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NEUROMONITORING OF CRITICAL CARE PATIENTS

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DOCTORAL DISSERTATION

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"It seems to me that the natural world is the greatest source of excitement; the greatest source of visual beauty; the greatest source of intellectual interest. It is the greatest source of so much in life that makes life worth living." – David Attenborough

"I love deadlines. I like the whooshing sound they make as they fly by." – Douglas Adams

To my family and other animals

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Frontal electroencephalogram variables are associated with the outcome and stage of hepatic encephalopathy in acute liver failure.
Stewart JA, Särkelä M, Koivusalo A-M, Wennervirta J, Salmi T, Isoniemi H, Stenman U-H, Viertiö-Oja H, Lapinlampi P, Lindgren L, Salminen U-S, Vakkuri A.
Liver Transplantation 2014; 20: 1256-1265.

II Non-invasive neuromonitoring of hypothermic circulatory arrest in aortic surgery.
Stewart JA, Särkelä M, Salmi T, Wennervirta J, Vakkuri A, Vainikka T, Suojaranta R, Mäki K, Ilkka V, Viertiö-Oja H, Salminen U-S.
Scandinavian Journal of Surgery 2020; 109(4): 320-327.

III Long-term survival and quality of life after hypothermic circulatory arrest in aortic surgery. Stewart JA, Ilkka V, Jokinen J, Vakkuri A, Suojaranta R, Wennervirta J, Salminen U-S.
Scandinavian Journal of Surgery 2018; 107(4): 322-328.

IV Dramatic increase in serum trypsinogens, SPINK1 and hCGβ in aortic surgery patients after hypothermic circulatory arrest.
Stewart JA, Koistinen R, Lempiäinen A, Hotakainen K, Salminen U-S, Vakkuri A, Wennervirta J, Stenman U-H, Koistinen H.
Scandinavian Journal of clinical and laboratory investigation 2020; 80(8): 640-643.

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

ALF	Acute liver failure
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AUC	Area under curve
BBB	Blood-brain barrier
BIS	Bispectral index
BSI	Brain symmetry index
CABG	Coronary artery bypass grafting
CBF	Cerebral blood flow
CI	Confidence interval
CPB	Cardiopulmonary bypass
CT	Computer tomography
DNA	Deoxyribonucleic acid
DWT	Discrete wavelet transform
EEG	Electroencephalogram
EMG	Electromyogram
FFT	Fast Fourier transform
GABA	γ-aminobutyric acid
HCA	Hypothermic circulatory arrest
hCG	Human chorionic gonadotropin
hCGβ	Human chorionic gonadotropin β-subunit
HE	Hepatic encephalopathy
HRQoL	Health-related quality of life
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IL-1	Interleukin 1
IL-6	Interleukin 6
kDa	Kilodalton
LOS	Length of stay
LT	Liver transplantation
MARS	Molecular adsorbent recirculating system
MCAR	Missing completely at random
MDF	Main dominant frequency

MPF	Median power frequency
MRI	Magnetic resonance imaging
NCSE	Nonconvulsive status epilepticus
NIHSS	National Institutes of Health Stroke Scale
NIRS	Near-infrared spectroscopy
NMDA	*N*-methyl-D-aspartate
NSE	Neuron-specific enolase
OPCAB	Off-pump coronary artery bypass surgery
OR	Odds ratio
pdBSI	Pairwise averaged revised spatial brain symmetry index
PI	Pulsatility index
P_K	Prediction probability
POD	Postoperative day
PSTI	Pancreatic secretory trypsin inhibitor
RE	Response Entropy
ROC	Receiver operating characteristic
r-sBSI	Revised brain symmetry index
rSO2	Regional tissue oxygen saturation
S100β	Protein S100 beta
SCP	Selective cerebral perfusion
SE	State Entropy
SEF	spectral edge frequency
SPINK1	Serine peptidase inhibitor Kazal type 1
SIRS	Systemic inflammatory response
2-API	α_1-antitrypsin
TATI	Tumour-associated trypsin inhibitor
TBI	Traumatic brain injury
TCD	Transcranial Dopper ultrasound
TGF-β	Tumour growth factor β
TNF-α	Tumour necrosis factor α
TP	Total power
WSE	Wavelet subband entropy

ABSTRACT

In critical illness the risk of neurological insults is high, whether because of the illness itself, or as a treatment complication. As a result, the length of hospital stay and the risk of both further morbidity and mortality are all roughly doubled.[1-5] One of the major challenges is the inability to monitor a sedated, mechanically ventilated patient's neurological symptoms during intensive care treatment, due to a lack of reliable methods.[6-8]

The aims of this thesis research were to identify and test potential non-invasive methods, which would be predictive of neurological outcome, showing potential as neuromonitoring methods of critical care patients unable to self-report. As a guiding theme, all tested methods could be applied to actual critical care with relative ease.

Patients were included from two groups with a notably high incidence of neurological complications, namely acute liver failure patients with hepatic encephalopathy (**I**), and aortic surgery patients operated during hypothermic circulatory arrest (**II**). The first group included 20 patients, and the latter 30 patients. Late mortality and quality of life was assessed for the aortic surgery patients (**III**), and the postoperative development of certain blood biomarkers (**IV**).

The tested non-invasive neuromonitoring methods included electroencephalogram (EEG) variables from frontal or fronto-temporal abbreviated monitoring, frontal near-infrared spectroscopy, transcranial Doppler ultrasound measurements of the intracranial blood flow, and finally biomarkers. The last included established biomarkers with an association with neurological complications, namely neuron-specific enolase, and protein S100β, and several interesting biomarkers normally associated with tumours and pancreatitis.

Of the tested methods, the frontal EEG variables showed greatest promise, but the addition of the temporal channels did not increase sensitivity. Spectral EEG variables were predictive of the stage of hepatic encephalopathy (**I**), while a novel EEG variable called wavelet subband entropy was predictive of neurological outcome (**I**). The hemispheric asymmetry of frontal EEG was reasonably predictive of neurological outcome after aortic surgery (**II**). None of the other tested methods were predictive of outcome (**I, II, IV**), except protein S100β, which was significantly higher in the poor outcome group 48 to 72 hours after hypothermic circulatory arrest (**II**). The quality of life of aortic surgery patients was good after 5 to 8 years, and comparable with the general population of chronically ill patients (**III**).

The aim of this explorative research was to identify and test non-invasive neuromonitoring methods, suitable for use in critical care. Based on the results, frontal EEG variables are promising and predict the grade of hepatic encephalopathy and neurological outcome. The other tested methods were not predictive of neurological outcome. The long-term quality of life of aortic surgery patients is very good, despite the high risk for neurological complications.

TIIVISTELMÄ

Kriittisissä sairauksissa neurologisen komplikaation riski on suuri, sekä itse kriittisen sairauden että varsinaisen hoidon seurauksena. Haittatapahtuman johdosta sairaalahoidon kesto sekä sairastuvuuden ja kuolleisuuden riskit kaksinkertaistuvat.[1-5] Yksi suurimmista haasteista on luotettavien menetelmien puute, joilla voitaisiin arvioida mekaanisen hengitystuen varassa olevan ja rauhoittavia lääkkeitä saavan potilaan neurologisia oireita tehohoidon aikana.[6-8]

Tämän väitöskirjatyön tarkoituksena oli tunnistaa ja testata lupaavia ei-kajoavia menetelmiä, jotka ennustaisivat neurologista lopputulosta, ja jotka soveltuisivat kriittisesti sairaan tehohoitopotilaan neuromonitorointiin. Kantavana teemana kaikki testatut menetelmät voitaisiin soveltaa kliiniseen työhön suhteellisen helposti.

Potilaita kerättiin kahteen ryhmään, joissa neurologisten komplikaatioiden esiintyvyys on huomattavan suuri. Ensimmäinen ryhmä käsitti akuuttia maksan vajaatoimintaa ja hepaattista enkefalopatiaa sairastavat potilaat (**I**), toinen hypotermisen verenkierron pysäytyksen aikana rinta-aortan leikkauksen läpikäyvät potilaat (**II**). Ensimmäiseen ryhmään kuului 20 potilasta, jälkimmäiseen 30 potilasta. Aorttaleikatuilta potilailta arvioitiin myös elämänlaatua sekä myöhäiskuolleisuutta (**III**), lisäksi tiettyjen biomerkkiaineiden aorttaleikkauksen jälkeistä kehitystä ja soveltuvuutta neuromonitorointiin arvioitiin yhdessä osatyössä (**IV**).

Tutkimuksessa arvioituihin ei-kajoaviin neuromonitorointimenetelmiin lukeutuivat otsa- ja ohimolohkon elektroenkefalografia (EEG), lähi-infrapunaspektroskopia, transkraniaalinen Doppler-ultraäänimittaus sekä verestä mitattavat biomerkkiaineet. Biomerkkiaineet kattoivat sekä vakiintuneita aivovauriota heijastavia merkkiaineita (hermostoperäinen enolaasi, proteiini S100β) että useita mielenkiintoisia merkkiaineita, jotka liittyvät kasvaintauteihin ja haimatulehdukseen.

Testatuista menetelmistä otsalohkon EEG muuttujat olivat lupaavia, mutta ohimolohkon EEG lisääminen ei parantanut menetelmien herkkyyttä. EEG spektrimuuttujat ennustivat hepaattisen enkefalopatian astetta (**I**) luotettavasti, kun taas kokeellinen EEG-muuttuja (aalloke-alitaajuuden entropia) ennusti luotettavasti neurologista lopputulosta akuutin maksan vajaatoimintaa sairastavilla potilailla (**I**). Otsalohkon aivopuoliskojen EEG-rekisteröinnin hetkellinen epäsymmetria ennusti kohtalaisella tarkkuudella neurologisten päätetapahtumien esiintymisen aorttaleikatuilla potilailla (**II**). Muut testatut menetelmät eivät ennustaneet neurologista lopputulemaa (**I, II, IV**), paitsi proteiini S100β, joka oli merkittävästi korkeampi 48–72 tuntia leikkauksen jälkeen niillä potilailla, joiden neurologinen toipuminen oli huono (**IV**). Aorttaleikattujen potilaiden elämänlaatu oli hyvä 5–8 vuotta leikkauksen jälkeen ja verrattavissa kroonisesti sairaan väestön elämänlaatuun (**III**).

Tämän kartoittavan tutkimuksen tarkoituksena oli tunnistaa ja testata ei-kajoavia neuromonitorointimenetelmiä, jotka soveltuvat tehohoitoon. Tulosten perusteella otsalohkon EEG-muuttujat ennustavat hepaattisen enkefalopatian astetta sekä potilaan neurologista toipumista. Muut testatut menetelmät eivät ennustaneet neurologista toipumista luotettavasti. Aorttaleikattujen potilaiden pitkäaikainen (5–8 vuoden) terveyteen liittyvä elämänlaatu on erittäin hyvä, vaikka leikkaukseen liittyy korkea aivovaurion riski.

1 INTRODUCTION

Neurological complications in critical care and the perioperative period of aortic surgery increase further morbidity, mortality, and decrease later quality of life.[1-5] Similarly, oversedation is associated with increased morbidity, and longer ICU and hospital stays.[9-11] The ability to monitor the well-being of the brain in sedated, mechanically ventilated patients is crucial, to guide sedation, therapeutic interventions, and for the evaluation of the prognosis of critical care.

Unfortunately, few reliable methods of neuromonitoring exist, and all have confounding factors that need to be addressed. A major challenge is the difficulty in defining and objectively measuring the abstract concepts of consciousness, pain, and sedation.

Several potential methods do exist, some of which have been used in different scenarios earlier. Indices derived from EEG, such as spectral EEG, Bispectral Index (BIS), and Entropy, have been used to assess the depth of anaesthesia during surgery, and with changes to the algorithms might serve in the critical care setting and neurological prognostication.[6-8]

Critical care differs in many ways from the operating room, with infrequent use of neuromuscular blockage and lighter sedation instead of surgical anaesthesia. Critical care patients react more due to lighter analgesia and sedation, treatment times are long, and several extrinsic factors interfere with the neuromonitoring devices. Therefore, methods developed for the purpose of surgical anaesthesia monitoring are not directly applicable in the critical care setting. Similarly, in aortic surgery the use of hypothermic circulatory arrest (HCA) can confound these methods.

The purpose of this prospective, explorative thesis research is to identify and test potential non-invasive methods, which would be predictive of neurological outcome and applicable to critical care. It was inspired by the clinical need seen in clinical work with critical care patients, especially patient groups with a high risk of neurological complications, such as acute liver failure (ALF) with hepatic encephalopathy (HE), and surgery of the thoracic aorta with HCA.

2 REVIEW OF THE LITERATURE

2.1 Historical perspective

Archaeology has uncovered human skulls from the Neolithic era, with burr holes as evidence of trepanation as a prehistoric surgical treatment of neurological ailments.[12] Following thousands of years of slow progress, the understanding of the brain and its function has developed mostly in the late modern, even contemporary history.

The first recording of the electrical activity of the human brain was performed by the English scientist Richard Caton, and the first human electroencephalogram (EEG) was recorded in 1924 by a German physiologist and psychiatrist Hans Berger.[7, 13] Followed by the identification and characterization of different EEG phenomena, the field of clinical electroencephalography was later created.

2.2 Neurological injury

2.2.1 Hypoxic-ischaemic brain injury and secondary cascades

Hypoxic-ischemic brain injury leads to neuron damage with serious consequences, including coma, epileptic seizures, ischaemic stroke, neurocognitive impairment, and death.[14, 15] In critical care, the non-traumatic reason for hypoxic-ischemic brain injury is typically a regional or generalised loss of cerebral blood flow (CBF) or depletion of blood oxygen levels, causing a critical lack of oxygen and energy in neurons.[14, 16] The brain consumes approximately 25 % of total body energy expenditure and 20 % of total oxygen consumption, and without a constant flux of oxygen and energy (mainly glucose), neurons and glial cells suffer ischemia and die.[15, 17-20] Loss of CBF may be a result of an occluding thromboembolism, severe generalised hypotension or markedly increased intracranial pressure (ICP). Depleted blood oxygen due to lack of breathing or asphyxiation can cause cerebral hypoxia and even anoxia, despite adequate blood flow.[14, 15, 18-20]

In physiological conditions, the arteries and arterioles of the brain have a considerable basal tone, contributing to a constant and highly regulated vascular resistance, ensuring adequate blood flow to all brain areas despite changes in systemic blood pressure. With a high degree of local control, called metabolic coupling, the blood flow to active areas can be autonomously increased to meet the increased oxygen and energy demands (functional hyperaemia), without simultaneously weakening the blood flow to other brain areas. Cerebrovascular pressure reactivity and vessel wall myogenic mechanisms are key components of cerebrovascular autoregulation. CBF is maintained at approximately 50 ml per 100 g of brain tissue per minute, as long as the cerebral perfusion pressure is between 60 to 160 mmHg. Beyond these limits the autoregulation is progressively lost, and CBF becomes dependent on mean arterial pressure. The mechanisms behind cerebral autoregulation are not fully understood, however the main components seem to be the myogenic responses of smooth muscles of the cerebral arteries and arterioles in response to changes in intraluminar pressure changes, and vasoactive substances causing vasodilatation (such as H^+, K^+, O_2, adenosine, nitric oxide, and neurotransmitters released by the astrocytes). In pathological conditions, such as severe hypotension or after brain injury[21], the cerebral pressure autoregulation is impaired, rendering the brain more susceptible to ischaemic insults.[17, 19, 22]

Ischaemic depolarization of neurons occurs when CBF decreases to approximately 18 ml/100 g brain tissue/min. Different areas of the brain vary in their sensitivity to prolonged ischaemia, with typically the most sensitive (caudate, putamen, frontal gyri) being damaged within 3 to 5 minutes of full ischaemia and up to 15 to 20 minutes for the more resistant parts.[14, 20, 23, 24]

The pathophysiology of non-traumatic neurological injury is complex, with a secondary phase of pathological cascades aggravating the primary insult.[14, 25] Secondary cascades include continued hypoxia or hypotension, brain oedema and a pathological increase in ICP, hypercapnia and metabolic disturbances, excitotoxicity due to imbalances in neurotransmitter release, endothelial dysfunction, increased release of free oxygen radicals, inflammation, mitochondrial damage, apoptosis, and necrosis.[14, 15, 19, 25-27] A schematic illustration of the brain damage cascades is presented in **Figure 1**.

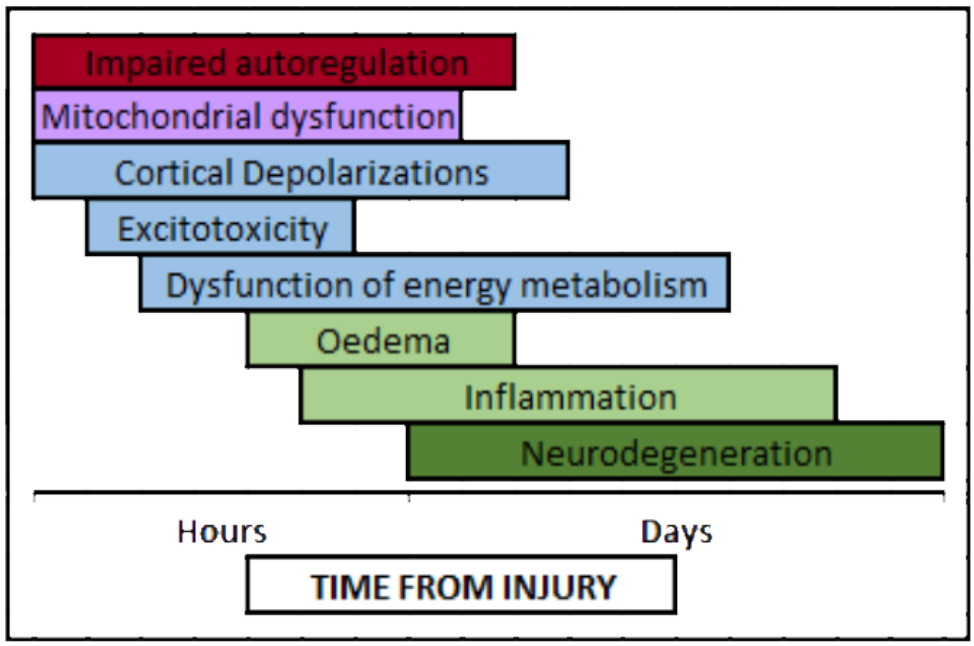


Figure 1. An illustrative example of different brain damage cascades and their temporal relations to the time of the primary injury.[19]

2.2.2 Intracranial pressure

As the brain is encased in an unyielding skull, increases in the intracranial volume (for instance brain oedema, intracranial hematomas, or tumours) lead to a steep increase in ICP, which in turn leads to decreased cerebral perfusion pressure, blood flow and an increased risk of eventual transtentorial herniation.[19, 21, 28]

Normal ICP in adults is 7 to 15 mmHg[21, 29], and elevated ICP (over 20 mmHg) is associated with increased mortality after acute traumatic brain injury (TBI), and other critical conditions[21, 29, 30], although no randomised controlled studies have yet addressed this effect.[19, 21, 28]

2.2.3 Hypoxia and Hypercapnia

Hypoxia causes cerebral vasodilatation, increasing CBF up to 400 % from resting levels during severe hypoxemia. In general, the increase of CBF due to hypoxemia begins when the partial pressure of tissue oxygen falls below 7 kPa.[17]

Carbon dioxide is a potent vasodilator, and hypercapnia causes strong vasodilatation of the cerebral blood vessels. This leads to a sharp increase in cerebral blood flow and increases intracranial oedema in situations where the normal homeostasis and blood brain barrier is disrupted. This may lead to increased ICP.[17]

2.2.4 Excitotoxicity

The damaging effect of glutamate on new-born murine neurons was shown by Olney half a century earlier.[31, 32] Later studies describe the cascade of events where the normally efficient glutamate uptake by astrocytes is disturbed, leading to a combination of impaired uptake and a massive increase in glutamate efflux due to cellular depolarization. Ischaemia or direct toxic effects cause neuron membrane depolarization, leading to increased release of glutamate. Glutamate activates several neuron receptors, including the NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors. These in turn open cellular calcium channels, leading to an increased calcium influx, an intracellular calcium overload, and further membrane depolarization. Tissue acidosis, which is also a result of ischaemia, further exacerbates the intracellular calcium overload. The result of all this is a loss of membrane ionic gradients and membrane potentials, spontaneous depolarization waves, and finally calcium-dependant cell death of neurons. The damaging process actives also cell apoptosis. Glutamate is the most abundant excitatory neurotransmitter in the brain, but other neurotransmitters have been similarly linked to the excitotoxicity of neurons, including aspartate, NMDA, homocysteine, and cysteine.[14, 15, 27, 33]

Excess release of intracellular calcium causes other complex damaging cascades, including the activation of catabolic enzymes, DNA fragmentation, and mitochondrial dysfunction resulting in an increase in free radical formation.[14, 24, 27, 32]

2.2.5 Reactive oxygen and nitrogen species

Previously called radicals, certain oxygen and nitrogen derived molecules are chemically aggressively reactive, and in excessive amounts disrupt normal cell membranes and physiological functions, leading to cell damage in the human body. Examples of reactive oxygen species include peroxides, superoxide, and hydroxyl radical, while examples of reactive nitrogen species include nitric oxide, and peroxynitrite.[14, 15, 26]

Their combined effect is called oxidative (and nitrative) stress, which in physiological conditions is mostly buffered by biological antioxidants (such as glutathione, superoxide dismutase, catalase, and blood transferrin, caeruloplasmin, haptoglobin and albumin). However, in hypoxic or hyperoxic conditions the buffering capacity is overrun, and the resulting oxidative distress is thought to be a part of the secondary neuron damage pathway and neuron apoptosis. [14, 15, 24, 26, 33]

2.2.6 Inflammation

Brain injury and ischemia is followed by an inflammation response, which includes a cellular response, cytokine response, and the activation of toll-like receptor 4 proteins. The cellular response leads to accumulation and activation of neutrophils, lymphocytes, and monocytes, which in turn cause tissue damage by releasing reactive oxygen species and proteolytic enzymes. The cytokine response is a result of increased production of cytokines (IL-1, IL-6, TNF-α, TGF-β) by several cell types activated in the inflammation processes (endothelial cells, microglia, neurons, platelets, leukocytes, fibroblasts). These cytokines contribute to secondary cell damage in only partly understood ways, which include causing fever, enhancing NMDA-mediated excitotoxicity, stimulating nitric oxide synthesis, increasing recruitment and adhesion of neutrophils, increasing production of acute-phase

proteins, and disrupting the blood-brain barrier. B cells, macrophages, endothelial cells, microglia, astrocytes, oligodendrocytes, and neurons express toll-like receptors, which act as the first-line defence against pathogens. Activation of toll-like receptors leads to increased cytokine and chemokine production and a localised inflammatory response, which correlates with increased neuron damage.[15, 30, 33]

2.3 Cerebral insults in critical care

2.3.1 Epidemiology, morbidity, and mortality

Neurological complications, especially when including reversible complications such as delirium, are common in critical care, and often recognised with a delay in intubated and sedated patients. Complications can develop because of the critical illness itself, such as TBI or intracerebral haemorrhage (ICH), or due to thromboembolic complications associated with the critical illness, or as complications of therapies and interventions (hypoxia during intubation, vessel thrombosis due to cardiopulmonary bypass cannulation). Surgical treatment, especially aortic surgery with HCA carries a high risk of perioperative insults and neurological complications.[20, 34] Neurological complications can also arise as an exacerbation of an underlying primary neurological disease.[1]

The highest incidence of neurological complications in non-neurosurgical critical care is seen in sepsis, with aortic and cardiac surgery carrying the second highest incidence.[1, 2, 35] In a 1993 published study of medical ICU patients by Bleck *et al*., up to 12.3 % of 1758 admitted medical ICU patients suffered neurological complications. The complications were divided into metabolic encephalopathy (28.6 %), seizure (28.1 %), hypoxic-ischemic encephalopathy (23.5 %), and ischaemic stroke (22.1 %). In this study, the highest incidence of 38.8 % of neurological complications was seen in ICU patients treated for sepsis.[2]

Encephalopathy of different stages is the most common neurological complication of the ICU, with a myriad of different aetiologies (traumatic, increased ICP, excitotoxic, epileptic, metabolic, inflammation). In septic patients the prevalence of impaired consciousness can be as high as 70 %, with 10 to 12 % suffering from more severe encephalopathy. More severe symptoms include seizures and coma, with the severity of septic encephalopathy correlating with an increased mortality.[1]

Epileptiform seizures in critical care patients have an incidence of 8 to 11 %, and nonconvulsive status epilepticus (NCSE; continuous cortical epileptiform discharge without visible seizures) has an estimated incidence of 8 % in comatose patients, and over 50 % in TBI patients. Nonconvulsive seizures secondary to a brain insult increase the mortality to 27 %.[1, 36, 37]

The incidence of delirium is high in ICU patients, up to 18 to 50 % according to most studies and depending on the definition.[1, 10]

Neurological complications can be devastating, leading to an increased short- and long-term mortality, longer ICU and hospital stays, increased disability, and increased morbidity.[1, 2, 20] Bleck *et al.* in their 1993 study reported an almost doubled mortality risk for patients with neurological complications (45.7 % versus 26.6 %).[2]

2.3.2 Length of stay

Critically ill patients with neurological complications experience over twice as long stays in the ICU and in the hospital. In the 1993 study by Bleck *et al.,* ICU patients with neurological complications had 2.5-fold longer ICU stays and 2-fold longer hospital stays.[2]

In a cohort of 2121 cardiac surgery patients, postoperative ischaemic strokes were detected in 1.7 % of all patients. Compared to the patients who did not suffer an ischaemic stroke, these patients had a two to three times longer ICU length of stay (LOS) (13.8 ± 14.7 days versus 5.7 ± 12.1 days; $p < 0.001$) and hospital LOS (53.0 ± 72.8 days versus 18.4 ± 29.2 days; $p < 0.001$).[5] Perioperative seizure patterns on the EEG are relatively rare in cardiac surgery, with an incidence of approximately 3 %, and have little effect on mortality or LOS.[36]

2.3.3 Quality of Life

Apart from morbidity and mortality, the health-related quality of life (HRQoL) has arisen as an important determinant of the success of medical care. HRQoL reflects in a broad and multidimensional way the outcome of treatment, highlighting the diffuse neurocognitive complications which are easily missed in initial evaluations, but present later challenges in daily life.[4, 38] As such, it can be seen as a powerful tool in estimating the long-term treatment success, and even the overall effects of neurological complications in everyday life.[4, 38]

Several different HRQoL measurement tools have been developed, which are based on structured interviews. These surveys or scores can be generic, or disease/condition specific, and are a quantitative way of representing an individual's self-perceived HRQoL.[38] Nationwide and other generic population survey data bases have been collected in many countries, to use as comparison groups.[38-40] One of the widely used generic HRQoL measures is the RAND-36, with 36 questions grouped in eights scales (physical functioning, role limitations caused by physical problems, role limitations caused by emotional problems, mental health, energy/vitality, bodily pain, and general health).[41]

Liver failure patients who have undergone liver transplant show significant improvement of HRQoL, however several HRQoL domains show significantly lower scores compared to the general population. Cirrhotic patients have the lowest HRQoL scores.[3]

The HRQoL of patients after surgery of the thoracic aorta is reasonably good, and even comparable to that of the age- and sex-matched general population.[4, 42, 43] Several previous studies have shown higher long-term HRQoL scores in aortic surgery patients with shorter (<20 min) HCA times, and in patients with bilateral selective cerebral perfusion (SCP) during HCA.[4, 40, 42] With no difference in primary neurological outcome, but lower HRQoL scores for the group of patients with longer HCA, it is speculated whether HRQoL instruments could be sensitive in detecting long-term neurological challenges in later life. While HRQoL questionnaires do not always include specific cognitive items, the evaluated aspects of life are highly affected by neurological, social, and cognitive functions and defects therein.[4, 40, 42]

2.4 Specific critical care conditions with increased risk of neurological complications

2.4.1 Acute liver failure

In ALF the failing liver function leads to HE, severe coagulopathy, multiorgan failure, and death. Chronic and intermediate forms of liver failure share similar complications, but with a slower disease progression. In the pretransplant era mortality in ALF was high, up to 80 %.[3] The most effective treatment for severe ALF is liver transplantation (LT), but even with modern critical care treatment the mortality remains still very high, approximately 30 (20 to 40) %.[3] The typical aetiology of ALF is excessive alcohol consumption, paracetamol intoxication, and viral hepatitis. Mycotoxins from the *genus Amanita* mushrooms can also cause severe ALF, for instance *Amanita phalloides*, commonly known as Death cap, and *Amanita virosa*, commonly known as the Destroying angel.[44-49]

2.4.1.1 Hepatic encephalopathy

HE is the syndrome of neuropsychiatric disturbances in liver failure, where the failing liver functions lead to an accumulation of neurotoxic substances, hyperammonaemia-induced brain oedema, and increased ICP.[31, 50, 51] These pathological changes lead to a progressively slowing of brain activity, deepening coma, and eventual brain herniation and death.[45, 48, 49] The exact mechanism behind the development of HE remains complex and only partially understood. One major contributor is hyperammonaemia (excess of ammonia), which leads to overactivation of the glutamate pathway and excitotoxic damage.[30, 45] Ammonia has also direct neurotoxic effects at high concentrations, but not typically at the concentrations found in grade I to III HE (100 to 400 µmol/l).[50] In liver failure, the ammonia-urea metabolism is impaired, leading to hyperammonaemia. In the brain, astrocytes metabolise ammonia and glutamate into glutamine, which causes osmotic cellular oedema and increases ICP.[30, 31, 50, 51] Hyperammonaemia causes also increased excitatory glutamate release by the astrocytes.[30, 31, 44-48, 50, 51]

Neuroinhibitory neurotransmitters, such as γ-aminobutyric acid A ($GABA_A$), are produced by the gut bacteria, among other sources. A failing liver function leads to an increase in their blood concentrations, and in combination with a leaking blood-brain barrier (BBB) the inhibitory effect via the $GABA_A$/benzodiazepine receptors lead to impaired motor functions, cognitive slowing, and eventual coma. The receptor is the same that is used by sedatives, such as barbiturates and benzodiazepines, to achieve pharmacological sedation. Interestingly, the application of a high affinity $GABA_A$/benzodiazepine receptor antagonist, such as flumazenil, decreases HE severity and corrects HE-related EEG changes (for instance preventing triphasic waves) temporarily in approximately 60 % of patients.[30, 50]

Systemic inflammatory response (SIRS), with an increased release of TNF-α and an increased cytokine production (IL-1, IL6) of the glial cells causes neuroinflammation, contributing to the development of encephalopathy and brain oedema.[33, 44, 45, 50]

Cerebral oedema is strongly associated with ALF, leading to an increased ICP in up to 80 % of fulminant hepatic failures. Mortality is worse in patients who develop an elevated ICP, and the reason for death is often brain herniation. The mechanisms behind cerebral oedema in ALF are still only

partially understood, however a functional breakdown of the BBB (vasogenic oedema) and a complex combined effect of the metabolic disturbances (high bilirubin, ammonium, and sodium) and impaired regulation of cellular osmosis are the main drivers. In severe ALF and HE the autoregulation of CBF is also impaired.[30, 44-46, 48, 50]

The severity of HE is graded according to the West Haven criteria (**Table 1**), which evaluates the altered mental functions and consciousness.[30, 33, 45]

Table 1. Hepatic Encephalopathy West Haven criteria

Grade	
I	Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks.
II	Lethargy or apathy; disorientation; inappropriate behavior; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
III	Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech.
IV	Coma, with (IVA) or without (IVB) response to painful stimuli.

Progressive HE presents with certain EEG patterns, such as a generalised slowing of brainwave activity, increased theta and delta activity, and decreased alpha and beta activity.[30] Triphasic waves are common in severe HE, while progressive coma leads to a suppressed, low-voltage EEG patterns, and eventually even burst suppression.[30] Epileptiform EEG patterns are relatively rare, seen in approximately 15 % of HE patients, and are associated with a poorer prognosis.[44, 52, 53]

The neurological changes of HE are partly reversible before brain herniation and death, thus the timely detection of developing neurological complications and increasing ICP is crucial. The traditional method of ICP monitoring is placing a pressure-sensitive catheter in the brain through a burr hole in the skull.[30] This invasive monitoring method carries an increased risk of bleeding, especially in ALF patients with a severe coagulopathy, with an estimated complication rate of 10 to 20 %.[44, 49]

2.4.1.2 Molecular adsorbent recirculating system (MARS)

Extracorporeal albumin dialysis, such as the Molecular adsorbent recirculating system (MARS), can be used to treat and stabilise patients while they are waiting for a suitable donor graft for LT. During treatment the patient's blood is perfused through an albumin-impregnated membrane, which allows small (< 50 kDa) molecules to pass freely, but prevents the passage of larger molecules (albumin, clotting factors, cells). At the same time, albumin-binding toxins are cleared from the blood by the membrane albumin. Combined with a traditional haemodialysis or hemofiltration method, the treatment reduces blood concentrations of both albumin bound and water-soluble toxic substances, as well as neuroactive amino acids. Albumin dialysis can provide time for the liver to recover without the need for LT and is, therefore, often used in the intensive care unit (ICU) for ALF patients requiring critical care.[44, 46, 47, 50, 54]

Treatment with MARS improves the stage of HE, and partially corrects hyperbilirubinemia and hyperammoniemia[44, 54], but most of the randomised, controlled studies show no effect on mortality in ALF.[44, 54, 55] A meta-analysis by Vaid *et al.* from 2012 analysed 10 trials (9 randomised, controlled) of MARS therapy, showing a significant decrease in bilirubin levels, an improvement in HE, but no statistically significant effect on mortality.[56]

However, a few studies have suggested that MARS treatment could enhance survival and decrease the need for a liver transplant.[44, 46, 47] A prospective cohort of consecutive ALF patients treated with MARS (N = 49) had a survival rate of 80 %, and 23 (51 %) patients' livers recovered without the need for a transplant.[47] In another cohort of 113 ALF patients, a trend for higher survival was seen in liver transplant patients treated with MARS (94 % versus 77 %; p = 0.06).[46]

2.4.2 Cardiac and aortic surgery

Both cardiac and aortic surgery carry a high risk of neurological complications. The incidence of postoperative delirium depends on the definition, with transient stroke-like symptoms seen in 4.6 % of cardiac surgery patients[57], while some level of neurocognitive dysfunction is seen in 9 to 25 %[58], and postoperative delirium in up to 25 to 45 % of all cardiac patients.[20, 59] The incidence of ischaemic stroke after coronary artery bypass grafting (CABG) is approximately 1 to 3 %[5, 14, 35], and in aortic surgery as high as 5 to 11 %.[20, 43] A wide spectrum of other potential neurological complications has been described, including postoperative delirium and cognitive decline, seizures, coma, ischaemic stroke, and neurocognitive impairment.[5, 14, 20, 35, 43, 58]

Neurological complications increase the morbidity and mortality of surgical patients. The hospital mortality after cardiac surgery is around 2 to 5 %[5, 35] and for aortic surgery around 9 to 10 %[16, 43], but for patients who suffer a perioperative ischaemic stroke the hospital mortality increases over five-fold to 20 to 30 %.[5] Similarly, the LOS can be quadrupled from one to four weeks.[5] According to a Japanese review, perioperative neurological complications in cardiovascular surgery increase the risk of perioperative death by sevenfold, and triples the 10-year mortality.[20]

The aetiology of neurological complications is typically due to cerebral hypoperfusion and thromboembolic events arising from the heart, valves, aortic atheroma, or use of cardiopulmonary bypass (CPB). Macroembolisms result from atheromatous material detaching from the aortic valve or aorta during manipulation, while microembolisms are typically caused by gaseous or solid particles released during cannulation, opening of the heart chambers and incomplete de-airing during surgery. Especially in aortic surgery the use of HCA causes notable global hypoperfusion. The developing neurological damage can be exacerbated by SIRS, arising from the surgery itself and from the use of CPB.[14, 23, 60]

2.4.2.1 Cardiopulmonary bypass

In cardiac surgery the use of CPB (extracorporeal blood circulation and gas exchange) is commonplace. Cannulas are placed in the venous system (femoral vein, vena cava, or right atrium) and the arterial system (aorta, femoral artery, or axillary artery). To prevent thromboembolisms, the patient is fully heparinised (local practises vary, typically activated clotting time maintained at over 400 s).[34, 61] To protect the myocardium from ischaemia during cardiac arrest, a cardioplegia solution (typically potassium-based) is used to cause an electromechanical arrest of the myocardium.[61] Complications include cannula malpositioning, iatrogenic dissection, platelet dysfunction,

haemodilution, and bleeding complications. Hypotension and SIRS can cause end-organ dysfunction and injury, presenting typically either as cerebral injury (ischaemic stroke) or as acute kidney injury. The BBB is temporarily weakened by CPB, and microemboli generated in the system may play a part in later cognitive functions and neurological complications.[61, 62]

Off-pump coronary artery bypass surgery (OPCAB) is performed on a beating heart, without aortic clamping or the use of CPB. It was thought to reduce the surgical risk of ischaemic stroke or death, but the clinical evidence remains inconclusive.[57, 62, 63]

In a retrospective analysis of 16 184 patients, the frequency of ischaemic stroke was 3.8 % in the CABG group and 1.9 % in the OPCAB group. Valvular surgery and combination surgery with CABG carried the highest risk of stroke, from the 4.8 % for aortic valve surgery to the 9.7 % for multiple valve surgery.[57] Similarly, in a cohort of 557 OPCAB and 445 CABG patients there was a non-significantly higher incidence of stroke in the group with perfusion (OPCAB 1.8 % versus CABG 2.5 %; $p = 0.45$).[63] In a randomised, controlled but underpowered study of the 5-year cognitive and cardiac outcomes of 281 low-risk patients referred to surgical treatment (142 OPCAB, 139 CABG), the researchers found that in both groups 50% presented with detectable cognitive decline (a 20 % or higher decline in the performance of neuropsychological tests), and similar rates for cardiovascular events (21 % OPCAB, 18 % CABG).[62]

2.4.2.2 Hypothermic circulatory arrest and selective cerebral perfusion

To protect the brain and other organs during circulatory arrest, cardiac and aortic surgery patients are cooled down to sub-physiological temperatures, using the slowing effect of hypothermia on cell metabolism. Originally the technique required the use of deep hypothermia (<25 ºC) and was named deep HCA, but later evidence has allowed the use of moderate or even mild HCA with SCP. According to expert consensus hypothermia is classified[64] as profound (≤14 ºC), deep (14.1 to 20 ºC), moderate (20.1 to 28 ºC), or mild (28.1 to 34 ºC).[16, 20, 27, 34, 64, 65]

A meta-analysis by Tian *et al.* in 2013 included the data of nine major studies of aortic arch surgery comparing deep HCA and moderate HCA with antegrade SCP. Permanent neurological injury was significantly higher in the deep HCA group without SCP (12.8 % versus 7.3 %, OR 1.8 with a 95% CI of 1.28 to 2.52; $p = 0.0007$), while no difference was detected in temporary neurological symptoms (8.0 % versus 10.3 %, OR 0.82 with a 95% CI of 0.46 to 1.48) or mortality (13.5 % versus 11.1 %, OR 1.39 with a 95% CI of 0.88 to 2.20).[65]

Deep hypothermia (nasopharyngeal temperature 14 to 20 ºC) allows 20 to 30 min of relatively safe cerebral ischemic time.[16, 20, 27, 34, 64, 65] A schematic of the effect of temperature on safe circulatory arrest time is presented in **Figure 2**.[27]

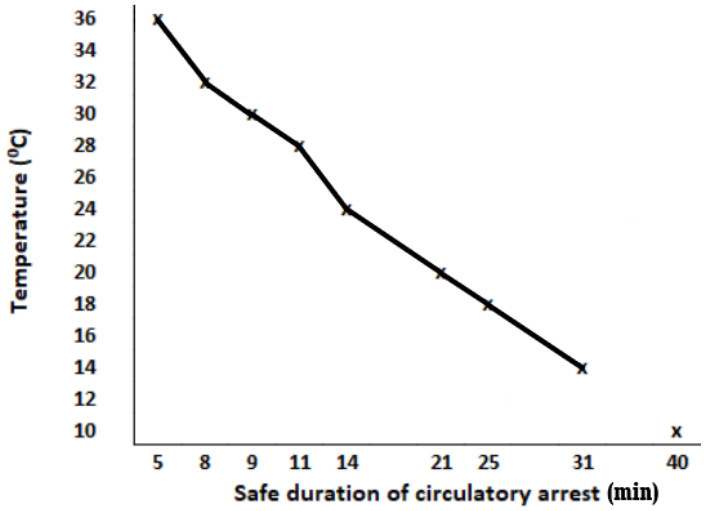


Figure 2. The relation of brain temperature with the duration of circulatory arrest considered safe, in relation to neurological complications.[27]

Hypothermia slows down neuron activity and metabolism, so that a 10 ºC drop reduces brain metabolism by 65-70 %, and at 20 ºC the metabolic activity is around 20-25 % of normal. However, even at severe hypothermia there remains a basal metabolic level, so that at 8 ºC approximately 11 % of brain metabolism is still present. Thus, the protective effect of HCA is not complete. CBF autoregulation is partially lost at 22 ºC, and totally at 8 ºC, decreasing the ability of the brain to ensure adequate perfusion.[16, 22, 64]

Glutamine and dopamine release are inhibited by even mild hypothermia (33 ºC), possible decreasing the adverse effects associated with the neurotransmitters on developing cellular injury.[22]

The use of HCA is associated with disturbances of normal physiology, and with complications.[16, 27, 34] Hypothermia interferes with physiological enzyme and organ function, causing oedema formation and even organ damage.[27] Hypothermia also aggravates bleeding and can cause electrical instability of the heart.[16] After HCA, the incidence of renal dysfunction is 5 to 14 % and left ventricular failure (depending on definition) has an incidence of 7 to 34 %.[27] As the protective effect of hypothermia is not complete, the combined effect of circulatory arrest and CPB carry a significant risk of neurological complications. After HCA, approximately 25 % suffer from temporary neurological dysfunction (including disorientation, confusion, agitation, delirium), and approximately 10 % suffer an ischaemic stroke.[16, 27]

2.4.2.3 Selective Cerebral Perfusion

SCP is achieved with additional CPB cannulas feeding the CBF via vessels of the brain, and it allows independently continuing the perfusion and temperature control of the brain during circulatory arrest. Antegrade SCP is achieved with a cannula in one of the arteries leading to the carotid artery, and retrograde SCP is achieved via a cannula in the superior vena cava (rarely in clinical use). The

technique can be modified to include bilateral cannulations, or even rarely the cannulation of just the left common carotid artery.[16, 27, 66]

Antegrade SCP is the most common technique, and it carries a risk of thromboembolic complications due to artery manipulation and possible iatrogenic artery dissection. The retrograde technique is thought to protect from atheroma release from the vessel wall, however, it is not physiological circulation and carries a risk of venous congestion and less reliable cerebral perfusion. Bilateral cannulation increases procedure complexity.[16, 20, 27, 66]

The use of SCP during HCA prolongs the circulatory arrest time considered acceptable, with right SCP to approximately 30 to 50 minutes, and with bilateral SCP up to 80 minutes. In circulatory arrests of over 40 minutes, the rate of cerebral infarction is around 1.7 % with SCP, while without SCP the rate of cerebral infarction is over 30 %. In HCA with shorter arrest times the use of SCP has been reported to reduce mortality from 6.5 % to 2.4 %, and ischaemic stroke rates from 9 % to 3 %.[16, 20, 27, 65]

The circle of Willis (*lat. Circulus arteriosus cerebri*) is an arterial system around the brain stem, responsible for delivering blood to the cerebral arteries, and has the only collateral circulation of the brain (**Figure 3**). Unfortunately, the circle of Willis is often incomplete, and may predispose certain cerebral areas to ischaemia during SCP. Autopsy studies have detected a significantly incomplete circle of Willis in approximately 15 % of patients.[42] Other studies have shown that in 46 % of patients at least one communicating artery is missing, and a fully complete circle of Willis is found in approximately 34 % of patients.[16, 65]

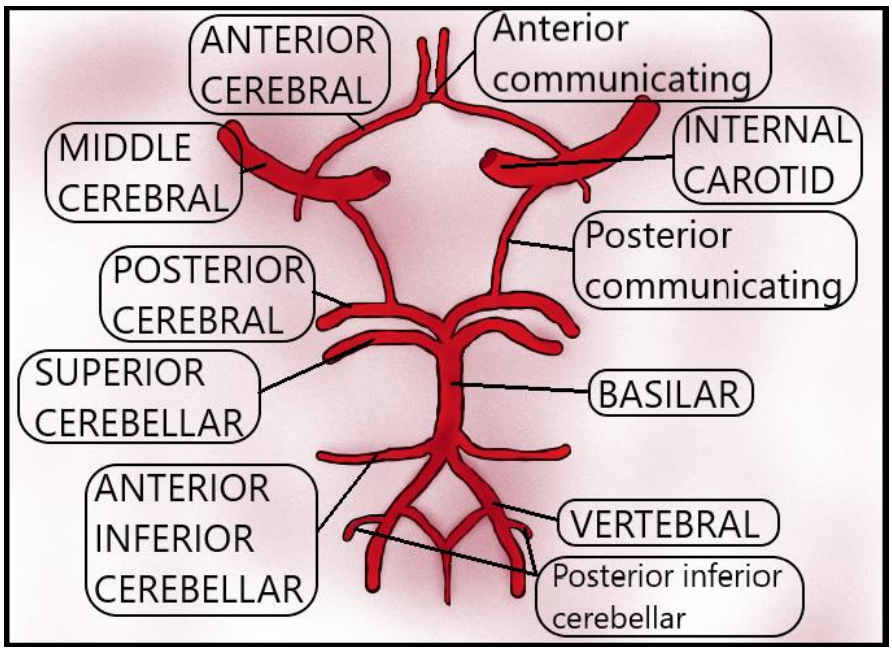


Figure 3. A complete circle of Willis (*lat. Circulus arteriosus cerebri*), showing the major afferent and efferent intracranial arteries connected to the system. Blood from the heart is pumped into the system via two vertebral and internal carotid arteries.

2.5 Sedation in critical care

2.5.1 Pain, anxiety, and *Primum non nocere*

Mechanically ventilated, critical care patients suffer pain and stress as a part of the illness, as a result of the preceding surgery, and from medical procedures, such as intubation tube irritation, bronchoscopy, catheters, and daily handling.[9, 11] Sedation and analgesic medication are utilised to decrease and to provide adequate analgesia. Unfortunately, over-sedation increases morbidity, mortality, time to extubation, and LOS in the ICU.[11, 67] On the other hand, insufficient sedation and analgesia leads to unnecessary patient suffering, a higher risk of spontaneous extubation, and increases the stress experienced among the staff.[11, 67]

One of the main Hippocratic principles in medicine is *primum non nocere*, or "first, do no harm". In critical care sedation and analgesia this translates to adequate sedation and pain medication, while avoiding oversedation, as is reflected by critical care guidelines.[11, 67]

2.5.2 Sedation medication

Sedatives commonly used in critical care include propofol, diazepam, midazolam, and dexmedetomidine. Opioids are the backbone of analgesic treatment, including typically fentanyl, morphine, or oxycodone. Ketamine has become another tool for both sedation and analgesia in critical care.[9, 11, 67, 68]

Propofol is an intravenous anaesthetic, with a rapid onset, a short half-life and minimal accumulation in serum. Propofol does not have an analgesic component, however it does have a moderate and dose-dependent cardiovascular depressive effect.[9, 67, 69, 70] Midazolam is an intravenous benzodiazepine, with an initially short half-life that increases dramatically with repeated or continuous administration. After prolonged midazolam sedation weaning becomes challenging, with both extubation and discharge from the ICU can be delayed.[9, 67, 69, 70]

Ketamine, a drug causing dissociative anaesthesia, has analgesic properties which are mediated through NMDA receptor blockage. Ketamine improves pain relief and reduces opioid requirements, but has side-effects also (nausea, delirium, hallucinations, pruritus, over-sedation). It has a fast onset and is short acting, and unlike most other sedative medications it does not depress respiration.[9, 67, 68] Guidelines recommend using low-dose ketamine as an adjunct to opioid therapy.[9]

Opioids are potent analgesic agents, with several dose-dependent adverse side-effects, such as excessive sedation, depression of the respiratory function, and ileus.[9, 68]

2.6 Neuromonitoring in Critical Care

2.6.1 Objectives of neuromonitoring in critical care

The objectives of neuromonitoring and areas of interest for future research are defined[19, 28] as follows:

- Identify primary and secondary cerebral insults, that may benefit from specific treatment, or affect treatment outcome
- Improve understanding of the pathophysiology of neurological diseases in critical illness
- Provide physiological data to guide critical care
- Assist with prognosis prediction and treatment allocation
- Guide future research and help develop specific therapies for neurological diseases in critical illness

2.6.2 Invasive intracranial pressure monitoring

ICP can be directly monitored via a burr hole in the skull, by placing a stable, pressure transducer intracranially. The benefits include direct and accurate pressure monitoring, and an indirect monitoring of cerebral perfusion pressure (difference of mean arterial blood pressure and ICP). However, the procedure carries a risk of ICH. An increased ICP of over 20 mmHg is associated with increased mortality in TBI[19, 21, 29] and severe HE.[30, 48, 49] Guidelines of TBI recommend considering invasive ICP measurement in all severe TBI patients.[21] Deep coma of non-traumatic aetiology is also often considered an indication for invasive ICP monitoring.[28]

Severe HE has traditionally been considered as an indication for ICP monitoring, however the associated coagulopathy increases bleeding risks notably and the evidence of improved survival is lacking. Invasive ICP monitoring is also typically considered or even recommended in subarachnoid haemorrhage and acute hydrocephalus, and sometimes considered in brain tumours, intracerebral haemorrhages, and central nervous infections. The bleeding risk and the potential for exacerbating brain damage limits the use of invasive ICP measuring. [19, 28, 30, 48, 49]

2.6.3 Non-invasive neuromonitoring

2.6.3.1 Clinical assessment

The basic evaluation of a critical care patient includes physiological monitoring and a clinical neurological examination. Hemodynamic variables, such as blood pressure and heart rate, are associated with both brain insults and sedation, but are typically not sensitive or specific enough for reliable neuromonitoring However, just as a unilaterally dilated pupil or new onset hemiplegia, these hemodynamic changes might be the first indications of developing brain injury.[19, 21, 28]

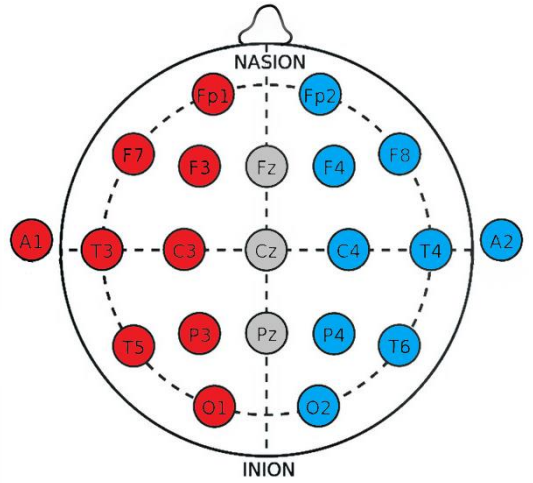
Radiological imaging modalities, such as computer tomography (CT) and magnetic resonance imaging (MRI), are used to diagnose CNS injuries and insults. However, taking a mechanically ventilated patient to the imaging laboratory is challenging and time consuming, and as such these methods are not suitable for continuous or even repetitive monitoring of critical care patients.[21]

2.6.4 Electroencephalography (EEG)

Using scalp electrodes, the voltage fluctuations of the ionic currents of the cortical neurons can be detected by electroencephalography (EEG).[6, 13] Similarly, the voltage fluctuations of the ionic currents of muscle myocytes can be detected by electromyogram (EMG).[71] Measurement is performed as a difference in potentials between two points, the recorded signal is then amplified and filtered (removing movement artefacts and exterior electrical currents). The resulting continuous signal waveforms, frequencies and amplitudes can be categorised in different ways. The most common placement of electrodes is the International 10-20 system for diagnostic purposes (**Figure 4**), while for sedation and neuromonitoring 2- or 4-channel montages are more typical.[6, 13, 23, 71]

Figure 4.

A schematic showing the electrode placements on a patient's scalp according to the International 10-20 EEG system. Electrodes on the left have odd numbers (colour-coded red) and electrodes on the right have even numbers (colour-coded blue). The letters refer to the areas they cover (*i.e.,* "F" = frontal, "T" = temporal, "C" = cranial, "P" = parietal, "O" = occipital, "A" = auricular), and the "z" denotes electrodes which are typically used as references). The 10-20 refers to the distance between electrodes, which equals 10 % or 20 % of the skull distance from the nasion to the inion.



The rhythmic activity of EEG is divided into waves according to frequency (**Figure 5**). Beta waves (β) represent frequencies from 14 Hz to 30 Hz, alpha-waves (α) represent frequencies of 8 to 14 Hz, theta waves (θ) from 4 to 8 Hz, and delta waves (δ) under 4 Hz.[6, 71] In addition, high-frequency gamma waves (γ) represent frequencies of 25 to 140 Hz, and are found in the somatosensory cortex (25 to 35 Hz) and in muscle EMG.[6, 71] Typically, EEG signals are considered to represent the 0.5 to 30 Hz band, while EMG signal represents higher frequencies of 30 to 300 Hz.[6-8, 13]

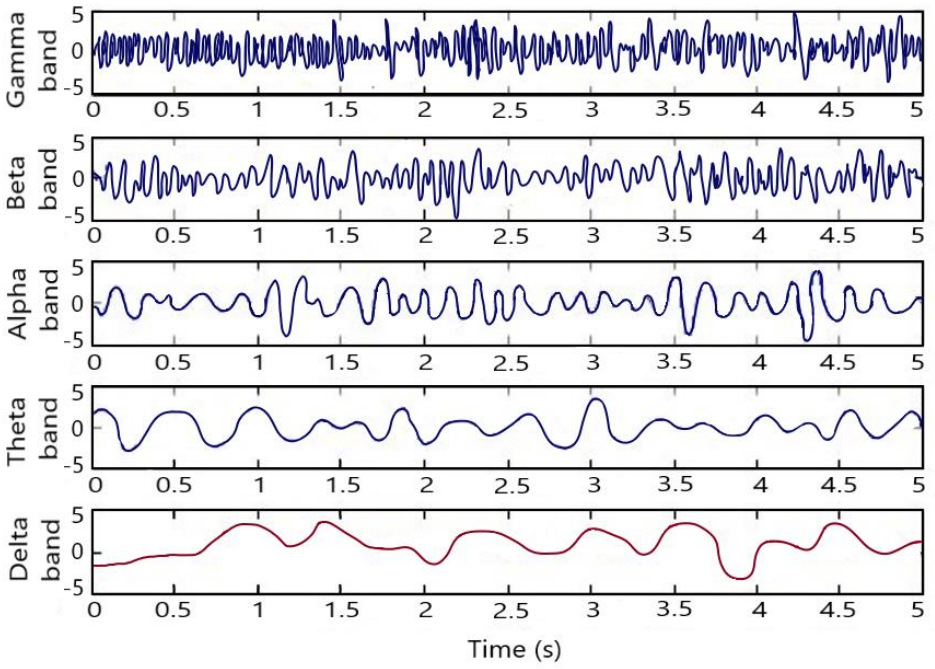


Figure 5. EEG frequency bands from higher to lower frequency range (gamma, beta, alpha, theta, delta), showing example wave forms for each band.

Beta waves are the dominant rhythm in an alert person, while alpha waves emerge typically in a calm, relaxed state with closed eyes. Theta waves are seen with drowsiness, and in relaxed, meditative states, however excessive theta wave activity is typically abnormal and may be associated with diffuse disorders, anaesthesia, or metabolic encephalopathy. Delta waves tend to have the highest amplitude and emerge during sleep and with metabolic encephalopathy.[6, 7, 13, 71]

A multitude of EEG patterns have been identified and named, with attempts to unify findings. One of the basic descriptive specification is the categorization of a EEG waveform into very low (<20 μV), low (20 to 49 μV), medium (50 to 199 μV) or high (≥200 μV) amplitude.[72] Usually a dominant activity with a very low (<20 μV) amplitude is associated with a poor outcome.[72, 73]

Physiological EEG is a combination of millions of individual neuron action potentials, and because of this appear asynchronous. In an epileptic seizure millions of neurons activate simultaneously, creating massive synchronous action potentials, which can be detected as typical large amplitude "spikes", or "sharp waves". The diagnosis of an epileptic seizure from EEG is based on the presence of repetitive spikes with a typical morphology.[72, 73]

Burst suppression is an EEG pattern, where intermittent electrical activity is interspersed with electrocerebral silence. It is a phenomenon seen in different states where cerebral metabolic activity is reduced significantly (*e.g.,* trauma, hypothermia, deep anaesthesia).[13, 37, 73]

Triphasic waves are EEG phenomena, typically seen in HE. Defined as three phases of waves, with each longer than the previous wave, with the highest amplitude (usually over 70 μV) in the positive phase, and with the polarity of the wave form switching for every consecutive wave in a negative-positive-negative pattern. Triphasic waves are usually bilateral and synchronous, seen more dominantly in the frontal regions, and repeat periodically with a 1.5 to 2.5 Hz frequency. Differentiating features from epileptiform patterns are a slightly lower mean frequency (epileptic typically around 2.5 Hz) and an increase of triphasic waves in response to stimuli, which is not seen in epileptiform patterns.[37, 72, 74] An EEG recording with triphasic waves can be seen in **Figure 6**.

Periodic lateralised epileptiform discharges are large (100–300 μV or higher), sharp, and repetitive (0.5 to 1 Hz) EEG potentials in the lateral electrode areas, typically seen in patients with serial seizures and acute structural brain lesions.[37, 75, 76]

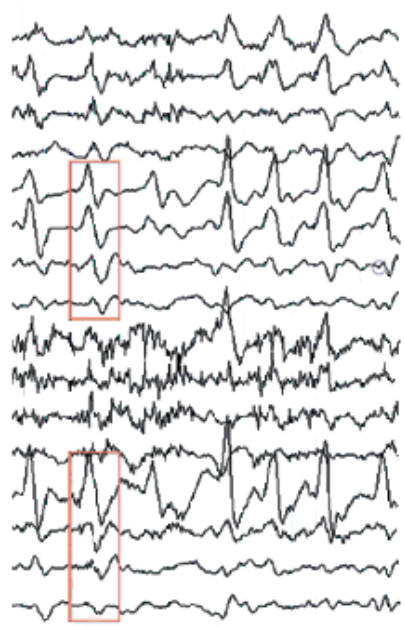


Figure 6. Example EEG recording with typical triphasic waves (marked with a red box).

2.6.4.1 EEG Time and frequency domain algorithms

The raw EEG signal can be processed to facilitate interpretation, typically by deriving the spectral content of the signal for further analysis. The most common technique is power spectral analysis with the fast Fourier transform (FFT). According to the Fourier theorem, any complex wave can be decomposed into the sum of a series of sine or cosine waves, as long as the original waveform is repetitive (**Figure 7**).[13] With a few corrections, this method can be applied to the raw EEG signal to decompose it into its frequency components and present it as a power spectrum of the standing wave. Here in lies the challenge of using FFT for EEG analysis, as it treats the examined epoch as a standing waveform, which is repeated until a new epoch is examined.[13, 77] The FFT method allows examination of the signal activity as a function of frequency. The exact method is described by Rampil *et al.* and a generic example of the frequency content of a wave is presented in **Figure 8**.[6, 13, 23]

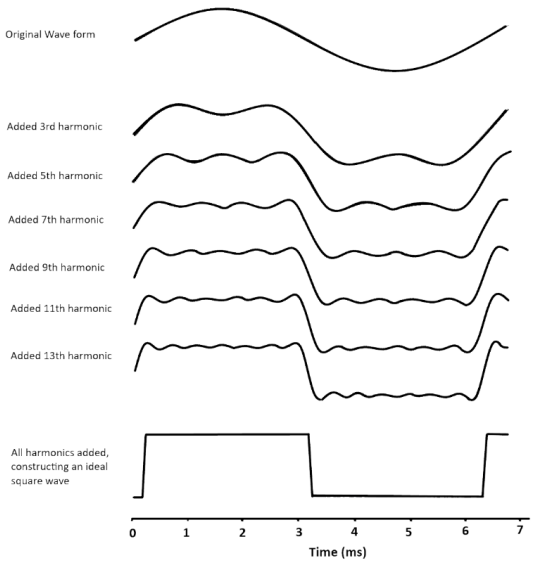


Figure 7. An example of the Fourier theorem of expressing a continuous complex wave as the sum of sine or cosine terms, leading finally to an ideal square wave.

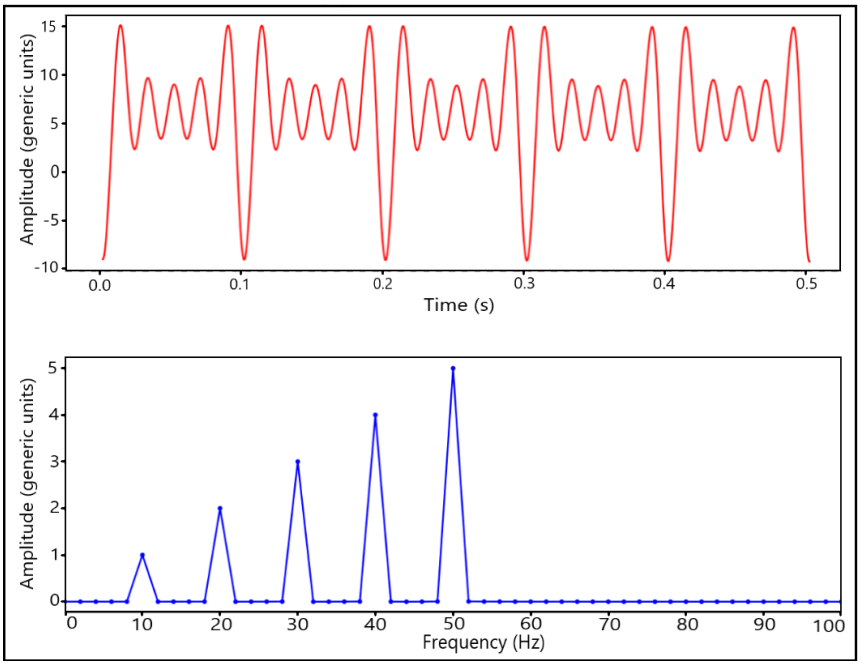


Figure 8. Example of the decomposition of a wave-form signal (upper box, in red) into its component frequencies (lower box, in blue), illustrating in a simplified manner the function of the fast Fourier transform.

Quantitative frequency and power variables can be extracted from the EEG spectra. Typical frequency variables are the *spectral edge frequency 95* (*SEF95*; frequencies under which 95 % of total power is contained), *spectral edge frequency 50* (*SEF50*; frequencies under which 50 % of total power is contained), *median power frequency* (*MPF*; frequencies under which 50 % of total power is contained), *main dominant frequency* (*MDF*; highest mean frequency in the 8 to 15 Hz frequency band). Quantitative power variables extracted from the spectra are *total power* (*TP*; the sum of the power of individual frequencies between 1 Hz and 32 Hz) and relative power band (power ratio between a given frequency band and total power).[23, 77]

As a nondeterministic (meaning that future epochs cannot be exactly predicted based on past epochs) and non-stationary signal (changing wave forms, amplitudes, and frequencies), a rapidly changing EEG signal is not ideally suited for FFT analysis, especially when transient and highly localised signals (such as spikes and bursts) are present. A more suitable technique in these situations is wavelet analysis with discrete wavelet transform (DWT), which allows a high-resolution breakdown of the signal. Wavelets are wave-like oscillations with amplitudes (signal energy) oscillating around the zero level in the time domain, exhibiting certain defined mathematical properties. Similarly to FFT, in which the signal is broken down into sine and cosine functions, a "mother wavelet" can be broken down into a function of the different scale components called "daughter waves". The different wavelet signals can be represented by discrete wavelets, for example the Daubechies wavelets, a family of orthogonal wavelets used to define DWT (**Figure 9**). Daubechies wavelets represent well spiky EEG waveforms, such as epileptiform and triphasic waves, and have been used previously in detecting spiky EEG waves in anaesthetised patients.[78] Whereas FFT only produces information on the frequency content of the signal, DWT produces information of both scale and time of each signal component.[77-79]

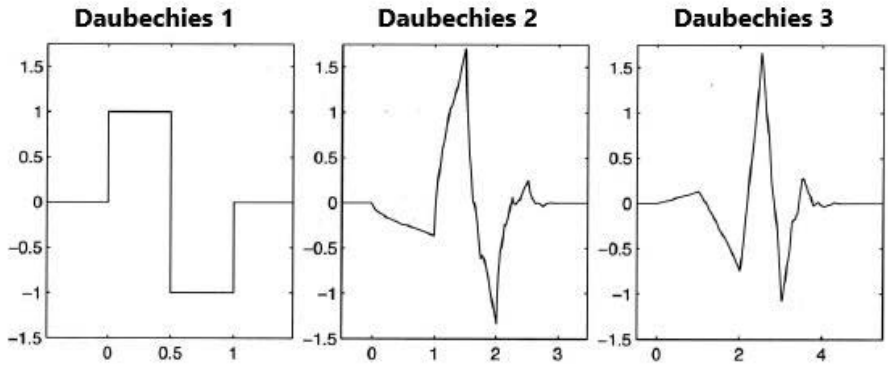


Figure 9. Daubechies 1 to 3 mother wavelets, which can be used with the discrete wavelet transform to achieve a high-resolution breakdown of a signal. These three mother wavelets have a waveform which can represent spiky and triphasic EEG waves, allowing for the quantitative detection of these EEG phenomena.

Mallat's algorithm is used to compute the multiresolution (multiscale) representation of a sampled function on a finite number of scales (from the finest to the coarsest scale), using a cascade of discrete-time low- and high-pass filters. This produces an approximate representation function of the sampled

data. The decomposition produces wavelet coefficients, with the low-pass filtering producing a coarse characterization of the original signal (approximation coefficients), and the high-pass filtering producing a fine degree characterization of the original signal (detail coefficients).[78-80]

2.6.4.2 EEG in clinical use

EEG can be used to evaluate the homeostasis of cortical neurons and the bioelectrical network, and the pharmacodynamic effect on brain function of anaesthesic drugs. Cerebral damage, brain tumours, hypoxia and hypoperfusion, metabolic encephalopathy, seizures, and sedation can all cause detectable and discriminating changes in the EEG. With the use of continuous EEG monitoring, the rapid identification and localisation of brain insult is possible, allowing for rapid interventions and providing a method for monitoring treatment results.[13, 81]

Cortical hypoperfusion (CBF below 22 ml/g/min) suppresses cortical neuron activity, leading to neuron ischaemia, a decrease in EEG amplitude, and a slowing of EEG frequencies. The slowing of frequencies presents as a decrease in the relative power of α and β waves, with a simultaneous increase in the relative power of θ and δ waves). Severe hypoperfusion and ischaemia (CBF 7 to 15 ml/g/min) suppresses the EEG signal all together, causing electrocerebral silence (*i.e.,* no EEG activity).[8, 18, 23, 28, 82]

EEG criteria for cortical ischaemia during cardiovascular surgery (aortic, carotid, cardiac) include a more than 50 % attenuation of the fast background activity (8 to 15 Hz activity of the α and β bands), a reduction of over 60 % of EEG amplitude, a two-fold increase of delta activity (0 to 4 Hz), and severe suppression of all EEG activity.[82]

In a prospective cohort of 151 ischaemic stroke patients, qualitative EEG indices (high delta power, low alpha power, and low relative beta power) were predictive of a poor neurological outcome at discharge and 12 months after the event.[81]

2.6.4.3 EEG and hypothermia

Hypothermia attenuates the EEG signal, lowering progressively the frequency and amplitude of EEG activity. The dampening of EEG by hypothermia begins around 32 ºC, and is clearly detectable around 25 ºC.[83, 84] With a lowering temperature a progressive amplitude decrease is seen, until the eventual cessation of all EEG activity (called electrocerebral silence), which happens around 20 to 22 ºC. There is a high degree of individual variability to these findings, however at 17.5 ºC practically all patients have reached electrocerebral silence.[16, 64, 73, 83-86]

Levy *et al.* showed with a 4-channel EEG in patients undergoing HCA how total spectral power and the peak power frequency of the high-frequency band correlated with temperature (both decreasing with increasing hypothermia), while SEF and average frequency did not correlate with temperature. During hypothermia Levy *et al.* detected a bimodal spectrum, with a high and low frequency peak exhibiting simultaneous changes in two different bands. Because of this bimodality, any univariate descriptors (such as spectral edge or average frequency) cannot adequately represent the EEG changes seen in hypothermia. Based on their results, the researchers concluded also that the change in average voltage between 27 ºC and 37 ºC was only 2 %/ºC. Below 26 ºC several patients exhibited a burst suppression pattern, while under halothane anaesthesia, before electrocerebral silence in deeper hypothermia.[84]

2.6.4.4 EEG and anaesthesia

Drugs used in anaesthesia have notable effects on neuron and myocyte activity, and thus an effect on EEG and EMG recordings, and derived EEG variables. After an initial excitatory stage of deorganised high frequency activity, common EEG patterns seen with deepening anaesthesia include a generalised slowing of frequency, followed by an increase in amplitude, and finally a more pronounced slowing until burst suppression and finally an isoelectric EEG is reached.[8, 13, 68, 73, 78, 87] For an example of the typical EEG patterns seen in deepening inhalation anaesthesia, see **Figure 10**.[68]

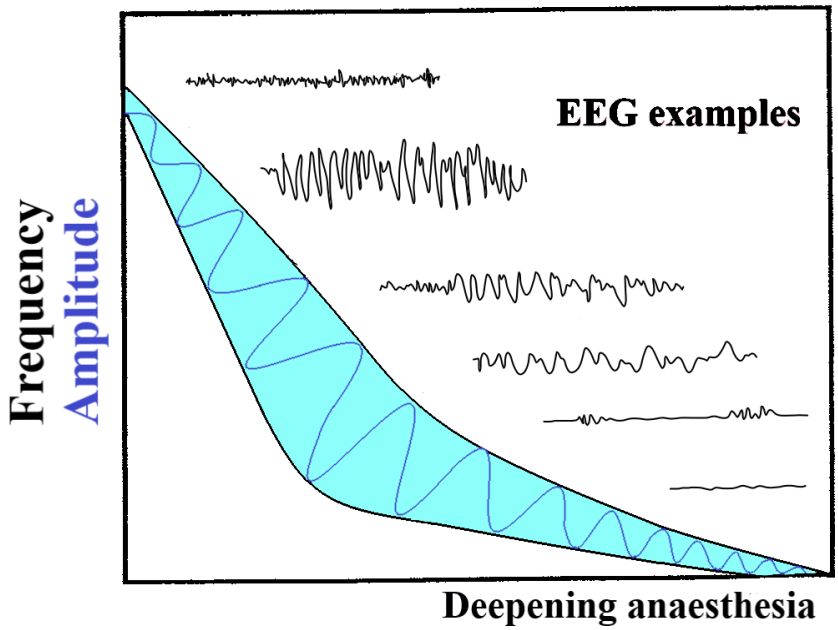


Figure 10. A schematic representation of the EEG changes seen with a deepening level of anaesthesia. Typically, a slowing of frequency and an increase in amplitude is seen at first, followed by a decrease of amplitude, and finally burst suppression and even electro-cerebral silence. Example EEG waveforms are presented at different levels of anaesthesia.

Low dose benzodiazepines increase frontal beta activity, while decreasing alpha activity. Sometimes spikelike activity can also emergence, which is not associated with seizures. At higher doses a generalised slowing of EEG into the theta and delta band is seen. Benzodiazepines do not produce burst suppression patterns typically.[68]

Opioids do not have a pronounced effect on EEG or EMG, but with high doses they express a dose-dependent decrease of EEG frequency into the delta range. Opioids do not influence amplitude, nor do they produce burst suppression or electrical silence even at high doses. While opioids do not have an initial excitatory phase, they slightly and dose-dependently increase muscle tone.[88, 89] Ketamine, an agent causing dissociative anaesthesia and analgesia, increases high-amplitude gamma (30 Hz), theta and beta activity.[68, 88]

Muscle relaxants have minimal effect on cortical electrical activity and the raw EEG, but in a dose-dependent manner attenuate or block all together EMG activity. As EMG causes interference and is even a part of some EEG variables (*e.g.,* BIS, which includes frequencies up to 47 Hz), muscle relaxants can have an indirect effect on EEG-derived variables.[7, 8, 68, 90, 91]

2.6.4.5 EEG and critical care

The primary need for neuromonitoring in critical care can be described as the ability to gain a generalised estimate of cortical function, with the ability to detect potentially damaging changes as fast as possible. Abbreviated 2- or 4-channel EEG montages have become popular in critical care, as the setup is much easier and with fewer electrodes the monitoring assemble is easier to check and maintain. Also, with only a few EEG channels the interpretation of major findings affecting the brain globally are easier to evaluate without years of formal training.[72, 92, 93] Abbreviated montages do not have the diagnostic power of a full montage EEG, but have excellent negative predictive values of over 90 %, and reach an acceptable sensitivity of 60 to 68 % in detecting epileptiform activity.[92-94]

The need for EEG monitoring in critical care has been established, and even partly implemented in modern critical care.[23, 73, 93] The possible benefits of EEG monitoring include detecting critical care encephalopathy (also called acute brain dysfunction and critical care delirium), which is frequent in critical care patients and is associated with increased morbidity and mortality.[1, 95] Similarly, neurological complications (mainly ischaemic strokes) may be detected, which have a major impact on survival, prognosis of critical care, later disability, and HRQoL.[1, 96] Certain critical illnesses have specific EEG abnormalities, which are associated with the overall prognosis. Epileptic seizures in sedated patients are difficult to detect without EEG, and nonconvulsive seizures impossible, but both increase the morbidity and mortality of critical care patients.[1, 96] A continuous EEG monitoring provides continuous real-time data of the physiological function of the brain, even in sedated patients on mechanical ventilation.[6, 37, 92, 95, 96]

A full montage EEG (*e.g.,* the International 10-20 set up) is used in the ICU mainly for on-demand diagnostics, as the full monitoring montage is not very practical for long-term continuous monitoring. The main challenges include a time-consuming monitoring set-up, increased risk of poor electrode contact especially in hairy areas or head parts in constant pillow contact, and the need of a clinical neurophysiologist for interpretation and diagnostics (generally not available after hours).[23, 37, 72, 92]

As a general overview, EEG patterns seen in critical care include a slowing of EEG frequency and a shift to theta and delta patterns, suppression patterns including burst suppression (both associated with sedation and deep hypothermia, as well as pathological conditions), low-amplitude EEG (amplitude <5 μV), electro-cerebral silence, epileptiform spike and seizure patterns, periodic lateralised epileptiform discharges, epileptic seizures, nonconvulsive seizures, and certain wave patterns (such as triphasic waves in hepatic and metabolic encephalopathy).[37, 72, 75, 95] See Hirsch *et al*. for a more detailed explanation of critical care EEG terminology and EEG patterns.[72]

Suppression patterns, including burst suppression, and low-amplitude EEG (amplitude <5 μV) in critically ill patients are associated with a poor outcome.[97-99] Sivaraju *et al*. showed in a large prospective cohort (N = 100) that comatose patients after cardiac arrest with low-amplitude features had all a poor outcome[99], while Rossetti *et al.* showed in a smaller (N = 34) study that patients presenting with prolonged burst suppression after therapeutic hypothermia for cardiac arrest had a poor outcome (positive predictive value for mortality of 100 %; 95% CI 74 to 100 %).[98] A large prospective study (N = 277) of comatose patients after resuscitation from cardiac arrest showed that

the presence of low-amplitude EEG or continuous burst suppression during the first 24 hours was associated with a poor outcome.[97]

Seizures are relatively common, with a prevalence of 3 % for cardiac ICU patients, 8 to 11 % for general ICU patients, and up to 35 % in neuro-critical care patients.[1, 37, 93] The different occurrence rates of epileptic activity in critical care patient populations are presented in **Table 2**.[37] Nonconvulsive seizures are a challenge in critical care, as they are only detectable by EEG and represent approximately 70 to 90 % of all seizure types in critical care.[1, 36, 37] Looking at history, over two decades ago the presence of nonconvulsive seizures increased critical care mortality from 33 % to 57 % in a study with 49 patients, with seizure duration and the delay in diagnosis associated with the increase in mortality.[96] Before the use of continuous EEG monitoring the incidence of nonconvulsive epileptiform activity in critical care patients was around 10 %, while with monitoring up to 67 % of critical care patients experience intermittent nonconvulsive epileptiform activity.[6, 28, 36, 37, 93, 95]

Table 2. Rate of seizures and status epilepticus in critical care patients with different CNS pathologies, using continuous EEG monitoring.

Critical Illness	Seizures	Status epilepticus
Generic ICU patients	4 to 15 %	0.4 %
Ischaemic stroke	5 %	1 to 10 %
Hypoxic-ischaemic encephalopathy	5 to 40 %	30 %
Traumatic brain injury	12 to 50 %	8 to 35 %
Intracerebral haemorrhage	10 to 30 %	1 to 21 %
Subarachnoidal haemorrhage	4 to 16 %	10 to 14 %

2.6.4.5.1 EEG in hepatic encephalopathy

Cirrhotic patients without clinically detectable mental changes have an increase in alpha power, while HE is associated with progressive EEG abnormalities.[100] In mild encephalopathy a diffuse slowing is seen, with a shift of power to theta activity (4 to 8 Hz), and later with progressive encephalopathy a further shift to delta activity (<4 Hz). With further progress a generalised suppression (amplitude <5 μV) or burst-suppression pattern emerges.[30, 100, 101] A typical, but nonspecific finding in HE is the emergence of triphasic waves[101], which together with delta waves and suppression patterns are associated with a poor prognosis. In deeper stages of HE (grade III to IV), nonconvulsive seizures can also be seen.[30, 33, 48, 52, 100, 101]

2.6.4.5.2 EEG in cardiac and aortic surgery

Cardiac and aortic surgery carry a high risk of neurological complications, which may develop prior to or during surgery, or later in postoperative critical care.[5] Preventing and detecting these complications is paramount, as they tend to have a high mortality and disability rate.[5] The outcome of cardiac surgery with significant neurological complications is poor, whether we look at human suffering, HRQoL, wasted resources, or cost of healthcare.[5, 14, 20, 22, 57, 60]

Generalised hypoperfusion during and after cardiac surgery can be detected by EEG as a general decrease in amplitude, and an increase in first theta, and later delta waves. Progressive hypoperfusion and neuron damage leads to suppression, low-amplitude EEG and finally electro-cerebral silence.[84]

Thromboembolic events cause typically localised or hemispheric EEG changes and a generalised slowing of EEG. Seizure-type discharge patterns and spikes develop sometimes after the thromboembolic insult.[75, 102] Unfortunately, as shown in the previous chapters, hypothermia causes similar slowing and suppression patterns, and the circulatory arrest used in aortic surgery causes electro-cerebral silence, decreasing the value of EEG in monitoring during HCA.[16, 58, 64, 83-85]

2.6.4.6 Derived EEG variables

Several variables derived from EEG are in clinical or research use, originally developed for anaesthesia monitoring but later the use has expanded to critical care monitoring. Presented in 1996, one of the most documented is BIS, with Response Entropy (RE) and State Entropy (SE) similarly in wide clinical use. Some of the more experimental variables include Brain symmetry index (BSI)[75, 103, 104] and wavelet subband entropy (WSE).[78, 79, 86, 105]

2.6.4.6.1 BIS

Originally developed to monitor hypnosis and later to reduce awareness during anaesthesia, the BIS is a complex parameter combining subparameters from the time domain, frequency domain, and spectral subparameters into a single variable (see Rampil *et al.* 1998).[7, 13] Included frequencies (0.5 Hz to 47 Hz) overlap slightly into the EMG low frequency bands (frontal muscle EMG frequency range of 30 to 300 Hz).[71] The exact algorithm for calculating BIS has not been published, but the complex formula has gone through several revisions, includes advanced artefact rejection techniques, and produces a single dimensionless value from 0 (isoelectric EEG, electrocerebral silence) to 100 (alert and oriented). The variable correlates with sedation, while remaining insensitive to the chosen specific anaesthetic agent. The obvious exception to this is ketamine, which disturbs the calculations by increasing gamma activity.[7] Different BIS values have been suggested for different levels of sedation and anaesthesia, with a BIS between 40 to 60 recommended for general anaesthesia (**Figure 11**).[6, 7, 13, 106, 107]

BIS	Sedation	Description
100		Awake.
	Anxiolysis	Response to normal voice.
80	Moderate sedation	Response to loud commands or mild to moderate physical stimuli.
60	Deep sedation	Low probability of explicit recall. Unresponsive to verbal stimuli.
40		
20		Burst suppression.
0		Electro-cerebral silence, suppressed

Figure 11. A schematic showing the recommended BIS Ranges associated with the level of sedation and anaesthesia, with BIS 40 to 60 recommended for surgical anaesthesia.

Hundreds of studies, including several reviews, have shown the ability of BIS to monitor cortical activity during anaesthesia, to reduce the use of anaesthetics (~20 %), to shorten extubation time (~35 %), and to shortened recovery time from anaesthesia.[7, 8, 106]

In a study comparing elective CABG patients operated during mild (32 ºC, $n = 14$) or normothermic ($n = 14$) CPB, Schmidlin *et al.* found that the hypothermic patient group had lower BIS values. For the hypothermic group the BIS median was 41 (95% CI 39 to 42), while the normothermic group had a median BIS of 49 (95% CI 48 to 51); $p < 0.0001$. There is, however, a possibility that the lower BIS values are partly associated with deeper sedation, as slower metabolism during hypothermia might increase blood concentrations of the anaesthesia agents.[108]

The usefulness of BIS in monitoring and detecting neurological diseases has been speculated on, with studies showing abnormally low BIS values in patients with severe brain injury and dementia. Critical care in the ICU presents challenges for EEG-based brain monitoring, including electrical interference, lack of neuromuscular blockage, metabolic disturbances, and complex neurological disease processes. Traditionally, frontal muscle EMG has been considered an artefact affecting BIS calculations.[7, 8, 71, 107] Liu *et al.* showed that neuromuscular blocking agent administration decreased BIS, SEF, RE, and EMG activity in anaesthetised patients.[91]

Neurological outcome prediction with BIS has shown some value. Patients treated with hypothermia after cardiac arrest who had a very low BIS (BIS <10) during the first 48 hours had a poor outcome, while patients with a higher lowest BIS value (BIS 10-35) had a good outcome.[109] Other studies have shown similar possible associations of increased mortality with low BIS values after cardiac surgery.[8] A reduction of BIS might be associated with neuron ischaemia, but confounding factors (anaesthesia, neuromuscular blockage, hypothermia) and a 30 to 60 s delay in BIS devices present a problem.[8, 82]

2.6.4.6.2 Entropy

Entropy in physics describes the amount of disorder in a system, by quantifying the number of microstates that characterise a system. The concept of entropy can be applied to the power spectrum, and in this context the derived entropy variable is called spectral entropy.[110] As an example, the spectral entropy of zero would be a sine wave (single frequency component, completely regular) while white noise (containing all possible frequencies) would have high irregularity, and thus high spectral entropy.[87, 111]

In an EEG signal, spectral entropy describes the number of different frequencies within the measured EEG wave. In an awake patient, EEG is highly irregular and contains many different frequencies, and has thus a high spectral entropy. With increasing depth of anaesthesia, EEG slows down and begins to show more regular patterns, thus decreasing the spectral entropy. Very deep anaesthesia induces burst suppression and finally full suppression (electrocerebral silence), with the entropy of the signal approaching zero.[87, 111]

The spectral entropy of an EEG signal can be calculated either in the time domain or in the frequency domain. The commercial Entropy monitor uses an algorithm based on combined and balanced time-frequency spectral entropy to calculate the parameters in two frequency ranges: the SE from 0.8 to 32 Hz (reflecting mostly EEG activity) and the RE including frequencies up to 47 Hz (reflecting EEG and frontal muscle EMG activity). Due to a different time window (SE time window 15 to 60 s, RE time window 1.92 to 15.36 s), RE responds faster to EEG changes. The RE parameter ranges from 0 (total suppression) to 100 (awake), while the SE parameter ranges from 0 to 91. Decreasing values indicate deeper anaesthesia.[6, 87, 111]

The Entropy parameters (RE, SE) have performed well in detecting loss of consciousness, estimating the depth of anaesthesia during surgical anaesthesia, and detecting burst suppression in EEG, comparing well with the performance of BIS.[87] In a study ($N = 30$) of hypothermia-treated patients resuscitated from cardiac arrest, at 24 h a slightly higher RE and SE were predictive of a good neurological outcome (RE $p = 0.011$, SE $p = 0.008$).[86] A case report of two patients undergoing urgent CABG showed an abrupt decrease to isoelectric values in RE and SE during anaesthesia. The low values persisted throughout the intraoperative period, both patients showed delayed awakening and on a postoperative brain CT both patients had new temporo-parietal cerebral infarctions.[112]

2.6.4.6.3 Wavelet subband entropy

WSE is a multiresolution decomposition of the DWT, which can be used to detect transient, non-stationary EEG signals, such as spikes and bursts. The variable can be derived from a certain frequency range (for EEG phenomena, typically from 4 to 32 Hz), and be used to detect certain specific waveforms by choosing a suitable mother wavelet (for instance Daubechies 3 for epileptiform spikes).[78, 79, 86]

The variable gives a numerical value, which decreases with increasing transient patterns (spikes, bursts) in a continuous EEG recording. In a study of sevoflurane-induced anaesthesia, WSE was used successfully to detect and quantify epileptiform EEG activity in continuous EEG recordings.[78]

A study of hypothermia-treated patients ($N = 30$) resuscitated from cardiac arrest used WSE to detect epileptiform EEG and predict treatment outcome. A good outcome was associated with slightly higher WSE values 24 to 48 h after resuscitation, while all patients with status epilepticus had lower WSE values and a poor outcome (none of them survived). For outcome prediction WSE sensitivity was reasonable (67 to 89 %), but specificity (52 to 71 %) and the positive prediction value (44 to 50 %) were low.[86] Another study showed higher WSE values in hypothermia-treated cardiac arrest survivors.[105]

2.6.4.6.4 Brain Symmetry Index

There exists a level of asymmetry between the activity of the two brain cortices even in normal, physiological conditions. This is based on slight differences in cortical anatomy, and local activity in specific brain areas. This symmetry, or lack of it, can be described by a single digit variable called BSI, which is derived from the difference of the left and right hemispheric spectral power (calculated by FFT, 1 to 25 Hz range). The variable reaches values from 0 to 1, with the lower bound of 0 representing perfect symmetry in all channels, and the upper bound of 1 representing maximal asymmetry.[103, 104, 113, 114] The exact mathematical function of BSI was defined[104] and later developed into the revised BSI function (r-sBSI)[114] by van Putten *et al.*, and finally a single channel, pairwise averaged revised spatial BSI (pdBSI) was further developed by Sheorajpanday *et al.*[103] All formulas are presented in **Figure 12**.

$$\mathrm{BSI}(t) = \left\| \frac{1}{N} \frac{1}{M} \sum_{i=1}^{N} \sum_{j=1}^{M} \frac{R_{ij}(t) - L_{ij}(t)}{R_{ij}(t) + L_{ij}(t)} \right\|$$

Brain Symmetry Index (BSI)

N is the number of channel pairs and *M* the number of Fourier coefficients.

$$\text{r-sBSI}(t) = \frac{1}{K} \sum_{n=1}^{K} \left| \frac{R_n^*(t) - L_n^*(t)}{R_n^*(t) + L_n^*(t)} \right|$$

with

$$R_n^*(t) = \frac{1}{M} \sum_{\mathrm{ch}=1}^{M} a_n^2(\mathrm{ch},t)$$

Revised BSI (r-sBSI)

a_n(ch,t) is the Fourier coefficient with index *n* of channel *ch*, evaluated at time *t*, corresponding to a particular epoch [*t* − *T*,*t*] with duration *T*. Similar expression for both hemispheres.

$$\mathrm{pdBSI} = \frac{1}{NM} \sum_{j=1}^{M} \sum_{i=1}^{N} \left| \frac{R_{ij} - L_{ij}}{R_{ij} + L_{ij}} \right|$$

Single channel pair averaged revised spatial Brain Symmetry Index (pdBSI)

R_{ij} and L_{ij} are the FFT based power spectral densities of the signal, obtained from a right and left channel of a homologous channel pair (with *i* = 1, 2, ..., *M*) at frequency *j* (or Fourier coefficient, with index *j* = 1, 2, ..., *N*).

Figure 12. Presenting three versions of the Brain Symmetry Index function, the original on top and the two revised BSI formulas below. The exact differences are explained in the accompanying text, and the revisions increase the sensitivity of detecting hemispheric EEG changes. The first revised (r-sBSI)[114] was used in the **II** study.

In physiological conditions of a healthy adult, normal BSI is 0.042 ± 0.005.[115] With very low amplitude (<20 μV) EEG, BSI is extremely sensitive to even small changes in amplitude symmetry and therefore reliability is limited in very-low amplitude settings.[113] During HCA with SCP a hemispheric asymmetry can be detected during active cooling and warming, which is not associated with neuron damage.[66] Furthermore, BSI can react to most forms of cortical damage, and other significant hemispheric changes, and is therefore not ischaemia-specific.[115] In a study testing several different parameters, BSI performed best (90% sensitivity) in detecting unilateral temporal seizures.[116]

Brain damage is typically unilateral, or at least affects irregularly different areas of the brain, leading to notable cortical asymmetry between the two brain cortices. The predictive value of BSI to detect hypoxia and an increased risk for neurological complications was first shown in carotid endarterectomy, where BSI has been suggested as an additional way to assess the need for perioperative shunting. In a retrospective study of 57 patients undergoing carotid endarterectomy, a BSI increase of ≥0.06 was associated with visual changes in EEG and two patients with a BSI increase of ≥0.16 suffered neurological complications.[104]

Stroke reperfusion with successful thrombolysis is an excellent example of a situation where notable hemispheric EEG differences should be detected. In a pilot study, acute ischaemic stroke patients (*N* = 16) had higher initial BSI values (mean BSI 0.20, range 0.10 to 0.38), which either stayed constant or decreased significantly following successful reperfusion. The BSI values correlated in a linear manner with clinical improvement (assessed with the National Institutes of Health Stroke Scale, or

NIHSS) after thrombolysis, with a correlation coefficient ρ of 0.74 ($p < 0.01$).[113] Similarly, BSI of the subacute phase of a ischaemic stroke (2 to 4 hours after the insult) correlated with clinical improvement (NIHSS) during the first 24 h after acute ischaemic stroke ($\rho = 0.86$, $p < 0.01$).[115]

Another, larger study ($N = 110$) showed that the pair-wise single channel pdBSI had prognostic value in determining the functional outcome of patients 6 months after suffering an ischaemic stroke, which was determined using a modified Rankin Scale. The correlation coefficient of pdBSI measured after ischaemic stroke with the 6 month modified Rankin Scale score was $\rho = 0.47$ ($p < 0.0005$), and pdBSI had a strong, independent association with permanent disability 6 months after suffering a ischaemic stroke (OR 4.07, 95% CI 1.32 to 12.58; $p = 0.015$).[117]

2.6.5 Near-infrared spectroscopy (NIRS)

Light with a slightly longer wavelength than visible light is called near-infrared light (wavelength 750 to 2500 nm). Jöbsis first showed how near-infrared light penetrates organic tissue (including bone, myocardium and brain matter) with relative transparency, while the haemoglobin of red blood cells absorbs the radiation energy of near-infrared light.[118] Using these properties, near-infrared spectroscopy (NIRS) is used to estimate noninvasively regional cerebral tissue oxygen saturation (rSO2) by calculating the light (700 to 1000 nm) absorption spectrum of oxygenated and deoxygenated haemoglobin in the tissues of the frontal lobe.[20, 119] The physics of the phenomena is based on a modified version of *Beer-Lambert's Law*, which states that a portion of light transmitted through a solution containing a coloured compound is absorbed by the compound.[20, 120] The absorption spectra for deoxyhaemoglobin ranges from 650 to 1000 nm and for oxyhaemoglobin from 700 to 1150 nm, with the maximal differentiation in absorption between 700 and 850 nm (**Figure 13**).[20, 118-122] A schematic of the function of a NIRS transmitter is presented in **Figure 14**.[120]

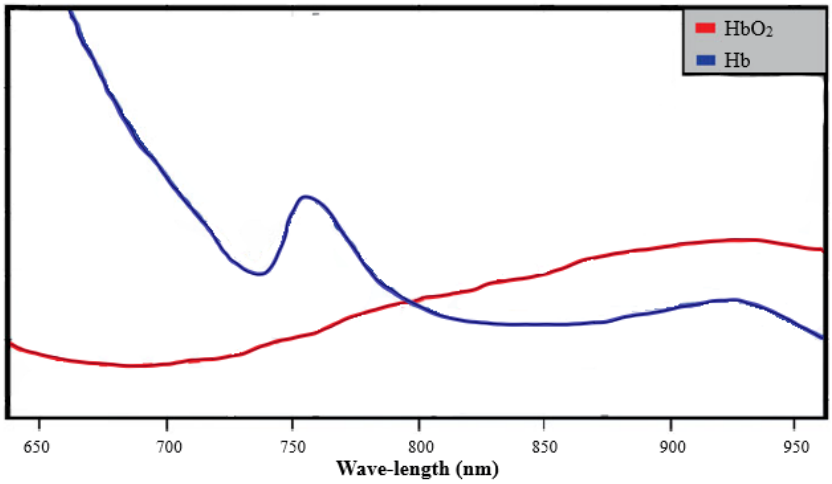


Figure 13. Optical Properties of oxyhaemoglobin ($Hb0_2$, red line) and deoxyhaemoglobin (Hb, blue line), showing the distinctive absorption patterns at different light wave lengths.

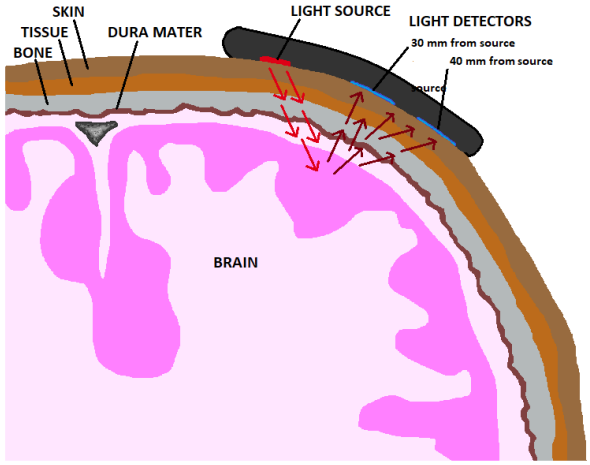


Figure 14. A schematic of a NIRS monitor, depicting how the emitted near-infrared light from the NIRS monitor's light source passes through the skin and skull, partially reflecting from intracranial tissue and blood, and then detected by the two receptors. The emitted light, after absorption, reflection, scatter, and frequency shift, is then detected and analysed to provide an estimate of tissue oxygenation.

The haemoglobin content of larger blood vessels absorbs all near-infrared photons, thus NIRS examines primarily small vessels with a diameter of less than 1 mm (arterioles, venules, and to a small extent capillaries). With a penetration depth of a few centimetres for near-infrared light in human tissue and given the greater volume of the venous system in the frontal lobe at this depth, the NIRS evaluation area includes approximately 85 % of cerebral tissue[119, 123], and reflects mostly venous oxygenation (approximately a 75-85 % contribution).[119, 120, 123] NIRS cannot differentiate between venous and arterial blood, but it does not require pulsatile flow and maybe therefore used in nonpulsatile states (such as cardiac arrest, CPB).[120] NIRS monitoring of the equilibrium between oxygen supply and consumption is continuous and bilateral, giving separate estimates for the left and right frontal lobe.[20] The signal is contaminated by abnormal collection of haemoglobin or other chromophores, for instance pools of haemorrhagic blood, hyperbilirubinemia in jaundice[124], and impaired venous return in cardiac tamponade create large photon sinks that affect NIRS measurements.[20, 23, 119-121, 125]

2.6.5.1 Neuromonitoring with NIRS

The traditional use of NIRS monitoring has been in cardiac and aortic surgery to guide initiation of intraoperative neuroprotective strategies (such as SCP, increasing blood pressure, shorter operating times), but in recent years it has seen new applications in carotid surgery, acute brain injury and functional neuropsychology.[23, 25, 119, 120, 124, 126] The NIRS values range from 0 to 100 % saturation, with a normal value of 60 to 80 %.[121, 123-125] NIRS is affected by changes in blood oxygenation,

hypothermia, blood pressure, cerebral pressure autoregulation, and haemoglobin levels. During CPB up to 85 % of rSO2 is determined by the level of Hb, temperature, blood pH and the partial pressure of carbon dioxide in blood.[119, 121, 125, 127]

NIRS monitoring is based on detecting trend changes in rSO2, and specific saturation levels have not been reliably linked to neuron damage or outcome.[23, 25, 119] Traditionally a drop of 20 % from baseline is considered significant, and a rSO2 lower than 50 % has been associated with an increase in ischaemic stroke[20, 119, 121, 124] and prolonged LOS[128] in cardiac surgery, and an increase in the incidence of perioperative ischaemic strokes in aortic surgery.[126, 129] Depending on local practise, the acceptable range for perioperative rSO2 is typically around 55 to 80 % during cardiac and aortic surgery. A notable decline of over 20 % from the baseline, or a decline to very low values (below 20) is usually met with corrective interventions, such as initiation of SCP.[20, 122, 125]

Looking at the other end of the equation, actively keeping rSO2 levels higher than 75 % from baseline during cardiac surgery is associated with a decreased hospital LOS[130] and even a decrease in morbidity and mortality.[131]

A retrospective review compared the outcomes of CABG surgery before (n = 286) and after (n = 332) the application of NIRS monitoring, with a correction protocol (increasement of blood pressure and perfusion flow) for significant desaturation (drop of >20% in rSO2 values). The incidence of major neurological complications was significantly (p = 0.03) higher in the non-monitored group (6.1 %) than in the monitored group (3.0 %), with an even more pronounced difference in favour of the monitored group in short-term cognitive decline and seizures (3.0 % versus 0.3 %; $p < 0.001$). However, these significant results are probably partly explained also by the development of surgical, anaesthesiogical and critical care techniques.[132]

In critical care the use of NIRS is not established.[29, 120] In cardiac tamponade, one of the first warning signs is a sudden fall in rSO2, suggesting that a continued NIRS monitoring after cardiac or aortic surgery might be helpful.[133, 134] In cardiac arrest survivors a lower rSO2 was associated with a poor neurological outcome (58 % versus 68 %; $p < 0.01$).[135] Postoperative brain hypoxemia after major neurosurgery can be detected by NIRS.[29]

While NIRS seems a promising tool for non-invasive and continuous neuromonitoring, it has several significant hindrances. There is considerable intra- and interpatient variability in measured NIRS values, with a lack of clearly definable cut-off values.[20, 23, 120] On the other hand, NIRS works even in the absence of flow, and is the only non-invasive monitoring method which works during HCA.[20, 23, 120]

2.6.5.2 Hemispheric asymmetry of NIRS

An interesting application of left and right NIRS monitoring is detecting hemispheric asymmetry in rSO2 values, signifying a cortical imbalance of cerebral oxygenation. Spatial NIRS analysis, or hemispheric asymmetry, has been actively used in functional neuropsychological research.[136] Hemispheric differences have been noted in only a few cardiac surgery studies previously, and asymmetry in and of itself has not been studied in cardiac surgery.[126, 137, 138] Patients with severe carotid stenosis may present with a hemispheric asymmetry or develop asymmetry even from head rotation during anaesthesia.[121, 139] In a study of 46 head-injury patients, a hemispheric difference of NIRS was used to detect intracranial haematomas, and the detected asymmetry resolved after surgical evacuation.[140]

2.6.6 Transcranial Doppler ultrasound

Doppler shift is a phenomenon described first in 1842 by a physicist called Christian Doppler. In essence, it is the change of frequency of a wave due to the movement of the wave source in relation to the observer. Movement "bunches together" waves in the direction of the movement, causing an increase in frequency, while waves travelling in the opposite direction take more time to reach the observer, resulting in a reduced frequency. A real-life example of the phenomenon is heard as the higher pitched siren of an approaching ambulance, which then becomes significantly lower as the ambulance passes the observer.

In medical use, Doppler Ultrasound can be used to noninvasively detect changes in blood flow.[141] As the temporal bone is partially ultrasound lucent, the temporal window can be used to measure the flow in the middle cerebral artery, which provides up to 70 % of the blood flow to the ipsilateral cerebral hemisphere.[23] Transcranial Doppler (TCD) measures changes in the blood flow using 2 MHz ultrasound and the Doppler shift to assess changes in the flow velocity of red blood cells.[18, 23, 82, 141, 142] Neuromonitoring with TCD has been used during CPB and carotid endarterectomy, after traumatic head injuries, ischaemic strokes, subarachnoid haemorrhages, and in HE.[18, 19, 142] Limitations include being an operator-dependent technique, low reproducibility, and an absence of a signal during severe hypotension. Finally, approximately 10 % of adult patients cannot be assessed by ultrasound through the temporal window at all.[23, 82]

2.6.6.1 Pulsatility Index

Pulsatility Index (PI), also called the Gosling index, is a variable used as a non-invasive and indirect estimation of blood flow in the cerebral arteries. It is calculated by measuring the systolic and diastolic flow velocities of the Doppler ultrasound waveform of the middle cerebral artery, using as a window the thin temporal skull called the pterion. The formula is presented in **Figure 15**.[141, 142]

$$\text{Pulsatility Index (PI)} = \frac{\text{Systolic flow velocity - diastolic flow velocity}}{\text{Mean flow velocity}}$$

Figure 15. The mathematical formula for calculating the Pulsatility Index from the systolic and diastolic velocity of arterial blood, as measured by transcranial Doppler ultrasound.

The normal value of PI is 0.5 to 1.19, with proximal obstructions decreasing the value and distal partial obstructions increasing the value. A pathologically elevated PI is associated with an increased ICP and increased mortality.[142]

2.6.6.2 Neuromonitoring with transcranial Doppler ultrasound

In HE a PI over 1.6 carries a poor prognosis.[48] A small ($N = 6$) study of hepatic failure patients showed that in the two patients with fulminant failure and a deteriorating disease progress, the PI values increased from baseline (~0.55 to 0.65) to over 1 (~1.0 to 1.2).[143] In another study of 27 ALF patients undergoing orthotopic LT, a median (IQR) decrease of 20.8 % (6.9 to 28.0 %) in PI along with a correction of HE was observed after transplantation.[144] In cardiac and aortic surgery, TCD is a potential monitoring tool to indirectly evaluate cerebral blood flow during surgery.[58] In cardiac arrest

patients treated with hypothermia ($N = 30$), a higher median PI was associated with a poor outcome (1.18 versus 0.85; $p = 0.004$).[86] Similarly, a higher PI was associated with poor neurological outcome at hospital discharge in 42 comatose cardiac arrest survivors (PI 1.49 versus 1.12; $p = 0.01$).[145] In TBI, several studies have shown that a PI of over 1.2 is associated with a poor neurological outcome (OR 3.87, 95% CI 2.97 to 5.04; $p < 0.00001$).[146]

As bubbles in the blood stream are highly echogenic and are easily picked up by TCD as high-intensity transient signals, Doppler ultrasound can be used to reliably detect microemboli.[147, 148] High counts of microembolic signals are associated with thromboembolic complications[142, 147-149], postoperative neuropsychological symptoms after CABG[147, 149, 150], longer hospital stays[147], and postoperative strokes.[147-149] The detection of microemboli during cardiac surgery and cardiopulmonary perfusion led to the application of arterial line filters, which have become a part of the standard setup of cardiac surgery.[150]

2.6.7 Biomarkers associated with neuron damage

Certain biochemical markers are released by damaged cells of the central nervous system, and the blood levels of these markers can be measured to detect brain injury. An optimal neurobiomarker would be released only from neurons, would be small enough to pass the BBB easily, and would have a short, uniphasic half-life to allow discrimination from later neuron injury. In practise, none of the potential neurobiomarkers have all these properties, some (NSE, S100β) are released from other sources, and most do not pass freely through a healthy BBB. As neuron damage is often accompanied by BBB dysfunction, large molecules, which normally cannot pass the BBB, may be released into the blood stream during acute brain injury.[151, 152]

The two most widely known and researched neurobiomarkers are the neuron-specific enolase (NSE) and protein S100 beta (S100β). For a schematic representation of the kinetic profile of NSE and S100β after a brain insult, see **Figure 16**. A lot of other potential neurobiomarkers have been identified, but none of them have performed significantly better, nor have they been adopted in clinical work.[19, 73, 151, 153-156]

The main challenges of NSE and S100β as serum neurobiomarkers are the release from other sources, and the delay in detecting neuron damage. The main challenge of the related research is the varying design of different studies, with varying outcome variables, different laboratory analysis kits, and differing normal values of the potential neurobiomarkers.[151, 153, 156]

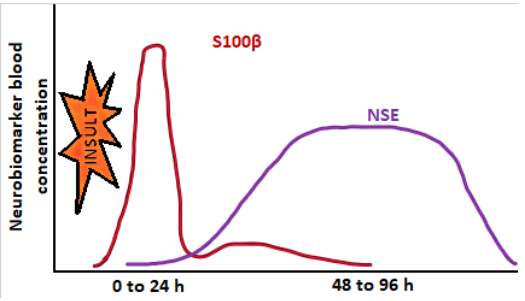


Figure 16. The blood concentration and kinetics of two biomarkers, neuron-specific enolase (NSE, purple) and S100β protein (red), after a brain insult causing neuron damage.[73, 153, 154, 157, 158]

2.6.7.1 Neuron-specific enolase

A glycolytic enzyme, NSE is a 78 kDa γγ-isoform of enolase, and is found predominantly in neurons, but is also secreted by neuroendocrine cancer cells (small-cell lung cancer, neuroblastoma). As it is also present in platelets and erythrocytes, haemolysis increases serum concentrations independently. NSE is a reasonably big molecule, and does not cross an intact BBB easily, which is evident in epileptic seizures where the spinal fluid concentration of NSE is increased, but the serum concentration is not. The biological half-life of NSE is approximately 24 hours.[152-154, 158] In normal conditions the serum concentration of NSE is <18 µg/l. Despite limitations, NSE is mainly released from damaged neurons and can be used as a potential neurobiomarker.[73, 151-154, 157, 158]

2.6.7.2 S100β protein

The S100β protein is a small acidic 21 kDa dimer protein that belongs to a family of calcium-ion binding proteins, named for their solubility in 100% saturated ammonium sulphate at neutral pH. Various isoforms exist, depending on the chain structure (two chains combining α, β or γ chains). The ββ-form occurs mainly in astroglia and Schwann cells, the αβ-form in astroglia cells. The S100β used as a neurobiomarker combines two isoforms – the S100αβ1 and S100ββ. The biological half-life of S100β protein is 25 ± 5 minutes and is not dependent on kidney function.[152-154, 158] In normal conditions the serum concentration of S100 is <0.05 to 0.15 µg/l. Approximately 90 % of all S100β is found within the brain, but small amounts have been identified in adipose tissue, skin, melanoma tumours, and T-lymphocytes.[73, 151-154, 157, 158]

2.6.7.3 Neuromonitoring with biomarkers

High, and especially increasing, serum concentrations of NSE and S100β have been linked to brain injury and poor neurological outcome after cardiac surgery and CPB[151, 153], surgery of the thoracic aorta[153], ischaemic stroke[159], and cardiac arrest.[73, 86, 154, 157, 158] Following neuron damage, the peak levels of NSE occur after 48 hours and the peak levels of S100β occur after 48 to 60 hours. Based on the body of evidence of slightly differing study results, the commonly accepted threshold of NSE for *possible* neuron damage is 33 µg/l, however several studies have shown good outcomes in patients with NSE levels as high as 80 µg/l. For S100β, the optimal cut-off point for predicting neurological outcome remains undefined, with previous studies suggesting values ranging from 0.12 to 0.80 µg/l.[19, 73, 151-154, 156, 157, 159, 160]

A study of hypothermia-treated cardiac arrest patients (n = 107 for S100β, n = 102 for NSE) a poor outcome was associated with a S100β of over 0.51 µg/l at 24 h (specificity 96%, sensitivity 62%), and with a NSE of over 28 µg/l at 48 h (specificity 100%, sensitivity 67%), and finally with a rise in NSE of over 2 µg/l from 24 h to 48 h (OR 9.8, 95% CI 3.5 to 27.7).[158] In another cardiac arrest cohort (N = 195) lower NSE and S100β levels were associated with a good outcome (**Table 3**).[157]

Table 3. Biomarkers (NSE, S100β) and neurological outcome in patients resuscitated from cardiac arrest (N = 195).

Timepoint	Biomarker	Good outcome	Poor outcome	*p*
At admission	NSE	28.0 (85 to 253.0)	36.9 (6.6 to 170.4)	0.059
	S100β	2.25 (0.15 to 19.40)	7.66 (0.20 to 145.00)	<0.0083
24 h after ROSC	NSE	21.7 (5.7 to 84.5)	34.9 (4.1 to 935.9)	<0.0083
	S100β	0.30 (0.05 to 1.30)	1.78 (0.20 to 124.00)	<0.0083
72 h after ROSC	NSE	15.6 (5.4 to 63.9)	60.98 (7.0 to 436.4)	<0.0083
	S100β	0.20 (0.10 to 0.50)	1.40 (0.09 to 102.00)	<0.0083

Results are given as median (range).
NSE = Neuron specific enolase; ROSC = return of spontaneous circulation; S100β = S100 protein.

However, SIRS and reversible BBB dysfunction associated with CPB also increases the serum concentrations of the neurobiomarkers, even without detectable neuron damage.[153, 161, 162] The time course of both markers was described in 1999 by Gao *et al*. in a study of 18 CABG patients operated during HCA with CPB. NSE and S100β followed similar time courses, increasing sharply, and reaching peak concentrations at the end of rewarming (mean WSE 25.5 and S100β 1.65 µg/l), decreasing significantly by the end of the operation, and reaching normal levels by the second postoperative day (POD) (**Figure 17**). None of the patients suffered neurological complications.[161] In a study of 21 on-pump (CABG, with CPB) and 20 off-pump (OPCAB, without CPB) coronary artery bypass surgery patients, the postoperative levels of neurobiomarkers were significantly higher in the group with CPB (for NSE $p < 0.001$, for S100β $p = 0.03$). For the on-pump group the peak mean NSE was 15.9 ± 1.8 µg/l and mean S100β was 4.0 ± 1.5 µg/l, while for the off-pump group the mean NSE was 8.0 ± 2.3 µg/l and mean S100β was 0.83 ± 0.21 µg/l.[162]

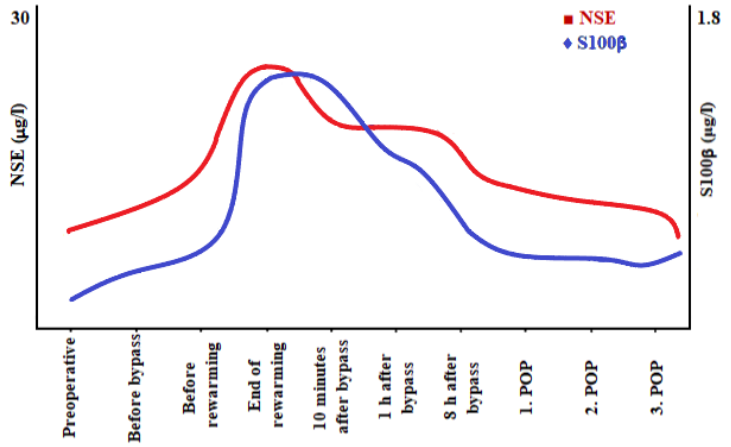


Figure 17. Time-course of the blood concentration of neuron-specific enolase (NSE, red) and S100β protein (blue) after coronary bypass surgery with hypothermic circulatory arrest and selective cerebral perfusion.

In a study of 190 patients undergoing cardiac surgery (elective CABG and valve surgery) by Georgiadis *et al*., postoperative S100β and NSE were higher in patients with a poor neurological outcome (new ischaemic stroke or coma). S100β specifically had an 89 % sensitivity and a 79 % specificity in identifying these patients.[163] In a cohort of cardiac surgery patients suffering a perioperative ischaemic stroke ($N = 20$), high levels of S100β were associated with the size of the brain infarction and an increased 2-year mortality risk.[164]

Ramlawi *et al*. showed in a study of 40 cardiac surgery patients (CABG, valve surgery, or both) with CPB that NSE and S100β levels increased 6 h after surgery and returned to preoperative levels by the 4. POD (at 6h NSE 8.49 ± 0.67 and S100β 0.44 ± 0.04). The author's used neuropsychological tests to determine the neurocognitive function of all patients before and after surgery and determined postoperative neurocognitive dysfunction as a significant drop from baseline (1 SD decline from baseline on 2 or more of the measures). Using this definition, the NSE levels at 6 h after surgery were significantly higher in patients with neurocognitive decline than in patients without a significant decline (NSE 8.69 ± 0.82 versus 5.98 ± 0.61; $p = 0.018$) The S100β levels did not differ significantly between the two groups, and even the highest NSE levels were significantly lower than the modern cut-off point of 33 µg/l. The study confirmed a similar time-course of NSE and S100β during and after surgery, as was shown by Gao *et al.* in 1999.[161, 165]

Bhattacharya *et al.* described the time-course of S100β during complex aortic operations with or without HCA, showing a peak concentration of 0.5 to 0.6 µg/l at skin closure and a decrease to 0.01 µg/l within 24 hours. The level of S100β at 24 h after the operation were higher in the group with HCA ($p = 0.01$) and were associated with the length of arrest ($r = 0.63$, $p = 0.02$). One of the patients suffered an ischaemic stroke, and had a steadily increasing level of S100β, peaking with a concentration of 1.0 µg/l at 24 hours after the operation.[166]

Despite the positive evidence, several studies have also failed to show any association between S100β levels and neurological outcome in cardiac surgery. Bokesch *et al.* presented the results of 557 patients undergoing high risk cardiac surgery (CABG and valve surgery), of which 10 % suffered a neurological complication. Using a cut-off value of the normal upper limit of S100β, a binomial division into "normal" or "abnormal" levels was used, and with this definition the preoperative values did not differ significantly between patients with a good or poor neurological outcome. Despite a prospective, blinded study with a large patient population, a dichotomous division of S100β leads to loss of information, as later studies have clearly shown that the level of S100β is associated with outcome. Also, the study only reports preoperative S100β values, but later studies have clearly shown that the levels of 24 to 48 hours after surgery are typically associated with outcome.[167]

2.6.7.4 Other biomarkers

The search for the perfect neurobiomarker continues, as does the attempt to use neurobiomarkers for disease characterization (diagnostics, outcome prediction, treatment efficacy evaluation, follow-up). Several markers have shown promising results, but one of the challenges in critical care is differentiating whether the marker is increased due to specific organ damage, or because of the associated severe disturbance of normal homeostasis and SIRS. For instance, lipase and amylase are used to diagnose and assess the severity of pancreatitis, however both markers are elevated in critical illness even without evidence of associated pancreatitis.[155, 168, 169] Similarly, amylase is significantly elevated after CABG, even without clinical pancreatitis.[170]

Several biomarkers associated with pancreatic cancer are increased also during acute pancreatitis, including Trypsinogen-1, Trypsinogen-2, Trypsinogen-3, serine peptidase inhibitor Kazal type 1 (SPINK1), pancreatic secretory trypsin inhibitor (PSTI), Trypsin-2 (activated complex of trypsinogen), and α_1-antitrypsin (2-API). SPINK1 has also been called tumour-associated trypsin inhibitor (TATI), but SPINK1 has become the accepted form in modern research.[168, 169, 171-173] Of these, trypsin-2 and 2-API measured at admission are predictive of severe acute pancreatitis.[174] Other prognostic biomarkers associated with pancreatic cancer, such as human chorionic gonadotropin β-subunit (hCGβ), are not elevated in acute pancreatitis, but have not been researched in critical illness.[175, 176] None of these have previously been tested as biomarkers of neuron damage, nor have they been defined after HCA.[172, 175]

Evaluating the origin and cause of elevated biomarkers is a complex process. Defining in which cells, tissues, and organs a specific biomarker is found can be helpful, however none of the know biomarkers are absolutely organ specific. Simultaneous measurement of different markers can reveal an association in the dynamics of biomarker concentrations, and a close enough association might suggest a common cause – such as SIRS, instead of specific brain damage.

3 AIMS OF THE STUDY

The aims of this prospective, explorative research were to study promising, non-invasive methods suitable for neuromonitoring of critical care patients in two specific patient groups: severe ALF patients with HE (**I**), and patients undergoing aortic surgery with HCA and postoperative critical care (**II**). The scope of the study covers critical care and long-term outcome, including HRQoL as a measure of neuropsychological (**II**) and neurological outcome (**III**), as well as the behaviour of certain biomarkers after HCA (**IV**).

The specific aims of this study are listed as follows:

1. To test whether continuous EEG monitoring with an abbreviated, 2-channel montage is predictive and a reliable method of non-invasive neuromonitoring in a critical care setting (**I**, **II**). Additionally, would a 4-channel fronto-temporal montage increase performance? (**II**)

2. To test whether spectral EEG variables are predictive of the stage of HE in ALF patients requiring critical care. (**I**)

3. To test whether a novel EEG variable WSE is predictive of neurological outcome in HE patients. (**I**)

4. To test the predictive power of neurological outcome of the frontal EEG hemispheric asymmetry (BSI) in aortic surgery patients operated with HCA. (**II**)

5. To test the predictive power of neurological outcome of perioperative NIRS and hemispheric asymmetry of NIRS in aortic surgery patients operated with HCA. (**II**)

6. To test the predictive power of neurological outcome of transcranial Doppler measurements reflecting indirectly intracranial blood flow (PI) in critical care ALF with HE, and aortic surgery patients operated with HCA. (**I**, **II**)

7. To evaluate the long-term survival and HRQoL of aortic patients operated with HCA. (**III**)

8. To test the predictive power of neurological outcome of NSE and protein S100β in aortic surgery patients operated with HCA. (**II**, **IV**)

9. To describe the postoperative kinetics, and test for neuromonitoring potential, certain interesting biomarkers (Trypsinogens, SPINK1, hCG and hCGβ) in aortic surgery patients with HCA. (**IV**)

4 MATERIALS AND METHODS

This study was inspired by the clinical need of non-invasive neuromonitoring methods in critical care for sedated, mechanically ventilated patients. Some of the researched methods have originally been developed for anaesthesia monitoring (*e.g.,* BIS, Entropy) and some for neuromonitoring in other settings (*e.g.,* TCD, NIRS). Certain biomarkers were included, of which some have an established association with neuron damage (NSE, S100β), and others are novel biomarkers which might show potential in neuromonitoring.

4.1 Study population

4.1.1 Studies I-IV

The study population included 81 patients altogether, with 50 study patients (**I**, **II**), and 31 comparison patients (**III**). The cohort sizes were decided upon *a priori*, based on an acceptable anticipated single-centre recruitment time. All studies included adult critical care patients and excluded patients with previous neurological injury.

The first study (**I**) included 20 patients with ALF and HE, referred to a tertiary centre for MARS treatment and evaluation for LT. Suitable, successive patients were recruited prospectively. Patient outcome was deemed poor if a liver transplant was required for recovery, or the patient died during the study period. The studied neuromonitoring methods included frontal EEG, TCD, and biomarkers (NSE, S100β). These were tested for predictive power in defining the grade of HE, and neurological outcome.

The second study (**II**) included 30 patients undergoing surgery of the thoracic aorta with HCA, optional SCP, and planned postoperative critical care. Suitable, successive patients were recruited prospectively. All patients were evaluated perioperatively and during the postoperative critical care for neurological outcome, which was defined as poor if the patient suffered significant neurological complications (*e.g.,* ischaemic stroke) or perioperative death. The studied neuromonitoring methods included frontal EEG, TCD, and biomarkers (NSE, S100β). These were tested for predictive power of neurological outcome. All suitable patients underwent a neuropsychological evaluation approximately 6 months after surgery.

The third study (**III**) included a cohort of 30 study patients (the same cohort as in the second study, **II**), with an additional comparison group of 31 patients undergoing elective coronary bypass surgery. The comparison group included 15 patients without CPB (off-pump, OPCAB), and 16 patients with CPB (on-pump, CABG). Originally both groups were planned to include 15 patients, but one recruited control was converted during surgery to on-pump, resulting in an extra patient. To limit selection bias, all recruited control patients were included. All patients were followed for a median (range) of 6.0 (0.0 to 8.0) years and were interviewed with a HRQoL questionnaire (RAND-36).

The fourth study (**IV**) included 17 patients from the **II** study cohort, from whom all researched biomarker measurements were available at all pre-specified time-points. In this study we describe the postoperative changes of several biomarkers, of which two have previously been used in neuromonitoring (NSE, S100β). The other biomarkers are specific markers associated with pancreatic cancer, and possibly SIRS and neuron damage (few anecdotal, unpublished clinical observations). In the **Results** chapter the unpublished results of all collected biomarkers are presented, in addition to the ones presented in the publication (**IV**).

4.2 Data collection

The research monitoring was set up by dedicated study nurses, who also collected all relevant data and performed the planned assessments defined by the study protocols.

All monitoring equipment and electrodes were applied to the patients' head, according to a setup scheme seen in **Figure 18**.

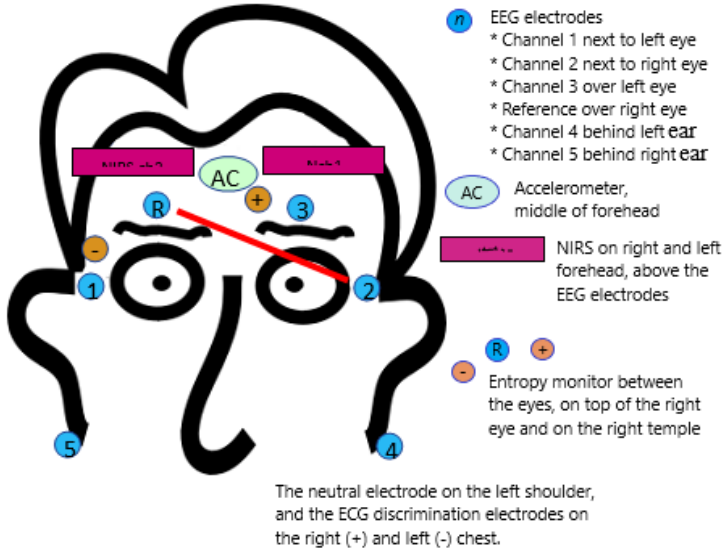


Figure 18. The neuromonitoring setup used in this thesis, showing the placement of the NIRS monitor, EEG electrodes, accelometer, Entropy monitor and a neutral electrode.

4.2.1 Electroencephalogram data collection

During the monitoring period, continuous EEG recordings of all study patients were collected using an Entropy monitor. In the **I** study a 2-channel signal was recorded with the S/5 Collect Program (GE Healthcare), using self-adhesive EEG electrodes attached to positions on the forehead, corresponding roughly to the frontal polar (Fp1, Fp2) locations of the international 10-20 system. In the **II** study a four-channel signal was recorded, adding bilateral temporal electrodes on the mastoid processes (**Figure 18,** channel 4 and 5).[177]

Off-line EEG data analysis included power spectral analysis, wavelet analysis and derived variables. In the **I** study we analysed WSE (described in detail by Särkelä *et al.*)[78], and in the **II** study we analysed BSI (described in detail by Van Putten *et al.*).[114]

The raw EEG signal was reviewed by a clinical neurophysiologist (T.S.), and in the **II** study classified into non-malignant, malignant, or highly malignant EEG, in accordance to the guidelines described by Westhall *et al.*[178]

4.2.2 Near-infrared spectroscopy data collection

In the **II** study a dedicated two-channel INVOS™ 5100C Cerebral/Somatic Oximeter (Medtronic) was used to measure bilaterally the continuous frontal venous-weighted rSO_2. The NIRS data were not blinded to the operating surgeon, as it was deemed unethical to deprive the surgeon of the only neuromonitoring method available, and which is considered a part of the routine setup for surgery with HCA.

Data were collected from the preoperative period and before anaesthesia induction, until 6 hours after surgery (thus including the first hours of cardiac ICU treatment). As tissue oxygenation is affected by several factors that change during anaesthesia induction and preparation for aortic surgery (level of Hb, temperature, oxygenation of blood, blood pressure), the initiation of circulatory arrest was chosen as a baseline for NIRS analyses.

Hemispheric rSO_2 data were used in two analyses. The first analysis included the surface integral of rSO_2 values against time, tested against patient outcome. The second analysis tracked the evolution of absolute hemispheric difference of bilateral NIRS values during circulatory arrest.

4.2.3 Transcranial Doppler ultrasound data collection

Transcranial Doppler measurements in the **I** study were performed daily at irregular times, by the treating ICU physicians and as a part of the clinical assessment of standard care of ICU-treated ALF patients with HE.

In the **II** study a dedicated study nurse performed the TCD measurements at end of surgery and 24 hours after weaning from CPB.

Measurements were gathered using Pioneer TC 4040 Doppler ultrasound (Nicolet-EME, Überlingen, Germany) and the middle cerebral artery was sonographed at a depth of 49 to 55 mm. From the measurements the PI was calculated (**Figure 15,** chapter **2.6.6.1 Pulsatility Index**).

4.2.4 Biomarker data collection

Blood samples were drawn every 6 hours in the **I** study and every morning in the **II** study. The specific biomarkers of the **IV** study were collected at baseline (before the operation), and on the 1st, 2nd, 3rd, 5th to 7th, and 8th to 10th POD. Of the biomarkers, S100β and NSE were analysed after sample collection, while the novel biomarkers were stored at -20 ºC and analysed later using in-house immunofluorometric assays.

4.2.5 Health-related Quality of Life and long-term survival

For the long-term survival and HRQoL data in the **III** study, patient survival was confirmed from the National cause of death registry and all available patients were then interviewed by either a postal or telephone questionnaire.

The questionnaire used was the Finnish version of the RAND 36-item Health Survey, which has been validated in the Finnish adult population ($N = 2175$, year of survey 1995). The questionnaire has eight health-related dimensions which are scored according to a 0 to 100 scale (physical functioning, role—physical, bodily pain, general health, vitality, social functioning, role—emotional, mental health), according to the personal experience of the subject.[39, 41]

For comparative analysis, data from two age- and sex-matched general populations were used. The first included chronically ill people (self-reported chronic illnesses), and the second included healthy people.[39]

4.2.6 Neuropsychological evaluation

All available study patients of the **II** study were evaluated by a neuropsychologist approximately 6 months after surgery. The neuropsychological performance of tested patients was classified as good if minor or no cognitive deficits were detected, and poor when significant cognitive deficits were present. Two patients were unable to undergo the evaluation due to persistent and disabling stroke symptoms and were classified in the poor performance category.

The neuropsychological examination covered cognitive domains of memory, executive functions, processing and motor speed, language skills and visuospatial skills.

No baseline evaluation was attempted, as most cases were anticipated to be emergency operations.

4.3 Ethical Aspects

No experimental interventions were included in this study. All monitoring results were evaluated after the monitoring period and were not used to guide clinical care. The only exception to this was NIRS in the **II** study, which was used by the operating surgeon according to established clinical practises in guiding the initiation of SCP during HCA. Due to a lack of neuromonitoring methods and the widely accepted use of NIRS during surgery, it was deemed unethical to blind the operating surgeon to NIRS for the purposes of this explorative study.

All patients, or next of kin when the patient was unavailable, gave their written informed consent. All studies were reviewed and accepted by an ethical committee. The **I** study was approved by the ethics committee of Helsinki University Hospital (reference number 165/E6/01), and the **II-IV** studies by the Helsinki University Hospital Surgical Ethics Committee, Helsinki, Finland (HUS 133/E6/07).

4.4 Statistical Analysis

All collected data were first analysed for normality. Based on a visual analysis and the results of a Shapiro-Wilk test of normality, all data were considered to have a non-gaussian distribution. Therefore, data is presented and analysed with non-parametric statistical tools. Continuous data are presented as median (range), except all **IV** study data is presented as median (IQR), and HRQoL data are presented as median (95% CI). All categorical data are presented as *n* (%).

For the **I** study, outcome was defined as good if the patient recovered without the need for a liver transplant, while a poor outcome was defined as a clinical deterioration leading to either liver transplant or death during the study period. For the II and **IV** study a poor outcome was defined as perioperative death or a new postoperative brain lesion detected by brain CT (including ischaemic strokes and haemorrhages). In the **III** study the early and long-term mortality and long-term HRQoL was determined.

Statistical testing for continuous data were performed with the Mann Whitney *U* test, and categorical data with the Pearson χ^2 test.

Prediction probability (P_K) analysis, designed for studying ordinal variables and commonly used in assessing the performance of anaesthetic depth indicators, was used to test EEG variable performance in all studies. A P_K value of 0.5 represents complete lack of prediction and describes complete randomness, while a value of 0.0 or 1.0 represent an absolute relationship.

In the **I** study the jackknife method was used to estimate P_K and it's standard error (SE) for the relationship of median EEG variables with the stage of HE. Assessments were assumed to be independent. The predictive power of each value (*i.e.,* whether it's P_K differed from 0.5) was evaluated by a paired *t*-test. Association of highest PI with outcome was assessed by P_K and the OR of a poor outcome was determined using a cut-off of PI >1.6.

In the **II** study the median values of EEG and NIRS were fed to a ROC analysis, deriving the AUC and it's standard error (SE) with the jack-knife analysis. Neuropsychological data analysis was performed with the Fisher's exact test.

In the **III** study, long-term survival was plotted with the Kaplan-Meier analysis and survival time comparison was performed with the log rank test. Groupwise comparison of HRQoL was performed with the Mann Whitney *U* test, and reference population comparison was performed with the Wilcoxon one-sample signed rank test. In the study missing data presented a challenge, leading to a *post hoc* sensitivity analysis with the multiple imputation method to assess the robustness of the results and conclusions. The pattern of missing data was determined with the Little's MCAR test (missing completely at random). The binomially categorised neuropsychological performance data were analysed with the Fisher's exact test.

In the **IV** study differences between baseline and maximal biomarker levels were evaluated with the Wilcoxon signed-rank test, and groupwise differences were analysed with the Mann Whitney *U* test. The unpublished outcome results of all the biomarker data were analysed with the Mann Whitney *U* test.

A two-sided α error of 0.05 was set in all studies. Due to the explorative nature of this research, multiple comparison was not used. When necessary, the Bonferroni method was used for correction of multiple comparison.

Statistical analyses were performed using the IBM SPSS Statistics (IBM Corporation, NY, USA) and MatLab (MathWorks, Inc., Natick, MA) for EEG analysis.

5 RESULTS

5.1 Demographics and outcome

The median (range) age of the whole study population of 50 patients was 56 (21 to 75) years, with 32 of 50 (64 %) being male patients. A good outcome was seen in 30 of 50 (60 %) patients. The **III** study included a comparison group of elective coronary bypass surgery patients (N = 31), with a median (range) age of 64 (37 to 80) years, and 25 (81 %) male patients.

In the **I** study of 20 patients with a median (range) age of 51.5 (21 to 71) years, four (20 %) patients died and 10 (50 %) received a liver transplant, resulting in poor outcome in 14 (70 %) patients. MARS treatment was received by 18 (90 %) of the patients, but one patient died of brain herniation after admittance and the first treatment cycle was cut short (15 h, target treatment cycle 22 hours).

In the **II** study 10 study patients of 30 (33 %) had a poor outcome, of these 8 (27 %) suffered a neurological insult and 2 (7 %) died in the perioperative period. The overall 90-day mortality was 10 % (3 of 30), with all deaths deemed to be of ischaemic aetiology.

The long-term mortality (up to 8 years) of the **III** study patients was 5% (3 of 58 patients surviving the study period), with a median (range) time of 1.3 (0.0 to 5.5) years from recruitment. The aetiology of the later deaths was cardiovascular in only 1 (33 %) patient. A censored Kaplan-Meier plot of long-term survival for the study and comparison group of the **III** study is presented in **Figure 19**.

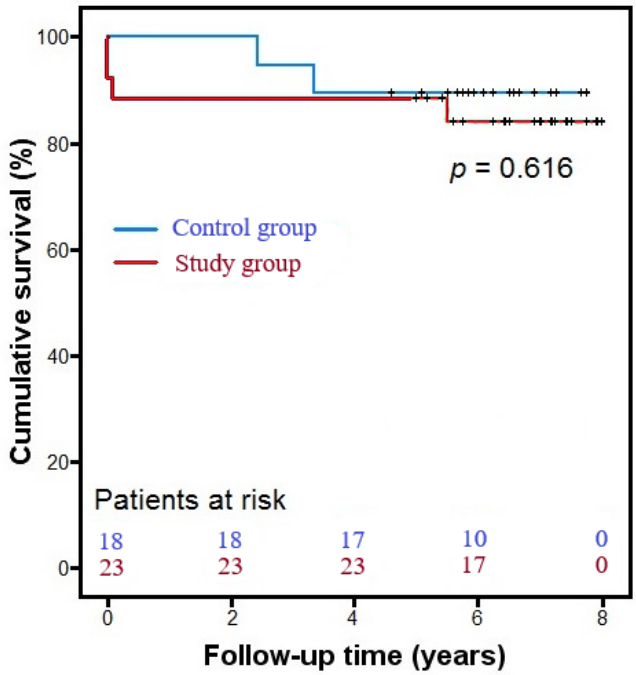


Figure 19. A censored Kaplan-Meier plot of the long-term survival of the study (green) and control (blue) groups in the **III** study. Despite slight trends in favour of a better early and late survival in the control group, no statistical difference could be detected (p = 0.616) within the maximum of eight years follow-up.

5.2 Electroencephalogram (EEG)

In the **I** study a deepening stage of HE was associated with an increase in delta activity and a decrease in alpha and beta band power. Of all the tested spectral variables, SEF50 (P_K 0.23, SE 0.03) and delta power (P_K 0.76, SE 0.03) were most predictive of the stage of HE. A P_K of over 0.5 indicates an increasing variable with deepening stage of HE, while a P_K below 0.5 indicates a decreasing variable with deepening stage of HE (a P_K of 0.5 means that the tested variable has no predictive power at all, while a P_K of 0 or 1 represent excellent predictive power). The distribution of these two variables with the stage of HE is shown in **Figure 20**.

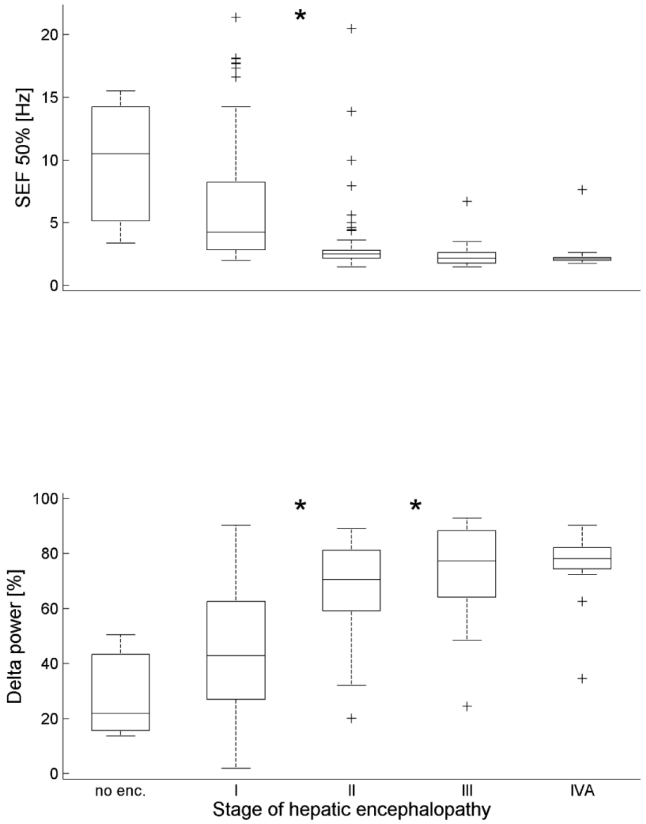


Figure 20. The most predictive EEG variables of 50 % spectral edge power (SEF50) and delta power, set against the stage of hepatic encephalopathy. Tested with prediction probability, SEF50 had a P_K of 0.23 (SE 0.03) and delta power a P_K of 0.76 (SE 0.03) of predicting the stage, with SEF50 decreasing with an increase in the stage of hepatic encephalopathy (P_K <0.5), while delta power increased with an increase in the stage of hepatic encephalopathy (P_K >0.5).

All tested EEG spectral variables and their associated P_K (SE) values for predicting the stage of HE are presented in **Table 4**.

Table 4. Spectral EEG and hepatic encephalopathy

All tested spectral EEG variables and their Prediction probabilities (P_K) and standard errors (SE) for distinguishing the stage of hepatic encephalopathy (HE). Variables which decrease with a deepening HE are on the left, while variables which increase with a deepening stage of HE are on the right. The variables with the best performance (i.e. a P_K value farthest away from 0.5) are on the top of the lists. Variables readily available in commercial EEG monitors are bolded.

EEG variable	P_K (SE)	EEG variable	P_K (SE)
50% spectral edge frequency	**0.23 (0.03)****	**Delta power %**	**0.76 (0.03)****
Mean dominant frequency	0.24 (0.03)**	Delta–fast theta ratio	0.75 (0.03)**
Spectral entropy total (1–30 Hz)	0.26 (0.03)**	Delta–theta ratio	0.74 (0.03)**
Slow beta power %	0.27 (0.03)**	Delta–slow beta ratio	0.74 (0.03)**
Beta power %	**0.28 (0.03)****	Delta alpha ratio	0.74 (0.03)**
95% spectral edge frequency	**0.28 (0.03)****	Delta beta ratio	0.73 (0.03)**
Alpha power %	**0.29 (0.03)****	Delta–fast beta ratio	0.73 (0.03)**
Fast beta power %	0.29 (0.03)**	Slow theta–fast theta ratio	0.71 (0.03)**
Spectral entropy of theta	0.30 (0.03)**	Delta power absolute	0.71 (0.03)**
Total WSE Daubechies 2	0.33 (0.03)**	Delta–slow theta ratio	0.70 (0.03)**
Fast theta %	0.34 (0.03)**	Slow theta–slow beta ratio	0.70 (0.03)**
Total WSE Daubechies 1	0.34 (0.03)**	Slow theta–alpha ratio	0.70 (0.03)**
Total WSE Daubechies 3	0.35 (0.03)**	Slow theta–beta ratio	0.69 (0.03)**
WSE 16–32 Daubechies 3	0.35 (0.03)**	Slow theta–fast beta ratio	0.69 (0.03)**
Spectral entropy of alpha	0.39 (0.03)*	Theta alpha ratio	0.69 (0.03)**
Fast beta power absolute	0.39 (0.04)*	Theta–slow beta ratio	0.68 (0.03)**
Slow beta power absolute	0.39 (0.04)*	Theta–beta ratio	0.68 (0.03)**
Beta power absolute	0.40 (0.04)*	Total power (1–30 Hz)	0.68 (0.03)**
Theta power %	**0.41 (0.03)***	Theta–fast beta ratio	0.68 (0.03)**
Spectral entropy of beta	0.45 (0.04)	Slow theta power absolute	0.66 (0.03)**
Spectral entropy of delta	0.46 (0.04)	Fast theta–slow beta ratio	0.66 (0.03)**
		Fast theta–beta ratio	0.65 (0.03)**
		Theta power absolute	0.65 (0.03)**
		Fast theta–alpha ratio	0.65 (0.03)**
		Fast theta–fast beta ratio	0.65 (0.03)**
		Alpha–slow beta ratio	0.64 (0.03)**
		Alpha–beta ratio	0.63 (0.03)**
		Alpha–fast beta ratio	0.62 (0.03)**
		Fast theta power absolute	0.61 (0.03)**
		Slow beta–fast beta ratio	0.55 (0.04)
		Slow theta power %	0.52 (0.04)
		Alpha power absolute	0.52 (0.04)

The novel EEG variable of WSE was tested with three Daubechies mother wavelets against neurological outcome in the **I** study, and all three were found to have predictive value – total WSE of Daubechies wavelet 1 had a P_K of 0.88 (SE 0.09, $p = 0.01$), Daubechies 2 a P_K of 0.85 (SE 0.12, $p = 0.02$), and Daubechies 3 a P_K of 0.82 (SE 0.12, $p = 0.04$). The distribution of the two outcome groups of the median total WSE of Daubechies wavelet 1 is presented in **Figure 21**. The lowest total WSE results were observed in a patient who perished due to brain herniation.

An increase in spiky waveforms decreases the value of WSE, which can be seen in the raw EEG signals of six patients with accompanying total WSE values in **Figure 22** (poor outcome marked with an *).

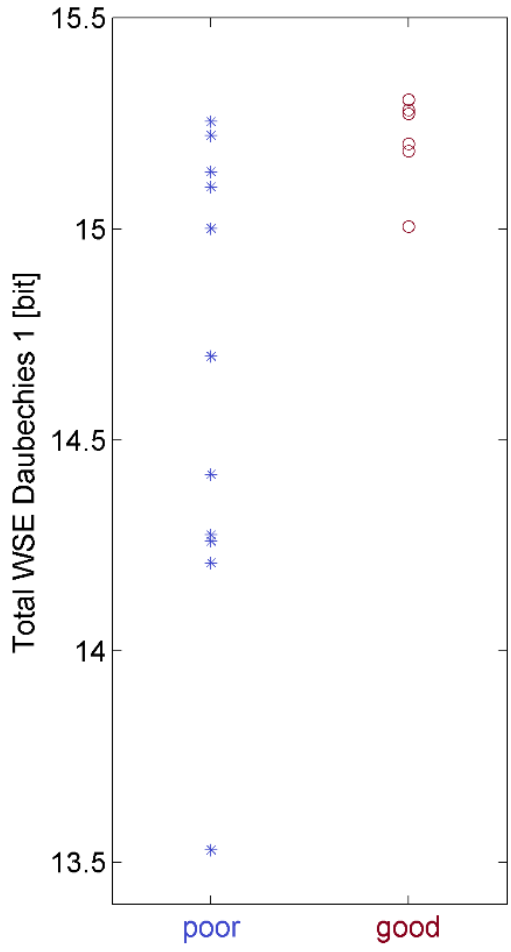


Figure 21. The distribution of the novel EEG variable of total WSE of Daubechies wavelet 1 in **I** study, set against neurological outcome and showing predictive value of neurological outcome (P_K 0.88, SE 0.09; $p = 0.01$). As evident, a low total WSE is associated with a poor neurological outcome, and accordingly the patient with the lowest WSE died early in the study due to brain herniation.

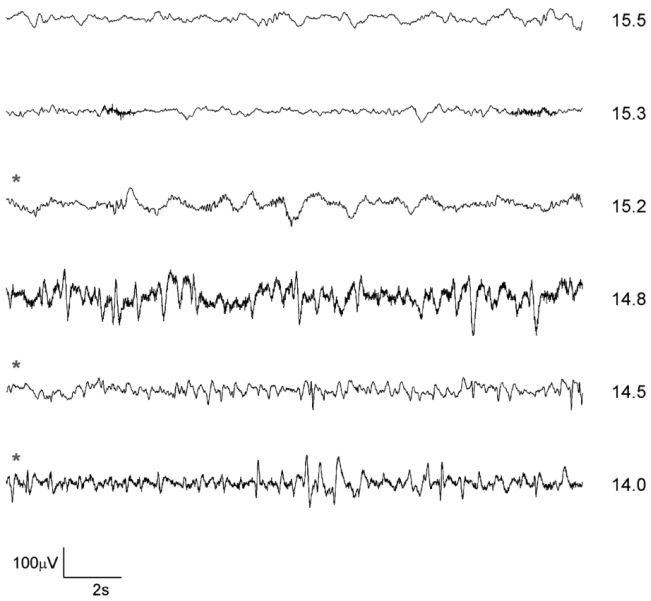


Figure 22. Exemplary EEG recordings from six HE patients (**I**), with the total wavelet subband entropy (WSE) on the right of each recording. In recordings presenting with increased spiky wave activity the WSE is lower. The three patients with a poor neurological outcome marked with an asterisk (*).

In the **II** study the hemispheric difference of frontal EEG was measured using the variable BSI. Temporal measurements did not perform as well and were dropped from subsequent analysis. A threshold value of BSI = 0.51 was identified (maximizing the sensitivity and specificity, see **II** study for details), and then used to classify patient outcomes. A higher BSI represents a more notable hemispheric asymmetry, which should be associated with poor neurological outcome. After artefact removal, the median (IQR) percentage of correctly classified EEG samples was 75 % (62 to 87 %). Based on these results, the threshold BSI value of 0.51 had a median (IQR) sensitivity of 79 % (62 to 88 %) and specificity of 71 % (61 to 84 %) to predict outcome.

The box-and-whisker plots of the BSI values of all patients are presented in **Figure 23**, with a dash line marking the threshold value (BSI = 0.51). Patients with a good neurological outcome are marked with blue boxes, while patients with a poor neurological outcome are marked with red boxes.

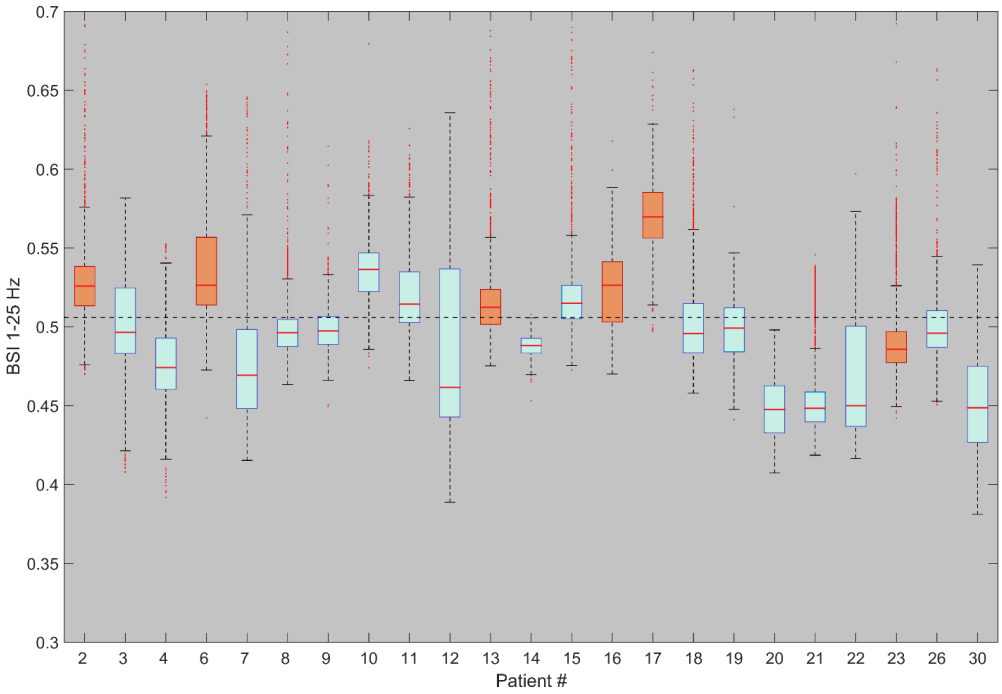


Figure 23. Presenting the box-and-whisker plots of BSI (1 to 25 Hz) values of all aortic surgery patients with HCA (**II**). The median values are shown with a line within the boxes, which represent the interquartile range, and the whiskers encompass the 95 % confidence interval, with individual dots representing outliers. The threshold value identified in the study for optimal neurological outcome detection of BSI = 0.51 is marked with a dash line, and each patient's results are colour coded according to outcome (blue for good outcome, red for poor outcome).

Example BSI spectra of two patients from both outcome groups are presented in **Figure 24**.

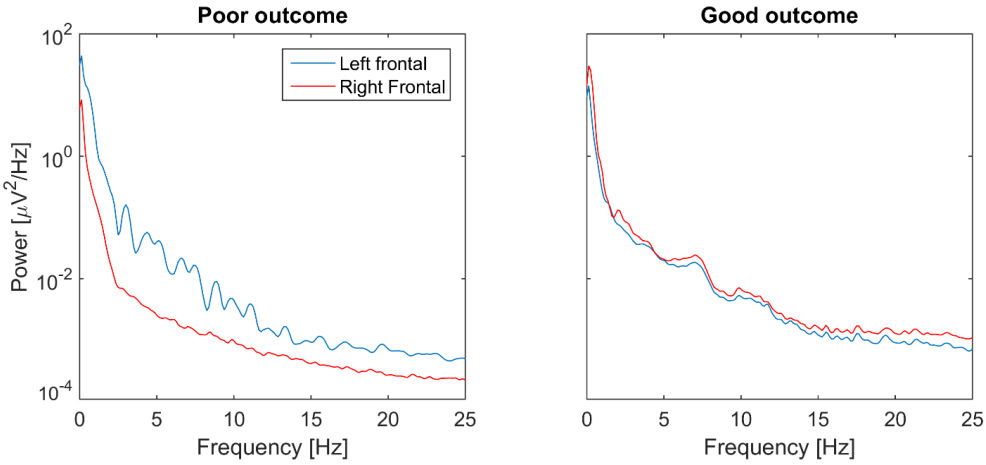


Figure 24. Illustrative representations of the mean spectra of the left (blue) and right (red) frontal EEG derivations of two aortic surgery patients with HCA (**II**), at two separate time points. On the left a patient's spectra with a poor outcome can be seen, with notable hemispheric asymmetry. On the right, a patient with a good outcome and little hemispheric asymmetry is presented.

5. 3 Near-infrared spectroscopy (NIRS)

In the **II** study, the hemispheric asymmetry of left and right rSO2 values had little predictive power, with an AUC value of only 0.56 (SE 0.13).

The asymmetry and area-time surface integral of rSO2 did not differ significantly between the outcome groups. Only at the timepoint of "rewarmed to 30 ºC" could a slight trend be detected, with a median (range) of 2 (0 to 8) for the good outcome group and 4 (0 to 13) for the poor outcome group ($p = 0.09$).

5. 4 Transcranial Doppler ultrasound (TCD)

In the **I** study population, the highest PI values measured during the study period did not differ significantly between the outcome groups ($p = 0.47$), nor were they predictive of outcome ($P_K = 0.39$, SE 0.16). However, as anecdotal evidence the highest measured PI of 3.0 was seen in a patient who died of brain herniation (the same patient had the lowest total WSE score). The maximum PI values

are shown in **Figure 25**. A threshold value of PI ≥ 1.6 had an OR of 1.1 (95% CI 0.1 to 9.3) for predicting poor outcome.

In the **II** study population, measured PI was not predictive of outcome at the end of surgery (p = 1.00) or 24 h after surgery (p = 0.21). The median (range) PI for the good and poor outcome group at the end of surgery were 1.3 (0.8 to 2.2) and 1.2 (0.9 to 2.3), respectively. Similarly, the median (range) PI for the outcome groups at 24 h after surgery were 1.1 (0.5 to 2.1) and 1.2 (0.9 to 3.4), respectively.

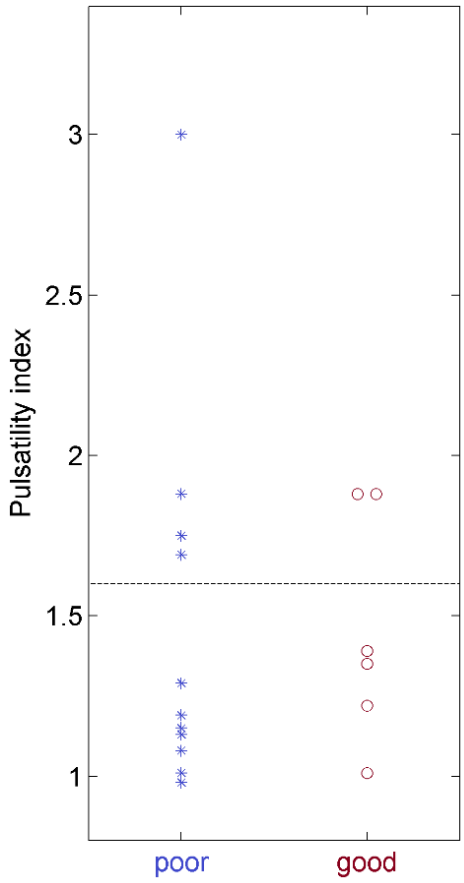


Figure 25. The highest recorded Pulsatility Index (PI) values by transcranial Doppler ultrasound for all HE patients from the **I** study, divided into two groups according to neurological outcome (poor on the left in blue, good on the right in red), with the threshold value of PI ≥ 1.6 used for the prediction of outcome (OR 1.1; 95% CI 0.1 to 9.3).

5. 5 Health-related quality of life (HRQoL)

The HRQoL interview was answered by 88% (23 of 26 survived) of the study patients, but a lower-than-anticipated response rate of only 59% (17 of 29 survived) for the two comparison groups lead to *post hoc* merging of the groups. The interviews were performed a median (range) of 6.8 (5.0–8.0) years after surgery for the study group, and 6.3 (4.6–7.8) years for the combined comparison group.

The study patients HRQoL was comparable to both the comparison group results, and the age- and sex-matched general populations of the chronically ill, and the healthy. For a visual representation, see **Figure 26**.

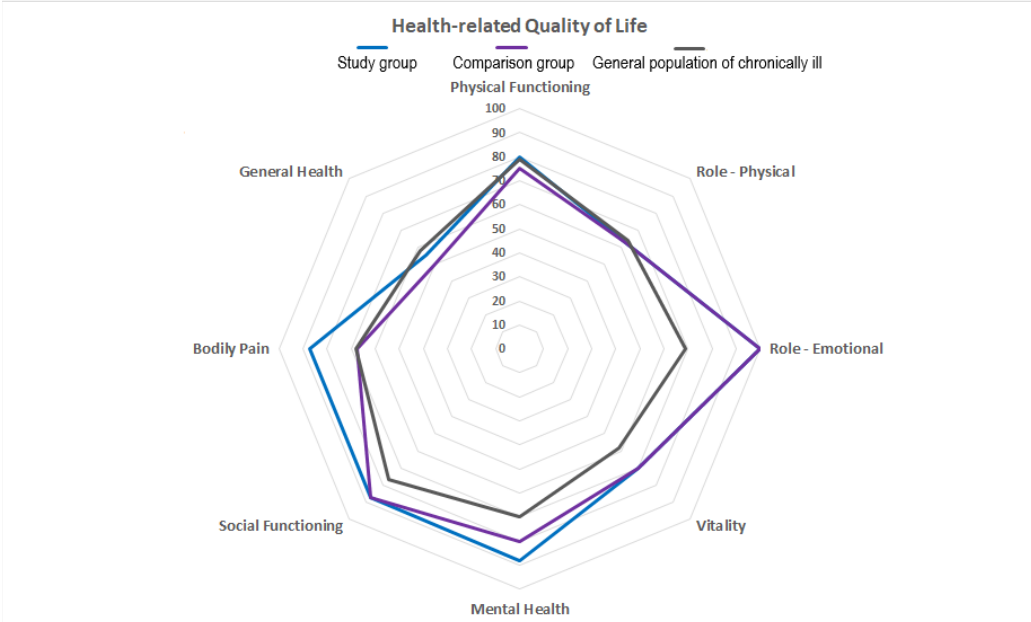


Figure 26. A radar plot of the health-related quality of life (HRQoL) results of the **III** study patients, showing the results of the study group, the comparison group, and the reference group of a general population of the chronically ill (self-reported). The results are comparable across the eight dimensions provided by the used HRQoL questionnaire, showing no statistically significant difference between the groups.

5. 6 Biomarkers

The median (IQR) of all gathered biomarkers (including those patients with missing results) from the **IV** study are presented in **Table 5**, along with the Mann Whitney *U* test of outcome difference of the two outcome groups. Only S100β on the 2nd and 3rd POD had a significantly higher median in the poor outcome group ($p = 0.03$, and $p = 0.002$, respectively).

Table 5. The median (IQR) of all biomarkers of the aortic surgery patients with HCA (IV), by neurological outcome. Only S100β on the 2nd and 3rd POD was significantly higher in the poor outcome group.

		Good outcome	Poor outcome	*p*		Good outcome	Poor outcome	*p*
Baseline	**S100β**	0.4 (0.03 to 0.06)	0.06 (0.05 to 0.12)	0.18	**Trypsinogen-2**	25 (14 to 40)	20 (12 to 28)	0.43
1. POD		0.16 (0.10 to 0.37)	0.21 (0.17 to 0.30)	0.54		40 (23 to 80)	80 (24 to 119)	0.54
2. POD		0.11 (0.07 to 0.16)	0.18 (0.15 to 0.82)	0.03*		44 (22 to 81)	48 (43 to 81)	0.50
3. POD		0.09 (0.07 to 0.13)	0.19 (0.17 to 0.97)	0.002*		74 (37 to 182)	94 (47 to 176)	0.89
5.–7. POD		0.08 (0.05 to 0.10)	0.11 (0.04 to 0.45)	0.38		199 (84 to 522)	305 (101 to 890)	0.57
8. – 10. POD		0.06 (0.05 to 0.09)	0.10 (0.04 to 0.26)	0.35		233 (91 to 479)	330 (173 to 841)	0.61
Baseline	**NSE**	12 (10 to 13)	13 (10 to 16)	0.56	**Trypsin-2-API**	4.9 (3.5 to 11.4)	4.2 (2.0 to 6.4)	0.26
1. POD		43 (30 to 53)	39 (34 to 64)	0.65		9.8 (6.3 to 16.6)	9.2 (5.8 to 16.1)	0.94
2. POD		30 (19 to 37)	36 (26 to 44)	0.35		12.8 (7.0 to 15.9)	11.9 (10.5 to 12.4)	0.74
3. POD		19 (14 to 27)	29 (24 to 45)	0.06		17.3 (8.7 to 29.2)	17.5 (15.3 to 21.5)	1.00
5.–7. POD		16 (13 to 18)	15 (11 to 31)	0.88		38.2 (14.7 to 75.5)	27.6 (21.0 to 147.1)	0.65
8. – 10. POD		18 (12 to 24)	16 (13 to 25)	0.76		26.0 (11.2 to 59.0)	56.9 (21.3 to 116.2)	0.26
Baseline	**Amylase**	41 (30 to 51)	63 (25 to 139)	0.56	**Trypsinogen-3**	0.01 (0.01 to 1.50)	0.61 (0.01 to 1.70)	0.71
1. POD		47 (43 to 104)	112 (32 to 206)	0.32		1.60 (0.01 to 2.25)	2.40 (0.01 to 4.45)	0.70
2. POD		54 (25 to 171)	59 (26 to 226)	0.93		0.01 (0.01 to 1.43)	1.70 (0.01 to 2.75)	0.30
3. POD		48 (22 to 101)	59 (24 to 137)	0.62		1.30 (0.01 to 2.95)	1,80 (0.01 to 4.60)	0.78
5.–7. POD		63 (26 to 98)	97 (53 to 112)	0.33		2.50 (1.10 to 11.10)	4.80 (1.80 to 15.30)	0.51
8. – 10. POD		69 (49 to 86)	99 (52 to 138)	0.48		4.30 (0.01 to 8.23)	-	0.71
Baseline	**SPINK1**	11 (9 to 16)	9 (5 to 17)	0.39	**hCGβ**	0.54 (0.47 to 0.91)	0.56 (0.25 to 1.02)	0.52
1. POD		24 (16 to 33)	35 (16 to 47)	0.54		0.60 (0.46 to 0.83)	0.46 (0.28 to 1.50)	0.70
2. POD		75 (42 to 164)	83 (46 to 303)	0.61		0.61 (0.54 to 0.92)	0.55 (0.32 to 1.61)	0.74
3. POD		106 (73 to 261)	86 (60 to 598)	0.89		0.92 (0.64 to 1.53)	0.59 (0.39 to 1.86)	0.30
5.–7. POD		111 (58 to 168)	71 (37 to 563)	0.80		2.99 (2.20 to 3.98)	4.37 (1.16 to 8.46)	0.72
8. – 10. POD		53 (31 to 230)	229 (67 to 676)	0.26		4.47 (2.10 to 9.85)	7.15 (3.19 to 9.93)	0.76
Baseline	**Trypsinogen-1**	33 (17 to 38)	22 (12 to 33)	0.29	**hCG**	0.23 (0.11 to 0.67)	0.42 (0.19 to 2.05)	0.48
1. POD		33 (21 to 63)	36 (81 to 109)	0.94		0.40 (0.10 to 0.99)	0.18 (0.04 to 0.95)	0.62
2. POD		17 (12 to 35)	20 (10 to 29)	1.00		0.19 (0.08 to 0.58)	0.31 (0.09 to 0.72)	0.73
3. POD		27 (18 to 68)	26 (22 to 34)	0.82		0.13 (0.03 to 0.55)	0.28 (0.06 to 0.65)	0.60
5.–7. POD		92 (41 to 226)	77 (32 to 245)	0.96		0.06 (0.01 to 0.49)	0.31 (0.12 to 0.38)	0.41
8. – 10. POD		123 (40 to 197)	116 (69 to 254)	0.76		0.22 (0.06 to 0.41)	-	0.63

Median (IQR), with groupwise comparison with Mann Whitney U test. Significant values of *p* below 0.05 marked with an asterisk (*).
1 Abbreviations: hCG, human chorionic gonadotropin; NSE, neuron specific enolase; POD, postoperative day.

The development of all tested biomarkers from baseline to the 8th to 10th POD is visualised for all patients (unpublished results) in **Figure 27**. Both S100β and NSE increase sharply after the operation, peaking on the 1st POD and then slowly declining. The significantly higher S100β medians of the poor outcome group is easily visualised. All other tested biomarkers show a different development, with a slow increase in values, peaking around the 5th to 10th POD. There is little difference between the values of the two outcome groups.

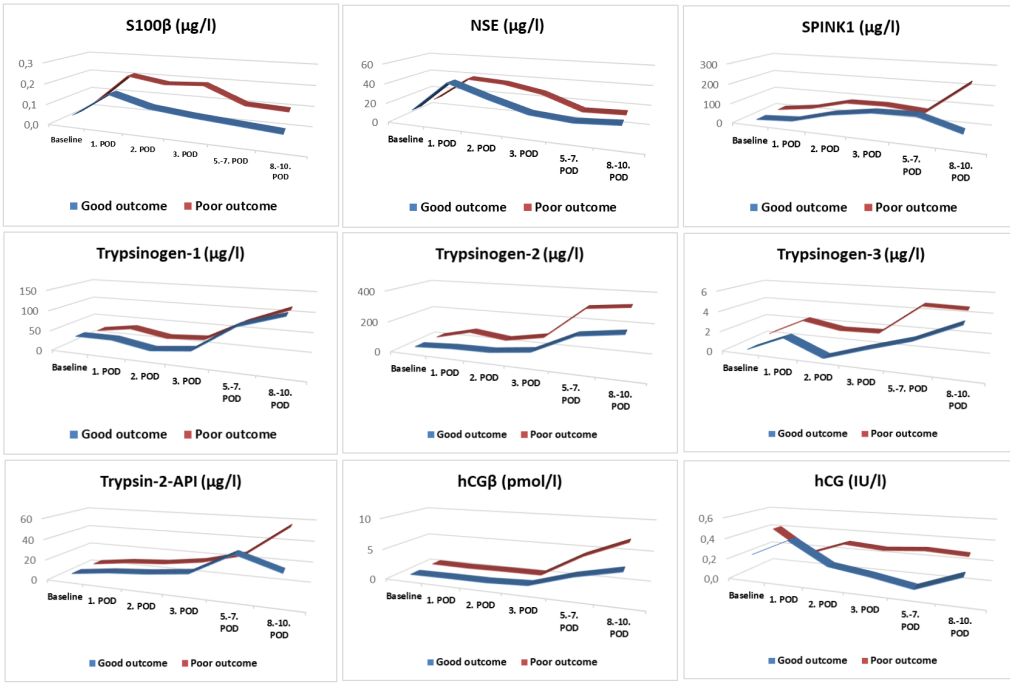


Figure 27. The time-course of all tested biomarkers in the **IV** study from baseline to the 10th POD, showing the median results divided into the good (blue) and poor (red) neurological outcome groups. The known neurobiomarkers of neuron-specific enolase (NSE) and S100β protein increase early and show a trend for higher values in the poor outcome group, but all other tested biomarkers increase later and show no difference between the outcome groups. The tested biomarkers include the pancreatic markers Trypsinogen-1, Trypsinogen-2, Trypsinogen-3, Trypsin-2- α_1-antitrypsin (Trypsin-2-API), Serine peptidase inhibitor Kazal type 1 (SPINK1), and human chorionic gonadotropin (hCG, hCGβ with β unit).

5.7 Neuropsychological evaluation

Of all surviving **II** study patients (n = 27), 21 (78 %) patients were evaluated by a neuropsychologist at median (range) of 6 (3-14) months after surgery. Three (14 %) patients presented with major neuropsychological complications, and all of these were from the poor neurological outcome group, as was expected. The patients with a poor neuropsychological outcome had major challenges in memory functions and concentration tasks.

6 DISCUSSION

6.1 Main findings

The main result of this research is that continuous, abbreviated frontal EEG monitoring is predictive of neurological outcome, and is a potential method for critical care neuromonitoring. Another important finding is the excellent long-term HRQoL of aortic patients operated with HCA.

The decision to include the tested methods of EEG, NIRS, TCD and biochemical markers was based on previous studies and academic opinions of potential non-invasive neuromonitoring methods.[23, 25, 29, 48, 73, 93] An exception from this were the tested biochemical markers (other than NSE and S100β) researched in the **IV** study, which have no prior evidence of being potential neuronal biomarkers. The **IV** study describes the behaviour of certain tumour-related biomarkers after aortic surgery with HCA, to evaluate whether any of these would present potential use as a neurobiomarker. Based on clinical, unpublished, and anecdotal observations of a few patient cases, these markers seemed to have increased concentrations in blood and spinal fluid after neurological insults. To explore the biomarkers behaviour, the postoperative concentrations during critical care were measured with simultaneous NSE and S100β measurements and other organ-associated biomarkers in a descriptive fashion. All biomarkers were also tested against neurological outcome.

The aims of this thesis were to explore non-invasive methods, which would offer reliable clinical tools for the neuromonitoring of mechanically ventilated, sedated critical care patients. The research concentrated on identifying and testing potential variables, with a realistic potential for clinical development.

Further study and development of suitable EEG algorithms and variables is called for and based on the results of this thesis, such research has great potential. None of the other monitoring methods showed any truly significant potential, and the benefits of future research is uncertain.

6.1.1 Electroencephalogram

In the **I** study, several spectral EEG variables predicted the stage of HE, allowing for neuromonitoring of ALF patients and detecting the progression of HE. The driving force seems to be the increase of delta power, which is seen also as a general slowing of frequencies with a deepening stage of HE.

Neurological outcome in **I** study was predicted by WSE, a group of EEG variables that detects spiky wave activity (triphasic waves), while the tested spectral EEG variables were not predictive of outcome. Similar results of neurological outcome prediction with WSE has been shown after cardiac arrest[86, 105], and triphasic waves with suppression patterns have been associated with increased mortality in HE.[101]

In a previous study by Wennervirta *et al.*[86], WSE of 16 to 32 Hz was predictive of outcome in cardiac arrest patients, a patient group in which a poor neurological outcome is often associated with epileptiform activity. In the **I** study the same variable was not predictive, probably as epileptiform activity is not as common in even severe HE.

The ability to differentiate and detect changes in the stage of HE addresses the clinical challenge of monitoring critically ill ALF patients, especially those requiring sedation and mechanical ventilation. As the decision for a LT and the outcome of ALF patients is strongly linked to the stage of HE, these

results show that abbreviated EEG could be a potential tool in neuromonitoring ALF patients with HE.

In the **II** study, the frontal EEG hemispheric asymmetry was defined by BSI, which was predictive of neurological outcome in patients undergoing surgery of the thoracic aorta with HCA and postoperative critical care (first 6 hours). Using the identified BSI threshold value, neurological outcome was predicted with reasonable reliability (sensitivity 79 %, specificity 71 %). A previous study shows a similar correlation between high BSI and permanent disability in ischaemic stroke patients.[117]

Six of the **II** study patients had a brain CT scan performed during the monitoring period, with five (83 %) presenting with acute ischaemic cerebral lesions on imaging and a BSI score of over 0.51. The single patient with a BSI lower than 0.51 had similar bilateral lesions in the cerebellum, which would be almost impossible to pick up on BSI. EEG, and therefore BSI, are based on the activity of cortical electricity, not cerebellar, and similar bilateral lesions would not typically cause a notable hemispheric difference.

An important quality of BSI is its relative resistance to global confounding factors, such as hypothermia and anaesthesia. These effects blunt EEG variables but exert a generalised effect on both frontal channels equally, which translates to minor hemispheric differences.

The temporal BSI did not perform as well as the frontal BSI, probably due to anatomical, neuroanatomical, and circulatory differences. As additional electrodes and a bulkier monitoring setup is not preferable for critical care patients, there seems little advantage in a four-channel fronto-temporal montage over a simpler two channel frontal montage.

In the **II** study, the visual classification of EEG was not predictive of outcome. Certain EEG patterns, which are easily detected by visual analysis, correlate with a poor outcome in comatose patients, such as prolonged isoelectric or low-voltage EEG.[97] Accordingly, in the **II** study similar low-voltage EEG patterns were seen during the first sedation break in two patients with a poor neurological outcome.

Visual analysis is not well suited to detect gradual changes and changes in trends, while computerised and qualitative analysis is. Visual EEG analysis is best suited to detect rapid changes (from seconds to minutes), and notable high amplitude or periodic patterns (such as epileptiform bursts or burst suppression). Computerised, qualitative EEG analysis, on the other hand, performs well in detecting gradual changes in spectral power, or the frequency of tracked transient patterns.[77, 97]

The results of abbreviated frontal EEG monitoring are promising, potentially providing a method with applications in neurological outcome prediction and neuromonitoring in critical care patients. The EEG findings of this study are in line with other study results, showing potential in neuromonitoring in critical care. The concept of monitoring hemispheric differences is probably an important part of future neuromonitoring development, especially as asymmetry is more resistant to sedation and hypothermia. With future research, the potential EEG variables and the algorithms can be fine-tuned to the critical care setting, to increase the sensitivity and specificity of the monitoring methods.

All the researched spectral EEG variables are easily applicable and can be found from modern monitoring setups.

6.1.2 Near-infrared spectroscopy

The asymmetry of brain activity has been researched previously in neuropsychology, but the concept of hemispheric asymmetry of NIRS values in cardiac surgery has been researched only in a few smaller studies.[126, 137, 138]

As a significant portion of changes in NIRS have been linked to physiological changes that occur during anaesthesia and CPB[119, 127], the beginning of circulatory arrest was used as a baseline for analysis in the **II** study. With such a baseline, the confounding effects mentioned previously were minimised.

NIRS was not predictive of outcome, neither the magnitude of decrease during circulatory arrest, nor the hemispheric asymmetry during and after circulatory arrest (**II**). However, these results are heavily biased as the surgeon could not be blinded to NIRS during surgery, and therefore threatening neurological complications detected by NIRS might have been avoided by the initiation of SCP. While NIRS has an accepted value in perioperative surgery, this study failed to identify factors which would be beneficial in critical care neuromonitoring.

6.1.3 Transcranial Doppler ultrasound

In this research PI measured by TCD was not predictive of neurological outcome in HE (**I**) or aortic surgery patients operated with HCA (**II**). Although a few of the most severe HE cases with a poor outcome did show a notable increase (PI over 2.0) later during treatment, even these patients did not have significantly higher PI values during the first 24-hours of treatment. It is probable that a poor neurological outcome in these patient groups is related to several aetiologies, in addition to a pathologically increased ICP, and thus with small cohorts the usefulness of TCD may be lost.

The results suggest that TCD might be useful in detecting severe increases in ICP, but it is not a precise enough method for reliable neuromonitoring in hepatic encephalopathy. For the timing of therapeutic interventions, such as LT, TCD monitoring does not seem to provide information early enough to have an impact on treatment outcome.

6.1.4 Biomarkers

Biomarkers performed poorly in neurological outcome prediction, which is probably partially related to small sample sizes and large dispersion of the analysed data. Also, the effects of CPB and HCA might have some unknown effects on the biomarker levels. (**II**, **IV**)

In the **IV** study the postoperative release of different tumour-related biomarkers (**Table 5**, in the **5.6 Biomarkers chapter**) was characterised, alongside two accepted biomarkers related to neuronal and astroglia damage (NSE and S100β). The highest values of all biomarkers were compared between the outcome groups, but no statistically significant difference was detected. There is a slight trend for higher NSE and S100β values in the poor outcome group, with significant difference for S100β on the 2nd POD. These results would have probably been more defined with a larger patient cohort and should therefore not be used to disqualify NSE and S100β as potential tools after aortic surgery with HCA.

The results reflect the prevailing opinion that while some biomarkers can be useful in detecting cerebral damage, there is a lot of confounding factors and uncertainty which diminishes the usefulness of biomarkers in critical care neuromonitoring. In addition, even reliable findings are typically

measured well after the time of cerebral damage, and thus have little value in guiding timely treatment or early outcome prediction.[151, 153, 154, 157]

The **IV** study failed to identify potential new neurobiomarkers but defines the evolution of these biomarkers after aortic surgery with HCA and critical care, along with NSE and S100β. As such, the increase of the studied biomarkers probably reflects transient global ischaemia, organ hypoperfusion, and SIRS. These results reflect the findings of previous studies, such as the increase of circulating SPINK1 in severe inflammation[179] and the increase of the pancreatic biomarkers (Trypsinogen-1 to -3, and SPINK1) in acute pancreatitis.[172]

The increase of hCG and hCGβ, with a slight trend of higher values in the poor outcome group, is interesting. These markers have not shown increased values previously in men without cancer, and the source of release of the hormone and hormone subunit remains unclear. However, as the increase was detected after the 2nd or 3rd POD, and no statistical significance or association with NSE and S100β was established, the biomarkers seem to have little value as neurobiomarkers.

6.1.5 Health-related quality of life

The long-term (5 to 8 years after surgery), self-reported HRQoL of aortic surgery patients undergoing HCA is almost surprisingly good, comparing favourably with the results of the general population with chronic illnesses, and even with the healthy general population. (**III**) These results, however, are in line with previous HRQoL studies on aortic surgery patients, reflecting several aspects.[4, 40, 42, 43] Patients surviving major cardiac surgery might express a more positive and healthier mental attitude concerning chronic illnesses and normal adversities of life, due to a near-death experience. In addition, aortic disease, unlike atherosclerotic heart disease for instance, does not have a similarly strong link to other chronic diseases (such as diabetes), which independently lower HRQoL.[4, 43]

There is also a certain bias inherent to HRQoL studies, as patients who do not survive cannot be included in the HRQoL interviews, and therefore are lost from the study. Even major neurological disability can affect the use of HRQoL instruments, for instance patients with severe speech impediments or challenges in understanding spoken or written questions might not be able to finish the interview.

The long-term HRQoL has potential as an indirect and alternative measure of the overall effects of neurological outcome, picking up on social and mental challenges in later life that might be missed in the acute phases of critical illness. While objective damage detected on a brain CT is the common outcome measure, HRQoL can catch social and neuropsychological problems which are associated with even minor brain damage. This concept is supported by previous study results, which show higher long-term HRQoL in patients with shorter HCA times, or bilateral SCP during HCA, without differences in postoperative neurological dysfunction.[4, 40, 42]

This is probably partly due to the psychological effect of surviving major prophylactic surgery to a life-threatening condition. In addition, aortic disease, unlike atherosclerotic heart disease for instance, does not have a strong link to other chronic diseases (such as diabetes), which independently lower HRQoL.[4, 43]

6.2 Methodological considerations

6.2.1 Study design, sample size and study population

The explorative nature of the research was the basis by which the study group cohort sizes were decided upon, with enough patients to be able to identify potential monitoring variables, but also to limit the costs and patient recruitment to a level acceptable for an explorative research.

The cohort sizes were deemed sufficient for the purposes of this prospective, explorative, and hypothesis-generating study, while considering the anticipated slow recruitment time. Extensive EEG recordings were collected from the study patients, with approximately 75 days (over 1700 hours) worth of continuous EEG data for both cohorts (**I**, **II**).

Patient recruitment was not randomised, instead all consecutive patients were included that could be recruited to the study. The study populations were recruited from actual critical care patients, and thus the results are potentially applicable to clinical work.

6.2.2 Data collection

All patient cohorts in this study included emergency patients also, and therefore no earlier baseline could be determined.

Patient recruitment was planned as consecutive, but this was not always possible as the monitoring equipment was sometimes still in use with the previous patient. Also, a research nurse was not always available for recruitment and monitoring setup.

One of the main challenges of EEG data collection and interpretation is the susceptibility to artefacts and data corruption. High quality electrodes and frequent electrode changes are crucial in eliminating these artifacts, and more extensive 4 or more channel montages might increase the risk of poor electrode contact during continuous monitoring. Automatic sensor impedance functions have become a standard in EEG recording but were not available in this research. EEG data were processed and analysed off-line during this study, but the processes could be easily automated and used for real-time monitoring.

In the **III** study the response rate of the comparison groups was lower than expected, and the lack of data led to *post hoc* combining of the two comparison groups and the use of statistical tools to compensate and check for data robustness.

6.2.3 Data analyses and interpretation

Neurological outcome (**I**, **II**, **IV**) and HRQoL analyses (**III**) are affected by the choice of inclusion of patient death as a poor outcome feature. Patient death during the monitoring period was decided to be considered as a poor neurological outcome (as it includes significant neuron damage), and the HRQoL data analysis included only the data of surviving patients. It is also possible, that a patient receiving a liver transplant might have survived without a transplant, but as the clinical situation can deteriorate rapidly and a delayed transplantation increases mortality significantly, it would have been unethical to postpone transplantation beyond the clinical recommendations.

All data analyses were performed off-line and did not affect treatment, except NIRS in the **II** study. Being a part of standard care, and the singular perioperative neuromonitoring device available, it was deemed unethical to blind the surgeon for NIRS values.

In the **III** study the long-term HRQoL of patients was assessed at a single time point, and other illnesses and surgery during the follow up where not assessed specifically. Therefore, any possible confounding factors cannot be controlled or evaluated, and there is no way of implying a direct causal link between the aortic surgery with HCA, and later HRQoL.

Despite missing data, the cohorts later HRQoL is described reliably, and the results of *post hoc* testing remain robust. Also, despite a poor neurological outcome in several patients, with postoperative strokes detected in brain CT scans, the long-term HRQoL of surviving, ambulatory patients remains very good. This raises the question of how a neurological poor outcome should be defined, and whether the immediate detection of a neurological complication is the best end point.

6.2.4 Generalizability

As a study of specific critical care patient populations with a high risk of neurological damage, namely ALF with HE and the surgery and postoperative critical care of the thoracic aorta with HCA, this explorative study aimed to identify and test potential neuromonitoring methods in the described patient groups. These results need to be validated by further study, preferable randomised and double-blinded trials with sufficient cohort sizes.

6.3 Clinical implications and future directions

Despite promising findings, the reliable and continuous monitoring of the brain functions of sedated, mechanically ventilated, critical care patients remains inadequate. The ability to detect brain insults as the damage is happening would allow for the testing of possible experimental treatments and would enable monitoring of treatment response. As extensive neuron damage increases notably the morbidity, mortality, and cost of treatment, neuromonitoring would be helpful in guiding treatment and in guiding the decision to withdraw treatment in poor outcome cases.

The results of this prospective, explorative research identifies abbreviated frontal EEG as a potential tool for future research. As modern monitors carry most of the studied variables, possible applications could be instituted easily. Further study is needed to confirm and further develop these methods. However, this research is in part laying down the foundations for future critical care neuromonitoring.

Abbreviated frontal EEG montages are easy to set up when compared to a standard EEG montage, provide continuous data, and do not need a clinical neurophysiologist to interpret the results.

The other tested methods show little predictive power and based on these results, might not play a significant part in future neuromonitoring of critical care patients.

7 CONCLUSIONS

1. Abbreviated, 2-channel EEG monitoring is a potential and easily applied method for neuromonitoring and outcome prediction in critical care. A 4-channel fronto-temporal montage showed no additional benefit. (**I**, **II**)
2. Spectral EEG variables are predictive of the stage of HE in ALF patients, and could be used to detect deepening HE during critical care. The best performing spectral variables are 50% SEF and delta power. (**I**)
3. The novel EEG variable WSE is designed to pick up spiky transient EEG waves (such as triphasic waves) and is predictive of neurological outcome in HE patients. (**I**)
4. The frontal hemispheric asymmetry of EEG can be defined by BSI, and high BSI values (increased asymmetry) are predictive of neurological outcome in aortic surgery patients operated with HCA. (**II**)
5. NIRS and the hemispheric asymmetry of NIRS are not predictive of neurological outcome in aortic surgery with HCA. These results are strongly biased, as NIRS monitoring could not be blinded during surgery. (**II**)
6. PI, a transcranial Doppler ultrasound variable which measures indirectly intracranial blood flow, is not predictive of outcome in HE or aortic surgery patients with HCA. Very high PI values might be associated with poor neurological outcome. (**I**, **II**)
7. Long-term HRQoL and survival of aortic patients operated with HCA is very good, even in surviving patients who had a poor primary neurological outcome. (**III**)
8. Of the two biomarkers commonly associated with neurological damage, protein S100β was predictive of neurological outcome in aortic surgery patients operated with HCA, but only on the second POD. NSE was not predictive. Neither biomarker seem to offer much additional information for the non-invasive neuromonitoring of critical care patients. (**II**, **IV**)
9. Biomarkers commonly associated with certain cancer types (Trypsinogens, SPINK1, hCG and hCGβ) increase slowly and remain high for days after aortic surgery. None of these show any correlation with neurological outcome, nor with traditional neurobiomarkers (NSE, S100β). (**IV**)

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Finland, January MMXXI

Juhani Stewart

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