Anesthesiological aspects on acute ischemic stroke and traumatic brain injury

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To my family

Abstract

Background
Endovascular treatment (EVT) of acute ischemic stroke (AIS) requires that patients are immobilized during the procedure. Retrospective studies have shown worse neurological outcome for patients receiving general anesthesia (GA) compared with patients receiving conscious sedation (CS) during EVT. Some suggested explanations for worse outcome in the GA group have been peri-operative hypotension, hypocapnia and attenuated cerebral autoregulation. However, the retrospective studies experienced pronounced selection bias, with more severe stroke in the GA groups, which could also explain the worse outcome.

Regarding traumatic brain injury (TBI), studies have shown that autonomic nervous system (ANS) dysfunction is associated with neurological outcome. However, the most severely injured patients treated in an intensive care unit, were excluded in those studies.

Methods
Paper I was a retrospective study on neurological outcome in relation to peri-operative blood pressure in patients managed with GA during EVT. In Paper II, a prospective study, stroke patients were randomized to GA or CS before EVT and neurological outcome was analyzed. Paper III investigated the impact of off-hour stroke admission on in-hospital lead times for EVT, in a cohort merged from Paper I and II.

Patients with severe TBI, receiving standard treatment in a neuro intensive care unit (NICU), were retrospectively studied with the aim to analyze ANS dysfunction in relation to late neurological outcome (Paper IV).

Results
Profound blood pressure fall (MAP fall > 40% from baseline) during EVT was an independent predictor of poor (modified Rankin Scale (mRS) > 2) neurological outcome. Patients randomized to GA or CS had equal mRS at 3 months (primary end-point). Furthermore, there were no differences in short-term neurological outcome (National Institutes of Health Stroke Scale (NIHSS) 24 h), infarction volume, recanalization grade or complications between the groups. Patients admitted during off-hours, experienced a longer time interval from admission non-contrast computed tomography to recanalization. This time interval was an independent predictor of poor neurological outcome.

In patients with severe TBI treated in a NICU, analyzes of ANS were feasible with ongoing full scale NICU care. ANS dysfunction was associated with worse long-term neurological outcome.

Conclusion
The results of this thesis on EVT in AIS, does not support the theory that anesthesia technique per se influences neurological outcome, provided that severe hypotension is avoided. Stroke management must be organized so that recanalization in EVT can be achieved as fast as possible around-the-clock. ANS analyzes might be adjunct tools in multi-monitoring of TBI patients in the NICU.

Keywords: acute ischemic stroke, endovascular treatment, general anesthesia, conscious sedation, traumatic brain injury, autonomic nervous system, heart rate variability, baroreflex sensitivity

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List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. P Löwhagen Hendén, A Rentzos, J-E Karlsson, L Rosengren, H Sundeman, B Reinsfelt, S-E Ricksten. **Hypotension during endovascular treatment of ischemic stroke is a risk factor for poor neurological outcome.** *Stroke 2015; 46:2678-2680*

II. P Löwhagen Hendén, A Rentzos, J-E Karlsson, L Rosengren, B Leiram, H Sundeman, D Dunker, K Schnabel†, G Wikholm, M Hellström, S-E Ricksten. **General anesthesia vs. conscious sedation for endovascular treatment of acute ischemic stroke The AnStroke trial.** *Accepted for publication in Stroke*

III. P Löwhagen Hendén, A Rentzos, J-E Karlsson, L Rosengren, H Sundeman, S-E Ricksten. **Does off-hour admission have an impact on lead times and neurological outcome in endovascular treatment for acute ischemic stroke? – the Gothenburg experience.** *Manuscript*

IV. P Löwhagen Hendén, S Söndergaard, B Rydenhag, B Reinsfelt, S-E Ricksten, A Åneman. **Can Baroreflex Sensitivity and Heart Rate Variability Predict Late Neurological Outcome in Patients With Traumatic Brain Injury?** *J Neurosurg Anesthesiol 2014; 26(1):50-59*

Summary in Swedish Populärvetenskaplig sammanfattning

Var tjugonde minut insjuknar någon i stroke i Sverige (20–25 000 personer per år). Stroke är den vanligaste orsaken till invaliditet och den tredje vanligaste orsaken till dödsfall i vårt land. Majoriteten av alla stroke är s.k. ischemiska stroke, vilket betyder att orsaken är en propp, som stoppar blodflödet i ett av hjärnans kärl. Vanliga symtom på stroke är hängande mungipa, sluddrigt tal, oförmåga att hitta ord och svaghet samt känselstörning i armen.

Länge fanns det ingen akutbehandling för stroke, men 2002 godkändes ett propplösande läkemedel. 2015 kom stora studier som visade att en annan metod, propputdragning, i kombination med läkemedlet, gav bättre resultat efter stroke än behandling med enbart propplösande läkemedel. Ett bra resultat anses vara om man kan återgå till ett självständigt liv efter sin stroke. På flera sjukhus, bl.a. på Sahlgrenska Universitets Sjukhuset, har propputdragning funnits i behandlingsarsenalen sedan 1990-talet.

Vid propputdragning förs en mikrokateter in via ljumskkärlet, upp till hjärnans kärl och proppen dras ut. Under ingreppet är det viktigt att patienten ligger helt stilla och därför behövs någon form av nedsövning. Det finns två huvudsakliga sätt att söva en patient inför propputdragning; fullnarkos eller lugnande medicinering. I många år, fr.a. efter 2010, har det varit en debatt om vilken av dessa metoder som är att föredra. Flera studier har visat sämre resultat för de patienter som fått fullnarkos. Dock var patienterna i de nämnda studierna inte lottade till sina respektive sövningssätt och de sjukaste patienterna (allvarligare stroke, mer samsjuklighet) återfanns i grupperna som fått fullnarkos. Detta faktum skulle kunna vara en förklaring till varför det gick sämre för dom.

Avhandlingsarbetet handlar till största delen om hur patienter, som genomgår propputdragning, ska handläggas av narkospersonalen för att det neurologiska resultatet ska bli så bra som möjligt.

I delarbete I studerade vi en grupp patienter som alla hade fått fullnarkos. Vi visade att stora blodtrycksfall, som är vanligt förekommande när man sövs, kan vara en förklaring till att det går sämre för patienter som genomgår propputdragning i fullnarkos.

I delarbete II, AnStroke studien, lottade vi patienter som skulle genomgå propputdragning, till fullnarkos eller lugnande medicinering. I båda grupperna var vi noga med att undvika stora blodtrycksfall. De neurologiska resultaten visade att det var lika stor andel i båda grupperna som återgick till ett självständigt liv.

I delarbete III undersökte vi effekterna av att söka vård för stroke på jourtid jämfört med att söka på kontorstid (mån-fre, kl. 8–16). Vi fann att tiden från att röntgenundersökningen av hjärnan görs tills att proppen är utdragen, förlängs med ca 20 minuter under jourtid, sannolikt p.g.a. lägre numerär och lägre kompetens i flera personalgrupper. Fördröjningen har potential att påverka det neurologiska resultatet negativt.

Delarbete IV handlar om det icke viljestyrda, s.k. autonoma nervsystemet, hos patienter som vårdas för svår skallskada på en neurologisk intensivvårdsavdelning. Studieresultaten visade att störningar i det autonoma nervsystemet under vårdtiden var kopplat till det neurologiska resultatet efter ett år.

Sammanfattningsvis har delarbeten I–III visat att det sannolikt inte är sövningsmetoden i sig som är avgörande för det neurologiska resultatet efter propputdragning vid stroke, utan det totala omhändertagandet av patienten. Att undvika blodtrycksfall under ingreppet är mycket viktigt. Narkospersonal är involverade i ledtiderna från första röntgen undersökningen efter inkomst till avslutad propputdragning och det är av stor vikt att omhändertagandet är lika effektivt dygnet runt.

Hos patienter med svåra skallskador är signaler från det autonoma nervsystemet möjliga att mäta med pågående full intensivvård och de är associerade till det neurologiska resultatet.

Table of Contents

Abbreviations

ACA	Anterior cerebral artery
A1	First segment of anterior cerebral artery
ADL	Activities of daily living
AIS	Acute ischemic stroke
ANS	Autonomic nervous system
APACHE II	Acute Physiology and Chronic Health Evaluation II
ASPECTS	Alberta Stroke Program Early CT score
AUC	Area under the curve
BP	Blood pressure
BRS	Baroreflex sensitivity
CB	Contusion bleeding
CPP	Cerebral perfusion pressure
CS	Conscious sedation
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
DBP	Diastolic blood pressure
DSA	Digital subtraction angiography
ECG	Electrocardiogram
EDB	Epidural bleeding
$ETCO_2$	End-tidal carbon dioxide
EVT	Endovascular treatment
GA	General anesthesia
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale Extended
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
IVT	Intravenous thrombolysis
LF	Low frequency
LOS	Length of stay
LR	Likelihood ratio
MAP	Mean arterial pressure
MCA	Middle cerebral artery

M1	First segment of middle cerebral artery
M2	Second segment of middle cerebral artery
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis In Cerebral Ischemia/Infarction
MVA	Motor vehicle accident
NCCT	Non-contrast computed tomography
NICU	Neuro intensive care unit
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
rtPA	Recombinant tissue plasminogen activator
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
sICH	Symptomatic intracerebral hemorrhage
TBI	Traumatic brain injury
TP	Total power

Introduction

Stroke

In Sweden, stroke is the main reason for neurological disability and the third most common cause of death after myocardial infarction and cancer. Every year, 20–25 000 people are diagnosed with stroke. This corresponds to one person having a stroke almost every twenty minutes. Mean age for the stroke patient is 74 years with a higher incidence in men than in women (Riksstroke, The Swedish Stroke Register 2015).

Approximately 85% of all strokes are ischemic, thus caused by a vessel occlusion and only 15% are hemorrhagic, i.e. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). For ischemic stroke, the main risk factors are atrial fibrillation, hypertension, hypercholesterolemia and diabetes mellitus.[1] The cerebral vessel occlusion is caused by an embolus from the heart or carotid vessels in 55% of the cases and blood clot formation in small brain vessels accounts for another 20%. In the remaining 25% of the cases, the cause is unknown or uncommon, such as trauma, dissection and arteritis. The anterior cerebral circulation, i.e. internal carotid artery (ICA), the middle cerebral artery (MCA) and anterior cerebral artery (ACA), is involved in 85% of the patients.[2] Posterior stroke, e.g. occlusion in the vertebral or basilar artery, has worse prognosis compared to anterior stroke and the two entities should be studied separately.[3]

This thesis addresses only management and treatment of acute ischemic stroke (AIS) in the anterior circulation.

Treatment of acute ischemic stroke

There are three milestones in modern stroke treatment. The first milestone was the establishment of specialist multi-disciplinary stroke units in the 1980s and 1990s. Medical care in a stroke unit gave an odds ratio (OR) of 1.28 for good neurological outcome compared to post-stroke care in a general ward.[4] The approval of recombinant tissue Plasminogen Activator (rtPA) for intravenous thrombolysis (IVT), in 1996 (USA) and 2002 (Europe), was the second milestone. IVT increased the incidence of a good neurological outcome (ADL (activities of daily living) independence) by 10 percentage units, compared to placebo treatment.[5] Patients with AIS are eligible for IVT within 4.5 hours from symptom onset if a non-contrast computed tomography (NCCT) excludes ICH and a large demarcated cerebral infarction. Furthermore, the patient must have no contraindications for rtPA treatment.

In Sweden in 2015, 13% of all AIS patients received IVT and 91% were treated in a specialist stroke unit after their stroke. The seemingly low figure for IVT of 13% reflects the fact that patients often arrive to hospital outside the time window. Only 37% of the AIS patients arrive within 4.5 hours from stroke onset and moreover, almost every fourth patient has a contraindication for IVT.

The third milestone for stroke treatment was reached during 2015, when endovascular treatment (EVT) in combination with IVT, was proven superior to IVT as single treatment, above all for patients with large vessel occlusions (occlusion in the internal carotid artery, the first two segments of the medial carotid artery or the first segment of the anterior carotid artery). The combination of EVT and IVT almost doubled the chance of a good neurological outcome, compared to therapy with IVT only.[6] EVT was performed in 390 patients (approximately 2% of all AIS) in Sweden in 2015 (Riksstroke, The Swedish Stroke Register 2015).

Thus, AIS has, over a fairly short period of time, evolved into an emergency condition with significant therapeutic potential and outcome figures in Sweden now show a 3-month mortality of 13% and a 3-month ADL independency of 84%. However, for the group of patients with large vessel occlusions, the prognosis is worse, and ADL independency is achieved only in approximately 40% of the cases after treatment with IVT in combination with EVT.[7]

Endovascular treatment (EVT)

Patients are eligible for EVT if the stroke severity score National Institutes of Health Stroke Scale (NIHSS) is ≥ 6, an occlusion is visible on a computed tomography angiography (CTA) and a NCCT excludes ICH and a large demarcated cerebral infarction. Computed tomography perfusion (CTP) is used in many centres to differentiate between manifest cerebral infarction versus penumbra ("tissue at risk").

Vascular approach for EVT is mainly via the femoral artery, but puncture of the common carotid artery is sometimes required due to arteriosclerosis and vessel tortuosity. A micro-catheter is advanced, under fluoroscopy and angiographic imaging guidance, into the intracranial vessel of interest. In the beginning of the EVT era, arterial rtPA was infused for local thrombolysis and the first industrial specialised embolectomy device (Merci® retriever) was approved in 2003. However, in our institution, successful endovascular embolectomies have been performed since 1994, initially by Gunnar Wikholm.[8]

EVT devices can be divided into two main groups: those with a proximal approach and those with a distal approach. In a proximal approach, the device never deliberately

passes the embolus during the procedure (Penumbra aspiration system®, Goose-Neck® snare). For a distal approach, there are so called stent retrievers (Solitaire®, Trevo®). The stent retriever passes the embolus and the stent then expands into the embolus and extracts it when withdrawn (Figure 1 and Figure 2). A potential problem with stent retrievers is that passing the embolus might cause fragmentation of it and thereby peripheral micro embolization.

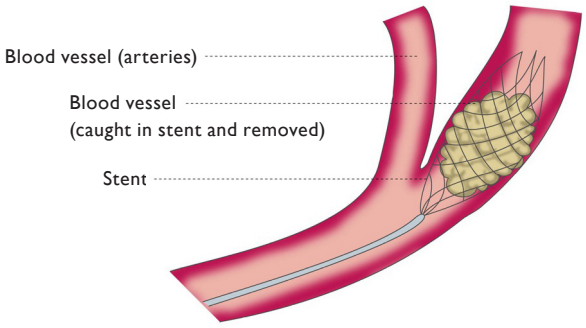


Figure 1. A stent retriever, with the stent expanded into an embolus. Figure reprinted with permission from the publisher (CIRCE; Cardiovascular and Interventional Radiological Society of Europe).

Figure 2. Embolus withdrawn from a cerebral vessel.

The main target group of patients for EVT are those with large vessel occlusions, since these occlusions seldom are resolved by intravenous thrombolysis solely. It is estimated that about 6–10% of all AIS are caused by large vessels occlusions that could benefit for EVT.

Time is brain

The time interval from stroke onset to revascularization of the occluded vessel is of paramount prognostic importance both in IVT and EVT. "Time is brain" is a phrase used to emphasize that for every minute without revascularization, 1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers are destroyed and consequently the treatments should be instituted as soon as possible in every single case.[5, 9, 10] The goal for "door-to-needle" time in IVT is < 40 min in Sweden and the time window for secure IVT is 4.5 hours from stroke onset. After 4.5 h, the risk of intracerebral hemorrhage might outweigh the benefit of treatment (Riksstroke, The Swedish Stroke Register 2015).

For EVT, national and international benchmark lead times are missing. The region of Västra Götaland guidelines propose a CT to groin puncture time of < 60 minutes. The time window for EVT is now established to be 6 hours from stroke onset, based on several randomized trials, but it can be expanded to > 6 hours when image-based selection criteria are used to identify patients with salvageable brain tissue.[6]

On-hour versus off-hour

Continuous work is done in hospitals to minimize all lead times in the stroke chain, both pre-hospital and in-hospital. The "weekend effect" refers to the assumption that stroke admissions off-hour (on-call time) have longer in-hospital lead times compared to on-hour (office hours) admissions. This phenomenon is described in several studies for IVT [11-16], but for EVT it is not well studied.[17-19] Obviously, EVT is a more complex procedure than IVT and during off-hours, hospital staffing is inevitably reduced. This might alter an otherwise well-organized work flow achieved on-hour in the neurology-, radiology- and anesthesiology departments, which are all involved in in-hospital stroke care.

Anesthesia during endovascular treatment

During EVT it is necessary that the patient is immobile and usually some type of anesthesia/sedation is required. In parallel to the studies proving the efficacy of EVT in the 2010s, there has been a debate on whether the type of anesthesia administered to these patients affects the neurological outcome.[20-37] The two alternatives compared are general anesthesia (GA) with intubation and conscious sedation (CS) with spontaneous breathing. Both alternatives have their potential advantages and disadvantages (Table 1).

Table 1. Potential advantages and disadvantages of GA and CS.

	Potential advantages	Potential disadvantages
General anesthesia	• Airway protection during the intervention • Less time consuming due to total immobilization • Less risk for intra-procedural complications due to total immobilization • Control of ventilation ($PaCO_2$) and oxygenation (PaO_2) • Neuroprotective effects of drugs?	• Hypotension during anesthesia induction and during the intervention • Time delay due to intubation • Risk of aspiration during the anesthesia induction • Attenuation of cerebral auto-regulation by anesthetic drugs • Need for longer postoperative recovery • Risk of delayed extubation and pneumonia • Stress and shivering during anesthesia recovery – risk of cardiac arrhythmias/ischemia
Conscious sedation	• Less risk of hypotension during the intervention • Possible to perform repeated neurological assessments during the intervention • Earlier mobilization	• Risk of aspiration during the intervention • Time delays due to patient movements • Risk of intra-procedural complications due to patient movements • Hyperventilation leading to hypocapnia • Hypoventilation leading to hypoxia • Patient discomfort, stress – risk of cardiac arrhythmias/ischemia

Not less than sixteen retrospective studies have been published, comparing GA with CS for EVT [38-55], together with review articles [56-63], guidelines [64-66] and one meta-analysis[67]. All retrospective studies show that GA patients have worse neurological outcome compared to CS patients. The reasons for this are suggested to be intra-operative hypotension and/or hypocapnia in the GA group. Furthermore, GA is described as a more time-consuming procedure and the GA patients could suffer from ventilator-associated complications due to delayed extubation. However, all retrospective studies experience pronounced selection bias, with the GA groups having more severe strokes and in some studies a higher proportion of posterior strokes, compared to the CS groups.

Randomized trials have been repeatedly requested. In 2013–2015, the AnStroke trial, the SIESTA trial[68] and the GOLIATH trial[69] were therefore launched with the aim of comparing the neurological outcome after GA and CS during EVT for AIS.

Blood pressure in acute ischemic stroke

At hospital admission, over 85% of the stroke patients have a systolic blood pressure (SBP) >150 mmHg, that spontaneously declines over several days. Several studies have shown a U-shaped relationship between the spontaneous blood pressure at admission and the neurological outcome after stroke, with the best outcome achieved at a SBP around 150 mmHg.[70] The term U-shape means that very low and very high blood pressures are associated with worse outcomes. However, a causal relationship between the spontaneous BP and outcome has never been proven. For a patient treated with IVT, BP < 180/105 mmHg is recommended for 24 hours, to minimize the risk of symptomatic ICH.[71]

Relevant in both IVT and EVT is that, during the time from stroke onset to reperfusion, the brain tissue distal to the occlusion is completely dependent on collateral circulation. The effectiveness of the collateral circulation, in turn, relies on sufficient cerebral perfusion pressure (mean arterial pressure minus intracerebral pressure), especially in the ischemic situation when the cerebral autoregulation is likely to be disturbed.[72]

Collateral circulation

The four blood vessels supplying the cerebral hemispheres (left- and right carotid artery and left- and right vertebral artery) are all connected at the skull base through the circle of Willis. This collateral system is complete in only 40–50% of all individuals and is of importance in AIS only if the occlusion is situated proximal to the circle. If the occlusion is more distal, effective collateral circulation depends on the leptomeningeal collaterals extending over the brain surface, seen in approximately 80% of AIS patients (Figure 3). These collaterals are dormant under normal conditions, but are recruited when one of the large vessels are occluded, although the exact temporal onset of recruitment is not yet known. Existence and extent of leptomeningeal collaterals demonstrate individual variations and they are an important prognostic factor for infarction size and neurological outcome in AIS.[73]

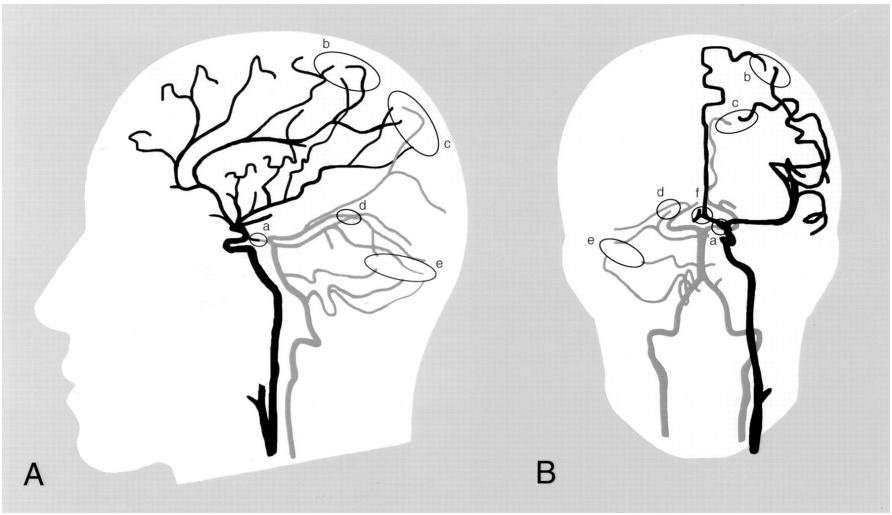


Figure 3. Intracranial arterial collateral circulation in a lateral (A) and frontal (B) view. Shown are posterior communicating artery (a); leptomeningeal anastomoses between anterior and middle cerebral arteries (b) and between posterior and middle cerebral arteries (c); tectal plexus between posterior cerebral and superior cerebellar arteries (d); anastomoses of distal cerebellar arteries (e); and anterior communicating artery (f). Figure reprinted from Liebeskind et al Stroke. 2003;34:2279-2284 with permission from the publisher.

Cerebral autoregulation

Autoregulation is defined as the intrinsic ability of an organ to maintain a constant blood flow despite changes in the perfusion pressure. This is mediated by metabolic- and myogenic intrinsic mechanisms, among others. Human cerebral circulation shows an excellent autoregulatory capacity and when cerebral perfusion pressure falls or increases, arteries and arterioles dilate or constrict, respectively, keeping the cerebral blood flow relatively constant through a range of mean arterial pressure (MAP) 50–150 mmHg in healthy subjects.[74]

However, both illness and pharmacological substances can diminish the autoregulatory capacity, e.g. hypertension, stroke and sedative drugs.[72, 74] Impaired autoregulation leads to a more pressure-dependent blood flow. Thus, AIS patients during anesthesia are very dependent on an adequate perfusion pressure to maintain the collateral circulation until the occluded vessel is recanalized.

Traumatic brain injury

Traumatic brain injury (TBI) is the most common cause of death and disability in young people, both worldwide and in Sweden. The most common causes for TBI in Sweden are falls, motor vehicle accidents and abuse. Seventy-five percent of the patients are male, most often < 30 years old and 25–50% are intoxicated at admission. In Sweden, the incidence of traumatic brain injury is about 260/100 000 inhabitants/year. Severe TBI, defined as Glasgow Coma Scale (GCS) 3–8 at admission, has an incidence of approximately 700 cases/year.[75-77]

This thesis addresses the autonomic dysfunction in the acute phase of severe acute TBI, defined by requiring neuro intensive care, although some of the patients initially were scored GCS > 8.

Autonomic nervous system

The autonomic nervous system (ANS) has two components: the sympathetic nervous system and the parasympathetic nervous system, both affecting the sinoatrial node in the heart. A constant and varying influence from both these nervous systems makes the heart rate change a little from beat to beat. This creates variability in the length of the R-R interval – the "heart rate variability" (HRV).

The baroreceptor reflex is a homeostatic mechanism that helps to maintain blood pressure at a nearly constant level, by modulating the sympathetic and parasympathetic nervous systems, which lead to changes in heart rate in response to changes in blood pressure. Important arterial baroreceptors are located in the carotid sinus and in the aortic arch. Baroreflex sensitivity (BRS) is a measure of the activity/sensitivity of the reflex. The baroreceptor reflex is one of many processes affecting the HRV (Figure 4).

Measurements of HRV and BRS thus give indirect measurements of the ANS activity.[78] The requirement for HRV analysis is detection of R-R intervals by a routine continuous ECG. For BRS also measurement of arterial blood pressure is required. The term autonomic dysfunction refers to lower HRV and lower BRS than normal.

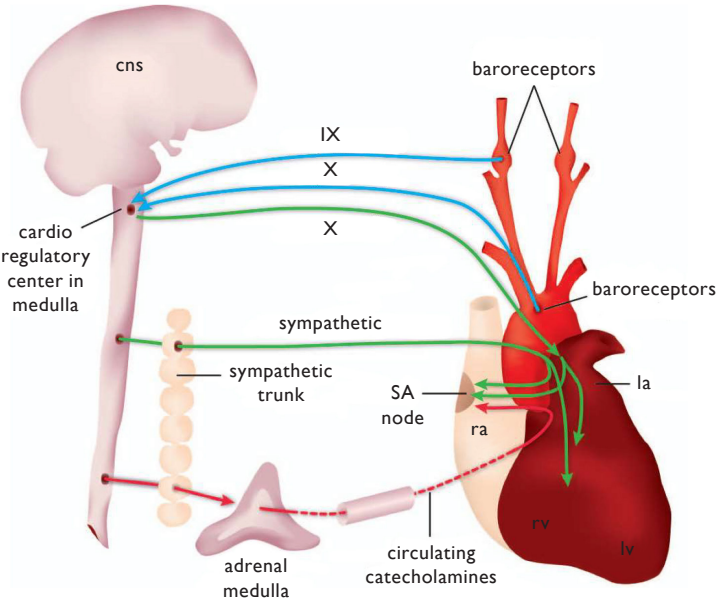


Figure 4. Sympathetic and parasympathetic regulation of the heart and the baroreceptor reflex. CNS; central nervous system, la; left atriu, lv; left ventricle, ra; right atrium, rv; right ventricle, SA; sinoatrial node, IX; glossopharyngeal nerve, X; vagus nerve. Figure reprinted from McNeill et al. Neural Development 2010, 5:6 with permission from the publisher.

Autonomic nervous system and outcome

The link between HRV and clinical outcome was first suggested in the 1960s in fetal monitoring studies, and fetal HRV monitoring (CTG, Cardiotocography) is now standard in maternity care. In anesthesia and intensive care, autonomic dysfunction has been described as an adverse prognostic sign in several different entities such as myocardial infarction, sepsis, multi-trauma and brain injury.[79]

It has been shown in several studies that autonomic dysfunction in TBI correlates with increased morbidity and mortality.[80-83] However, most studies did not include the severe TBI patients, treated in the ICU with anesthetic drugs and mechanical ventilation. The autonomic nervous system is affected by a numerous factors inherent to the intracranial injury as well as by the clinical management in the ICU.[84-95] Studies of HRV and BRS in patients with severe TBI treated with standard intensive care, including mechanical ventilation, analgesia, sedatives and vasoactive drugs were lacking when Paper IV was published.

Aim

The aims of this thesis were:

- To evaluate the impact of intra-procedural hypotension on neurological outcome for patients with acute ischemic stroke undergoing embolectomy under general anesthesia. (Paper I)

- To compare neurological outcome after embolectomy for acute ischemic stroke in patients randomized to general anesthesia or conscious sedation. (Paper II)

- To evaluate the effect of off-hour admission on in-hospital time intervals for patients undergoing embolectomy for acute ischemic stroke. (Paper III)

- To test the hypothesis that autonomic dysfunction in patients with acute traumatic brain injury, treated with standard intensive care treatment protocols, can predict poor late neurological outcome. (Paper IV)

Patients and Methods

Paper I–III

Stroke alarm organization

All patients primarily admitted to our institute as acute stroke alarms are transported directly to the CT laboratory in the Radiology department, bypassing the emergency room to save time. The stroke team, consisting of a vascular neurologist, a neurology nurse responsible for intravenous thrombolysis and a neuroradiologist, is waiting for the patient in the CT room. The neurointerventionist is contacted prior to the CT scan if a suspicion for large vessel occlusion exists. Also the anesthesiologist receives the stroke alarm to be prepared if EVT is appropriate. During night shifts the stroke team consists of a neurologist, an anesthetist nurse responsible for intravenous thrombolysis and a radiologist on call.

There is a parallel workflow and the NIHSS evaluation is done by the neurologist simultaneously as the patient is prepared for the non-contrast computer tomography (NCCT) scan and interrupted when the CT staff is ready. If needed the NIHSS evaluation is completed during evaluation of the NCCT. A computed tomography angiography (CTA) is performed in case of a large vessel occlusion suspicion, according to NIHSS evaluation (NIHSS ≥ 6) and/or radiological indirect signs. As soon as a proximal (internal carotid artery, M1 and M2 segments of middle cerebral artery, A1 segment of anterior cerebral artery) occlusion is detected in the CTA, a computed tomography perfusion (CTP) is performed and the patient is transported to the neurointerventional suite. The CTP is evaluated while the patient is transported to the neurointervention unit. Patients admitted via a regional hospital have already undergone NCCT and CTA and are transported directly to the neurointerventional suite.

Imaging for stroke

NCCT (non-contrast computed tomography) is performed to rule out stroke mimics (e.g. tumors), intracerebral hemorrhage and to evaluate the infarction expansion (ASPECT score).

CTA (computed tomography angiography) is a contrast enhanced examination. By using intravenous radiopacity, arterial or venous vessels can be visualized, depending on in which phase the image is taken. The CTA confirms a vessel occlusion, gives details on occlusion site and is also used to grade the collateral circulation.

CTP (computed tomography perfusion) gives information on the relation between manifest cerebral infarction versus penumbra ("tissue at risk"). After an intravenous radiopacity injection, mean transit time (MTT) for blood through the brain tissues is calculated, as well as the cerebral blood flow (CBF) and the cerebral blood volume (CBV). Compared to the unaffected brain tissue, the infarction core has a prolonged MTT, a decreased CBF and a reduced CBV. Potentially salvageable tissue, the penumbra, also has a prolonged MTT and to a lesser degree decreased CBF but, importantly, a normal or even increased CBV (if vasodilatory autoregulation is active).

In *DSA* (digital subtraction angiography), intra-arterial radiopacity is injected into the cerebral vessels of interest, in a catheter inserted via the femoral artery. By "subtracting" all other tissues (bone, brain) visible in the pre-contrast image, the DSA image clearly visualizes only the contrasting intracerebral vessels. DSA confirms the existing vessel occlusion and the images are used when performing the embolectomy and also for evaluation of the result.

Time intervals

Time intervals in this thesis were calculated based on the following time points:

Stroke onset is the time for onset of symptoms or the time when the patient was last seen normal.

CT refers to the start (time-log on the first NCCT slice) of the NCCT examination.

Arrival to neurointervention suite is the time the patient arrives to the neurointervention suite from the CT room or from a regional hospital with ambulance transport.

Groin puncture is the time when the neurointerventionist punctures the femoral artery.

Recanalization is defined by the time for the first angiographic image where recanalization is visible.

End of procedure is determined by the time for the final angiographic run in case of an unsuccessful recanalization.

Several important time intervals (Figure 5) were calculated from these time points.

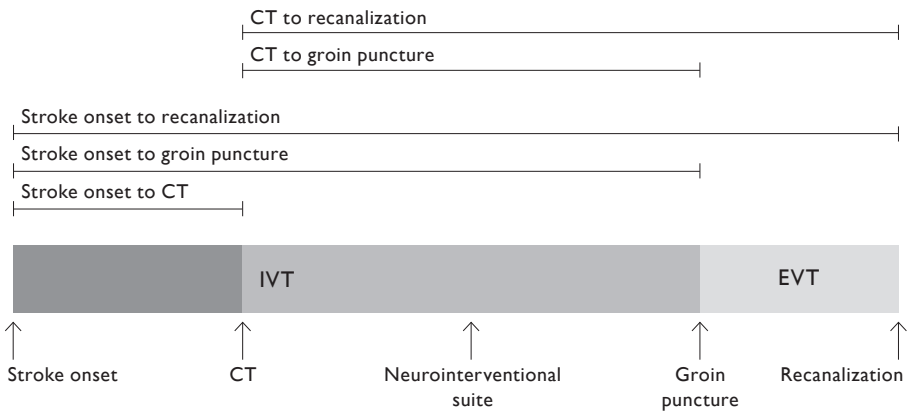


Figure 5. Time intervals in endovascular treatment for acute ischemic stroke.

Devices for endovascular treatment

During the years 2007–2016, several different endovascular devices were used in our institution at the discretion of the attending neurointerventionist. The three main devices used were: The GooseNeck® snare, Penumbra aspiration system® and Solitaire® stent retriever (Figure 6 – 8). Sometimes, in case of distal small fragmentation embolus, intra-arterial rtPA was used.[96]

Figure 6. GooseNeck® snare. Reprinted with the permission from Medtronic.

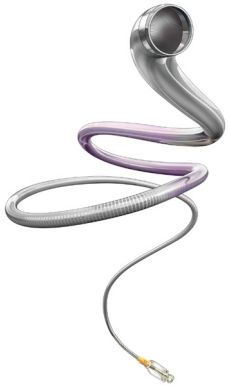


Figure 7. Penumbra Aspiration system®. Reprinted with the permission from Penumbra, Inc.

Figure 8. Solitaire® stent retriever. Reprinted with the permission from Medtronic.

Baseline and outcome measurements

NIHSS

NIHSS (National Institutes of Health Stroke Scale) developed 1983, is a tool for quantitative measuring of stroke severity. It can be administered bedside and is used to determine appropriate treatment, follow treatment effects and has been shown to be a predictor of both short and long term outcomes of stroke patients.[97] The neurological examination evaluates the level of consciousness, language, neglect, visual-field loss, ocular movements, motor strength, ataxia, dysarthria, and sensory loss. The scale is valid for occlusions in the anterior circulation. The range of score is 0 – 42 points (Figure 9).

An approximate grading can be presented as:

NIHSS	0 – 1	Normal
NIHSS	1 – 4	Minor Stroke
NIHSS	5 – 15	Moderate Stroke
NIHSS	15 – 20	Moderately Severe Stroke
NIHSS	> 20	Severe Stroke

ASPECT

ASPECT (Alberta Stroke Program Early CT) score is a 10-point score that rates the presence of early ischemic changes in 10 predefined regions of the MCA territory on a NCCT. The score can be used before eventual therapy to guide decision making and after therapy to evaluate outcome.[98]

A NCCT with ASPECT score of 10 is without signs of ischemia in the MCA territory. Scores ≤ 7 correlate with both poor functional outcome and symptomatic intracerebral hemorrhage if revascularization is achieved.

Figure 9. NIHSS (National Institutes of Health Stroke Scale).
Image created by Å Kuntze Söderqvist. Reprinted with permission.

Category	Score/Description		Score
1a. Level of Consciousness (LOC)	0 = Alert; keenly responsive 1 = Arouses to minor stimulation 2 = Requires repeated stimulation to arouse 3 = Unresponsive, coma		
1b. LOC Questions (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
1b. LOC Commands (Open/close eyes, squeeze hands)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect		
2. Best Gaze (Eyes open – patient follows examiner's finger or face)	0 = Normal 1 = Partial Gaze Palsy 2 = Forced deviation		
3. Visual Fields (Introduce visual stimulus/threat to patients visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)		
4. Facial Paresis (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete		
5a Motor Arm – Left **5b Motor Arm – Right** (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left Right	
6a Motor Leg – Left **6b Motor Leg– Right** (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left Right	
7. Limp ataxia (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs		
8. Sensory (Pin prick to face, arm, trunk and leg – compare sides)	0 = Normal 1 = Partial Loss 2 = Severe loss		
9. Best language (Name items, describe a picture and read a sentence)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute		
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate alluring of words 2 = Near to unintelligible or worse x = Intubated or other physical barrier		
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect		

mTICI

mTICI (modified Thrombolysis In Cerebral Ischemia/Infarction) grading system was developed in a consensus statement in 2013 and is a tool for classifying the degree of revascularization after endovascular treatment for stroke.[99, 100]

The range of score is 0–3 with subgroups 2a and 2b (Figure 10). Score 2b and 3 are considered as successful recanalization.

Modified Treatment in Cerebral Ischemia/Infarction (mTICI)

Score	Definitions
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion.
2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g., in 1 major division of the MCA and its territory)
2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g., in 2 major division of the MCA and their territories)
3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches.

Figure 10. mTICI (modified Thrombolysis In Cerebral Ischemia/Infarction). Image created by Å Kuntze Söderqvist. Reprinted with permission. MCA; middle cerebral artery.

mRS

mRS (modified Rankin Scale) was originally introduced in 1957 and modified in the late 1980s. It is a commonly used outcome rating scale for stroke patients, categorizing the level of functional independence at three months after the stroke. The range of score is 0 – 6 (Figure 11).

In most studies mRS ≤ 2 is defined as good neurological outcome. A person with mRS ≤ 2 is ADL independent. mRS ≤ 1 is sometimes referred to as excellent neurological outcome.[101]

The modified Rankin Scale (mRS)

Score	Definitions
0	No Symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance or unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden.
6	Dead

Figure 11. mRS (modified Rankin Scale). Image created by Å Kuntze Söderqvist. Reprinted with permission.

Paper I and III

Patients

The studies were approved by the Gothenburg Regional Ethical Review Board, documents no 455-12 and no 013-13. Patients from the prospective hospital stroke database for endovascular treatments of AIS were reviewed for eligibility between 2007 and 2012 (Paper I) (Figure 12).

Study inclusion criteria were: a) no intra-cerebral hemorrhage on the admission NCCT, b) NIHSS score of ≥ 14 when no CTA was performed or proven occlusion when CTA was performed, c) treatment initiation within 6 hours and d) anterior circulation stroke. Exclusion criteria were: a) patient managed by CS, b) missing outcome data and c) missing blood pressure recordings.

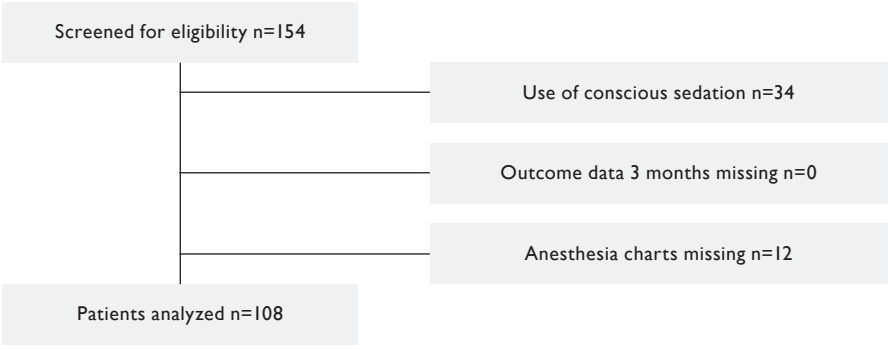


Figure 12. Consort diagram Paper I.

Paper III, combined the retrospective patient material from Paper I with the prospectively collected patient cohort in Paper II.

Methods

Patient- and stroke characteristics were retrieved from medical journals and from the hospital stroke database. Anesthesiological data were collected from anesthesia charts.

Analyzed variables were age, sex, co-morbidities, baseline NIHSS, occlusion site, time intervals, mTICI, blood glucose, $ETCO_2$ and intra-procedural relative changes in MAP from baseline. Modified Rankin Scale (mRS) at three months was used as outcome variable.

In Paper III, the patients were divided and analyzed according to time for the admission NCCT. This time point is referred to as "admission" in the paper. We defined on-hour as office hours, e.g. weekdays between 8 a.m. and 16 p.m. and off-hour, as on-call time, e.g. weekdays between 16 p.m. and 8 a.m. and weekends.

Statistics

In Paper I, the cohort was divided and analyzed according to two outcome groups; good neurological outcome, defined as mRS ≤ 2 or poor neurological outcome, defined as mRS > 2.

In Paper III, differences in baseline and outcome data between the on-hour and the off-hour groups were checked by t-test or Mann-Whitney test for continuous variables and Fisher's exact test for dichotomous data. In a second step, the cohort was divided and analyzed according to two outcome groups; good neurological outcome or poor neurological outcome.

Independent predictors of poor neurological outcome were assessed by uni- and multivariate logistic regression. Predictors with a p-value < 0.1 in the univariate analysis were finally included in the multivariate regression analysis (Paper I and III). Statistical significance was set to $p < 0.05$.

Paper II

Patients

The study was approved by the Gothenburg Regional Ethical Review Board, document no 013-13 and registered on https://clinicaltrials.gov Unique identifier: NCT01872884. All patients with acute ischemic stroke admitted to our institution from November 2013 to July 2016 were reviewed for eligibility. Inclusion criteria were: a) ≥ 18 years of age, b) proven occlusion in anterior cerebral circulation by CT-angiography (CTA) and/or NIHSS score ≥ 10 (if right sided occlusion) or ≥ 14 (if left sided occlusion), c) treatment initiated within 8 hours after onset of symptoms.

Exclusion criteria were: a) the patient was not eligible for randomization due to anesthesiological concerns (airway, agitation etc.) at the discretion of the attending anesthetist b) occlusion of posterior cerebral circulation c) intracerebral hemorrhage d) neurological recovery and/or recanalization before or during angiography e) premorbidity mRS ≥ 4 or other comorbidity contraindicating embolectomy (Figure 13).

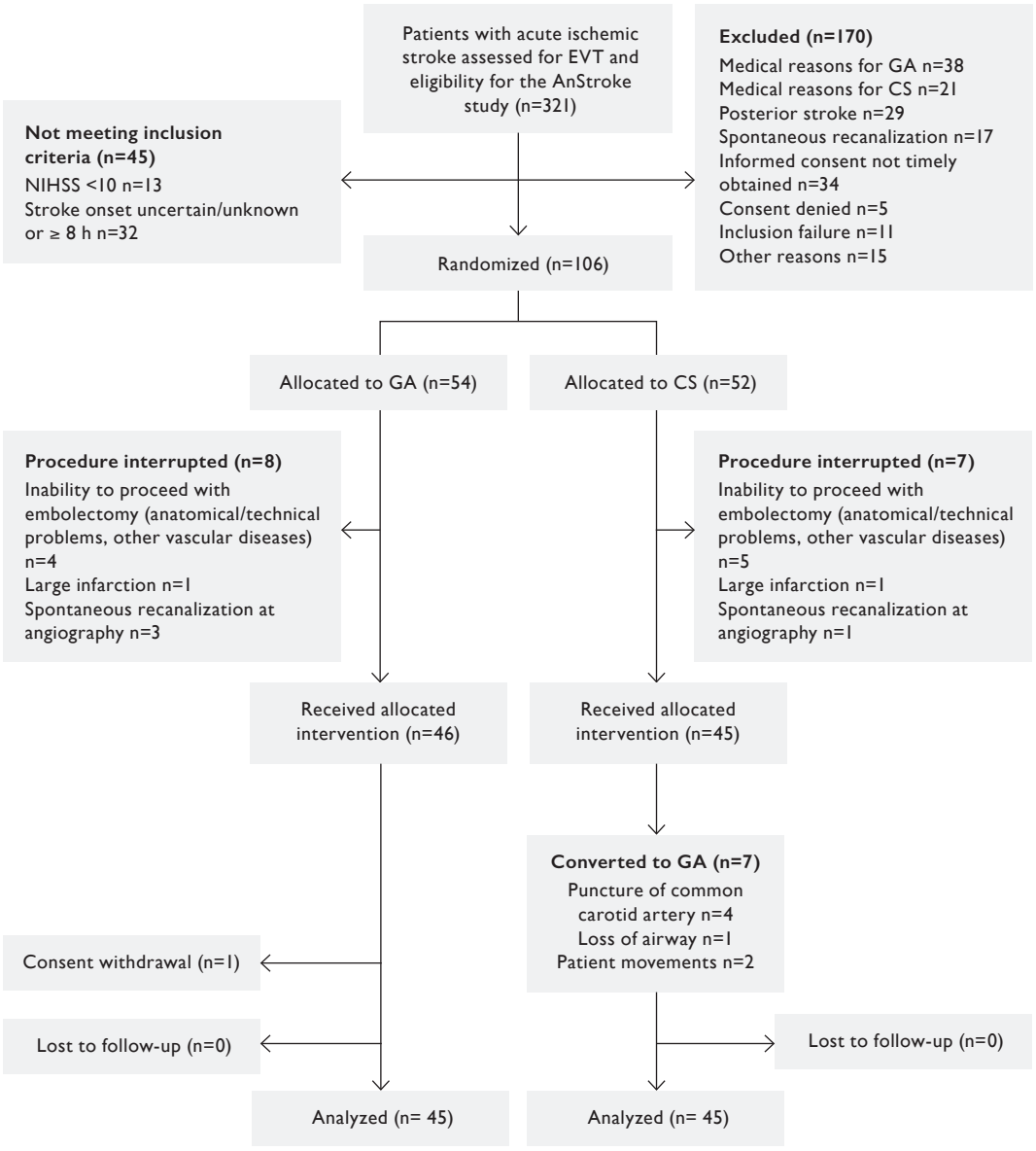


Figure 13. Consort diagram Paper II. EVT; endovascular treatment, NIHSS; National Institutes of Health Stroke Scale, GA; general anesthesia, CS; conscious sedation.

Methods

After informed consent, patients were randomly allocated in blocks to either general anesthesia or conscious sedation in a 1:1 ratio using sealed non-transparent envelopes.

Anesthesiologists were involved in all procedures. General anesthesia was induced by propofol and remifentanil, maintained with sevoflurane and remifentanil and with ventilator settings aiming for normoventilation. Conscious sedation was maintained with remifentanil infusion.

Systolic-, diastolic- and mean arterial pressure (MAP) were recorded every 5 minutes in all patients from before the start of induction of anesthesia until extubation in the neurointerventional suite. Blood pressure was measured by a radial arterial catheter, inserted as soon as possible during the procedure in all patients. Before obtaining intra-arterial measurements, arterial blood pressure was measured non-invasively. The last recorded MAP before induction of anesthesia, was defined as the baseline MAP. Intra-procedural MAP was expressed as fractions of baseline MAP. The occurrence of a > 20% and > 40% fall in MAP from baseline was noted and total time spent under these limits was calculated. Dopamine, ephedrine, phenylephrine or norepinephrine was used for inotropic and/or vasoactive treatment at the discretion of the attending anesthesiologist. The treatment goal was a systolic blood pressure of 140 – 180 mmHg in all patients before recanalization.

The main embolectomy techniques were: Solitaire® stent retriever, Penumbra aspiration system®, The GooseNeck® snare and combinations of these techniques. The choice of technique was at the discretion of the neurointerventionist in charge. Substantial patient movements, quality of angiography and vessel tortuosity were registered, as well as neurointerventional and anesthesiological complications.

Age, sex, co-morbidities, administration of IVT, occlusion site, ASPECT score, collateral circulation, blood glucose, partial pressure of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) and relevant time intervals were recorded. Neurological impairment was assessed as NIHSS, by a neurologist at admission as well as after 24 hours, at day 3 and at discharge or day 4–7.

The angiographic result of the endovascular treatment was defined according to the modified Thrombolysis In Cerebral Ischemia/Infarction (mTICI) score. A NCCT scan for detection of postoperative hemorrhage was done at day 1 after treatment. A magnetic resonance imaging (MRI) was performed at day 3 for infarction volume calculation. The review of the neuroradiologic and angiographic data was done by neuroradiologists, blinded to neurological outcome.

A vascular neurologist, blinded to treatment allocation and mTICI score, assessed mRS three months after stroke (primary end-point). Also at 3 months, an MRI was done to detect any new cerebral infarcts in the postoperative period that could affect the mRS.

Statistics

The intention-to-treat principle was used for the primary analysis.
Differences in outcome data between the GA and CS group were checked by t-test or Mann-Whitney test for continuous variables and Fisher's exact test for dichotomous data. The mRS scores three months after the stroke, were compared using a 2 x 7 Chi-square test. Statistical significance was set to $p < 0.05$.

Paper IV

Baseline and outcome measurements

GCS

GCS (Glasgow Coma Scale) described in 1974, is a scale for level of consciousness of patients with an acute brain injury, evaluating eye opening, verbal response and motor response. It is used for guiding initial decision making and to monitor neurological status evolution. Range of score is 3–15 (Figure 14). Unconsciousness is defined as GCS ≤ 8.[102]

Category	Score/Description	Score
Best eye response (E)	1 = None 2 = To pressure 3 = To speech 4 = Spontaneous	
Best verbal response (V)	1 = None 2 = Sounds 3 = Words 4 = Confused 5 = Oriented	
Best motor response (M)	1 = None 2 = Extension 3 = Abnormal flexion 4 = Normal flexion (withdrawal) 5 = Localising 6 = Obeying commands	

Figure 14. GCS (Glasgow Coma Scale). Image created by Å Kuntze Söderqvist. Reprinted with permission.

APACHE II

APACHE II (Acute Physiology and Chronic Health Evaluation II) from 1985, is one of many prognostic severity scores for ICU patients, predicting ICU- and hospital mortality based on a number of laboratory values and patient signs. The range of score is 0–71 and an increased score correlates to a subsequent risk of mortality.[103]

GOSE

GOSE (Glasgow Outcome Scale Extended) from 1981 is an outcome rating scale for traumatic brain injury patients categorizing the level of functional independence in the range of 1– 8.[104]

In most studies GOSE ≥ 5 is defined as good neurological outcome. A person with GOSE ≥ 5 is ADL independent.

Patients

The study was approved by the Gothenburg Regional Ethical Review Board, document no 292-08. Nineteen consecutive patients with isolated TBI, requiring mechanical ventilation, sedation and analgesia, and with arterial- and intracranial pressure monitoring for at least one week, were included 2007–2010.

The exclusion criteria were: a) multiple trauma, b) autonomic dysfunction (e.g. diabetes, ischemic heart disease, hypertension), c) patients with arrhythmias precluding analysis of HRV and BRS, d) patients treated with angiotensin converting enzyme inhibitors or ß-adrenergic blockers, e) registration of invasive blood pressure, intracranial pressure and 3-lead ECG for less than seven consecutive days and f) mechanical ventilation for less than seven days (Figure 15).

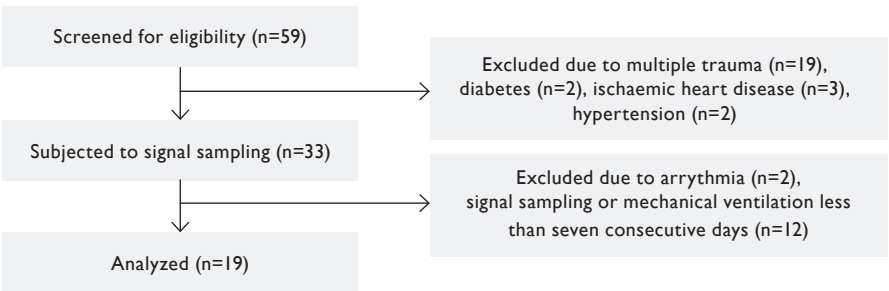


Figure 15. Consort diagram Paper IV. Figure reprinted from Löwhagen Hendén et al, J Neurosurg Anesthesiol 2014;26:50–59 with permission from the publisher.

Methods

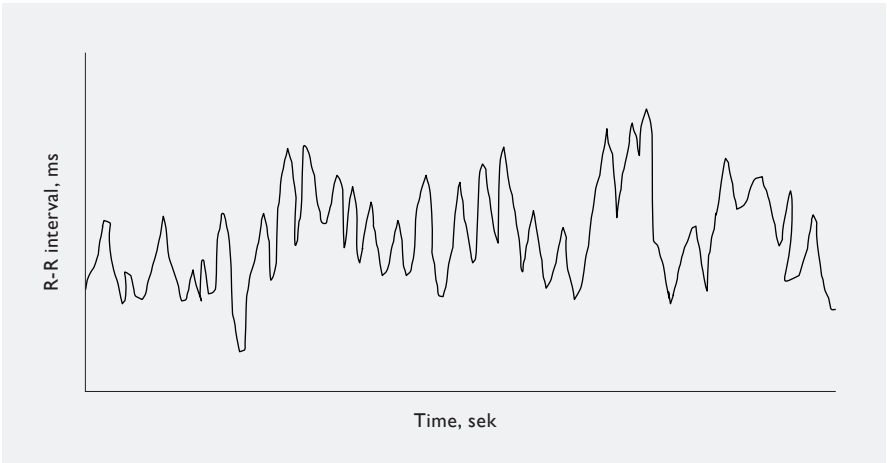
Acquisition of data for HRV and BRS calculations were commenced in NICU and timing was standardized to a period of 60 minutes in the early morning (5–7 a.m.) free of nursing interventions. Data on clinical management (sedation, inotropes, vasopressors, ventilatory support, and surgical procedures) as well as the GOSE score one year later, were obtained from clinical records.

Heart rate variability (HRV)

HRV is analyzed mainly in time domain and in frequency domain. Time-domain analyzes give a measure of the total ANS activity and frequency domain analyzes give a measure on the relative contribution of sympathetic- and parasympathetic nervous system respectively. In Paper IV, only frequency domain analyzes were used. All measurements of HRV followed the "Standards for heart rate variability measurements".[78] Figure 16 explains the (computerized) process/pathway from R-R intervals in the ECG to HRV variables in the frequency domain.

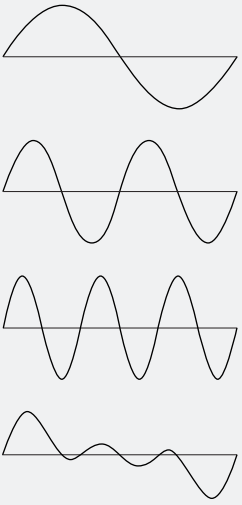
Panel A
R-R interval R-R tachogram

A software program is used to analyze the R-R intervals from the ECG. The R-R intervals can be plotted along a timeline in a so called tachogram with time (seconds) on the x-axis and R-R intervals (milliseconds) on the y-axis. The "waveform" of this R-R tachogram is then subjected to a so called Fourier's transformation.



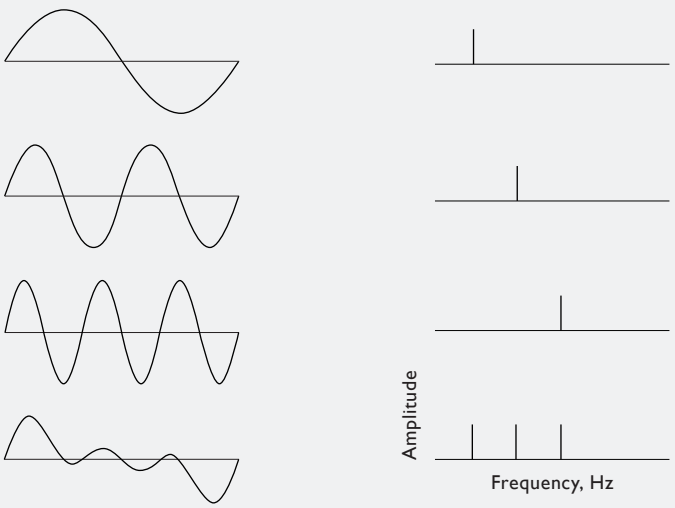
Panel B
A Fourier's transformation

The figure shows three cosine curves on the top, with different frequency but the same amplitude. If they are merged, one more complex curve form (at the bottom) is created. A Fourier's transformation runs this process in reverse, i.e it separates one complex curve form into the single cosine curves it consists of. Obviously, many more than three different cosine curves are needed to built up the real R-R tachogram "waveform" in panel A.



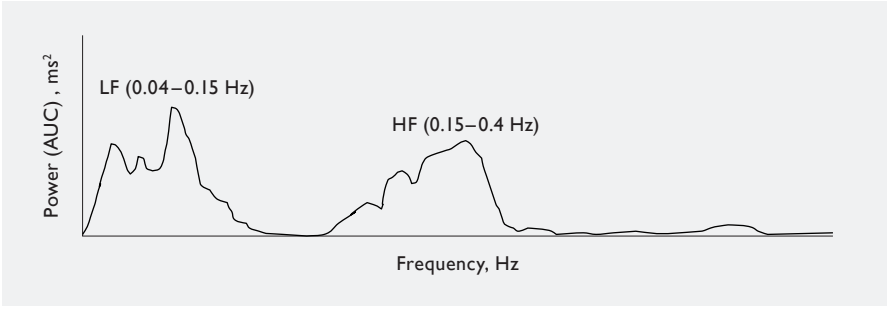
Panel C
Frequency Amplitude

The separated cosine curves, are plotted according to their different frequencies and amplitude. In heart rate variability (HRV) analyzes, a 5 minutes sampling time is used as standard. The sum of the amplitudes, at one frequency during this period, is termed the power of that frequency (ms^2).



Panel D
Frequency domain

In humans, the different frequencies prove to be clustered in defined domains; the low frequency (LF) domain (0.04–0.15 Hz) and the high frequency (HF) domain (0.15–0.4 Hz). The sum of amplitudes for all the frequencies in each domain during the 5 minutes sample period, is termed the power of that frequency domain, representing the AUC (area under the curve) in the figure.



Panel E
High frequency (HF) Low frequency (LF)

In animal- and human research, it has been shown that when manipulating the parasympathetic nervous system by e.g. vagotomy, atropine use or deep breathing, the amplitudes in the high frequency (HF) domain diminish. When manipulating the sympathetic nervous system by e.g. stress test and stellatum blockage, the amplitudes in low frequency (LF) domain diminish and also, to a lesser extent, the high frequency amplitudes. The conclusion has therefore been that the HF component is primarily associated with parasympathetic activity, whereas the LF component is the result of mixed sympathetic and parasympathetic control.[54] The LF/HF ratio gives a measure of sympathetic/ parasympathetic balance with a a high value reflecting a preponderance of sympathetic activity and inversely a low value reflecting a preponderance of parasympathetic activity. The total power of all frequency domains is termed total power (TP).

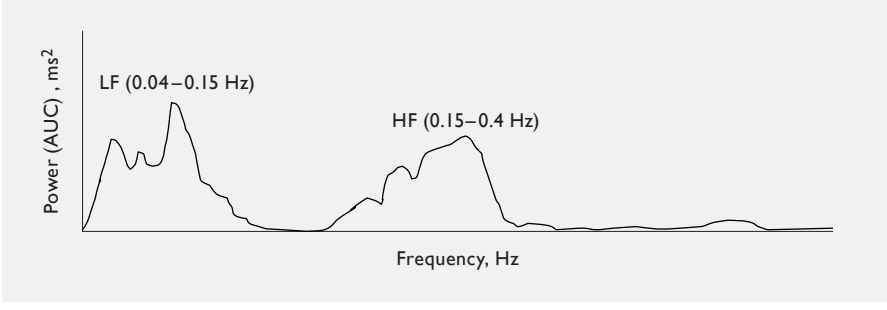


Figure 16 A-E. The pathway from R-R intervals in the ECG to HRV variables in the frequency domain. Images by the author of this thesis.

HRV in the high (HF) and low frequency (LF) domains, as well as, LF/HF ratio and total power (TP), were investigated in Paper IV. Several sequential software programs were used for the HRV and BRS analyzes: Datex Collect ver.5 (Helsinki, Finland), TestPoint™ ver.7 (Measurement Computing Corporation, Norton, MA, USA), MatLab ver.8.1, Baro Reflex Analysis (BRA) Software ver.5.9 and BioSpect ver.1.8.

Baroreflex sensitivity (BRS)

With an intact baroreceptor reflex, an increase in blood pressure results in a decreased heart rate, i.e. a longer R-R interval in the ECG. A decrease in blood pressure consequently results in a shorter R-R interval. The baroreceptor reflex is activated in fractions of a second, mainly by the activation/deactivation of the parasympathetic nervous system. The slope for change in the R-R interval per mmHg change in blood pressure (ms/mmHg) is taken as an index of the baroreflex sensitivity (BRS) (Figure 17).[105]

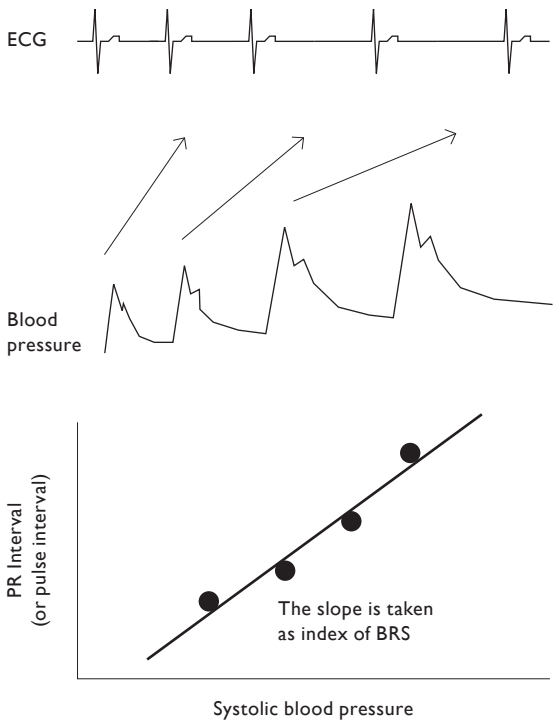


Figure 17. Schematic of the sequence technique for the estimation of the baroreflex sensitivity (BRS). ECG; electrocardiogram. Reprinted from Persson et al, Journal of Hypertension. 2010;19(10):1699-1705 with permission from the publisher.

Statistics

The patients were divided in two outcome groups according to late (1 year) neurological outcome using the GOSE score. GOSE ≥ 5 was defined as favorable and GOSE < 5 as unfavorable outcome. Differences in demographic data between the two groups were compared, by t-test or Mann-Whitney test for continuous variables and Fisher's exact test for dichotomous data.

A two-way ANOVA for repeated measurements were used to assess differences in physiological and autonomic variables between the two outcome groups.

The predictive performance of HRV and BRS (day 7) vs. GOSE < 5 was analyzed by receiver operating characteristics to calculate the Area Under Curve (AUC).

Statistical significance was set to $p < 0.05$.

Results

Paper I

We investigated the impact of intra-procedural hypotension on neurological outcome in 108 AIS patients undergoing EVT in GA. Median age of the cohort was 70 (62–77) years. Median NIHSS was 21 (18–24) and successful recanalization was achieved in 77% of the cases with a median time from stroke to recanalization/end of procedure of 278 (227–345) min. Favorable outcome with mRS ≤ 2 was seen in 41 patients (38%). In the good outcome group (mRS ≤ 2), admission NIHSS was lower, successful recanalization was more common, time from stroke onset to recanalization/end of procedure was shorter and importantly, blood pressures were higher compared to the poor outcome group.

Over 3200 blood pressure recordings were reviewed. Almost all patients experienced a substantial fall in arterial blood pressure during the general anesthesia. There was a trend for lower fractions of baseline MAP in the poor outcome group (p=0.069) (Figure 18).

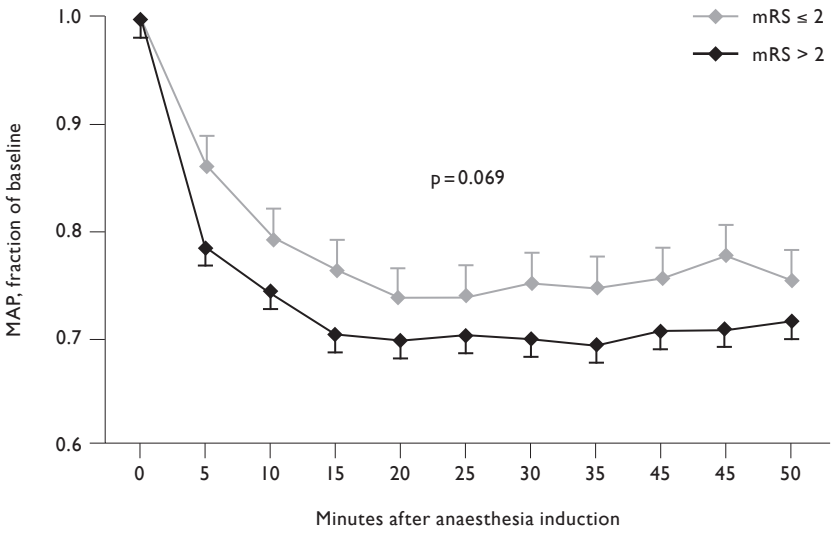


Figure 18. Changes in mean arterial pressure (MAP), expressed as a fraction of baseline MAP. In patients with poor neurological outcome (mRS > 2), a more pronounced fall in MAP was seen after induction of anesthesia. Mean±SEM.

The incidence of a fall in MAP > 40% from baseline was higher in the poor outcome group (p = 0.040) and patients with a fall in MAP > 40% from baseline had a worse neurological outcome and no patient recovered without a neurological deficit (Figure 19).

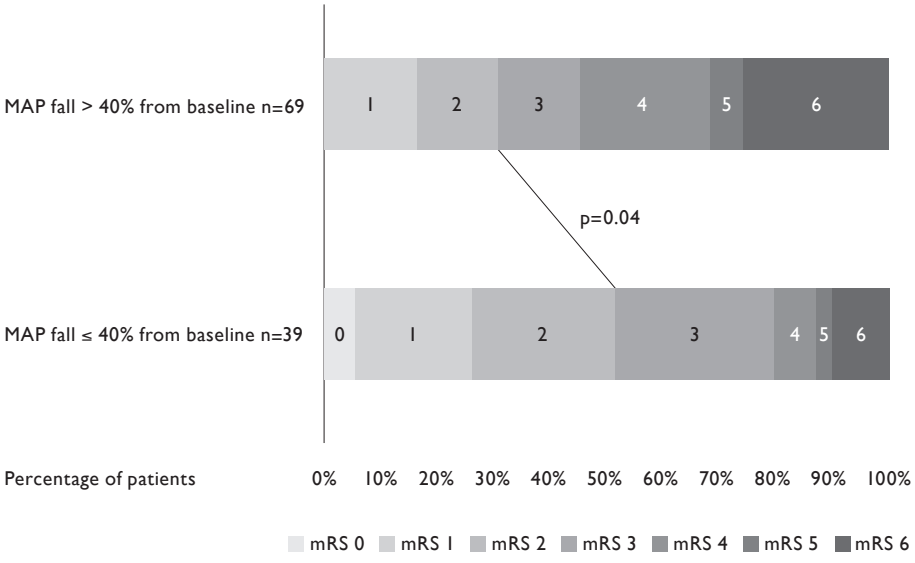


Figure 19. Neurological outcome expressed as modified Ranking Scale (mRS) at 3 months in patients with and without a fall in MAP > 40% from baseline during general anesthesia. The proportion of patients with poor neurological outcome (mRS > 2) was higher in patients experiencing a fall in MAP > 40% from baseline. Figure reprinted from Löwhagen Hendén et al, Stroke 2015;46(9):2678-80 with permission from the publisher.

The independent predictors of poor neurological outcome are shown in Table 2. The odds ratio (OR) of poor neurological outcome, for a patient experiencing a fall in MAP of > 40% from baseline during the EVT, was 2.8.

Table 2. Independent predictors of poor neurological outcome (mRS > 2) with their adjusted OR and 95% CI. mRS; modified Rankin Score, NIHSS; National Institutes of Health Stroke Scale, MCA; middle cerebral artery, ICA; internal carotid artery, CT; computer scan tomography, mTICI; modified Thrombolysis In Cerebral Ischemia/Infarction, MAP; mean arterial pressure, $ETCO_2$; end-tidal partial pressure of carbon dioxide

	OR unadjusted	95% CI	p-value	OR adjusted	95% CI	p-value
Age, years	1.02	0.99–1.06	0.11			
Sex	1.01	0.45–2.24	0.98			
NIHSS	1.13	1.02–1.25	0.022	1.18	1.05–1.34	0.008
Hypertension	0.88	0.40–1.93	0.76			
Atrial fibrillation	0.92	0.40–2.12	0.84			
Ischemic heart disease	0.99	0.37–2.65	0.99			
Diabetes mellitus	3.03	0.62–14.8	0.17			
Smoker	1.08	0.30–3.94	0.91			
Hyperlipidemia	0.48	0.15–1.54	0.22			
Obesity	1.23	0.11–14.0	0.87			
Glucose mmol/L	1.18	0.94–1.48	0.17			
First segment of MCA	1.19	0.54–2.63	0.67			
Second segment of MCA	0.98	0.30–3.21	0.97			
Top of, or distal, ICA	0.98	0.45–2.13	0.95			
Left hemisphere	1.50	0.66–3.40	0.33			
Time from stroke onset to CT	1.02	0.95–1.09	0.64			
Time from stroke onset to groin puncture	1.01	0.96–1.05	0.82			
Time from stroke onset to recanalisation/end of procedure	1.01	1.00–1.01	0.07	1.002	0.996–1.008	0.513
Lack of successful recanalization	22.3	2.9–172.8	0.003	25.6	2.96–250	0.003
Interventional complications	2.54	0.27–23.5	0.41			
Ambulance MAP, mmHg	1.02	0.99–1.05	0.12			
Baseline MAP pre anaesthesia, mmHg	1.02	1.00–1.04	0.13			
Intra-procedural						
MAP, mmHg	1.02	0.97–1.07	0.46			
MAP (fraction of baseline MAP)	0.15	0.01–2.46	0.18			
Highest MAP, mmHg	1.02	0.99–1.04	0.20			
Lowest MAP, mmHg	0.99	0.94–1.03	0.51			
Lowest MAP, fraction of baseline MAP	0.05	0.00–1.04	0.053			
Occurrence of >20% fall in MAP compared to baseline	1.74	0.52–5.81	0.37			
Time spent with >20% fall in MAP compared to baseline	1.01	1.00–1.01	0.057			
Occurrence of >40% fall in MAP compared to baseline	2.41	1.07–5.41	0.034	2.80	1.09–7.19	0.032
Time spent with >40% fall in MAP compared to baseline	1.00	0.9–1.01	0.756			
Use of inotropes	1.16	0.48–2.85	0.731			
Use of vasopressors	2.94	0.57–3.85	0.419			
$ETCO_2$, kPa	0.89	0.45–1.77	0.737			

The main finding in Paper I was that intra-procedural hypotension was more frequent and pronounced in patients with poor neurological outcome. Furthermore, a fall in MAP > 40% from baseline was an independent predictor of poor neurological outcome.

Paper II

In the AnStroke trial, 90 patients were randomized to GA or CS during EVT for AIS. Median age was 72 (65–80) years, median NIHSS 18 (15–22) and median ASPECT score 10 (8–10). Sixty-six patients (77%) received intravenous thrombolysis before EVT. For the whole group, the median time from stroke onset to recanalization/end of procedure was 253 (213–355) minutes.

The GA and CS groups were well balanced for patient characteristics. For stroke characteristics, the admission NIHSS was 20 (15.5–23) in the GA group compared to 17 (14–20.5) in the CS group. There were no differences between the GA and CS group in any of the time intervals. As expected, substantial patient movements were more frequent and angiographic quality was lower in the CS group.

Over 2200 blood pressure recordings were reviewed. During EVT, mean MAP was slightly lower in the GA group, but importantly the average MAP fraction during the anesthesia was similar in both groups. A more frequent occurrence of a fall in MAP > 20% from baseline was seen in the GA group but there were no differences between groups with respect to the occurrence of a fall in MAP > 40% from baseline MAP (Figure 20).

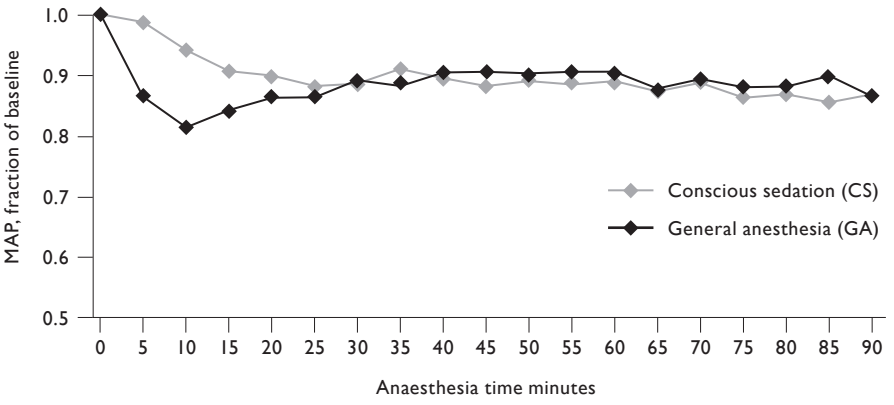


Figure 20. Changes in mean arterial pressure (MAP), expressed as a fraction of baseline MAP in patients under GA versus CS. Mean values.

Successful recanalization was achieved in 81 out of 90 cases (90%) and a favorable neurological outcome with a mRS ≤ 2 was seen in 37 out of 90 patients (41%).

The NIHSS shifts at 24 hours, day 3 and at hospital discharge, as well as cerebral infarction volume day 3, ASPECTS day 3, hospital mortality and incidence of a new stroke at three months, were equal for both groups. There were no differences in the occurrence of anesthesiological or interventional complications and frequency of successful recanalization was also similar for both groups (Table 3).

Table 3. Anesthesiological complications
a Therapy resistant hypertension leading to premature termination of the procedure
b Delayed extubation was defined as extubation after leaving the interventional suit
c Patients converted from CS to GA
d Postoperative pneumonia was defined as the institution of antibiotic therapy due to a clinical or radiological suspected bronchpulmonary infection on day 1–3 after the procedure

	GA	CS	p-value
Anesthesiological complications, n (%)	2 (4.4)	4 (8.9)	0.6766
Loss of airway	0	2	
Aspiration	1	2	
Hemodynamic instability [a]	1	0	
Delayed extubation [b], n (%)	3 (6.7)	3 (6.7) [c]	1.000
Postoperative pneumonia requiring treatment [d], n (%)	6 (13.3)	7 (15.6)	1.000

The main finding in the AnStroke trial was that we found no difference between the two anesthesia techniques with respect to mRS at 3 months (primary end-point) (Figure 21).

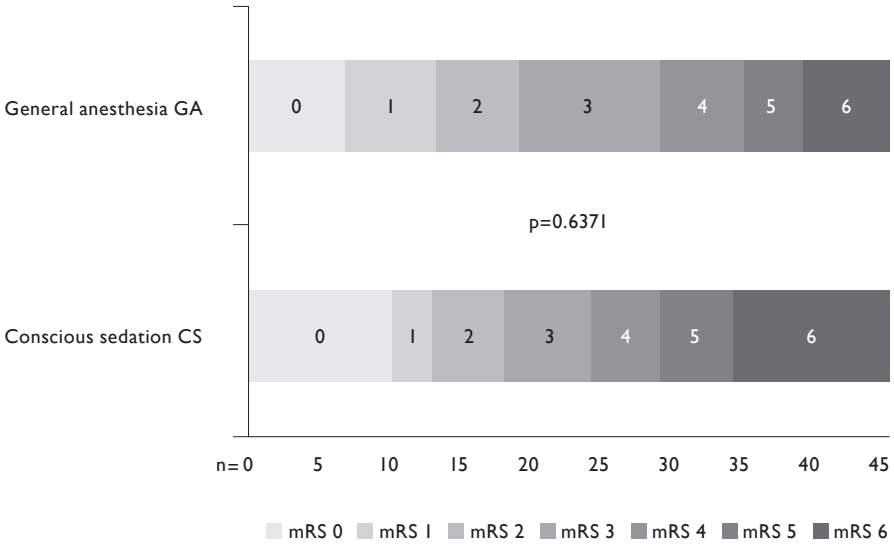


Figure 21. Neurological outcome expressed as modified Ranking Scale (mRS) at 3 months in the GA versus CS group.

Paper III

In this study we investigated the impact of on-hour versus off-hour hospital admission on lead times from stroke onset to recanalization in 198 AIS patients undergoing EVT. Median age was 71 (64–79) years and median NIHSS was 20 (16–23). Sixty-one (31%) of the patients were admitted via a regional hospital and 101 (52%) of all patients received IVT before EVT.

The patients were divided in two groups, the on-hour group or the off-hour group. The proportions of patients from regional hospitals and the proportion of patients having IVT did not differ between the on- and off-hour group.

The NIHSS as well as the incidence of ischemic heart disease was higher in the on-hour group. Time intervals were longer in the off-hour group, except the time interval from stroke onset to CT and the time interval from groin puncture to recanalization (Figure 22).

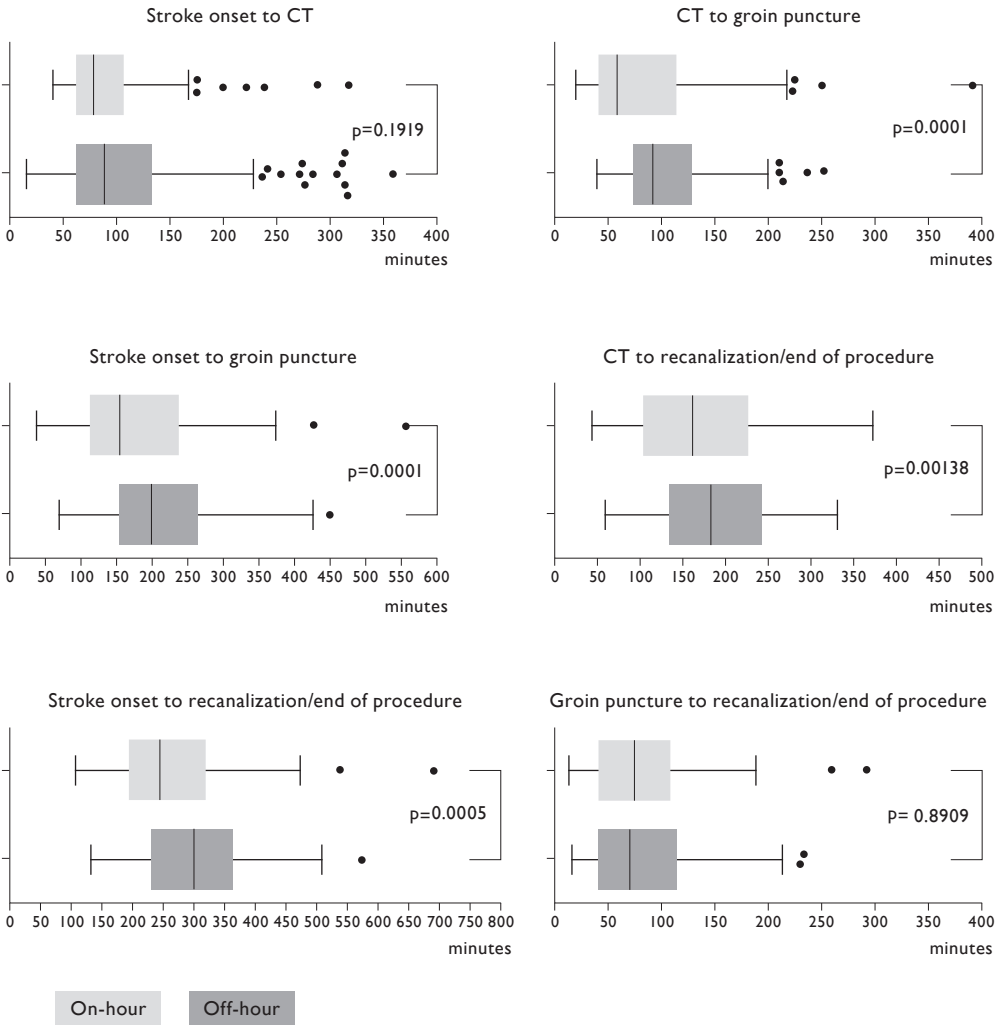


Figure 22. Time intervals from stroke onset to recanalization after EVT for patients admitted on-hour versus off-hour.

General anesthesia with tracheal intubation was performed in 153 (77%) of the patients. The proportion of patients having general anesthesia was similar in both groups. During the procedure the MAP fraction was lower in the off-hour group (0.79 ± 0.13 off-hour versus 0.84 ± 0.14 on-hour, p=0.0293). The occurrence of a > 20% and > 40% fall of MAP from baseline did not differ between groups.

Successful recanalization was achieved in 164 (83%) of the cases and a favorable neurological outcome with a mRS ≤ 2 was seen in 78 (39%) of the patients. We found no statistical significant differences between the groups with respect to good neurological outcome (mRS ≤ 2) at 3 months or the rate of successful recanalization.

In the uni- and multivariate analysis of predictors of poor neurological outcome (mRS > 2) only patients that received recanalization (mTICI 2b-3) were included (n=164). The time intervals included in the analysis were time from stroke onset to CT and time from CT to recanalization, due to co-linearity between the other time intervals. Variables with p < 0.1 in the univariate analysis were included in the multivariate model. The variables with p < 0.1 were age, NIHSS, time from CT to recanalization, occurrence of a fall in MAP > 40% from baseline and blood glucose. Off-hour admission, per se, was not associated with an increased risk of poor outcome (p=0.574).

Only two of the factors in the multivariate analysis made a unique statistically significant contribution to the model, namely age and the time interval CT to recanalization. The odds ratio (OR) for poor outcome was, for age 1.045 (per year increment) and for the time interval CT to recanalization 1.009 (per minute increment) (Table 4).

Table 4. Predictors and odds ratios (OR) of poor neurological outcome (mRS > 2) after successful recanalization (mTICI 2b-3). mRS; modified Rankin Score, mTICI; modified Thrombolysis In Cerebral Ischemia/Infarction, NIHSS; National Institutes of Health Stroke Scale, MAP; mean arterial pressure.

	OR unadjusted	95% CI	p-value	OR adjusted	95% CI	p-value
Age, years	1.045	1.017–1.074	0.001	1.045	1.011–1.080	0.010
NIHSS	1.114	1.032–1.203	0.006	1.092	0.997–1.197	0.059
Time from CT to recanalization, minutes	1.007	1.002–1.012	0.003	1.009	1.003–1.015	0.005
Occurrence of MAP fall >40% from baseline	1.948	1.033–3.671	0.039	1.790	0.839–3.820	0.132
Glucose, mmol/L	1.227	1.029–1.463	0.022	1.203	0.992–1.459	0.060

Paper IV

In Paper IV, 19 patients with traumatic brain injuries aged 33 (± 17) years and with a median Glasgow coma scale (GCS) of 6 (3–13), were studied during the NICU stay. A GOSE score ≥ 5 (favorable neurological outcome) was seen in eleven patients (58%) and a GOSE score < 5 (unfavorable neurological outcome) was seen in eight patients (42%).

BRS and HRV in the LF and HF domains were significantly lower day 3–7 in patients with GOSE score < 5, while the LF/HF ratio did not differ significantly between groups (Figure 23).

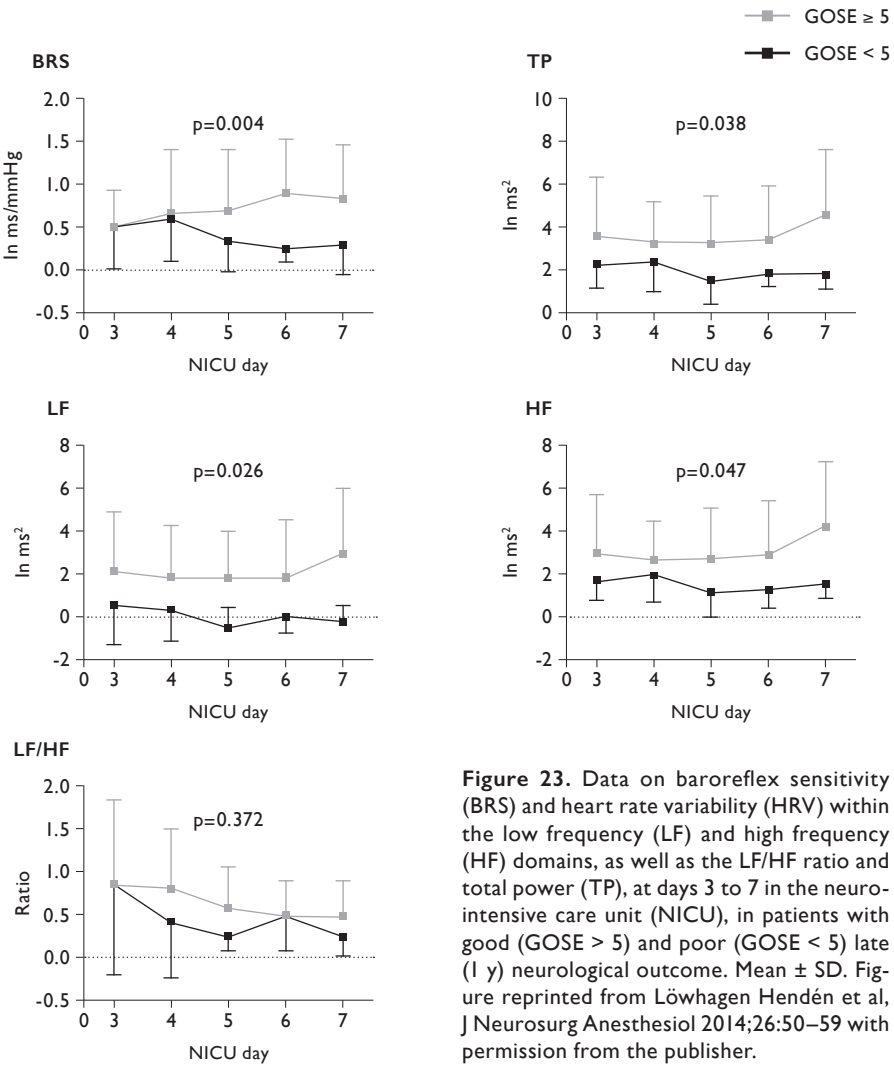


Figure 23. Data on baroreflex sensitivity (BRS) and heart rate variability (HRV) within the low frequency (LF) and high frequency (HF) domains, as well as the LF/HF ratio and total power (TP), at days 3 to 7 in the neurointensive care unit (NICU), in patients with good (GOSE > 5) and poor (GOSE < 5) late (1 y) neurological outcome. Mean ± SD. Figure reprinted from Löwhagen Hendén et al, J Neurosurg Anesthesiol 2014;26:50–59 with permission from the publisher.

There were no differences in age, gender, admission GCS, APACHE II score or the need for de-compressive craniectomy comparing patients with unfavorable outcome to patients with favorable outcome. No statistical differences in intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), heart rate (HR) or arterial partial pressure of carbon dioxide ($PaCO_2$) were detected between the two outcome groups. The differential use of sedation, analgesia and vasoactive drugs in the two groups at day 7 are described in the manuscript.

Receiver operating characteristic (ROC) curve for the abilities of BRS and HRV (TP, LF domain, HF domain) at day 7 to predict poor late neurological outcome showed that BRS, as well as the HRV variables all had ROC areas > 0.78. Day seven was chosen as it exhibited the largest difference in HRV parameters between the groups in the two-way ANOVA analysis. A HF cut-off value of < 2.179 had the highest sensitivity (88%) and specificity (82%) to predict poor late neurologic outcome in this group of patients (Figure 24).

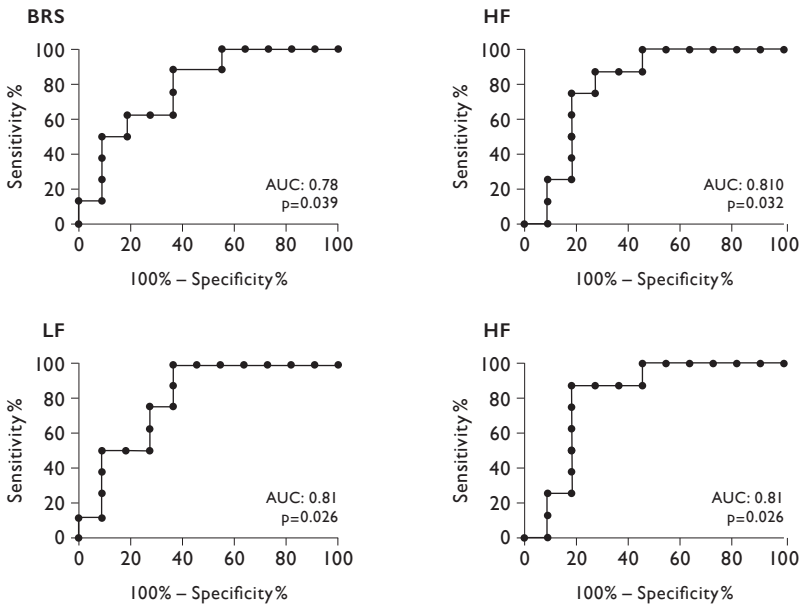


Figure 24. Receiver-operating characteristic (ROC) curves for the abilities of baroreflex sensitivity (BRS) and heart rate variability (HRV) within the low-frequency (LF) and high-frequency (HF) domains and total power (TP) at day 7 to predict poor late neurological outcome. AUC indicates area under curve. Figure reprinted from Löwhagen Hendén et al, J Neurosurg Anesthesiol 2014;26:50–59 with permission from the publisher.

The main finding in Paper IV was that consecutive daily measurements of HRV and BRS are feasible in TBI patients with sedation, analgesia and mechanical ventilation and that the measurements may identify patients with poor late (≥ 1 year) neurological outcome.

Discussion

Anesthesiological aspects on acute ischemic stroke

Anesthesia technique – retrospective studies

In all the retrospective studies, comparing GA with CS for EVT in AIS, there was a considerable risk of patient selection bias, since the NIHSS was higher in the GA group and there was an uneven distribution of posterior strokes [38-40, 43, 45, 46, 48, 49, 54] and co-morbidities [40, 48, 52] between the groups in several of the studies (Table 5).

Table 5. The retrospective studies on anesthesia technique in EVT for AIS. The table shows the proportions of patients receiving GA in each study and further, stroke severity (NIHSS), proportions of posterior stroke, proportion of successful recanalization (mTICI 2b-3) and proportion of favorable neurological outcome (mRS ≤ 2) in the GA and CS groups respectively. NIHSS; National Institutes of Health Stroke Scale, mTICI; modified Thrombolysis In Cerebral Ischemia/Infarction, mRS; modified Rankin Scale, IVT; intravenous thrombolysis, EVT; endovascular treatment.

				Admission NIHSS Median			Posterior circulation %			Successful recanalization %			mRS ≤ 2 at 3 months %		
Author	Year	n=	GA%	GA	CS	p-value	GA	CS	p-value	GA	CS	p-value	GA	CS	p-value
Abou-Chebl	2010	980	43	NA	NA	NA				NA	NA	NA	25	45	<0.0001
Jumaa	2010	126	42	18	15	0.004				70	82	0.103	23	46	0.009
Nichols	2010	75	35	21	19	0.03				35	73	0.01	23	60	<0.01
Sugg	2010	66	14	28	17	<0.01	1	0	0.1493	77[e]	70[e]	0.331	11	51	0.033
Davis	2012	96	50	19	16	0.03	40	21	0.08				15	60	<0.0001
Hassan	2012	136	39	NA	NA	0.0001							17	45	0.0009
Langner	2013	124	15	NA	14		63	17	<0.001	58	59	ns			
Abou-Chebl	2014	281	70	19	16	0.002	13	3	0.3	74	73	0.9	37	53	0.01
John	2014	190	48	16	15	0.364				58	48	0.182	15	23	0.293
Li	2014	109	32	18	15	0.059	20	4	0.018	63[e]	76[e]	0.392	11	15	0.631
McDonald	2014	1014	50												c
Whalin	2014	216	61	20	17	0.009				72	84	0.039	30	49	0.007
van den Berg	2015	348	20	16	15	0.76				49	43	0.37	14	26	0.04
Abou-Chebl[a]	2015	434	34	18	16	<0.0001	4	3	ns	76[e]	73[e]	0.48	31	48	0.0006
Berkhemer[b]	2016	216	37	18	17	ns				52	63	0.19	23	38	0.024
Just	2016	109	39	13	13	0.771	NA	NA	NA				33	46	0.182
Jagani	2016	99	38	16	18	0.67	34	2	<0.0001				16	39	0.02
Bekelis	2017	1174	38				NA	NA	NA						d

a Post-hoc analysis of data from IMS III, a randomized trial for IVT ± EVT
b Post-hoc analysis of data from MR CLEAN, a randomized trial for IVT ± EVT
c Hospital mortality 25 % (GA) vs 12 % (CS) p<0.0001
d Case fatality difference for GA vs CS 7.2% (95% CI: 2.6-12%)
e TICI score 2-3 defined as sucessful recanalization

Three of these retrospective studies, found that GA was an independent predictor of poor neurological outcome (mRS ≤ 2), after adjusting for other known prognostic factors such as stroke severity (NIHSS), age and recanalization rate.[45, 51, 52] In five other studies, the degree of recanalization was not adjusted for, which is a major limitation, as timely recanalization is the major determinant of neurological outcome.[47, 48, 50, 54, 55] Furthermore, adjusting for NIHSS, may not capture all aspects of stroke severity and pre-interventional events seen in a larger proportion in GA patients, which may influence outcome.

In most of the retrospective studies several known and possibly predictive factors of neurological outcome are missing, such as peri-procedural blood pressure, blood glucose, ventilatory parameters (end-tidal carbon dioxide, arterial blood gases, pulse oximetry, respiratory frequency, tidal volumes) and administered anesthetic- and vasoactive drugs (Table 6). Thus, prospective randomized studies, with complete data capturing, were repeatedly requested for several years before the AnStroke trial (Paper II) was launched in 2013.

Table 6. Data presented in the retrospective studies. BP; Blood pressure.

			The retrospective studies present data on:						
Author	**Year**	**n=**	**BP baseline**	**BP Periop**	**Blood glucose**	**Ventil Periop**	**Anesth drugs**	**Vasoactive drugs**	**Time intervals**
Abou-Chebl	2010	980							•
Jumaa	2010	126			•				•
Nichols	2010	75	•		•				•
Sugg	2010	66							•
Davis	2012	96		•	•				•
Hassan	2012	136							•
Langner	2013	124					•		•
Abou-Chebl	2014	281	•						•
John	2014	190	•	•			•	•	•
Li	2014	109	•		•		•		•
McDonald	2014	1014							
Whalin	2014	216	•	•				•	•
van den Berg	2015	348							
Abou-Chebl	2015	434			•				•
Berkhemer	2016	216							•
Just	2016	109							•
Jagani	2016	99	•	•	•		•	•	•
Bekelis	2017	1174							

In comparison to the retrospective studies published on EVT for AIS, the GA cohort in Paper I was slightly older, with similar frequencies of co-morbidities, a higher frequency of occluded internal carotid artery and comparable admission NIHSS (median 21). Our regression analyzes showed that the most important factor for good neurological outcome was occurrence of successful revascularization and 77% of our patients reached mTICI score 2b-3, which is comparable or better than in other retrospective studies. The neurological outcome result (38% of patients achieving mRS ≤ 2) was more favorable than for GA patients in all of the retrospective studies (Table 5).

Blood pressure

The worse neurological outcome for GA patients in the retrospective studies, could be explained by a more pronounced peri-procedural hypotension in this group during the EVT. It is well-known that the vasodilatory side-effect from most anesthetic drugs causes hypotension, correlating to the depth of anesthesia.[106]

In only four of the cited retrospective studies, the role of intra-procedural hypotension for neurological outcome was addressed[40, 42, 44, 48]. Only one of the studies[42] expressed the intra-procedural changes in blood pressure as fractions of baseline values, which is important, as baseline MAP varies considerably between AIS patients.[70]

In two of the studies, that did present data on perioperative BP, it was shown that GA was an independent predictor of worse neurological outcome. To evaluate whether intra-procedural hypotension could be a potential contributor to poor outcome in the GA patients, a second regression model was constructed in both studies, substituting lowest SBP < 140 mmHg[48] or lowest MAP < 70 mmHg[42], for anesthesia type. In such a second regression model, low intra-procedural blood pressure was associated with poor neurological outcome in both studies. The problem with these analyzes was that type of anesthesia and blood pressure are co-linear variables, making it difficult to identify the role of hypotension, per se, for neurological outcome. The strength of the retrospective study presented in Paper I, was that the confounding of anesthesia type was eliminated, as all patients were subjected to GA.

A recently published retrospective study from Whalin et el have analyzed a cohort were all patients were subjected to CS during EVT.[107] Their results showed that patients with a 10 % MAP fall from baseline, had an OR for poor neurological outcome of 4.38 and for every 10 mmHg fall in MAP < 100 mmHg, the OR for poor neurological outcome was 1.28. These findings certainly emphasize the role of hypotension for poor outcome after EVT.

Intra-procedural hypotension, typically seen after induction of anesthesia, may impair important collateral perfusion to the penumbra, especially as the cerebral autoregulation capacity could be diminished during ischemia and accordingly, hypotension could hasten the progression of manifest infarction.[72] Although the data on blood pressure during EVT is scarce, international guidelines recommend that the SBP should be maintained between 140–180 mmHg during the endovascular procedure.[64] This approximately corresponds to a SBP drop of 10 % from common baseline values. In Paper I, both the occurrence of and actual time spent with MAP more than 20% and 40% below baseline values were common findings, despite the fact that > 70% of all patients were treated with vasopressors. Whalin et al[42] reported a > 20% fall in MAP in more than 50% of the patients receiving GA. Eighty percent of their patients received vasopressor therapy. Thus, GA for endovascular therapy in AIS is associated with pronounced aberrations of arterial blood pressure from baseline, despite vasopressor therapy in the majority of the patients.

Notably, despite the unsatisfactory blood pressure control in Paper I, 38% of the patients had a mRS score ≤ 2 at 3 months, which is a better result compared to GA patients in the other retrospective studies.[67] Comparisons of blood pressure parameters in the retrospective studies and in Paper I and Paper II are shown in Table 7 and Table 8.

Table 7. Comparisons of blood pressure parameters (baseline values and lowest peri-procedural values) between the retrospective studies, Paper I and Paper II. MAP; mean arterial pressure, SBP; systolic blood pressure.

Blood pressure comparisons		Baseline MAP mmHg		Baseline SBP mmHg		Lowest MAP mmHg		Lowest SBP mmHg	
Author	**Year**	**GA**	**CS**	**GA**	**CS**	**GA**	**CS**	**GA**	**CS**
Davis	2012					72	86	104	137
John	2014	106	107	152	157	72	89	109	110
Whalin	2014	108	105	156	155	69	74		
Jagani	2016					62	79	94	119
Nichols	2010			147	150				
Abou-Chebl	2014			143	147				
Li	2014	110	105						
Abou-Chebl	2015								
Löwhagen Hendén	2015	107	NA	154	NA	61	NA	89	NA
Löwhagen Hendén	2017	105	108	156	163	68	77	101	119

Table 8. Comparisons of more specific data on peri-operative blood pressure measures presented in the retrospective studies with corresponding results from Paper I and Paper II. MAP; mean arterial pressure, SBP; systolic blood pressure.

Blood pressure comparisons

Author	Year	GA	CS
Davis	2012	0% of patients reached target SBP 140–180 mmHg	44% of patients reached target SBP 140-180 mmHg
John	2014	15% of patients experienced a MAP < 60 mmHg	13% of patients experienced a MAP < 60 mmHg
Whalin	2014	54% of patients experienced a 20% fall in baseline MAP	28% of patients experienced a 20% fall in baseline MAP
Jagani	2016		
Nichols	2010		
Abou-Chebl	2014		
Li	2014		
Abou-Chebl	2015		
Löwhagen Hendén	2015	0% of patients reached target SBP 140–180 mmHg 42% of patients experienced a MAP < 60 mmHg 89% of patients experienced a 20% fall in baseline MAP	
Löwhagen Hendén	2017	2% of patients reached target SBP 140-180 mmHg 27% of patients experienced a MAP < 60 mmHg 93% of patients experienced a 20% fall in baseline MAP	4% of patients reached target SBP 140-180 mmHg 11% of patients experienced a MAP < 60 mmHg 60% of patients experienced a 20% fall in baseline MAP

Due to the poor blood pressure control during EVT in our institution, detected in Paper I, we changed our institutional guidelines, with a more aggressive treatment of intra-operative hypotension. As a result, the MAP fraction was considerably higher in Paper II than in Paper I (Figure 25) and the occurrence of a MAP fall > 40% from baseline was markedly lower.

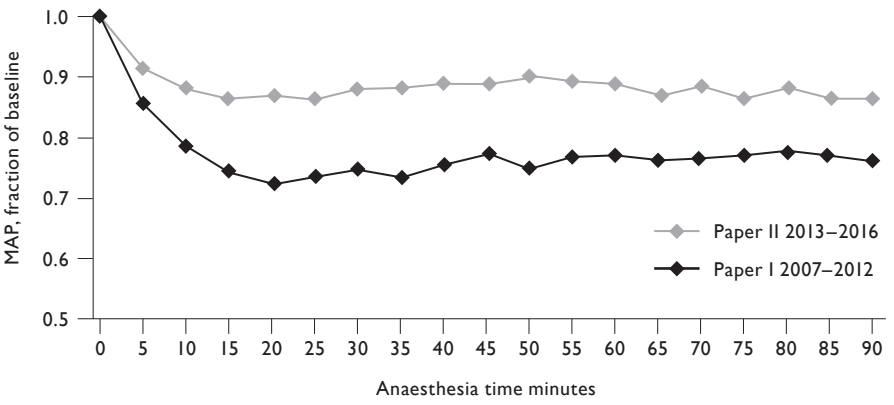


Figure 25. MAP fraction during EVT for patients in Paper I versus patients in Paper II. Mean values.

The more accurate treatment of hypotension resulted in only a minor difference between the blood pressures in the GA versus the CS group in Paper II. Thus, one explanation for equivalent neurological outcomes between the GA and CS groups in the AnStroke trial, despite the higher NIHSS at admission in the GA group, could be the fact that arterial blood pressure was now only marginally lower in this group. Notably though, also in the AnStroke trial there was a trend for worse outcome in the patient group experiencing a MAP fall of > 40% from the baseline value, comparable with the result from Paper I (Figure 26).

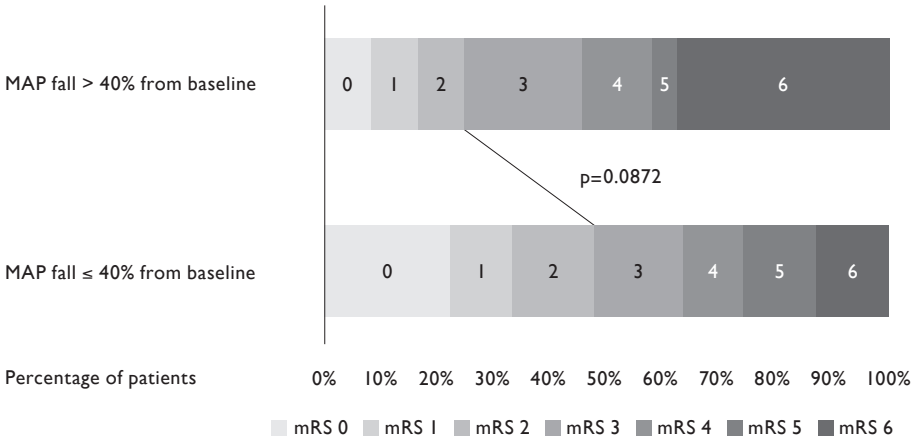


Figure 26. Neurological outcome expressed as modified Ranking Scale (mRS) for patients in Paper II (AnStroke trial) with MAP fall > 40 % and ≤ 40 % from baseline respectively.

In summary, hypotension during EVT is common, both in GA and CS, and AIS patients are particularly sensitive to hypotension until revascularization is achieved. Hypotension is an independent predictor for poor neurological outcome and should be treated aggressively.

Ventilation

Hypercapnia

Hypercapnia (defined as $PaCO_2 > 6$ kPa), has been postulated as a benefit for the CS patients in the retrospective studies, presuming that the patients hypoventilate and that the resulting hypercapnia facilitates cerebral blood flow by cerebral vasodilation.[50] This theory however, has at least two limitations. First, there are hardly no studies on ventilator parameters during EVT and it has not been shown that patients under CS for EVT do hypoventilate. On the contrary, Mundiyanapurath et al, showed that patients under CS were hyperventilating.[108] Whether the CS patients hyper- or hypoventilate is of course largely dependent on the dose of sedative anesthetics administered. In Paper II, the CS group was normoventilated, probably due to a higher dose of remifentanil administered, compared to the study by Mundiyanapurath et al.

The second limitation is that, even if CS does in fact cause hypoventilation and hypercapnia, the assumption that blood flow to penumbra tissue increases might be wrong. If the vessels in the penumbra tissue are already maximally dilated, due to the pressure-autoregulation mechanism, dilation only occurs in the surrounding vessels. This might cause a "steal phenomenon" with diminished, instead of increased, blood flow to the penumbra region. Notably, it has also been shown that vessels in ischemic tissues have reduced vasodilatory capacity in response to hypercapnia.[109]

Hypocapnia

Well-known effects of hypocapnia (defined as $PaCO_2 < 4.5$ kPa) are cerebral vasoconstriction and a left-ward shift of the oxygen dissociation curve, possibly impairing the oxygen delivery to the penumbra.[63] Existing data suggest that hypocapnia is associated with poor prognosis in stroke patients and it has been suggested that anesthesia staff routinely hyperventilate neurological patients during GA.[110, 111] As mentioned, the vessels in ischemic tissues have reduced vasodilatory capacity in response to hypercapnia, but on the contrary, the ability to constrict in response to hypocapnia is preserved.[63, 109, 112]

Indeed, Takahashi et. al. showed that hypocapnia was associated with poor neurological outcome in patients undergoing EVT in GA for AIS. Mean $ETCO_2$ was 4.7 kPa for patients with favorable outcome and 4.3 kPa for patients with unfavorable

outcome, with an OR for unfavorable outcome of 1.3 per 0.13 kPa decrease in $ETCO_2$.[113] In Paper I (only GA patients), $ETCO_2$ values were in the lower range as compared to values presented in the study by Takahashi. However, values were similar in both outcome groups (median values 4.4 kPa and 4.3 kPa in the favorable vs unfavorable outcome group respectively) and we did not find an association between $ETCO_2$ and neurological outcome in a logistic regression analysis (Table 2).

Importantly, the GA group in Paper II was not hyperventilated (median $PaCO_2$ 5.4 kPa in the GA group, which can be compared to 5.2 kPa in the CS group). In Paper II, $PaCO_2$ was not associated with neurological outcome in a univariate logistic regression analysis (data not published).

In summary, the influence of hypercapnia and hypocapnia on penumbra blood flow in AIS is not extensively studied. International guidelines recommend normocapnia ($PaCO_2$ 4.7-6.0 kPa) in the GA group and to avoid hypercapnia in the CS group.[64] Worth noticing is that $ETCO_2$ does not always accurately represent the true $PaCO_2$, due to situations with ventilation/perfusion mismatch.[114] Thus, in future studies, arterial blood gases should be drawn repeatedly for accurate measurements of $PaCO_2$, together with close blood pressure monitoring.

Oxygenation

Hypoxemia

Hypoxia is a common feature in patients admitted for stroke although there is no consensus on the hypoxia definition (hemoglobin oxygen saturation ranging from < 90% to < 96% and PaO_2 < 8 kPa in different studies).[115, 116] In one study, 63% of AIS patients experienced hemoglobin oxygen saturation < 96 % for more than 5 minutes during the initial 48h from admission.[116] In a healthy subject experiencing hypoxia, brain vessels vasodilate to compensate for a decrease in blood oxygen content.[117] However, in the penumbra region, vessels have reduced capacity to vasodilate in response to eventual hypoxia.[118]

The occurrence of hypoxia is associated with worse neurological outcome after stroke; Rocco et al reported an OR of 15 for poor outcome in hypoxic patients compared to non-hypoxemic patients (hypoxic defined as occurrence of pulse oximetry values < 92% during hospitalization).[119] However, it remains unclear whether hypoxemia is the cause, or just a sign, of poor prognosis. Also, limited and divergent data exist on the benefit of supplemental oxygen. In the published randomized studies on supplemental oxygen, the oxygen was administered within 12–48 hours after stroke onset, often without data on hemoglobin oxygenation saturation or PaO_2 and without

data on reperfusion strategies or reperfusion results.[120-124] Thus, the interpretation of the results and their relevance in an acute setting during EVT can be questioned.

Hyperoxia

In the literature, there have been concerns about negative effects of oxygen supplementation, as oxygen encourage the formation of toxic free radicals, that could harm the vulnerable penumbra. However, studies showing toxic free radical production in AIS, used late treatment onset, animal models, long-term oxygen therapy and often hyperbaric treatments.[125] Another concern has been that oxygen supplement could result in hyperoxia (PaO_2 > 13 kPa), known to induce cerebral vasoconstriction, that could theoretically compromise blood flow to the penumbra tissue. However, in the ischemic brain, hyperoxia is described to paradoxically increase cerebral perfusion by vasodilation.[123]

In conclusion; whether or not oxygen supplement is beneficial when administered before revascularization, in order to extend the reperfusion window, is not studied. Nonetheless, in international guidelines, supplemental oxygen in EVT is only recommended if hemoglobin oxygen saturation is < 92%.[64]

In Paper II, all patients received supplemental oxygen, according to our institutional guidelines, and hemoglobin oxygen saturation as well as PaO_2 were higher than the international recommendations, and also significantly higher in the GA group compared to the CS group. Hemoglobin oxygen saturation and PaO_2 were not associated with neurological outcome in a univariate logistic regression analysis (data not published).

Anemia

In addition to hemoglobin oxygen saturation, the hemoglobin concentration is of importance for the blood oxygen content. Many of the AIS patients are anemic (defined as hemoglobin concentration < 120 g/L for women, < 130 g/L for men) at admission; 25% in a study by Barlas et al and the common routine to administer intravenous crystalloid solutions might result in a dilution anemia.[126]

Hemoglobin concentrations in AIS are associated with infarction growth[127] and mortality[126, 128] and describes a U-formed curve in relation to the neurological outcome, outcome being worse with very low and very high hemoglobin concentrations.[129] Dilution with crystalloid solutions to lower the hemoglobin concentration and theoretically improve the blood rheology in AIS, has not been demonstrated beneficial.[130] Furthermore, erythrocyte transfusions to rise the concentration, did not improve neurological outcome in NICU treated AIS patients in a study by Kellert et al.[131]

The impact of acute erythrocyte transfusions on neurological outcome in the anemic AIS patient, has not been studied and no target hemoglobin concentration is available in international guidelines.[64] In Paper II, 33% of the patients were anemic (definition above) at admission. Two patients received erythrocyte transfusions during the EVT. Hemoglobin concentration was not associated with neurological outcome in a univariate logistic regression analysis in our study (data not published).

Blood glucose

Forty percent of the AIS patients are hyperglycemic (defined as blood glucose > 7.8 mmol/L) at admission according to Alvarez-Sabin et al.[132] Blood glucose was seldom reported in the cited retrospective studies, although hyperglycemia is a well-known negative prognostic factor for neurological outcome in AIS and associated with reduced benefit from recanalization with IVT.[132-135]

Blood glucose during EVT was studied by Kim et al, showing that patients with hyperglycemia were less likely to achieved an excellent outcome (mRS ≤ 1) at 3 months compared to patients without hyperglycemia.[134] Li et al and Davis et al also presented data on hyperglycemia as an independent predictor of mortality and poor neurological outcome after EVT.[43, 48]

Randomized studies on insulin therapy in AIS in general have failed to show any outcome benefit when therapy was initiated 6–24 hours after stroke onset.[136] Instead, there was an increased risk of hypoglycemic episodes in the treatment group. Hypoglycemia is a well-known devastating condition, with the potential to cause secondary brain injury. For hyperglycemia, the question remains whether this, per se, worsens the prognosis (hyperglycemia leads to cerebral acidosis and could potentially exaggerate the neuronal injury) or if hyperglycemia merely is a physiological stress response indicating a more severe stroke.

In international guidelines, target blood glucose is set to 7.8–10 mmol/L.[64] In Paper I and Paper II, the patients had mean blood glucose values under the hyperglycemia-limit and blood glucose was not associated with neurological outcome in univariate logistic regression analyzes (Table 2) (Data for Paper II not published).

Anesthetic drugs

In several of the retrospective studies, it is suggested that higher doses of anesthetic drugs during GA attenuate the cerebral autoregulation, contributing to the worse outcome in the GA group.[40, 45, 49, 52-55] On the other hand, some authors mention the possibility of a dose-dependent neuroprotective effect by the anesthetics.[42, 45, 52]

Anesthetics do attenuate the cerebral autoregulation, although to varying extent; inhalation anesthetics more pronounced than propofol while isoflurane has a more pronounced effect than sevoflurane.[137-139] Dexmedetomidine also has a negative impact on cerebral autoregulation,[140] while opioids, on the other hand, preserve autoregulation.[137] Whether the influence from anesthetics on autoregulation is important or not during EVT is unknown. As mentioned earlier, autoregulation in ischemic tissues is already diminished or lost.

Regarding the neuroprotective effects, inhalation anesthetics reduce cerebral metabolic rate (CMR) but retain cerebral blood flow (CBF) in contrast to propofol, which diminishes CMR but also the CBF.[137] Opioids and dexmedetomidine, exhibit a less pronounced decrease in both CMR and CBF compared to inhalation anesthetics and propofol.[137] Indeed, Sivansankar et al reported better neurological outcome after EVT in GA if patients received inhalation anesthesia (desflurane or sevoflurane) when compared to intravenous anesthesia (propofol).[141]

All patients in Paper I and the GA patients in Paper II, were subjected to inhalation anesthesia (sevoflurane plus remifentanil). In Paper II the CS group received remifentanil. The GA group in Paper II had, due to chance, higher NIHSS, higher incidence of proximal occlusions and left-sided lesions, yet equivalent neurological outcome to the CS group.

Thus, one could speculate on GA showing a neuroprotective effect in Paper II (AnStroke trial). A randomized trial on intravenous versus inhalation anesthesia would be of interest in the future.

Anesthetic complications

Another matter of debate in the retrospective studies, has been the rate of complications with GA and CS respectively. One reason for worse outcome in the GA group was considered to be more frequent aspiration pneumonia in this group. Undoubtedly, there was a higher incidence of pneumonia in the GA group in the AnStroke trial, as in several previous studies.[41, 46, 47, 50] Most likely this is due to the invasive ventilation, since the risk of aspiration, per se, applies to both GA and CS.[142] However, all patients with pneumonia in Paper II were treated with antibiotics and postoperative pneumonia was not associated with neurological outcome in a univariate logistic regression analysis (data not published).

Regarding interventional complications, patient agitation and patient movements during CS are considered to possibly hamper catheterization and degrade angiography quality, which can lead to an increased complication frequency.[67] This has not been

proven in previous studies and in the AnStroke trial, even though the angiographic quality was worse and substantial patient movements were more frequent in the CS group; this was not associated with more complications, e.g. vessel perforation.

Time is brain

It has been claimed that one major disadvantage of GA and intubation for EVT is the potential risk of delaying the procedure start time. This means a prolonged CT to groin puncture time, which could affect the treatment outcome.[44, 53, 55, 68] The CT to groin puncture time in the AnStroke trial, was almost identical for the two groups (≈ 90 minutes) and there was no difference in the CT to recanalization time (≈ 160 minutes).

The specific time intervals that could be affected by anesthesia technique are rarely presented in previous studies, namely time "from arrival to neurointervention suite to groin puncture" (possibly longer for GA due to induction of anesthesia and intubation) and "from groin puncture to recanalization" (possibly shorter for GA because of better working conditions for the neurointerventionist). In the AnStroke trial, there was a trend towards longer "from arrival to neurointerventional suite to groinpuncture" time interval in the GA group, which was compensated by a shorter "from groin puncture to recanalization" time interval.

On-hour versus off-hour

In Paper III, we found a substantial delay in the time interval from admission CT to recanalization for AIS patients admitted for EVT during off-hours (median 20 minutes). Time from groin puncture to recanalization was similar during on- and off-hours, suggesting that no delay in treatment was caused by the responsible neurointerventionists. The longer CT to recanalization time during off-hours could not immediately be explained by differences in patient characteristics, differential use of general anesthesia, the extent of IVT or proportion of admissions from regional hospitals, as all these factors were similarly distributed between the on- and off-hour group. Most likely, the time delay during off-hours was due to a reduced hospital staffing, experience and competence of the involved professional teams during nights and weekends. Importantly though, the off-hour admission per se, was not an independent predictor for poor outcome.

Delay in the CT to recanalization time seen off-hour is previously described, and the 20 minutes delay in the present study is well in agreement with the results presented in some earlier studies.[17, 18] Several authors suggest that CT to recanalization time is a relevant in-hospital performance metrics, since it can be modified by the hospital personnel.[19, 143] Furthermore, the time interval is shown to be an important indepen-

dent predictor of the neurological outcome after EVT. In the ESCAPE trial, every 30 minutes increase in CT to recanalization time, reduced the probability of achieving good neurological outcome (mRS ≤ 2) by 8.3%.[19] These figures are in line with the results from Paper III, showing an OR of 0.991 for good neurological outcome for every minute delay in the time interval CT to recanalization.

Although there was a substantial time delay in off-hour EVT treatment for AIS in the present study, the observed delay did not translate into a statistically significant difference in the proportions of good neurological outcome between the on-hour and off-hour groups (43% and 37% respectively, p=0.47). This could be explained by the fact that the groups were unbalanced with respect to NIHSS and incidence of ischemic heart disease. The NIHSS was significantly higher in the group of patients admitted on-hour, which could level out the beneficial effects of shorter lead times on neurological outcome. Furthermore, the incidence of ischemic heart disease was more than twice as high in the on-hour group, indicating that this group had a more pronounced arteriosclerotic disease. Similarly, neither Almekhlafi et al nor Mpotsaris et al, both including about 100 patients in their studies, with similar off-hour delay (approximately 20 minutes), could detect differences in neurological outcome.[17, 18] Also in those studies, group imbalances were demonstrated. In the study by Mpotsaris et al, for example, patients admitted on-hour were significantly older.

After several randomized trials reporting efficacy of EVT over standard medical care with IVT in AIS, the number of patients eligible for EVT is estimated to increase three- to five-fold in the coming years.[6] This will put a harder strain on the stroke organization during off-hours (as well as during on-hours) and the results in Paper III mandate further analysis and measures to correct the imbalance between time intervals for on- versus off-hour admittance. Increased resources will have to be allocated to EVT in AIS, investments that soon will repay themselves, as short- and long-term costs diminish for every patient achieving an independent neurological outcome.[144]

Anesthesia technique – prospective studies

To our knowledge, the AnStroke trial (Paper II) is the second prospective randomized trial comparing GA with CS for EVT in AIS. The recently published SIESTA trial[68] showed that CS did not result in better early neurological recovery (primary outcome), as assessed by NIHSS 24h, a finding that was confirmed in our study. On the other hand, in the SIESTA trial, the proportion of patients having good neurological outcome (mRS ≤ 2) at three months (secondary outcome) was significantly higher in the GA group (37%) compared to the CS group (18%).

In the AnStroke trial, including patients with equally high admission NIHSS as the SIESTA trial, the proportion of patients having a mRS ≤ 2 at three months was approximately 40% in both groups. The low incidence of good neurological outcome in the CS group in the SIESTA trial could be explained by the fact that the staff, according to the authors, was less experienced with the CS technique at the time of their study start.

The SIESTA trial results emphasize the importance of staff familiar with both anesthesia techniques. Most importantly, neither the SIESTA nor the AnStroke trial could demonstrate that GA results in worse neurological outcome compared to CS, as suggested by previous retrospective studies.

Methodological considerations Paper I–III

Paper I

- The major limitation of the study is its retrospective design.
- Although intra-arterial blood pressure was continuously monitored during the EVT procedure, the accuracy of the anesthesia chart recorded blood pressures was limited to ± 5 mmHg.
- The MAP limit of more than 20% fall from baseline, was chosen in accordance with international guidelines which propose a maximum drop of BP of 10-20% from baseline during EVT. As all patients had a 10% MAP fall from baseline, the 20% limit was selected. A 40% fall in MAP from baseline represents, in average, the BP at which the cerebral autoregulation curve reaches its steep part and the cerebral blood flow becomes linearly dependent on the cerebral perfusion pressure.

Paper II

- The power calculation in Paper II was based on published retrospective studies on anesthesia for EVT before 2012, showing large differences in neurological outcome for GA versus CS groups. The incidence of good outcome varied as much as 20-40 percent units between the GA and CS groups. The AnStroke trial was powered to detect a difference of that magnitude with an inclusion of 80 patients, a reasonable number in a single-center setting. We included 90 patients, assuming a 10% loss to follow-up. However, the size of the study was limited and a small difference in outcome would have been difficult to interpret, had it occurred.
- The NIHSS limits of ≥ 10 was the institutional limit used for EVT eligibility at the time of study design (≥ 14 if there was a dominant hemisphere occlusion) since this magnitude of NIHSS is associated with large vessel occlusions. Since recently discovered evidence was published, supporting the efficacy of EVT also for lower

NIHSS, all patients with NIHSS ≥ 6 are now eligible for EVT.

- We did not use a detailed study protocol for the anesthesia procedure per se, which would have been ideal, but at the time for the trial design, that approach was not considered feasible. The study patients were managed according to our institutional guidelines for anesthesia during EVT. All patients in the GA group received maintenance anesthesia with sevoflurane and remifentanil and all patients in the CS group received remifentanil.
- The study was blinded in all relevant aspects: The neuroradiologists reviewing the CT and MRI examinations were blinded to anesthesia type, recanalization grade and neurologic outcome. The angiographic data were reviewed by neuroradiologists blinded to the CT and MRI reviews, as well as to neurologic outcome (but not to the anesthesia type, as a tracheal tube can be seen on the angiographic images).
- The primary endpoint was evaluated by a vascular neurologist, blinded to treatment allocation and recanalization grade, assessing mRS by direct examination of 81 patients (90%). In most studies, as the recently published SIESTA trial, only telephone interviews are performed by a modified Rankin Scale–certified investigator.[68]
- No patient was lost to follow-up.
- As the AnStroke trial was a single center study, the results cannot automatically be applied to other centers with different neuroanesthesiological and neurointerventional approaches.

Paper III

The cohort in Paper III was a merger of the retrospective cohort in Paper I and the prospective cohort in Paper II and the patients were thus not consecutive. However, for the purpose of the study, namely to assess the differences in time intervals between on- and off hour stroke admittances, the new cohort was adequate. The number of included patients was twice the number in earlier studies and collected data included extensive information on prognostic factors for stroke outcome.

Ethical considerations Paper I–III

The studies were approved by the Gothenburg Regional Ethical Review Board, documents no 455-12 and no 013-13.

Paper I was a retrospective observational study.

The two anesthesia techniques used in Paper II (a prospective study) were both standard procedures in our institution before the start of the trial. We did not consider the randomization as an ethical dilemma, as patients with medical indication or contraindication, for any of the two techniques, were excluded. Nevertheless, oral

informed consent was collected, as required by the Regional Ethical Review Board before randomization, from the patient or next of kin (if the patient was aphasic). This was done without prolonging the treatment initiation, and a written consent was mandatory after the treatment was completed, either from the patient if possible, or otherwise from next of kin.

Due to the urgent circumstances, oral consent could not be awaited. For this reason, 14% of the otherwise eligible patients could not be included. In those cases, the patient was subjected to one of the two anesthesia techniques chosen by the anesthesiologist in charge.

Autonomic nervous system and traumatic brain injury

The main finding in Paper IV was that ANS dysfunction, during the first week in NICU, was associated with poor late neurological outcome. It was the first study to report longitudinal measurements of both HRV and BRS in a homogenous group of patients with traumatic brain injury, requiring mechanical ventilation, sedation, analgesia and cardiovascular support. In some previous studies, patients requiring sedation were excluded [80, 81] or the patients were subjected to early discontinuation of sedatives and analgesics.[83] In other studies, data on the use of sedatives, analgesics, vasoactive drugs and mechanical ventilation were not presented.[81, 82, 145] The results from our study however, showed that monitoring signals from ANS was feasible during ongoing full scale intensive care.

It is well known that thiopental, opioids, benzodiazepines and propofol reduce HRV [86, 87, 89, 91, 94, 95] and BRS.[84, 85, 90, 92, 93] There were however no evident differences between the two outcome groups in Paper IV with respect to the doses used, although the limited number of patients precluded statistical calculations on this matter. Further on, mechanical ventilation may induce a decrease in LF and an increase in HF.[146] Importantly mechanical ventilatory modes were maintained constant throughout the study period, with no patient regaining spontaneous breathing during that time.

In previous studies, several attempts have been made to predict outcome from HRV analysis, such as brain death[147], ICU mortality [80, 83], 30-day mortality and GOSE < 5 at three months.[81] Paper IV was the first study on the power of autonomic variables to predict long-term neurological outcome. The power of BRS and HRV variables to predict GOSE < 5 at one-year follow-up were acceptable.

The association of autonomic dysfunction with worse neurological outcome in TBI is thus reported in several studies.[80-83] The mechanisms of the poor outcome are suggested to be cardiovascular complications, insulin resistance, attenuated cerebral

autoregulation, brain edema and immunological effects mediated via the cholinergic anti-inflammatory pathway, causing immune suppression and infection susceptibility.[148, 149] In Paper IV we lack data on cerebral autoregulation, infectious complications and insulin requirements and thus cannot have an opinion on the contribution of such factors on outcome.

In 2016, Sykora et al presented a large retrospective study on 262 TBI patients, all treated in the ICU with sedation and mechanical ventilation. The showed that BRS and HF power were independent predictors of mortality and unfavorable neurological outcome.[148] Thus, their findings are in line with our results, yet the strength of our study is the longitudinal capture of data, making a temporal resolution possible. In the study by Sykora et al, mean values for the whole length of stay were used.

In summary, the findings in Paper IV, suggest that HRV, as well as BRS can be used to predict outcome in TBI patients with advanced neuro intensive care treatment. Although signals from the autonomic nervous system are attenuated during ICU treatment, they are still detectable and offer information on prognosis. With new automated devises, the HRV and BRS values can be followed on line as a part of a multi-modal monitoring of TBI patients. With a temporal resolution, a patient at risk of worse outcome can be identified, and diagnostic- and therapeutic actions intensified. Whether the autonomic impairment per se is a possible therapeutic target, as suggested by Sykora et al[148], remains to be elucidated.

Methodological considerations Paper IV

- The weaknesses of the study lie within the retrospective design, hampering complete data acquisition, and the limited number of patients.
- The observed ICU mortality (one out of 19 patients) precluded any mortality outcome analyzes (as reported in previous studies) with HRV and BRS as predictors. Therefore, only the 1-year GOSE score was used as the outcome variable.
- HRV measured in frequency domain is sensitive to arrhythmias, commonly seen in brain injured patients. In our study all data were manually checked for ectopic beats.
- Acquisition of data was standardized to a 60-minute period free of nursing interventions, in the early morning (5–7 a.m.). However, we cannot exclude the possibility that some measurements were influenced by factors in the ICU care.

Ethical considerations Paper IV

This strictly observational study was approved by the Gothenburg Regional Ethical Review Board, document no 292-08.

Conclusions

Concerning patients undergoing endovascular treatment for acute ischemic stroke, we found that profound intra-procedural hypotension during general anesthesia is an independent predictor of poor neurological outcome (mRS ≤ 2) at 3 months.

Randomizing patients to general anesthesia or conscious sedation did not result in any difference in mRS at 3 months; neither in early neurological recovery, in cerebral infarction volume or in angiographic outcome between the two groups.

Off-hour admissions result in a substantial delay in the time interval from CT to recanalization. This time interval is an independent predictor of poor neurological outcome.

Regarding patients with acute traumatic brain injury (TBI), autonomic nervous system dysfunction, as assessed by heart rate variability (HRV) and baroreflex sensitivity (BRS), during the first week of neuro intensive care, is associated with poor late neurological outcome.

Future perspectives

For years, the main focus in anesthesia during EVT has been on *anesthesia form* more than on *anesthesia performance*. Most aspects of anesthesia management during EVT are not yet studied, except for the blood pressure control.

Factors as ventilation, oxygenation and glucose control might be important for penumbra salvage and can be controlled and corrected by anesthesia- and intensive care staff in the acute setting, before, during and right after the recanalization. Both optimal oxygen delivery and glucose control may be beneficial as bridging therapies during the transient ischemic period before revascularization. In addition, some anesthetics might be preferable in providing neuroprotection. Whether these theories are relevant or not will have to be explored in future studies.

Monitoring of heart rate variability and baroreceptor reflex sensitivity might be adjunct tools in multi-modal monitoring of traumatic brain injury in the future since on-line devices now are available.

Finally, as a bridge between paper I–III and Paper IV: In acute ischemic stroke (AIS), ANS dysfunction, as assessed by HRV or BRS, is repeatedly shown to be associated with stroke severity, early and late complications, dependency and mortality.[150] Early diagnosis of ANS dysfunction in stroke may have prognostic and possibly also therapeutic values in acute stroke, as stated in the review by Yperzeele et al.[150]

Furthermore, several aspects of ANS dysfunction in AIS are yet to be investigated; for example, the effect on HRV and BRS of recanalization. Are on-line measurements of HRV and/or BRS a method to non-invasively monitor the process of recanalization in IVT and EVT? This question can be addressed in future studies.

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Appendix I–IV