Clinical Bedside Studies of Cerebral Blood Flow in Severe Subarachnoid Hemorrhage Using Xenon CT

HENRIK ENGQUIST
Aneurysmal subarachnoid hemorrhage (SAH) is frequently complicated by delayed cerebral ischemia (DCI), contributing to poor outcome. Particularly for patients in poor neurological state, prediction of the acute clinical course is difficult, as is the early detection of DCI. Repeated measurement of global and regional cerebral blood flow (CBF) could potentially identify patients at risk of deterioration and guide in the clinical management.

The studies in this thesis are based on bedside measurements of CBF by xenon-enhanced CT with the aim to assess and characterize global and regional CBF disturbances at different phases in the acute course after severe SAH. Furthermore, the effects of hemodynamic augmentation by hypervolemia, hemodilution and hypertension (HHH-therapy) on CBF and cerebral energy metabolism in patients with DCI are addressed.

In Paper I, CBF disturbances at the early phase (day 0–3) after SAH were found common and often heterogeneous with substantial regions of near ischemic CBF. Older age and more severe hemorrhage (graded according to Fisher from CT) were factors associated with more compromised CBF. In Paper II, exploring the temporal dynamics of CBF, low initial CBF was associated with a persistent low level of CBF at day 4–7. The association was more pronounced when patients receiving HHH-therapy were separated, and indicates that patients with low CBF, even without clinical signs of DCI, could benefit from careful surveillance and optimization of circulation. In Paper III, the effects on CBF from HHH-therapy in patients with DCI was assessed. Hematocrit decreased during treatment, while the increase in systemic blood pressure was modest. Global CBF and CBF of the worst perfused regions increased, and the proportion of regions with critically low flow decreased accordingly. In Paper IV, the effects of HHH was further assessed in patients also monitored with cerebral microdialysis (CMD). CBF improved during HHH-therapy, while the cerebral energy metabolic CMD parameters stayed statistically unchanged. None of the patients developed metabolic signs of severe ischemia, but a disturbed energy metabolic pattern was common, possibly explained by mitochondrial dysfunction.

Keywords: Subarachnoid hemorrhage, delayed cerebral ischemia, cerebral blood flow, HHH-therapy, triple-H, xenon CT, XeCT, cerebral microdialysis

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List of Papers

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<tbody>
<tr>
<td>ACA</td>
<td>anterior cerebral artery</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
</tr>
<tr>
<td>rCBF</td>
<td>regional cerebral blood flow</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CMD</td>
<td>cerebral microdialysis</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<tr>
<td>CT</td>
<td>computerized tomography, computed tomography</td>
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<tr>
<td>DCI</td>
<td>delayed cerebral ischemia</td>
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<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>GCSmotor</td>
<td>Glasgow coma scale, motor component</td>
</tr>
<tr>
<td>GOS</td>
<td>Glasgow outcome scale</td>
</tr>
<tr>
<td>H&amp;H</td>
<td>Hunt and Hess scale</td>
</tr>
<tr>
<td>HHH-therapy</td>
<td>hypervolemia, hemodilution and hypertension</td>
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<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>lactate/pyruvate ratio</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MCA</td>
<td>middle cerebral artery</td>
</tr>
<tr>
<td>MR, MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin scale</td>
</tr>
<tr>
<td>NIC</td>
<td>neurosurgical intensive care</td>
</tr>
<tr>
<td>NICU</td>
<td>neurosurgical intensive care unit</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PCA</td>
<td>posterior cerebral artery</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SAH</td>
<td>subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission CT</td>
</tr>
<tr>
<td>TCD</td>
<td>transcranial doppler</td>
</tr>
<tr>
<td>WFNS</td>
<td>World Federation of Neurosurgical Societies</td>
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<tr>
<td>XeCT</td>
<td>xenon enhanced computerized tomography</td>
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Introduction

As an estimated worldwide average, 10 in 100,000 people suffer from spontaneous subarachnoid hemorrhage (SAH) each year [1]. SAH constitutes a small part of all stroke cases but carries a high rate of mortality and morbidity, despite the last decades of improvement in the treatment of cerebral aneurysms and neurosurgical intensive care (NIC) [2, 3]. In as many as 20–30 percent of the patients surviving the initial hemorrhage, the acute course is complicated by delayed cerebral ischemia (DCI), which contributes to poor outcome [4, 5]. The complex pathophysiological mechanisms leading to DCI, including vasospasm, inflammatory response and microcirculatory disturbances, are insufficiently understood [6], and scientific evidence supporting prophylactic strategies and therapeutic interventions is scarce [7-9]. Furthermore, there is a lack of clinical tools for early identification of patients at risk of deterioration, especially for unconscious or sedated patients. Compromised cerebral blood flow (CBF) is a crucial factor in the development of DCI, and repeated measurement of global and regional CBF may potentially help in the clinical management of these patients.

The studies in this thesis are based on bedside measurement of CBF using xenon-enhanced computerized tomography (XeCT) and investigates the global and regional CBF disturbances occurring at different phases in the acute course after severe SAH.
A brief overview of aneurysmal subarachnoid hemorrhage

History

The macroscopic vascular anatomy of the brain has been known for centuries, with the description of the collateral vascular circle by Thomas Willis in 1664 as a landmark [10]. In 1813, Blackall wrote one of the first known clinical reports on aneurysmal intracranial hemorrhage after postmortem observations in a young woman [11]. Hodgson later concluded that the blood from an aneurysmal hemorrhage was contained under the arachnoid membrane [12]. Initially the term “meningeal apoplexy” was used for aneurysmal subarachnoid hemorrhage, which was thought always to be fatal. With the introduction of lumbar puncture by Quincke in 1891 [13], the diagnosis of subarachnoid hemorrhage became possible also in non-fatal cases. The clinical description of subarachnoid hemorrhage, with sudden onset of headache and the following confirmation of the diagnosis by lumbar puncture, was published by Symonds in the 1920s [14]. The development of radiology, and later cerebral angiography by Moniz in 1933 [15], made diagnosis and treatment of intracranial aneurysms possible. A further fundamental step in neuroradiology was made in the 1970s, when the British engineer Hounsfield invented computed tomography (CT) [16] in collaboration with the American physicist Cormack, both later Nobel Prize laureates. The high risk of re-bleeding after SAH was known, but treatment was usually conservative. However, surgical extracranial ligation of the carotid artery was attempted in the 1880s (Horsley, cited by Beadles in 1907 [17]), and an intracranial direct surgical approach to the aneurysm was later described by Dott in 1931 [18]. Use of a silver clip to occlude the neck of the aneurysm was introduced by Dandy in 1937 [19]. Improvements in the surgical technique have since decreased the hazards of intracranial aneurysm surgery. An important contribution was later made by Guglielmi, who developed the method for intravascular occlusion of aneurysms with platinum coils in the 1980s [20]. In addition to the imminent risk of re-bleeding after SAH, there has been a gradual understanding of cerebral ischemia of various presentations as a major contributor to poor outcome. The radiological finding of cerebral vasospasm related to aneurysmal SAH was described in 1951 by Ecker and Riemenschneider [21].
Epidemiology, risk factors and etiology

According to de Rooij et al (2007) [22] the worldwide average incidence of aneurysmal SAH is 9/100,000/year. There are regional variations with higher incidences in some of the Nordic countries (Finland 19.7/100,000/year) and Japan (22.7/100,000/year), and lower incidences in China (2.4/100,000/year) and South America (4.2/100,000/year). As reported by Koffijberg et al [3], the risk for SAH in Sweden is higher in the northern part compared to the southern part; 15.2 vs. 11.4 per 100,000/year.

Historically, aneurysms of the cerebral vessels were thought to be congenital malformations [23], but today the formation and evolvement of aneurysms are explained mainly by anatomical features and wall shear stress in combination with genetic predisposition and acquired risk factors [24, 25]. Hypertension, smoking, female sex, old age, and a family history of intracranial aneurysm are known risk factors for formation of intracranial aneurysms [26-28]. The incidence is higher in some genetic disorders – markedly in polycystic kidney disease and to a lesser extent in the Marfan and Ehler-Danlos connective tissue syndromes [29, 30]. Arteriosclerosis and dissection are important mechanisms leading to formation and rupture of aneurysms. Hypertension, as well as the location and size of the aneurysm, are risk factors for rupture [31].

Clinical manifestations

Most aneurysms remain unrecognized and never cause symptoms, whereas some cause neurological symptoms due to location and size or are incidentally detected, requiring delicate decisions in the clinical management.

The rupture of an intracranial aneurysm is associated with sudden onset of intense headache. The extravasation of blood into the subarachnoid space will cause meningeal irritation and often neck rigidity. In more severe cases, the arterial extravasation will cause an instant rise in intracranial pressure (ICP), leading to compromised cerebral perfusion and unconsciousness. In the worst scenario, this is followed by respiratory and circulatory arrest. According to the Swedish Cause of Death and Hospital Discharge registries, 12% of patients with aneurysmal SAH die before they reach hospital [3]. The systemic sympathetic surge to preserve cerebral perfusion can be tremendous [32], and both cardiac failure and pulmonary edema may develop in patients surviving the initial ictus. As ICP rises and the extravasation decreases, there may be clot formation and temporary cessation of the bleeding. The risk of re-bleeding is high in the next few days [33, 34] and gradually diminishes over time. The initial hemorrhage may have caused intracerebral hematoma or bleeding into the ventricular system, depending on the location and direction of the
rupture. Clot formation and disturbed circulation of cerebrospinal fluid may lead to acute hydrocephalus, or there may be a gradual development of hydrocephalus at a later stage because of disturbed absorption [35].

After the initial ictus and the risk of re-bleed, the major contributor to morbidity and mortality is delayed cerebral ischemia (DCI) [36]. The risk of DCI has a peak at day 4–7 and thereafter slowly decreases. The cause of DCI is today considered multifactorial, and not only the effect of vasospasm, as will be discussed in the following sections.

### Grading scales

It is established, that morbidity and mortality from SAH are influenced by the acute neurological impact of the hemorrhage. A grading system for prediction of the surgical risk in relation to aneurysm repair was developed by Hunt and Hess (H&H) [37]. At admission, patients are categorized as grade I–V depending on the degree of meningeal symptoms and neurological deficit. The World Federation of Neurosurgical Societies (WFNS) scale is similar [38], combining the Glasgow Coma Scale [39] with grading of focal neurological deficits. The severity of the hemorrhage, graded as the amount of blood detected on the first CT scan, is predictive of cerebral vasospasm, as described by Fisher et al [40]. The neurological outcome after SAH, usually at 6 or 12 months, is generally reported according to the Glasgow Outcome Scale (GOS) [41], its extended (GOSE) version [42, 43] or the modified Rankin Scale (mRS) [44, 45], the latter mostly used in stroke patients. An overview of the most commonly used grading scales is presented in [Table 1].

### Table 1. Grading Scales for assessment of severity and outcome in SAH

<table>
<thead>
<tr>
<th>Hunt and Hess scale [37]</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Grade I</td>
<td>Asymptomatic, or minimal headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>Grade II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>Grade III</td>
<td>Drowsiness, confusion, or mild focal deficit, and vegetative disturbances</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity</td>
</tr>
<tr>
<td>Grade V</td>
<td>Deep coma, decerebrate rigidity, moribund appearance</td>
</tr>
</tbody>
</table>

(continued on next page)
**Table 1 (continued).** Grading Scales for assessment of severity and outcome in SAH

<table>
<thead>
<tr>
<th>World Federation of Neurosurgical Societies (WFNS) scale [38]</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>15</td>
<td>absent</td>
</tr>
<tr>
<td>Grade II</td>
<td>14 – 13</td>
<td>absent</td>
</tr>
<tr>
<td>Grade III</td>
<td>14 – 13</td>
<td>present</td>
</tr>
<tr>
<td>Grade IV</td>
<td>12 – 7</td>
<td>present or absent</td>
</tr>
<tr>
<td>Grade V</td>
<td>6 – 3</td>
<td>present or absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glasgow Coma Scale [39]</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td>Verbal response</td>
<td>Motor response</td>
</tr>
<tr>
<td>6 – obeys commands</td>
<td>5 – oriented</td>
<td>5 – localizes pain</td>
</tr>
<tr>
<td>4 – confused conversation</td>
<td>4 – flexion, withdrawal</td>
<td></td>
</tr>
<tr>
<td>3 – inappropriate words</td>
<td>3 – flexion, abnormal</td>
<td></td>
</tr>
<tr>
<td>2 – incomprehensible sounds</td>
<td>2 – extension</td>
<td></td>
</tr>
<tr>
<td>1 – none</td>
<td>1 – none</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Fisher scale [40]</th>
<th>Findings of subarachnoid blood on first CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>None</td>
</tr>
<tr>
<td>Group 2</td>
<td>Diffuse only</td>
</tr>
<tr>
<td>Group 3</td>
<td>Clot or thick layer</td>
</tr>
<tr>
<td>Group 4</td>
<td>Intraventricular or intracerebral blood</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale [41]</th>
<th>Key definitions (text modified after Jennett et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good recovery (GR)</td>
<td>Capable of resuming normal occupational and social activities (minor deficits may persist)</td>
</tr>
<tr>
<td>Moderate disability (MD)</td>
<td>Fully independent (in daily life), but disabled</td>
</tr>
<tr>
<td>Severe disability (SD)</td>
<td>Conscious but needs assistance (in daily life activities)</td>
</tr>
<tr>
<td>Vegetative status (VS)</td>
<td>No meaningful responsiveness (eyes may be open and may follow objects)</td>
</tr>
<tr>
<td>Death (D)</td>
<td></td>
</tr>
</tbody>
</table>


Neurosurgical treatment and neurointensive care

In modern neurosurgical care, early treatment of aneurysms has lowered the risk of re-bleeding and contributed to favorable outcome [46]. Guidelines now propose treatment as soon as possible, preferably within 72 hours, to reduce the risk of re-bleeding [47]. Neurosurgical clipping has been the standard treatment, but with the development of interventional radiology, endovascular coil occlusion of aneurysms has gradually become the dominating treatment in most centers. The superiority of one technique over the other has been debated, but endovascular treatment is now preferred when feasible [48]. Other endovascular approaches, e.g., placement of stents and flow diverters, are options in specific cases.

As in neurocritical care of patients with traumatic brain injury, the importance of secondary brain injury has been recognized also in the care of patients after SAH [49, 50]. Cornerstones of modern neurointensive care are multimodal monitoring of systemic and cerebral physiological and biochemical parameters, repeated clinical neurological examination and CT scans, which enable early detection of avoidable factors and prompt interventions to minimize secondary brain injury. This concept is included in the Uppsala standardized NIC protocol for SAH [50]. Furthermore, patients with altered level of consciousness after severe SAH receive a ventriculostomy catheter for monitoring of ICP and treatment of hydrocephalus if indicated. Unconscious patients, not responding to commands, are kept intubated and mechanically ventilated. In caring for SAH patients, focus is also on reducing the risk of vasospasm and DCI. Aside from prevention from secondary insults, the medical management includes ensuring normovolemia and normotension, whereas prophylactic hyperdynamic therapy does not convincingly improve outcome [51]. Strategies for therapeutic CBF augmentation upon suspicion of DCI will be discussed in a later section. Several pharmacological therapies to prevent and overcome vasospasm and DCI have been proposed. Vasodilatory drugs such as magnesium-sulfate [52], calcium-channel blockers, the endothelin receptor antagonist clazosentane [53], as well as corticosteroids [54] and anti-inflammatory statins [55, 56] have been tested in randomized controlled trials. However, as of today, only the calcium-antagonist nimodipine has a proven effect on outcome and is included in routine care of SAH patients [57, 58].
Mortality and neurological outcome

Aneurysmal subarachnoid hemorrhage accounts only for less than 5% of the incidence of stroke, but the average age in this group of patients is lower, and the rates of morbidity and mortality are high. The 28-day case fatality among all SAH cases in the WHO MONICA study was 42% [1], and in a study of Swedish Hospital Discharge and Cause of Death Registries (1987–2002) the 28-day fatality rate was 32% [3]. In a Swedish hospital series of SAH patients (N=648), good neurological outcome at > 5 months was concluded in 74% of patients in H&H I–II, 45% in H&H III and 34% in H&H IV–V [2]. Thus, a majority of patients presenting in H&H grades III, IV and V were severely disabled or had poor outcome according to GOS.
Cerebral blood flow disturbances and delayed cerebral ischemia following subarachnoid hemorrhage

Early brain injury
The sudden and intense rise of intracranial pressure at the rupture of an intracranial aneurysm compromises cerebral perfusion and causes transient global ischemia, which is believed to trigger mechanisms leading to early brain injury and onset of inflammatory cascades [59-62]. The “jet-stream” of extravasated blood may in some cases also cause an intraparenchymal hematoma with mass-effect contributing to further tissue damage. Furthermore, acute vasoconstriction has been shown in experimental and clinical studies [63-65]. The pathophysiology of early brain injury is complex with disturbances occurring at the cellular and molecular level, and includes blood-brain barrier disruption, endothelial damage, activation of platelets, microthrombosis and compromised energy metabolism, followed by neuronal damage and apoptosis [66].

Delayed cerebral ischemia (DCI) and vasospasm
Already in the early descriptions of subarachnoid hemorrhage, it was noted that patients who survived the initial ictus might deteriorate neurologically later in the course, not only due to re-bleeding, but also due to the onset of ischemic changes [67-69]. The highest risk for deterioration is between days 4 to 14 after the hemorrhage, with a peak on day 7. For many years, this phenomenon was thought to be primarily caused by large-vessel vasospasm, triggered by the degradation of blood in the subarachnoid space [70, 71]. Angiographic vasospasm is found in up to 50% of SAH patients, but only causes symptoms in 30–50% of these cases, and the total incidence of infarctions is about 25% [72]. In about 15–25% of patients with delayed neurological deterioration, there is no evidence of angiographic vasospasm [4, 5]. The preferred term is now delayed cerebral ischemia [73], and this is clinically diagnosed as the onset of persistent neurological deterioration in the absence of other detectable causes. To the clinical diagnosis is added any finding of new infarcts on CT that are not immediately procedure related. The modern understanding
of DCI is that the causes are multifactorial, with vasospasm being one of many contributing factors. The onset of the process is already at the time of early brain injury, and it is then further escalated by blood degradation products, inflammatory processes, endothelial damage, microthrombosis and microcirculatory disturbances [6, 74, 75].

Early global and regional CBF disturbances

Following the ictus of transient global ischemia at the rupture of an aneurysm, there is evidence of disturbed cerebral blood flow (CBF) in the subsequent early acute stage after SAH [60, 76]. As previously mentioned, this might be partly caused by local large-vessel vasoconstriction at the site of rupture. However, the early reduction in CBF is usually globally distributed, and additionally explained by impaired pressure autoregulation and widespread microvascular constriction [77, 78]. On the other hand, there are also contrary reports of cerebral hyperemia after SAH [79]. Several reports support the correlation between early CBF disturbances and the subsequent occurrence of vasospasm, DCI and poor outcome [80-82].

CBF dynamics during the clinical course after SAH

An extensive study assessing CBF daily in the course after SAH was presented by Meyer in 1983 [83]. In this series of notably mostly good-grade, conscious patients, CBF declined progressively during day 1–14 and then gradually returned to the “baseline” level. In a study by Jakobsen in 1990, stratification of patients revealed a similar pattern for good-grade patients, whereas CBF in poor-grade patients was very low at baseline and then slowly recovered to a still low level [60]. Other sequential series support these findings with lower CBF in unconscious, poor-grade patients and decline in CBF corresponding to symptomatic vasospasm or DCI [69, 84].
Assessment of CBF in the clinical setting

Monitoring of intracranial pressure (ICP), mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP) is essential in neurointensive care [85-87]. Assessment of CBF would in many situations provide additional important information for clinical decisions and guidance of therapy [88, 89]. However, most methods for measurement of CBF are not readily available for bedside use. In positron emission tomography (PET), selected molecules are labelled with short-lived radionuclides (e.g., oxygen-15) and injected or inhaled to serve as tracers for uptake in tissues, thus enabling quantitative measurement of regional blood flow [90]. In PET, the choice of certain tracers can also enable assessment of oxygen extraction and metabolic rate [90, 91]. Single photon emission CT (SPECT) has similarities with PET but is less resource-intensive and uses radio isotopes with longer half-life, e.g., technetium-99m or inhaled xenon-133 [92]. Generally, the image quality of SPECT is lower, and the method only allows for calculation of relative blood flow. Blood-flow studies can also be obtained through CT with intravenous non-radioactive iodine as a contrast agent; CT perfusion. Modern CT scanners provide high resolution color-coded images and calculation of cerebral blood volume, mean transit time and relative CBF [93]. Magnetic resonance imagining (MRI) is widely used for anatomical and functional imagining of the brain. There are several techniques for perfusion weighted MRI to give insight into perfusion of tissues, e.g., dynamic contrast enhanced MR perfusion and arterial spin labelling MR perfusion [94].

An alternative to intravenous iodine contrast for CT perfusion imaging, is inhaled nonradioactive (stable) xenon. Xenon-enhanced CT (XeCT) using a mobile CT scanner enables bedside measurement of CBF in the neurointensive care unit [95]. XeCT will be described in more detail in the methods section below.

There is a range of other, indirect methods to study cerebral hemodynamics. Transcranial Doppler (TCD) uses ultrasound and the Doppler effect to measure blood flow velocity in cerebral arteries [96]. In brief, the blood flow velocity is a function of vessel diameter and blood flow, and TCD is mainly used to detect proximal vasospasm in SAH patients. Oximetry of venous blood in the jugular bulb is used to mirror changes in CBF and/or metabolism. Near infrared spectroscopy (NIRS) is a non-invasive method that uses multiple wavelengths of red light to estimate the oxygen saturation of hemoglobin in capillaries of cerebral tissue, and would theoretically reflect CBF in a similar manner, if metabolism and arterial oxygen saturation are constant [97].
Therapies to augment CBF

The medical management to prevent vasospasm and development of DCI has been discussed in a previous section. As compromised CBF may be both the result of vasospasm and microcirculatory disturbances, and further contribute to the progression of DCI, it is considered essential to augment CBF upon suspicion of DCI. The original concept for hyperdynamic augmentation of CBF includes hypervolemia, hemodilution and hypertension (triple-H therapy, HHH-therapy) to improve systemic cardiac output and cerebral perfusion pressure, and to optimize blood rheology [98-100]. There have been conflicting results from prophylactic use of this therapy [51, 100, 101] and later consensus that outcome is not improved by prophylactic HHH [7]. However, it is established that hypovolemia and hypotension contribute to DCI and worsen outcome [102-105], and guidelines propose attentive fluid management with maintenance of normovolemia and normotension [8, 47]. Concerning therapeutic use of HHH upon clinical suspicion of DCI, there are several small and uncontrolled studies with divergent results [106-112]. The potentially positive effects of hyperdynamic hemodilution might be outweighed by intracranial, pulmonary and cardiovascular side-effects of too aggressive therapy [106, 113-116]. The evidence is also scarce regarding which of the three components of HHH that is most important [117], and sufficiently powered randomized controlled trials have thus far been difficult to conduct [118, 119]. Based on scarce and relatively weak evidence, international guidelines recommend normovolemia and induced hypertension in treatment of DCI, but no specific blood pressure targets are proposed in these guidelines [8, 47].

HHH-therapy in accordance with the Uppsala standardized clinical NIC protocol for SAH is cautious with a moderately elevated blood pressure target, as described in Paper III. The patient is kept in supine position, and focus is on maintaining adequate intravascular volume status by daily infusions of dextran 40 and additionally albumin, if tolerated. Vasoactive agents are used as needed to maintain a systolic blood pressure above 140 mmHg. Dobutamine is used as first line of treatment for inotropy, and norepinephrine as second line if a vasopressor is needed. The hemodynamic therapy is carefully monitored and re-evaluated to avoid serious side-effects.

Cerebral energy metabolism and DCI

Due to the intense activity in the neuronal tissue of the awake brain, the energy requirements are high. Cerebral energy metabolism consumes roughly 1/5 of the whole-body resting energy expenditure and is dependent on a cerebral blood flow of 700–800 ml/min (50 ml/100 g of brain tissue per min) to meet the demand for energy substrates and oxygen [120, 121]. Under aerobic
conditions, glucose is the main substrate in cerebral energy metabolism. In cytoplasmic aerobic glycolysis, glucose is transformed into pyruvate, which enters the mitochondria and is further oxidized through dehydrogenation in the citric acid cycle, where intermediate energy-carrying (electron transporting) NADH, FADH₂ and GTP is gained in successive steps [120]. The actual utilization of oxygen occurs in the electron transport chain at the inner mitochondrial membrane, where (simply put) high energy electrons are passed from NADH to oxygen, forming NAD⁺ and water (H₂O), and hydrogen ions (protons) are pumped through the membrane. The hydrogen ion gradient is the driving force for enzymatic phosphorylation of ADP, forming energy-carrying ATP molecules that can be utilized in the mechanisms of the cell. Also simply put, glycolysis under anaerobic conditions will cause accumulation of lactate instead of pyruvate, and less energy (ATP) is gained, as lactate cannot be utilized as a substrate for the citric acid cycle. However, in recent years, the classic view of the role of lactate vs. pyruvate has been challenged [122], and there is an evolving view that lactate serves as an important energy substrate under certain conditions. Furthermore, there is an intrinsic coupling between metabolic activity and local cerebral blood flow, mediated by astrocytes that are closely connected to the intracerebral vessels and neuronal cells, forming “neurovascular units” [123]. The physiological mechanisms for this neurovascular coupling are still not completely elucidated.

Using interstitial cerebral microdialysis (CMD), the low molecular weight substances glucose, lactate and pyruvate, can be retrieved for measurement by diffusion through a semi-permeable membrane in a micro-catheter introduced into the parenchyma [124, 125]. (CMD is further described in the methods section.) Thus, the energy metabolic state of the cerebral tissue can be reflected by the local levels of, e.g., glucose, lactate and pyruvate. Changes in the pattern of these energy metabolic parameters has been studied for a number of different conditions with cerebral pathology, primarily traumatic brain injury and SAH. There is evidence supporting clinical use of CMD for monitoring of delayed cerebral ischemia after SAH [126-128]. Threshold levels for pathological cerebral energy metabolism have been defined in a consensus statement 2014 [129]: glucose <0.2–0.8 mmol/L, lactate >4 mmol/L and lactate/pyruvate ratio (L/P ratio) >25–40. Combined patterns of these parameters have also been discussed for patients with SAH or traumatic brain injury, where high L/P ratio and low pyruvate suggests ischemia, whereas moderately elevated L/P ratio in combination with normal or high pyruvate is compatible with non-ischemic energy crisis, e.g., mitochondrial dysfunction [130, 131].
Aims of the investigations

General aim

The studies in this thesis investigate the global and regional CBF disturbances occurring at different phases in the acute course after severe SAH with the general aim to provide better insight into the pathophysiological processes that potentially evolve into delayed cerebral ischemia. A further general aim of the studies was to evaluate whether repeated bedside measurements of CBF using XeCT could serve as a tool in the clinical care of poor-grade SAH patients for early recognition and management of patients at risk of deterioration.

Specific aims

Paper I

The first aim in Paper I was to assess CBF disturbances at the early stage (day 0–3) after SAH, and relate the findings to age, clinical characteristics and severity of the hemorrhage. The second aim was to investigate the distribution of regional CBF disturbances and assess the extent of regions with critically low CBF. The final aim was to get an indication of whether early CBF disturbances may identify patients at risk of deterioration by studying the relation to early clinical course outcome.

Paper II

In Paper II, the first aim was to investigate sequential changes in the CBF parameters; early day 0–3, day 4-7 when the risk of DCI is considered to increase, and at the later stage day 8–12. Additional aims were to explore whether the early initial level of CBF determines the continued course of CBF, and whether the course of CBF is affected by the therapy for hemodynamic augmentation used in patients with suspected DCI.
Paper III
The aim in *Paper III* was to specifically evaluate the effect of therapeutic HHH on CBF in patients with the clinical diagnosis of DCI, with the primary hypothesis that HHH-therapy increases not only global CBF but also regional CBF in regions at risk of ischemia.

Paper IV
The aim in *Paper IV* was to investigate cerebral energy metabolic changes in relation to CBF during HHH-therapy, using CMD. The hypothesis was that the cerebral metabolic state would improve in concordance with increased CBF during HHH-therapy, i.e., decrease in CMD lactate level and L/P ratio.
Methods and patient population

Patients
The patients in the cohort studied in this thesis work had all suffered from severe spontaneous SAH and were treated in the neurointensive care (NIC) unit of Uppsala University Hospital during the time-period 2013 to 2016. The diagnosis of SAH was determined from admission CT. Since ventilator treatment is mandatory for bedside XeCT in our setting, only patients who required endotracheal intubation due to their neurological state at admission or due to deterioration at day 0–1 were included. Patients with severe intracranial hypertension, deep sedation with thiopental, respiratory problems requiring FiO2 > 0.6, futility or a “do not resuscitate” order were excluded from the study.

Methods
Patient selection, study protocol and data collection
Following the clinical NIC routine for SAH, mechanically ventilated SAH patients should undergo XeCT procedures for measurement of CBF at day 0–3, 4–7 and 8–12, if logistically possible. Additional XeCT procedures are performed when clinically indicated. During the study period, SAH patients scheduled for XeCT were consecutively screened for inclusion. The studies in Paper I, II, III and IV were all clinical observation studies, and data were collected prospectively.

Paper I – SAH patients with XeCT measurements within the early acute phase, day 0–3 from admission, were included (n = 64, 72% female, mean age 61 years).

Paper II – SAH patients with valid baseline XeCT measurements at day 0–3 from admission were included (n = 81, 72% female, mean age 60 years). To study the temporal course of CBF, patients who subsequently had XeCT measurements also at day 4–7 (n = 51) or at day 4–7 and 8–12 (n = 27) were allocated into corresponding subgroups (subgroup 04 and 048).
Paper III – SAH patients clinically diagnosed with DCI during their course in NIC, who had XeCT measurements within 0–48 hours prior to initiation of HHH-therapy and a second measurement during ongoing therapy, were included (n = 20). Non-DCI patients with measurements in corresponding time-windows were also identified and included as a reference group (n = 28).

Paper IV – SAH patients with clinical diagnose of DCI and subsequent HHH-therapy, who had XeCT measurements meeting the same criteria as in Paper III, and additionally had CMD monitoring at the time of the CBF measurements, were included (n = 12). Again, in this study, non-DCI patients with XeCT and CMD measurements in corresponding time-windows were included for reference (n = 11).

Data from the XeCT measurements of CBF and from the CMD were collected as described in the sections below. Physiological monitoring data and clinical characteristics of the patients were collected into the clinical research database of the Uppsala University NIC unit.

Xenon CT procedures for measurement of CBF

The procedures for measurement of CBF in mechanically ventilated patients in the NIC unit are performed using bedside XeCT, following the principles originally developed by Gur et al and Yonas et al [132-135]. The inert xenon gas is lipid soluble, dissolves readily in blood and tissues, and acts as a contrast agent due to its relatively high atomic mass (131 u) causing radiopacity. Hence, inhaled stable xenon can serve as a diffusible tracer during a repeated series of axial CT scans to estimate the uptake in cerebral tissue. The calculations of local blood flow in each pixel of the resulting CT images during wash-in of xenon are based on the Fick principle as applied by Kety for inert gas uptake in tissue [136, 137]. During the XeCT procedures, 28% xenon in a mixture of oxygen/air (pre-set to the patient requirements) is administered to the patient’s ventilator circuit for 4 ½ minutes by a computer-controlled delivery system, Enhancer 3000 (Diversified Diagnostic Products Inc, Huston, USA). The arterial xenon concentration is approximated by end-tidal measurement from the breathing circuit [Figure I].
CT scans synchronized to the xenon inhalation are acquired by a mobile scanner, CereTom (Neurologica, Boston, USA). Routinely, four axial sections of the brain are examined through a series of eight scans per section, two at baseline and six during xenon wash-in. Local CBF corresponding to each CT pixel is calculated and displayed as color-coded maps. Twenty cortical regions of interest (ROIs) are then symmetrically set out in the image of each section, and mean blood flow in each ROI is calculated by the Enhancer software for further analysis [Figure 2].

![Figure 1. End-tidal measurements of CO₂ and xenon (mmHg) illustrating the xenon wash-in, steady state and wash-out phases during the synchronized CT scans.](image-url)
Calculated CBF parameters

Scan sections with extensive artifacts from bone structures, endovascular coils or surgical material were excluded, and typically three axial sections were used for calculations. ROIs containing radiological artifacts or located in areas of hematoma were manually excluded.

**Global cortical CBF** (ml/100 g/min) was calculated as the mean of all specified cortical/subcortical ROIs (weighted average by the individual ROI size) at all scan levels included, typically twenty ROIs per scan level and a total of sixty ROIs [Figure 2].

**Regional CBF** (rCBF) for each of the major vascular territories was calculated as the mean of the ROIs included in the vascular territory at all scan levels: Right anterior cerebral artery (ACA) ROI 1–2, middle cerebral artery (MCA) ROI 3–8, posterior cerebral artery (PCA) ROI 9–10, and equally for the left side ROI 11–20 [Figure 3].

The worst vascular territory in each patient was identified by comparing regional CBF of the six major vascular territories described above.
CBF index of worst vascular territory was calculated as rCBF of the worst vascular territory divided by the best hemispheric blood flow.

Ischemic thresholds. To detect and quantify the extent of areas with low and near ischemic blood flow, thresholds for local CBF were set to 20 and 10 ml/100 g/min [138-140]. The proportion of area with local CBF below these thresholds was calculated as the sum of ROI-area below the specified threshold divided by the total analyzed ROI-area in each patient.

Figure 3. Regional CBF for each vascular territory was calculated as the mean of the corresponding ROIs of that vascular territory at all scan-levels.

Interstitial cerebral microdialysis (CMD)
The CMD technique for assessment of the energy metabolic state in cerebral tissue has been established in clinical NIC during the last two decades [125, 126, 128, 129]. Glucose, lactate and pyruvate levels are measured in a microdialysis fluid circulated through a semipermeable micro-catheter and allowed to equilibrate with the interstitial environment. Unconscious SAH-patients routinely receive a ventriculostomy catheter for CSF drainage, and an intraparenchymatous CMD catheter is placed in the cortex of the frontal lobe, usually on the right side, during the same procedure. However, CMD was not applied in all SAH patients, for logistical and technical reasons. The CMD catheter used had a membrane length of 10 mm, cut-off 20 kDa, ‘70 Brain Microdialysis catheter’ (M Dialysis AB, Stockholm, Sweden). The microdialysis fluid had a composition of NaCl 147 mmol/L, KCl 2.7 mmol/L, CaCl₂ 1.2 mmol/L, MgCl₂ 0.85 mmol/L (Perfusion Fluid CNS, M Dialysis AB), and was perfused through the catheter at a rate of 0.3 µl/minute by a microinjection.
pump (CMA-106, M Dialysis AB). Catheter performance was validated by monitoring of the CMD urea level. CMD samples were collected hourly and analyzed bedside using the CMA 600 or ISCUS Clinical Microdialysis Analyzer (M Dialysis AB).

CMD parameters and classification of CMD metabolic patterns

As described in the previous section, hourly samples were collected from the equilibrated microdialysis fluid. To reflect the metabolic situation at the time of CBF-measurement, the mean of CMD measurements (glucose, lactate and pyruvate, respectively) for two hours before and two hours after the XeCT procedure was used. The L/P ratio for each CMD sample was also calculated.

In addition to interpretation of the separate CMD parameters, different patterns of the parameters have been recognized, reflecting the energy metabolic state of the monitored cerebral tissue [130, 131]. In Paper IV, three patterns of the CMD parameters were defined to reflect the cerebral energy metabolic state of each patient: Normal (lactate < 4 mmol/L, L/P ratio < 30), mitochondrial dysfunction (L/P ratio > 30, pyruvate > 70 µmol/L) or ischemia (L/P ratio > 30, pyruvate < 70 µmol/L).

Early clinical course outcome parameters

As a measure of short-term outcome at the time of discharge from NIC, patients were graded as good – responding to commands and GCS motor component 6 points, poor – unconscious and GCS motor ≤ 5 points, or dead. For Papers II and III, the presence and size of cerebral infarcts, visible on follow-up CT at > day 12, was also assessed as no infarct, 20–40 mm infarct, or >40 mm infarct (or multiple infarcts).
Statistical analysis

SPSS statistics 23.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis of the collected data. CBF data for groups of patients are presented as median values and interquartile ranges (IQR) because of non-normal distribution. Differences in CBF parameters between groups, independent samples, were tested for statistical significance using the Mann-Whitney U test, and for related samples using the Wilcoxon signed-ranks test. Friedman’s test was used to analyze data comparing measurements from multiple time-windows. The Chi-squared test or Fisher’s exact test was used to compare proportions between groups. Systemic physiological data are presented as mean values with confidence intervals, and differences in these parameters were tested using Student’s t-test or the paired samples t-test. The relationship between CBF and other physiological parameters was analyzed using the Pearson correlation coefficients, and for discrete or non-normal distributed parameters, the Spearman correlation was used. The statistical significance level was set at P < 0.05.

Ethical considerations

The studies in this thesis were all performed in compliance with the 1964 Helsinki Declaration and its later amendments [141]. The study protocol was approved by the Uppsala University Regional Ethical Review Board, and informed consent was obtained from the patients included in the studies or from their next of kin. The project was also approved by the local Radiation Safety Authority.
Results, main findings

Paper I

In this study, concerning CBF impairment in the early acute phase after spontaneous SAH, 64 patients were included and had XeCT measurements of CBF within day 0–3 after admission to NIC. All patients were in need of mechanical ventilation at the time of inclusion due to their neurological state; forty-five patients were in Hunt and Hess (H&H) grades III–V at admission, and 27 of the patients initially graded as H&H I–III had deteriorated during day 0–1. Systemic physiological parameters, ICP and CPP were clinically stable with small alterations from start to end of the XeCT procedures.

Median global cortical CBF for all patients was 34.9 ml/100 g/min (IQR 26.7–41.6). Correlation analysis did not reveal any significant relationship between CBF and the systemic physiological variables, MAP, CPP, arterial pCO₂, or sedation dose (propofol).

Heterogeneity with regional disturbances in CBF was common; in 43 of the 64 patients more than 10% of the analyzed ROI-area had local CBF below a threshold of 20 ml/100 g/min, and in 18 patients the proportion of such low flow area exceeded 30% [Figure 4].

CBF in the vascular territory corresponding to the location of lateralized aneurysms (ipsilateral rCBF) was compared with the that on the contralateral side. No statistically significant difference was found between ipsilateral and contralateral vascular territories related to the location of the aneurysms.

Early CBF was analyzed in relation to age and the severity of SAH. Median global CBF was higher in the younger group (30–49 years), 43.4 ml/100 g/min (IQR 35.9–50.8), compared with in the intermediate and elderly groups, 34.5 (IQR 23.7–40.4) (P = 0.048) and 29.3 (IQR 26.9–37.8) ml/100 g/min, respectively [Table 2]. No significant differences in global or regional CBF parameters were found in relation to severity of SAH as graded on the H&H scale. Severity graded according to Fisher from admission CT showed a significant difference in median global cortical CBF between patients in Fisher grades 3 and 4, 39.5 (IQR 28.9–48.3) versus 31.9 (IQR 23.7–39.9) ml/100 g/min (P = 0.034) [Table 2].
Among patients initially in H&H grades I–III, those with subsequent poor clinical course outcome had lower median global CBF compared with patients with good outcome, 25.5 (IQR 21.3–28.3) vs. 37.8 (IQR 30.5–47.6) ml/100 g/min, (P = 0.002). In patients H&H IV–V at admission, no significant difference in CBF related to outcome was detected.

**Figure 4.** Proportion of low flow ROI-area. Cases presented by increasing proportion of low flow area, showing percentage of ROI-area where rCBF < 20 ml/100 g/min (blue bars). In cases where ROIs with rCBF < 10 ml/100 g/min were detected, this proportion of ROI-area is displayed accordingly (purple bars).
Table 2. Global and regional CBF parameters presented in relation to age groups, Hunt & Hess and CT Fisher grade.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>30–49</th>
<th>50–69</th>
<th>70–85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td><strong>glob CBF</strong></td>
<td>43.4 (35.9–50.8)</td>
<td>34.5 (23.7–40.4)</td>
<td>29.3 (26.9–37.8)</td>
</tr>
<tr>
<td><strong>% of cortical ROI area &lt; 20 ml/100 g/min</strong></td>
<td>4.9 (1.6–12.1)</td>
<td>20.0 (6.7–43.2)</td>
<td>18.9 (6.0–25.2)</td>
</tr>
<tr>
<td><strong>rCBF best territory</strong></td>
<td>53.1 (45.1–61.3)</td>
<td>42.1 (31.5–54.3)</td>
<td>45.1 (35.6–50.6)</td>
</tr>
<tr>
<td><strong>rCBF worst territory</strong></td>
<td>35.7 (26.0–43.2)</td>
<td>21.5 (17.8–30.2)</td>
<td>23.4 (20.1–30.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H &amp; H I–III</th>
<th>H &amp; H IV–V</th>
<th>CT Fisher 3</th>
<th>CT Fisher 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td><strong>glob CBF</strong></td>
<td>35.1 (27.1–45.1)</td>
<td>32.3 (23.6–41.4)</td>
<td>39.5 (28.9–48.3)</td>
</tr>
<tr>
<td><strong>% of cortical ROI-area &lt; 20 ml/100 g/min</strong></td>
<td>15.8 (3.3–31.1)</td>
<td>12.3 (5.6–44.5)</td>
<td>10.4 (1.65–26.4)</td>
</tr>
<tr>
<td><strong>rCBF best vascular territory</strong></td>
<td>45.3 (34.2–54.3)</td>
<td>45.6 (33.8–54.8)</td>
<td>49.1 (39.4–57.7)</td>
</tr>
<tr>
<td><strong>rCBF worst vascular territory</strong></td>
<td>22.4 (18.8–36.4)</td>
<td>25.3 (18.5–30.8)</td>
<td>31.3 (19.7–41.0)</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow, mL/100 g/min, values presented as median (interquartile range); rCBF regional cerebral blood flow; ROI regions of interest; * P < 0.05
Eighty-one patients with valid XeCT procedures at baseline, day 0–3, were included in this study of temporal dynamics of CBF after SAH. Fifty-one patients had CBF measurements at both day 0–3 and 4–7 (subgroup 04) and out of these there were 27 patients who also had measurements at day 8–12 (subgroup 048). All patients were in CT Fisher group 3 or 4, and all were mechanically ventilated at the time of inclusion due to their neurological state at admission or following early deterioration.

For the entire subgroup 04, there was no significant change in global or regional CBF–parameters from day 0–3 to 4–7; median global cortical CBF was 32.8 (IQR 28.0–40.1) vs. 35.0 (IQR 25.4–41.3) ml/100 g/min. Nor did the three measurements in subgroup 048 reveal any significant change in median CBF during the course from baseline to day 8–12.

In the further analysis, patients in subgroup 04 were stratified depending on high or low initial (baseline) CBF (cut-off 30 ml/100 g/min). Global and regional CBF for the high-CBF group stayed statistically unchanged from baseline to day 4–7, whereas the low-CBF group showed an increase in global cortical CBF from 23.6 (IQR 21.0–28.1) ml/100 g/min to 28.4 (IQR 22.7–38.3) \( (P = 0.025) \), though still markedly lower compared with the high-CBF group \( (P = 0.016) \) [Figure 5]. Regional CBF parameters followed the same pattern.

Patients were also stratified depending on whether they had clinical signs of DCI and consequently received HHH-therapy. Twenty-two of the 51 patients were receiving HHH-therapy at the second measurement. Patients with low initial CBF and standard treatment (no suspicion of DCI) remained at low CBF; baseline 27.1 (IQR 21.7–28.7) ml/100 g/min vs. 26.6 (IQR 21.9–28.9) at day 4–7 [Table 3]. In contrast, patients with low initial CBF who received HHH-therapy showed a marked increase in CBF from 21.3 (IQR 20.8–25.9) ml/100 g/min to 37.8 (IQR 23.6–41.0) at day 4–7 \( (P = 0.006) \). In the group with high initial CBF there was a slight decrease in CBF among the standard treated patients, but no significant change among those receiving HHH-therapy [Table 3].

Poor clinical course outcome was concluded in 11 of the 20 patients (55%) who still had low CBF at XeCT day 4–7 compared with 11 of 31 patients (35%) with high CBF at day 4–7. The differences in proportion of patients with poor outcome did not reach statistical significance.
Figure 5. Global cortical CBF and proportion of ROI-area with local CBF < 20 ml/100 g/min at different phases in the acute course of SAH for patients grouped by high or low early global CBF at day 0–3, cutoff 30 ml/100 g/min. a, b Boxplots (median, IQR) for subgroup 04 (n = 51) with measurements at day 0–3 and 4–7. c, d Boxplots for subgroup 048 (n = 27) with measurements at day 0–3, 4–7, and 8–12.
Table 3. Calculated XeCT-CBF parameters at the different phases of the acute course after SAH day 0–3 and 4–7 (subgroup 04). Patients are stratified by high or low early global CBF at day 0–3 (cut-off 30 ml/100 g/min), and by whether HHH-therapy was given during the ICU-course. Systemic physiological parameters and sedation dose at the start of the XeCT procedures.

<table>
<thead>
<tr>
<th></th>
<th>High early CBF (n = 21)</th>
<th>Low early CBF (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0–3</td>
<td>Day 4–7</td>
</tr>
<tr>
<td><strong>Standard treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glob CBF, ml/100g/min</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
</tr>
<tr>
<td></td>
<td>40.0 (34.9–48.5)</td>
<td>35.0 (28.6–41.4)</td>
</tr>
<tr>
<td><strong>P = 0.002</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF worst territory, ml/100g/min</td>
<td>30.4 (22.9–33.0)</td>
<td>24.2 (18.9–30.3)</td>
</tr>
<tr>
<td><strong>P = 0.004</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ROI-area [rCBF&lt; 20 ml/100g/min]</td>
<td>10.0 (2.4–16.5)</td>
<td>10.0 (0.9–31.8)</td>
</tr>
<tr>
<td>% ROI-area [rCBF&lt; 10 ml/100g/min]</td>
<td>1.3 (0.0–5.0)</td>
<td>0.0 (0.0–8.3)</td>
</tr>
<tr>
<td><strong>Clinical DCI, HHH-therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glob CBF ml/100g/min</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
</tr>
<tr>
<td></td>
<td>34.5 (31.9–41.7)</td>
<td>39.4 (33.9–48.8)</td>
</tr>
<tr>
<td><strong>P = 0.008</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF worst territory ml/100g/min</td>
<td>26.5 (22.2–33.0)</td>
<td>30.0 (21.1–40.7)</td>
</tr>
<tr>
<td><strong>P = 0.008</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ROI-area [rCBF&lt; 20 ml/100g/min]</td>
<td>11.3 (3.8–22.5)</td>
<td>3.3 (1.2–21.7)</td>
</tr>
<tr>
<td><strong>P = 0.021</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ROI-area [rCBF&lt; 10 ml/100g/min]</td>
<td>0.0 (0.0–1.4)</td>
<td>0.0 (0.0–2.1)</td>
</tr>
</tbody>
</table>

CBF cerebral blood flow, glob global, r regional, ROI-area region-of-interest area, MAP mean arterial pressure, PaCO2 arterial PCO2.
In Paper III, concerning the effect of HHH-therapy on CBF, mechanically ventilated SAH patients who had XeCT procedures during NIC were screened for inclusion. Twenty patients clinically diagnosed with DCI were identified, where XeCT was performed 0–48 hours before the start of HHH-therapy and during the five-day therapy. Twenty-eight non-DCI patients with CBF measurements in corresponding time-windows were identified for a reference group.

Among DCI patients, the systolic blood pressure (SBP) increased slightly during HHH-therapy compared to baseline, from 151.2 mmHg (CI 142.1–160.3) to 157.3 mmHg, (CI 150.7–163.8), but the difference did not reach statistical significance [Table 4]. Hematocrit decreased from 36.4% (CI 34.7–38.0) to 31.7% (CI 30.2–33.2), (P < 0.001) after the initiation of HHH-therapy [Table 4].

At baseline, global cortical CBF was significantly lower for the DCI group compared with the non-DCI group; median 29.5 ml/100 g/min (IQR 24.6–33.9) versus 34.9 (IQR 29.0–41.7) (P = 0.005) [Table 4]. During HHH-therapy in the DCI patients, there was an increase in median global cortical CBF from 29.5 (IQR 24.6–33.9) to 38.4 (IQR 27.0–41.2) ml/100 g/min (P = 0.001), while no significant change over time was seen among the reference patients [Table 4] [Figure 6].

Concerning regional CBF during HHH-therapy, the most important findings were the increase in rCBF of the worst vascular territory from median 19.6 (IQR 15.0–24.2) to 27.3 (IQR 17.8–34.1) ml/100 g/min (P = 0.006), and similarly the reduction in the proportion of ROI-area with local blood flow below the threshold of 20 ml/100 g/min from median 26.2% (IQR 13.4–44.5) to 8.55% (IQR 2.4–34.8) (P = 0.019) [Table 4] [Figure 6].

Favorable clinical course outcome was concluded in 65% of the patients in the group receiving HHH-therapy (DCI group) and in 57% of the non-DCI patients. The proportion of patients with no infarcts larger than 20 mm at follow-up CT was 65% for the DCI group and 46% in the non-DCI group.
Table 4. Systemic hemodynamic parameters, ventilation, sedation and vasoactive medication at the time of XeCT measurements (upper part). Calculated XeCT CBF parameters (lower part).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DCI (n = 20) Baseline</th>
<th>mean (CI)</th>
<th>during HHH</th>
<th>mean (CI)</th>
<th>No DCI (n = 28) Baseline</th>
<th>mean (CI)</th>
<th>No DCI Day 5-8</th>
<th>mean (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP mmHg</td>
<td></td>
<td>151.2</td>
<td>157.3</td>
<td>150.0</td>
<td>152.9</td>
<td>157.3</td>
<td>150.0</td>
<td>152.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(142.1–160.3)</td>
<td>(150.7–163.8)</td>
<td>(143.5–156.4)</td>
<td>(145.9–159.8)</td>
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<td>(87.0–93.6)</td>
<td>(88.2–96.7)</td>
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<td>(15.0–24.2)</td>
<td>(17.8–34.1)</td>
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<tr>
<td>Index [rCBFworst / best hemisph]</td>
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<td>0.70</td>
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<td>(0.60–0.79)</td>
<td>(0.52–0.73)</td>
<td>(0.46–0.75)</td>
<td>(0.55–0.83)</td>
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<td>* P</td>
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<td>&lt; 0.001</td>
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* Indicates P < 0.05, CBF cerebral blood flow, CI confidence interval, CPP cerebral perfusion pressure, DCI delayed cerebral ischemia, HHH-therapy therapeutic hypervolemia, hemodilution and hypertension, IQR interquartile range, MAP mean arterial pressure, rCBF regional cerebral blood flow, ROI region of interest, SBP systolic blood pressure
Figure 6. Boxplots of global cortical CBF and regional CBF of the worst vascular territory for patients clinically diagnosed with DCI at baseline and during HHH-therapy, and patients with no suspicion of DCI at corresponding time-windows (upper charts). Similarly, proportion of ROI-area with CBF below specified thresholds (lower charts).
Twelve patients with subsequent clinical diagnosis of DCI met the inclusion criteria, i.e., had XeCT procedures within the defined time-windows (prior to the start of HHH-therapy and during therapy) and also had valid CMD monitoring. Among non-DCI patients with CBF measurements in corresponding time-windows, CMD data were available for eleven patients. The results of CBF and CMD measurements are presented below and in [Table 5].

In patients receiving HHH-therapy, there was an increase in median global cortical CBF from 30.4 ml/100 g/min (IQR 25.1–33.8) to 38.4 (IQR 34.2–46.1) ml/100 g/min (P = 0.006). Regional CBF during HHH-therapy showed a similar pattern with a statistically significant increase in rCBF of the worst vascular territory and a decrease in proportion of low-flow ROI-area (local CBF < 20 ml/100 g/min). The non-DCI (reference) group had markedly higher global and regional CBF at baseline compared with the DCI group, and the CBF parameters remained at an unchanged level at the second time-window.

Concerning the CMD measurements at the time of baseline XeCT, median CMD lactate for patients who later developed clinical signs of DCI was 4.37 mmol/L (IQR 3.41–5.58) compared with 2.42 mmol/L (IQR 2.13–2.97) (P = 0.026) for non-DCI patients. CMD pyruvate in the DCI group was 162.0 µmol/L (IQR 113.2–179.1) vs. 117.5 µmol/L (IQR 85.7–174.1) (n.s.). The baseline L/P ratio was higher in the DCI-group compared with the non-DCI group; 26.9 (IQR 22.9–48.5) vs. 20.3 (IQR 18.8 vs. 26.2) (P = 0.044). There was no difference in baseline CMD Glucose between the groups.

During HHH-therapy there was no significant change in CMD lactate; 4.37 mmol/L (IQR 3.41–5.58) at baseline vs. 4.78 mmol/L (IQR 3.71–5.15) during HHH. CMD pyruvate and L/P ratio also stayed statistically unchanged. For the non-DCI patients, there was a small increase in CMD lactate from 2.42 mmol/L (IQR 2.13–2.97) at baseline to 3.19 (IQR 2.42–3.97) (P = 0.041), while pyruvate and L/P-ratio stayed statistically unchanged.

When patients were categorized by different energy metabolic CMD patterns at baseline (normal, mitochondrial dysfunction or ischemia), the DCI group showed four patients with mitochondrial dysfunction, one with ischemia, and seven with a normal pattern [Figure 7]. During HHH-therapy, eight patients were categorized with a pattern of mitochondrial dysfunction and four were normal. In the reference group, all patients were categorized as normal both at baseline and at the second time-window [Figure 7].
Table 5. XeCT CBF parameters and CMD data for patients subsequently diagnosed with DCI at baseline and during HHH-therapy. The reference group (non-DCI patients) had measurements at corresponding time-windows. The lower part of the table shows systemic hemodynamic parameters, ventilation, sedation and vasoactive medication at the time of XeCT measurements.

![Table Image]

DCI (n = 12)  
Baseline | During HHH  | No DCI (n = 11)  
Baseline  | Day 5–8  |
|---|---|---|---|
glob CBF mL/100g/min | 30.4 (25.1–33.8)  | 38.4 (34.2–46.1)  | 40.1 (31.5–60.1)  | 38.4 (29.2–46.2)  |
P<0.05  
% ROI-area [rCBF< 20] | 27.7 (9.8–39.4)  | 7.2 (2.0–23.0)  | 6.7 (1.7–16.7)  | 4.0 (2.0–23.9)  |
P=0.019  
rCBF worst mL/100g/min | 19.6 (12.1–26.5)  | 31.5 (22.1–38.5)  | 30.4 (21.4–53.2)  | 29.7 (18.4–36.2)  |
P=0.005  
rCBF CMD mL/100g/min | 25.6 (22.5–35.9)  | 37.4 (30.2–46.5)  | 36.1 (27.7–54.4)  | 33.4 (29.2–49.8)  |
CMD Lactate mmol/L | 4.37 (3.41–5.68)  | 4.78 (3.71–5.15)  | 2.42 (2.13–2.97)  | 3.19 (2.42–3.97)  |
P=0.041  
CMD Pyruvate µmol/L | 162.0 (113.2–179.1)  | 153.2 (133.4–166.9)  | 117.5 (85.7–174.1)  | 139.5 (115.6–187.1)  |
CMD L/P ratio | 26.9 (22.9–48.5)  | 31.6 (22.4–35.7)  | 20.3 (18.8–26.2)  | 21.6 (18.6–24.7)  |
CMD Glucose mmol/L | 1.79 (1.24–2.73)  | 1.82 (0.89–3.16)  | 2.52 (1.27–2.87)  | 1.77 (0.74–2.60)  |
P=0.050  
CMD Glutamate µmol/L | 10.0 (1.89–66.0)  | 9.02 (0.89–3.16)  | 2.26 (0.68–6.80)  | 1.18 (0.88–6.81)  |
|---|---|---|---|
SBP mmHg | 152.9 (141.5–164.3)  | 160.7 (151.6–169.9)  | 150.0 (136.2–163.7)  | 154.1 (139.8–168.3)  |
MAP mmHg | 93.3 (86.8–99.8)  | 98.5 (92.0–105.0)  | 89.8 (82.7–97.0)  | 94.3 (86.2–102.4)  |
CPP mmHg | 81.5 (75.4–87.6)  | 84.7 (78.6–90.8)  | 76.0 (68.7–83.4)  | 82.9 (74.4–91.5)  |
Hematocrit % | 34.9 (33.2–36.6)  | 30.6 (29.0–32.2)  | 33.4 (31.3–35.5)  | 31.6 (29.6–33.5)  |
P=0.001  
pCO2 mmHg | 39.9 (37.4–42.1)  | 41.7 (39.4–44.1)  | 38.1 (36.2–40.1)  | 42.6 (38.5–46.7)  |
Temp, °C | 37.9 (37.4–38.3)  | 38.3 (38.0–38.6)  | 37.8 (37.5–38.1)  | 38.2 (37.7–38.6)  |
propofol mg/kg/h | 2.44 (1.95–2.95)  | 2.61 (2.05–3.18)  | 3.11 (2.17–4.05)  | 2.56 (1.3–3.82)  |
|---|---|---|---|
Dobutamine, n [μg/kg/min] | 0 [–]  | 2 [1.8–4.5]  | 2 [1.3–2.9]  | 3 [1.8–4.5]  |
Norepinephr, n [μg/kg/min] | 0 [–]  | 2 [0.0–0.07]  | 2 [0.05–0.05]  | 2 [0.05–0.05]  |

DCI = delayed cerebral ischemia, CBF = cerebral blood flow, glob = global, r = regional, ROI-area = region-of-interest area, CMD = cerebral microdialysis, L/P ratio = lactate/pyruvate ratio, SBP = systolic blood pressure, MAP = mean arterial pressure, CPP = cerebral perfusion pressure, PaCO2 = arterial PCO2, Temp = body temperature, IQR = interquartile range, CI = confidence interval.
Figure 7. Patients categorized by three cerebral microdialysis patterns: NORM – Normal (lactate < 4 mmol/L, L/P ratio < 30), MDYS – Mitochondrial dysfunction (L/P ratio > 30, pyruvate > 70 µmol/L), ISC – Ischemia (L/P ratio > 30 and pyruvate < 70 µmol/L).
Discussion

SAH patients are, despite early aneurysm repair and generally improved NIC, still at substantial risk of deterioration and of having poor clinical outcome due to development of DCI. Particularly for patients in poor neurological state, prediction of the acute clinical course is difficult, as is detection of early signs of DCI. To some extent, risk stratification at the group level is possible from risk factors and severity scoring, but there is still uncertainty at the individual level. Repeated measurement of CBF could potentially add valuable information in identifying patients at risk of deterioration and guide in the clinical management of these patients.

Patient selection

The patients studied in the four papers had all suffered from severe SAH, and were all requiring intubation due to their initial neurological state or early deterioration within day 0–1 in NIC. Hence, the study cohort consisted of poor-grade SAH patients. The CBF measurements in our setting are only performed in intubated patients, why those who improved sufficiently to be extubated did not have further measurements during the course. This inherent selection of patients to undergo repeated measurements of CBF to some extent limits the generalizability of the results.

Influence of systemic physiological conditions

Alterations in CBF are expected from changes in ventilation, systemic hemodynamics, and from changes in metabolic rate due to anesthesia and sedation. As all patients were sedated, mechanically ventilated and treated in accordance with our standardized NIC protocol for SAH, alterations in the systemic physiological conditions could be kept to a minimum. This is demonstrated in Paper I, where no correlation between these factors and CBF was found in the patients studied. During HHH-therapy (Papers III–IV), the systemic physiological changes over time in hematocrit and blood pressure are considered to be related to the intended effect of the treatment studied.
Early CBF disturbances in SAH.

In accordance with earlier studies, the study in Paper I showed that global CBF was reduced in most patients at the early acute stage after SAH [60, 76], median global cortical CBF 34.9 ml/100 g/min (IQR 26.7–41.6). However, there were also patients with unexpectedly high global CBF and/or regional hyperemia.

Heterogeneous CBF with hypoperfused regions was common, also in patients with global CBF in the intermediate or high range. In one third of the patients, the proportion of cortical ROI-area with near-ischemic CBF (below 20 ml/100 g/min) exceeded 30%. The pathophysiology for ischemia after SAH is different from thromboembolic stroke, and there are no established CBF thresholds for progression to infarction [140]. However, these findings emphasize the importance of considering regional CBF, and not only global measures.

As the historical presumption was that compromised CBF mainly depended on vasospasm at the site of aneurysm rupture, regional hypoperfusion would be expected mainly in ipsilateral regions. For patients with lateralized aneurysms in our study, there was no difference in rCBF for the ipsilateral vascular territory compared with the corresponding contralateral territory. This supports the view that also the early CBF disturbances have a multifactorial pathogenesis [6, 66, 75].

Age and Fisher grade from CT were factors found to influence global cortical CBF, but our results did not show any significant relationship with H&H grade. The latter is in contrast with other studies [60, 142], and is probably explained by the fact that only patients in poor neurological state at admission or with early deterioration were included in our study.

To evaluate the clinical significance of the early CBF disturbances, the results were related to neurological state at discharge from NIC, as a short-term outcome parameter. The pattern was complex but indicated that patients in good-grade at admission, with early neurological deterioration and low early CBF, may have increased risk for a poor clinical course. For patients in poor neurological state already at admission, there was no significant difference in CBF related to the short-term outcome.
Temporal course of CBF after SAH

There are few clinical studies of the temporal course of CBF after SAH. In an early study including mainly good-grade patients, Meyer et al found that CBF typically declined gradually to reach the lowest level at day 7–10 after the hemorrhage, followed by a slow restitution over weeks [83]. The aim of our study in Paper II was to assess the temporal dynamics of CBF in poor-grade SAH patients during their course in NIC.

Global cortical CBF at baseline (median 34.5 ml/100 g/min for all patients) was in accordance with previous studies of intubated poor-grade SAH patients in NIC [76, 143]. The changes in CBF parameters over time during the acute course of SAH were small when data were analyzed for the entire group of patients. Hence, we did not find the hypothesized pattern with a decrease in CBF at day 4–7. This may be coherent with another early study by Jakobsen et al, where the most severely graded SAH patients had very low initial CBF and recovered slowly [60]. To reveal the temporal CBF dynamics after SAH, it seems necessary to stratify patients by severity grade and also by differences in the clinical management.

Based on the CBF measurements at baseline in Paper II, patients were dichotomized depending on high or low CBF. The group with high initial CBF had no significant changes in CBF parameters from baseline to day 4–7. In contrast, the low-CBF group showed a moderate increase in CBF at day 4–7, but to a level still significantly lower compared with the high-CBF group. Corresponding changes in regional CBF parameters were seen in the low-CBF group. In the subset of patients also examined at day 8–12, there was an apparent further increase in median CBF for the low-CBF group, but the change was not statistically significant. These findings may be of relevance for the clinical management of patients found to have low initial CBF.

During their course in NIC, more than 30% of the patients had clinical signs of DCI and were subjected to HHH-therapy. Among patients who received HHH therapy, there was a marked increase in CBF at day 4–7 for those with low initial CBF, but no significant change for patients with high initial CBF. It is probable that the hemodynamic augmentation therapy had some influence on CBF in these patients, even if the benefits of such treatment is still in question [117]. It should be noted that this study was not intended to evaluate HHH-therapy, and the increase in CBF may alternatively be explained by a natural recovery of CBF after the initial impact or by correction of covert hypovolemia.

Among patients with standard treatment (no HHH-therapy), those with high initial CBF showed a moderate decrease in CBF at day 4–7, whereas patients
with low initial CBF remained at low CBF at day 4–7. As DCI is difficult to
detect in unconscious patients, it is possible that some of the standard-treated
patients with persistent low CBF were suffering from unrecognized DCI.

Inference of outcome related to CBF parameters is difficult in this small study.
However, to reflect the short-term outcome of the different subgroups, the
neurological state at discharge from NIC was determined. The numeric dif-
ference found in the proportion of patients with poor outcome between the
high- and low-CBF groups did not reach statistical significance, but the pic-
ture was that a larger proportion of patients with persistent low CBF at day 0–
3 and day 4–7 had poor outcome.

The study of temporal dynamics highlighted the importance of considering
differences in initial presentation and subsequent clinical management, and to
study the SAH patients in NIC divided into relevant subgroups, as the results
for the entire SAH cohort may be blunted.

Effect on CBF from hemodynamic augmentation in
DCI

The benefit of therapeutic HHH to improve CBF in patients with clinical signs
of DCI has been questioned, and several authors conclude that there is limited
scientific support only for induced hypertension [8, 117]. For the study in Pa-
per III, we aimed to investigate the effect of HHH-therapy in our setting, fol-
lowing our standardized NIC protocol for SAH with cautious institution of
HHH-therapy, moderate blood pressure targets, focus on intravascular volume
status, and frequent reevaluation of the treatment to avoid side effects [114-
116].

As this was an observational study, all patients clinically diagnosed with DCI
received HHH-therapy, and there was no valid control group. For reference,
patients with no suspicion of DCI and who had XeCT in corresponding time-
windows were identified. Data comparing these groups must be interpreted
with caution, as CBF dynamics might differ between the groups due to factors
other than the HHH-therapy.

Global cortical CBF at baseline was lower in DCI patients than non-DCI pa-
ients. During HHH-therapy, there was a marked elevation of global CBF,
whereas there was no significant change over time among the non-DCI pa-
ients. The observed increase in CBF may be related to the HHH-therapy, but
a time-dependent natural recovery of CBF cannot be ruled out.
When DCI is suspected, the most important therapeutic goal is to restore adequate perfusion in regions with near-ischemic CBF. Our results showed an increase in regional CBF in the previously worst perfused vascular territories and a corresponding decrease in the proportion of low-flow ROI-area (with CBF below 20 ml/100 g/min). This supports the view that HHH-therapy has an actual effect on restoration of CBF in poorly perfused regions.

The elevation of SBP during HHH-therapy was small and there was no significant change in CPP, but there was a more pronounced reduction in hematocrit. This indicates that the controlled hypervolemia, intravascular volume status and rheological effects are of importance. There are still uncertainties as to whether the increase in CBF improves oxygen delivery on the microvascular level as hemodilution may reduce the oxygen-carrying capacity, and further studies of both CBF and cerebral metabolism would be of value in the assessment of HHH-therapy.

Although there was a significant improvement in CBF during HHH-therapy, it is not evident that this correlates with better outcome. Definitive conclusions on outcome should not be drawn from this observational study, but it was noted that the frequencies of infarction and good clinical course outcome at discharge from NIC were at similar levels for HHH-treated DCI patients and non-DCI patients.

CBF and cerebral energy metabolism during HHH-therapy

The intention in the study in Paper IV was to investigate whether the cerebral energy metabolic pattern changes in concordance with improvement in CBF during HHH-therapy (as found in Paper III).

In our standardized NIC protocol, as described in Paper III, HHH-therapy is instituted cautiously with moderate blood-pressure targets, which is partly in contrast to other protocols aiming for higher blood pressure levels [111, 144, 145].

At baseline, median global cortical CBF was lower among the patients who subsequently developed DCI compared with patients in the reference group, which is in line with other studies [93, 146]. There were corresponding differences in the regional CBF parameters. The results of the CMD measurements showed a higher lactate level in the DCI group at baseline, and the L/P ratio was also higher in this group. The pathological energy metabolic state in DCI patients corresponds with the findings in earlier CMD studies [126, 127].
When the DCI patients were categorized by energy metabolic CMD patterns, only one patient had an ischemic pattern at baseline and four were in mitochondrial dysfunction, indicating that the energy metabolic derangement was moderate in most of these patients.

During HHH-therapy, both global cortical CBF and rCBF of the worst vascular territory increased markedly in the DCI patients, and the proportion of low-flow ROI-area showed a corresponding decrease. Regarding the CMD measurements, there was statistically no change in the levels of lactate, pyruvate or L/P ratio. Following diagnosis of DCI and HHH-therapy, the proportion of patients with an energy metabolic CMD pattern of mitochondrial dysfunction increased from four to eight, and four remained in a normal CMD pattern. The low number of patients and lack of a control group makes it difficult to draw firm conclusions from these observations. There is a possibility that the CMD levels and CMD patterns would have become worse without HHH-therapy, but this cannot be elucidated. Speculatively, increased CBF may have been beneficial for the microcirculation in compromised regions, albeit with a varying degree of disturbed energy metabolism remaining, addressed as mitochondrial dysfunction, despite improved blood flow [127, 130].

Feasibility and safety of bedside xenon CT

Regarding safety issues, XeCT using 28% inhaled xenon is previously reported as safe in a multicenter study on adverse events related to use of this technique [147]. The XeCT procedures in our NIC unit are performed with an intensive care physician on site, and all patients are mechanically ventilated and fully intensive-care monitored. The patients in our studies were all physiologically stable, and there were no adverse events during the procedures. The radiation exposure, which is estimated to 3 mSv (effective dose), is comparable to the exposure in a regular head CT scan and substantially less than that in a perfusion CT procedure [148]. We found XeCT to be a feasible method for bedside measurements of rCBF in unconscious SAH patients, but careful preparation and a trained team of radiology and NIC personnel are essential.
Conclusions

Already at the early acute stage after SAH, impairment of CBF is common and often heterogeneous, with substantial regions of low rCBF. Age and severity of the hemorrhage as graded in accordance with Fisher were found to influence global cortical CBF.

Low initial CBF was associated with a persistent low level of CBF later in the course, and this association was more pronounced when patients receiving HHH-therapy were separated from those with standard treatment. These results indicate that patients with early low CBF, even without clinical signs of DCI, could benefit from careful surveillance and optimization of circulation.

Patients diagnosed with DCI had lower initial CBF compared with non-DCI patients, and global CBF increased significantly during HHH-therapy. Similarly, regional CBF in the worst perfused vascular territories increased, which indicates a true effect of the HHH-therapy in our setting.

Intravascular volume status and blood rheology seem to be important factors in augmentation of CBF, as the increase in SBP during HHH-therapy was small, while there was a pronounced decrease in hematocrit.

Combining CBF measurements and CMD monitoring during HHH-therapy in DCI-patients revealed that global and regional CBF improved while the cerebral energy metabolic CMD parameters stayed statistically unchanged. None of the patients studied developed metabolic signs of severe ischemia, but a disturbed energy metabolic pattern was common, possibly explained by mitochondrial dysfunction, despite a proposed beneficial effect from HHH on the cerebral microcirculation.

In general, we found XeCT to be a feasible method for bedside measurement of CBF in NIC, which provides additional important information for the medical management of SAH patients. Unconscious and/or sedated SAH patients may have critically low CBF without detectable neurological deterioration and would benefit from early recognition and hemodynamic optimization.
Future perspectives

The findings in the studies of this thesis underline the importance of hemodynamic management to optimize CBF in poor-grade SAH patients. There is a need for further studies designed to elucidate the effects of different strategies of hemodynamic augmentation on CBF, cerebral energy metabolism and oxygen utilization, respectively, and ultimately also on neurological outcome.

Combined studies of CBF and cerebral metabolism by CBF imaging and multimodality monitoring are warranted. In this aspect, PET studies of CBF, oxygen extraction and cerebral metabolism would be of great value. Hopefully, also mobile CT scanners in combination with the XeCT technique or other modes of perfusion CT will be subject for future development enabling broader routine-use bedside in NIC.

Although restoration of CBF in regions with critically low flow seems fundamental in the treatment of DCI, our findings also imply that other factors impairing the cerebral energy metabolism at the cellular level should be addressed in future research.
Subaraknoidalblödning (SAB) till följd av ett brustet aneurysm (pulsåderbräck) i hjärnans blodkärl är ett allvarligt tillstånd med hög dödlighet och stor risk för bestående neurologiska handikapp. Detta trots de senaste decenniernas tekniska framsteg i behandlingen av aneurysm samt förbättrad neurokirurgisk intensivvård. Det akuta förloppet efter SAB komplicerar ofta av störningar i hjärnans blodflöde, ”delayed cerebral ischemia” (DCI), vilket kan bidra till ett mer svårt endast förlopp med risk för utveckling av bestående skador i hjärnan, hjärninfarkter. De biokemiska och fysiologiska störningar som leder till DCI, bland annat vasospasm (sammandragning av blodkärlen), inflammationsvar och störningar på mikroskopisk nivå i hjärnans blodkärlsnät, är komplicerade och ofullständigt kända. Förloppet är svårt att förutsöga, särskilt för neurologiskt påverkade patienter med medvetandesänkning där tidiga tecken på DCI kan vara svåra att upptäcka. Försämrat blodflöde i hjärnan, cerebralt blodflöde (CBF), är en avgörande faktor för utveckling av DCI, och upprepade mätningar av CBF både globalt (i hela hjärnan) och regionalt i hjärnans olika blodförsörjningsområden skulle kunna bidra till identifiering av riskpatienter och ge vägledning i den medicinska handläggningen.

Studierna i de fyra delarbeten som ingår i denna avhandling baseras på mätningar av CBF hos patienter med svår SAB som respirator-behandlats på intensivvårdsavdelning. Mätningarna har genomförts med hjälp av mobil utrustning för datortomografi och en teknik med samtidig tillblandning av ädelgasen xenon i andningsluften från respiratorn, vilket ger en röntgenkontrasteffekt och möjliggör beräkning av blodflödet, ”xenon-CT”. Målsättningen har varit att undersöka och karaktärisera globala och regionala störningar i CBF i olika faser av det akuta förloppet efter SAB. Vidare har effekten på CBF av den behandling som ges för att försöka öka blodflödet vid misstanke om DCI undersöpts. Effekten av behandlingen vid DCI även studerats med hjälp av ”cerebral microdialysis” via en tunn kateter i hjärnvävnaden, där biokemiska parametrar som speglar hjärnans energiomsättning kan mätas och ställas i förhållande till CBF.

_Delstudie I_ visade att stört/reducerat CBF var vanligt redan tidigt i förloppet (dag 0–3) efter SAB. Blodflödet var ofta heterogent med betydande områden
med blodflöde nära kritisk nivå för hjärnvävnadens överlevnad. Vidare konstaterades att patientens ålder samt svårighetsgraden av SAB (graderad från datortomografiundersökningen enligt Fisher) var faktorer som påverkade CBF.

*Delstudie II*, där CBF undersöktes vid flera tidpunkter under det akuta förloppet, påvisade ett samband mellan lågt initialt CBF och fortsatt lågt CBF även dag 4–7. Sambandet befanns starkare när patienter som erhållit blodflödesökande behandling separerades från dem med standardbehandling. Dessa resultat talar för att patienter med lågt CBF, även när det inte föreligger kliniska tecken på DCI, kan ha nytta av noggrann övervakning och optimering av blodcirkulationen.

I *delstudie III* undersökte effekten på CBF av den behandling som ges för att befrämja blodflödet (bl a höjning av blodtrycket och ökad vätsketillförsel). Både globalt CBF och CBF i områden med lägst blodflöde ökade. På motsvarande sätt minskade utbredningen av områden med kritiskt lågt blodflöde, vilket talar för att den blodflödesökande behandlingen haft avsedd effekt.

I *delstudie IV* gjordes vidare undersökning av effekten av den blodflödesbefrämjande behandlingen hos en grupp patienter som även hade övervakning med ”cerebral mikrodialys” enligt ovan. CBF ökade i samband med den blodflödesbefrämjande behandlingen, och de biokemiska ”energimetaboliska” parametrarna uppmätta genom mikrodialys i hjärnvävnaden (glukos, laktat, pyruvat och laktat/pyruvat-kvot) var statistiskt oförändrade. Ett biokemiskt mönster motsvarande kritiskt lågt (ischemiskt) blodflöde kunde inte ses hos någon patient under behandlingen, men ett mätligt störta mönster var vanligt. Detta kan möjligen förklaras av störningar i cellernas förmåga att utnyttja syrgas och glukos som tillförs hjärnvävnaden via blodflödet.
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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)