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Pressure autoregulation of cerebral blood flow in traumatic brain injury and aneurysmal subarachnoid hemorrhage

ULF JOHNSON



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Abstract

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The ability of the brain to keep a stable and adequate cerebral blood flow (CBF) independently of fluctuations in systemic blood pressure is referred to as cerebral pressure autoregulation (CPA). When the brain is injured by trauma or hemorrhage, this ability may be impaired, leaving the brain vulnerable to events of high or low blood pressure. The aims of this thesis were to study CPA in patients with severe traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH), the relation between CPA and other physiological parameters, and the influence of CPA on outcome. Four retrospective studies are included in the thesis. All patients were treated at the neurointensive care unit, Uppsala University hospital.

In paper I, 58 TBI patients were studied. In patients with impaired CPA, cerebral perfusion pressure between 50-60 mm Hg was associated with favorable outcome while CPP > 70 and >80 mm Hg was associated with unfavorable outcome. In patients with intact CPA there was no association between CPP and outcome.

In paper II, 107 TBI patients were studied. High CPP was associated with unfavorable outcome in patients with focal injuries. In patients with diffuse injury and impaired CPA, CPP > 70 mm Hg was associated with favorable outcome.

In paper III, 47 SAH patients were studied. CBF was measured bedside with Xenon-enhance CT (Xe-CT). Patients with impaired CPA had lower CBF, both in the early (day 0-3) and late (day 4-14) acute phase of the disease.

In paper IV, 64 SAH patients were studied. Optimal CPP (CPP_{opt}) was calculated automatically as the level of CPP where CPA works best for the patient, i.e., where PR_x is lowest. Patients with actual CPP below their calculated optimum had higher amounts of low-flow regions (CBF < 10 ml/100g/min).

The findings in this thesis emphasize the importance of taking CPA into account in the management of TBI and SAH patients, and suggest that treatment should be individualized depending on status of autoregulation. PR_x and CPP_{opt} may be used bedside to guide management according to status of autoregulation. In the future CPA-guided management should be tested in prospective studies

Keywords: cerebral blood flow, autoregulation, traumatic brain injury, subarachnoid hemorrhage

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Till min familj

List of Papers

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

- I Johnson U., Nilsson P., Ronne-Engström E., Howells T., Enblad P. (2011) Favorable outcome in traumatic brain injury patients with impaired cerebral pressure autoregulation when treated at low cerebral perfusion pressure levels. *Neurosurgery*, 68(3):714–21.
- II Johnson U., Lewén A., Ronne-Engström E., Howells T., Enblad P. (2014) Should the neurointensive care management of traumatic brain injury patients be individualized according to autoregulation status and injury subtype? *Neurocritical Care*, 21(2):259–65.
- III Johnson U., Engquist H., Howells T., Nilsson P., Ronne-Engström E., Lewén A., Rostami E., Enblad P. (2016) Bedside Xenon-CT shows lower CBF in SAH patients with impaired CBF pressure autoregulation as defined by pressure reactivity index (PRx). *Neurocritical care*, 25(1):47–55
- IV Johnson U., Engquist H., Lewén A., Howells T., Nilsson P., Ronne-Engström E., Rostami E., Enblad P. (2016) Increased risk of critical CBF levels in SAH patients with actual CPP below calculated optimal CPP. *Submitted*

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Abbreviations

20-HETE = 20-Hydroxyicosatetraenoic acid
ASL = arterial spin labelling
BBB = blood-brain barrier
BOLD = blood oxygen level dependent
BPs = systolic blood pressure
CBF = cerebral blood flow
CBV = cerebral blood volume
CMRO = cerebral metabolic rate of oxygen
CPP = cerebral perfusion pressure
CPPopt = optimal cerebral perfusion pressure
CT = computed tomography
CVR = cerebrovascular resistance
DCE = dynamic contrast enhancement
DCI = delayed cerebral ischemia
DSA = digital subtraction angiography
DSC = dynamic susceptibility contrast
EML = evacuated mass lesion
FLAIR = fluid attenuation inversion recovery
GCS = Glasgow coma scale
GMT = good monitoring time
GOSE = Glasgow outcome scale extended
ICP = intracranial pressure
MAP = mean arterial blood pressure
MLCK = myosin light chain kinase
MRI = magnetic resonance imaging
NEML = non-evacuated mass lesion
NICU = neurointensive care unit
NIRS = near infra-red spectroscopy
NIVA = neurointensivvårdsavdelning
PET = positron emission tomography
PRx = pressure reactivity index
ROCK = Rho-associated kinase
SAB = subarachnoidalblödning

SAH = subarachnoid hemorrhage

SPECT = single-photon emission computed tomography

SWI = susceptibility weighted imaging

TBI = traumatic brain injury

TCD = trans cranial Doppler ultrasound

VOI = volume of interest

Introduction

The human brain is an organ with high metabolism, but very limited storage capacity for oxygen and glucose. The brain is therefore dependent on a continuous supply of oxygenated and nutrient-rich blood. Even brief periods of diminished cerebral blood flow (CBF) may rapidly cause irreversible damage to the neurons. Markedly elevated CBF, on the other hand, may also be harmful due to cerebral edema and increased intracranial pressure because of the rigid nature of the skull ^[1-4].

To prevent events of hypo- and hyperperfusion, the brain has the remarkable ability to keep a steady CBF despite fluctuations in systemic blood pressure. This phenomenon is referred to as pressure autoregulation, or simply autoregulation ^[5].

When the brain is injured by trauma or hemorrhage, autoregulation may be impaired to different extents. The injured brain that no longer can regulate CBF by itself becomes vulnerable to events of systemic hypo- or hypertension with associated risks of ischemia or hyperperfusion, respectively.

In the care of patients with severe neurological conditions, such as traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), maintaining CBF is of paramount importance. Success or failure may mean the difference between a good or bad outcome, or even life or death. A brain with impaired autoregulation cannot keep an adequate CBF by itself and is obviously more vulnerable than one with intact autoregulation. The status of autoregulation should therefore be a key parameter to take into account in the management of these patients. This is, however, not the case in routine neurointensive care today. Despite a large and growing body of literature on autoregulation during almost a century there is still no clear view on how information on autoregulation should be used in the clinical setting.

The aims of this thesis were to study cerebral pressure autoregulation in patients with TBI and SAH, the impact on outcome, and the relation between autoregulation and other physiological parameters including CBF.

Background

Below follows a brief review of autoregulation of CBF, and the two diseases in focus in this thesis, namely traumatic brain injury and aneurysmal subarachnoid hemorrhage.

Cerebral blood flow

Because of the combination of high consumption and limited storage capacity, the brain is dependent on a steady supply of oxygen and substrates. The brain comprises only 2% of the body weight but receives 15% of the cardiac output, because of its high oxygen consumption (average 3-3.8 ml/100 g of brain tissue/min) ^[6,7]. Mean global CBF is normally around 50 ml/100g/min and declines with age to approximately 40 ml/100g/min after the age of 50 years ^[6,8,9]. Normal CBF ranges from 20 ml/100g/min (white matter) to 70 ml/100g/min (grey matter), and varies according to neuronal activity ^[10]. There is some data supporting a gender difference in CBF with higher values in females ^[11], although other studies have been unable to demonstrate this ^[12]. When CBF drops below 18 ml/100g/min reversible neuronal dysfunction ensues, but the neurons are still capable to survive for a limited amount of time if CBF normalizes ^[13,14]. CBF < 10 ml/100g/min quickly leads to irreversible dysfunction and neuronal death ^[14,15]. Since the brain can withstand only brief periods of reduced blood flow, the precise regulation of CBF is a top priority of the body.

Historically it was believed that CBF was dependent only on arterial blood pressure and that the brain had no ability to modulate CBF. In 1783 Monro stated that cerebral blood volume has to be constant due to the non-compliant nature of the skull and that CBF therefore is a function of the combination of arterial inflow and venous outflow ^[16]. In 1890, Roy and Sherrington proposed that CBF was determined by both arterial blood pressure and intrinsic mechanisms capable of independently regulating CBF, such as products of metabolism and direct innervation of intracranial vessels ^[17]. In 1902, Bayliss observed vasoconstriction in peripheral arteries during increased blood pressure ^[18]. This phenomenon, later named the Bayliss Effect, is an intrinsic property of vascular smooth muscle cells and a key component in the regulation of CBF, as discussed below. In 1934, Fog observed the Bayliss

effect in feline pial arteries using a cranial window preparation and proposed an active CBF-regulating mechanism based on changes in transmural arterial pressure ^[5].

Measuring cerebral blood flow

In 1945 Kety and Schmidt presented a method for quantification of CBF ^[19]. By measuring the concentration of a tracer substance (N₂O) in arterial and venous blood, global CBF could be calculated according to the Fick principle. In the late 1950's, scintigraphic methods were developed for regional CBF measurement with radioactive ⁸⁵Kr as a tracer substance ^[20,21]. Since then several methods for quantitative and qualitative assessment of CBF have been described, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), various magnetic resonance imaging (MRI) techniques and near infra-red spectroscopy (NIRS) ^[22-27]. At present, ¹⁵O-water PET is considered the reference standard for CBF measurement, but is impractical due to the procedural complexity and the need of an on-site cyclotron. Characteristics of different CBF measurement methods used today are outlined in Table 1.

One method of particular interest in this thesis is Xenon-enhanced CT (Xe-CT), which may be used at the neurointensive care unit (NICU) with a mobile scanner. This method uses CT with inhaled Xenon gas as a contrast agent and CBF is calculated by a modified Kety-Schmidt equation ^[28-31]. The method is described more thoroughly below (see Materials and methods, CBF-measurement).

Table 1. Overview of CBF measurement techniques currently in use. PET = positron emission tomography, MRI = magnetic resonance imaging, ASL = arterial spin labelling, DSC = dynamic susceptibility contrast, DCE = dynamic contrast enhancement, CT = computed tomography, CTP = computed tomography perfusion, Xe-CT = Xenon-enhanced computed tomography, NIRS = near infra-red spectroscopy, CM = contrast medium.

Technique	Tracer/contrast medium	Advantages	Limitations	Radiation
PET	H ₂ [¹⁵ O]	Accurate quantitative CBF	Impractical in emergency situation	Yes (1.7 mSv*)
MRI (ASL)	Endogenous H ₂ O	Quantitative CBF Simultaneous anatomical imaging	Over/underestimation of CBF	No
MRI (DSC)	Gadolinium-based CM	Simultaneous anatomical imaging	Semi quantitative	No
MRI (DCE)	Gadolinium-based CM	Simultaneous anatomical imaging	Semi quantitative	No
CT (CTP)	Iodine-based CM	Widely available	Semi quantitative Radiation Iodine-based CM	Yes (5.5 mSv*)
CT (Xe-CT)	Stable Xenon	Accurate quantitative CBF Bedside measurement possible	Sedative effect of xenon Prone to motion artifacts	Yes (2.7 mSv*)
Trans-cranial Doppler	-	Noninvasive Continuous monitoring	Surrogate measure User dependent	No
NIRS	-	Noninvasive Continuous monitoring	Small superficial examined volume	No

* Data from Uppsala University Hospital

Regulation of cerebral blood flow

The brain does not only need to keep a continuous steady blood flow despite fluctuations in systemic blood pressure, but also has to adapt CBF according to neuronal activity. The regulation of CBF is accomplished through a complex interplay of different mediators.

In brief, the regulation of CBF can be divided into three major mechanistic groups: global metabolic, neurogenic and pressure autoregulation.

Global metabolic regulation of CBF

The factors involved in the global metabolic regulation of CBF are circulating agents such as CO₂, O₂ and glucose.

Cerebral perfusion is highly sensitive to changes in PaCO₂ [32]. The high sensitivity of CO₂ is unique to the cerebrovasculature [33], and is manifest both intracranially and in the major arteries of the neck [34,35]. Elevated levels of CO₂ lead to vasodilatation and vice versa, which in turn affects cerebrovascular resistance and CBF [36]. This effect is utilized in neurointensive care to treat elevated intracranial pressure. Since intracranial vasoconstriction also leads to decreased intracranial blood volume, moderate hyperventilation leading to decreased PaCO₂ and vasoconstriction can be used to decrease intracranial blood volume and intracranial pressure [37].

Decreased PaO₂ increases CBF, but this does not take effect until rather severe hypoxemia (PaO₂ < 50 mm Hg / 6.6 kPa) [38].

Blood glucose level also has the potential to influence CBF, but an increase in CBF does not occur until severe systemic hypoglycemia (blood glucose level < 2 mmol/L) [39].

Neurogenic regulation of CBF

It has been known for a long time that local cerebral activity is coupled with increased local CBF to meet the metabolic demands of the neurons, termed neurovascular coupling or flow-metabolism coupling [40]. At resting state, local CBF is proportional to cerebral metabolism measured by metabolic rate of oxygen (CMRO) [41]. At neuronal activation, however, there is an increase in CBF that surpasses the increase in cerebral metabolism [42]. The change in CBF in response to neuronal activation can be observed as the blood oxygen level dependent response (BOLD response) which is used in functional MRI (fMRI) to identify which region of the brain is activated in a particular task [43]. The signaling pathways involves neurons as well as astrocytes and vascular cells [44,45].

Pressure autoregulation of CBF

Pressure autoregulation of -CBF is defined as the ability of the cerebral vascular bed to keep a steady CBF over a range of different systemic blood pressures.

In 1959 Lassen noted that CBF was relatively constant between mean arterial blood pressure (MAP) of approximately 50-150 mm Hg [46]. Within this interval (the autoregulatory plateau), he proposed that the cerebral vasculature could maintain constant CBF by vasodilatation and vasoconstriction. Beyond the autoregulatory plateau, i.e. beyond the maximal

capacity of vasodilatation/constriction, CBF would have a linear association with mean arterial blood pressure (MAP) (*Figure 1*).

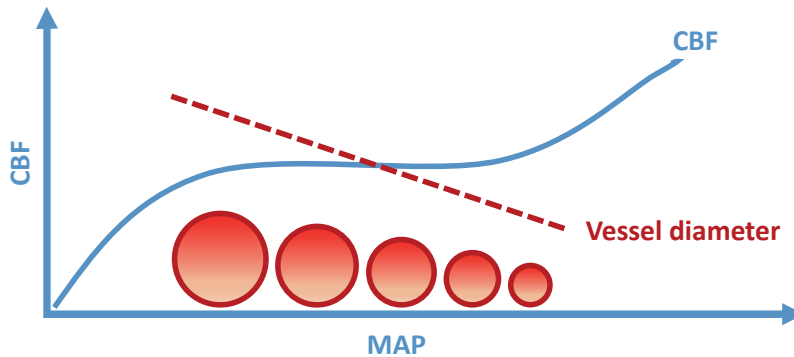


Figure 1. The autoregulatory plateau according to Lassen. Between MAP approximately 50 – 150 mmHg, CBF will be kept stable by vasodilatation and vasoconstriction.

The concept of the autoregulatory plateau has obvious clinical implications and has prevailed relatively unchallenged. More recent studies however indicate that the plateau region may be smaller and not as flat as previously thought [47,48]. Also, the autoregulatory response have been shown to be asymmetric with a stronger reaction to hypotension than hypertension [49].

The vasodilatation and vasoconstriction in pressure autoregulation is triggered by changes in transmural pressure that activate mechano-sensors in the vessel wall [50,51]. This in turn activates different pathways:

- Membrane depolarization opens voltage-gated Ca^{++} channels and causes influx of Ca^{++} into the smooth muscle cell [52]. This activates myosin light chain kinase (MLCK) which in turn activates myosin by phosphorylation. Phosphorylated MLCK leads to increased actin-myosin interaction and causes contraction of the muscle cell and vasoconstriction.
- Activation of RhoA, which is a small GTPase. This in turn activates the Rho-associated kinase (ROCK), which inhibits myosin light chain phosphatase. This inhibits dephosphorylation of MLCK, which potentiates actin-myosin interaction and vasoconstriction [53].
- Activation of protein kinase C (PKC) stabilizes the actin-myosin interaction and potentiates vasoconstriction [54].
- 20-hydroxyeisetetraoic acid (20-HETE) inhibits voltage-gated Ca^{++} channels and opens L-type Ca^{++} channels [55]. 20-HETE also activates PKC [56].

Increased transmural pressure will be accompanied by increased flow as well. There is evidence that flow may activate vasoconstriction/vasodilatation independently of pressure changes. In an experimental setting, human cerebral arteries have been shown to constrict in response to increased flow when pressure was kept constant ^[57]. In animal studies, however increased flow has been associated with both vasodilatation and vasoconstriction ^[58].

Measuring pressure autoregulation

Initially, pressure autoregulation was assessed by calculating CBF at different steady-states of arterial blood pressures. With this methodology, CBF is measured at baseline blood pressure. Blood pressure is thereafter increased pharmacologically, and when blood pressure is stabilized at a higher level CBF is measured again. The change in CBF relative to the change in MAP is a numerical representation of the status of autoregulation ^[59]. This methodology is referred to as static autoregulation measurement.

After the introduction of transcranial Doppler ultrasound (TCD) with the ability to visualize short-term changes in blood-flow velocity, the concept of dynamic autoregulation measurement was introduced ^[60]. Dynamic autoregulation refers to how fast autoregulation acts. As TCD cannot measure CBF directly, blood flow velocity is used as a surrogate measure of CBF. With this methodology a rapid change in blood pressure is induced, e.g. by releasing inflated leg cuffs or by carotid compression ^[60,61]. Flow velocity in innominate intracranial vessels will be affected differently depending on status of autoregulation. Instead of induced blood pressure challenges, spontaneous fluctuations of systemic blood pressure can be correlated with blood flow velocity in intracranial vessels as a measure of autoregulatory status ^[62]. This type of methodology makes continuous monitoring of cerebral autoregulation possible.

In 2000 Lang and Chesnut introduced the relationship between intracranial pressure and blood pressure as a measure of cerebral autoregulation ^[63]. With intact autoregulation an increase in systemic blood pressure will evoke a compensatory vasoconstriction, causing decreased cerebral blood volume (CBV) and decreased intracranial pressure. With intact autoregulation MAP will therefore be negatively correlated with intracranial pressure (ICP) (pressure-active response, *Figure 2*). If autoregulation is impaired, the correlation will be positive (pressure-passive response, *Figure 3*).

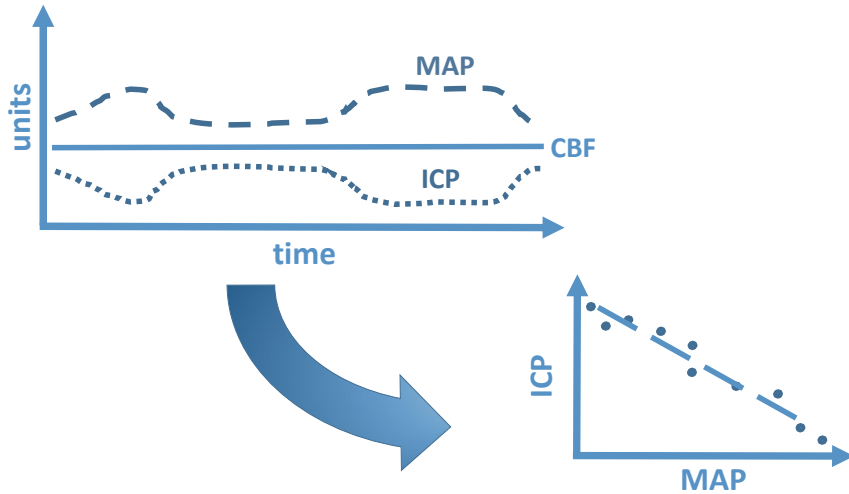


Figure 2. Pressure-active response. Normal autoregulatory function. Changes in MAP cause compensatory changes in CVR to keep CBF Stable. The changes in CVR cause changes in CBV and ICP. ICP and MAP are negatively correlated.

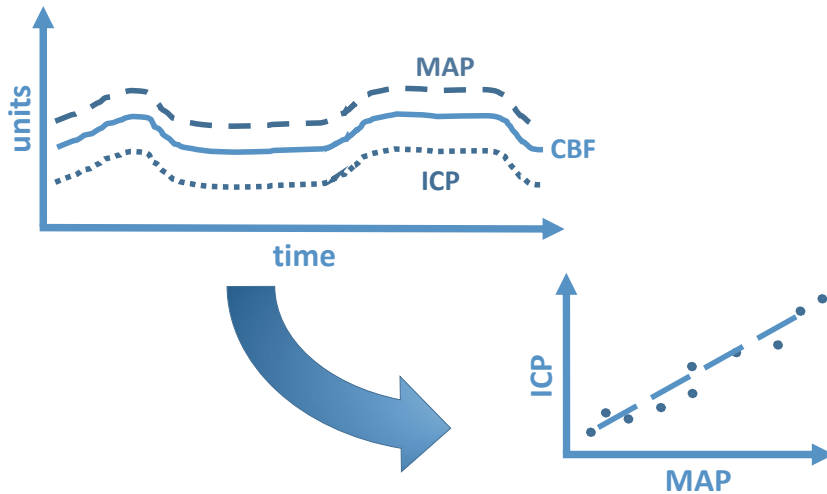


Figure 3. Pressure-passive response. Impaired autoregulatory function. Changes in MAP are not followed by compensatory changes in CVR. CBV and ICP are passively related to MAP. ICP and MAP are positively correlated.

The concept of pressure reactivity was developed further when Czosnyka introduced the Pressure Reactivity Index, PRx^[64]. PRx is calculated as the moving correlation coefficient between spontaneous fluctuations in ICP and MAP and provides a method for continuous bedside monitoring of pressure reactivity in patients with brain injury. PRx has been extensively validated as

a measure of pressure reactivity, and is highly correlated with outcome after traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) ^[65-67]. In theory, PRx allows for real-time monitoring of autoregulatory status, but despite promising possibilities it has not been widely adopted in clinical routine, probably due to the noisy nature of the parameter ^[68].

Traumatic brain injury

Epidemiology

Traumatic brain injury (TBI) is a major cause of death and disability worldwide ^[69,70]. Reported mortality ranges from 30-40 %, and about 50-60 % of the patients achieve a favorable outcome ^[71,72]. TBI often affects young and middle-aged people and lifelong disability is common in survivors. The socio-economic cost as well as individual suffering and the burden on the relatives is therefore considerable ^[73]. The most common cause of TBI in young and middle-aged people is road traffic accidents, while fall is the most common cause in small children and people > 65 years ^[74]. The global incidence of TBI is increasing due to increased use of motor vehicles in low- and middle-income countries. In high-income countries there is an ongoing epidemiological shift from younger to older. Safety regulations and preventive measures have decreased traffic-related TBI in the young and middle-aged ^[75]. In the elderly, absolute incidence of TBI is increasing due to increased life expectancy and greater mobility among the elder population ^[74]. In older TBI-patients pre-existing morbidities and anticoagulant/antiplatelet drugs are common, which aggravates the injury and prolongs rehabilitation.

According to statistics from the Swedish National Board of Health, TBI was the cause of death in 966 persons in 2015. Death from TBI was twice as common in men as in women, 660 compared to 306 (personal communication).

Of the TBI patients treated at the NICU at Uppsala University Hospital between 2008-2010, 64% achieved a favorable outcome, 5% died at the NICU and 8% were dead within 6 months after discharge ^[76].

Pathophysiology

The final damage to the brain after trauma is comprised by a combination of primary and secondary injury. The primary injury is inflicted immediately upon the traumatic event and includes hematoma, contusion and diffuse injury. The primary injury also triggers a cascade of cellular mechanisms that may be protective as well as destructive. In the latter case these mechanisms, such as inflammatory and neurotoxic processes, may lead to secondary injury,

i.e. brain damage that occurs at different time points, hours to weeks, after the trauma itself^[77-79].

Other causes of secondary injury are secondary insults. These are adverse events that occur after the trauma such as increased ICP due to e.g. expanding hematoma, systemic hypotension, hypo/hyperglycemia, seizures, fever and infection. Although these insults may be of relatively mild magnitude, they may cause damage to the vulnerable injured brain. The concept of secondary insults was introduced by Reilly in 1975, who noted that some patients were able to talk after head trauma, but still had an adverse outcome^[80]. The relation between primary/secondary injury, secondary insults and outcome is outlined in *Figure 4*.

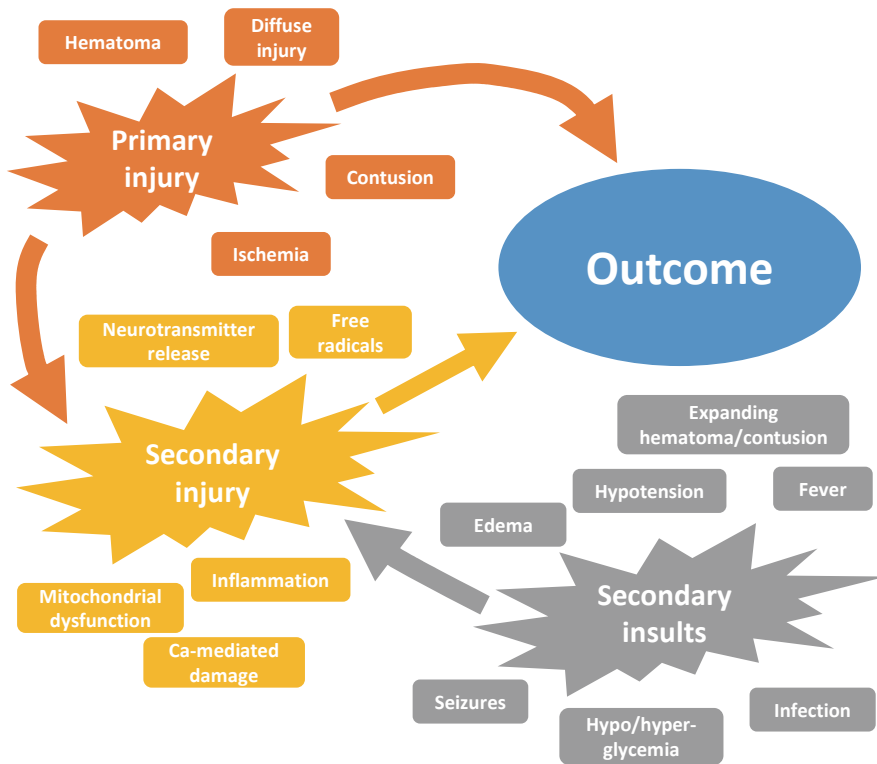


Figure 4. Outcome after TBI is dependent on the relation between primary/secondary injury and secondary insults.

Intensive care

The management of acute TBI is mainly focused on avoiding secondary insults. After the recognition of the impact of secondary insults, dedicated neurointensive care focused on avoiding these adverse events started to

evolve. At Uppsala University Hospital a specialized neurosurgical neurointensive care unit was inaugurated in 1990. The clinical outcome after TBI was substantially improved after the introduction of dedicated and systematic care (increased rate of favorable outcome increased from 40% to 84%, decreased rate of death from 40% to 2.8%)^[81].

Autoregulation in traumatic brain injury.

After TBI, cerebral autoregulation may be impaired to various extents. The impairment may vary regionally and also over time^[82–85]. Autoregulation has been shown to be impaired even after relatively minor head trauma^[86]. In 1997, Howells et al studied two patient groups from Uppsala and Edinburgh, treated with different approaches (ICP-oriented protocol in Uppsala and cerebral perfusion pressure (CPP)-oriented protocol in Edinburgh) and found that impaired autoregulation was a negative prognostic factor in one of the patient groups, and a positive prognostic factor in the other^[87]. The authors concluded that in an ICP-oriented treatment protocol, impaired autoregulation was associated with better clinical outcome and vice versa in an CPP-oriented protocol. This was later adopted in the Brain Trauma Foundation treatment guidelines from 2007, that emphasizes that autoregulation should be taken into account in the intensive care management of patients with TBI^[88].

Aneurysmal subarachnoid hemorrhage

Epidemiology

Aneurysmal subarachnoid hemorrhage (SAH) is a type of hemorrhagic stroke that accounts for about 5 % of all strokes^[89]. The overall global incidence is approximately 9/100 000 person years^[90]. Incidence varies globally^[91], with higher rates of SAH in for example Finland^[92] and Japan^[93]. SAH mortality is decreasing due to better supportive care and more aggressive aneurysm treatment^[94,95]. Although SAH is a relatively uncommon disease, the rates of mortality and morbidity are high. Approximately 30–40% die, and of those who survive, 30 % do not regain full independence^[96,97].

Pathophysiology

Aneurysmal SAH occurs when an intracranial aneurysm ruptures. An aneurysm is a bulge on an intracranial artery that is prone to rupture. When the aneurysm ruptures, blood spreads in the subarachnoid space and there is a sudden sharp rise in ICP. If ICP rises high enough, cerebral perfusion is compromised with resulting transient global ischemia, which may cause temporary loss of consciousness or death. If the patient survives the transient

global ischemia, increased sympathetic activity may cause pulmonary edema or cardiac dysfunction.

After the early brain injury, caused by the hemorrhage and its systemic effects, unfavorable outcome may be caused by aneurysm re-rupture, hydrocephalus or delayed cerebral ischemia (DCI). DCI is ischemic neurologic deficit attributed to the combined effect of adverse events that occur in a time window of approximately 5-15 days after the initial hemorrhage. DCI was originally only thought to be the result of arterial spasm with subsequent hypoperfusion and ischemia ^[98-100]. Hypoperfusion and ischemia, however, may occur without angiographic vasospasm, and vasospasm may occur without ischemia ^[101]. The cause of DCI is now considered multifactorial, with elements of endothelial dysfunction causing blood-brain-barrier disruption, cortical spreading depolarizations, microvascular thrombosis and failure of autoregulation; as well as vascular spasm ^[102-104]. Various clinical secondary insults are probably also involved ^[105,106].

Presentation and diagnosis

SAH typically presents with sudden “worst ever” headache, nausea, photophobia, neck stiffness or loss of consciousness. Computed tomography (CT) reveals the diagnosis, but may be false negative if performed too long after ictus. One study of 296 patients with SAH showed 100% sensitivity if CT scan was performed < 6 days after onset ^[107]. Another study of 760 patients with acute headache reported negative predictive value of 100% in CT scans done < 6 hours after onset ^[108]. MRI with susceptibility weighted (SWI) and fluid-attenuated inversion recovery (FLAIR) sequences may be equal, or even superior to CT, but is rarely performed in the acute setting due to limited availability and logistic reasons ^[109]. In case of negative CT scan lumbar puncture with CSF analysis has high diagnostic yield if performed > 12 hours after onset ^[110]. After diagnosis, CT angiography or digital subtraction angiography (DSA) is done to detect and map the aneurysm for treatment planning.

Treatment

Patients often require intensive care, and even in case of favorable clinical course the patients are monitored closely for early detection and treatment of complications or adverse events. Re-bleeding is an avoidable and potentially fatal complication of aneurysmal SAH. The risk of re-bleeding is highest on the first day after onset, and declines thereafter ^[111,112]. Treatment by surgical clipping or endovascular coil embolization should therefore be done as early as possible. Clipping or coiling both almost abolishes the long-term risk of re-bleeding, although coiling may require repeated treatment sessions ^[113,114].

Choice of treatment is dependent on several factors such as patient age, comorbidity and aneurysm size, configuration and relation to adjacent vessels [115]. If the aneurysm is suitable for endovascular treatment, however, coiling is the treatment modality of choice due to its less invasive nature.

Autoregulation in aneurysmal subarachnoid hemorrhage

Several studies have shown impaired autoregulation to be associated with vasospasm, DCI and poor neurologic outcome, respectively, in aneurysmal SAH [116–118]. With vasospasm and loss of autoregulation, CBF will be vulnerable to low CPP and the risk of ischemia increased.

The Hagen-Poiseuille law states that flow in a vessel is a function of pressure gradient, vessel radius and length, and viscosity. With vascular spasm the vessel radius will be fixed and the only way to increase flow is therefore to alter the pressure gradient and viscosity. This is the rationale behind triple-H therapy (hypertension, hypervolemia, hemodilution) which is a common treatment against symptomatic vasospasm and DCI [115,119]. Triple-H therapy has been used since the 1970's and is an effective but also dangerous therapy. Adverse effects occur in 10-20% of the patients; pulmonary edema is the most common complication [120,121].

Aims

General aim

The general aim was to study cerebral pressure autoregulation in patients with TBI and SAH, the impact on outcome, and the relation between autoregulation and other physiological parameters including CBF.

Specific aims

- I To study autoregulation in relation to other physiological parameters, treatment and outcome in TBI patients (*paper I*).
- II To study the impact of autoregulation and CPP on outcome in patients with different TBI subtypes (*paper II*).
- III To study the relation between autoregulation and CBF in SAH patients, and if PRx can be used to predict DCI (*paper III*).
- IV To study “optimal CPP” in relation to CBF in SAH patients (*paper IV*).

Materials and methods

Study design, patients, and treatment protocol

Paper I-II

Study designs were retrospective studies of prospectively collected data. Inclusion criteria were TBI, invasive MAP and ICP monitoring and age > 15 years. Patients with previous brain injury or intracranial surgery were not included.

A standardized treatment protocol with the goals to keep ICP < 20 mm Hg and CPP > 60 mm Hg was used. In case of hypotension, clear fluids and colloids were used primarily. Vasopressors were added if needed, but generally used sparingly. Elevated ICP was treated with sedation, slight hyperventilation and if possible CSF drainage. Second tier treatment for elevated ICP was pentobarbiturate coma or decompressive craniectomy.

Paper III-IV

Study designs were retrospective studies of prospectively collected data. Inclusion criteria were aneurysmal SAH, mechanical ventilation, invasive MAP and ICP monitoring and valid Xe-CT CBF data. As a consequence of the Xe-CT methodology where Xenon is administered to the patients via a ventilator, only unconscious patients were included, i.e. patients with severe disease.

The patients were treated according to a standardized protocol aiming at ICP < 20 mm Hg and CPP > 60 mm Hg, normotension, normovolemia/slight hypervolemia, body temperature < 38° and normal electrolyte levels. Aneurysms were treated early with surgical clipping or endovascular coiling. DCI was diagnosed clinically and triple-H therapy (hypertension, hypervolemia, hemodilution) used in these patients. All patients received prophylactic Nimodipine.

Measures of autoregulation

Paper I

For each patient, corresponding minute-averaged values of ICP and MAP were plotted with ICP on the Y-axis and MAP on the X-axis. A regression line was then fitted to the data points, and the slope of the regression line used as an overall estimate of the patient's status of autoregulation for the whole monitoring time^[85,87]. With intact pressure autoregulation, an increase in MAP will cause a compensatory vasoconstriction and a decrease in ICP, and vice versa. With non-functioning pressure autoregulation on the other hand, changes in MAP will not cause vasomotor responses, and ICP will be positively correlated with MAP. Therefore, a positive slope of the regression line represents a pressure-passive response, i.e. disturbed autoregulation. Negative or near-zero values represent a pressure-active response, i.e. intact autoregulation (*Figure 5*).

In addition to calculations using data from the whole monitoring time, calculations using data from only the first 24 hours were done on each patient.

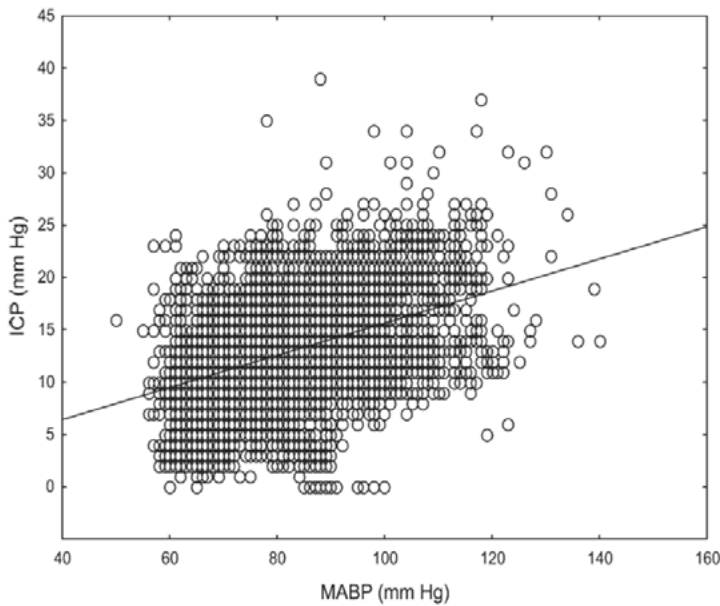


Figure 5. Example of autoregulation calculation in paper I. Corresponding minute-averaged values of ICP and MAP are plotted and a regression line is fitted to the data points. The slope of the regression line is taken as an overall measure of autoregulation. Separate calculations were done using data from all monitoring time and the first 24 hours, respectively. In this particular patient with totally 8226 minutes of monitoring, the slope is positive, signifying impaired autoregulation.

Paper II-IV

The pressure reactivity index, PRx, was used to measure autoregulation. PRx is an autoregulatory index that relies on the correlation between spontaneous fluctuations of MAP and ICP. PRx has been used extensively to study autoregulation in TBI, and to some extent also in SAH, and is highly correlated with outcome ^[64,68]. PRx was calculated as a moving correlation coefficient between ICP and MAP as follows: The correlation between 30 contiguous averaged 10-second segments of ICP and MAP was calculated. This 5-minute window was then moved forward in increments of 12 seconds, generating 5 values of PRx per minute. The median value for each minute was then calculated ^[122]. Positive PRx values signify a pressure-passive response and disturbed autoregulation, whereas negative or near-zero values signify a pressure-active response and intact autoregulation. In situations with high craniospinal compliance (high capacity to compensate for added intracranial volume) the relation between vasoconstriction/vasodilatation and ICP will be less pronounced, and PRx less reliable. This may be the case after decompressive craniectomy or potentially also when CSF is drained through an open ventricular drainage system. In paper II, all data recorded after the opening of a ventricular drainage was omitted to avoid this. In paper III and IV, SAH patients were studied. CSF drainage is common in these patients to treat hydrocephalus, and PRx data derived from open ventricular drains was used in order not to lose information (see discussion section, paper III for elaboration on this approach).

In paper II mean PRx for the first 96 hours of monitoring was calculated. In paper III, mean PRx was calculated for 6, 4 and 2 hours before each Xe-CT CBF-measurement.

Measurement of cerebral blood flow with Xenon-enhanced computed tomography

In paper III and IV CBF was measured bedside with Xe-CT using a mobile CT scanner ^[123]. Stable Xenon is an inert, radio opaque gas that diffuses freely over the blood-brain barrier and can be used as a contrast agent. Inhaled Xenon has complex pharmacokinetics, with several measurable compartments in vivo with half-times ranging from 22 seconds to 17 hours ^[124]. In Xe-CT however, the body will not be saturated with xenon, and the gas will be washed out below measurable end-tidal levels in less than one minute. Xe-CT has been validated against CBF measurement with microspheres and 14C-iodoantipyrine in animals ^[30,125] and provides reliable quantitative values.

A gas mixture with 28% Xenon was administered to the patient through the ventilator. After two unenhanced baseline scans, repeated scanning was done during the wash-in phase of Xenon. CBF was calculated with a modified Kety-

Smith equation. Four 1-cm thick slices were scanned. The cortical mantle in these slices was subdivided into regional volumes of interest (rVOI) (*Figure 6*). CBF in each cortical rVOI was used to calculate CBF parameters as presented below.

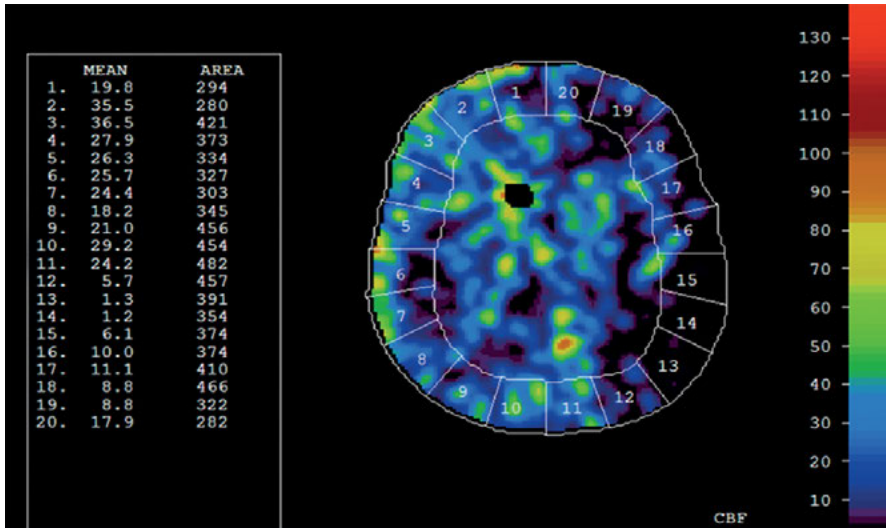


Figure 6. Example of CBF measurement with Xenon-CT. The cortical mantle is divided into regional volumes of interest. In this particular patient, CBF is decreased in the posterior part of the left hemisphere.

In paper III and IV three CBF parameters were calculated: Mean global CBF, CBF%<20 and CBF%<10. The two last parameters were chosen to signify tissue at risk/high risk of ischemia and calculated as follows:

$$CBF\% < 20 = \frac{rVOI \text{ volume with } CBF < 20 \text{ ml}^{-1} \times 100g^{-1} \times \text{min}^{-1}}{\text{total } rVOI \text{ volume}}$$

$$CBF\% < 10 = \frac{rVOI \text{ volume with } CBF < 10 \text{ ml}^{-1} \times 100g^{-1} \times \text{min}^{-1}}{\text{total } rVOI \text{ volume}}$$

Optimal cerebral perfusion pressure

In paper IV, optimal CPP (CPP_{opt}) was calculated. CPP_{opt} is the CPP level within a predefined range where PR_x is lowest. This CPP level is assumed to be where autoregulation functions best for the patient. To calculate CPP_{opt}, CPP values between 40 and 120 are binned in intervals of 5 mm Hg in a given time window ^[126]. Mean PR_x values are then plotted against the binned CPP values and a quadratic function fitted. If a clear U-shaped curve is identified,

CPPopt is the CPP on the curve with the lowest PRx value (*Figure 7*). If no clear U-shaped curve is identified, the lowest point on an ascending or descending convex curve is accepted if the curve follows a quadratic function to some extent, assuming that a U-shaped curve would have been identified with a larger range of CPP. If the curve does not meet these criteria, CPPopt is not calculated. In this paper CPPopt was calculated using a four-hour time window and an automatic calculation algorithm as described by Aries et. al. [127].

In TBI, patients with CPP close to CPPopt have been found to achieve better outcome than those with large deviations, and treatment protocols focusing on CPPopt have been proposed [128-130]. In SAH, CPP above CPPopt has been associated with better outcome [131].

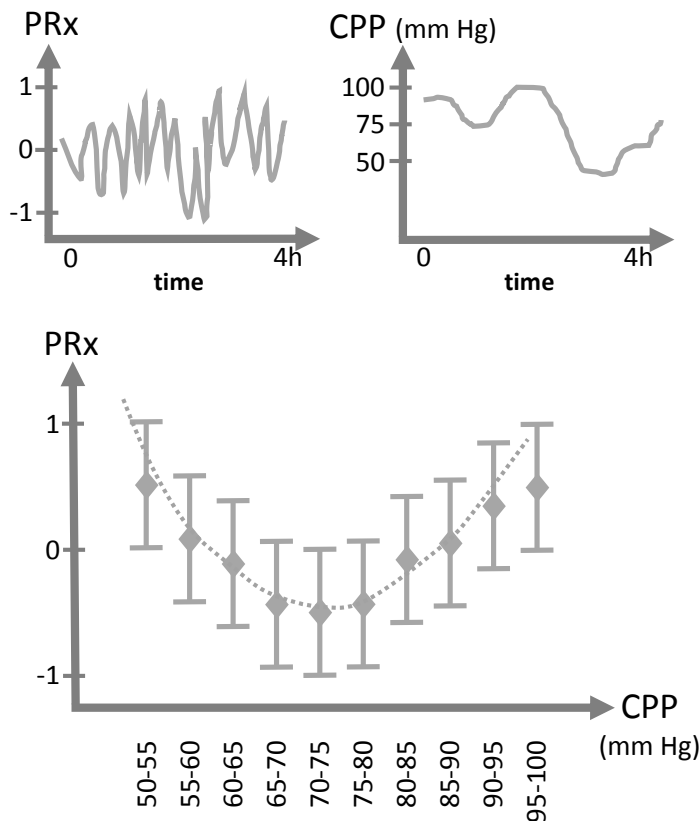


Figure 7. Calculation of CPPopt, simplified. In a given time interval (four hours) CPP values are binned in intervals of 5 mm Hg. Mean PRx in each CPP interval is calculated and plotted against CPP (bars denote dispersion). If a U-shaped curve can be fitted to the data points, CPPopt is the CPP level with lowest associated PRx, i.e. the CPP level where pressure autoregulation is assumed to function best. In this example, CPPopt is between 70 and 75 mm Hg.

Other physiological and epidemiological parameters

In all papers, ICP, MAP and CPP data were recorded and stored in a database by a multimodality monitoring system^[87]. In paper I and II the first CT scan was classified according to Marshall CT class by one of the authors (U. Johnson) (Table 2)^[132]. Neurological status at admission was assessed with Glasgow coma scale (GCS, Table 3) and functional outcome with Glasgow outcome scale extended (GOSE, Table 4)^[133,134].

In paper III and IV neurological status at admission was assessed with the Hunt and Hess scale (Table 5), and the first CT classified according to the Fisher CT classification by one of the authors (U. Johnson) (Table 6).

Table 2. *Marshall CT classification of TBI.*

Class	Definition
Diffuse injury I	No visible pathology on CT scan.
Diffuse injury II	Cisterns present, midline shift < 5 mm. No high/mixed density lesion > 25 cc.
Diffuse injury III	Cisterns compressed, midline shift < 5 mm. No high/mixed density lesion > 25 cc.
Diffuse injury IV	Midline shift > 5 mm. No high/mixed density lesion > 25 cc.
Evacuated mass lesion (EML)	Any lesion surgically evacuated.
Non-evacuated mass lesion (NEML)	High- or mixed density lesion > 25 cc, not surgically evacuated.

Table 3. *Glasgow coma scale: The score from best eye response, best verbal response and best motor response are added to a maximum score of 15. Minimum score is three.*

Category	Description	Score
Best eye response	Spontaneous, open eyes	4
	Opens to verbal commands	3
	Opens to pain	2
	None	1
Best verbal response	Oriented	5
	Confused, but answers questions	4
	Inappropriate responses	3
	Incomprehensible speech	2
	None	1
Best motor response	Obeys commands	6
	Purposeful movement to pain stimulus	5
	Withdraws from pain	4
	Flexion	3
	Extension	2
	None	1

Table 4. *Glasgow outcome scale extended for assessment of clinical outcome in TBI.*

GOSE score	Description
1	Death
2	Vegetative state
3	Lower severe disability (needs help with most activities of daily life)
4	Upper severe disability (needs help with some activities of daily life such as shopping, local travelling)
5	Lower moderate disability (unable to work or participate in social activities)
6	Upper moderate disability (reduced ability to work or participate in social activities)
7	Lower good recovery (some problems related to the injury)
8	Upper good recovery (No problems related to the injury)

Table 5. *Hunt and Hess scale for clinical grading of SAH.*

Score	Description
1	Asymptomatic / mild headache
2	Moderate/severe headache, nuchal rigidity, no neurological deficit other than cranial nerves
3	Drowsiness, confusion, mild focal neurological deficit
4	Stupor, moderate/severe hemiparesis
5	Coma, decerebrate posturing

Table 6. *Fisher CT classification of SAH.*

Score	Description
1	No hemorrhage evident
2	Subarachnoid hemorrhage < 1 mm thick
3	Subarachnoid hemorrhage > 1 mm thick
4	Subarachnoid hemorrhage with intraventricular/ intraparenchymal extension

Patient groups and data analysis

Paper I

The relation between pressure reactivity, physiological parameters and outcome was studied in two ways: First the slope of MAP/ICP regression line was used to dichotomize patients into pressure-passive (MAP/ICP slope above median) and pressure active (MAP/ICP slope below median). Differences in ICP, MAP and CPP between patients with unfavorable and favorable outcome (GOSE score 1-4 and 5-8, respectively) were assessed with Mann-Whitney U test. Separate calculations were made in the pressure-passive / pressure-active groups. ICP, MAP and CPP were expressed as % of the monitoring time spent above or below predefined thresholds.

Secondly, patients were also dichotomized into high-CPP and low-CPP groups (above or below median CPP), and differences in proportions of

favorable outcome in different combinations of high/low-CPP and pressure passive/pressure active were assessed with 2x2 tables (Fisher's exact test).

Patients were also grouped according to GCS score at admission, Marshall CT class at admission and GOSE score at 6 months. Differences in MAP/ICP slope between GCS and Marshall CT class groups were assessed with Kruskal-Wallis ANOVA. Correlation between GOSE and MAP/ICP slope was assessed with Spearman rank order correlation.

In the patients who were treated with pentobarbiturate, the difference in MAP/ICP slope before, during and after treatment was calculated with Friedman's ANOVA. In the patients treated with hemicraniectomy, the difference in MAP/ICP slope before and after the procedure was calculated with Mann-Whitney U-test.

Non-parametric statistics were chosen because of mostly non-normal data distribution. A p-value < 0.05 was considered statistically significant.

Paper II

Marshall CT class was dichotomized into Diffuse injury group (Marshall class D1, D2 and D3) or Focal injury group (D4, EML and NEML). The aim was to separate patients with mass lesions from those with diffuse injury. Marshall classes D3 and D4 both includes high or mixed density lesions up to 25 cc, but in group D4 a midline shift > 5 mm is present. To balance borderline cases, D3 was included in the Diffuse group and D4 in the Focal injury group. Mean PRx, was divided into high-PRx (>0.1) intermediate-PRx (0.05 – 0.1) and low-PRx (<0.05) groups. These thresholds were chosen to separate patients with severely deranged (high-PRx) from those with normal pressure autoregulation (low-PRx). In the intermediate group were patients with slightly – moderately disturbed autoregulation. Mean CPP was dichotomized into high-CPP (>70 mm Hg) or low-CPP (<70 mm Hg).

Differences in PRx and CPP between groups with unfavorable/favorable outcome (GOSE score 1-4 and 5-8, respectively) were assessed with Mann-Whitney U-test. Separate calculations were done for the diffuse and focal injury group, as well as for the two groups combined.

Differences in proportions of favorable outcome in groups with different combinations of CPP and PRx were assessed with 2x2 tables (Fisher's exact test).

Non-parametric statistics were chosen because of non-normal data distribution and small n in the 2x2 tables. A p-value < 0.05 was considered statistically significant.

Paper III

Mean PRx was calculated for each 6- 4- and 2-hour period before Xe-CT. Patients were divided into high-PRx (<0.1) and low-PRx (<0.1) groups,

signifying highly disturbed and intact/moderately disturbed autoregulation. Differences in CBF variables between high-PRx and low-PRx groups were calculated with Mann-Whitney U-test, with separate calculations in the two different time windows, roughly corresponding to before and during expected peak incidence of DCI (day 0-3 and day 4-14).

Differences in CBF and physiological parameters between patients who did and did not develop DCI were calculated with Mann-Whitney U-test. DCI was diagnosed clinically as neurological deficits/deterioration occurring that could not be explained by other factors such as infection, hematoma, hydrocephalus etc. Differences in PRx and CBF variables between DCI / non-DCI patients were calculated with Mann-Whitney U-test.

A p-value < 0.05 was considered significant. Non-parametric statistics were chosen because of non-normal data distribution.

Paper IV

The difference between CPPopt and actual CPP (mean value for 30 minutes before Xe-CT scan) was calculated (CPP Δ). Positive CPP Δ signifies actual CPP > CPPopt and vice versa. Correlations between CPP Δ and CBF parameters were calculated with Spearman's rank order correlation. In addition to calculations on all patients (day 0-14), separate calculations were done in day 0-3 and day 4-14 after onset. The reason for the subgrouping was vasospasm, which occurs in about $\frac{2}{3}$ of SAH patients with highest prevalence day 4-14 after onset ^[135,136]. Vasospasm may affect CPA ^[137], and potentially also PRx and CPPopt calculations (*Figure 9*), and the two subgroup time windows were chosen to correspond approximately to before and during peak prevalence of vasospasm. If a patient had multiple Xe-CT scans with calculated CPPopt in the same time window, only data from one scan (the first) was used. In order to evaluate if CPP had an effect on CBF, correlations between CPP and CBF were also calculated. A p-value < 0.05 was considered significant. Non-parametric statistics were chosen because of non-normal data distribution.

Ethical considerations

All studies were approved by the regional ethical review board. In addition, study IV was approved by the local radiation safety authority.

Results

Paper I

Fifty-eight TBI patients (44 male, 14 female, mean age 38.7 years, GCS score 4 - 13, median 7) treated between Oct 2003 and Sept 2006 were included. The main finding was that favorable outcome in patients with disturbed pressure autoregulation was associated with low CPP and low MAP; whereas unfavorable outcome was associated with high CPP (Table 9). In patients with preserved pressure autoregulation there was no association between physiological parameters and outcome (Table 9).

This relationship was also reflected by the fact that in patients with disturbed pressure autoregulation, low CPP was associated with a higher proportion of favorable outcome, and that in patients with preserved pressure autoregulation, no such association was seen (Table 7 and Table 8). There was no difference in autoregulation status (MAP/ICP slope) between GCS score and Marshall CT class. Patients who died had worse autoregulation during the first 24 hours ($p = 0.009$, Mann-Whitney U-test), but there was no difference when considering the whole monitoring time ($p = 0.141$, Mann-Whitney U-test).

In survivors, there was a positive correlation between MAP/ICP slope and GOSE score in the first 24 hours (Spearman $R = 0.33$, $p = <0.05$), but not when data from the whole monitoring time was used.

Table 7. Proportions of favorable outcome in patients with disturbed pressure autoregulation. $p =$ Fischer's exact test.

Group (n)	Favorable outcome; n (%)	p
Low CPP (16)	15 (94)	0.0067
High CPP (13)	6 (46)	

Table 8. Proportions of favorable outcome in patients with preserved pressure autoregulation. $p =$ Fischer's exact test.

Group (n)	Favorable outcome; n (%)	p
Low CPP (13)	10 (77)	0.135
High CPP (16)	8 (50)	

Table 9. Physiological variables in patients with disturbed / preserved pressure autoregulation divided by favorable / unfavorable outcome. *p* = Mann-Whitney U-test. GMT = Good monitoring time (monitoring time after removal of artefacts). BPs = systolic blood pressure

variable	Disturbed pressure autoregulation		Preserved pressure autoregulation		p
	Favorable	Unfavorable	Favorable	Unfavorable	
Mean ICP, mm Hg	12.6 (10.5-4.6)	10.8 (9.5-13.8)	13.1 (10.5-15.5)	11.3 (9.1-16.7)	0.93
Mean MAP, mm Hg	85.9 (81.3-89.4)	90.7 (86.3-94.8)	85.6 (84.4-94.9)	87.4 (84.4-94.9)	0.79
Mean CPP, mm Hg	69.8 (67.4-74.8)	78.2 (75.1-82.1)	71.7 (68.9-80.8)	75.0 (70.9-81.9)	0.35
CPP < 60 mm Hg, % GMT	14.8 (9.34-19.19)	2.8 (1.7-3.4)	17.0 (8.1-22.1)	9.6 (4.0-22.2)	0.39
CPP < 50 mm Hg, % GMT	1.2 (1.0-2.4)	0.2 (0.1-0.2)	2.9 (0.9-4.1)	0.9 (0.3-2.9)	0.23
CPP > 70 mm Hg, % GMT	48.8 (39.1-63.3)	81.6 (70.4-88.3)	53.5 (38.1-71.3)	61.7 (48.3-84.0)	0.45
CPP > 80 mm Hg, % GMT	19.1 (10.6-33.0)	43.4 (30.0-55.2)	24.2 (17.7-51.3)	34.1 (27.6-53.9)	0.37
ICP > 25 mm Hg, % GMT	3.2 (1.2-4.4)	0.9 (0.5-1.3)	4.5 (0.8-6.3)	3.5 (0.1-11.6)	0.61
ICP > 35 mm Hg, % GMT	0.4 (0.1-0.8)	0.1 (0.1 - 0.2)	0.6 (0.1-1.1)	0.5 (0.0-1.3)	0.91
BPs < 100 mm Hg, % GMT	3.2 (0.8-4.6)	0.4 (0.2-1.0)	1.9 (0.7-3.3)	1.2 (0.8-5.3)	0.93
BPs < 90 mm Hg, % GMT	0.5 (0.1-1.1)	0.1 (0.0-0.2)	0.3 (0.1-0.7)	0.2 (0.1-1.2)	0.89
BPs > 160 mm Hg, % GMT	9.4 (3.8-23.0)	12.1 (7.4-25.8)	10.9 (5.9-33.8)	15.1 (2.1-24.4)	0.16
BPs > 180 mm Hg, % GMT	0.9 (0.5-3.5)	1.6 (0.4-4.5)	1.6 (0.5-11.0)	1.8 (0.4-7.8)	0.37
MAP < 80 mm Hg, % GMT	35.6 (22.5-48.3)	16.1 (9.1-25.8)	29.5 (16.5-41.9)	27.2 (14.5-36.8)	0.37
MAP < 70 mm Hg, % GMT	10.3 (5.3-11.8)	1.7 (0.4-2.8)	4.7 (2.2-8.8)	3.4 (1.7-4.5)	0.37
MAP > 110 mm Hg, % GMT	2.6 (0.9-8.0)	4.2 (1.7-11.3)	4.2 (1.9-18.2)	4.8 (2.6-15.9)	0.93
MAP > 120 mm Hg, % GMT	0.6 (0.2-2.9)	1.4 (0.5-1.8)	0.9 (0.5-6.4)	1.4 (0.5-6.9)	0.96

In the small number of patients who were treated with pentobarbiturate coma (n=7), there was no difference in MAP/ICP slope before, during and after treatment. Nine patients were treated with decompressive hemicraniectomy, but in only three patients MAP/ICP slope could be calculated before and after the procedure (due to the fact that most patients underwent the procedure immediately upon admission). In these three patients MAP/ICP slope showed a reduction after hemicraniectomy (-0.092 ± 0.047).

Paper II

One hundred seven TBI patients (84 male, 23 female, mean age 40.6 years) treated between Jan 2008 and Feb 2011 were studied. Low PRx (i.e. intact autoregulation) was associated with favorable outcome in the combined group ($p = 0.002$) and the diffuse injury group ($p = 0.04$), but not in the focal injury group ($p = 0.06$). In the focal injury group, unfavorable outcome was associated with high CPP ($p = 0.02$). In the combined group and the focal injury group, CPP was not associated with outcome.

In the 2x2 table analysis, patients in the diffuse injury group with PRx > 0.1 (worst autoregulation) and mean CPP > 70 mm Hg had a higher proportion of favorable outcome than those with CPP < 70 mm Hg (Table 10).

Table 10. *Proportions of favorable outcome in diffuse injury patients with PRx > 0.1 divided by high/low CPP. p = Fischer's exact test.*

CPP	Unfavorable outcome	Favorable outcome	p
<70	5	0	0.03
>70	2	5	

No difference in proportions of favorable outcome was found in the other PRx-groups when divided by CPP-level. In the focal injury group, there were no differences in the proportions of favorable outcome in the three PRx-groups when divided by CPP-level.

Paper III

Forty-seven SAH patients (13 male, 34 female; age 28-81 years, median 59 years; Hunt & Hess 1-5, median 3; CT Fisher 2-4, median 4) treated between Oct 2012 and Feb 2015 were included.

In the pre-vasospasm window (day 0-3 after admission), 38 patients had PRx and CBF data. High-PRx patients had significantly higher proportions of CBF% < 10 and a showed a trend towards lower mean global CBF (Table 11).

Table 11. CBF variables in SAH patients with PRx above/below 0.1, day 0-3 after onset. *p* = Mann-Whitney U-test

	PRx > 0.1	PRx < 0.1	<i>p</i>
Mean global CBF	30.2 (21.3-39.8)	37.6 (34.6-48.6)	0.06
CBF% < 20	23.3 (6.7-48.3)	10.0 (3.3-16.7)	0.10
CBF % < 10	5.0 (0.0-15.0)	0.0 (0.0-5.0)	0.04

In the vasospasm time window (day 4-14 after admission) 30 patients had PRx and CBF data. Patients in the high-PRx group (PRx > 0.1) had significantly higher CBF%<10 (Table 12).

Table 12. CBF variables in SAH patients with PRx above/below 0.1, day 4-14 after onset. *p* = Mann-Whitney U-test

	PRx > 0.1	PRx < 0.1	<i>p</i>
Mean Global CBF	27.8 (21.7-39.2)	36.0 (27.9-44.5)	0.15
CBF% < 20	28.6 (2.4-53.4)	11.7 (5.0-18.6)	0.27
CBF % < 10	5.9 (0.0-18.6)	0.0 (0.0-1.9)	0.03

There was no significant difference in PRx or CBF parameters between patients who did and did not develop DCI, although DCI patients had lower Mean global CBF with borderline significance (32.9 ml/100g/min vs 37.5 ml/100g/min. *p*=0.05, Mann-Whitney U-test).

Paper IV

One hundred forty-five Xe-CT scans were done in 82 SAH patients between Oct 2012 and Jan 2016. CPPopt could be calculated in adjunct to 87 of the 145 Xe CT scans (60%), in 64 of the 82 patients (78%). Of these 64 patients, 39 were examined day 0-3 and 35 day 4-14.

Using all data (day 0-14), CPPΔ was negatively correlated with CBF%<20 and CBF%<10 (Table 13). Patients with CPP below CPPopt had higher amounts of low-flow regions (*Figure 8*). In day 0-3 and day 4-14 subgroups, CPPΔ was negatively correlated with CBF%<10 (Table 14 and Table 15). CPP was not correlated with any of the CBF parameters in any of the time windows.

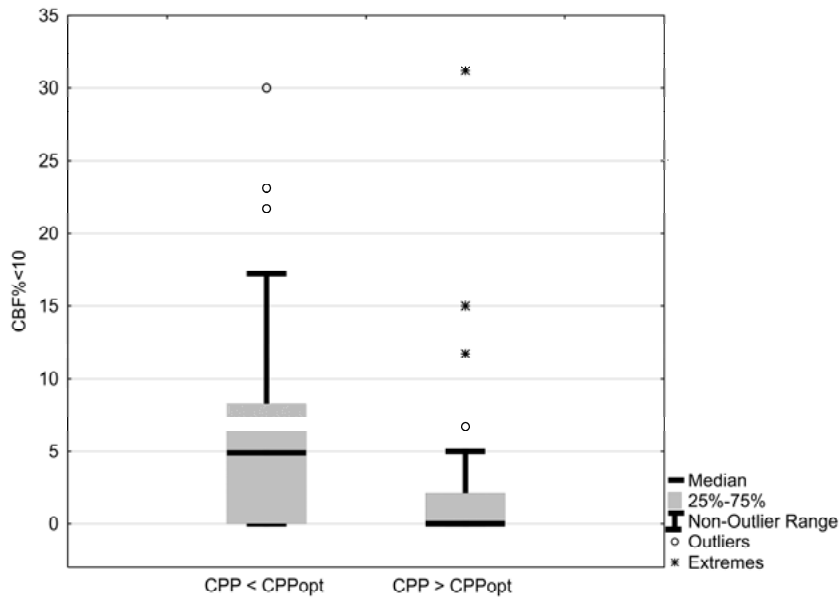


Figure 8. Patients with actual CPP below calculated optimum had higher amounts of regions with CBF < 10 ml/100g/min (median 5 vs 0, $p = 0.008$ Mann-Whitney U-test.)

Table 13. Correlations between CPP Δ and CBF parameters. R, p: Spearman's rank order correlation. Time window = day 0-14.

CPP Δ correlation with	R	p
Mean global cortical CBF	0.24	0.05
CBF%<10	-0.39	0.002
CBF%<20	-0.27	0.03

Table 14. Correlations between CPP Δ and CBF parameters. R, p: Spearman's rank order correlation. Time window = day 0-3.

CPP Δ correlation with	R	p
Mean global cortical CBF	0.15	0.37
CBF%<10	-0.38	0.02
CBF%<20	-0.19	0.25

Table 15. Correlations between CPP Δ and CBF parameters. R, p: Spearman's rank order correlation. Time window = day 4-14.

CPP Δ correlation with	R	p
Mean global cortical CBF	0.29	0.09
CBF%<10	-0.39	0.02
CBF%<20	-0.30	0.08

Discussion

All studies in this thesis include relatively few patients and are of an exploratory nature, i.e. hypothesis-generating, rather than hypothesis-testing. Small sample size is common in clinical research, and has a few associated risks regarding statistical significance testing. One risk is reduced ability to detect a true finding. Another, more counterintuitive risk is the decreased probability that a significant finding actually is true and over inflation of effect sizes ^[138,139]. An obvious cure for these problems would be increasing statistical power by increasing sample size. This is however not always possible in clinical research, where one must “make do” with the data at hand. The statistical methods are therefore chosen to be as robust as possible, and assumptions about effect sizes are generally conservative, but the results must still be interpreted with some caution.

Paper I

The measure of autoregulation in this paper have similarities with the pressure reactivity index (PRx), which is a well-validated and extensively studied measure of pressure reactivity. There are however differences to be considered when comparing the present findings with PRx-based studies. PRx is a dynamic index that reflects the status of autoregulation at a specific point in time. The MAP/ICP slope requires at least several hours to obtain a good estimate, and probably relates more to static autoregulation measurements.

In both the 2x2 tables and subgroup analyses, low CPP was associated with favorable outcome in patients with impaired pressure autoregulation. As CPP < 50 mm Hg was uncommon (only 2 patients had CPP < 50 mm Hg for more than 10 % of the monitoring time) no conclusions are drawn about CPP levels < 50 mm Hg. CPP between 50 and 60 mm Hg however seems beneficial in these patients. A common target CPP for TBI treatment protocol has been > 70 mm Hg ^[140], but some studies have been unable to demonstrate improved outcome with this approach ^[141], and artificial elevation of CPP has even been associated with decreased regional CBF ^[142].

In patients with more preserved pressure reactivity, higher levels of CPP were hypothesized to be associated with better functional outcome, but no such

association was found. Several reasons may explain this. The MAP/ICP slope threshold value was chosen to create groups of similar size and some patients with disturbed autoregulation may have been included in the “pressure active” group. Furthermore, the dispersion of CPP values was not large and it is possible that higher levels would have helped some patients in the group with intact pressure reactivity.

A previous study by Zweifel et al found a linear relationship between PRx and outcome with low PRx in patients with good recovery and high PRx in non-survivors ^[143]. We found the opposite in survivors, i.e. a significant positive correlation between MAP/ICP slope the first 24 hours and GOSE score. This discrepancy is interesting, but not necessarily contradictory. Impaired CPA has been shown to be a good prognostic factor in an ICP-based treatment protocol but a negative prognostic factor in a CPP-based protocol ^[87]. MAP/ICP slope was higher in non-survivors than survivors, which is in line with previous findings ^[144]. Very deranged autoregulation may be an indicator of severe trauma where the potentially treatable component is small regardless of treatment protocol.

No patterns regarding pressure autoregulation were found in patients treated with decompressive hemicraniectomy or pentobarbiturate coma; but due to small sample sizes no conclusions can be drawn.

Paper II

This study used PRx as a measure of pressure reactivity and the results are therefore possible to compare with the previous literature on PRx.

In the focal injury group, high CPP was associated with unfavorable outcome. The reason may be disruption of blood-brain barrier (BBB) in these patients, causing increased risk of capillary leakage and brain edema ^[145-148]. Hyperemia may also cause increased intracranial hypertension when cerebrospinal compliance is exhausted ^[149,150].

In diffuse injury patients with disturbed pressure autoregulation, high CPP was associated with favorable outcome. This does not necessarily contradict the findings in paper I. As discussed above these patients may be less prone to BBB-damage and edema formation, and slightly higher levels of CPP may help establish an adequate CBF.

Paper III

A methodological issue that must be discussed is the ICP data input into the PRx calculations. In this paper, ICP values for PRx calculation were derived from ventricular drains. In case of CSF drainage through an open catheter system, craniospinal compliance is altered. In that case changes in ICP

following changes in MAP may be smaller, and PRx values may be unreliable. However, the ventricular drains used in this study (HanniSet® Xtrans, Smith medical, GmbH, Glasbrunn, Germany) have a rubber valve at the outflow tube that causes an outflow resistance so the ICP pulsations are visible even when the system is open for CSF drainage. Quick changes in MAP may therefore induce enough changes in ICP to produce relatively accurate PRx values. Previous investigators have used different approaches to this issue. When Bijlenga studied PRx in SAH, monitoring data from time periods with open ventricular drains were excluded [65]. Eide came to similar results without excluding open-ventricular drain data [151]. Since acute hydrocephalus and CSF drainage with ventricular drains is common in these patients, excluding data derived from open-ventricular drains means discarding a lot of information. We therefore chose to include PRx data from open ventricular drains in order not to lose data. This approach is supported by a small publication that concluded that PRx values derived from open drains are valid as long as the ICP curve has a normal configuration [152]. Another recent study by us found a small and clinical insignificant difference in PRx values derived from open/closed drains [153].

In the pre-DCI window (day 1-3 after admission), high PRx, i.e. disturbed autoregulation was associated with higher amounts of CBF < 20 ml/100g/min; as could be expected from previous studies. There was no association between CPP and CBF parameters. CPP in this time window was not low (mean 75.0, range 58.6 – 92.3 mm Hg), and as this was before expected onset of vasospasm, CPP was probably not critical for upholding CBF.

In the DCI window (day 4-14 after admission) the high-PRx group (PRx > 0.1) had higher a proportion of CBF% < 10, but no difference in mean global CBF or CBF% < 20.

Previous studies have found an association between autoregulatory dysfunction and DCI [66,117], but we found no association between PRx and development of DCI. PRx relies on spontaneous fluctuations of MAP and ICP, and it is important to consider how these parameters are affected by vascular spasm or loss of vascular tone at different levels of the vascular tree. In case of distal vasospasm, the modulation of vessel diameter in response to changes in CPP will be lost, i.e. there will be a purely mechanistic reason for measured loss of pressure reactivity [154]. In case of proximal vasospasm with preserved autoregulation, distal vasodilatation will be an adequate compensatory response, but will shift the autoregulatory curve [155]. In both instances PRx may not be a reliable indicator of autoregulatory status (*Figure 9*).

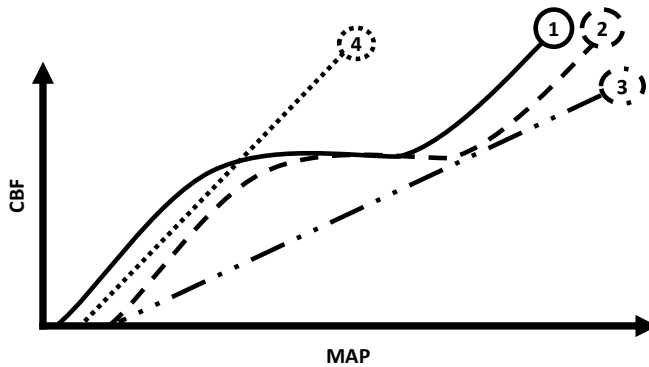


Figure 9. Theoretical implications of vasomotor tonus and autoregulation. 1) Normal vasomotor tonus and normal autoregulation. PRx is valid. 2) Proximal vasospasm and normal distal vasomotor reactivity. Normal autoregulation. PRx is valid, but the curve is shifted to the right. 3) Distal vasospasm, loss of autoregulation. PRx is invalid with false low values. 4) Loss of vasomotor tonus, loss of autoregulation. PRx is valid.

Paper IV

In this study CPPopt could be calculated in adjunct to 60 % of the Xe-CT scans (78% of the patients), which is in line with previous findings ^[126] and seems adequately high for CPPopt to be useful in clinical monitoring. CPP below calculated optimum was associated with higher amounts of low-flow regions. This was not attributed to CPP levels. The correlations found were only weak to moderate, and CPPopt is of course not the only determinant of CBF. However, CPPopt seems to be a useful guide in the clinical setting since it provides an indicator on how to individualize treatment according to status of autoregulation.

As discussed in paper III, PRx calculations may be affected by high craniospinal compliance (high capacity to compensate for added intracranial volume) such as when CSF is drained by an open ventricular drainage system, but PRx is probably valid as long as the ICP curve has a normal configuration. Vasospasm at different levels of the vascular tree may also affect PRx and therefore CPPopt calculations. In this study vasospasm was not assessed with trans cranial Doppler or angiography, and the effect of vasospasm on CPPopt could therefore not be studied. However, it is unlikely that vasospasm would occur in the early time window (day 0-3) and the results were consistent in all three time windows.

Taken together, the study demonstrates the physiological CBF properties of CPPopt and that CPPopt may be a valuable tool to monitor SAH patients and individualize CPP treatment to avoid regional hypoperfusion. This is, to our knowledge, the first study to show this. Further studies are warranted to evaluate the utility of CPPopt in the clinical management of SAH patients.

Conclusions

Paper I

In TBI patients with disturbed autoregulation, slightly lower levels of CPP (50-60 mm Hg) are well tolerated and seem beneficial.

Paper II

In TBI patients with focal lesions high CPP may be harmful, possibly because of BBB-disruption. In TBI patients with diffuse injury and disturbed pressure autoregulation, higher levels of CPP may be beneficial.

Paper III

In patients with severe SAH, high PRx (disturbed autoregulation) is associated with low CBF. PRx may be an unreliable indicator of autoregulation in some situations, such as during vasospasm.

Paper IV

CPPopt calculation with an automated algorithm is possible in a majority of patients with severe SAH. CPPopt may be a valuable tool to guide treatment. CPP should be kept above calculated optimum in patients with severe SAH.

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Sammanfattning på svenska

Hjärnan är ett organ med hög ämnesomsättning men liten kapacitet att lagra näring och syre. Hjärnan måste därför ständigt förses med dessa ämnen via blodet. Redan en måttlig sänkning av hjärnans blodflöde (cerebralt blodflöde, CBF) kan innebära att neuronernas (nervcellernas) och hjärnans funktion påverkas. Ytterligare sänkning av CBF innebär oåterkallelig skada och celledöd. För högt CBF kan även det vara farligt, då det kan öka det intrakraniella trycket och utöva ett skadligt tryck på hjärnan. Att upprätthålla CBF är därför en av kroppens viktigaste funktioner. Det finns flera mekanismer för att reglera CBF; tex via neuronal aktivitet och koldioxidnivå i blodet. En nyckelmekanism i sammanhanget, som studeras i denna avhandling, är autoregulation. Autoregulation definieras som hjärnans egen förmåga att upprätthålla ett jämnt och tillräckligt CBF trots variationer i kroppens blodtryck. Ett tillfälligt lågt blodtryck får inte medföra lågt CBF, eftersom det skulle äventyra neuronernas funktion och liv. Vice versa får ett tillfälligt högt blodtryck inte orsaka ett för högt CBF vilket kan ge ökat intrakraniellt tryck.

Autoregulationen kan beskrivas genom en ekvivalent till Ohms lag:

$$CBF = \frac{CPP}{CVR}$$

där CPP är cerebralt perfusionstryck, d.v.s. blodtrycket minus intrakraniellt tryck, och CVR är cerebrovaskulär resistens, d.v.s. flödesmotståndet i hjärnans blodkärl. När blodtrycket, och därigenom CPP, ändras kommer detta att utlösa en kompensatorisk förändring i CVR, och CBF hålls konstant.

Särskilda receptorer i kärlväggen känner av förändringar i CPP i form av ändrad spänning i kärlväggen och utlöser en dilatation eller kontraktion av blodkärlet. Med kontraherade trängre kärl blir motståndet högre medan dilaterade vida kärl erbjuder ett lägre motstånd.

Vid akuta skador eller sjukdomar i hjärnan kan förmågan till autoregulation bli nedsatt. Detta medför en hög risk för hjärnan eftersom tillfälligt lågt eller högt blodtryck då kan medföra för lågt eller högt CBF, vilket kan ha skadliga effekter på hjärncellerna. Att upprätthålla ett adekvat CBF är därför av yttersta vikt i intensivvård av sådana patienter, och att ta hänsyn till autoregulationsstatus är önskvärt, men i praktiken mycket svårt. Trots att det

finns många metoder för mätning av autoregulation har dessa hittills varit redskap för forskningen och inte kunnat tas i bruk i den kliniska vardagen.

Den metod för mätning av autoregulation som används i denna avhandling utnyttjar förhållandet mellan blodtryck och intrakraniellt tryck (ICP). När blodkärl kontraheras eller dilateras för att reglera CVR, kommer detta också att påverka den intrakraniella blodvolymen (CBV). Kontraktion medför minskad CBV medan dilatation medför ökad. Ökning av CBV betyder också ökat intrakraniellt tryck (ICP) och vice versa. När autoregulationen fungerar normalt kommer därför en ökning i blodtryck att medföra en sänkning i ICP genom de CBF-reglerande mekanismerna; matematiskt uttryckt blir blodtryck och ICP negativt korrelerade. När autoregulationen är störd blir förhållandet det omvända, d.v.s. blodtryck och ICP är positivt korrelerade.

Detta förhållande har använts i forskning framförallt på patienter med skullskador, men även patienter med hjärnblödningar, och har visats vara starkt kopplat till det kliniska utfallet. Att använda sådan information för att individualisera vården vore önskvärt men har visat sig vara svårt. Trots att många förslag funnits har inget av dessa tagits i kliniskt rutinbruk.

Syftet med denna avhandling var att studera autoregulation hos patienter med skullskada och subaraknoidalblödning för att öka kunskapen om hur samspelet mellan autoregulation och andra fysiologiska parametrar är kopplat till utfall.

Avhandlingen består av fyra delarbeten där data har insamlats fortlöpande, och analyserats i efterhand. Samtliga studerade patienter vårdades vid Akademiska Sjukhusets neurointensivvårdsavdelning (NIVA). I intensivvården mäts blodtryck genom en tunn kateter i en artär i handleden. ICP mäts med en tryckgivare som införs i hjärnvävnaden, eller med en tunn kateter som införs i hjärnans ventrikelsystem. CPP beräknas som medelartärblodtrycket (MAP) – ICP.

I delarbete I studerades 44 patienter med skullskada som vårdats mellan oktober 2003 och september 2006. Samtliga patienter vårdades enligt ett standardiserat protokoll, och i efterhand analyserades hur autoregulation, CPP, MAP och ICP påverkade utfallet efter sex månader. Autoregulationen mättes genom att motsvarande värden för MAP och ICP för varje minut under vårdtiden plottades i ett diagram, och en regressionslinje anpassades till punkterna. Regressionslinjens lutning togs som ett mått på patientens autoregulationsstatus under vårdtiden.

Vi fann att de patienter som dog hade sämre autoregulation under vårdens första dygn än de som överlevde. Bland de överlevande fann vi däremot att sämre autoregulation var kopplat till bättre kliniskt utfall. Patienterna delades även in i två grupper med god respektive dålig autoregulation. I gruppen med

dålig autoregulation fann vi att lågt CPP var kopplat till bättre kliniskt utfall. I gruppen med god autoregulation fanns ingen koppling mellan CPP och utfall.

Resultaten kan förklaras med att patienter med dålig autoregulation blir känsliga för högt CPP som kan medföra ökat intrakraniellt tryck och ödem, d.v.s. vätskeutträde, i hjärnan. Det behandlingsprotokoll som användes är sannolikt särskilt fördelaktigt för patienter med dålig autoregulation, eftersom man generellt inte strävar efter att höja blodtrycket med läkemedel. Lågt CPP borde också vara skadligt för dessa patienter, men inte i de nivåer som vi såg i studien. Sammanfattningsvis drar vi slutsatsen att hos patienter med skullskada och störd autoregulation skall man inte höja CPP.

I delarbete II studeras om relationen mellan autoregulation, CPP och utfall är olika vid olika typer av skullskada. Studien innefattade 107 patienter med skullskada som vårdats mellan jan 2008 och feb 2011. Autoregulation mättes här med pressure reactivity index (PRx), som är den fortlöpande korrelationen mellan MAP och ICP mätt under en 5-minutersperiod. PRx är en väl etablerad markör för autoregulation inom forskning och kan användas för klinisk övervakning. Patienternas första datortomografi klassificerades efter skadetyper enligt Marshalls klassifikationssystem för skullskador. Detta system delar in skador efter diffusa eller fokala hjärnskador.

I analysen såg vi att högt PRx, d.v.s. dålig autoregulation var associerat med sämre kliniskt utfall. I gruppen med fokal hjärnskada var högt CPP associerat med sämre kliniskt utfall, vilket kan bero på att denna typ av skada kan medföra skada på blod-hjärn-barriären, och att ett högt CPP då kan innebära vätskeutträde i vävnaden och ett skadligt ökat intrakraniellt tryck. Hos patienter med diffus skada och dålig autoregulation var däremot högt CPP associerat med gott kliniskt utfall. Detta kan förklaras med att dessa patienter har mer intakt blod-hjärn-barriär, och därför är hjälpta av ett måttligt ökat CPP för att upprätthålla CBF. Det förefaller således som att både typen av skullskada och förmågan att autoreglera CBF skall styra CPP-behandlingen.

Delarbete III var en studie av patienter med aneurysmal subaraknoidalblödning, SAB. SAB är en blödning under den mjuka hjärnhinnan, som drabbar c:a 9 av 100 000 personer årligen. Även om antalet drabbade är få är dödligheten hög, och bland de som överlever är bestående men av olika allvarlighetsgrad vanliga. Även vid SAB kan autoregulationen vara störd, och man har i forskning sett en koppling mellan autoregulationsstatus och kliniskt utfall vid SAB. I denna studie ville vi studera hur PRx påverkar CBF och om PRx kan förutsäga delayed cerebral ischemia (DCI), vilket är en fruktad komplikation i den tidiga fasen av sjukdomen. DCI innebär infarktutveckling med oåterkalleliga neurologiska bortfall. DCI drabbar c:a 30 % av patienterna med SAB och kan bero på många

faktorer som kramp i blodkärl, blod-hjärn-barriärskada, autoregulationsstörning, etc.

I denna studie mätte vi CBF med Xenon-förstärkt datortomografi (Xe-CT). Xenon är en ädelgas som när den tillförs via inandningsluften kommer att lösas upp i blodet och fördela sig i kroppen på samma sätt som syrgas. Xenon har också egenskapen att dämpa röntgenstrålning, och genom att utföra datortomografi medan Xenon tillförs kan man bestämma CBF. Tack vare ett system med en flyttbar datortomograf kunde patienterna undersökas på NIVA i sina sängar under pågående intensivvård, vilket är en fördel då det kan vara svårt eller omöjligt att transportera dessa svårt sjuka patienter för undersökning på annan plats. Autoregulation mättes även här med PRx.

I den här undersökningen studerades 47 patienter med SAB, vårdade mellan okt 2012 och feb 2015. Eftersom Xe-CT metoden använder en respirator för Xenontillförsel innebär det att undersökningen endast omfattar medvetslösa patienter med andningsstöd av respirator, d.v.s. patienter med svår sjukdom. Eftersom förekomsten av DCI är låg omedelbart efter insjuknandet och högre efter c:a en vecka, gjordes olika analyser i tidsfönstren dag 0-3 och dag 4-14 efter insjuknandet.

I analysen fann vi ingen skillnad i autoregulation mellan patienter som drabbades respektive inte drabbades av DCI. Detta var förvånande, men kan förklaras av att behandlingen som används mot DCI, s.k. Triple-H, är effektiv. Man måste också vara försiktig med tolkningen av data då antalet studerade patienter var relativt litet. Då vi analyserade autoregulationens relation till CBF fann vi att dålig autoregulation var associerat med dåligt CBF, både i det tidiga och sena tidsfönstret. PRx kan alltså ha potential att förutsäga CBF, men även här bör man vara försiktig i tolkningen då studien är liten. Ett ytterligare observandum är att PRx beror på förhållandet mellan ICP och MAP, och att detta förhållande kan påverkas vid kramp i blodkärlen, s.k. vasospasm. Eftersom vasospasm är vanligt vid SAB kan PRx påverkas och måste tolkas med varsamhet.

I delarbete IV studerades om s.k. ”optimalt CPP” (CPPopt) kan beräknas hos patienter med SAB, och om det kan förutsäga CBF mätt med Xenon-CT. CPPopt är det värde på CPP där autoregulationen teoretiskt fungerar bäst. CPPopt beräknas genom att man tar flera korresponderande värden på PRx och CPP och plottar dessa mot varandra med PRx på Y-axeln och CPP på X-axeln i intervall om 5 mm Hg. Det CPP-värde där PRx är lägst antas vara det värde där autoregulationen fungerar bäst, och benämns CPPopt. Beräkning av CPPopt kräver relativt mycket data, motsvarande minst flera timmars övervakning. I studien användes ett tidsintervall på fyra timmar för beräkning av CPPopt.

Skillnaden mellan ”verkligt” CPP och CPPopt beräknades som ΔCPP . Positivt ΔCPP innebär att verkligt CPP var högre än beräknat CPPopt, och vice versa. I tre olika tidsfönster (dag 0-14, dag 0-3 och dag 4-14 efter

insjuknandet) beräknades korrelationen mellan Δ CPP och olika CBF-parametrar. Även korrelationen mellan CPP och CBF beräknades för att undersöka om en eventuell koppling mellan Δ CPP och CBF enbart är relaterad till CPP-nivå.

Resultaten från beräkningarna visade CPPopt gick att bestämma hos c:a 60% av patienterna. Δ CPP var negativt korrelerat med CBF, dvs CPP under beräknad optimal nivå var associerat med högre förekomst av lågt blodflöde (CBF < 10 ml/100g/min). Det fanns ingen korrelation mellan enbart CPP och CBF.

Sammantaget verkar CPPopt vara en användbar markör för individualisering av behandling med avseende på autoregulation. CPP bör inte ligga under beräknat optimalt CPP hos patienter med svår SAB.

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