission and K^+-dependant glutamate release (Rudolphi, Schubert, Parkinson, & Fredholm, 1992). It also inhibits the presynaptic Ca^{2+} efflux and the mitochondrial Ca^{2+} influx during ischaemia, mitigating the ischaemic cascade (O'Rourke et al., 2005). Moderately increased ROS production is also present, leading to the antioxidative properties discussed earlier (Ravati, Ahlemeyer, Becker, Klumpp, & Krieglstein, 2001). However, the most important protective function of the activated K_{ATP} channels involves limiting the opening of MTPTs, preventing mitochondrial swelling, AD, and failure from I/R injury (O'Rourke et al., 2005). The same phenomenon has also been studied in humans (Loukogeorgakis et al., 2007). Studies regarding the cerebral protective effects of K_{ATP} channels remain absent (Meller & Simon, 2015).

2.4.6 Clinical applications of RIPC

Encouraged by the promising results of RIPC in cardiac protection, small clinical studies were conducted to reproduce these results in humans. The first clinical study concerning RIPC involved children undergoing cardiac surgery. It was published in 2006 by Cheung et al.; they noted a smaller release of cardiac enzymes after surgery (Cheung et al., 2006). Attenuation of myocardial injury by RIPC was also noted in adults undergoing CABG (Hausenloy et al., 2007; Yang, Wang, Du, Ji, & Zheng, 2014). Positive results regarding the prevention of acute kidney injury (AKI)

by RIPC were also noted (Zimmerman et al., 2011). In addition to mitigating myocardial injury, RIPC was also shown to reduce mortality after CABG in a randomized, controlled study by Thielman et al (Thielmann et al., 2013). RIPC has also been shown to reduce the release of cardiac enzymes and the infarct size after percutaneous coronary intervention (PCI) in both elective and acute settings compromised by ST-elevation myocardial infarction (Bøtker et al., 2010; Eitel et al., 2015; Pei et al., 2014; White, S. K. et al., 2015). In the CRISP stent study by Hoole et al., there were significantly less cerebral and cardiac adverse events in the RIPC group than in the control group six months after percutaneous coronary intervention (PCI) (Hoole et al., 2009). Surprisingly, that difference was also present six years after PCI (Davies et al., 2013).

Two randomized, controlled, multi-centre trials were conducted with the goal of endorsing a wider use of RIPC in cardiac surgery; RIPHeart and ERICCA (Hausenloy et al., 2015; Meybohm et al., 2015). RIPC was applied with a blood pressure cuff through four cycles of 5 minutes of ischaemia and 5 minutes of reperfusion to an upper limb before subsequent CABG. However, these studies revealed that there were no significant differences regarding mortality, MI, repeat revascularisation, stroke, and AKI (Hausenloy et al., 2015; Meybohm et al., 2015). The same result was also noted in a large meta-analysis (Pierce, Bole, Patel, & Brown, 2017).

Even though these multi-centre trials were carefully planned and executed, there are certain limitations to these studies that have to be taken into account before forming permanent conclusions. First of all, these patients were very sick, with mean EuroSCOREs of 4.2 and 6, respectively. Most of the patients had hypertension, diabetes mellitus, and hypercholesterolemia, all of which could have interfered with the effects of RIPC. Routine protective measures, such as CPB, hypothermia, and cardioplegia solutions might have concealed the positive effects of RIPC (Hausenloy et al., 2015; Meybohm et al., 2015). In addition, it seems that the anaesthetic agents isoflurane and propofol protect the heart and other vulnerable organs from the ischaemic insult by using different mechanisms, simultaneously blocking the pathways associated with RIPC (Kottenberg et al., 2012; Kottenberg et al., 2014; Lucchinetti et al., 2012; Pierce et al., 2017; Zaugg, Lucchinetti, Clanachan, & Finegan, 2012). One of these molecular mechanisms is STAT5, which is closely associated with the SAFE pathway (Kottenberg et al., 2014). Additionally, propofol has been shown to impair cerebral metabolism during ischaemia and hypothermia (Dahlbacka et al., 2006). A recent meta-analysis revealed that RIPC reduced the incidence of AKI when propofol was not used,

though this effect disappeared with the use of propofol. However, there were no differences in ischaemic protection of other vital organs, even without the usage of propofol (Pierce et al., 2017). Moreover, the anaesthesia, perfusion methods, and postoperative care were not unified in the multi-centre studies. Additionally, most of these patients had propofol at some point during anaesthesia, which complicates the interpretation of these results. Finally, it has to be noted that the three big studies (CRISP Stent, RIPHeart, and ERICCA) all used the upper limb as the source of RIPC, which could create a more subtle response that might not be enough to elicit protection from greater ischaemic insult. It is worth noting that most of the human studies with a positive result applied RIPC to a lower limb (Johnsen et al., 2016).

These results proved that RIPC would not be effective in cardiac protection for all patients undergoing cardiac surgery, especially CABG, but did not necessarily mean that it would have to be removed from other procedures, such as aortic arch surgery. The PCI studies showed better results, possibly due to a less significant use of anaesthetics. Promising news has also come from the fields of vascular surgery and neurology, as RIPC-enhanced cerebral protection in carotid endarterectomies (Walsh et al., 2010) reduced the size of brain infarctions when applied with thrombolysis (Hougaard et al., 2014) and enhanced motor learning in healthy adults (Cherry-Allen, Gidday, Lee, Hershey, & Lang, 2015). However, RIPC failed to reduce white matter injury on children undergoing cardiac surgery with CPB (Gaynor et al., 2018). In summary, the patient population, procedure, and protected organ in regard to RIPC need to be studied further for it to gain a permanent position in the realm of protection from ischaemic injury.

Large animal studies in cardiac surgery on cerebral protection by RIPC

Studies regarding the cerebral protection of RIPC have been mostly performed on smaller animals and without either cardiac surgery or CPB (Dave et al., 2006; Vlasov et al., 2005). Our research group utilized our well-established porcine model to this matter to obtain a more realistic clinical setting.

The initial study was conducted by Jensen et al. with the help of personnel led by Professor Tsang from the Great Ormond Street Hospital in London. It proved to be a landmark paper in RIPC-induced cerebral protection as it suggested that RIPC lowered the lactate discharge, hastened the recovery of EEG, improved neurological recovery, lowered the leakage of glial-specific S100 calcium binding protein B, and reduced cerebral injury in histopathological analyses after 60 minutes of HCA at 18°C (Jensen et al., 2011). This mode of ischaemia was used in

all subsequent studies. The findings indicating a faster recovery of EEG were repeated in the next study. Microdialysis analysis also showed changes in glucose, glycerol, lactate, and pyruvate, indicating a better metabolism pattern in the RIPC group (Yannopoulos et al., 2010). The metabolic changes also extended to the oxygen metabolism, as RIPC preserved higher cerebral oxygen tension throughout the 60-minute HCA period as compared to the control group (Yannopoulos et al., 2012). RIPC seemed to also be effective in preserving the cerebellar ERs, reducing the number of adherent leukocytes in the cerebral circulation and providing better respiratory chain function, as indicated by the higher NADH content (Yannopoulos et al., 2014).

The findings regarding respiratory chain function guided subsequent studies toward oxidative stress. Lower levels of oxidative stress marker 8-hydroxydeoxyguanosine were found after HCA in two different studies (Arvola et al., 2016a; Arvola et al., 2016b). The most recent study revealed the previously noted mitigation of glial-specific S100 calcium binding protein B release and lactate discharge but also showed a favourable antioxidant response to RIPC (Herajärvi et al., 2017).

As the use of HCA is limited to a maximum duration of 30 minutes at deep hypothermic temperatures (Krüger et al., 2011), and the concrete advantage of RIPC was still unclear, we decided to examine whether RIPC could prolong the calculated permissible period of HCA and lead to better rates of survival and neurological recovery after clinically applicable durations.

3 Aims of the study

The purpose of these studies was to evaluate the efficacy of RIPC in cerebral protection before experimental HCA. The safety of an alternative cannulation in a surgical model of ATAAD was also investigated.

I

To assess the safety of DTLC after venous exsanguination in terms of cerebral and global ischaemia.

II

To study whether RIPC suppresses cerebral metabolism during cooling with CPB and prolongs the permissible period of HCA.

III

To evaluate the synergistic effect of RIPC and moderate hypothermia on neurologic outcome after HCA and to confirm that RIPC prolongs the permissible period of HCA during cooling with CPB.

4 Author's contribution

The author of the present thesis played a crucial role in all the original publications (Studies I, II, and III) that this dissertation is based on. These studies were supervised primarily by Professor Tatu Juvonen, along with the other senior researchers. The author's contributions were as follows:

He was the first author in them all and therefore was responsible for data curation and analysis, interpretation of the results, manuscript draft writing, and editing of the final versions. He was responsible for the main surgical procedures: thoracotomies, heart cannulation, cerebral procedures, and exposure of the common carotid artery. He and H-P Honkanen were responsible for the monitoring periods and intensive care unit supervision postoperatively. He participated in the daily follow-up and pain medication delivery to the pigs and fed them if necessary. He was also responsible for obtaining the brain post-euthanisation.

He also had administrative duties, including research grant acquisitions, obtaining of laboratory animal licenses, and material subscriptions. The author of the present thesis held two oral presentations on study II, one at the 2017 annual meeting of the Scandinavian Association of Thoracic Surgery (SATS) in Helsinki and one at the 2018 Aortic Symposium of the American Association of Thoracic Surgery in New York. In Helsinki, he was awarded the SATS prize for Best Presentation. He also gave oral presentations on study I at the 2018 SATS annual meeting in Copenhagen and at the Finnish Operative Days 2018 in Helsinki, receiving one of the two prizes. He also orally presented study III at the 2019 SATS annual meeting in Stockholm, receiving the C. Walton Lillehei Young Investigator's award.

5 Materials and methods

This thesis involves three experimental studies on a porcine model. Studies I and III were completed with a surviving porcine model; the pig lived for seven days postoperatively. Study II was performed with an acute porcine model. All studies were randomised and controlled. The same basic HCA model was used for all three studies. The most important differences are presented in Table 1.

Table 1. The most important differences between the studies.

Study	I	II	III
Number of pigs	12	20	16
Donor pigs	yes	no	yes
Surviving model	yes	no	yes
Intervention	DTLC	RIPC	RIPC
HCA temperature	25°C	11°C	18°C or 24°C
HCA duration	25 min	45 min	30 min

5.1 The porcine model

The porcine model that was used in these studies was originally developed by Professor Randall B. Griepp and his associates from Mount Sinai School of Medicine in New York. Professor Tatu Juvonen brought the model to Finland after working under Professor Griepp's guidance at Mount Sinai. The first experiments were conducted with Kai Kiviluoma and Vesa Anttila at the Cardiothoracic Research Laboratory in Oulu in the autumn of 1997. The porcine model has been used ever since and has been refined for different study purposes.

5.2 Experimental animals and preoperative management

Pigs from a native stock (Utajärvi, Finland) were used in these studies. The pigs weighed from 22 kg to 30 kg in studies I and III. In study II, larger pigs were used (39 to 45 kg) to avoid the need for donor pigs. All pigs received humane care in accordance with the European Union directive on the protection of animals used for scientific purposes (2010/63/EU) and the Finnish act on the protection of animals used for scientific purposes (FINLEX 497/2013). The study protocol was approved by the Finnish National Animal Experiment Board. Continuous communication between researchers and professional animal caretakers took place

during the experiments. The 3Rs, the rules of reduction, refinement, and replacement, were used in planning the experiments. The pigs arrived at the facilities of the Laboratory Animal Centre one week prior to operation and were monitored numerous times throughout the day by researchers and animal caretakers.

5.3 Anaesthesia and monitoring

Anaesthesia induction was carried out similarly in all animals via an intramuscular injection of ketamine hydrochloride (15 mg/kg), midazolam (2 mg/kg), and medetomidene (0.075 mg/kg). A peripheral venous cannula was inserted in both ears to facilitate infusion of medications and fluids. Intravenous fentanyl (50 μg/kg) was administered for pain relief and relaxation prior to endotracheal intubation. Continuous intravenous infusion of fentanyl (25 μg/kg/h), midazolam (0.25 mg/kg/h), and rocuronium (1.5 mg/kg/h) was used to maintain anaesthesia during the operation and intensive follow-up. Prophylactic antibiotic cefuroxime (1.5 g) and glycopyrronium bromide (0.2 mg) were given prior to the operation. The pigs were placed in a respirator system (GE Healthcare, Madison, WI, USA) and ventilated with 40/60% oxygen-air and sevoflurane (1.0 % end-tidal concentration). An end-tidal carbon dioxide level of 4.7-5.0% was maintained by adjusting the tidal volume. An ECG lead II was used to monitor the heart and an 8 Fr urinary catheter was placed in the bladder to monitor diuresis. A temperature probe was inserted into the rectum for body temperature monitoring.

In studies I and II, an arterial needle was placed in the left femoral artery for blood pressure monitoring and arterial blood sampling while the right femoral artery was used in study III. In studies I and II, a pulmonary artery catheter (CritiCath; Ohmeda GmbH & Co, Erlangen, Germany) was inserted via the left femoral vein and introduced into the pulmonary artery to permit mixed venous blood sampling and to measure pulmonary artery pressure, central venous pressure, CO, pulmonary capillary wedge pressure, and blood temperature. In study III, the right femoral vein was used for same purposes. In all studies, PaO2, PaCO2, pH, haematocrit, haemoglobin, sodium, and potassium were measured from arterial and sagittal sinus or central venous blood samples. In addition, blood glucose, ionized calcium, and lactate were measured from the venous blood samples. A blood gas analyser (i-STAT Analyser; i-STAT Corporation, East Windsor, NJ, USA) was used for the measurements. Haemodynamic measurements were recorded, and arterial and venous blood samples were collected in studies I and III at six time points: at

baseline, immediately prior to the HCA, and at 30 minutes, 2 hours, 4 hours, and 6 or 8 hours after the beginning of re-warming.

5.4 Cranial operations

In studies II and III, a cranial window was created over the superior sagittal sinus with a 12 mm cranial perforator (200-253 DGR-II, Agra Cut Inc., Acton MA, USA), exposing the dura mater, after a rectangular opening was created in the cranial skin. The superior sagittal sinus was then cannulated with a 22 G venous cannula for collecting cerebral venous blood. A temperature probe was then inserted deep into the brain parenchyma through the dura mater for monitoring brain temperature throughout the experiment.

5.5 Cardiopulmonary bypass

In studies I and II, a right-sided thoracotomy to the 4th intercostal space was made to expose the heart and the great vessels. A left-sided approach to the 3rd intercostal space was used in study III. The ascending aorta was cannulated with a 16 Fr aortic cannula and the right atrial appendage with a 24 Fr atrial cannula through purse-string sutures. In study III, the left ventricle was decompressed with a 12 Fr cannula inserted via the left atrial appendage. 500 IU/kg of heparin were administered for anticoagulation two minutes prior to cannulation. A membrane oxygenator (D905 Eos, Dideco or Inspire 6, Livanova, Mirandola, Italy) with a venous reservoir was used. Priming of the CPB circuit was done with 15000 IU of Heparin and 500-800 ml of Ringer-acetate; 1000 ml of donor blood from a porcine universal donor was used in studies I and III but not in study II.

CPB was initiated with a pump flow rate of 80 ml/kg/min and then adjusted to a MAP of 60-80 mmHg. The perfusion was performed using an alpha-stat strategy to mimic clinical practise. Cooling and warming gradient was kept at 7°C between the brain temperature and blood temperature in studies II and III. In study I, the same gradient was used between the rectal temperature and the blood temperature. After the cooling period, the ascending aorta was clamped distally to the cannula and 40mmol of potassium chloride was injected to achieve diastolic cardiac arrest during the HCA period. Ice-cold topical saline was used as myocardial protection. Warming perfusion was started after the HCA period. At the beginning of the warming perfusion, furosemide (40 mg), mannitol (15 g), methylprednisolone (80 mg), lidocaine (40 mg), and calcium gluconate (1375 mg) were administered to

induce diuresis and to prevent brain oedema, inflammation, and arrhythmias, respectively. If necessary, the heart was defibrillated at 30 °C. After reaching the target temperature of 36 °C, the heart was decannulated and protamine was administered.

5.6 Donor pigs

Donor pigs (35 kg to 45 kg) were used in studies I and III to prevent haemodilution during CPB. Donor blood could be used because pigs do not have different blood types. The donor pigs were anaesthetised in the same way as the experimental pigs. After heparinisation (500IU/kg), 1000ml of whole blood was harvested from the right femoral artery into the CPB circuit. The pigs were then euthanised with sodium pentobarbital (90mg/kg).

5.7 Remote ischaemic preconditioning

In studies II and III, RIPC was performed with a children's blood pressure cuff prior to cooling with CPB. A static pressure of 300mmHg was used for five minutes before the cuff was deflated for five minutes. This cycle was repeated four times. The control group was monitored in the same setting without inflating the cuff. Occlusion of circulation was confirmed with invasive arterial pressure readings, pulse palpation, and capillary reactions. In study II, RIPC was performed on the right hind limb; the left hind limb was used in study III. CPB was instituted 20 minutes after the last cycle in study II and 30 minutes after the last cycle in study III.

5.8 Simulation of direct true lumen cannulation after venous exsanguination

In study I, the intervention group underwent a 5-minute circulatory arrest at 35 °C to simulate the time required for DTLC after venous exsanguination before the start of the cooling perfusion. In the control group, cooling perfusion was started as normal. Circulatory arrest in the intervention group was achieved via exsanguination from the venous cannula into the venous reservoir, clamping the ascending aorta distally to the aortic cannula, and injecting potassium chloride (40 mmol) through the aortic cannula into the coronary arteries. After 5 minutes, the aortic clamp was taken off and cooling perfusion was started.

5.9 Calculations of the permissible period of HCA

Calculations of the permissible period of HCA were used in studies II and III. Sagittal sinus and arterial blood samples were taken simultaneously to calculate the cerebral arteriovenous oxygen content difference. The cerebral metabolic rate for oxygen using CBF and cerebral arteriovenous oxygen content difference was calculated using the following formula:

$CMRO_2$ = CBF x (arterial oxygen content – sagittal sinus oxygen content)/100.

The cerebral arteriovenous oxygen content difference was calculated using the following formula:

A-V O_2 difference = (Hb x 0.1)(1.34)(AO_2 sat – VO_2 sat) + 0.003(ApO_2 – VpO_2)
where Hb is arterial haemoglobin (g/l), AO_2 is arterial oxygen saturation (with decimals), $V0_2$ is sagittal sinus oxygen saturation (with decimals), ApO_2 is arterial oxygen pressure (mmHg) and VpO_2 is sagittal sinus oxygen pressure (mmHg).

The Q10 for cerebral metabolism is defined as the ratio of two $CMRO_2$ values that are 10 °C apart from each other. First, an estimate of the slope (m(x)) of the line stating the natural logarithm of the $CMRO_2$ was plotted against temperature t in the cooling period:

$$\ln CMRO_2\,(x,t) = a(x) + m(x)t$$

where a(x) is a patient unique intercept, m(x) is the slope of the line for each animal and t is temperature. The mean slope m was then found for both groups, after which the Q10 could be solved as the ratio of the $CMRO_2$ at the temperature of t and t - 10. Assuming that the permissible period of circulatory arrest at 38 °C for pigs is 5 minutes and that cerebral protection is only achieved with metabolic suppression by hypothermia, the permissible periods of HCA can be calculated for any given temperature.

In study II, CBF, $CMRO_2$ and cerebral oxygen extraction were measured at seven time points: at baseline (before the RIPC cycle), during cooling at 28 °C and 22 °C along with during warming at 15 °C, at 22 °C, at 29 °C, and at 36 °C. Deep brain temperature was used to define the given temperature point. In study III, measurements were taken in both groups at baseline, during cooling at 30°C and at 24°C, and at 18°C for the control group. In addition to the samples taken for the measurements of the permissible period of HCA, measurements of lactate, partial

pressures of oxygen and carbon dioxide, and oxygen saturation were taken during the HCA at 15 minutes, during warming at 15 and 30 minutes, and at 2, 3, 4, 5, and 6 hours after the start of warming.

5.10 Postoperative management and neurobehavioral evaluation

In study II, the pigs were euthanised using sodium pentobarbital (90mg/kg) after the last measurements and blood samples were taken. In study I, all pigs underwent warming perfusion to 36 °C and were monitored for eight hours. After the monitoring period, the pigs were extubated, weaned off the anaesthesia, and observed until the next morning, at which point they were transferred back into stalls. The pigs were monitored for seven days postoperatively with adequate pain relief and then euthanised with sodium pentobarbital (90 mg/kg). The same protocol was used in study III, although the monitoring period was six hours.

During the seven-day follow-up period, a neurobehavioral evaluation was conducted daily at 1 p.m. by an experienced observer masked to the experimental set-up. A species specific, quantitative scoring system was used. The scoring system included an assessment of mental status (0 = comatose, 1 = groggy, 2 = depressed, 3 = habitual), appetite (0 = refuses liquids, 1 = refuses solids, 2 = decreased, 3 = normal), and motor function (0 = unable to stand, 1 = unable to walk, 2 = unsteady gait, 3 = normal). Scores were then summed; the maximum score of 9 was set to represent full recovery.

5.11 Histopathological analysis

After euthanisation, the brain was harvested and fixed into neutral 10% formalin for two weeks. Samples were collected from the cortex, thalamic region, hippocampus, cerebellum, and pons. Afterward, the samples were embedded in paraffin and stained with hematoxylin-eosin. An analysis was conducted by an experienced neuropathologist blinded to the study protocol. Samples were analysed using a semi-quantitative scoring system, including the presence of edema (0-3), haemorrhage (0, 2-3), neuronal degeneration (0, 2-3), and the presence of infarcted tissue (0, 3).

5.12 Neuron specific enolase analysis

In studies I and III, quantitative sandwich enzyme-linked immunosorbent assay (MyBioSource) was used to determine the plasma levels of neuron-specific enolase during the operation. The analysis was done according to the manufacturer's instructions by an experienced cell biologist who was blinded to the operative protocol. The baseline levels of neuron-specific enolase showed wide variance between different pigs, forcing us to analyse the values as a ratio to the baseline values.

5.13 Near-infrared spectroscopy

A NIRS sensor (INVOS cerebral oximetry, Medtronic, Minneapolis) was placed on the skin over the frontoparietal cortex to measure continuous regional cerebral oxygenation throughout the experiments in studies I and III. The NIRS values were recorded as absolute values but also compared to the baseline values for each pig. A 25% drop from the baseline values was considered clinically significant.

5.14 Statistical analysis

Statistical analyses were performed using SPSS (IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and SAS (Version 9.4; SAS Institute, Cary, NC) statistical software. Continuous and ordinal variables are presented as medians and 25th and 75th percentiles or means and 95% confidence intervals depending on the normality of the values. The Mann-Whitney U test was used to determine the P values between the groups for continuous variables. Fisher's exact test was used to determine the P values between the groups for categorical variables. A linear mixed model analysis was performed to analyse repeatedly measured data. The pigs were fitted at random, and the best covariance pattern was chosen using Akaike's information criterion. Reported P values were exact and two-tailed, and the analyses were exploratory in nature. The P value of <0.05 was considered significant. P between groups was marked with P_g and P between groups and time was marked as $P_{g \times t}$. An experienced biostatistician familiar with laboratory animal experiments assisted in the statistical analyses.

6 Results

6.1 Study I

6.1.1 Comparability of the study groups

There were no significant differences in the average sizes of the pigs in the intervention group (25.3 kg (24.6 – 26.9)) and the control group (25.2 kg (23.5 – 25.4)) (P = 0.509) nor in the amount of donor blood used (39.5 ml/kg [37.3-40.7] vs. 39.8 ml/kg [39.3-42.6], [P = 0.509]). In the baseline measurements, the cardiac index was higher in the control group (3.6 l x min^{-1} x m^{-2} (3.4 – 4.0)) than in the intervention group (3.2 l x min^{-1} x m^{-2} (2.8 - 3.4) (P = 0.04)). This difference, however, was not clinically significant, as both values indicate sufficient cardiac output. There were no differences in other baseline measurements.

6.1.2 Blood sampling

The 5-minute circulatory arrest at 35°C led to immediate mild lactatemia in the intervention group, as would be expected. Systemic lactate levels in the intervention group were higher throughout the experiment. A graphical presentation of the systemic lactate levels is shown in Figure 6.

6.1.3 Neuron specific enolase analysis

A significant amount of variance was present in the baseline values, weakening the reliability of the analyses. Each pig was compared to its own baseline value. There were no differences at any timepoint.

6.1.4 Near-infrared spectroscopy

During the circulatory arrest at 35°C, the NIRS values of the intervention group dropped steeply, as would be expected, and remained below the values of the control group at the halfway point of cooling (P=0.004). During the cooling period, the NIRS values remained significantly under 75% of baseline values in the intervention group (8.0 [5.0-11.5] minutes) as compared to the control group (1.5 [0.8-4.3] minutes) (P=0.017).

During the warming period, the control group tended to reach a higher NIRS value than the intervention group (58.0 % [55.5-66.8] vs. 68.5 % [63.5-69.0], [P=0.054]). NIRS curves are presented in Figure 7.

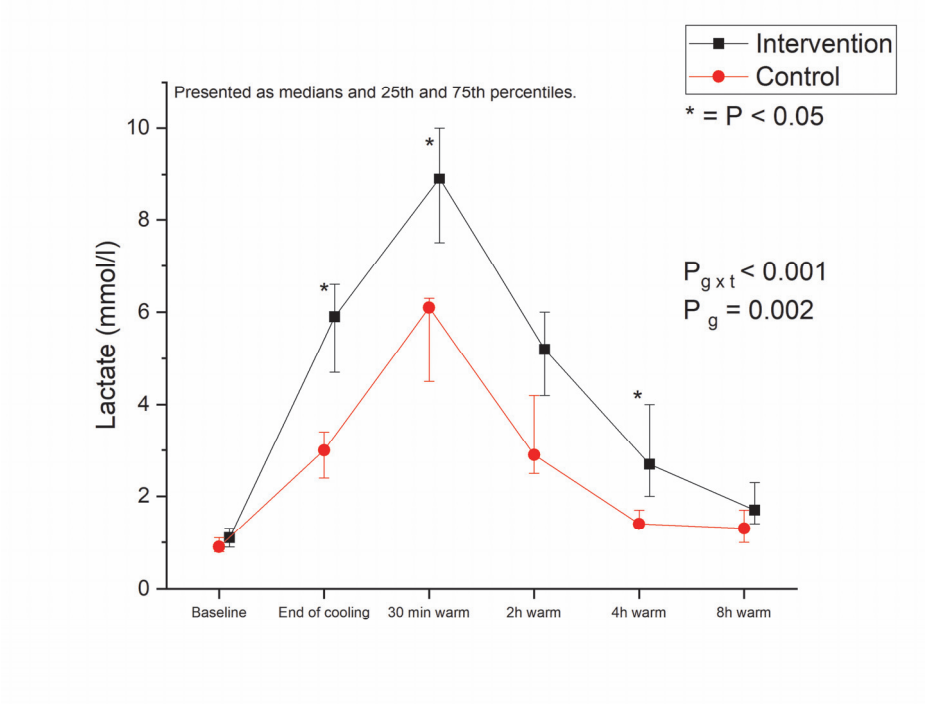

Fig. 6. Systemic lactate levels in study I. Reprinted with permission from Oxford academic.

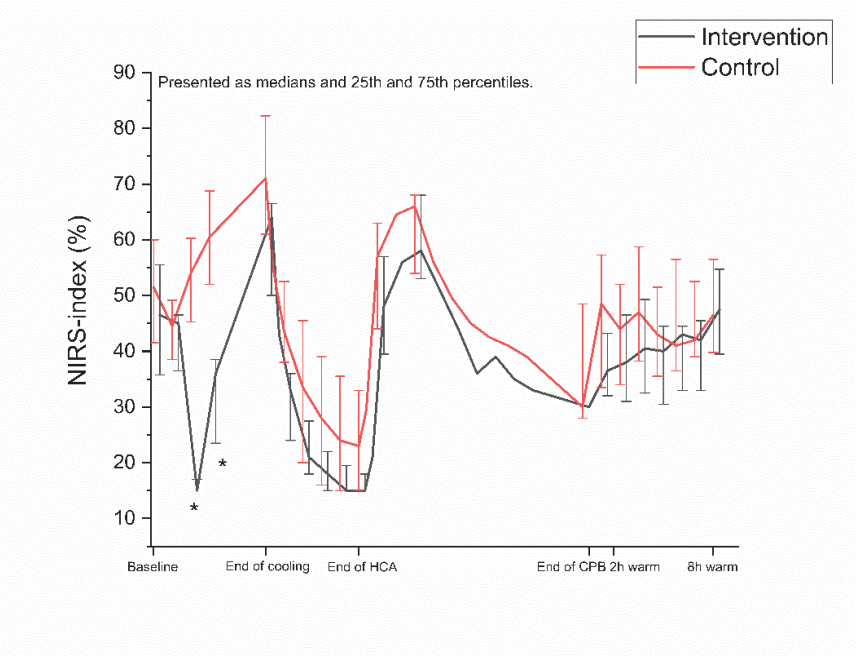

Fig. 7. Median NIRS-curves during the operation and the monitoring period in study I. * = *P* < 0.05 at a single timepoint. Reprinted with permission from Oxford academic.

6.1.5 Histopathological analysis

The histopathological analysis revealed only slight oedema and few haemorrhagic foci, which are considered signs of mild neuronal injury. Histopathological strokes were not present. There were no differences in any of the anatomical sections between the study groups.

6.1.6 Neurobehavioral evaluation

Normal neurological behaviour was reached in both groups on the 4th postoperative day the latest. On the second postoperative day, the intervention group tended to have slightly better scores than the control group (9 (8.75-9) vs. 6.5 (5.5-9)) (P=0.061). The sum of the mental status scores from the first two postoperative days was higher in the intervention group than in the control group (5.0 (4.0-5.0) vs. 3.0 (2.75-4.25)) (P=0.045). Graphical illustration is presented in Figure 8.

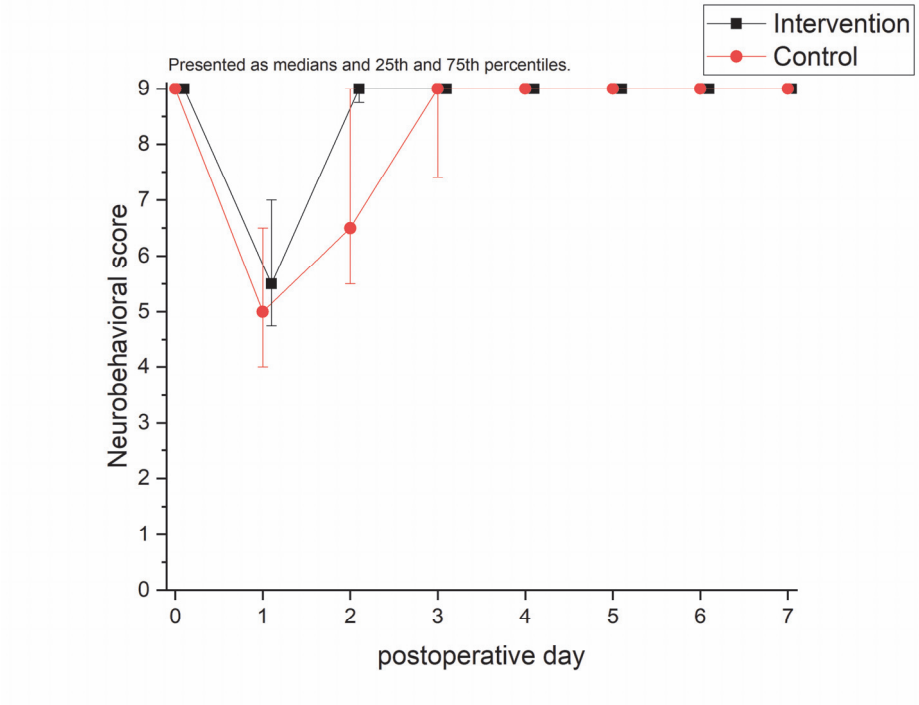

Fig. 8. Neurobehavioral scores in study I. Reprinted with permission from Oxford academic.

6.2 Study II

6.2.1 Comparability of the study groups

There were no differences between the groups in terms of the weight of the pigs (39.4 kg (38.5 – 41.4) in the RIPC group and 42.6 kg (38.7 – 45.1) in the control group) (P = 0.123) nor in the baseline haemodynamic measurements. The haematocrit level was higher in the RIPC group than in the control group at baseline (26.0 [25.5 – 28.5] vs. 23.5 [22.8 – 27.3], [$P < 0.05$]). The same finding was present during both cooling and warming at 22°C.

6.2.2 *Permissible period of HCA*

The Q10 value tended to be higher in the RIPC group than in the control group (2.27 [1.98 – 2.58] vs. 1.87 [1.61 – 2.25], [P = 0.063]). This was translated into a tendency toward a longer calculated permissible period of HCA at 18°C (26 [20 - 33] vs. 17 [13 - 26], [P = 0.063]). Permissible periods of HCA are presented in Figure 9.

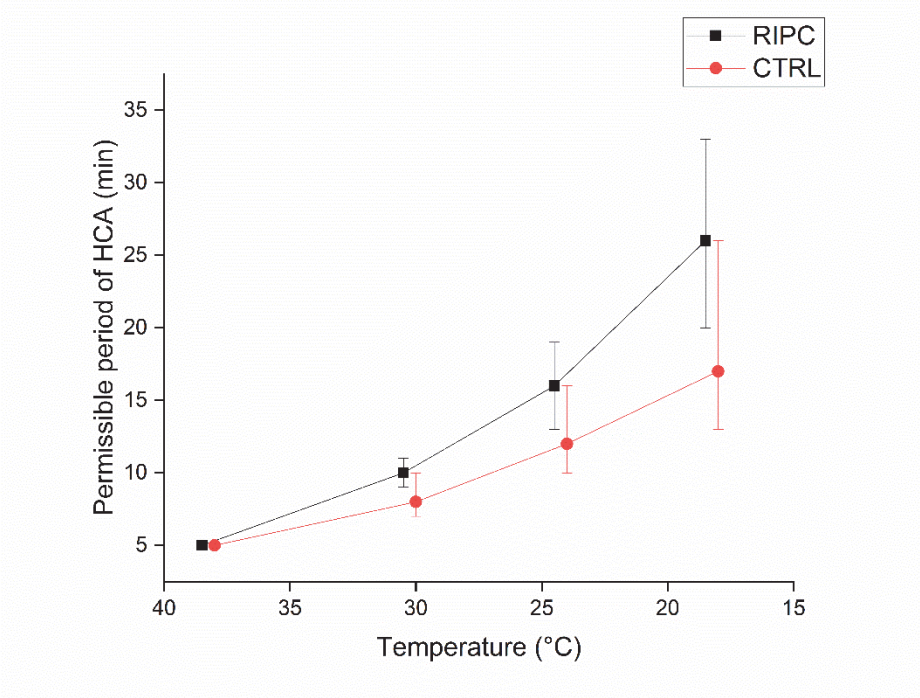

Fig. 9. Permissible periods of HCA in study I. Presented as medians and 25th and 75th percentiles. RIPC = remote ischaemic preconditioning group, CTRL = control group. Reprinted with permission from Taylor & Francis.

6.3 Study III

6.3.1 *Comparability of the study groups*

The median weight of the pigs was 23.5 kg (23.0 – 26.3 kg) in the RIPC group and 26.1 kg (23.9 – 28.0 kg) in the control group (P = 0.224). The groups received a

comparable amount of donor blood (43.1 ml/kg [40.7 – 44.2] vs. 40.3 ml/kg [37.7 – 46.0], P = 0.488). There were no differences in metabolic or hemodynamic measurements at baseline between the study groups.

6.3.2 Mortality

Two pigs in the RIPC group and six pigs in the control group died before the end of the follow-up period. The causes of death are presented in Table 2 and a Kaplan-Meier plot of survival is presented in Figure 10.

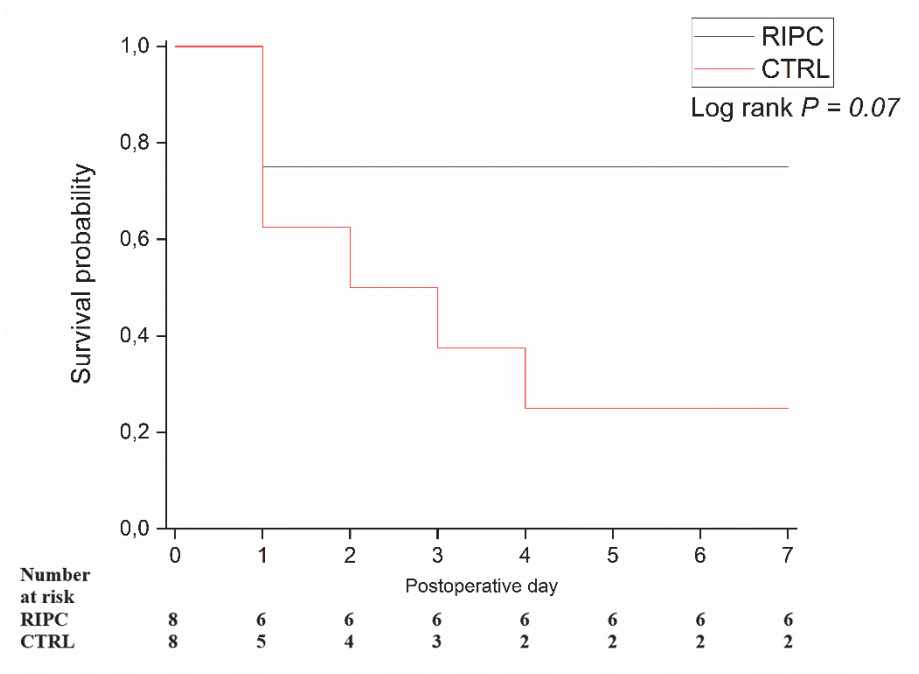

Fig. 10. Kaplan-Maier plot for overall survival in study III. RIPC = remote ischaemic preconditioning group, CTRL = control group. Reprinted with permission from Oxford academic.

Table 2. Mortality in study III.

Group	RIPC	Control
Global brain ischemia	0	1
Hemiplegia	0	1
LV failure	2	1
MOF	0	2
Unexplained	0	1

6.3.3 Blood sampling

After the HCA period, the lactate levels in the RIPC group increased more than the levels in the control group at 15 and 30 minutes since the start of the rewarming period (Figure). In the middle of the HCA period, the sagittal sinus saturation was lower in the RIPC group than in the control group 60 (52-70) vs. 79 (75-85), ($P < 0.05$).

6.3.4 Neuron specific enolase analysis

The baseline plasma neuron specific enolase levels ranged from 1.96 ng/ml to 22.79 ng/ml, which practically diminished the reliability of further analyses. There were not any differences between the groups at any timepoint.

6.3.5 Near-infrared spectroscopy

Despite the differences in the length of the cooling perfusion and HCA temperature, the RIPC group reached the same NIRS index as the control group at the end of the cooling perfusion. There were no differences in NIRS indexes during the HCA period, the warming perfusion, or the monitoring period. The NIRS curves are presented in Figure 11.

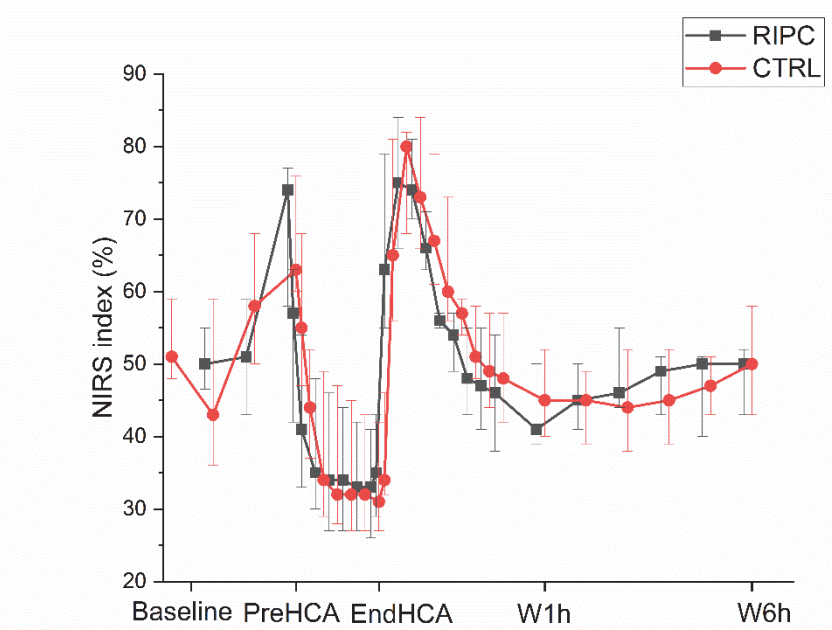

Fig. 11. Median NIRS-curves with interquartile ranges in study III. RIPC = remote ischaemic preconditioning group, CTRL = control group. Reprinted with permission from Oxford academic.

6.3.6 Histopathological analysis

Three pigs had a stroke in the control group; there was one haemorrhagic infarction with severe oedema and neuronal degeneration in the pons region and two smaller infarctions in the posterior cortex and cerebellum. One pig in the RIPC group had a small infarction area in the posterior cortex. The only difference between the study groups was the pons oedema score, which was worse in the control group than in the RIPC group (2.0 [1.0 – 2.3] vs. 1.0 [1.0 – 1.0]) (P = 0.042).

6.3.7 Permissible period of HCA

The Q10 value was higher in the RIPC group than in the control group (2.77 (2.36 – 3.13) vs. 1.80 (1.57 – 2.00)) (P = 0.007). This translated to a much longer

calculated permissible period of HCA at 24°C (21 min [17 – 25] vs. 11 min [9 – 13]) (P = 0.007). In addition, the permissible period of HCA in the RIPC group was significantly higher at 24°C than in control group at 18°C (21 min [17 – 25] vs. 16 min [12 – 20]) (P < 0.05). The permissible periods of HCA are presented in Figure 12.

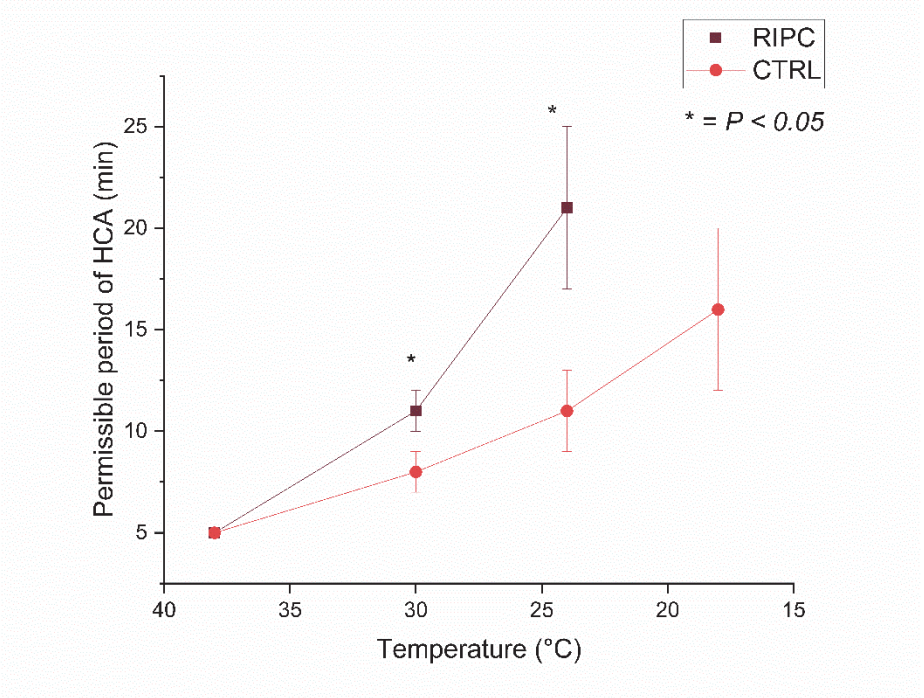

Fig. 12. Permissible periods of HCA in study III. Presented as medians and 25th and 75th percentiles. RIPC = remote ischaemic preconditioning group, CTRL = control group. Reprinted with permission from Oxford academic.

6.3.8 Neurobehavioral evaluation

The most important finding was that all six pigs in the RIPC group that survived from the operation day achieved normal neurological function but none of the pigs in the control group did (P = 0.007). The RIPC group also had higher scores than the control group on the second postoperative day (7.5 [5.8 – 8.3] vs. 4.0 [3.0 – 6.0]) (P = 0.031). In addition, the cumulative score of all postoperative days was

higher in the RIPC group than in the control group (55 [52 – 58] vs. 45 [39 -51], P = 0.026). Individual neurobehavioral scoring is presented in Figure 13.

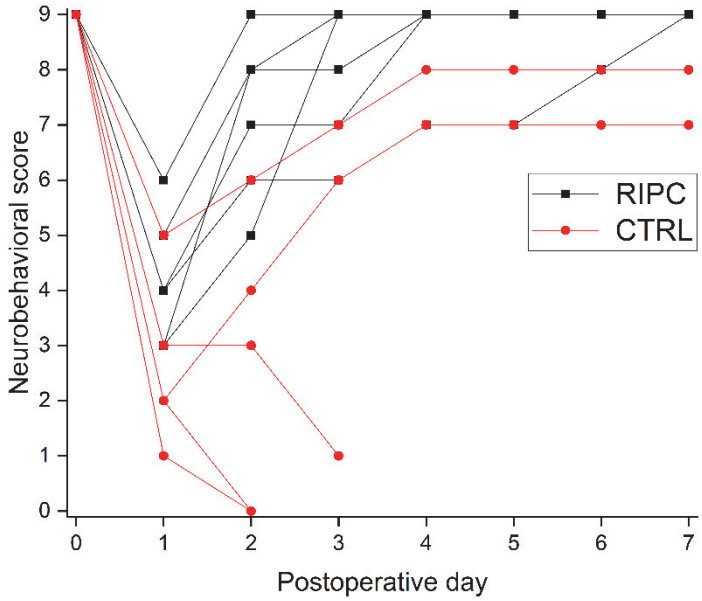

Fig. 13. Neurobehavioral scores in study III. RIPC = remote ischaemic preconditioning group, CTRL = control group. Reprinted with permission from Oxford academic.

7 Discussion

7.1 Study design

The HCA porcine model has proved to be of paramount importance in hypothesis testing for experimental cardiac surgery studies. The evidence from the pig model has been the scientific base of modern cerebral protection during aortic arch surgery since Dr Griepp's group developed it in the early 1990's. The main objectives in the present thesis were to test if it was safe to interrupt circulation at 35°C for 5 minutes followed by cooling with CPB and a subsequent HCA period, if RIPC could prolong the permissible period of HCA, and if RIPC with moderate hypothermia would improve cerebral protection and survival as compared to deep hypothermia alone. All these hypotheses could be tested adequately because of clinically similar monitoring and operational protocols that produce data that is understandable to clinicians. A seven-day evaluation period provides an accurate representation of the early recovery phase. Post-mortem histopathological analyses provide data on the brain that would not be procured in human studies. The experimental setting enables control of the HCA temperatures and the duration of the perfusion periods, which cannot be done in the clinical studies.

7.2 Near-infrared spectroscopy

The NIRS analyses did not reveal any major differences between the groups. As expected, the normothermic circulatory arrest in study I resulted in a rapid decrease in NIRS values. However, the intervention group reached the same level of brain oxygenation at the end of the cooling period. In study III, despite a shorter perfusion period and higher HCA temperature, the RIPC group reached the same NIRS values as the control group, indicating an enhanced suppression of global and brain oxygen consumption during cooling with CPB.

7.3 Histopathological analysis

In study I, there were no differences in histopathological findings between the groups. The HCA period was short and occurred at 25°C, which most likely preserved cerebral autoregulation. Thus, the findings mostly involved slight

oedema. Only few small haemorrhagic foci were present in both study groups. Cerebral infarctions and neuronal degeneration were not present in any of the pigs.

The histopathological findings were worse in study III than in study I. The three strokes in the control group were most likely caused by the longer HCA period. The one stroke in the RIPC group demonstrates that, even with enhanced suppression of cerebral oxygen consumption and preservation of cerebral autoregulation by moderate hypothermia, prolonged (> 30min) periods of HCA pose a risk for ischemic brain damage.

7.4 Permissible period of HCA

Study II proposed that there is a tendency toward a longer permissible period of HCA in the RIPC group at 18°C. However, the difference was not statistically significant. Another interesting proposition was that the RIPC group had the same permissible period of HCA at 24°C than the control group did at 18°C. This yielded the hypothesis of study III, that RIPC combined with moderate hypothermia would lead to a better neurologic outcome than deep hypothermia alone. Study III then revealed that RIPC enhances the suppression of cerebral metabolism during cooling with CPB at a rate even greater than what study II proposed.

Results regarding the Q10 and permissible periods of HCA are in line with the previous studies. The control group's Q10 was 1.80 in study III and 1.87 in study II. These matched the Q10 values in previous studies (2.05 in the human study). In study III, the RIPC group's Q10 of 2.77 was much higher than the Q10 of 2.27 in study II. This was most likely due to the avoidance of excessive haemodilution, which was present in study II.

7.5 Neurobehavioral evaluation

The neurological evaluation in study I showed only a slight advantage for the intervention group's total and mood scores after the first two postoperative days. Thus, no clear conclusions can be drawn.

Study III revealed that RIPC with moderate hypothermia provides a significantly better neurologic outcome than deep hypothermia alone. The finding was present both in the beginning of the postoperative period and at the end of the follow-up period, as six pigs in the RIPC group and none of the pigs in the control group achieved normal function.

7.6 Limitations

Though these studies were performed using a porcine model, the similarities in cerebrovascular physiology and anatomy between pigs and humans are commonly recognized and can result in strong extrapolation potential to human patients. The study protocol is highly traumatising for the animals and the 3R rules of animal research ethics (replacement, reduction, and refinement) urged us to use the smallest number of animals possible. This resulted in a small sample size in all of the studies; we therefore cannot exclude the possibility of a Type II statistical error, which can be considered the main limitation of the studies.

In studies I and III, the use of 10% formaldehyde could be considered a drawback, as the use formaldehyde can cause shrinking, which can result in artefacts. The use of whole blood priming of the CPB circuit was essential for avoiding the excessive haemodilution that occurred in study II and could have interfered with the results. Fortunately, the formula of cerebral arteriovenous oxygen content difference takes haematocrit into account through the use of haemoglobin in the equation, which diminishes the effect of haemoglobin differences between the groups; however, this could have resulted in worse suppression of cerebral metabolism as compared to study III.

In study III, the low survival rates in the control group interfered with our neurological evaluation analysis, as only eight pigs survived to the end of the follow up period. Another limitation is that the calculated permissible periods of HCA in studies II and III are only estimates. They are based on the assumption that hypothermia is the only factor contributing to cerebral metabolic suppression during cooling with CPB and that the permissible period of HCA at 38°C is 5 minutes.

7.7 Clinical implications

7.7.1 RIPC and HCA in aortic arch surgery

To date, the effects of RIPC in terms of cerebral protection during aortic arch surgery have not been studied in a clinical situation. As aortic arch surgery requiring circulatory arrest is mainly conducted on patients in a critical state that require emergency surgery, one could argue that RIPC could not be safely done to these patients. Completion of the RIPC cycles requires 40 minutes and an additional flush period of 30 to 60 minutes during which the neuronal, humoral, and immunological

effects of RIPC take place. However, the cooling perfusion usually lasts about 45 to 60 minutes before the circulatory arrest commences. RIPC can be performed during aortic imaging and transfer to operating room by automated blood pressure cuff systems or in the OR while the patient is prepped for surgery. There are few cases for utilizing RIPC in ATAAD patients, as dissection flaps causing malperfusion to the limbs could prevent the effects of RIPC by obstructing blood flow. Additionally, patients in deep shock or resuscitation will most likely not benefit from RIPC as the shock state and resuscitation itself cause hypoxia and ischaemia to all organs and tissues. Propofol should be avoided as an anaesthetic agent, a lower limb should be used for applying RIPC, and the perfusion and operative strategies should be as unified as possible to obtain optimal results with the lowest possible amount of interference.

Studies II and III showed that moderate hypothermia alone would lead to a permissible period of HCA of only 11-12 minutes at 24°C, which would safely allow for an inspection of the aortic arch during circulatory arrest. Hemiarch repair, however, can usually be completed within 20 to 30 minutes. RIPC could be used as an adjunctive cerebral protection strategy to avoid neurologic sequalae associated with prolonged HCA. With this combination, the need for deep or profound hypothermia and the associated longer perfusion periods could be avoided. Preservation of cerebral autoregulation, avoidance of coagulopathies, and permeability dysfunctions could be additional benefits.

One could argue that SCP provides the very same effects and even provides antegrade cerebral blood flow throughout the LBCA. However, the aorta and arch vessels of ATAAD patients are fragile and therefore prone to propagation, dissection, and increased embolic load. The additional manipulation and clamping associated with SCP could be harmful in ATAAD patients. The optimal use of SCP is well-described in the literature, as was shown earlier. However, SCP can easily lead to hypo- or hyperfusion of the brain, possibly impairing the neurologic outcome, in acute settings or inexperienced hands. On the other hand, large centres have utilized SCP with excellent results, even in ATAAD patients, for years. The use of SCP and a heavy caseload have led to a more aggressive primary operation strategy with routine total aortic arch repairs and FET implantations in some centres; the results have been surprisingly good but the rationale for this strategy remains unclear. The same strategy would most likely lead to a worse outcome in low-volume centres, such as all our Nordic Cardiothoracic hospitals. Therefore, a safe and effective adjunctive cerebral protection strategy would be still of use.

7.7.2 DTLC

DTLC after venous exsanguination is used as a primary cannulation strategy in patients experiencing malperfusion, shock, or resuscitation in a few centres. However, it is a relatively unknown cannulation method in most centres and is generally not even used as a bailout strategy in catastrophic situations. In the clinical situation, DTLC is performed under prior pure oxygen ventilation and the cannulation (normothermic circulatory arrest) itself lasts 60 to 120 seconds. However, in the most challenging circumstances or inexperienced hands, the duration used to establish DTLC can exceed this timeframe, increasing the risk of neurological sequalae. The purpose of study I was to simulate these extreme settings, and so we chose a longer, 5-minute normothermic circulatory arrest. The HCA period was completed at a moderate temperature of 25 °C for 25 minutes to simulate the average hemiarch procedure with open distal anastomosis for ATAAD patients. The cannulation procedure itself was not studied but the effects of the associated normothermic circulatory arrest on global and cerebral ischaemia were examined.

The clinical results with DTLC have been encouraging, as patients in a more critical state than the control group achieved similar short- and long-term outcomes (El Beyrouti et al., 2020). The results of the few clinical studies, as well as this one, should encourage surgeons to recognize DTLC as, at the very least, an effective bailout cannulation strategy when the primary cannulation method fails, or it is too time-consuming to complete in ATAAD patients in a critical state.

8 Conclusions

I

DTLC after venous exsanguination with a 5-minute period of normothermic global and cerebral ischaemia before CPB does not impair neurologic outcome following HCA.

II

RIPC tends to suppress cerebral metabolism during cooling with CPB and may prolong estimated permissible period of HCA.

III

RIPC suppresses cerebral metabolism during cooling with CPB, prolonging estimated permissible period of HCA. RIPC with moderate hypothermia improves neurological recovery.

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Original publications

I Mustonen C, Honkanen HP, Lehtonen S, Tuominen H, Mäkelä T, Kaakinen T, Yannopoulos F, Anttila V, Juvonen T. (2019) Safety of direct true lumen cannulation after venous exsanguination: a study in a surviving porcine model. Eur J Cardiothorac Surg. Sep 1;56(3):451-457. doi: 10.1093/ejcts/ezz047.

II Mustonen C, Honkanen HP, Anttila T, Herajärvi J, Yannopoulos F, Mäkelä T, Kaakinen T, Anttila V, Juvonen T. (2019) Remote ischaemic preconditioning may prolong permissible period of hypothermic circulatory arrest in a porcine model. Scand Cardiovasc J. Aug;53(4):192-196. doi: 10.1080/14017431.2019.1629005.

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