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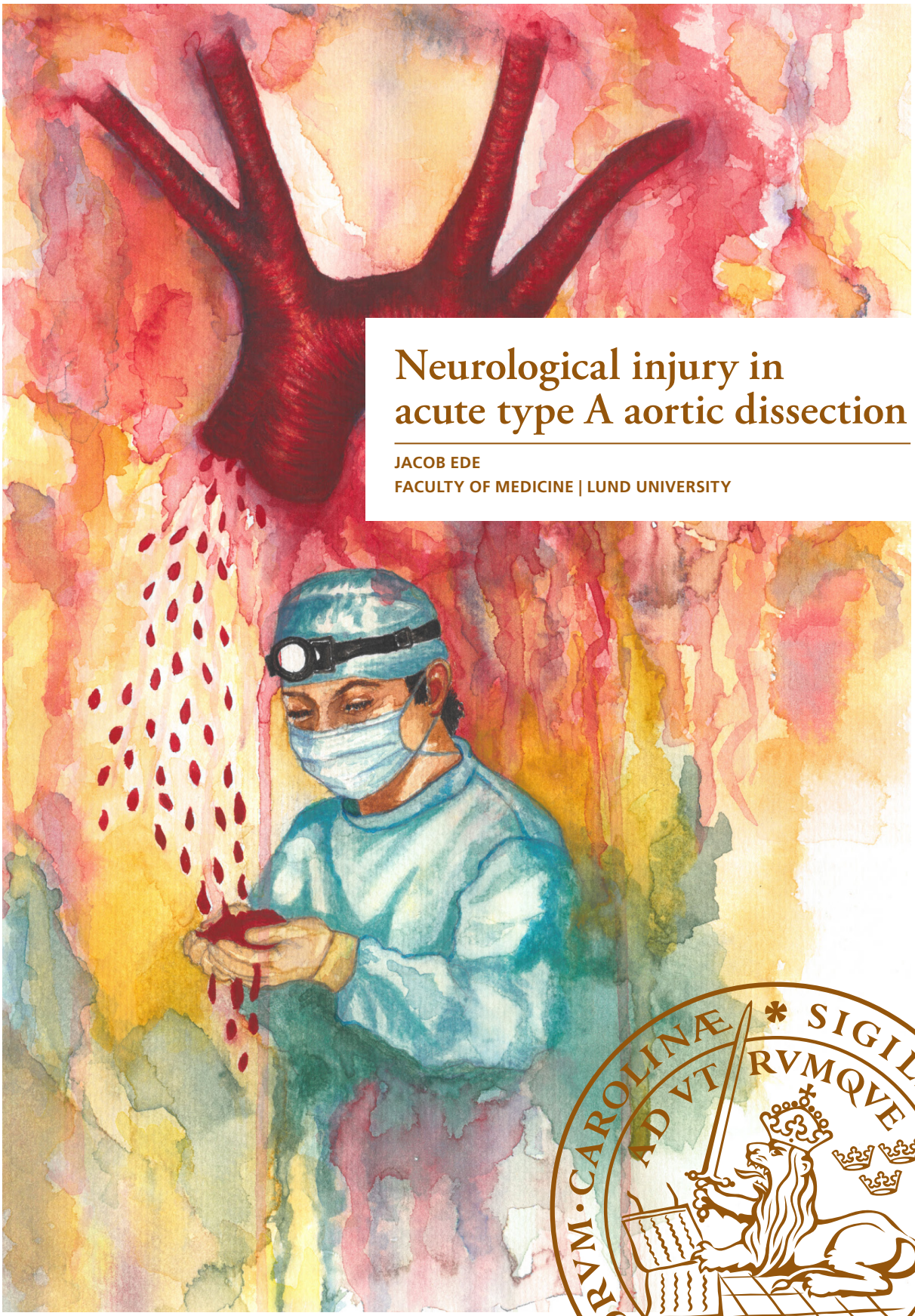

Neurological injury in acute type A aortic dissection

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 8th of May at 13.00 in Segerfalksalen, BMC, Lund

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Abstract:

Background: Acute type A aortic dissection (ATAAD) is a life-threatening condition with high mortality. Neurological injuries are among the most feared complications associated with ATAAD surgery and these complications significantly contribute to both short- and long-term morbidity and mortality.
Aims: I: Assess radiological characteristics of ATAAD-related neurological injury and identify predictors. II: Evaluate the neuroprotective effect of retrograde cerebral perfusion (RCP) III: Investigate patients with cerebral malperfusion and surgical outcomes. IV and V: Investigate whether carbon dioxide (CO_2) flooding of the surgical field reduces postoperative neurological injury in ATAAD patients.
Method: Studies I-III were retrospective studies of patients undergoing ATAAD surgery at Skåne University Hospital Lund. Study I compared patients with and without postoperative neurological injuries. Study II compared patients with and without RCP. Study III investigated patients who presented with cerebral malperfusion and compared those with and without persisting neurological deficit. Studies IV and V, based on a randomised controlled interventional trial, compared neurological outcomes in patients who received CO_2 flooding of the surgical field with those who did not.
Results: I: Embolic lesions causing symptoms of stroke were more common in the right hemisphere; basilary artery obstruction and watershed lesions were associated with postoperative coma; and RCP has a neuroprotective effect. II: Clinical neurological injury and embolic lesions were less frequent in patients with RCP. After multivariable logistic regression, RCP was associated with a significant reduction of watershed lesions. III: Patients with postoperative neurological deficit had significantly higher 30-day mortality. After repair, 52.2% of patients showed an improvement in their clinical neurological status. IV and V: The number of acute ischemic lesions on brain-MRI were 2 (0-6) in the intervention group and 5 (2-12) in the control group (p=0.08), and volume was 1.5 ml (0.0-10.0) in the intervention group and 2.8ml (1.0-7.8) in the control group (p=0.35). The incidence of clinical neurological injury was 14% in the intervention group vs 36% in the control group (p=0.035).
Conclusions: I: Radiological features are important to understanding the pathophysiology of neurological injury related to ATAAD repair. II: Retrograde cerebral perfusion reduces the risk of clinical neurological injury, embolic lesions and watershed lesions compared to hypothermic circulatory arrest alone. III: ATAAD patients with cerebral malperfusion have high risk of mortality and persisting neurological injury, but more than half show an improvement in postoperative neurological symptoms. IV and V: Carbon dioxide flooding shows a trend towards reducing the number of ischemic lesions after ATAAD repair and was also associated with a statistically significant reduction of clinical neurological injuries.

Key words: Aorta, Dissection, Brain ischemia, Cerebral perfusion, Carbon dioxide

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"Life before death. Strength before weakness. Journey before destination."

– Brandon Sanderson, The Stormlight Archive.

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Ede J, Teurneau-Hermansson K, Ramgren B, Moseby-Knappe M, Larsson M, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Radiological properties of neurological injury following acute type A aortic dissection repair. JTCVS Open. 2023 Jun 16;15:38-60.

Paper II

Ede J, Teurneau-Hermansson K, Ramgren B, Moseby-Knappe M, Åström DO, Larsson M, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Retrograde cerebral perfusion reduces embolic and watershed lesions after acute type A aortic dissection repair with deep hypothermic circulatory arrest. J Cardiothorac Surg. 2024 May 29;19(1):302.

Paper III

Ede J, Teurneau-Hermansson K, Ramgren B, Moseby-Knappe M, Larsson M, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Outcomes following repair of acute type A aortic dissection in patients with cerebral malperfusion. Scand Cardiovasc J. 2025 Dec;59(1):2514742.

Paper IV

Ede J, Teurneau-Hermansson K, Moseby-Knappe M, Ramgren B, Bjursten H, Ederoth P, Larsson M, Mattsson-Carlgren N, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Carbon dioxide flooding to reduce postoperative neurological injury following surgery for acute type A aortic dissection: a prospective, randomised, blinded, controlled clinical trial, CARTA study protocol - objectives and design. BMJ Open. 2023 May 25;13(5):e063837.

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Ede J, Teurneau-Hermansson K, Moseby-Knappe M, Ramgren B, Larsson M, Jespersson S, Bjursten H, Mattsson-Carlgren N, Åkesson C, Forsberg A, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Carbon dioxide flooding to reduce postoperative neurological injury following surgery for acute type A aortic dissection (CARTA): A prospective randomized controlled trial. Submitted for publication.

Populärvetenskaplig sammanfattning

(Summary in Swedish)

Aortadissektion är en livshotande sjukdom med hög dödlighet. Aortadissektion uppstår när det bildas ett hål i aortans (stora kroppspulsåderns) innersta lager och blodet således skiktar blodkärlet. Aortan försvagas som följd och riskerar att spricka. Förutom risken att spricka kan även blodet som skiktar kärlet leda till att det blir stopp i kärlets avgångar, och blodet hindras då från att nå sina målorgan. Beroende på vilket blodkärl som drabbas kan man till exempel utveckla hjärtinfarkt, stroke, eller skador på njurar och tarmar som i sig kan vara dödliga.

Typ A aortadissektion är den allvarligaste formen av aortadissektion, och drabbar den första uppåtstigande delen av aortan, mellan hjärtat och där blodkärlen till halsen avgår. Upp till hälften av patienterna som drabbas kommer aldrig ens till sjukhus, och de första 24 timmarna är det upp till 2.6% av drabbade som dör varje timme. Den vanligaste anledningen till att man avlider är att det börjar blöda ut från aortan in i hjärtsäcken som omger hjärtat. Detta leder till att trycket i hjärtsäcken ökar och komprimerar högersidiga hjärtrum, vilket gör att blod inte kan komma in i hjärtat. Detta leder i sin tur till lågt blodtryck och potentiellt dödlig cirkulationskollaps – så kallad hjärttamponad.

Behandlingen för akut typ A aortadissektion är akut operation där den första delen av aortan byts ut mot en kärlprotes. Trots att den kirurgiska tekniken och omhändertagandet av patienterna har utvecklats så är det 15-20% som inte överlever operationen och den efterföljande sjukhusvården.

Neurologiska skador i samband med operationen är tyvärr vanliga. När de drabbade patienterna kommer till sjukhus har 6-20% påverkan på hjärnan redan innan operationen (så kallad cerebral malperfusion). Det finns två huvudsakliga mekanismer som kan leda till hjärnpåverkan innan operationen: blodkärlen som försörjer hjärnan är påverkade av dissektionen med resulterande syrebrist eller otillräckligt blodflöde till hjärnan på grund av lågt blodtryck.

Efter operation för akut typ A aortadissektion drabbas 10-16% av stroke och 3-9% hamnar i koma. De potentiella mekanismerna bakom hjärnskadorna är flera. All kirurgi för att behandla akut typ A dissektion kräver att patienten kopplas till en så

kallad hjärt-lung-maskin som syresätter och cirkulerar patientens blod så att hjärtat temporärt kan stoppas. En förutsättning för att hjärt-lung-maskinen ska fungera är att man har tillgång till både patientens artärsystem och vensystem med kanyler i cirkulationssystemet. Kanylen i artärsystemet anses medföra en risk för att blodkoagler från den sjuka aortan lossnar och hamnar i hjärnan. Utöver detta kräver de flesta operationer för akut typ A dissektion att patientens cirkulation tillfälligt pausas helt. Detta sker genom att patienten kyls med hjälp av hjärt-lung-maskinen för att minska syreåtgången i hjärnan. När man nått sin måltemperatur så stannas cirkulationen helt. Detta möjliggör inspektion av kroppspulsåderns insida och åtgärd av eventuella skador. En kort cirkulationsarrest anses ej ge någon betydande risk för bestående neurologisk skada. Tidigare studier har dock visat att så kallad retrograd hjärnperfusion (baklänges cirkulation av hjärnans kärl från vensida till artärsida) som genomförs under cirkulationsarresten kan minska risken för hjärnskador. De exakta verkningsmekanismerna är dock inte helt klarlagda. I samband med cirkulationsarrest öppnas kroppspulsådern på ett sätt som gör att stora mängder luft kan komma in i kärlträdet. När cirkulationen återstartas kan luft som fastnat i blodomloppet hamna i hjärnan och orsaka syrebrist. I annan hjärtkirurgi använder man koldioxid i det operationssåret för att minska denna risk. Koldioxid är 25 gånger mer lättlösligt i blod än vad rumsluft är, vilket i teorin borde ha en skyddande effekt på hjärnan.

Denna avhandling består av fem delarbeten vars syfte är att undersöka mekanismer, riskfaktorer och möjliga strategier för att minska risken för hjärnskador vid kirurgi för akut typ A aortadissektion.

Delarbete I är en retrospektiv studie där vi undersökte 538 patienter som opererades för akut typ A dissektion på Skånes universitets sjukhus i Lund mellan 1998 och 2021. Vi undersökte sambandet mellan kliniska fynd och röntgenfynd för att bättre förstå hjärnskador som uppstår i samband med dissektionskirurgi. Vi fann att emboliska skador (material som färdas med blodet och täpper till ett blodkärl) som gav kliniska fynd var vanligare i höger hjärnhalva. Watershed lesioner (ett resultat av generell syrebrist) och stopp i basilarartären var kopplade till risken att hamna i koma efter operationen. Vi fann även att cerebral malperfusion och diabetes är viktiga i utvecklingen av hjärnskador i samband med operationen samt att retrograd hjärnperfusion verkar ha en skyddande effekt mot hjärnskador.

I delarbete II genomförde vi en retrospektiv studie där vi undersökte 515 patienter som opererades för akut typ A dissektion på Skånes universitets sjukhus i Lund mellan 1998 och 2022. Vi jämförde de patienter som hade opererats i cirkulationsstillestånd med retrograd hjärnperfusion med de patienter som hade opererats utan retrograd hjärnperfusion. Vi kunde visa att retrograd hjärnperfusion minskar risken för hjärnskador i samband med operationen, men att det inte var någon skillnad i överlevnad, varken på kort- eller lång sikt.

I delarbete III genomförde vi en retrospektiv studie där vi undersökte alla (93st) patienter som opererats för akut typ A aortadissektion på Skånes universitets sjukhus i Lund mellan 1998 och 2023 som inkom med cerebral malperfusion. Vi fann att dessa patienter hade hög dödlighet och risk för permanenta hjärnskador. Dock ledde operation till förbättring av neurologiska symptom hos mer än hälften av patienterna. Medvetslöshet innan operationen för förenat med högst risk för död.

I delarbete IV och V genomförde vi en randomiserad interventionsstudie där vi undersökte om koldioxid i operationssåret kan minska risken för att luftembolier i hjärnan i samband med kirurgi för att behandla akut typ A aortadissektion. I studien inkluderades 75 patienter som lottades till antingen behandling med koldioxid i operationssåret eller ej. I övrigt genomfördes operationen på liknande sätt i de båda grupperna. Vi fann att koldioxid i operationssåret hade en skyddande effekt och minskade antalet kliniska hjärnskador efter operationen. Vid magnetkameraundersökning efter operationen kunde vi se en trend mot minskade hjärnskador på undersökningen, men denna trend är ej statistisk säkerställd.

Sammanfattningsvis har vi i denna avhandling visat att både kliniska variabler och röntgenvariabler bidrar till förståelsen för hur hjärnskador uppstår vid akut typ A aortadissektion. Vi har vidare visat att retrograd hjärnperfusion minskar risken för hjärnskador i samband med operationen och att cerebral malperfusion innebär ökad risk för död och hjärnskador. Dock förbättras mer än hälften av patienterna neurologiskt efter kirurgi. Slutligen visade vi att koldioxid i operationssåret minskar risken för kliniska hjärnskador vid operationen för akut typ A aortadissektion.

Abbreviations

ACP	Antegrade cerebral perfusion
ATAAD	Acute type A aortic dissection
AVR	Aortic valve replacement
CABG	Coronary artery bypass grafting
CARTA	Carbon dioxide flooding to reduce postoperative neurological injury following surgery for acute type A aortic dissection
CCA	Common carotid artery
CKMB	Creatine phosphokinase-MB
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTA	Computed tomography angiography
DWI	Diffusion weighted imaging
FLAIR	Fluid attenuated inversion recovery
GCS-M	Glasgow Coma Scale motor score
GFAP	Glial fibrillary acidic protein
HCA	Hypothermic circulatory arrest
HR	Hazard ratio
ICA	Internal carotid artery
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale for neurologic disability
NFL	Neurofilament light-chain
NIHSS	National Institutes of Health Stroke Scale
NSE	Neuron specific enolase

OR	Odds ratio
PRBC	Packed red blood cells
PS	Propensity score
RCP	Retrograde cerebral perfusion
rFVIIa	Recombinant factor VIIa
S100B	S100 calcium-binding protein B
SCA	Straight circulatory arrest
t-Tau	total-Tau
TOE	Transoesophageal echocardiography
UCH-L1	Ubiquitin carboxy-terminal hydrolase L1
95% CI	95% confidence interval

Introduction

Aortic dissection

Anatomy and pathophysiology

The aorta, recently recognised as an organ, is the largest blood vessel in the human body responsible for delivering oxygenated blood from the heart to all end organs except the lungs (1). The aorta is divided into several segments from the heart to the aortic bifurcation: the aortic root, ascending aorta, aortic arch and descending aorta, the latter of which is further divided into a thoracic section above the diaphragm and an abdominal section below the diaphragm (2). To further refine classification, to facilitate description of surgical or endovascular intervention, the 12 Ischimaru zones (zone 0-11) were developed (3). The aortic wall consists of three distinct layers: the intima, the media and the adventitia. The intimal layer consists of a single layer of endothelial cells, a basal membrane and a layer of collagen fibrils. The media consists of smooth muscle cells and a network of collagen and elastic fibrils. The adventitia primarily consists of thick bundles of collagen fibrils arranged in helical structures, but also present are the vasa vasorum and nervi vasorum (4, 5).

The first known description of an aortic dissection was made by Frank Nicholls performing the autopsy of King George II of England in 1760. Nicholls described a cardiac tamponade: "…in the trunk of the aorta, we found a transverse fissure on its inner side about an inch and half long, through which some blood had recently passed under its external coat and formed an elevated ecchymosis" (6). Aortic dissection is the result of a tear in the intimal layer of the aorta, allowing circulating blood to enter the vessel wall and separate its layers longitudinally and/or circumferentially (7). As the dissection progresses, a false lumen of the vessel is created, compressing the true lumen and leading to obstruction of branch artery outflows with resulting organ ischemia. If the dissection continues towards the aortic root, this can create an aortic valve insufficiency, cardiac tamponade, and as the weakening of the aortic wall continues, increase the risk of aortic rupture (8-10).

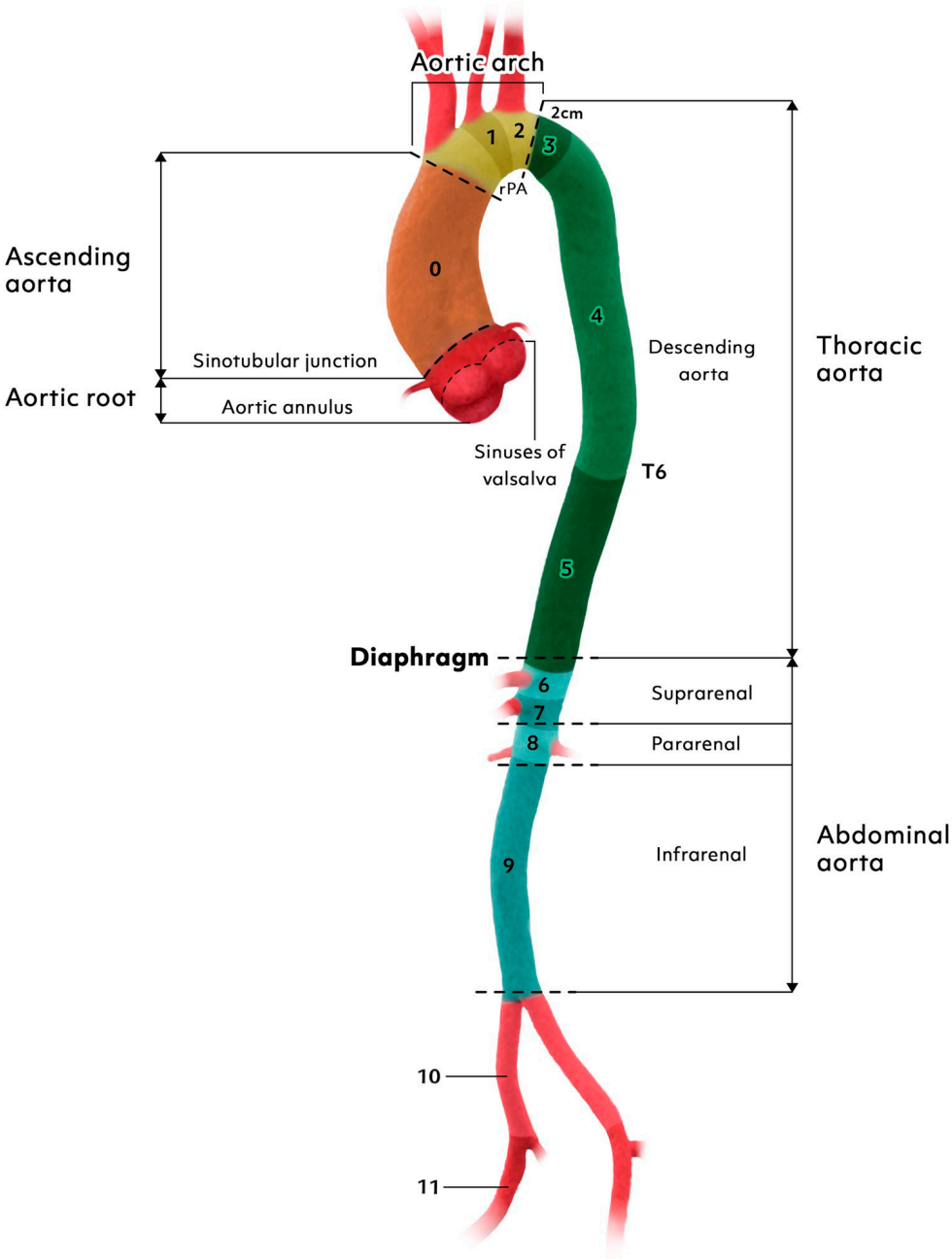

Figure 1. The anatomic segments of the aorta together with Ischimaru zones 0-11. Reprinted from Czerny M, Grabenwöger M, Berger T, et al., EACTS/STS Guidelines for diagnosing and treating acute and chronic syndromes of the aortic organ from Eur J Cardiothorac Surg, Volume 65 / Issue 2, / ezad426. by permission of Oxford University Press.

The predominant cell type in the aortic wall is the smooth muscle cell, which interacts with the extracellular matrix. Different models of aortic dissection describe changes in the aortic wall that leads to the loss of contractile function of the vascular smooth muscle cells. Decreased expression of proteins produced by vascular smooth muscle cells and increased expression of inflammatory proteins has been described in the context of aortic dissection (11). A key component of the extracellular matrix is Fibrillin-1, which plays a key role in transferring mechanical stress between the extracellular matrix and the vascular smooth muscle cells. Loss of elasticity in the diseased aorta is associated with increased extracellular collagen deposition and decreased elastin. Current data suggest that both the mechanical stress and the loss of elasticity play important roles in the development of aortic dissection (12, 13).

Epidemiology

The exact incidence of aortic dissection is hard to determine, largely because the diagnosis is often made post-mortem and autopsy rates are declining worldwide. Consequently, both incidence and mortality are likely underestimated (14). However, several population-based cohort studies have attempted to estimate the disease burden. In a study from Oxfordshire in the United Kingdom, the incidence of aortic dissection was 6 per 100.000 patient-years, with 48.6% of patients dying before reaching hospital care (15). Swedish population-based studies have reported comparable figures. In Malmö, the incidence was estimated at 5.5 per 100.000 patient-years, with a decreasing proportion of cases identified during autopsy (16). Another study in Malmö showed an incidence of 8.7 per 100.000 patient-years, with an acute and in-hospital mortality of 39% (17). A third Swedish study showed that the incidence of aortic dissection was 7.2 per 100.000 patient-years, where 29% died without hospital admission (18). A nationwide Icelandic study showed that the incidence of acute type A aortic dissection was 2.5 per 100.000 patient-years, and 17.6% died before reaching the hospital (19).

Male-sex is a recognised risk factor for aortic dissection, with males constituting 60-76% of all diagnosed cases (15, 18-20). Interestingly, females tend to present with aortic dissection five years later than men (18). Increasing age is also associated with increased risk of aortic dissection, with the highest incidence observed in males 64-75 years and 85 years plus. The highest incidence observed in females is 74-85 years (16). Some studies report increasing incidence of aortic dissection over time, whereas others report a stable trend; rising life-expectancy has been proposed as a contributing factor to any observed increase (16, 17, 19, 21). Hypertension is one of the strongest risk factors for aortic dissection, present in 74-86% of patients with aortic dissection. Other risk factors include smoking, atherosclerotic disease, known aortic aneurysm, previous cardiac surgery, Marfan syndrome and iatrogenic causes (17, 22).

The best treatment for aneurysm of the ascending aorta and/or the aortic root is prophylactic surgery. Current guidelines recommend surgery when the diameter is

≥55mm for most patients, ≥52mm in selected patients with low surgical risk and with "ascending phenotype", ≥50mm in selected patients with a low surgical risk and especially those with "root phenotype" and ≥45mm in patients undergoing aortic valve surgery. Additional factors influencing the decision to operate include family history of dissection, hypertension, coarctation of the aorta, aortic diameter growth rate and length of ascending aorta (1, 23, 24). Even though aortic diameter is considered the primary criterium for surgical intervention, it remains unclear which patients should undergo surgery for prevention of aortic dissection. Aneurysms of ≥6cm are reported to have a yearly dissection or rupture risk of 6.9% (25). However, most patients with type A aortic dissection have an aorta with a diameter less than 5.5 cm (59%), and 40% have an aortic diameter of less than 5.0 cm, meaning that the majority of patients with aortic dissection are not eligible for prophylactic aortic surgery (26). Recent data suggest that ascending aorta length may also be an important determinant of risk, with a length exceeding 11cm proposed as a potential surgical threshold (23, 27).

Several genetic connective-tissue disorders predispose patients to aortic dissection, including Marfan syndrome, Loeys-Dietz syndrome, vascular Ehler-Danlos syndrome and Turner syndrome (1). Marfan syndrome was the first to be described. It is a monogenic autosomal dominant disorder caused by a mutation in the FBN1 gene encoding the protein fibrillin-1, essential in the elastic fibres of the aortic wall (28, 29). Marfan syndrome has been reported in 3-7% of patients with aortic dissection (30-32). The mutated fibrillin-1 lacks the ability to form polymers, which leads to reduced strength of the aortic wall. Other features of Marfan syndrome include chest wall deformities, elongation of long bones and lens luxation. Typically, Marfan syndrome patients have an aortic-root aneurysm shaped as a pear, and prophylactic root-replacement has been shown to reduce the risk of aortic dissection (33). Vascular Ehler-Danlos is also a monogenetic autosomal dominant disorder caused by a mutation of the COL3A1 gene encoding type III procollagen. Patients with vascular Ehler-Danlos have thin and fragile skin, have hypermobility of joints and risk rupture in both arteries and organs, and account for 0.6% of patients with aortic dissection, according to a German registry (32, 34). Loeys-Dietz syndrome has been associated with six different genes all encoding proteins in the transforming growth factor-β pathway (28, 34, 35). Loeys-Dietz syndrome is associated with bifid uvula, also a severe disseminated arteriopathy resulting in both central and peripheral dissections, and the different associated genes have different risk profiles with gene-specific interventional guidelines (1). Turner syndrome affecting about 0.5% of females is the result of a missing, or partially missing, X chromosome. Turner syndrome is associated with an increased prevalence of aortic disease such as bicuspid aortic valve, aortic coarctation, ascending aortic aneurysm and aortic dissection (36, 37).

Non-syndromic heritable thoracic aortic disease is a condition with a genetic disposition for thoracic aortic aneurysm or dissection, but without the systemic features of, for example, Marfan syndrome or Ehler-Danlos (i.e., syndromic thoracic

aortic disease). It has been shown that up to 21.5% of patients with thoracic aortic disease have a family history with at least one first-degree relative with thoracic aortic disease (38). Studies have also shown that ascending pathologies are more likely to be hereditary than descending pathologies, which more often are a result of atherosclerosis, old age and hypertension (28, 38, 39). The presence of a bicuspid aortic valve is common and present in 0.5-1.4% of the normal population (40, 41). The association between bicuspid aortic valve and aortic aneurysms was made as early as 1928 and root and/or proximal ascending aneurysms is seen in 30-70% of patients with bicuspid aortic valve (40). In the Nordic consortium for acute type A aortic dissection for aortic dissection, 6% of patients had a bicuspid aortic valve (30).

Iatrogenic aortic dissections are uncommon, accounting for up to 5% of all aortic dissections (31, 42, 43). The most common cause is either cardiac surgery (e.g., arterial cannulation), transcatheter aortic valve replacement or coronary angiogram. Some studies suggest that mortality is higher in iatrogenic aortic dissection than in spontaneous aortic dissection, but other studies contradict these results (42, 44-46). The use of fluoroquinolones in interventional procedures has been shown in a Swedish study to increase the risk of aortic aneurysms or aortic dissection compared to the use of amoxicillin (43).

Although aortic dissection is more common in males than in females, the risk of aortic dissection increases during pregnancy. A Swedish study has shown that there is an almost 25-fold increase in aortic dissection risk during pregnancy, with an incidence of 0.06 per 100.000 patient-years in non-pregnant women compared to 1.45 per 100.000 patient-years in pregnant women of the same age (47). The mechanism of the disease is not fully understood in these patients, but the prevalence of family history of dissection or connective tissue disorder seems to be more common than in other patients (48, 49).

Inflammatory conditions of the aorta are uncommon and may be either infectious or non-infectious (e.g., giant cell aortitis or Takayasu arteritis) and can lead to the formation of aortic aneurysm and subsequent dissection (50).

Classification

Several different classification systems are used in the context of aortic dissection. A fundamental distinction is made between acute and chronic disease. In general, a dissection is considered acute the first 14 days after symptom onset and chronic when persisting beyond this period (7).

Intramural hematomas, aortic dissection and penetrating aortic ulcers together constitute the spectrum of acute aortic syndrome. Both intramural hematomas and aortic dissections are characterised by the presence of blood between the layers of the aorta; however, in intramural hematoma, no false lumen is formed. Intramural hematoma was previously believed to result from bleeding of the vasa vasorum

within the aortic wall, but a study from Leone et al. showed that 90% of patients with intramural hematoma had atherosclerotic lesions, suggesting that intimal injury is the more likely pathophysiological mechanism (51).

The classification system most commonly used in clinical practice is the Stanford classification, first published in 1970. This system was developed to guide clinical patient management by identifying patients requiring urgent life-saving surgery from those treatable by medical intervention alone. Dissections involving the ascending aorta, irrespective of the involvement of other segments of the aorta, is considered type A, whereas dissections confined to the descending aorta are classified as type B (52). Type A dissections require immediate surgery, while type B dissections can be managed medically. Dissections limited to the aortic arch are classified as non A-non B dissections. These can be further subdivided into arch type A if the dissection extends retrogradely in the ascending aorta, or as arch type B if it extends antegradely into the descending aorta (53, 54).

Michael DeBakey, the surgeon who was the first to successfully perform a surgical repair of an aortic dissection, also developed a classification system for aortic dissection (55). This system further divides Stanford type A and type B dissections. DeBakey type I dissections involve both the ascending and descending aorta, whereas DeBakey type II dissections are confined to the ascending aorta. DeBakey type III dissections are limited to the descending aorta, and are subdivided into type IIIa, which is limited to the thoracic descending aorta and type IIIb, which extends below the diaphragm (56, 57).

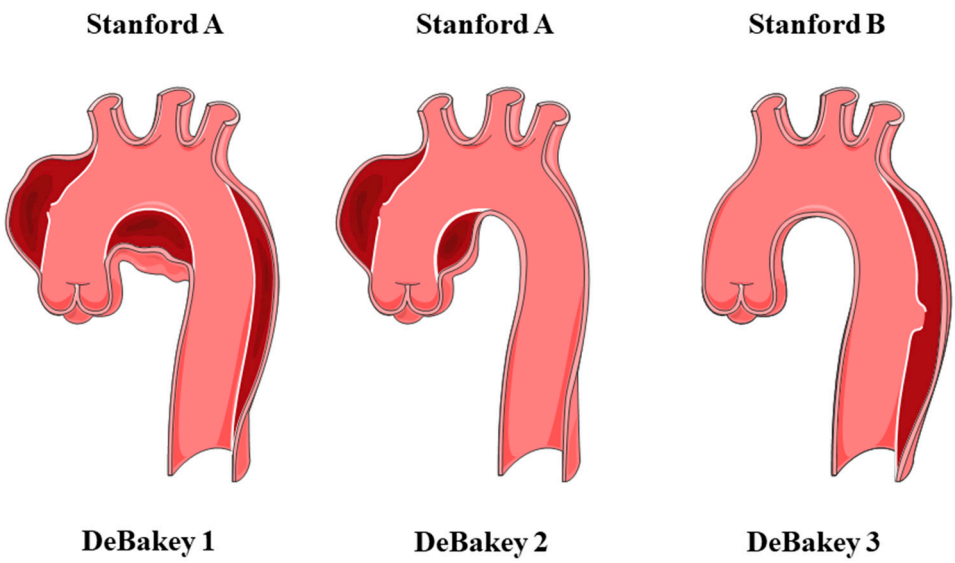

Figure 2. DeBakey and Stanford classification systems of aortic dissection. Illustrations from Servier Medical Art, used under CC BY 4.0 license.

The most common classification system for evaluating clinical presentation and associated risk is the Penn classification, developed in 2009 at the University of Pennsylvania (58). This system classifies patients into four groups based on their ischemic symptoms. Penn Aa is characterised by no ischemic symptoms, Penn Ab by localised ischemic symptoms, Penn Ac by generalised ischemic symptoms (i.e. circulatory collapse with or without cardiac involvement) and Penn Ab&c by both localised and generalised ischemia.

In an effort to further integrate radiological findings and clinical presentation, the Type-Entry-Malperfusion (TEM) classification system was proposed. The aim of the TEM system was to "add clarity regarding the extent of the disease process, enhance awareness of the disease mechanism, aid in decision-making regarding the extent of repair and help in anticipating outcome". The type component follows the Stanford classification, with the addition of non-A-non-B dissections. Entry is defined by the location of the primary entry of the dissection in either the ascending aorta (E1), aortic arch (E2), descending aorta (E3) or unknown (E0). Malperfusion is defined as either clinical (+) or radiological (-) evidence of malperfusion and is further subdivided into no malperfusion (M0), coronary arteries (M1), supra-aortic vessels (M2) or spinal, visceral and lower extremities (M3) (59).

Clinical presentation

The clinical presentation of acute type A aortic dissection (ATAAD) is often dramatic. Chest pain is the most common presenting symptom, occurring in approximately 85% of cases, with more than 90% of these patients reporting severe pain, often described as the worst pain ever experienced (60, 61). In addition to chest pain, a wide spectrum of symptoms may be present, muddling the clinical picture and resulting in an initial misdiagnosis of 45% according to a study from our research group (62). Common accompanying symptoms include back pain, abdominal pain, lower back pain, syncope, dizziness, nausea and difference of blood pressure between the arms. Additional symptoms may arise as a consequence of malperfusion, which occurs in one-third of patients and results from end-organ ischemia downstream in the aorta (60, 63, 64). In cerebral malperfusion, symptoms include hemiparesis, hemiplegia or unconsciousness. If coronary malperfusion is present, pathological changes may be seen on an electrocardiogram or echocardiogram, and elevated cardiac enzymes may be present. When arterial supply to the limbs is affected, the 5 P's of limb ischemia may be present (pain, pallor, pulselessness, paraesthesia and paralysis). Hypotensive shock is present in up to 25% of patients and might be result of severe aortic valve insufficiency due to dissection in the aortic root, cardiac tamponade or coronary malperfusion. Approximately 5% of patients undergo preoperative cardiopulmonary resuscitation (60, 61, 63).

The gold standard of aortic imaging is computed tomography angiography (CTA) with intravenous contrast, which is readily available in most hospitals, time efficient and highly accurate (1). Alternative diagnostic imaging includes transthoracic echocardiography, transoesophageal echocardiography (TOE), magnetic resonance imaging (MRI) and conventional angiogram. The use of CTA has increased over time whereas the use of echocardiograms has decreased; MRI and conventional angiograms are seldom used (60). A systematic review evaluating imaging modalities in thoracic aortic dissection showed that CTA, MRI and TOE are equally reliable in confirming or ruling out thoracic aortic dissection (65). The use of CTA has the advantage of being easily available in most hospitals and able to be performed quickly but comes with the risk of radiation exposure and possible kidney damage from the iodine contrast (66). MRI has the advantage of no radiation exposure, but it is time-consuming and most often only available during office-hours. Echocardiogram has the advantage of being relatively fast and easily available with no contrast or radiation exposure, but accurate results are highly dependent on the skill of the investigator. The use of echocardiography is used less and less, but it remains an important tool for the hemodynamically unstable patient who cannot be safely transported to the radiology department for imaging (65, 67). Conventional angiogram is rarely used, and almost only in cases of iatrogenic aortic dissection during the procedure or if acute coronary syndrome is suspected.

The role of biomarkers in the diagnosis of aortic dissection remains limited. Studies have shown that D-dimer levels are elevated in aortic dissection; however, D-dimer is also elevated in other conditions presenting with acute chest pain, such as pulmonary embolism (68, 69). It has been proposed that low levels of D-dimer could rule out aortic dissection, but it is not used in routine clinical practice for various reasons (69, 70).

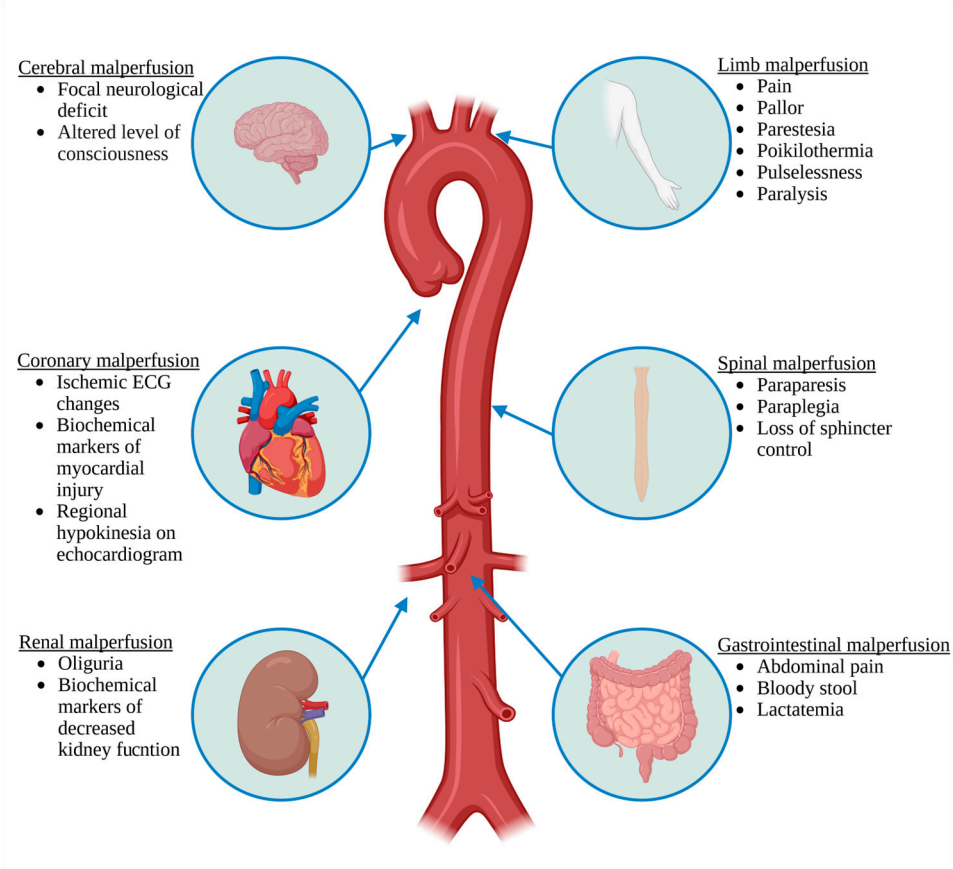

Figure 3. Malperfusion syndrome in acute type A aortic dissection and their clinical characteristics. Created in BioRender. Ede, J. (2026) https://BioRender.com/3q9y4h9

Natural history and medical treatment

ATAAD is a highly lethal disease, with 18-49% of patients dying before reaching the hospital (8, 15, 19, 21). During the first 24 hours, an hourly mortality rate of up to 2.6% has been reported in patients who do not undergo surgery, and 24-68% die within the first 48 hours (8, 21, 31, 71, 72). The prognosis for medically treated patients is particularly poor. One Swedish study observed that as few as 6% of medically treated patients survived hospital stay, and none survived beyond one year. The primary objective of medical treatment for non-surgical patients, or patients awaiting transfer to a cardiothoracic surgical centre, is to reduce aortic wall stress. This is achieved by strict blood pressure control and pain management. Target systolic blood pressure of 100-120mmHg and a heart rate of 60-80 beats per minute is recommended. Treatment involves the use of beta-blockers in combination with short-acting vasodilators (73-75).

Surgical management

The gold standard treatment of ATAAD is open surgical repair. The objectives of surgery is to restore blood flow within the true lumen of the aorta, prevent aortic rupture and, when feasible, remove or repair the intimal tear. The leading cause of death in patients with aortic dissection is aortic rupture resulting in either cardiac tamponade or exsanguination (76). The optimal surgical strategy remains under debate, and considerable variations exists regarding arterial cannulation, cerebral protection strategies and the extent of both proximal and distal repair.

Arterial cannulation

To establish cardiopulmonary bypass, one has to cannulate the arterial system. This can be achieved using several approaches, including the femoral artery, axillary-subclavian artery or direct aortic cannulation. Historically, femoral cannulation was the most commonly used technique; however, both axillary-subclavian and direct aortic cannulation have increased in recent years, with axillary-subclavian currently being the most common approach in Europe (77, 78). There are currently no randomised trials on cannulation strategies and their outcome. However, retrospective series from both Ghoreishi et al. and Rosinski et al. have shown a decrease in mortality and stroke with axillary-subclavian cannulation (79, 80). More recently, TOE-guided direct cannulation of the ascending aorta using the Seldinger technique has increased in popularity. Studies by Kreibich et al. and Jormalainen et al. showed comparable results between central and peripheral cannulation in terms of stroke and mortality (81, 82). Femoral cannulation has been associated with an increased risk of perioperative stroke possibly due to backwards flushing of embolic material from the dissected descending aorta (80, 83). However, it has been suggested that these findings may be influenced by significant selection bias and that the increased risk of stroke in patients with femoral cannulation may be related to surgical inexperience or hemodynamic instability (84).

Cerebral perfusion

The majority of ATAAD repairs are performed with an open distal anastomosis, as it has been shown to be superior to the cross-clamp strategy (85). During the procedure, hypothermia is induced to protect the cerebral parenchyma from ischemia as circulatory arrest is required for the completion of the distal anastomosis. Hypothermia could be classified as deep (≤20.0°C), moderate (20.1-28.0°C) or mild (>28.0°C). As an adjunct to hypothermic circulatory arrest (HCA), retrograde cerebral perfusion (RCP) and antegrade cerebral perfusion (ACP) have been introduced, potentially reducing the risk of ischemic injuries, especially in cases with expected prolonged HCA duration (86-88). ACP delivers oxygenated

blood directly to the brain during circulatory arrest via an arterial cannula in the axillary or subclavian artery or through separate arterial lines in the common carotid artery, brachiocephalic trunk or both. RCP perfuses the venous system via a snared cannula in the superior vena cava, during circulatory arrest. While ACP has been shown to provide a metabolic effect on the brain, the exact mechanism of action of RCP is not fully understood (89, 90). Proposed mechanisms include the washout of embolic debris, cooling of the brain parenchyma and a metabolic effect on the cerebral parenchyma. A large database study from The Society of Thoracic Surgeons demonstrated a protective effect of both ACP and RCP compared to HCA alone (91). However, large single-centre studies have shown excellent results using HCA alone (92, 93). A meta-analysis from Takagi et al. reported similar outcomes for ACP and RCP with respect to mortality and stroke (94). Nevertheless, The American Association for Thoracic Surgery guidelines support the use of either ACP or RCP during circulatory arrest (84).

Extent of repair

The optimal extent of repair is still under debate, and practices vary between surgical centres. A more extensive approach may lower the risk of reoperations or aortic events in the future; however, this potential benefit must be weighed against an increase in mortality and morbidity in the postoperative period. As stated by the Stanford group: "It must be remembered that the first and foremost goal of the operation is to have an operative survivor; additional measures to reduce late morbidity are secondary aspirations" (95).

Regarding proximal repair, the most conservative approach is to only resect the ascending aorta and resuspend the aortic valve without any resection of the aortic root if valve competence can be restored. One can also replace the aortic valve or aortic root if needed and either replace the valve or do a valve-sparing root replacement. Indications for root replacement include destruction by the dissection, dissection into the coronary ostia, presence of a root aneurysm exceeding 45mm and connective tissue disorder in selected cases. In large multicentre databases, patients undergo root replacement in 24-35% of cases (96-100). For patients replacing only the ascending aorta, some studies show an increased risk of reoperation while others show similar long-term results (96-100). Root replacement, especially valve-sparing root replacement, is more technically demanding than ascending replacement only, but different studies show conflicting results regarding outcomes. A study from Brown et al. showed similar short- and mid-term results in patients undergoing root replacement compared to those who did not (101). Another study from Geirsson et al. showed increased in-hospital mortality in patients undergoing root replacement compared to a more conservative approach (102). Finally, a third study from Hysi et al. showed lower in-hospital mortality in patients undergoing root replacement;

however, these patients were younger and presented less often with cardiogenic shock, which may have contributed to the better results for these patients (103).

The optimal approach for distal repair is also under debate. Some centres favour a conservative approach, reducing the complexity of the surgery by limiting it to ascending aortic or hemiarch replacement. Other centres advocate a more aggressive approach involving reconstruction of the aortic arch to resect as much as possible of the diseased aorta to promote false lumen thrombosis and aortic remodeling. In some studies, false lumen patency has been shown to be predictive of late mortality (104, 105). Studies on the extent of distal repair show conflicting results. The Stanford group showed similar survival in patients who underwent hemiarch replacement compared to total arch replacement, and the rates of reoperations of the descending aorta were similar (106). Data from Freiburg showed that total arch replacement was an independent predictor of perioperative mortality, but the incidence of distal reoperations was similar in patients with ascending, hemiarch or total arch replacement (107). However, data from Hannover showed excellent survival (12% in-hospital mortality) in patients with ATAAD dissection who underwent total arch replacement with frozen elephant trunk (108). Even though these data show inconclusive results regarding the extent of repair, one must bear in mind that more complex surgery usually requires longer operating time, cardiopulmonary bypass time, aortic cross-clamp time and hypothermic circulatory arrest time, all of which have been shown to increase perioperative mortality and morbidity (109-111).

Mortality

Perioperative mortality following ATAAD surgery is high and varies greatly from 2.8% to 28.6% (112). However, large international databases show similar in-hospital mortality rates with 18.4% in the international registry of aortic dissection, 17.6% in the Nordic Consortium for Acute Type A Aortic Dissection, 16.9% in the German Registry for Acute Aortic Dissection type A and 18.4% in the European Registry of Type A Aortic Dissection (22, 109, 113, 114). Long-term data is more limited. In 30-day survivors in the Nordic database, 1-year survival was 95%, 5-year survival was 86% and 8-year survival was 76% (113). Data from the international registry show 1-year survival at 96% and 3-year survival at 91% while the German database reports 1-year survival at 96%, 5-year survival at 84% and 10-year survival at 68% among 30-day survivors (115, 116).

Malperfusion has been shown to be a predictor of in-hospital mortality (58). In a recent publication from the University of Pennsylvania, the mortality risk increased with increasing Penn class. The 30-day morality in Penn class Aa (no ischemia) was 5%, Penn class Ab (localised ischemia) was 10%, Penn class Ac (generalised ischemia) was 15% and Penn class Ab&c (localised and generalised ischemia) was 35% (117) highlighting the consequences of malperfusion. Several studies have

shown that with an increasing number of organs malperfused, the risk of morality increases with an odds ratio of 1.66-2.56 with one organ, 2.44-2.72 with two organs and 3.39-7.19 for three or more organs (64, 109).

Stroke

Stroke is most commonly defined as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin,” and it is one of the leading causes of death and disability worldwide (118, 119). Three main subtypes are recognised: ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage. Ischemic stroke represents up to 85% of all strokes and is the most relevant type of stroke in the setting of ATAAD; it will, therefore, be the focus of the following discussion (120).

Pathophysiology of ischemic stroke

Ischemic stroke occurs when blood flow to a region of the brain is severely reduced or blocked resulting in lack of oxygen and glucose delivery (121). The reduced blood flow can be caused by thromboembolism or arterial dissection (122). The areas that are hypoperfused due to the lack of blood flow are defined as the penumbra (123). The penumbra quickly becomes hypoxic due to the high metabolism of the brain, and irreversible damage occurs after only a few minutes. Ischemic neuronal injury occurs through two principal pathways. Firstly, hypoxia leads to anaerobic glycolysis of adenosintriphosphate, resulting in increased lactate levels and reduced intracellular pH, ultimately resulting in neuronal cell death. Secondly, hypoxia induces the release of excitatory neurotransmitters leading to an increase in intracellular calcium-ions activating proteases and a disruption of the cell membrane, resulting in further neuronal cell death (124-126). As irreversible damage occurs in the centre of the penumbra, the area is instead defined as the ischemic core, and the area around the core becomes the penumbra. Unless cerebral perfusion is restored, the ischemic core expands progressively into the surrounding penumbra (121).

Cerebral malperfusion in aortic dissection

Cerebral malperfusion is defined as imaging evidence of either a dissected or occluded artery supplying the brain regardless of clinical symptoms. Whereas cerebral malperfusion syndrome is defined by focal neurological deficits or an altered state of consciousness.

Between 6% and 20% of patients with ATAAD present with symptoms of cerebral malperfusion. Data suggest that patients with cerebral malperfusion who receive only medical treatment have up to 100% mortality. Surgical treatment in these patients is also associated with a significant increase in both mortality and morbidity, and there is a two- to fourfold risk increase of permanent neurological injury in patients who present with cerebral malperfusion (22, 61, 64, 80, 127-132).

There are several pathophysiological mechanisms of cerebral malperfusion. They include the dissection of the supra-aortic blood vessels, embolism, and/or systemic hypotension due to shock, hypovolemia, severe aortic regurgitation or cardiac tamponade (133). Historically, cerebral malperfusion has been considered a relative contraindication to emergency surgery as patients presenting with cerebral malperfusion have a worse postoperative outcome, making the decision to perform acute surgery difficult (134-136). However, the most recent European guidelines recommend that surgery should be considered despite neurological symptoms or non-haemorrhagic stroke (1). However, the decision to perform surgery in patients with cerebral malperfusion should be individualised, as several factors may influence the outcome after surgery.

Stroke after type A aortic dissection surgery

Irrespective of cerebral malperfusion, 10-16% of all ATAAD patients develop stroke and 3-9% coma following surgical repair (61, 80, 127-130). Patients with permanent neurological injury have increased short- and mid-term mortality rates compared to patients without any signs of neurological injury (129). The surgical procedure surgical itself may also contribute to the development of neurological injury. All surgery for ATAAD relies on the use of cardiopulmonary bypass, and as previously discussed, the location of arterial cannulation may influence perioperative haemodynamics and the risk of perioperative stroke (80). Surgery for ATAAD is mainly performed under deep or moderate hypothermia with circulatory arrest. A short period of circulatory arrest (up to 30-40 minutes) has been considered neurologically safe for most patients (137, 138). However, shorter times can be detrimental if the brain metabolism is not sufficiently reduced. This is mainly achieved by hypothermia, and hypothermia has been shown to significantly reduce the brains metabolic need for oxygen and glucose by 5-7% per degree Celsius decreased (126, 139). If the metabolic need of the brain is sufficiently lowered, the metabolism could be sufficiently met by the additional use of cerebral perfusion during circulatory arrest (138, 140).

Surgery with an open-distal anastomosis allows large volumes of air to enter the arterial circulation, and air may become trapped in the cerebral vessels. When circulation is re-instituted, this air may embolise to peripheral organs and block arteries. A simple technique of de-airing is to re-institute circulation with the patient in the Trendelenburg position facilitating displacement of air from a lower point to

the aortic graft. More recently, the “shaggy aorta protocol” has been described. Here, circulatory arrest is initiated with a short period of RCP to wash out embolic debris and air followed by ACP to meet the metabolic needs of the brain. This protocol has been successful in reducing neurological injury by almost 60% (164, 165). An additional preventive measure is displacing air from the surgical field by means of carbon dioxide flooding. Carbon dioxide has 1.5 times the density of air, is 25 times more soluble in blood and may thereby reduce the risk of air embolism (141).

Aims

Study I

The aim of study I was to assess the radiological properties of ATAAD-related neurological injuries and to identify predictors of these neurological injuries based on their radiological profile rather than their clinical manifestations.

Study II

The aim of Study II was to assess whether the addition of retrograde cerebral perfusion has a neuroprotective effect in ATAAD repair.

Study III

The aim of Study III was to investigate types of preoperative neurological symptoms and radiological findings and their association with persisting neurological deficit and mortality following ATAAD repair.

Study IV and V

The aim of Studies IV and V was to assess whether the flooding of carbon dioxide in the surgical field may reduce postoperative neurological injury in patients undergoing ATAAD surgery.

Material and methods

Patients and study design

Study I

This study was a single-centre, retrospective, observational study and included all patients who underwent ATAAD surgery between January 1998 and December 2021 at our institution. Data was prospectively entered into our departmental surgical database, and additional data were collected by retrospective chart review and radiological assessment.

Patients with a postoperative neurological injury were compared with patients with no postoperative neurological injury.

The primary outcome measures for this study were clinical neurological injury, embolic cerebral lesions and watershed cerebral lesions. Clinical neurological injury was identified at wake up and was defined as focal neurological deficit or coma diagnosed by clinical assessment with or without radiological confirmation (CT or MRI) with a symptom duration of more than 24 hours. Embolic lesions were defined as ischemia spread in the brain parenchyma, whereas watershed infarctions were defined as ischemic lesions occurring at the border zones between major cerebral artery territories resulting from cerebral hypoperfusion.

Postoperative coma was defined as GCS-M <6, 48 hours after termination of pharmacological sedation. Patients who were comatose postoperatively and regained consciousness with persisting stroke symptoms were regarded as coma patients. The radiological assessment was performed by a senior consultant neuroradiologist. Postoperative stroke was defined as focal neurological symptoms with a duration of more than 24 hours confirmed by a neurologist and/or with radiological findings correlating with the symptoms. If a neurological injury was presumed, a neurologist would be consulted. When classification was unclear, a neurologist reviewed the documentation of neurological symptoms.

Study II

This study was a single-centre, retrospective, observational study and included all patients who underwent ATAAD surgery with HCA between January 1998 and December 2022 at our institution. Patients undergoing surgery without HCA or surgery with HCA with the adjunct of ACP were excluded. Data were prospectively

entered into our departmental surgical database, and additional data were collected by retrospective chart review and radiological assessment.

Patients undergoing ATAAD surgery with HCA with the adjunct of RCP were compared with patients undergoing ATAAD surgery with HCA alone.

The primary outcome measures were clinical neurological injury, defined as either stroke or coma as defined below, embolic cerebral lesions and watershed cerebral lesions diagnosed on CT or MRI. The secondary outcome measures were 30-day mortality and long-term mortality.

Study III

This study was a single-centre, retrospective, observational study and included all patients who presented with cerebral malperfusion and underwent ATAAD surgery between January 1998 and December 2023 at our institution. Data were prospectively entered into our departmental surgical database, and additional data were collected by retrospective chart review and radiological assessment.

Patients with persisting neurological deficit were compared to patients without persisting neurological deficit.

The primary outcome measures for this study were persisting neurological deficit and 30-day mortality. Persisting neurological deficit was defined as focal neurological symptoms with a duration of more than 24 hours confirmed by a neurologist and/or with radiological findings correlating with the symptoms or coma defined as Glasgow coma scale (GCS) motor score <6, 48 hours after termination of pharmacological sedation. The radiological assessment of preoperative CT was performed by a senior consultant neuroradiologist.

The main neurological symptom was identified by retrospective chart review. Postoperative neurological status was collected by retrospective chart review at the time of discharge. Syncope was defined as loss of consciousness lasting less than 5 minutes. Level of consciousness was defined as worst recorded level of consciousness ranked from best to worst as no impairment, syncope, reduced consciousness and unconsciousness. Reduced level of consciousness was defined as GCS <15 but with motor score of 6, and unconsciousness was defined as GCS<15 with a motor score <6. Preoperative symptom duration was defined as transient when the symptoms were in full remission at the time of anaesthesia induction and persistent when symptoms were not in full remission at the time of anaesthesia induction.

Studies IV and V

We performed a prospective, randomised, patient- and outcome assessor-blinded, controlled, interventional single-centre study entitled “Carbon dioxide flooding to

reduce postoperative neurological injury following surgery for acute type A aortic dissection (CARTA)".

From January 2022, all patients over the age of 18, presenting with an ATAAD with symptom duration <14 days who were offered open-heart surgery at Skåne University Hospital, Lund, were screened for inclusion. Exclusion criteria were previous open-heart surgery, new onset neurological symptoms at the time of inclusion, prior stroke with persisting disability, surgery performed without open distal anastomosis and presence of implants or devices not compatible with MRI. Preoperative neurological symptoms were defined as either focal neurological symptoms or coma defined as Glasgow Coma Scale motor score (GCS-M) <6.

After eligibility screening, patients were randomly assigned in a 1:1 ratio to undergo carbon dioxide flooding or no intervention. Randomisation was set up by external consultants (Clinical Studies Sweden, Forum South), and consecutively numbered randomisation envelopes were attached to each case report form. Randomisation was performed in blocks of variable size. Inclusion and randomisation were performed by study officials or the on-call physician at the cardiothoracic surgical unit.

The primary outcomes of this study were the number and volume of acute ischemic lesions observed using diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences on MRI post-surgery. The secondary outcomes were clinical signs of neurological injury after surgery defined as either coma according to clinical neurological assessment and/or clinical focal neurological injury assessed by a neurologist and verified by CT or MRI. Neurological function was assessed using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale for neurologic disability (mRS) and Glasgow Coma Scale motor score (GCS-M) at postoperative day 4 and 3 months after surgery. Levels of established blood-based biomarkers for brain injury—S100 calcium-binding protein B (S100B), neuron specific enolase (NSE), neurofilament light (NFL), glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) and total-Tau (t-Tau)—were measured preoperatively and postoperatively at 24 hours, 4 days and 3 months after surgery.

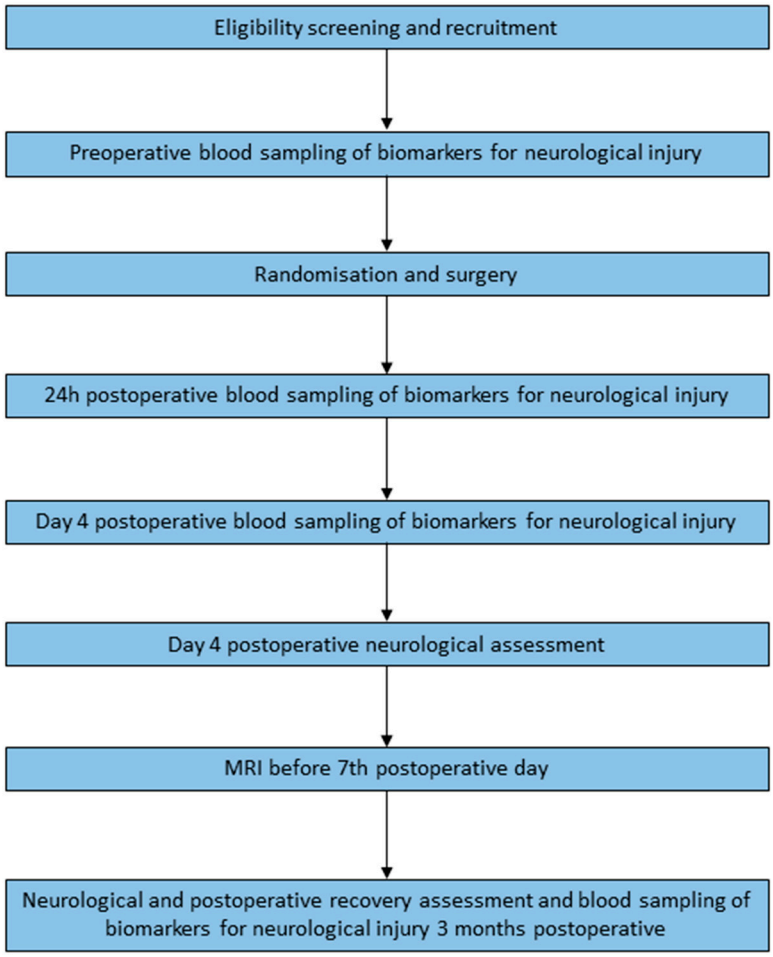

Figure 1. Flow chart for inclusion and assessment of study participants in the CARTA trial.

MRI assessment

Brain MRI was carried out as soon as external pacemaker wires were removed and the patient was clinically stable, if possible within the first seven days after surgery. A standard protocol was used with DWI-MRI and FLAIR images, and all lesions seen on DWI and apparent diffusion coefficient maps were considered positive and counted in the number of ischemic lesions.

A neuroradiologist blinded to the randomisation and clinical outcomes following surgery analysed the images and quantified the number and volume of ischemic lesions. The lesions were described as focal (related to embolism) or watershed (related to hypoperfusion) and according to their anatomical locations.

Biomarkers

A sample volume of 10 ml of blood was collected before surgery, 24 hours after the start of surgery, four days after surgery, and 3 months after the procedure. S100B and NSE were analysed immediately using electrochemiluminescence immunoassays, while NFL, GFAP, UCH-L1, and t-Tau were analysed using the Simoa 4-plex analysis kit in one batch. These samples were centrifuged at 2000g for 10 minutes and stored in a biobank until batch analysis.

Neurological assessment

Patients were assessed using the NIHSS, mRS and GCS-M four days after surgery. The occurrence of clinical postoperative stroke was defined as the presence of focal neurological symptoms persisting for more than 24 hours confirmed by a neurologist and a postoperative CT or MRI. Three months after surgery, patients' neurological function was re-evaluated using the NIHSS, mRS and Symbol Digit Modalities Test (SDMT).

Ethical aspects

All studies were performed according to the principles of Helsinki Declaration of Human Right and were approved by the Swedish Ethical Review Agency (for Studies I-III ref: 2021-01185 and for Studies IV and V ref: 2021-02039). For Studies IV and V, written informed consent was collected preoperatively when possible. In cases where patient consent could not be obtained preoperatively, an oral consent was obtained from next of kin, and in cases where the patient regained adequate cognitive abilities, written informed consent was collected postoperatively. For Studies I-III, individual patient consent was waived.

Surgical technique

General anaesthesia was commonly induced with propofol, fentanyl and rocuronium bromide and maintained with propofol and remifentanil.

Surgery was performed with median sternotomy, cardiopulmonary bypass and intermittent cold blood cardioplegic cardiac arrest. Arterial cannulation site varies by patient and surgeon, but commonly femoral artery or direct aortic cannulation was employed aided by guidewire and transoesophageal echocardiography to ensure access to the true lumen. Venous access was achieved through either bicaval cannulation or a two-stage atrial cannula.

Before circulation was stopped, our neuroprotective strategy included topical cooling of the head and administration of thiopental (1g) and hydrocortisone (500mg). An open distal anastomosis was performed under deep or moderate hypothermic circulatory arrest (usually <22°C) without prior use of aortic cross clamp.

The distal extent of repair was determined by the location of the intimal tear and the extension of the dissection. If the extent of the repair included resection of the lesser curvature of the aortic arch, it was defined as a hemiarch procedure. Any re-implantation of supra-aortic branches was defined as an arch procedure.

In selected patients, ACP or RCP may have been used. If RCP was used, the vena cava superior was cannulated separately and was snared proximal to the cannula before circulatory arrest. An RCP flow of 5-10ml/kg/min was used with a maximum pressure of 25 mmHg measured using the central venous catheter.

After circulatory arrest, perfusion was restarted using a side-branch of the vascular prosthesis with the patient in a Trendelenburg position, which enabled de-airing before the vascular graft was clamped. The proximal extent of the repair was performed during rewarming of the patient. The aortic valve competence was restored by commissural resuspension. If not possible, an aortic valve replacement was sometimes performed, while sparing the native aortic root. Aortic root replacement was performed if there was involvement of the coronary ostia or in the presence of a root aneurysm. Concomitant procedures e.g., coronary artery bypass grafting, was performed when necessary.

In Study IV and V, for patients who were randomised to surgical CO_2 flooding, a CO_2 diffuser was used at a flow of 5 l/min from the time of the chest being opened until the closure of the aorta.

Statistical analysis

All studies

Categorical variables were presented as numbers and percentages. Continuous data were reported as median with interquartile range or mean ± standard deviation depending on the distribution of data. Chi-square test, Fisher's exact test, two sample T-tests, and Mann-Whitney U-test were used for intergroup comparisons when appropriate.

Study I

Logistic regression was used for univariable and multivariable analyses to identify predictors of neurological injury and 30-day mortality. A p-value of <0.1 in the univariable model was required for a variable to be included in the full model. The

analyses were performed using the Backward Wald method, and the variables remaining at the last step were re-analysed using the Enter method to generate the final ORs. In models where neurological injury was tested, neurological injury was used in the baseline model, but radiological and clinical properties were analysed in separate models to generate the specific odds ratios (OR) for these variables.

Predictors of late mortality were assessed with Cox proportional hazard regression using stepwise backward elimination, and the analysis only included 30-day survivors. The results of the logistic regression analyses are expressed as ORs and those of the Cox regression analysis as hazard ratios (HR), both with 95% confidence intervals (95% CI). ORs and HRs were illustrated using forest plots. Late survival rates ±1 standard error were illustrated using the Kaplan-Meier method. For all tests, p-values <0.05 were considered statistically significant.

Study II

The hypothesised association between RCP and defined outcome measures was analysed using binary logistic regression. We performed separate crude and adjusted regressions for each outcome. The multivariable model was performed with a priori adjustment for clinical variables known to carry significant risk of neurological injury, i.e., age, diabetes mellitus, coronary artery disease, previous cardiac surgery, presentation with syncope, cerebral malperfusion, hypotensive shock, intramural hematoma and DeBakey type 1 dissection. We also adjusted for an interaction term between RCP and cerebral malperfusion to account for the potential bias of using or not using RCP in the presence of cerebral malperfusion.

Furthermore, we performed sensitivity analyses by removing patients with preoperative cerebral malperfusion from the analyses. In addition, we performed analyses on a data set where missing values had been imputed by a random forest approach, and patients were matched by propensity score using nearest neighbour matching with a caliper of 0.2 on all preoperative variables.

To evaluate overall survival, we generated Kaplan-Meier curves, and groups were compared using the log-rank test.

Study III

To evaluate overall survival, we generated Kaplan-Meier curves, and groups were compared using the log-rank test.

Study IV and V

Since there are no studies to indicate the effect of carbon dioxide flooding on postoperative neurological outcomes following ATAAD surgery, power calculation was based on a study by Leshnower et al, showing that RCP in conjunction with aortic surgery reduces the occurrence of ischemic lesions (142). We hypothesised that the beneficial effect of RCP demonstrated by Leshnower et al. was due to a

reduction of air embolism and we, therefore, used this data as a basis for our power calculation. A study sample of 25 patients in each arm would yield 80% power to detect a significant difference between the groups with a 0.05 significance level (alpha). A 50% reduction of ischemic lesions from a baseline prevalence of 70% (as in the study by Leshnower and colleagues) would require 31 patients in each arm to achieve similar statistical power. To account for mortality, loss to follow-up and withdrawn consent, a sample size of 80 was chosen.

Univariable logistic regression was used for generating odds ratios comparing the intervention and control groups. For univariable analysis for continuous variables, the median value was used as a cut-off.

Results

Study I

Study population

Between January 1998 and December 2021, 538 patients underwent ATAAD surgery at our institution, all of whom were included in the present study. Follow-up was conducted in January 2022 with a total of 3 346 patient-years (median 5.1 (1.2-10.1), mean 6.2±5.7). Twenty-three patients (4.3%) died intraoperatively. A total of 120 patients (22.3%) experienced postoperative neurological injury, of whom 74 patients (13.8%) suffered stroke and 36 patients (6.8%) coma. Fifteen patients (2.8%) were initially comatose and showed focal neurological symptoms after regaining consciousness. Ten patients (1.9%) had an unspecified neurological injury, and 78 patients (14.5%) presented with cerebral malperfusion.

Baseline characteristics are presented in Table I.1. A significantly higher proportion of patients with neurological injury had diabetes mellitus (23.3% vs 15.4%, p=0.045), higher preoperative creatinine (103 µmol/L vs 87 µmol/L, p<0.001) and lactate (2.6 mmol/L vs 1.8 mmol/L, p<0.001). These patients also presented significantly more often with syncope (26.7% vs 13.6%, p=0.002), hypotensive shock (31.0% vs 20.5%, p=0.030) and cardiac tamponade (23.0% vs 13.0%, p=0.016) and more frequently had any malperfusion (50.8% vs 30.9%, p<0.001) or cerebral malperfusion (30.0% vs 9.9%, p<0.001). However, there was no difference between the groups in the prevalence of carotid artery dissection (57.4% vs 47.4%, p=0.186).

Surgical data of the study population is presented in Table I.2. Patients with postoperative neurological injury underwent arch repair more often than the no neurological injury group (10.0% vs 4.3%, p=0.017) (Table I.2). They more often underwent surgery with straight circulatory arrest (52.5% vs 41.9%) or with ACP (9.2% vs 5.7%) and less often with RCP (35.0% vs 46.0%) (p=0.043).

Postoperative data of the study population is presented in Table I.3. Patients with neurological injury had significantly higher 24-hour bleeding volumes (730ml vs 610ml, p=0.011) and received more blood products (packed red blood cells: 5 (2-12) units vs 3 (2-7) units, p<0.001; plasma: 4 (0-8) units vs 3 (0-6) units, p=0.035; and platelets: 4 (4-6) units vs 4 (2-4) units, p<0.001).

Table I.1 Baseline characteristics

	All (538)	Neurological injury (120)	No neurological injury[1] (395)	*p*-value	*Missing*
Age	64.5±11.6	65.4±10.9	64.3±11.9	0.380	0
Female	192 (35.7)	43 (35.8)	144 (36.5)	0.901	0
Hypertension	275 (51.5)	65 (54.2)	198 (50.1)	0.438	0
Diabetes mellitus	96 (17.8)	28 (23.3)	61 (15.4)	0.045	0
COPD	28 (5.2)	4 (3.3)	22 (5.6)	0.327	0
History of smoking	171 (33.3)	41 (37.3)	122 (32.0)	0.303	25 (4.6)
Coronary artery disease	30 (7.0)	6 (5.9)	22 (7.1)	0.678	111 (20.6)
Known thoracic aneurysm	50 (11.7)	10 (10.0)	38 (12.3)	0.528	112 (20.8)
Marfan syndrome	28 (5.2)	4 (3.3)	23 (5.8)	0.284	0
Other connective tissue disease	5 (1.2)	1 (1.0)	4 (1.3)	1.000	111 (20.6)
Family history of dissection	22 (4.1)	4 (3.3)	18 (4.6)	0.562	0
Previous cardiac surgery	13 (2.4)	3 (2.5)	10 (2.5)	1.000	2 (0.4)
Previous aortic surgery	16 (3.0)	3 (2.5)	12 (3.0)	1.000	1 (0.2)
Preoperative creatinine (µmol/L)	89 (73-111)	103 (77-127)	87 (72-105)	<0.001	20 (3.7)
Preoperative lactate (mmol/L)	1.8 (1.2-3.3)	2.6 (1.3-4.7)	1.6 (1.2-2.8)	<0.001	126 (23.3)
Syncope	76 (17.8)	27 (26.7)	42 (13.6)	0.002	111 (20.6)
Hypotensive shock	100 (23.8)	31 (31.0)	62 (20.5)	0.030	117 (21.7)
Preoperative cardiac arrest	19 (4.4)	6 (5.9)	10 (3.2)	0.241	111 (20.6)
Cardiac tamponade	70 (16.4)	23 (23.0)	40 (13.0)	0.016	112 (20.8)
Any malperfusion	194 (36.1)	61 (50.8)	122 (30.9)	<0.001	0
Cerebral malperfusion	78 (14.5)	36 (30.0)	39 (9.9)	<0.001	1 (0.2)
Carotid dissection				0.186	72 (13.4)
None	236 (50.6)	46 (42.6)	179 (52.6)		
Unilateral	99 (21.2)	26 (24.1)	70 (20.6)		
Bilateral	131 (28.1)	36 (33.3)	91 (26.8)		
Intramural hematoma	62 (14.6)	12 (11.9)	49 (16.0)	0.319	112 (20.8)
Debakey type 1	419 (78.2)	95(79.8)	305 (77.4)	0.616	2 (0.4)

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). COPD: Chronic obstructive pulmonary disease. 1=Patients who died intraoperatively were excluded from the group “No neurological injury” (n=23).

Table I.2 Surgical data

	All (538)	Neurological injury (120)	No neurological injury[1] (395)	*p*-value	*Missing*
Cardiopulmonary bypass time (min)	190 (150-235)	197 (153-251)	187 (148-225)	0.050	2 (0.4)
Crossclamp time (min)	85 (60-128)	90 (57-140)	83 (60-122)	0.553	2 (0.4)
Hypothermic circulatory arrest technique				0.043	8 (1.5)
Cross clamp	31 (5.8)	4 (3.3)	25 (6.4)		
SCA	233 (44.0)	63 (52.5)	163 (41.9)		
ACP	37 (7.0)	11 (9.2)	22 (5.7)		
RCP	229 (43.2)	42 (35.0)	179 (46.0)		
Hypothermic circulatory arrest time (min)	22 (17-30)	22 (16-32)	22 (17-30)	0.902	43 (8.0)
Hypothermic circulatory arrest temperature (°C)	18.0 (16.8-20.0)	18.0 (17.0-20.4)	18.0 (16.7-20.0)	0.602	4 (0.8)
Arterial cannulation				0.595	3 (0.6)
Femoral	395 (73.6)	88 (73.3)	295 (74.7)		
Axillary	15 (2.8)	2 (1.7)	13 (3.3)		
Direct aortic	116 (21.6)	26 (21.7)	82 (20.8)		
Left ventricle/Unknown	9 (1.7)	3 (2.5)	5 (1.3)		
Distal surgical technique				0.017	1 (0.2)
Ascending	438 (81.6)	89 (74.2)	334 (84.6)		
Hemiarch	66 (12.3)	19 (15.8)	44 (11.1)		
Arch	31 (5.8)	12 (10.0)	17 (4.3)		
Other/Not completed	2 (0.4)	0 (0.0)	0 (0.0)		
Proximal surgical technique				0.192	0 (0.0)
Supracoronary graft	385 (71.6)	90 (75.0)	283 (71.6)		
Bentall procedure	114 (21.2)	19 (15.8)	88 (22.3)		
Supracoronary + isolated AVR	27 (5.0)	8 (6.7)	18 (4.6)		
Root replacement with aortic valve repair	8 (1.5)	2 (1.7)	6 (1.5)		
Other/not completed	4 (0.7)	1 (0.8)	0 (0.0)		
Additional CABG	43 (8.0)	12 (10.0)	26 (6.6)	0.210	0 (0.0)

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). SCA: Straight circulatory arrest, ACP: Antegrade cerebral perfusion, RCP: Retrograde cerebral perfusion, AVR: Aortic valve replacement, and CABG: Coronary artery bypass grafting. 1=Patients who died intraoperatively were excluded from the group “No neurological injury” (n=23).

Table I.3 Postoperative data

	All (538)	Neurological injury (120)	No neurological injury[1] (395)	*p*-value	*Missing*
rFVIIa	102 (36.3)	30 (44.1)	72 (34.1)	0.137	257 (47.8)
Fibrinogen (g)	4 (4-8)	6 (4-8)	4 (4-8)	0.070	257 (47.8)
Bleeding first 24 hours (ml)	640 (440-900)	730 (488-1345)	610 (420-855)	0.011	262 (48.7)
Reoperated for bleedning	77 (14.3)	23 (19.2)	54 (13.7)	0.142	1 (0.2)
PRBC units	4 (2-7.5)	5 (2-12)	3 (2-7)	<0.001	133 (24.7)
Plasma units	3 (0-6)	4 (0-8)	3 (0-6)	0.035	133 (24.7)
Platelet units	4 (2-6)	4 (4-6)	4 (2-4)	<0.001	133 (24.7)
Ventilator >48h	197 (39.7)	77 (66.4)	120 (31.6)	<0.001	42 (7.8)
Renal replacement therapy	52 (10.2)	18 (15.0)	34 (8.7)	0.046	27 (5.0)
Postoperative MI	20 (9.9)	8 (17.0)	12 (7.7)	0.090	335 (62.3)
Multiple organ failure	8 (2.6)	5 (6.6)	3 (1.3)	0.012	230 (42.8)
Postoperative peak CKMB (µg/L)	28.3 (18.1-55.0)	31.0 (22.8-65.0)	27.0 (17.0-53.4)	0.015	207 (38.5)
Postoperative peak creatinine (µmol/L)	122 (91-201)	155 (104-257)	117 (88-182)	<0.001	46 (8.6)
Postoperative peak lactate (mmol/L)	2.8 (2.0-3.8)	3.1 (2.2-5.0)	2.7 (2.0-3.5)	0.028	263 (48.9)
Intraop death	23 (4.3)	NA	NA	NA	0
30-day mortality	73 (13.7)	27 (22.7)	23 (5.8)	<0.001	7 (1.3)
In-hospital mortality	78 (14.6)	29 (24.4)	26 (6.6)	<0.001	4 (0.7)

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). rFVIIa: recombinant factor VIIa, PRBC: Packed red blood cells, MI: Myocardial infarction and CKMB: Creatine phosphokinase-MB. 1=Patients who died intraoperatively were excluded from the group “No neurological injury” (n=23).

Radiological properties of neurological injury

Radiological properties of neurological injuries are presented in Table I.4. Both hemispheres were affected in more than half of patients (53.4%), but unilateral embolic injuries were more common in the right hemisphere than the left in patients with stroke as well as coma (70.4% in stroke patients and 85.7% in coma patients). In patients with neurological injury, common carotid dissection was present on the left side in 6 patients (5.6%), right side in 20 patients (18.5%) and bilateral in 36 patients (33.3%). The middle cerebral artery was the most affected vascular territory in both groups (71.6% and 69.4%, respectively), but embolic lesions in the basilar artery territory were significantly more common in comatose patients (47.2% vs 20.3%, p=0.009) as were watershed lesions (41.7% vs 6.8%, p<0.001) and mixed lesions (30.6% vs 4.1%, p<0.001).

Table I.4 Radiological properties of neurological injury stratified by clinical presentation.

	All (n=120)	Stroke (n=74)	Coma[1] (n=36)	*p*-value	Missing
Carotid artery dissection				0.205	10 (8.3)
Left	6 (5.6)	5 (5.7)	0 (0)		
Right	20 (18.5)	12 (16.1)	6 (19.4)		
Both	36 (33.3)	28 (35.6)	8 (25.8)		
Postoperative imaging available				0.091	20 (16.7)
CT	89 (89.0)	55 (74.3)	34 (94.4)		
MRI	11 (11.0)	10 (13.5)	1 (2.8)		
Non-acute ischemic lesions/white matter disease	24 (24.0)	16(21.6)	8 (22.2)	0.84	20 (16.7)
Acute ischemic lesions	92 (92.0)	59 (79.7)	33 (91.7)	0.709	20 (16.7)
Embolic	88 (88.0)	58 (78.4)	30 (83.3)	0.748	
Watershed	20 (20.0)	5 (6.8)	15 (41.7)	<0.001	
Mixed	14 (14.0)	3 (4.1)	11 (30.6)	<0.001	
Embolic lesion hemisphere				0.699	20 (16.7)
Left	10 (10.0)	8 (10.8)	2 (5.6)		
Right	31 (31.0)	19 (25.7)	12 (33.3)		
Both	47 (47.0)	31 (41.9)	16 (44.4)		
Embolic lesion territory					20 (16.7)
Anterior	17 (17.0)	9 (12.2)	8 (22.2)	0.253	
Media	78 (78.0)	53 (71.6)	25 (69.4)	0.244	
Posterior	42 (42.0)	26 (35.1)	16 (44.4)	0.581	
Basilar	32 (32.0)	15 (20.3)	17 (47.2)	0.009	
Watershed lesion hemisphere				<0.001	20 (16.7)
Left	3 (3.0)	1 (1.4)	2 (5.6)		
Right	5 (5.0)	2 (2.7)	3 (8.3)		
Both	12 (12.0)	2 (2.7)	10 (27.8)		
Mixed lesions hemisphere				0.003	20 (16.7)
Left	2 (2.0)	0 (0)	2 (5.6)		
Right	4 (4.0)	1 (1.4)	3 (8.3)		
Both	8 (8.0)	2 (2.7)	6 (16.7)		

Values are presented as n (%). CT: computed tomography and MRI: magnetic resonance imaging. 1=Patients with coma and symptoms of focal neurological injuries (stroke) were categorised into the coma group.

Independent predictors of neurological injury

Independent predictors of neurological injury are presented in Figure I.1. Cerebral malperfusion (OR: 3.74; 95% CI 2.12-6.58, p<0.001) and cardiopulmonary bypass time (OR: 1.00; 95% CI 1.00-1.01, p=0.032) predicted neurological injury whereas RCP (OR: 0.58; 95% CI 0.37-0.91, p=0.015) had a protective effect.

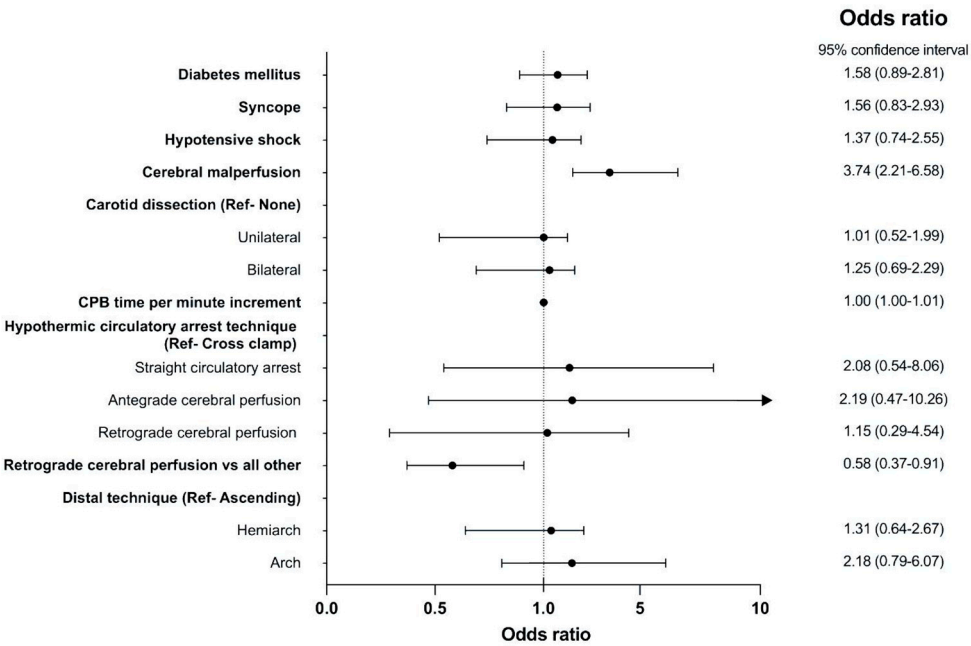

Figure I.1 Forest plot illustrating the association with neurological injury. Values are expressed as odds ratio with 95% confidence interval. CPB: Cardiopulmonary bypass. Ref: reference variable.

Independent predictors of embolic or watershed lesions

Independent predictors of embolic lesions are presented in Figure I.2. Cerebral malperfusion (OR: 2.77; 95% CI, 1.53-5.00, p<0.001), systemic hypotensive shock (OR: 1.97; 95% CI 1.13-3.43, p=0.011) and aortic arch replacement (OR: 3.08; 95% CI 1.17-8.08, p=0.020) predicted embolic lesions. Independent predictors of watershed lesions are presented in Figure I.3: diabetes mellitus (OR: 5.35; 95% CI 1.85-15.42, p=0.002), previous cardiac surgery (OR: 8.62; 95% CI 1.47-50.43, p=0.017), hypothermic circulatory arrest time (OR: 1.05; 95% CI 1.01-1.08, p=0.005), cardiopulmonary bypass time (OR: 1.01; 95% CI 1.00-1.01, p=0.041), ascending aortic-/arch cannulation (OR: 5.68; 95% CI, 1.88-17.12, p=0.002) and left ventricular cannulation (OR: 17.81; 95% CI 1.69-188.01, p=0.015). RCP had a protective effect when compared to hypothermic circulatory arrest alone (OR: 0.28; 95% CI, 0.01-0.84, p=0.023).

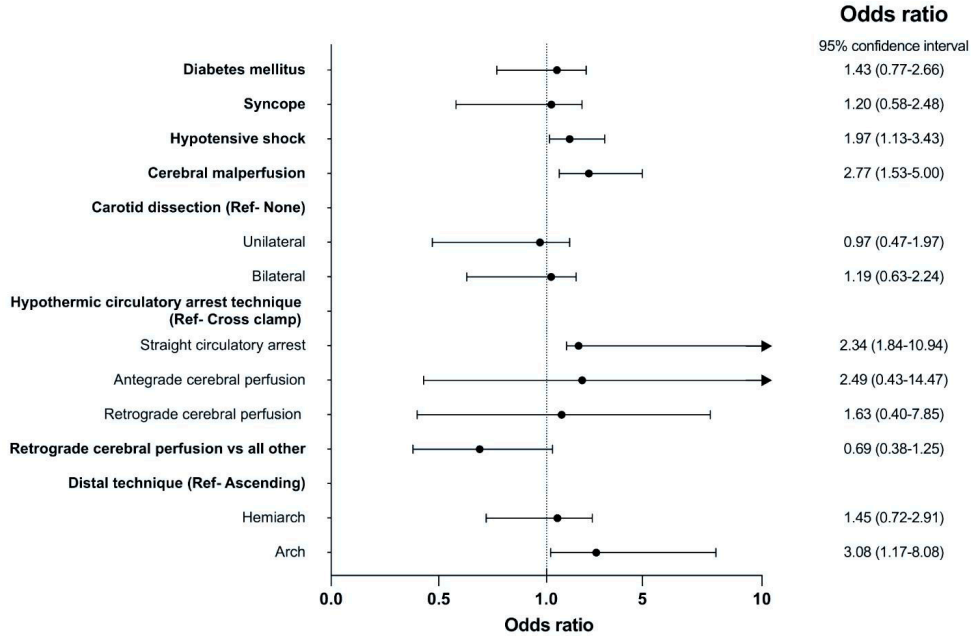

Figure I.2 Forest plot illustrating the association with embolic lesions. Values are expressed as odds ratio with 95% confidence interval. Ref: reference variable.

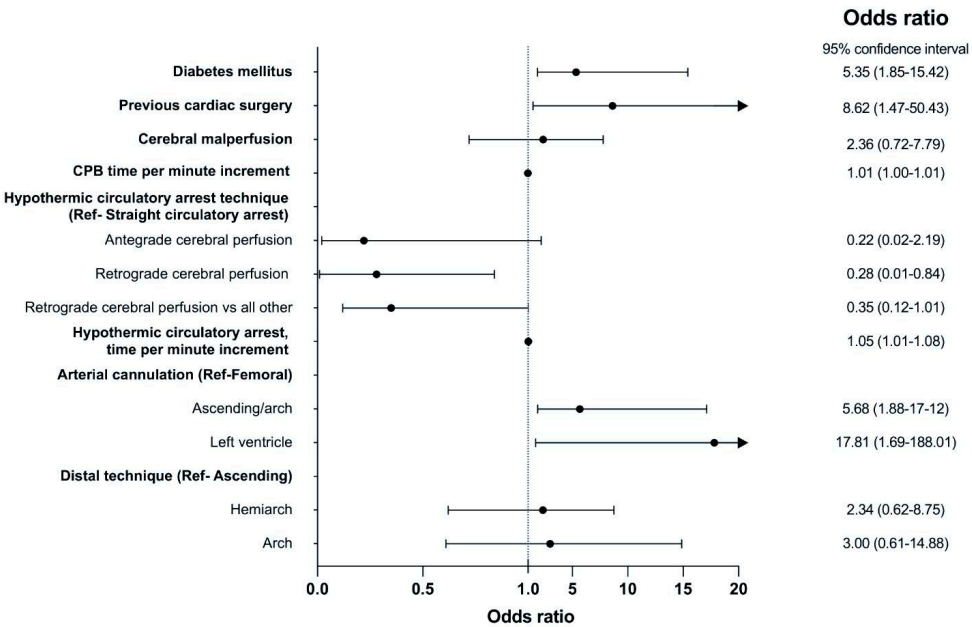

Figure I.3 Forest plot illustrating the association with watershed lesions. Values are expressed as odds ratio with 95% confidence interval. Ref: reference variable.

Postoperative mortality

Overall, 30-day mortality was 13.7%. In patients who survived surgery, 30-day mortality was 9.7% (22.7% vs 5.8% in the neurological injury and no neurological injury group, respectively (p<0.001).

Independent predictors of 30-day mortality

We identified several independent predictors of 30-day mortality, which are presented in Supplementary Table I.1. The predictors included malperfusion (OR: 4.62; 95% CI, 1.83-11.67, p=0.011), neurological injury (OR: 3.82; 95% CI, 1.62-9.05, p<0.001), coma (OR: 15.68; 95% CI, 5.23-47.09, p<0.001), neurological injury with embolic lesions (OR: 4.34; 95% CI, 1.78-10.59, p<0.001), and neurological injury with watershed lesions (OR: 13.48; 95% CI, 3.82-47.63, p<0.001).

Late survival

Kaplan-Meier estimates of late survival in patients who survived 30 days postoperatively are demonstrated in Supplementary Figure I.1 and indicate that postoperative neurological injury is associated with significantly poorer survival at 1, 5, 10 and 15 years after ATAAD surgery (96.6±0.9% vs 90.1±3.1%, 86.3±2.0% vs 71.1±5.2%, 68.1±3.1% vs 49.2±6.7%, and 46.4±4.1% vs 28.4±7.9%, respectively; log rank p<0.001). Independent predictors of late mortality are presented in Supplementary Table I.2.

Study II

Study population

Between January 1998 and December 2022, 598 patients underwent ATAAD surgery at our institution. A total of 515 patients underwent ATAAD surgery with HCA and were included in the present study. A total of 258 patients (50.1%) underwent repair with the use of RCP. In total, 83 patients were excluded: 42 because of surgery performed without circulatory arrest, 39 due to the use of ACP, and 2 patients because they died before the initiation of CPB. Follow-up was conducted in March 2023 with a total of 3 212 patient-years (median 5.0 (1.1-10.1), mean 6.2±5.8).

Baseline variables are presented in Table II.1. A significantly lower proportion of patients in the RCP group presented with hypotensive shock (19.5% vs 28.2%, p=0.029), any malperfusion (30.7% vs 40.5%, p=0.027) and intramural hematoma (7.4% vs 15.6%, p=0.005). DeBakey type 1 dissections were more frequently observed in the RCP group compared to the HCA only group (78.4% vs 86.0%, p=0.034). There was a lower frequency of cerebral malperfusion in the RCP only

group (11.3% vs. 17.6%, p=0.057), but it did not reach the level of statistical significance.

Intraoperative data are presented in Table II.2. RCP patients had longer time on cardiopulmonary bypass (202 min; 95% CI 168-248 min vs 168 min; 95% CI 134-213 min, p<0.001), longer cross-clamp time (98 min; 95% CI 71-142 min vs 67 min; 95% CI 50-106 min, p<0.001) and longer HCA time (26 min; 95% CI 20-34 min vs 18 min; 95% CI 14-23 min, p<0.001). Patients with RCP were operated on at a lower HCA temperature (17.0 ℃; 95% CI 16.0-19.0 ℃ vs 18.5 ℃; 95% CI 18.0-20.0 ℃, p<0.001) and underwent more extensive proximal aortic repair.

Postoperative data are presented in Table II.3. There were no significant differences except for the RCP group receiving fewer units of platelets (4 units (2-5) vs 4 units (2-6), p=0.036), and neurological outcomes as presented below. Mortality was equal between the groups with an intraoperative mortality of 3.9% vs 2.7%, 30-day mortality of 14.0% vs 12.3% and in-hospital mortality of 15.2% vs 13.4% (p=ns) in the RCP group and HCA only group, respectively.

Survival at 1, 5 and 15 years was similar for both groups with 82.0%±2.4% vs 80.9%±2.4%, 73.9±2.9% vs 68.9%±3.1%, and 34.3±3.8% vs 37.2%±6.5% in the RCP and HCA only group, respectively (p=0.594)(Supplementary Figure II.1.).

Table II.1. Baseline variables of the study population.

	RCP (n=258)	HCA only (n=257)	*p*-value	Missing
Age	64.90±11.7	64.6±10.7	0.723	0
Female	93 (36.0)	97 (37.7)	0.758	0
Hypertension	121 (46.9)	142 (55.3)	0.071	0
Diabetes mellitus	46 (17.8)	34 (13.2)	0.187	0
COPD	14 (5.4)	14 (5.4)	1.000	0
Smoking	84 (33.5)	86 (35.7)	0.673	23 (4.5)
Coronary artery disease	21 (8.1)	29 (11.3)	0.291	0
Thoracic aneurysm	24 (9.3)	28 (10.9)	0.639	1 (0.2)
Marfan syndrome	12 (4.7)	9 (3.5)	0.662	0
Family history of dissection	8 (3.1)	13 (5.1)	0.368	0
Previous cardiac surgery	5 (1.9)	7 (2.7)	0.760	1 (0.2)
Previous aortic surgery	8 (3.1)	11 (4.3)	0.634	0
Preoperative creatinine (µmol/L)	87 (73–110)	90 (74-112)	0.392	21 (4.1)
Syncope	39 (15.2)	49 (19.1)	0.292	1 (0.2)
Hypotonic shock	50 (19.5)	71 (28.2)	0.029	7 (1.4)
Preoperative arrest	7 (2.7)	14 (5.4)	0.181	1 (0.2)
Malperfusion (any)	79 (30.7)	104 (40.5)	0.027	1 (0.2)
Cerebral malperfusion	29 (11.3)	45 (17.6)	0.057	2 (0.4)
Intramural hematoma	19 (7.4)	40 (15.6)	0.005	1 (0.2)
DeBakey Type 1	221 (86.0)	200 (78.4)	0.034	1 (0.2)

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). HCA: hypothermic circulatory arrest, RCP: retrograde cerebral perfusion, COPD: chronic obstructive pulmonary disease.

Table II.2. Intraoperative data of the study population.

	RCP (n=258)	HCA only (n=257)	*p*-value	Missing
Cardiopulmonary bypass time (min)	202 (168-248)	168 (134-213)	<0.001	0
Crossclamp time (min)	98 (71-142)	67 (50-106)	<0.001	0
Hypothermic circulatory arrest time (min)	26 (20-34)	18 (14-23)	<0.001	2 (0.4)
Hypothermic circulatory arrest temperature (°C)	17 (16-19)	19 (18–20)	<0.001	3 (0.6)
Arterial cannulation			0.134	0
-Femoral artery	190 (73.6)	196 (76.3)		
-Axillary artery	2 (0.8)	6 (2.3)		
-Ascending aorta/Arch	65 (25.2)	51 (19.8)		
-Left ventricle	1 (0.4)	4 (1.6)		
Distal surgical technique			0.514	0
-Ascending aorta	209 (81.0)	218 (84.8)		
-Hemiarch procedure	36 (14.0)	29 (11.3)		
-Arch procedure	13 (5.0)	10 (3.9)		
Proximal surgical technique			0.012	0
-Supracoronary graft	174 (67.5)	207 (80.5)		
-Bentall procedure	62 (25.0)	41 (16.0)		
-Supracoronary graft + isolated AVR	4 (1.6)	3 (1.2)		
-Root replacement with aortic valve repair	17 (6.6)	6 (2.3)		
-Other/not completed	1 (0.4)	0 (0.0)		
Additional CABG	20 (7.8)	17 (6.6)	0.742	0

Values are presented as n (%) or median (interquartile range). HCA: hypothermic circulatory arrest, RCP: retrograde cerebral perfusion, AVR: aortic valve replacement, CABG: coronary artery bypass grafting.

Table II.3. Postoperative data of the study population.

	RCP (n=258)	HCA only (n=257)	*p*-value	Missing
Peak creatinine (µmol/L)	132 (91-219)	118 (94-202)	0.479	36 (7.0)
Peak lactate (mmol/L)	2.8 (2.2–3.8)	3.1 (2.2–4.2)	0.183	225 (43.7)
Bleeding first 24 hours (ml)	680 (450-920)	630 (435-855)	0.425	223 (43.4)
Peak CKMB (µg/L)	27 (17-52)	27 (18-54)	0.559	178 (34.6)
Packed red blood cells (units)	4 (2-8)	4 (2–7)	0.209	113 (21.9)
Plasma (units)	3 (0-8)	3 (0-6)	0.207	113 (21.9)
Platelets (units)	4 (2-5)	4 (2-6)	0.036	113 (21.9)
Fibrinogen (g)	4 (4-7)	6 (4-8)	0.193	222 (43.1)
rFVIIa	29 (31.2)	78 (39.0)	0.245	222 (43.1)
Reoperated for bleeding	41 (16.0)	35 (13.6)	0.522	2 (0.4)
Ventilator >48h	93 (39.9)	99 (39.8)	1.000	33 (6.4)
Renal replacement therapy	24 (9.9)	29 (11.6)	0.637	22 (4.3)
Postoperative MI	6 (4.5)	16 (15.7)	0.007	280 (54.4)
Multiple organ failure	3 (2.6)	6 (2.9)	1.000	192 37.3)
Clinical neurological injury	50 (20.2)	71 (28.4)	0.041	17 (3.3)
Stroke	36 (14.3)	45 (18.0)	0.349	17 (3.3)
Coma	14 (5.9)	26 (10.4)	0.067	17 (3.3)
Embolic lesions	32 (13.7)	57 (23.4)	0.010	38 (7.4)
Watershed lesions	7 (3.0)	15 (6.1)	0.156	38 (7.4)
Intraoperative death	10 (3.9)	7 (2.7)	0.628	0
30-day mortality	36 (14.0)	31 (12.3)	0.661	6 (1.2)
In-hospital mortality	39 (15.2)	34 (13.4)	0.652	4 (0.8)

Values are presented as n (%) or median (interquartile range). HCA: hypothermic circulatory arrest, RCP: retrograde cerebral perfusion, CKMB: creatine phosphokinase-MB, rFVIIa: recombinant factor VIIa and MI: myocardial infarction.

Neurological injury

Stroke or coma occurred postoperatively in 28.4% of HCA only patients and 20.2% of patients with RCP (p=0.041) regardless of preoperative symptoms. In patients with a clinical neurological injury, 78.9% underwent a CT-scan of the brain, 12.4% underwent brain-MRI, and 16.5% underwent no radiological imaging. The median duration from surgery to imaging was 3 days (2-6). Embolic cerebral lesions were more frequently observed in the HCA only group (23.4% vs 13.7%, p=0.010). There was no significant difference in the occurrence of watershed lesions (6.1% vs 3.0%, p=0.156).

After multivariable logistic regression with adjustment for covariates that may influence the risk of neurological injury, the use of RCP independently predicted a reduction of clinical neurological injury (OR: 0.60; 95% CI 0.36-0.99, p=0.047), embolic lesions (OR: 0.55; 95% CI 0.31-0.97, p=0.040) and watershed lesions (OR: 0.25; 95% CI 0.07-0.80, p=0.027) (Figure II.1, Table II.4).

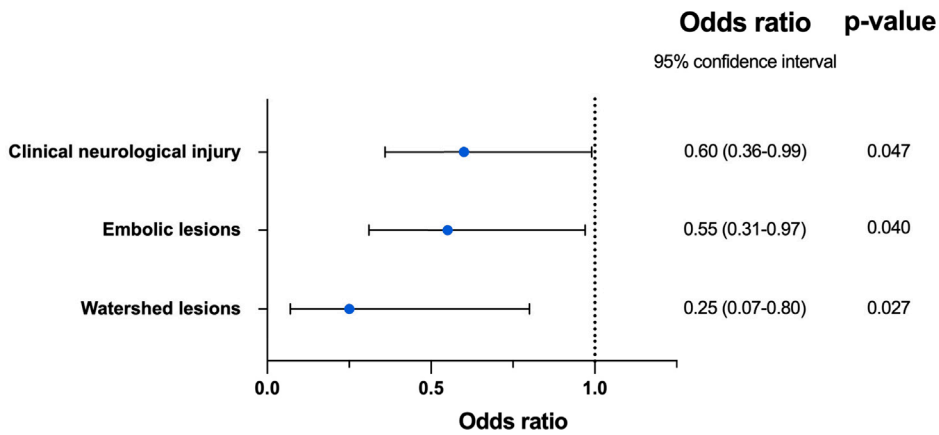

Figure II.1. The neuroprotective effect of retrograde cerebral perfusion compared to hypothermic circulatory arrest only on the primary outcomes (clinical neurological injury, embolic lesions and watershed lesions).

In order to evaluate the robustness of our findings, we performed a series of sensitivity analyses. First, we excluded patients who presented with cerebral malperfusion. In the remaining cohort (n=441), the use of RCP resulted in an adjusted OR of 0.61 (95% CI 0.36-1.02, p=0.061) for clinical neurological injury, 0.55 (95% CI 0.31-0.98, p=0.044) for embolic lesions and 0.24 (95% CI 0.06-0.77, p=0.024) for watershed lesions (Table II.4). Second, we performed a propensity score matched analysis generating 218 matched pairs. The matched variables and absolute standardised differences of the propensity score matching are presented in Supplementary Figure II.2. Using this set of data, our analysis generated an OR of 0.82 (95% CI 0.53-1.34, p=0.415) for clinical neurological injury, 0.68 (95% CI 0.40-1.15, p=0.156) for embolic lesions and 0.67 (95% CI 0.24-1.73, p=0.413) for watershed lesions. Supplementary Table II.1 illustrates the number of patients with cerebral malperfusion and neurological outcomes in each analysis, showing that both sensitivity analyses were performed on a study sample with a significant reduction of neurological outcomes, rendering them under-powered to detect some of the differences observed in the crude and adjusted primary analyses.

Table II.4. Crude and adjusted odds ratios for the primary outcomes in the full population and the population excluding patients with preoperative cerebral malperfusion.

Full population					
Clinical neurological injury		Embolic lesions		Watershed lesions	
Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
0.64 (0.42-0.96) p = 0.033	0.60 (0.36-0.99) p = 0.047	0.52 (0.32-0.83) p = 0.007	0.55 (0.31-0.97) p = 0.040	0.47 (0.18-1.14) p = 0.109	0.25 (0.07-0.80) p = 0.027
Study population without cerebral malperfusion					
Clinical neurological injury		Embolic lesions		Watershed lesions	
Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
0.65 (0.40-1.06) p = 0.089	0.61 (0.36-1.02) p = 0.061	0.60 (0.34-1.04) p = 0.070	0.55 (0.31-0.98) p = 0.043	0.34 (0.09-1.00) p = 0.066	0.24 (0.06-0.77) p = 0.024

Values are presented as odds ratio (95% confidence interval). Adjusted analyses were adjusted for the following variables: age, diabetes mellitus, coronary artery disease, previous cardiac surgery, presentation with syncope, cerebral malperfusion, hypotensive shock, intramural hematoma and DeBakey type 1. The full population was also adjusted for an interaction term between RCP and cerebral malperfusion.

Study III

Study population

Between January 1998 and December 2023, 629 patients underwent ATAAD surgery at our institution. Of these patients, 93 (14.7%) presented with cerebral malperfusion and were included in the present study. Of the patients who presented with cerebral malperfusion, 52 patients (57.1%) had persisting neurological deficit, and 39 patients (42.9%) did not. Two patients (2.2%) died intraoperatively and were, therefore, excluded from further group analyses.

Preoperative data

Preoperative data are presented in Table III.1. There were no differences in patients with and without persisting neurological deficit in preoperative variables. There was no significant difference in time from symptom onset to start of surgery between groups (6.6 (4.4-9.9) hours vs 5.7 (4.1-7.3) hours, *p*=ns).

Preoperative neurology

Preoperative neurological symptoms are presented in Table III.2 and Figure III.1B-D. Hemiparesis/hemiplegia was the most common presentation (45.2%) followed by altered level of consciousness (35.5%), monoparesis/monoplegia (6.5%), impaired vision (6.5%), facial palsy (2.2%), vertigo (2.2%) and aphasia (2.2%). Of all focal neurological symptoms, only hemiparesis/hemiplegia was significantly

more frequently observed in patients who developed postoperative neurological deficit (57.7% vs. 28.2%, p=0.005), and of those patients who presented with hemiparesis/hemiplegia, 73.2% developed persisting neurological deficit.

There was a significant difference in the level of consciousness between the groups. Syncope was less frequently observed in the group with persisting neurological deficit (5.8% vs. 23.1%, p=0.015), and 25.0% of patients with syncope had persisting neurological deficit. Of the patients who presented with unconsciousness, 83.3% had persisting neurological deficit, and preoperative unconsciousness was significantly more common in the group with persisting neurological deficit (19.2% vs. 5.1%, p=0.049). In patients who presented with transient neurological symptoms, 22.2% developed persisting neurological deficit.

Table III.1. Baseline variables of the study population.

	All* (n=93)	**Persisting neurological deficit (n=52)**	**No persisting neurological deficit (n=39)**	***p-value***	**Missing**
Age	67.3±10.6	67.2±11.2	67.3±9.9	0.911	0
Female	40 (43.0)	22 (42.3)	18 (46.2)	0.715	0
Hypertension	54 (58.1)	32 (61.5)	21 (53.8)	0.462	0
Diabetes mellitus	14 (15.1)	8 (15.4)	5 (12.8)	0.729	0
COPD	5 (5.4)	2 (3.8)	3 (7.7)	0.648	0
Smoking	26 (31.0)	12 (28.9)	13 (34.2)	0.603	9 (9.7)
Coronary artery disease	6 (6.5)	2 (3.8)	3 (7.7)	0.648	0
Thoracic aneurysm	7 (7.5)	2 (3.8)	5 (12.8)	0.134	0
Marfan syndrome	3 (3.2)	0	3 (7.7)	0.075	0
Family history of dissection	3 (3.2)	0	3 (7.7)	0.075	0
Previous cardiac surgery	1 (1.1)	1 (1.9)	0	1.000	0
Previous aortic surgery	1 (1.1)	0	1 (2.6)	0.429	0
Preoperative creatinine (µmol/L)	95 (78-125)	97 (77-122)	95 (78-127)	0.976	4 (4.3)
Hypotonic shock	32 (34.3)	20 (38.5)	11 (28.2)	0.307	0
Cardiac tamponade	25 (26.9)	17 (32.7)	7 (17.9)	0.114	0
Preoperative arrest	6 (6.5)	4 (7.7)	2 (5.1)	0.697	0
Malperfusion (any not cerebral)	37 (39.8)	24 (46.2)	13 (33.3)	0.218	0
Cardiac	13 (14.0)	8 (15.4)	5 (12.8)	0.729	0
Gastrointestinal	7 (7.5)	6 (11.5)	1 (2.6)	0.232	0
Renal	11 (11.8)	9 (17.3)	2 (5.1)	0.107	0
Limb	18 (19.4)	11 (21.2)	7 (17.9)	0.704	0
Duration to surgery (hours)	6.0 (4.4-9.2)	6.6 (4.4-9.9)	5.7 (4.1-7.3)	0.113	14 (15.1)
Intramural hematoma	7 (7.5)	3 (5.8)	4 (10.3)	0.456	0
DeBakey Type 1	80 (86.0)	45 (86.5)	33 (84.6)	0.795	0

*=2 patients died intraoperatively and were excluded from group analyses. Values are presented as mean ± standard deviation, n (%), or median (interquartile range). COPD: chronic obstructive pulmonary disease.

Preoperative radiology

Preoperative radiological data are presented in Table III.1 and Figure III.1A. Patients with persisting neurological deficit were significantly more likely to have common carotid artery (CCA) dissection compared to patients who did not develop postoperative neurological injury (8.0% vs. 34.2% had no CCA dissection, 22.0% vs. 36.8% had unilateral dissection and 70.0% vs. 28.9% had bilateral carotid artery dissection in the persisting neurological deficit vs no persisting neurological deficit groups ($p<0.001$)). Any carotid artery occlusion was significantly more common in patients with persisting neurological deficit (34.0% vs. 10.5%, $p=0.030$). Also, patients with persisting neurological deficit more often presented with right CCA occlusion (26.0% vs. 7.9%, $p=0.029$) than in patients with no persisting neurological deficit. Patients with internal carotid artery (ICA) occlusion (n=9) presented with either hemiparesis (n=5) or reduced consciousness or unconsciousness (n=4). In patients with any carotid artery occlusion, 81.0% developed neurological injury and 23.8% were not alive 30 days after surgery.

Fifty-eight patients (62.4%) underwent a preoperative CT of the brain, and early signs of cerebral ischemia were observed in 6 patients (6.5%). Three patients (3.2%) had a preoperative perfusion-CT of the brain with an ischemic core of 109ml, 27ml and 5ml, respectively, and penumbra was 424ml, 219ml and 418ml, respectively.

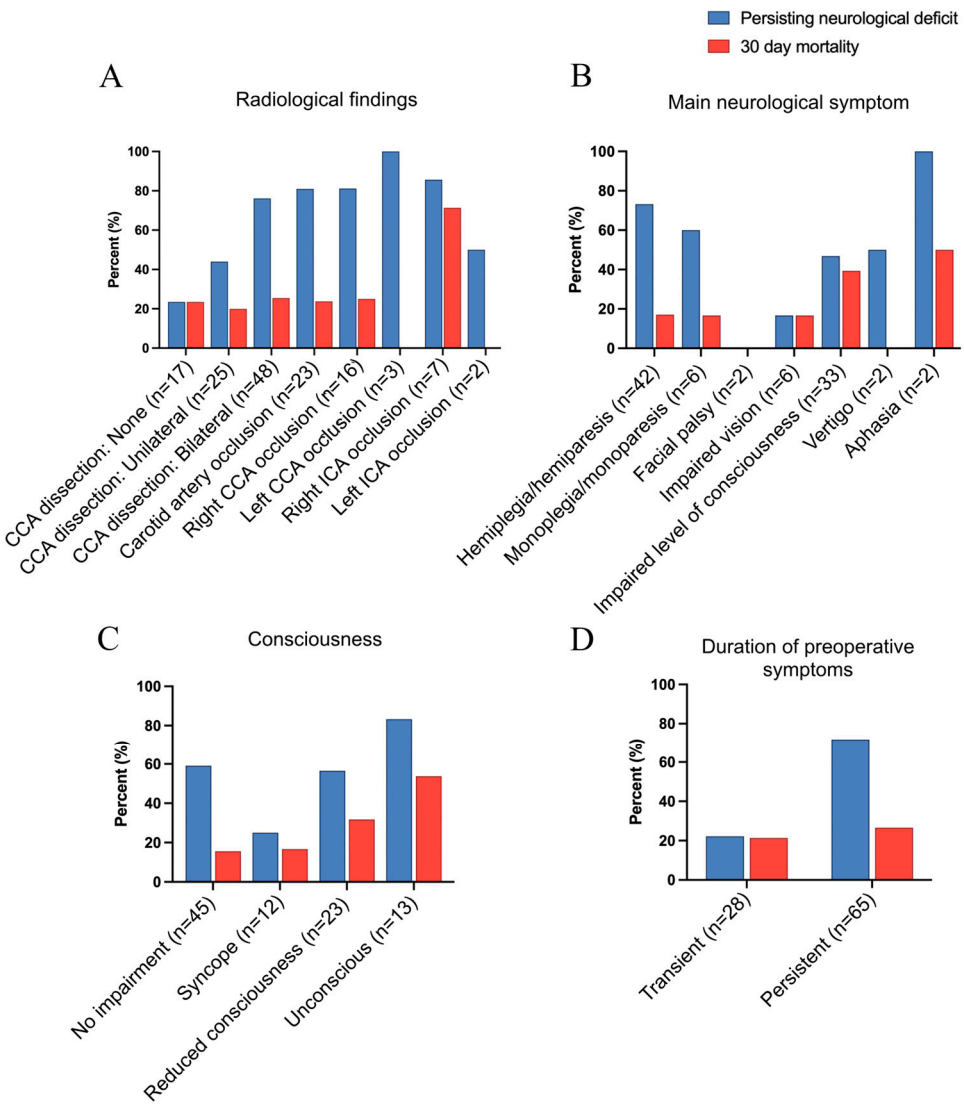

Figure III.1. Radiological and clinical neurological findings compared with neurological and 30-day mortality outcomes

Table III.2. Neurological and radiological data

	All* (n=93)	Persisting neurological deficit (n=52)	No persisting neurological deficit (n=39)	*p*-value	Missing
Common carotid artery dissection				<0.001	3 (3.2)
- None	17 (18.9)	4 (8.0)	13 (34.2)		
- Unilateral	25 (27.8)	11 (22.0)	14 (36.8)		
- Bilateral	48 (53.3)	35 (70.0)	11 (28.9)		
Carotid artery occlusion	21 (23.3)	17 (34.0)	4 (10.5)	.030	3 (3.2)
- CCA dexter occlusion	16 (17.8)	13 (26.0)	3 (7.9)	.029	
- CCA sinister occlusion	3 (3.3)	3 (6.0)	0	.255	
- ICA dexter occlusion	7 (7.8)	6 (12.0)	1 (2.6)	.135	
- ICA sinister occlusion	2 (2.2)	1 (2.0)	1 (2.6)	1.0	
Main neurological symptom					0
- Hemiparesis/hemiplegia	42 (45.2)	30 (57.7)	11 (28.2)	.005	
- Monoparesis/monoplegia	6 (6.5)	3 (5.8)	2 (7.7)	1.0	
- Facial palsy	2 (2.2)	0	2 (5.1)	.181	
- Impaired vision	6 (6.5)	1 (1.9)	5 (12.8)	.080	
- Impaired level of consciousness	33 (35.5)	15 (28.8)	17 (43.6)	.185	
- Vertigo	2 (2.2)	1 (1.9)	1 (2.6)	1.0	
- Aphasia	2 (2.2)	2 (3.8)	0	.505	
Level of consciousness				.034	0
- No impairment	45 (48.4)	26 (50.0)	18 (46.2)	.716	
- Syncope	12 (12.9)	3 (5.8)	9 (23.1)	.016	
- Reduced level of consciousness	23 (24.7)	13 (25.0)	10 (25.6)	.944	
- Unconscious	13 (14.0)	10 (19.2)	2 (5.1)	.049	
Duration of preoperative symptoms				<0.001	0
- Persistent	65 (69.9)	46 (88.5)	18 (46.2)		
- Transient	28 (30.1)	6 (11.5)	20 (53.8)		
Postoperative neurological status				<0.001	3 (3.2)
- Better	47 (52.2)	8 (15.7)	39 (100.0)		
- Same	23 (25.6)	23 (45.1)	0		
- Worse	20 (22.2)	20 (39.2)	0		

*=2 patients died intraoperatively and were excluded from group analyses. Values are presented as n (%). CCA: common carotid artery, ICA: internal carotid artery.

Intraoperative data

Intraoperative data are presented in Supplementary Table III.1. There were no differences in patients with and without persisting neurological deficit in intraoperative variables.

Postoperative data

Postoperative data are presented in Table Supplementary III.2. There were no differences in patients with and without persisting neurological deficit in postoperative variables apart from mortality

Perioperative neurological outcomes and mortality

Out of all patients, 52.2% improved their neurological status after surgery, 25.6% had similar status and 22.2% were in a worse neurological state after the procedure. Of the patients who presented with preoperative persistent neurological symptoms, 71.9% had a persisting neurological deficit after surgery.

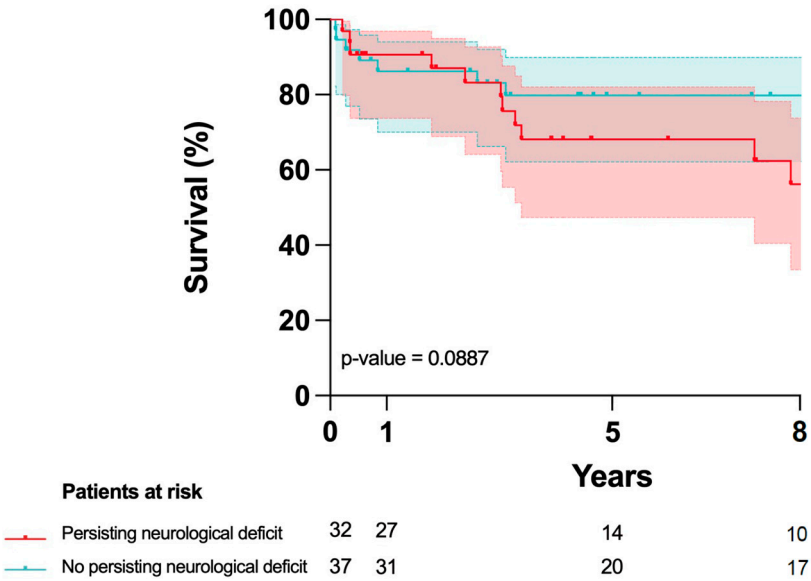

Figure III.2. Late survival for 30-day survivors.

Patients with persisting neurological deficit had a significantly higher 30-day mortality and in-hospital mortality compared to those without persisting neurological deficit (37.3% vs 5.1%, $p<0.001$ and 37.3% vs. 7.7%, $p=0.001$). In patients presenting with unconsciousness, 53.8% died within 30 days after surgery ($p=0.016$) and 4 out of 6 survivors developed neurological injury. Of the 13 patients (14.0%) presenting with unconsciousness, 84.6% died or had persisting neurological deficit. In patients who were unconscious before surgery (n=13), the time from symptom to surgery was longer in patients who died within 30-days of surgery (9.2 (4.9-21.6) hours vs. 5.3 (2.6-9.9) hours, $p=0.30$), but this difference was not statistically significant.

Late survival

Late survival for 30-day survivors is presented in Figure III.2. There was no statistically significant difference between the persisting neurological deficit and no persisting neurological deficit groups at 1, 5 and 8 years (90.6%±5.2% vs 86.2%±5.7%, 68.1%±8.9% vs 79.8%±6.9%, and 62.4%±9.8% vs 79.8%±6.9%, respectively ($p=0.089$)).

Study IV and V

Study population

A total of 117 patients were accepted for ATAAD repair from January 2022 until March 2025. A flowchart of the patients is presented in Figure V.1. Of these, 80 patients were randomised and 75 were included in the present study. Randomised patients who were later excluded, were excluded due to not being operated with an open distal anastomosis (n=3), death before establishing extracorporeal circulation (n=1) and unrecognised prior cardiac surgery at randomization (n=1). Thirty-seven patients were randomised to CO_2 flooding and 38 patients to the control group. Baseline characteristics are presented in Table V.1 and intraoperative data in Table V.2. There was a non-significant difference in hypothermic circulatory arrest technique between the groups where 59% (n=22) received RCP in the intervention, whereas 37% (n=14) received RCP in the control group (p=0.066).

Postoperative data and adverse events with the exception of neurological outcomes are presented in Table V.3. There were no significant differences between the groups. Intraoperative mortality occurred in 2 patients in each group (5.4% in the CO_2 flooding group vs 5.3% in the control group (p>0.999)) due to aortic rupture (n=2) and cardiac failure (n=2). Thirty-day mortality was 5.6% in the CO_2 flooding group vs 13% in the control group (p=0.431).

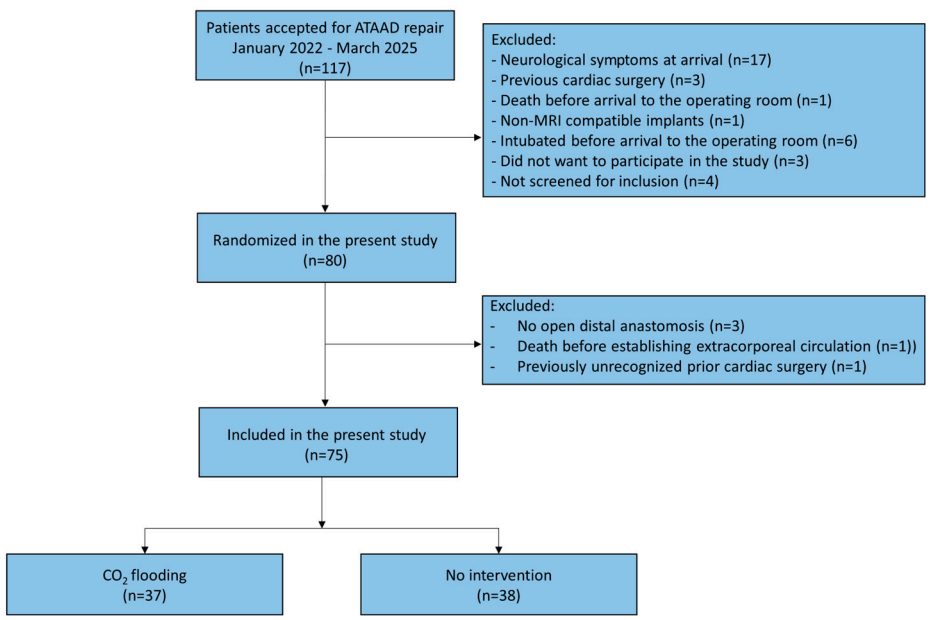

Figure V.1. Flowchart for the study participants

Table V.1. Baseline variables of the study population.

Characteristic	Intervention N = 37	Control N = 38	Missing, N (%)
Age	65 (58-73)	71 (62-75)	0 (0%)
Female	14 (38%)	14 (37%)	0 (0%)
Height (cm)	176 (168-184)	177 (168-182)	0 (0%)
Weight (kg)	82 (74-95)	85 (67-105)	0 (0%)
Hypertension	22 (59%)	21 (55%)	0 (0%)
Diabetes mellitus	1 (2.7%)	2 (5.3%)	0 (0%)
COPD	3 (8.1%)	1 (2.6%)	0 (0%)
Smoking	14 (38%)	13 (34%)	0 (0%)
Coronary artery disease	2 (5.4%)	1 (2.6%)	0 (0%)
Known thoracic aneurysm	4 (11%)	5 (13%)	0 (0%)
Connective tissue disorder	0 (0%)	0 (0%)	0 (0%)
Family history of dissection	2 (5.4%)	1 (2.6%)	0 (0%)
Previous non-cardiac aortic surgery	2 (5.4%)	0 (0%)	0 (0%)
Previous CVI	0 (0%)	0 (0%)	0 (0%)
Previous TIA	0 (0%)	1 (2.6%)	0 (0%)
Previous atrial fibrillation	6 (16%)	7 (18%)	0 (0%)
Preoperative P-creatinine (µmol/L)	98 (80-119)	92 (76-121)	7 (9.3%)
Preoperative P-lactate (mmol/L)	1.90 (1.40-3.20)	2.45 (1.80-3.70)	0 (0%)
Hypotensive shock	10 (27%)	12 (32%)	0 (0%)
Cardiac tamponade	11 (30%)	10 (26%)	0 (0%)
Preoperative cardiac arrest	0 (0%)	3 (7.9%)	0 (0%)
Malperfusion (any)	18 (49%)	18 (47%)	0 (0%)
- Cerebral	2 (5.4%)	2 (5.3%)	0 (0%)
- Cardiac	3 (8.1%)	4 (11%)	0 (0%)
- Gastrointestinal	0 (0%)	2 (5.3%)	0 (0%)
- Renal	8 (22%)	7 (18%)	0 (0%)
- Limb	7 (19%)	7 (18%)	0 (0%)
Symptom duration (hours)	6 (4-10)	7 (4-10)	12 (16%)
CCA dissection			1 (1.3%)
- None	22 (61%)	22 (58%)	
- Unilateral	5 (14%)	5 (13%)	
- Bilateral	9 (25%)	11 (29%)	
Intramural hematoma	3 (8.1%)	3 (7.9%)	0 (0%)
DeBakey Type 1	35 (95%)	35 (92%)	0 (0%)

Values are presented as n (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease, CVI: cerebrovascular insult, TIA: transient ischemic attack, CCA: common carotid artery.

Table V.2. Intraoperative data of the study population.

Characteristic	Intervention N = 37	Control N = 38	Missing, N (%)
Operating time (min)	269 (214-309)	279 (239-331)	5 (6.7%)
Cardiopulmonary bypass time (min)	141 (114-175)	147 (125-174)	0 (0%)
Crossclamp time (min)	85 (53-99)	62 (48-93)	0 (0%)
Hypothermic circulatory arrest time (min)	18 (15-21)	17 (14-21)	0 (0%)
Hypothermic circulatory arrest temperature (°C)	20.0 (19.7-21.0)	21.0 (20.0-22.0)	0 (0%)
Hypothermic circulatory arrest technique			0 (0%)
- Circulatory arrest only	15 (41%)	24 (63%)	
- Antegrade cerebral perfusion	0 (0%)	0 (0%)	
- Retrograde cerebral perfusion	22 (59%)	14 (37%)	
Arterial cannulation			0 (0%)
- Femoral artery	23 (62%)	19 (50%)	
- Ascending aorta/Arch	14 (38%)	19 (50%)	
Distal surgical technique			0 (0%)
- Ascending aortic replacement	30 (81%)	33 (87%)	
- Hemiarch procedure	4 (11%)	5 (13%)	
- Arch procedure	1 (2.7%)	0 (0%)	
- Unspecified	2 (5.4%)	0 (0%)	
Proximal surgical technique			0 (0%)
- Supracoronary graft	22 (59%)	29 (76%)	
- Bentall procedure	14 (38%)	9 (24%)	
- Supracoronary graft + isolated AVR	1 (2.7%)	0 (0%)	
Concomitant CABG	3 (8.1%)	1 (2.6%)	0 (0%)
Tranexamic acid (g)	4 (4-4)	4 (4-4)	3 (4.0%)
Fibrinogen (g)	6 (4-8)	6 (6-8)	3 (4.0%)
Prothrombin complex (U)	2000 (1000-2000)	2000 (1500-3250]	5 (6.7%)
Recombinant fVIIa (mg)	0 (0-0)	0 (0-3)	3 (4.0%)
Recombinant fVIIa	7 (20%)	12 (32%)	3 (4.0%)
Calcium (mmol)	6.75 (4.50-9.00)	7.90 (4.50-11.25)	5 (6.7%)

Values are presented as n (%) or median (interquartile range). AVR: aortic valve replacement, CABG: coronary artery bypass grafting.

Table V.3. Postoperative data and adverse events of the study population.

Characteristic	Intervention N = 37	Control N = 38	p-value	Missing N (%)
Length of ICU stay (hours)	51 (36-93)	80 (45-141)	0.080	5 (6.7%)
Ventilator time (hours)	10 (6-27)	16 (10-42)	0.052	5 (6.7%)
Duration of sedation (hours)	5 (3-20)	7 (2-32)	0.525	5 (6.7%)
Postoperative propofol dose (mg)	997 (424-2076)	1216 (592-3298)	0.524	5 (6.7%)
Postoperative use of anti-epileptic drugs	2 (5.9%)	5 (14%)	0.430	5 (6.7%)
Postoperative cardiac failure	1 (2.9%)	5 (14%)	0.199	4 (5.3%)
Postoperative mechanical support	0 (0%)	0 (0%)	>0.999	4 (5.3%)
Postoperative MI	2 (5.7%)	3 (8.3%)	>0.999	4 (5.3%)
Postoperative tromboembolic event*	1 (2.9%)	0 (0%)	0.493	4 (5.3%)
Postoperative atrial fibrillation	16 (46%)	18 (50%)	0.718	4 (5.3%)
Renal replacement therapy	2 (5.7%)	4 (11%)	0.674	4 (5.3%)
Reoperation due to bleeding	4 (11%)	2 (5.6%)	0.429	4 (5.3%)
Bleeding volume first 24 hours (ml)	630 (460-750)	515 (365-795)	0.348	4 (5.3%)
Packed red blood cells (units)	3 (0-5)	3 (1-6)	0.258	3 (4.0%)
Plasma (units)	1 (0-3)	2 (1-4)	0.166	3 (4.0%)
Platelets (units)	5 (4-6)	5 (4-6)	0.915	3 (4.0%)
Peak P-lactate (mmol/L)	3.5 (2.7-4.6)	3.6 (3.0-4.9)	0.523	4 (5.3%)
Peak P-creatinine (µmol/L)	103 (79-219)	152 [107; 218]	0.088	4 (5.3%)
Peak CKMB (µg/L)	18 (13-37)	24 (13-37)	0.531	4 (5.3%)
Intraoperative death	2 (5.4%)	2 (5.3%)	>0.999	0 (0%)
30-day mortality	2 (5.6%)	5 (13%)	0.431	1 (1.3%)
Death during index hospitalization	2 (5.6%)	5 (13%)	0.431	1 (1.3%)

Values are presented as n (%) or median (interquartile range). *=Other than cerebral or myocardial event. ICU: intensive care unit, MI: myocardial infarction, CKMB: Creatine Kinase-Myocardial Band.

Primary and secondary endpoints

Primary and secondary outcomes are presented in Table V.4, with additional neurological outcomes presented in Supplementary Table V.1. ORs comparing outcomes between the groups are presented in Figure V.2. The median number of ischemic lesions in the intervention group was 2 (0-6) and 5 (2-12) (p=0.080) in the control group (Figure V.3). The median volume of ischemic lesions was 1.5ml (0.0-10.0) in the intervention group and 2.8ml (1.0-7.8) in the control group (p=0.335), respectively. Carbon dioxide flooding was associated with significantly lower rates of postoperative clinical neurological injury (14% vs 36% p=0.035) compared with patients in the control group. In the intervention group, 14% of patients had stroke compared to 31% in the control group (p=0.101) whereas coma occurred in 5.7% vs 14% of patients, respectively (p=0.429). Neurological testing is presented in Figure V.3. Neurological assessment on postoperative day 4 showed no significant difference in NIHSS score between the intervention group and the control group (0 (0-2) vs 1 (0-9), p=0.102). There were no significant differences in GCS-M score between groups. However, the CO_2 group had significantly better mRS score on the 4th postoperative day (4 (4-4) vs 5 (4-5), p=0.022).

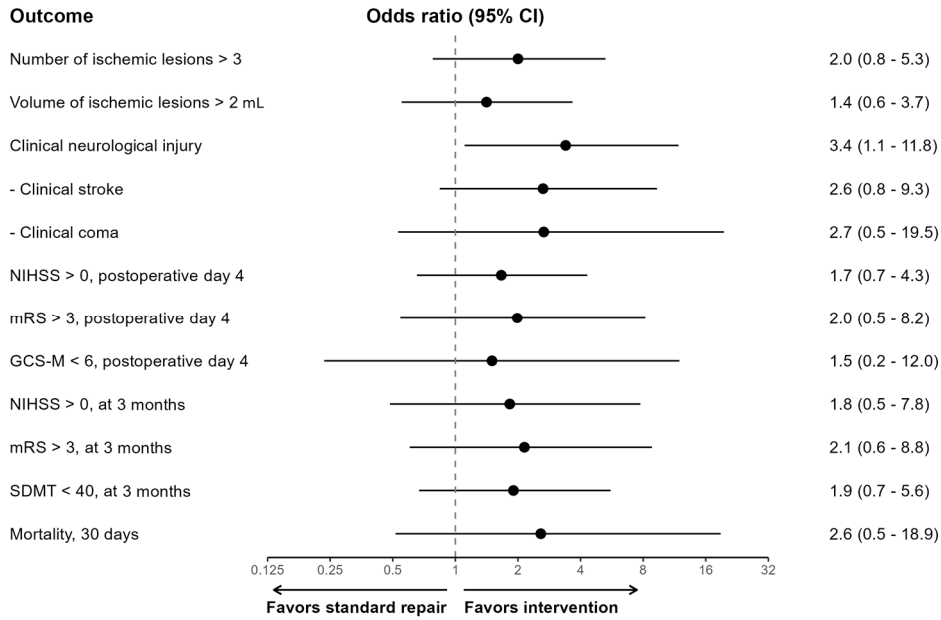

Figure V.2. Odds ratios for primary and secondary outcomes comparing the interventional and control group. For continuous variables, the median value was used as a cut-off NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale for neurologic disability, GCS-M: Glasgow Coma Scale motor score, SDMT: Symbol Digit Modalities Test.

Table V.4. Primary and secondary outcomes

Characteristic	Intervention N = 37	Control N = 38	p-value	Missing N (%)
Number of ischemic lesions	2 (0-6)	5 (2-12)	0.080	5 (6.7%)
Volume of ischemic lesions (mL)	1.5 (0.0-10.0)	2.8 (1.0-7.8)	0.335	5 (6.7%)
Clinical neurological injury	5 (14%)	13 (36%)	0.035	4 (5.3%)
- Clinical stroke	5 (14%)	11 (31%)	0.101	4 (5.3%)
- Clinical coma	2 (5.7%)	5 (14%)	0.429	4 (5.3%)
NIHSS day 4 postoperatively	0 (0-2)	1 (0-9)	0.102	4 (5.3%)
mRS day 4 postoperatively	4 (4-4)	5 (4-5)	0.022	0 (0%)
GCS-M day 4 postoperatively	6 (6-6)	6 (6-6)	0.697	4 (5.3%)
NIHSS 3 months postoperatively	0 (0-0)	0 (0-0)	0.345	17 (23%)
mRS 3 months postoperatively	2 (2-2)	2 (2-3)	0.082	7 (9.3%)
SDMT 3 months postoperatively	44 (35-49)	37 (23-46)	0.063	18 (24%)

Values are presented as n (%) or median (interquartile range). NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale for neurologic disability, GCS-M: Glasgow Coma Scale motor score, SDMT: Symbol Digit Modalities Test.

Three-month follow-up

Data from the 3-month follow-up are presented in Table V.4 and Figure V.3. No statistically significant differences were observed between the intervention and control group in NIHSS score (0 (0-0) vs 0 (0-0), p=0.345), but there was a trend towards better mRS score in the intervention group (2 (2-2) vs 2 (2-3), p=0.082). Cognitive assessment using the SDMT demonstrated a non-significant trend towards improved performance in the CO_2 group (44 (35-49) vs 37 (23-46), p=0.063).

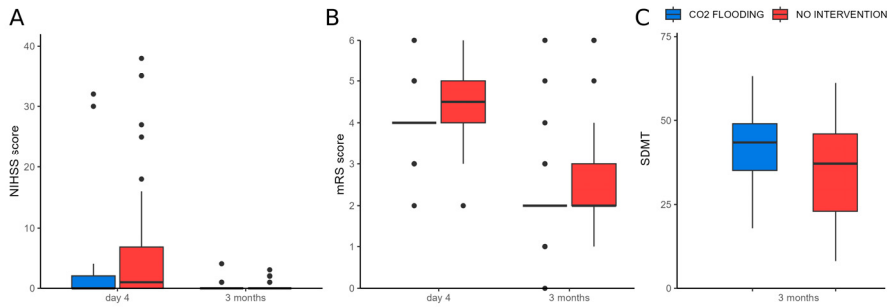

Figure V.3. Neurological and neurocognitive testing comparing the interventional group and the control group. A – National institute of health stroke scale at 4 days and 3 months postoperatively. B – modified Rankin scale score at 4 days and 3 months postoperatively. C – Symbol digits modalities testing score at 3 months postoperatively.

Biomarkers of neurological injury

Biomarkers of neurological injury are presented in Figure V.4 and in Supplementary Table V.2. No significant intergroup differences were observed for S100B, NSE, GFAP, UCH-L1 or t-TAU at any time point. However, NFL concentrations were significantly lower in the CO_2 group compared with controls preoperatively at 24 hours after surgery and on postoperative day 4. NFL was 9.9 pg/mL (8.6-14.2) vs 15.3 pg/mL (11.0-23.6) preoperatively, 17.4 pg/mL (13.4-38.3) vs 35.1 pg/mL (19.7-72.2) 24 hours after surgery and 28.7 pg/mL (21.2-42.1) vs 49.1 pg/mL (26.1-105.2) on postoperative day 4 (p=0.003, p=0.004 and p=0.027 respectively) in the intervention group and control group, respectively. No significant differences in NFL concentration could be seen at 3 months after surgery between the groups.

Sensitivity analyses

There were no significant differences between patients who received RCP compared to patients with circulatory arrest alone in the number (2 (0-10) vs 4 (1-8), p=0.379) or volume (1.0 mL (0.0-10.5) vs 2.1 mL (1.0-7.7), p=0.533) of ischemic lesions on MRI. Furthermore, there were no significant differences in clinical neurological injury (9 (27%) vs 9 (24%), p=0.729), stroke (8 (24%) vs 8 (21%), p=0.748) or coma (4 (12%) vs 3 (8%), p=0.697) after surgery between patients who received RCP compared with patients who underwent circulatory arrest alone. As preoperative

NFL concentrations were higher in patients in the control group compared to the intervention group we tested the association between preoperative NFL and postoperative clinical neurological injury using a logistic regression analysis. This analysis demonstrated no association between preoperative NFL and postoperative neurological injury (OR: 1.02 (95% CI 0.95-1.10, *p*=0.483).

Safety endpoints

There were no significant differences between groups in the predefined safety endpoints, presented in Supplementary Table V.3.

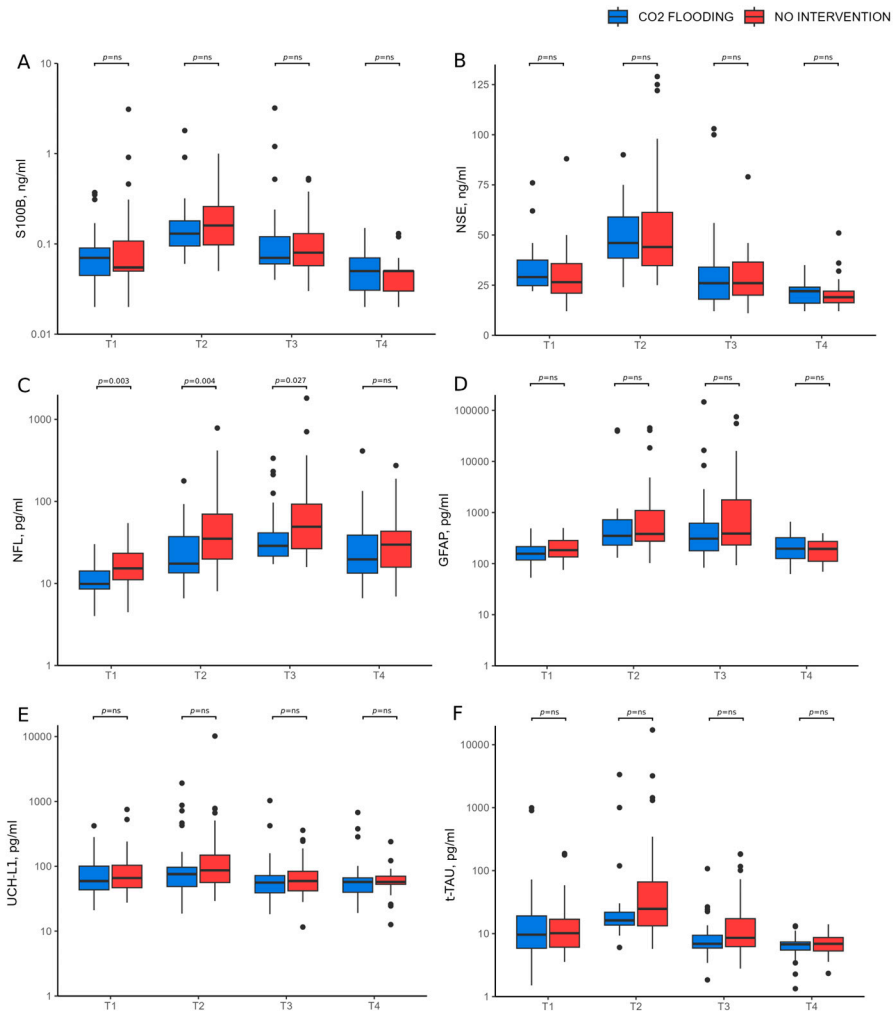

Figure V.4. Biomarkers of neurological injury compared between the interventional and control group taken at four different time points: T1 – preoperatively, T2 – 24 hours after surgery, T3 – 4th postoperative day and T4 – 3 months after surgery. A – S100B, B – NSE, C – NFL, D – GFAP, E – UCH-L1 and F – t-TAU.

Discussion

ATAAD is a highly lethal disease with high mortality and morbidity rates. Despite significant advances in both surgical techniques and perioperative care, the management of ATAAD continues to pose significant challenges, including associated neurological complications that significantly impact both short- and long-term mortality rates. Neurological injury, which ranges from minor focal deficits to coma and severe irreversible ischemic brain injury, is an important field of research in which even modest improvements may lead to substantial benefits for patient outcomes.

The overall aim of this thesis was to investigate factors influencing neurological injury in patients undergoing surgery for ATAAD, with a particular focus on operative strategies, cerebral malperfusion and radiological characteristics associated with neurological outcomes. Specifically, the thesis sought to characterize the radiological features of ATAAD-related neurological injury and identify predictors based on imaging profiles rather than clinical presentation (Study I); to determine whether retrograde cerebral perfusion confers additional neuroprotective benefit during ATAAD surgery (Study II); to examine the relationship between preoperative neurological symptoms, radiological findings and their association with persistent neurological deficits and mortality following surgical repair (Study III); and finally, to evaluate whether flooding the surgical field with carbon dioxide during ATAAD repair reduces the risk of postoperative neurological injury (Studies IV and V).

Risk factors for developing persisting neurological injury

In Study I, 22.3% of patients developed postoperative neurological injury, irrespective of their preoperative neurological status. Much of the published literature on ATAAD complications relies on surgeon-reported outcomes, in which stroke definitions include both clinical and radiological findings. This approach may underestimate the true incidence of postoperative injury as patients who die before radiological examination or do not undergo the examination for other reasons are

not included. Furthermore, systematic neurological assessment by neurologists are more likely to detect subtle deficits.

Diabetes mellitus is a well-established risk factor for stroke (143). In Study I, diabetes mellitus was associated with an increased risk of watershed injury. It is reasonable to believe that patients with diabetes mellitus, are more sensitive to perioperative systemic hypotension, owing to underlying vasculopathy. This may render them more sensitive to brief periods of circulatory arrest, both because of the general metabolic consequences of reduced blood flow, but also because hypoperfusion may lead to inadequate cooling of the cerebral parenchyma.

In Study III, we showed that patients with cerebral malperfusion and CCA dissection or carotid artery occlusion were significantly more likely to develop persisting neurological deficit. Preoperative hemiparesis or hemiplegia was also more frequent in patients who developed persisting neurological deficit. Patients who presented with unconsciousness had significantly higher rates of persisting neurological deficit and mortality. Only 15.4% of unconscious patients survived without neurological injury. In contrast, patients who presented with preoperative transient neurological symptoms had a significantly lower risk of persistent neurological deficit.

Previous studies have shown that femoral cannulation increases the risk of perioperative stroke, possibly due to backwards flushing of embolic material from the dissected descending aorta (80, 84). However, no randomised trials have been performed on cannulation strategies in the setting of ATAAD surgery, and the results from the previous studies may be influenced by significant selection bias as mentioned in the introduction. In Study I, patients with unilateral postoperative neurological injury were observed to have a higher frequency of embolic lesions in the right hemisphere compared to the left. The proposed mechanism of backward washing of embolic material using femoral cannulation would most likely lead to an increase of lesions in the left hemisphere as it is the first supra-aortic branch reached when blood flow is reversed. Furthermore, in Study I, we performed a post hoc analysis of patients with unilateral lesions and demonstrated that patients who had femoral artery cannulation had 78.8% of lesions in the right hemisphere compared to 55.6% in the right hemisphere when other cannulation sites were used (p=0.21).

By contrast, Fichadiya et al. did not identify any lateralisation of unilateral strokes in ATAAD patients, and a study of patients with cardioembolic stroke due to atrial fibrillation found that the lesions are equally distributed between the hemispheres, with a slightly higher proportion located in the left hemisphere (144, 145). In Study I, radiological imaging of the brain was only done upon clinical suspicion of neurological injury; left-sided symptoms may be more easily recognised clinically, which might increase the lateralisation frequency in favour of the left hemisphere (144). The higher occurrence of right-sided lesions in Study I may be because the

right common carotid artery was dissected more often than the left. This may contribute to the discrepancy observed between the studies (146). As the primary entry most often is located in the ascending aorta, it is logical that the dissection more often involves the first vessel arising from the aortic arch (131).

Patients who develop neurological injury after ATAAD surgery have previously been shown to have an increased early mortality, a finding corroborated by Studies I and III (80, 128). However, most studies show comparable mid- and long-term survival in patients who survive the initial 30-day postoperative period (116, 127, 132). In Study I, postoperative neurological injury was associated with reduced long-term survival, whereas in Study III, which included a smaller cohort of patients with cerebral malperfusion, no statistically significant difference between groups was observed, likely due to lack of power.

Retrograde cerebral perfusion

The first use of continuous flow RCP was described by Ueda and colleagues in 1990 (147). Despite more than three decades of clinical use, its precise mechanism of action is not fully understood. Proposed mechanisms include washout of embolic debris, cooling of the brain parenchyma and a possible metabolic effect on the cerebral parenchyma.

Data in Study II demonstrated that RCP reduces the risk of embolic lesions. In a small, randomised study of patients undergoing elective hemiarch repair under circulatory arrest, Leshnower et al. showed that the use of RCP resulted in a lower number of ischemic lesions and smaller volume of ischemic lesions on MRI than did ACP (142). Previous studies have shown that ACP accommodates the metabolic need of the brain during HCA (89, 90). Since ACP has been shown to provide a superior metabolic effect compared to RCP, one may speculate that the effect of RCP to some degree is related to the washout of air and other embolic material from the aortic arch branch vessels.

Consistent with this interpretation, Bonser et al. demonstrated that, in patients receiving topical head cooling with ice packs (which is regularly used in our centre), RCP did not provide any additional reduction in nasopharyngeal temperature, indicating that its contribution to cerebral cooling is limited (148).

No consensus has been reached whether blood delivered during RCP reaches the brain parenchyma. Experimental studies with animal models have shown that, during circulatory arrest with RCP, the majority of administered blood was returned to the heart via the inferior vena cava, with only a small fraction reaching the brachiocephalic trunk (149). Human cadaver studies have similarly suggested that the azygos system may be a major route of venous return during RCP (150). In

contrast, a small clinical study using fluorescein in administered blood during RCP showed that the fluorescein reached the retina, indicating that the blood reached the brain (151). Moreover, an animal experiment showed that RCP resulted in a superior oxygen extraction rate compared to ACP (89). Collectively, these data indicate that some of the blood provided by RCP reaches the cerebral parenchyma, albeit less than that provided by ACP. In Studies I and II, a reduced risk of watershed lesions was observed in patients with RCP despite these patients having longer circulatory arrest time, cardiopulmonary bypass time and aortic cross-clamp time, all known risk factors for neurological injury. Since watershed injuries are the result of global cerebral hypoperfusion, and the duration of circulatory arrest is a known risk factor for postoperative neurological injury and watershed lesions, our results from Studies I and II indicate that RCP may provide some metabolic effect sufficient for protecting the brain at relatively short circulatory arrest times at low temperatures.

Cerebral malperfusion

In line with previous findings, Study I demonstrated that cerebral malperfusion is an independent predictor of neurological injury (128, 129). ATAAD surgery is associated with high mortality and a high incidence of postoperative neurological injury. The risk of mortality and neurological injury is aggravated in patients presenting with cerebral malperfusion. In Study III, 14.7% of all ATAAD patients presented with cerebral malperfusion, and of these patients, 57.1% developed persisting neurological injury and 25% died within 30 days. Furthermore, in Studies I and III, we demonstrated that in about 50% of patients, cerebral malperfusion may be resolved by ATAAD repair.

The decision to perform surgery on patients presenting with cerebral malperfusion is complex, and historically, it has been considered a relative contraindication to surgery. However, in Study III, we could demonstrate that 52.2% of patients showed improvement in their clinical neurological status after repair. A large study from Di Eusanio et al. showed that among patients presenting with stroke or coma, the 30-day mortality for patients not undergoing surgery was 76.2% for stroke patients and 100% for comatose patients, whereas surgical mortality was 27.0% and 44.4%, respectively. This is clearly in favour of surgical treatment in these patients (128). An earlier study by Tanaka et al. reported 100% mortality (all six) for comatose patients, but more recent results from Tsukube et al. showed favourable outcomes in coma patients who underwent ATAAD repair within 5 hours of symptom onset (152, 153). In Study III, 83.3% of patients who were in a comatose state developed persisting neurological injury, with a 30-day mortality of 53.8%. Since the prognosis in comatose patients who are not treated with surgery is very poor, it seems reasonable to consider surgery only in carefully selected patients. In Study III, a post-hoc analysis of patients who presented with unconsciousness, the patients

who survived past 30 days had a median time from symptom onset to the beginning of surgery of 5.3 hours, compared to patients who did not survive beyond 30 days who had a median symptom duration of 9.2 hours (p=ns), further emphasizing the need for swift surgical management.

Rapid reperfusion of the cerebral parenchyma is essential to minimize the risk and severity of neurological injury. This can be achieved through several approaches, including central repair, extra-anatomic carotid bypass and endovascular reperfusion. The present study focused on central repair in accordance with current recommendations from the European Association for Cardio-Thoracic Surgery and The Society of Thoracic Surgeons (1). Nevertheless, extra-anatomic bypass can be valuable in specific cases with occlusion or severe stenosis of the CCA. Okita et al. described the use of carotid-femoral bypass with an extra-corporeal circuit prior to central repair to reduce cerebral ischemic time. In one case, the carotid-femoral bypass was established in the emergency room. The 30-day mortality in this case-series was 33.3%, and neurological injury was 55.6% (154). Luehr et al. also performed an extra-anatomic aorto-carotid bypass in the beginning of the ATAAD repair procedure to achieve faster reperfusion in 23 patients presenting with occlusion of the CCA with a hospital mortality of 13.0% and persisting neurological injury of 60.9% (155). The obstruction of the carotid artery can be either dynamic or static, with dynamic obstruction being the most common and present in up to 80% of cases (156). For static obstruction, endovascular treatment might be an option, but it is rare and only a few case reports have been published on endovascular treatment of cerebral malperfusion (157, 158). In Study III, 21 patients presented with carotid artery occlusion. In this cohort, the 30-day mortality was relatively low at 23.8%, but the persisting neurological injury rate was high at 81.0%. While available research has shown that extra-anatomic bypass may reduce the incidence of neurological complications, it does not appear to significantly improve 30-day mortality, likely reflecting the balance between achieving prompt cerebral reperfusion and delaying central repair.

In recent years, CT-perfusion imaging has been more common in stroke patients and is increasingly utilised in patients with ATAAD to assess cerebral malperfusion. Zhao et al. demonstrated that cerebral blood flow measured by CT perfusion was significantly lower in ATAAD patients with neurological symptoms or common carotid artery (CCA) dissection on CT angiography. Among the 44 patients (30.8%) who developed postoperative stroke, mean preoperative cerebral blood flow was approximately one third lower than in those who did not develop stroke. The CT-perfusion data in addition to clinical and angiographic findings improved prediction of postoperative stroke (159). Inoue et al. described a small cohort of six ATAAD patients with preoperative neurological symptoms who underwent CT perfusion. Four patients with penumbral volumes of 8–735 ml and ischemic cores of 0–31 ml had acceptable neurological outcomes, while two with ischemic cores of 51 ml and 73 ml both died from neurological complications. The authors concluded that an

ischemic core greater than 50 ml is likely incompatible with survival, but this very small cohort severely limits generalization (160). In Study III, one patient had an ischemic core above 50 ml (109 ml) and died due to extensive brain infarction and herniation. Two patients had ischemic cores <50 ml; one was discharged without neurological deficits and the other had partial recovery from hemiparesis and dysphasia. These findings suggest that preoperative CT perfusion may provide valuable prognostic information regarding cerebral perfusion and postoperative neurological recovery. It is also possible that CT perfusion could aid in planning cannulation and brain protection strategies when using ACP. For instance, studies show that 6-17% of patients have an incomplete Circle of Willis, and in these patients, unilateral ACP may not be enough for cerebral protection (161, 162). Currently, CT perfusion is rarely performed in ATAAD patients, but we believe it should be routinely used in all ATAAD patients who present with cerebral malperfusion. Furthermore, the management of these patients should be discussed with the on-call neurologist and/or neuro-interventionist to optimise the management of each patient.

Air embolism and carbon dioxide flooding

The incidence of stroke after ATAAD surgery is high and remains a substantial concern despite improvements in surgical technique, cerebral protection strategies and an overall reduction of mortality (60). This warrants an investigation into alternative mechanisms of neurological injury beyond those previously established, such as hypoperfusion, branch vessel dissection or occlusion, and thromboembolism (80). One potentially important mechanism is cerebral air embolisation. Surgical procedures involving an open distal anastomosis allow large volumes of air to enter the aorta, where air may become trapped. Upon restoration of circulation, this trapped air may embolise to peripheral organs and occlude arteries. One preventive strategy to mitigate this risk is the displacement of air from the surgical field using CO_2 flooding. Carbon dioxide has a density approximately 1.5 times that of air and is about 25 times more soluble in blood, properties that may reduce the risk of air embolism (141).

In Studies IV and V, CO_2 flooding was employed to displace air from the surgical field. Cerebral lesions detected by MRI after open-heart surgery are common, and silent embolic lesions have been reported in more than half of patients undergoing surgical aortic valve replacement (163). Previous studies evaluating CO_2 flooding have demonstrated a reduction in gaseous microemboli in the aorta during elective open left-sided valve surgery (164). Patients undergoing aortic surgery with an open distal anastomosis may theoretically derive even greater benefit from CO_2 flooding, as this surgical technique permits substantial air entry into the arterial circulation without the possibility of distal air venting. In the present trial, a trend towards a

reduced number of acute cerebral lesions on MRI was observed in the CO_2 flooding group compared with the control group.

More importantly, CO_2 flooding was associated with a significant reduction in clinical neurological injury (13% vs. 36%, p = 0.035). Neurological and cognitive assessments were performed on postoperative day 4 and at 3 months after surgery. While NIHSS scores were similar between groups at both time points, a significant difference in mRS scores was observed on postoperative day 4, with a non-significant difference favouring CO_2 flooding at 3 months. Compared with previous reports describing stroke rates of 10–16% and coma rates of 3–9%, the incidence of neurological injury in the present study was relatively high, with an overall stroke rate of 22.5% and a coma rate of 9.9%(80, 128, 129, 132). However, this elevated incidence likely reflects, at least in part, the inclusion of systematic neurological examinations not routinely performed in this patient population. Neurocognitive testing using SDMT demonstrated a trend towards better postoperative cognitive function in patients receiving CO_2 flooding. These findings are consistent with a randomised trial by Martens et al., in which patients undergoing elective open-heart surgery with CO_2 flooding exhibited lower P300 auditory evoked potentials, indicating less cerebral injury compared with controls (165). Similarly, Ganguly et al. reported a reduced risk of postoperative neurocognitive dysfunction associated with CO_2 flooding in a randomised trial of 300 patients undergoing elective cardiac surgery (166).

In the evaluation of biomarkers of brain injury in Studies IV and V, lower concentrations of NFL were observed in the intervention group at 24 hours postoperatively and on postoperative day 4 compared with the control group. Although baseline differences in preoperative NFL levels may have influenced these findings, a sensitivity analysis revealed no association between preoperative NFL concentrations and postoperative neurological injury. Research on biomarkers of neurological injury in the context of ATAAD surgery is limited, with most previous studies focusing on S100B or NSE (167). In other clinical settings, such as after cardiac arrest, several biomarkers have been shown to reflect cerebral injury, with NFL emerging as one of the most robust prognostic markers (168). Therefore, we believe that the increased postoperative concentrations of NFL in the control group are related to more frequent and more extensive perioperative neurological injury in the control group.

The only established risk associated with CO_2 flooding is the potential induction of acidosis, which may attenuate the effect of heparin and thereby increase the risk of thrombus formation during surgery. This effect may be exacerbated under hypothermic conditions, as present during circulatory arrest in ATAAD surgery (169). In the present study, no increased risk of thromboembolic events attributable to CO_2 flooding was identified. On the contrary, fewer patients in the intervention group experienced embolic cerebral lesions or myocardial infarction. One non-cerebral, non-cardiac thromboembolic event occurred in the intervention group;

however, this consisted of a pulmonary embolism in a patient with delayed sternal closure due to severe coagulopathy. Substantial amounts of procoagulant agents were administered, and the pulmonary embolism was diagnosed on postoperative day 2. A causal relationship with CO_2 flooding is therefore unlikely, particularly as pulmonary embolism originates in the venous system, which is not exposed to CO_2 flooding.

Limitations

Studies I-III are limited by their retrospective design and by reliance on a database potentially missing significant variables that cannot be retrieved. In addition, these are single-centre studies spanning nearly 25 years, during which time both surgical techniques and perioperative care have evolved, potentially influencing results.

For Studies I-III, but particularly for Study III, the database includes only patients who underwent surgery. Therefore, outcomes among patients who received medical treatment alone could not be assessed, limiting the generalisability of the findings.

Due to the urgency of ATAAD, preoperative brain imaging to confirm existing neurological injury are infrequently performed. Moreover, not all cases of neurological injury could be radiologically confirmed postoperatively, probably due to the relatively limited use of MRI and the timing of the CT-scan, which might influence its sensitivity to detect ischemic lesions. Some patients with clinical neurological injury did not undergo radiological examination, often due to being terminally ill, and they could therefore not be classified as having embolic or watershed lesions. Patients who did not have clinical neurological injury could still have small ischemic lesions, as seen in Studies I and II, and not all patients underwent a postoperative CT-scan or MRI of the brain. In Studies I and II, some radiological findings interpreted as embolic lesions could potentially have been intimal flaps or local atherosclerotic plaques causing regional hypoperfusion rather than a true embolism. The primary neurological assessments in Studies I–III were also seldom performed using standardised instruments, e.g., NIHSS, which would have strengthened the comparability of the neurological evaluations.

In Study I, ACP was primarily employed in more complex procedures and was seldom used, making it difficult to draw firm conclusions regarding its impact. In Study III, several clinical symptom subgroups comprised relatively small cohorts, which limits the ability to derive specific and generalizable conclusions. Finally, the limited use of CT perfusion imaging restricts the interpretation of findings in this area.

In Studies IV and V, there are several limitations to be considered when interpreting the results. First, two different CO_2 delivery devices were used during the study

period due to supply chain disruptions related to the COVID-19 pandemic and the Russian-Ukrainian war, which might have had an impact on the results. Second, the flow rate of 5 L/min may not be optimal, and alternative delivery devices or different flow rates could produce different results. Since there is no previous data on ATAAD patients, and limited data on neurological outcomes following CO_2 flooding, our power calculation was derived from the assumption that CO_2 has the same effect on air embolism as RCP in the setting of elective aortic surgery, likely rendering the study under-powered. Since we believed that a substantially larger study population would have been required to demonstrate differences in terms of clinical outcomes, we designed the study to assess radiological findings to test our hypothesis. Notably, despite these constraints, several statistically significant differences between the groups were observed. Although Type I errors cannot be ruled out, our results show consistent trends across neurological outcomes in favour of the intervention.

Moreover, variations in the application of RCP between the study groups could have affected the results. However, sensitivity analyses indicated that RCP was not significantly associated with either the primary endpoints or the incidence of clinical neurological injury. Even if an interaction with RCP was present, it would strengthen the hypothesis that air embolism contributes to neurological injury during ATAAD surgery as the flushing of air trapped in the arch branch vessels is one of the suggested therapeutical mechanisms of RCP. Baseline neuroimaging and preoperative cognitive testing were not feasible due to the emergent nature of the condition. Although preferable, MRI was not consistently performed within the first seven postoperative days, which may have resulted in missed ischemic lesions. Patients in the control group more frequently underwent MRI at later time points, and one patient died from neurological injury before imaging could be completed. Furthermore, since the likelihood of acute lesions being detectable with MRI is reduced over time and one patient in the control group did not live long enough to perform an MRI, the primary endpoints may have been underestimated, and was in one case, unreported in the control group.

Conclusions

Study I

Study I demonstrated that radiological features are at least as important as clinical manifestations in understanding the pathophysiology behind neurological injury related to ATAAD repair. Embolic lesions more often occurred in the right hemisphere causing symptoms of stroke. Basilar artery obstruction and watershed lesions were associated with postoperative coma. We also showed that cerebral malperfusion and diabetes mellitus play key parts in the development of neurological injury and that retrograde cerebral perfusion has a neuroprotective effect.

Study II

In Study II, we showed that RCP reduces the risk of clinical neurological injury, embolic lesions and watershed lesions compared to HCA alone. The reduced risk of embolic lesions suggests that the effect of RCP may partially be the consequence of washout of air and other embolic material, while the reduced risk of watershed lesions may be related to RCP having some metabolic effect on the cerebral parenchyma.

Study III

In Study III, we demonstrated that in ATAAD patients who present with cerebral malperfusion, the risk of persisting neurological deficit and 30-day mortality is high, but a significant proportion of patients survive, and more than half show an improved postoperative neurological state. Bilateral carotid artery dissection, carotid artery occlusion, hemiparesis/hemiplegia and unconsciousness were associated with the highest risk of persisting neurological deficit, and more than half of patients who were unconscious prior to surgery died within 30 days of the procedure. The addition of CT perfusion to current clinical assessment prior to surgery may be valuable in optimizing patient management.

Study IV and V

In Studies IV and V, carbon dioxide flooding was associated with a trend towards fewer ischemic lesions after ATAAD repair. More importantly, CO_2 flooding was associated with a statistically significant reduction of clinical neurological injury. Our findings suggest that air embolism plays a significant role in the development

of neurological injury related to surgery for ATAAD. Finally, this study proves the feasibility of performing randomised trials in ATAAD patients and provides a basis for more adequately powered future trials and further investigations into air embolism as a mechanism of neurological injury following aortic repair using an open distal anastomosis.

Future perspectives

In this thesis, we explored mechanisms and risk factors underlying neurological injury following surgical repair of ATAAD. We also investigated surgical strategies that potentially can reduce the risk of developing neurological injury.

In Studies I and II, we show that retrograde cerebral perfusion reduces neurological injury and provides a possible metabolic effect. Previous studies have yielded conflicting results regarding the metabolic effect of RCP. Future research should therefore focus on investigating its precise mechanisms of action and on identifying anatomical considerations that may influence its neuroprotective efficacy. Similarly, arterial cannulations strategies in ATAAD still lack evidence. Although some research suggests that femoral artery cannulation increases the risk of stroke, others suggest a bias as femoral artery cannulation is often used in the most critically ill patients and at the most inexperienced surgical centres. There is need for randomised studies to determine whether certain arterial cannulations sites are better than others.

Study III highlights the complexity of clinical decision-making in ATAAD patients presenting with cerebral malperfusion. In the present study, data from patients who did not undergo surgery were unavailable, and only a small cohort of patients underwent preoperative CT perfusion of the brain. Two lines of investigation could further refine patient selection for surgery. First, comparative studies of surgically and non-surgically managed patients with cerebral malperfusion would help identify factors influencing treatment decisions and outcomes. Second, in addition to CTA, routine incorporation of preoperative CT perfusion imaging in ATAAD patients with suspected cerebral malperfusion could improve risk stratification and guide patient management.

Finally, Studies IV and V demonstrate the feasibility of performing randomised controlled interventional trials for surgical strategies in ATAAD patients. More randomised controlled trails are needed to address evidence gaps, including those related to arterial cannulation strategies, the use of cerebral perfusion and the extent of repair. Regarding the use of carbon dioxide flooding, our findings suggest that air embolism may play an important role in the development of neurological injury related to surgery for ATAAD. Since no adverse effects of CO_2 flooding were identified, our study supports routine use of CO_2 in surgery for ATAAD.

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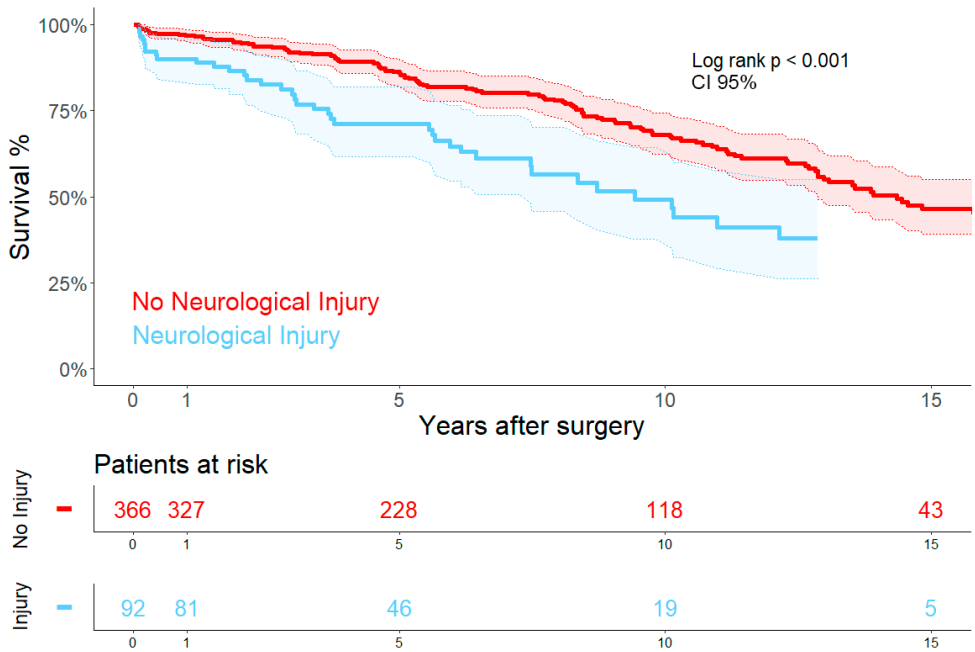
Supplementary material

Study I



Supplementary figure I.1 Kaplan-Meier survival curves of 30-day survivors demonstrating poorer survival in patients with neurological injury.

Supplementary Table I.1. Univariable and multivariable logistic regression analysis for predictors of 30-day mortality. Values are expressed as odds ratio (OR) with 95% confidence interval.

Characteristics	Univariable analysis (OR)	*p*-value	Multivariable analysis (OR)	*p*-value
Age per year increment	1.02 (1.00-1.04)	0.086		
Female	0.92 (0.55-1.54)	0.741		
Hypertension	1.04 (0.63-1.70)	0.878		
Diabetes Mellitus	1.46 (0.80-2.64)	0.215		
COPD	1.78 (0.69-4.54)	0.231		
History of smoking	0.80 (0.46-1.39)	0.424		
Coronary artery disease	1.19 (0.40-3.56)	0.760		
Known thoracic aortic aneurysm	1.04 (0.42-2.59)	0.932		
Marfan syndrome	0.47 (0.11-2.02)	0.308		
Other connective tissue disease	0	0.999		
Heredity for aortic dissection	0.99 (.29-3.43)	0.988		
Previous cardiac surgery	4.19 (1.33-13.18)	0.014		
Previous aortic surgery	1.46 (0.41-5.27)	0.560		
Preoperative lactate	1.21 (1.11-1.34)	<0.001		
Syncope	2.83 (1.48-5.42)	0.002		
Hypotensive shock	1.85 (0.98-3.49)	0.059		
Any malperfusion	1.90 (1.16-3.13)	0.011	4.62 (1.83-11.67)	0.015
Cerebral malperfusion	2.21 (1.21-4.02)	0.009		
Carotid dissection				
None	Ref			
Unilateral	1.10 (0.55-2.22)	0.791		
Bilateral	0.80 (0.40-1.61)	0.535		
Intramural hematoma	0.35 (0.10-1.15)	0.083		
Debakey 1	1.01 (0.56-1.84)	0.965		
Cardiopulmonary bypass time	1.01 (1.00-1.01)	<0.001		
Aortic cross-clamp time	1.00 (1.00-1.01)	0.104		
Hypothermic circulatory arrest technique				
Cross-clamp	Ref			
SCA	0.59 (0.22-1.55)	0.283		
ACP	0.81 (0.23-2.81)	0.736		
RCP	0.66 (0.25-1.73)	0.393		
Hypothermic circulatory arrest time per minute increment	1.03 (1.01-1.04)	0.005		
Hypothermic circulatory arrest temperature per degree Celsius increment	0.99 (0.94-1.05)	0.826		
Arterial cannulation				
Femoral	Ref			
Subclavian/brachiocephalic trunk	1.02 (0.25-5.09)	0.883		
Ascending/arch	1.94 (1.11-3.37)	0.019		
Left ventricle	2.62 (0.51-13.35)	0.248		

Characteristics	Univariable analysis (OR)	*p*-value	Multivariable analysis (OR)	*p*-value
Distal Technique				
Ascending	Ref			
Hemiarch	0.98 (0.44-2.17)	0.964		
Arch	2.01 (0.85-4.87)	0.125		
Proximal Technique				
Supracoronary graft	Ref			
Bentall procedure	0.84 (0.44-1.60)	0.589		
Supracoronary + isolated AVR	1.46 (0.53-4.03)	0.464		
Root replacement with aortic valve repair	0.92 (0.11-7.62)	0.937		
Other/not completed	19.29 (1.97-189.07)	0.011		
Additional CABG	3.64 (1.82-7.32)	<0.001		
rFVIIa	0.94 (0.36-2.45)	0.905		
Fibrinogen per g increment	1.16 (1.03-1.31)	0.014		
Reoperation for bleeding	2.01 (1.10-3.69)	0.024		
Ventilator >48 h	5.29 (2.68-10.45)	<0.001	5.94 (2.12-16.63)	<0.001
Renal replacement therapy	2.35 (1.06-5.18)	0.035		
Postoperative myocardial infarction	3.21 (0.94-11.01)	0.064		
Postoperative lactate per mmol increment	1.33 (1.16-1.53)	<0.001		
Neurological injury	4.67 (2.56-8.52)	<0.001	3.82 (1.62-9.05)	<0.001
Postoperative stroke	0.42 (0.15-1.12)	0.103	0.25 (0.02-2.61)	0.562
Postoperative coma	18.00 (8.41-38.55)	<0.001	15.68 (5.23-47.09)	<0.001
Non-acute lesions	1.40 (0.47-4.01)	0.568		
Acute lesions	3.81 (2.00-7.72)	<0.001		
Embolic lesions	3.40 (1.82-6.35)	<0.001	4.34 (1.78-10.59)	0.0095
Embolic territory				
Anterior	4.64 (1.55-13.84)	0.006		
Media	3.09 (1.59-6.08)	0.001		
Posterior	3.81 (1.72-8.40)	<0.001<		
Basilar	6.75 (3.00-15.18)	0.001		
Watershed lesions	8.92 (3.49-22.77)	<0.001	13.48 (3.82-47.63)	<0.001
Mixed lesions	16.27 (5.36-49.53)	<0.001		

OR: odds ratio, Ref: reference variable, COPD: Chronic obstructive pulmonary disease, SCA: Straight circulatory arrest, ACP: Antegrade cerebral perfusion, RCP: Retrograde cerebral perfusion, AVR: Aortic valve replacement, CABG: Coronary artery bypass grafting and rFVIIa: recombinant factor VIIa.

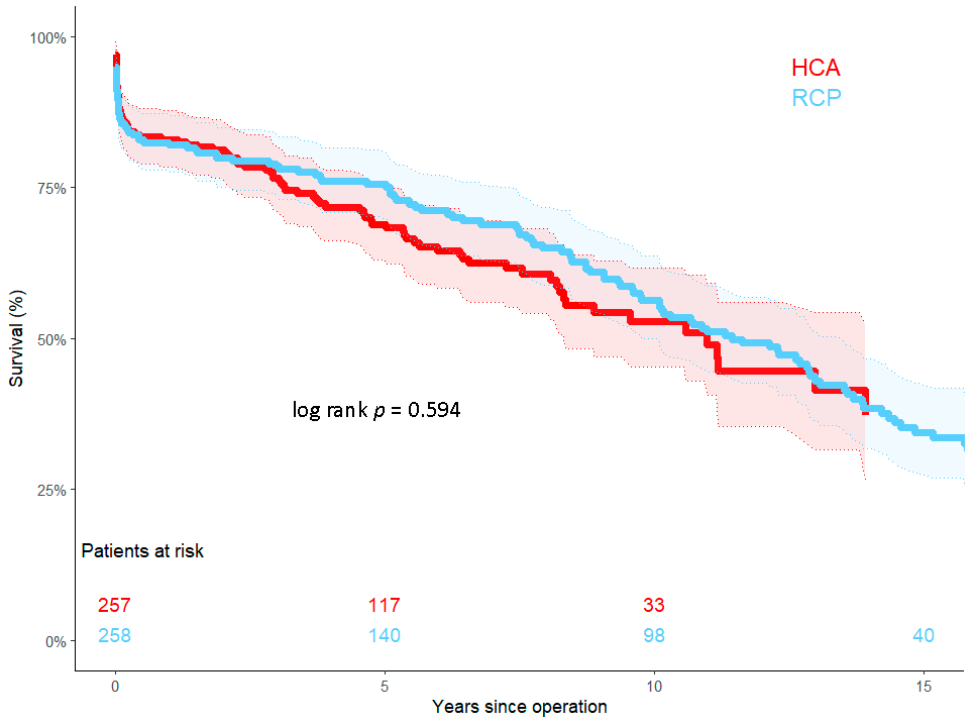
Supplementary Table I.2. Univariable and multivariable Cox regression analysis for predictors of late mortality. Values are expressed as hazard ratio (HR) with 95% confidence interval.

Characteristics	Univariable analysis (HR)	*p*-value	Multivariable analysis (HR)	*p*-value
Age per year increment	1.06 (1.05-1.08)	<0.001	1.07 (1.05-1.09)	<0.001
Female	1.09 (0.79-1.49)	0.606		
Hypertension	1.20 (0.89-1.65)	0.231		
Diabetes Mellitus	0.97 (0.66-1.43)	0.867		
COPD	3.06 (1.82-5.14)	<0.001	3.08 (1.78-5.33)	<0.001
History of smoking	1.13 (0.82-1.57)	0.462		
Coronary artery disease	1.51 (0.78-2.91)	0.222		
Known thoracic aortic aneurysm	1.50 (0.82-2.78)	0.190		
Marfan syndrome	0.43 (0.19-0.97)	0.042	0.76 (0.31-1.89)	0.553
Other connective tissue disease	0.54 (0.08-3.91)	0.545		
Heredity for aortic dissection	0.37 (0.12-1.15)	0.084		
Previous cardiac surgery	1.35 (0.55-3.31)	0.506		
Previous aortic surgery	3.66 (1.70-7.89)	<0.001	2.79 (1.24-6.25	0.022
Preoperative lactate per mmol increment	1.05 (0.97-1.13)	0.250		
Syncope	1.159 (0.67-2.01)	0.598		
Hypotensive shock	1.37 (0.18-0.86)	2.17		
All malperfusion	1.20 (0.86-1.68)	0.280		
Cerebral malperfusion	1.21 (0.75-1.95)	0.442		
Carotid dissection				
None	Ref			
Unilateral	1.24 (0.80-1.91)	0.334		
Bilateral	0.93 (0.60-1.45)	0.753		
Intramural hematoma	0.83 (0.47-1.46)	0.520		
Debakey 1	0.92 (0.63-1.34)	0.661		
Cardiopulmonary bypass time	1.00 (1.00-1.00	0.811		
Aortic cross-clamp time	1.00 (1.00-1.00)	0.775		
Hypothermic circulatory arrest technique				
Cross-clamp	Ref		N/A	
SCA	2.47 (1.16-5.25)	0.019	Ref	
ACP	1.16 (0.42-3.20)	0.780	0.35 (0.15-0.78)	0.004
RCP	2.01 (0.98-4.144)	0.059	0.75 (0.51-1.11)	0.074
Hypothermic circulatory arrest time per minute increment	1.02 (1.00-1.03)	0.027	1.03 (1.01-1.04)	<0.001
Hypothermic circulatory arrest temperature per degree Celsius increment	0.99 (-0.96-1.03)	0.671		
Arterial cannulation				
Femoral	Ref			
Subclavian/brachiocephalic trunk	0.53 (0.17-1.66)	0.273		
Ascending/arch	1.25 (0.86-1.82)	0.245		
Distal Technique				
Ascending	Ref			
Hemiarch	0.99 (0.61-1.61)	0.972		
Arch	0.61 (0.31-1.21)	0.156		

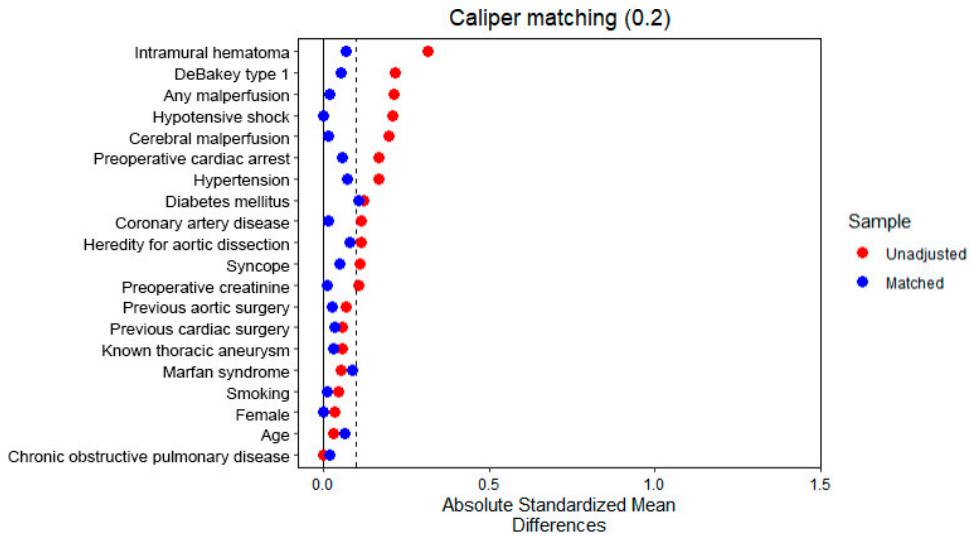
Characteristics	Univariable analysis (HR)	*p*-value	Multivariable analysis (HR)	*p*-value
Proximal Technique				
Supracoronary graft	Ref			
Bentall procedure	0.58 (0.38-0.87)	0.006		
Supracoronary + isolated AVR	1.82 (0.98-3.37)	0.059		
Root replacement with aortic valve repair	0.63 (0.16-2.58)	0.526		
Additional CABG	1.34 (0.82-2.20)	0.248		
rFVIIa	0.89 (0.48-1.63)	0.697		
Fibrinogen per g increment	1.07 (0.99-1.16)	0.082		
Reoperation for bleeding	2.06 (1.42-2.97)	<0.001	1.45 (0.95-2.19)	0.082
Ventilator >48 h	1.60 (1.17-2.21)	0.004	1.00 (0.69-1.46)	0.982
Renal replacement therapy	0.93 (0.54-1.61)	0.794		
Postoperative myocardial infarction	2.24 (0.86-5.83)	0.099		
Postoperative lactate per mmol increment	1.17 (1.01-1.35)	0.041		
Neurological injury	1.98 (1.39-2.82)	<0.001	2.10 (1.41-3.11)	<0.001
Postoperative stroke	1.50 (0.81-2.77)	0.198		
Postoperative coma	1.76 (0.86-3.60)	0.119		
TIA	0.49 (0.97-3.48)	0.473		
Non-acute lesions	2.05 (0.93-4.52)	0.076		
Acute lesions	1.92 (1.28-2.91)	0.002		
Embolic lesions	1.75 (1.14-2.68)	0.010	1.96 (1.23-3.12)	0.003
Watershed lesions	2.10 (0.92-4.75)	0.076	2.19 (0.88-5.43)	0.067
Mixed lesions	2.00 (0.64-6.29)	0.237		

HR: hazard ratio, Ref: reference variable, COPD: Chronic obstructive pulmonary disease, SCA: Straight circulatory arrest, ACP: Antegrade cerebral perfusion, RCP: Retrograde cerebral perfusion, AVR: Aortic valve replacement, CABG: Coronary artery bypass grafting and rFVIIa: recombinant factor VIIa.

Study II



Supplementary Figure II.1. Kaplan-Meier survival curves of 30-day survivors demonstrating equal survival between patients receiving HCA only and RCP.



Supplementary Figure II.2. The propensity score matching variables and their absolute standardised mean differences.

Supplementary Table II.1. Number of patients with cerebral malperfusion and neurological outcomes in each analysis.

Population	Grouping	Clinical Neurological injury
Full population	HCA only	71 (28.4)
	RCP	50 (20.2)
Full population with cerebral malperfusion excluded	HCA only	47 (23.0)
	RCP	36 (16.4)
PS matched population	HCA only	53 (24.6)
	RCP	46 (21.9)

Population	Grouping	Embolic lesions
Full population	HCA only	57 (23.4)
	RCP	32 (13.7)
Full population with cerebral malperfusion excluded	HCA only	37 (18.4)
	RCP	25 (12.0)
PS matched population	HCA only	42 (19.9)
	RCP	28 (14.4)

Population	Grouping	Watershed lesions
Full population	HCA only	15 (6.1)
	RCP	7 (3.0)
Full population with cerebral malperfusion excluded	HCA only	11 (5.5)
	RCP	4 (1.9)
PS matched population	HCA only	11 (5.2)
	RCP	7 (3.6)

Population	Grouping	Cerebral malperfusion
Full population	HCA only	45 (17.6)
	RCP	29 (11.3)
PS matched population	HCA only	30 (13.7)
	RCP	29 (13.2)

Values are presented as n (%). HCA: hypothermic circulatory arrest, RCP: retrograde cerebral perfusion, PS: propensity score.

Study III

Supplementary Table III.1 Intraoperative data of the study population.

	All* (n=93)	Persisting neurological deficit (n=52)	No persisting neurological deficit (n=39)	*p*-value	Missing
Cardiopulmonary bypass time (min)	174 (136-226)	175 (140-226)	174 (133-216)	0.767	1 (1.1)
Crossclamp time (min)	74 (51-118)	77 (50-119)	71 (52-109)	0.745	1 (1.1)
Hypothermic circulatory arrest time (min)	20 (15-26)	19 (15-26)	22 (15-27)	0.298	5 (5.4)
Hypothermic circulatory arrest temperature (°C)	19 (18-21)	18 (17-20)	19 (18-22)	0.232	5 (5.4)
Hypothermic circulatory arrest technique				0.807	1 (1.1)
- No circulatory arrest	3 (3.3)	1 (1.9)	2 (5.1)		
- Circulatory arrest only	50 (54.3)	29 (55.8)	21 (53.8)		
- Antegrade cerebral perfusion	8 (8.7)	4 (7.7)	4 (10.3)		
- Retrograde cerebral perfusion	31 (33.7)	18 (34.6)	12 (30.8)		
- Arterial cannulation				0.414	1 (1.1)
- Femoral artery	63 (67.6)	37 (71.2)	25 (64.1)		
- Axillary artery	3 (3.2)	1 (1.9)	2 (5.1)		
- Ascending aorta/Arch	24 (25.8)	12 (23.1)	12 (30.8)		
- Left ventricle	2 (2.2)	2 (3.8)	0		
Distal surgical technique				0.728	0
- Ascending aorta	75 (80.6)	43 (83.7)	31 (79.5)		
- Hemiarch procedure	12 (12.9)	7 (13.5)	5 (12.8)		
- Arch procedure	5 (5.4)	2 (3.8)	3 (7.7)		
- Not completed	1 (1.1)	0	0		
Proximal surgical technique				0.116	0
- Supracoronary graft	69 (74.2)	39 (75.0)	30 (77.0)		
- Bentall procedure	17 (18.3)	9 (17.3)	7 (18.0)		
- Supracoronary graft + isolated AVR	5 (5.4)	4 (7.7)	1 (2.6)		
- Root replacement with aortic valve repair	1 (1.1)	0	1 (2.6)		
- Not completed	1 (1.1)	0	0		
Concomitant CABG	5 (5.4)	3 (5.8)	2 (5.1)	1.000	0

*=2 patients died intraoperatively and were excluded from group analyses. Values are presented as n (%) or median (interquartile range). AVR: aortic valve replacement, CABG: coronary artery bypass grafting.

Supplementary Table III.2. Postoperative data of the study population.

	All* (n=93)	Persisting neurological deficit (n=52)	No persisting neurological deficit (n=39)	*p*-value	Missing
Peak creatinine (µmol/L)	145 (101-216)	139 (108-211)	149 (96-217)	0.960	4 (4.3)
Peak lactate (mmol/L)	3.3 (2.4-4.9)	3.5 (2.4-5.3)	2.9 (2.3-4.0)	0.103	38 (40.9)
Bleeding first 24 hours (ml)	660 (410-1130)	600 (403-1010)	760 (450-1170)	0.439	8 (8.6)
Peak CKMB (µg/L)	30 (19-48)	33 (21-53)	22 (17-46)	0.233	24 (25.8)
Packed red blood cells (units)	4 (2-7)	5 (2-8)	4 (2-7)	0.677	10 (10.8)
Plasma (units)	2 (0-5)	2 (0-4)	2 (0-6)	0.825	10 (10.8)
Platelets (units)	4 (4-6)	4 (4-6)	4 (2-6)	0.107	10 (10.8)
Fibrinogen (g)	6 (4-8)	6 (4-8)	6 (4-10)	0.640	25 (26.9)
rFVIIa	28 (41.8)	18 (46.2)	10 (37.0)	0.461	26 (28.0)
Reoperated for bleeding	8 (8.6)	6 (11.5)	2 (5.1)	0.459	0
Ventilator >48h	43 (47.8)	28 (53.8)	15 (39.5)	0.178	3 (3.2)
Renal replacement therapy	4 (4.4)	3 (5.8)	1 (2.6)	0.632	2 (2.2)
Postoperative MI	4 (8.5)	3 (10.0)	1 (5.9)	1.000	46 (49.5)
Multiple organ failure	3 (4.1)	2 (4.5)	1 (3.3)	1.000	19 (20.4)
Intraoperative death	2 (2.2)	0	0	N/A	0
30-day mortality	23 (25.0)	19 (37.3)	2 (5.1)	<0.001	1 (1.1)
In-hospital mortality	24 (26.1)	19 (37.3)	3 (7.7)	0.001	1 (1.1)

*=2 patients died intraoperatively and were excluded from group analyses. Values are presented as n (%) or median (interquartile range). CKMB: creatine phosphokinase-MB, rFVIIa: recombinant factor VIIa, MI: myocardial infarction.

Study IV and V

Supplementary Table V.1. Neurological outcomes

Characteristic	Intervention N = 37	Control N = 38	*p*-value	Missing, N (%)
Clinical neurological injury	5 (14%)	13 (36%)	0.035	4 (5.3%)
- Clinical stroke	5 (14%)	11 (31%)	0.101	4 (5.3%)
- Clinical coma	2 (5.7%)	5 (14%)	0.429	4 (5.3%)
NIHSS day 4	0 (0-2)	1 (0-9)	0.102	4 (5.3%)
mRS day 4	4 (4-4)	5 (4-5)	0.022	0 (0%)
GCS-M day 4	6 (6-6)	6 (6-6)	0.697	4 (5.3%)
Days from surgery to MRI	5 (4-6)	6 (4-9)	0.384	5 (6.7%)
Acute ischemic lesions on MRI	25 (71%)	29 (83%)	0.255	5 (6.7%)
Non-acute ischemic lesions on MRI	12 (34%)	15 (43%)	0.461	5 (6.7%)
Number of patients with embolic lesions	25 (71%)	29 (83%)	0.255	5 (6.7%)
Number of patients with watershed lesions	1 (2.9%)	2 (5.7%)	>0.999	5 (6.7%)
Area of embolic lesions				
Left anterior	0 (0%)	1 (2.9%)	>0.999	5 (6.7%)
Right anterior	1 (2.9%)	1 (2.9%)	>0.999	5 (6.7%)
Left media	16 (47%)	18 (51%)	0.717	6 (8.0%)
Right media	16 (47%)	21 (60%)	0.281	6 (8.0%)
Left posterior	5 (14%)	11 (31%)	0.088	5 (6.7%)
Right posterior	6 (17%)	5 (14%)	0.743	5 (6.7%)
Basilar	10 (29%)	16 (47%)	0.113	6 (8.0%)
Number of embolic lesions				
Total	2 (0-6)	5 (2-12)	0.084	5 (6.7%)
Left	1 (0-4)	2 (0-5)	0.267	5 (6.7%)
Right	1 (0-3)	2 (0-6)	0.096	5 (6.7%)
Volume of embolic lesions				
Total	1.5 (0.0-10.0)	2.8 (1.0-7.8)	0.391	5 (6.7%)
Left	0.5 (0.0; 2.8)	1.0 (0.0-5.0)	0.510	5 (6.7%)
Right	0.5 (0.0-5.7)	1.0 (0.0-3.3)	0.360	5 (6.7%)
Number of watershed lesions				
Total	0 (0-0)	0 (0-0)	0.547	5 (6.7%)
Left	0 (0-0)	0 (0-0)	0.558	5 (6.7%)
Right	0 (0-0)	0 (0-0)	0.547	5 (6.7%)
Volume of watershed lesions				
Total	0 (0-0)	0 (0-0)	0.547	5 (6.7%)
Left	0 (0-0)	0 (0-0)	0.547	5 (6.7%)
Right	0 (0-0)	0 (0-0)	0.547	5 (6.7%)
Number of ischemic lesions	2 (0-6)	5 (2-12)	0.080	5 (6.7%)
Volume of ischemic lesions	1.5 (0.0-10.0)	2.8 (1.0-7.8)	0.335	5 (6.7%)

Values are presented as n (%) or median (interquartile range). NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale for neurologic disability, GCS-M: Glasgow Coma Scale motor score, MRI: magnetic resonance imaging.

Supplementary table V.2. Biomarkers for neurological injury

Characteristic	Intervention N = 37	Control N = 38	p-value	Missing, N (%)
S100B preoperative (ng/mL)	0.07 (0.04-0.09)	0.06 (0.05-0.11)	0.876	2 (2.7%)
S100B 24 hours after surgery (ng/mL)	0.13 (0.09-0.18)	0.16 (0.10-0.27)	0.284	4 (5.3%)
S100B postoperative day 4 (ng/mL)	0.07 (0.06-0.12)	0.08 (0.06-0.13)	0.782	4 (5.3%)
S100B 3 months postoperative (ng/mL)	0.05 (0.03-0.07)	0.05 (0.03-0.05)	0.495	16 (21%)
NSE preoperative (ng/mL)	29 (25-38)	27 (21-36)	0.185	17 (23%)
NSE 24 hours after surgery (ng/mL)	46 (38-60)	44 (35-62)	0.886	4 (5.3%)
NSE postoperative day 4 (ng/mL)	26 (18-34)	26 (20-37)	0.851	8 (11%)
NSE 3 months postoperative (ng/mL)	22 (16-24)	19 (16-22)	0.252	21 (28%)
NFL preoperative (pg/mL)	9.9 (8.6-14.2)	15.3 (11.0-23.6)	0.003	0 (0%)
NFL 24 hours after surgery (pg/mL)	17.4 (13.4-38.3)	35.1 (19.7-72.2)	0.004	4 (5.3%)
NFL postoperative day 4 (pg/mL)	28.7 (21.2-42.1)	49.1 (26.1-105.2)	0.027	4 (5.3%)
NFL 3 months postoperative (pg/mL)	19.7 (13.1-40.1)	29.7 (15.8-43.3)	0.294	16 (21%)
GFAP preoperative (pg/mL)	156.4 (118.2-215.0)	183.7 (134.9-284.5)	0.265	0 (0%)
GFAP 24 hours after surgery (pg/mL)	349.9 (222.2-747.1)	381.4 (267.7-1 424.5)	0.295	4 (5.3%)
GFAP postoperative day 4 (pg/mL)	308.4 (178.0-717.4)	387.7 (230.7-1 792.0)	0.209	4 (5.3%)
GFAP 3 months postoperative (pg/mL)	195.6 (120.0-322.5)	193.9 (111.1-271.5)	0.593	16 (21%)
UCH-L1 preoperative (pg/mL)	59.2 (43.5-100.6)	65.9 (46.8-104.3)	0.524	0 (0%)
UCH-L1 24 hours after surgery (pg/mL)	75.8 (48.1-101.4)	86.7 (55.7-164.7)	0.201	4 (5.3%)
UCH-L1 postoperative day 4 (pg/mL)	56.0 (37.7-73.2)	59.3 (41.2-90.0)	0.447	4 (5.3%)
UCH-L1 3 months postoperative (pg/mL)	57.3 (38.5-66.5)	57.3 (52.7-70.4)	0.769	16 (21%)
t-TAU preoperative (pg/mL)	9.6 (5.9-19.1)	10.2 (5.8-17.0)	0.962	0 (0%)
t-TAU 24 hours after surgery (pg/mL)	16.2 (13.3-22.5)	24.7 (13.0-79.2)	0.099	4 (5.3%)
t-TAU postoperative day 4 (pg/mL)	6.9 (5.6-9.5)	8.6 (6.1-17.9)	0.150	4 (5.3%)
t-TAU 3 months postoperative (pg/mL)	6.8 (5.4-7.4)	6.9 (5.3-8.7)	0.668	16 (21%)

Values are presented as median (interquartile range). S100B: S100 calcium-binding protein B, NSE: neuron specific enolase, NFL: neurofilament light polypeptide, GFAP: glial fibrillary acidic protein, UCH-L1: ubiquitin carboxy-terminal hydrolase L1, t-Tau: total-Tau.

Supplementary Table V. 3. Safety endpoints

Characteristic	Intervention N = 37	Control N = 38	p-value	Missing, N (%)
Intraoperative death	2 (5.4%)	2 (5.3%)	>0.999	0 (0%)
30-day mortality	2 (5.6%)	5 (13%)	0.431	1 (1.3%)
Clinical stroke	5 (14%)	11 (31%)	0.101	4 (5.3%)
Clinical coma	2 (5.7%)	5 (14%)	0.429	4 (5.3%)
Postoperative MI	2 (5.7%)	3 (8.3%)	>0.999	4 (5.3%)
Postoperative tromboembolic event*	1 (2.9%)	0 (0%)	0.493	4 (5.3%)

Values are presented as n (%). *=Other than cerebral or myocardial event. MI: myocardial infarction.

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