Carotid intima-media thickness and cerebrovascular vasoreactivity in patients with intracranial aneurysms

A sonographic study of potential predictors for aneurysm rupture risk and delayed cerebral ischemia

Marianne Lundervik Bøthun

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Tenke sjæl og mene, måtte stå for det du sa
Ikke vri deg unna, ikke være likeglad
Ikke late som du ikke mente det du sa
Ikke si som andre
Du må tenke sjæl

Trond-Viggo

Scientific environment

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Department of Global Public Health and Primary Health Care, University of Bergen

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Department of Neurology, Haukeland University Hospital

Department of Radiology, Haukeland University Hospital

Bergen Stroke Research Group

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2. LIST OF ABBREVIATIONS

AHA	The American Heart Association
ASA	The American Stroke Association
aSAH	Aneurysmal subarachnoid hemorrhage
AZ	Acetazolamide
BFV	Blood flow velocity
BIF	Carotid bifurcation
BMI	Body mass index
CCA	Common carotid artery
CI	Confidence interval
CO_2	Carbon dioxide
CT	Computed tomography
CTA	Computed tomography angiography
CVR	Cerebrovascular reactivity
CSF	Cerebrospinal fluid
DCI	Delayed cerebral ischemia
$DCI_{clinical}$	Clinical deterioration due to delayed cerebral ischemia
$DCI_{infarction}$	Cerebral infarction due to delayed cerebral ischemia
GCS	Glasgow Coma Scale
IA	Intracranial aneurysm
ICA	Internal carotid artery
IMT	Intima-media thickness
IQR	Interquartile range

LI	Lindegaard Index
MCA	Middle cerebral artery
MFV	Mean blood flow velocity
MFV_{AZ}	Maximal mean blood flow velocity after acetazolamide
$MFV_{BASELINE}$	Baseline mean blood flow velocity (before acetazolamide)
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
NOR-SYS	Norwegian Stroke in the Young Study
OR	Odds ratio
PAASH	Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage
RIA	Ruptured intracranial aneurym
RRR	Relative risk ratio
SAH	Subarachnoid hemorrhage
SD	Standard deviation
TCCS	Transcranial color-coded duplex sonography
TCD	Transcranial Doppler
TCU	Transcranial ultrasound
UIA	Unruptured intracranial aneurysm
VSP	Vasospasm
WFNS	World Federation of Neurological Surgeons

3. LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by the Roman numerals I-IV. The published papers are reprinted with permission from International Journal of Stroke, World Stroke Organization, Blackwell publishing and The Journal of Neurological Sciences, Elsevier. All rights reserved.

I **Carotid intima-media thickness – a potential predictor for rupture risk of intracranial aneurysms**
Lundervik M, Fromm A, Haaland ØA, Waje-Andreassen U, Svendsen F, Thomassen L, Helland CA.
International Journal of Stroke. 2014 Oct;9(7):866-72.

II **Cerebrovascular reactivity after treatment of unruptured intracranial aneurysms - A transcranial Doppler sonography and acetazolamide study**
Bøthun ML, Haaland ØA, Logallo N, Svendsen F, Thomassen L, Helland CA.
Journal of the Neurological Sciences, 2016 Apr 15;363:97-103.

III **Time-course of cerebrovascular reactivity in patients treated for unruptured intracranial aneurysms - A one-year transcranial Doppler and acetazolamide follow-up study**
Bøthun ML, Haaland ØA, Logallo N, Svendsen F, Thomassen L, Helland CA.
BioMed Research International, 2018 Apr 26;2018:6489276.

IV **Impaired cerebrovascular reactivity may predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage**
Bøthun ML, Haaland ØA, Moen G, Logallo N, Svendsen F, Thomassen L, Helland CA.
Journal of the Neurological Sciences, 2019. Dec 15:2019:407:116539.

4. ABSTRACT

Background and aims

Intracranial aneurysms can rupture and cause an aneurysmal subarachnoid hemorrhage (aSAH), a bleeding under the arachnoid meninges covering the brain. This is a devastating event, in which delayed cerebral ischemia (DCI) is a major cause of death and disability. In this thesis, we assess two possible ultrasonographic predictors for aneurysm rupture risk and DCI: carotid intima-media thickness (IMT) and cerebrovascular reactivity (CVR).

Carotid IMT is the combined thickness of the inner two layers of the carotid artery wall. IMT provides information about the degree of atherosclerosis and is an established risk marker for myocardial infarction and ischemic stroke. Persons with atherosclerosis have an increased prevalence of intracranial aneurysms, and smoking and hypertension are shared risk factors for aneurysm rupture, myocardial infarction and ischemic stroke. We thus hypothesized that IMT also could be associated with risk of aneurysm rupture.

Cerebral arterioles regulate vascular resistance and play an important role in maintaining constant cerebral blood flow during variations in cerebral perfusion pressure. CVR is defined as the change in cerebral blood flow, or blood flow velocity, in response to a vasoactive stimulus. Proximal arterial narrowing in vasospastic vessels causes a poststenotic pressure drop and compensatory arteriolar dilation. The suggested theory is that when vasospasm develops, pre-existing compensatory arteriolar dilation limits the capacity for further arteriolar dilation in a CVR test. Literature have indicated that impaired CVR may be a potential predictor for DCI after aSAH. Still, sample sizes have been limited and varying methodology and inconsistent and outdated definitions of DCI have been used.

Material and methods

Patients treated for unruptured and ruptured intracranial aneurysms at the Department of Neurosurgery, Haukeland University Hospital between February 2011 and May 2013 were included. Clinical, ultrasonographic and radiographic assessment were done after aneurysm treatment and at one-year follow up. Carotid ultrasound was performed with evaluation of IMT, and CVR was assessed by transcranial Doppler and acetazolamide test. Patients were followed prospectively for development of delayed cerebral ischemia (DCI), separated into clinical and radiographic findings.

Results

Carotid IMT was higher in patients treated for ruptured aneurysms than in patients with unruptured aneurysms. The probability of belonging to the aneurysm rupture group increased with higher IMT values.

CVR was reduced on the ipsilateral side in all patients after aneurysm treatment, regardless of rupture status or DCI development. Patients with clinical deterioration due to DCI had lower CVR, and the difference was bigger on the contralateral side. Including CVR in a prediction model with established predictors increased the area under the receiving operator curve, indicating improved prediction of DCI.

Conclusions

There is an association between carotid IMT and aneurysm rupture status at the time of aneurysm treatment. Carotid IMT is a potential predictor of aneurysm rupture, and is a possible adjunct in the assessment of aneurysm rupture risk, and thus a helpful tool in patient counseling.

Impaired CVR is a potential independent predictor of clinical deterioration due to DCI, and may assist in identifying patients at risk after aSAH. Our prediction model can be useful in clinical practice, but first needs to be validated. Ipsi- and contralateral CVR needs to be considered separately.

5. GENERAL INTRODUCTION

An intracranial aneurysm is a localized bulging or ballooning of an artery, caused by local weakness of the arterial wall. Aneurysms can rupture and (depending of the location) cause a subarachnoid hemorrhage, a bleeding under the arachnoid - one of the meninges covering the brain. This is a devastating event, with high morbidity and mortality rates for affected patients. Delayed cerebral ischemia (DCI) is a potentially severe complication following subarachnoid hemorrhage, and is a major contributor as a cause of death and disability after aneurysmal subarachnoid hemorrhage (aSAH).

This thesis is based on a prospective ultrasonographic study of patients treated for saccular intracranial aneurysms. The overall aim was to investigate whether neurosonological examinations can aid in assessments of risk of 1) rupture of intracranial aneurysms and 2) development of delayed cerebral ischemia. Two ultrasonographic parameters were studied: “carotid intima-media thickness” and “cerebrovascular reactivity”.

First, existing knowledge will be presented.

Clarifications

The literature search in sections 6 to 8 was concluded 01.01.2019.

The abbreviation aSAH describes only aneurysmal subarachnoid hemorrhage, whereas the abbreviation SAH is used for all types of spontaneous subarachnoid hemorrhage (aneurysmal and non-aneurysmal).

TCU is the joint abbreviation for all transcranial ultrasound examinations, whereas the non-imaging technique is termed TCD (transcranial Doppler) and the imaging technique is termed TCCS (transcranial color-coded duplex sonography).

6. INTRACRANIAL ANEURYSMS

6.1 Intracranial aneurysms

An aneurysm is a localized bulging or ballooning of an artery, caused by local weakness of the arterial wall. Intracranial aneurysms (IAs) are most commonly located at the branching points of the major arteries coursing through the subarachnoid space at the base of the brain (Figure 1). There are four main types of IAs: saccular, fusiform, dissecting, and mycotic. The saccular type accounts for approximately 90% of IAs.[1]

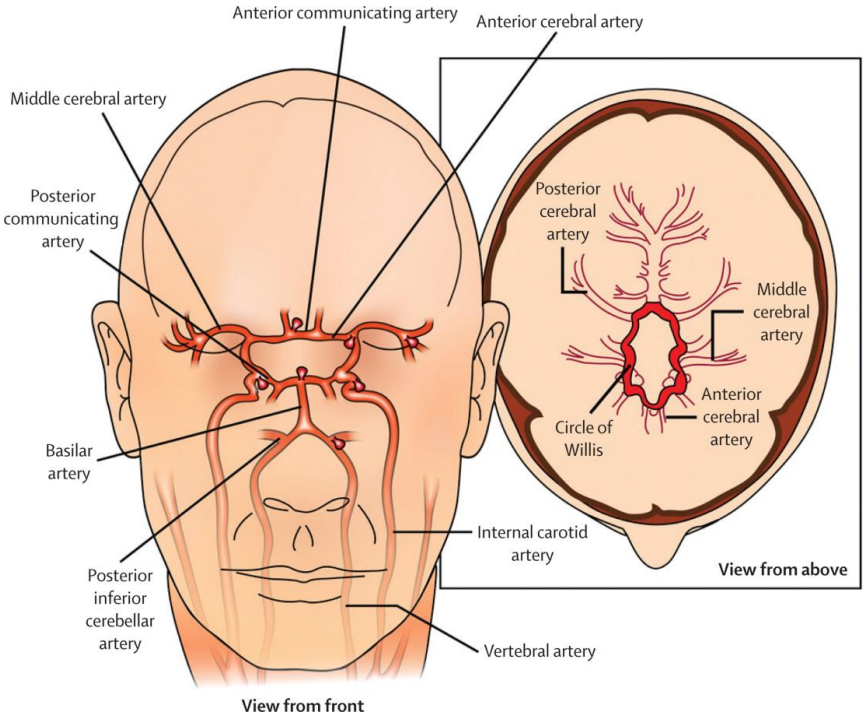

Figure 1. Common locations for intracranial saccular aneurysms.
Reprinted from Williams, Brown and Broderick[2, 3] with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

The prevalence of IAs is aproximately 3% in the general population.[4] In Norway, the prevalence of intracranial saccular aneurysms on MRA is 1.9% (95%CI: 1.2-2.9%).[5] IAs are often discovered as random findings in asymptomatic patients. There has been a considerable increase in incidentally detected aneurysms due to improved availability and sensibility of modern neuroimaging tools such as CT and MRA angiography.[6, 7]

The process underlying aneurysm formation, growth and rupture is not yet fully understood, but inflammation and hemodynamic stress are assumed to play central roles in the pathogenesis. The existing theory is that hemodynamic stress induces endothelial dysfunction, which is followed by an inflammatory response, involving macrophages and smooth muscle cells in the artery wall. Finally, a degradation of the extracellular matrix facilitates aneurysm rupture.[8-10]

6.2 Aneurysmal subarachnoid hemorrhage

The majority of IAs remains asymptomatic throughout life.[2, 11-14] However, some aneurysms rupture and cause a subarachnoid hemorrhage, a bleeding localized under the subarachnoid mater. The bleeding can also reach into brain parenchyma (intracerebral hemorrhage), the ventricular system, or sometimes even the subdural space.[15]

The incidence of SAH varies widely from region to region. There is a tenfold difference in incidence worldwide, with lowest rates in China (2.0 per 100.000 person-years) and highest rates in Japan and Finland (respectively 22.7 and 19.7 per 100.000 person-years).[16, 17]

With an incidence rate of 10.3 per 100.000 person-years (13.3 for women and 7.1 for men),[18] the incidence in Norway is comparable to the overall worldwide incidence

(9.1 (95% CI 8.8–9.5) per 100.000 person-years).[17, 19] The incidence of SAH increases with age and is higher in females,[17] and the average age of onset is >50 years of age.[16, 20, 21]

6.3 Risk factors for aneurysm formation, growth and rupture

IAs are acquired lesions that develop throughout life. Female sex, family history of SAH (two or more affected first-degree relatives), and autosomal dominant polycystic kidney disease are known non-modifiable risk factors for **formation** of IA.[4] Smoking and hypertension are major environmental risk factors, and seem to have an additive effect.[22]

Risk factors for aSAH can be divided into risk factors for aneurysm formation, growth and rupture. Most risk factors for aneurysm **growth** are consistent with risk factors for aneurysm rupture.[23, 24] This suggests that aneurysm growth and rupture are processes with, in part, shared pathogenesis, a suggestion supported by reports of markedly increased rupture risk in growing aneurysms.[25-27] However, there are some differences between risk factors for aneurysm growth and rupture. Although there is heterogeneity in reports, multiple IAs may be associated with increased risk of aneurysm growth,[23] and still have a limited predictive value for aneurysm rupture.[28] Conversely, a family history of SAH and IAs is related to aneurysm rupture,[28, 29] but has limited predictive value for aneurysm growth.[23] In addition, Finnish and Japanese populations have reduced risk for aneurysm growth,[23] but still a high risk of aneurysm rupture.[28, 30]

Established risk factors for aneurysm **rupture** are age >60 years, female sex and Japanese and Finnish descent.[28, 30, 31] Reported aneurysm-specific risk factors are size >5mm,[30] location in the posterior circulation[30], symptomatic aneurysm,[30] and irregular

aneurysm shape.[32] Whether smoking and hypertension increase the risk of aSAH only through an increased risk of aneurysm formation and growth, or also through an increased risk of rupture is under debate.[11, 12, 22, 28, 30, 33-39]

Additional risk factors have been suggested for aneurysm formation, growth and rupture; such as hypercholesterolemia, ischemic heart disease, diabetes mellitus, low body mass index, and excessive alcohol consumption. Data is however limited and conflicting.[11, 12, 22, 28, 34, 38, 40-42]

6.4 Clinical presentation

Most aneurysms go unnoticed unless they are very large, rupture or are (incidentally) discovered with brain imaging. The clinical manifestations of unruptured aneurysms (UIAs) are subtle. Only 10-15% of UIAs are symptomatic.[11, 14, 43] Symptoms are primarily caused by mass effect of large aneurysms, alternatively by minimal leakage of blood which irritates the meninges.[44] The most common presentation is headache or third nerve palsy. Other symptoms and signs include visual field defects, trigeminal neuralgia, cavernous sinus syndrome, brain-stem dysfunctions and seizures.[45] Occasionally UIAs can cause arterial embolisms and ischemia.[46, 47] Symptomatic UIAs carries a higher risk of subsequent rupture (RR 4.4; 95% CI, 2.8-6.8).[30] Headache may be a warning sign of impending rupture. A sentinel headache in the three months preceding aneurysm rupture has been reported in 10% to 43% of patients with aSAH.[48]

The typical symptoms of aSAH result from blood spilling into the cerebrospinal fluid (CSF) and the immediately increased intracranial pressure and later the subsequent breakdown of blood products. The hallmark feature of aSAH is hyperacute onset of severe headache (“thunderclap-headache”, “the worst headache in my life”).[44, 49] The headache is often accompanied by nausea and vomiting, photophobia, neck stiffness

or loss of consciousness.[50] Patients may also experience seizures[51], or show focal neurological deficits[52] particularly in cases with parenchymal hematomas.[52]

6.5 Diagnostics

The majority of UIAs are detected incidentally during neuroimaging for unrelated conditions.[53] Some aneurysms are diagnosed due to relevant symptoms (se section 6.4), or screening patients with familial aSAH (two or more first-degree relatives with SAH).[54] Lastly, some patients have multiple aneurysms and UIAs are discovered as part of assessment of and/or follow-up after aSAH.[54]

Non-contrast cerebral computer tomography (CT) is the first line diagnostic test when SAH is suspected, and should be performed as soon as possible after symptom onset.[54-56] CT has nearly 100% sensitivity for detecting subarachnoid blood if scanning is performed within six hours after ictus.[57, 58] However, sensitivity decreases with resorption and redistribution of subarachnoid blood over time after the initial bleeding: five days after the initial bleeding SAH is detectable in approximately 85% of cases, and after two weeks in under 30% of cases.[59] A negative non-contrast CT is thus supplemented with a lumbar puncture if there is a strong suspicion of SAH, especially if the patient presents days after ictus.[54, 56] Detection of xanthochromia in CSF due to metabolites of hemoglobin supports the diagnosis of SAH.[60] The term xanthochromia comes from the Greek words xanthos (yellow) and chroma (color), due to the yellow discoloration of CSF caused by hemoglobin catabolism. Xanthochromia can be determined by spectrophotometry (measuring the absorption of particular wavelengths of light) or simple visual examination (Figure 2). As blood degradation takes some hours, lumbar puncture is recommended performed 6–12 hours after the initial SAH.

Figure 2. Xanthochromic cerebrospinal fluid
Visual examination shows yellow discoloration of CSF (xanthocromia) in the left bottle, and normal CSF in the right bottle. Reproduced with permission from Williams,[61] copyright BMJ Publishing Group Ltd.

After the diagnosis of SAH is established one needs to identify the source of the bleeding. This is usually done by CT angiography (CTA), due to the method's non-inasiveness and high sensitivity and specificity for detecting IAs.[62, 63] The sensitivity is nearly 100% for aneurysms greater than 4 mm,[64-66] and 97% for all aneurysm sizes.[67] Additionally, CTA visualizes the configuration of the aneurysm and surrounding blood vessels, which is helpful in deciding which treatment modality to use. If CTA is negative, conventional four vessel catheter digital subtraction angiography (DSA) is recommended, as this is considered the gold standard for imaging IAs.[68]

Although MRI with multiple sequences might be equally sensitive as CT/CTA in detecting SAH within 24 hours,[54] limitations in availability, logistics, predisposition

to motion artefacts, patient complicance, longer study time and higher cost cause MRI to not routinely being used in the diagnostics of aSAH.[56]

6.6 Management

Individual assessment of patients with UIA to determine the best management is challenging, and a thourough assessment of rupture risk versus interventional risks is necessary. Multiple factors are considered, including aneurysm size, location, and morphology, symptoms, patient age, family or personal history of SAH, comorbidity, and patient's perspective regarding an interventional procedure.[2, 3, 54] Ruptured intracranial aneurysms (RIAs) should be treated with intervention as early as logistically and technically possible to reduce the risk of rebleeding.[54, 56]

There are three main strategies in the management of IAs: 1) conservative approach with regular neuroimaging follow-ups, 2) endovascular treatment, or 3) surgical clipping. Figure 3 illustrates the methods used in aneurysm intervention. Aneurysm clipping is performed during an open craniotomy, where the aneurysm is dissected out and a metallic clip is placed across the neck to isolate the aneurysm sack from the parent artery. The basic endovascular aneurysm treatment is coiling, in which soft platinum coils are placed directly into the aneurysm, causing local thrombosis and isolation of the aneurysm from the parent blood vessel.[69, 70] For some aneurysms, other endovascular techniques such as stent-assisted coiling is necessary. The stent prevents the coils from becoming displaced from the aneurysm sack and entering the parent artery.

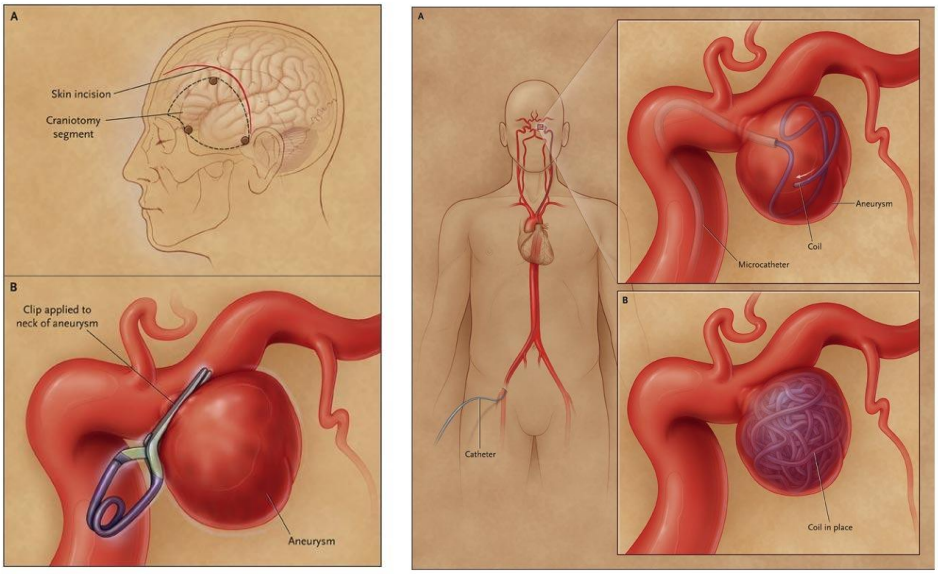

Figure 3. Aneurysm interventions

The left side of the figure illustrates craniotomy and clipping of aneurysm. The skin is incised and a craniotomy performed (A), before a clip is placed across the aneurysm neck (B). The right side of the figure shows endovascular coiling, where a small microcatheter is incerted transfemorally (A), and platinum coils are placed into the aneurysm sack (B). Reproduced with permission from Brisman, Song, and Newell,[71] copyright Massachusetts Medical Society.

Treatment of aSAH also includes appropriate neurocritical care, and prevention and treatment of potential complications.[54, 56]

6.7 Complications

Aneurysm intervention carries a risk of complications, including arterial dissection, hemorrhage, cerebral infarction, aneurysm rupture/perforation, cardiac and thromboembolic events, infections and acute organ failure. Complications are more

common in acute treatment for aSAH compared with elective treatment for UIA, but occur in both settings.[72-74]

The three most important neurological complications after SAH are aneurysm rebleeding, delayed cerebral ischemia and hydrocephalus.[55]

Aneurym rebleeding is a feared early complication after aSAH.[75] Aproximately 15% of patients rebleed in the first few hours after the initial bleeding.[76] If patients survive the initial 24 hours after the hemorrhage and the aneurysm is not occluded, the risk of rebleeding in the following weeks is aproximately 30%.[77] Rebleeding is associated with high mortality and poor outcome. Aproximately 60% of patients who rebleed die, and additional 30% remain dependent in activities of daily living.[78, 79] A ruptured aneurysm should be occluded early (usually within 24 hours after ictus) to prevent rebleeding.[54, 56] Antifibrinolytic medications reduces the risk of rebleeding by 35%, but since they also increase the risk of cerebral ischemia, there is no proven effect on case fatality or clinical outcome.[80]

Delayed cerebral ischemia is another major source of disability and death after aSAH.[81-83] This complication is thouroghly presented in section 7.

aSAH can also disrupt the production and absorption of cerebrospinal fluid (CSF) and cause hydrocephalus (HC). The range of reported incidence of HC after SAH is wide (6-67%),[84] still most studies report that 20-30% of patients with SAH develop HC.[85-87] The onset can be acute[88] (within 72 hours after SAH) or chronic[89] (weeks or months after the initial event), and HC may complicate aSAH in both the short and long term. Symptoms include headache, reduced level of consciousness, urinary incontinence and gait disturbances, and neuroimaging (CT/MRI) show enlarged ventricles. The excess fluid needs to be drained, and treatment options are either lumbare puncture or drainage, or in case of obstruction of CSF flow within the ventricular system, external ventricular drainage. Patients with symptomatic chronic

hydrocephalus may require permanent ventriculo-peritoneal or ventriculo-atrial shunting.[54, 56]

Systemic complications are also common after aSAH. Non-neurological complications include fever, anaemia, hypertension and hypotension, electrolyte disturbances, glucose abnormalities, cardiac failure, arrhythmias, thromboembolism, pulmonary oedema, pneumonia and sepsis.[56, 90, 91]

6.8 Outcome

aSAH is a devastating event associated with high rates of morbidity and mortality.[18, 92] Althoug there has been a reduction in mortality in the last decades, case fatality rates still remains high.[20, 93] Precise outcome statistics vary among publications, but in summary approximately one-third of patients with aSAH die, one-third survive with significant permanent disabilities, and one-third make a good recovery with little or no long-term disabilities.[20, 93, 94] Most deaths occur within two weeks after the bleeding, with approximately 10-15% occurring before the patient receives medical care and 25% within 24 hours after ictus.[75, 95, 96]

In addition to focal neurological deficits, survivors of aSAH often have cognitive sequelae, with impairment in memory, language, visuospatial and executive function.[97, 98] Fatigue, sleeping disturbances, and mood disorders are also common.[97] aSAH leads to a substantial decrease in health related quality of life, not only in the acute phase, but also the first years after the bleeding.[99, 100] However, reports indicates improvement in quality of life in the long term after aSAH, despite of persistant restrictions in function.[100] This indicates that long-term survivors of aSAH apply psychological adaptation and coping mechanisms, as described in other chronic diseases[101] and ischemic stroke.[102]

aSAH cause considerable socioeconomic burden on the society, individual patients and their families.[103] Although SAH accounts for only 1% to 7% of all strokes,[104] the loss of productive life years is comparable to that of cerebral infarction (the most common type of stroke), due to the poor outcome and relatively young age of onset in SAH.[17, 104, 105] Overall, SAH accounts for 5% of stroke deaths, but for 27% of all stroke-related years of potential life lost before the age of 65.[106]

Persons who survive aSAH have increased risk of vascular events and death.[107-110] Possibly due to overlapping vascular risk factors like hypertension and smoking,[34] they have increased risk of ischemic stroke, hemorrhagic stroke and cardiovascular events,[107, 111] in addition to being at risk for developing new aneurysms[112, 113] and having new episodes of aSAH.[92, 114-117] Prevention of new vascular events after aSAH by managing risk factors appears important and cessation of smoking and regular blood pressure check-ups are recommended.[54, 56]

6.9 Management of patients with unruptured intracranial aneurysms

The number of patients with incidentally discovered IAs is rapidly growing due to increasing use of modern neuroimaging tools,[6, 7] and incites a challenge in patient counselling and clinical decision making. Although as many as up to 3% of the worldwide population harbors an UIA,[4] the incidence of SAH from aneurysmal rupture is relatively low (9.1 per 100.000 person-years).[17, 19] This discrepancy indicates that the majority of IAs do not rupture. Still, the consequences of aneurysm rupture are potentially devastating.[18, 92] Treatment of the aneurysm (surgical or endovascular) can effectively eliminate the risk of aSAH. However, treatment of all UIAs is not prudent, because of the risk of complications caused by aneurysm treatment and the high financial cost.[118] To decide whether to perform a potentially harmful prophylactic procedure or not, tools to predict the risk of rupture in the given

individual is needed. Although some predictors are known and prediction models have been proposed,[28] counselling of individual patients with UIA remains challenging and increased knowledge of predictors for aneurysm rupture is needed.

7. DELAYED CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

7.1 Early descriptions

The earliest description of delayed cerebral ischemia (DCI) after SAH likely dates back to Hippocrates (460-370 BC). «When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days.»[119] It took an additional 2000 years before comparable descriptions appeared in medical literature. In 1859, the british physician Sir William Gull described the first case of neurological deterioration after aSAH consistent with DCI.[120] A 30-year old female fainted after an episode of acute headache and nausea, and was admitted with "increasing coma" and right-sided hemiplegia. Over the next few days her clinical status improved, until an acute worsening occurred. Her pupils became dilated and fixed, and she died five days after hospital admission. The autopsy revealed two aneurysms on the middle cerebral artery, one of which had ruptured, subarachnoid blood in the left Sylvian Fissure, and infarction in the left hemisphere. Over the next 100 years additional reports were added,[121] including the first angiographic description of constriction of cerebral arteries after aneurysm rupture.[122] This firmly established the concept of vasospasm after aSAH. In 1975, Fisher illuminated the clinical spectrum and time-course of DCI after aSAH.[123, 124]

7.2 Pathogenesis

For decades, the classic understanding was that arterial narrowing, called vasospasm (VSP), was the sole cause and explanation for secondary brain injury after aSAH. Blood byproducts from the aneurysm rupture cause contraction of the walls of nearby arteries (Figure 4). This leads to cerebral ischemia, and potentially infarction.

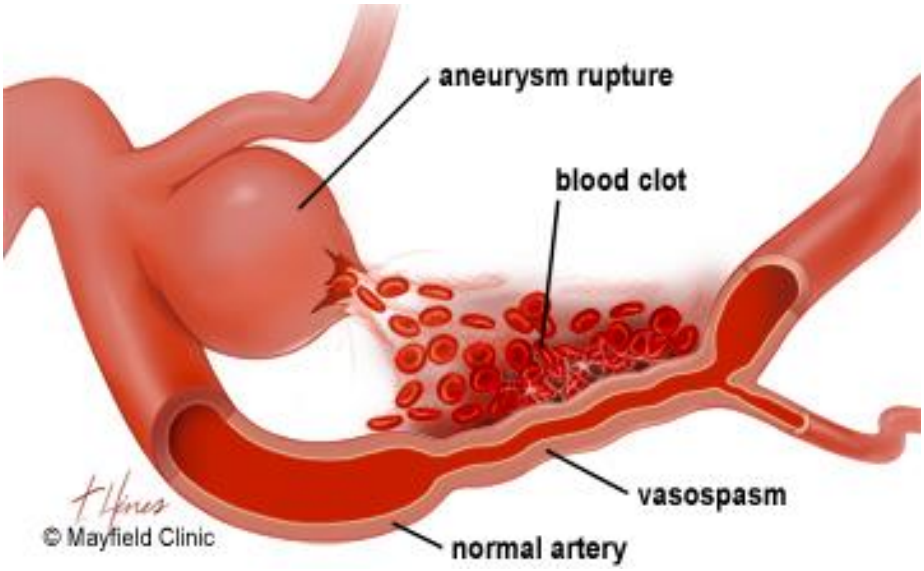

Figure 4. Arterial narrowing due to aneurysm rupture

The traditional idea of cerebral ischemia secondary to vasospasm has, however, been challenged. Patients may have severe arterial narrowing but still maintain adequate brain perfusion.[125] Reversely, patients can have delayed cerebral ischemia without any signs of arterial narrowing on angiography.[125] Additionally, clazosentan, an endothelin receptor antagonist, was found successful in reversing vasoconstriction, but failed to improve patient outcome.[126-129] Furthermore, nimodipine, a calcium channel antagonist, does improve patient outcome, although it has no impact on large-vessel caliber.[130] These findings led to a paradigm shift, where the pathogenesis of delayed cerebral ischemia was presumed to be complex and multifactorial; and not exclusively explained by arterial narrowing.[131] One is now looking beyond vasoconstriction for alternative explanations of cerebral ischemia after SAH.[132-134] The current theory is that several other factors are important in the pathophysiology of DCI,[135-137] as illustrated in Figure 5. Possible mechanisms besides large vessel

vasospasm include microcirculatory constriction,[138] microthromboebolism,[139-141] cortical spreading depression,[142] failed autoregulation,[143] early brain injury,[144] inflammation,[145, 146] blood brain barrier disruption,[147] oxidative stress,[148] and delayed cellular apoptosis.[149] Despite extensive efforts in elucidating the pathogenic mechanisms, the pathogenesis of DCI remains incompletely understood, and research is ongoing.

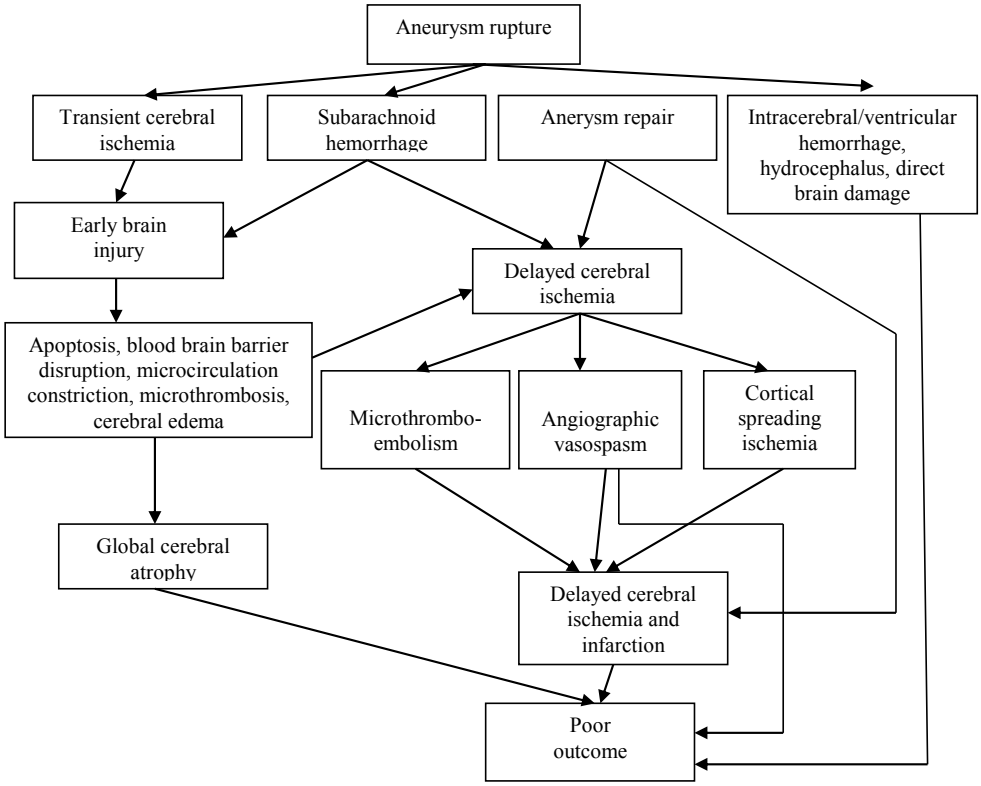

Figure 5. Pathophysiology of cerebral ischemia and poor outcome after aneurysmal subarachnoid hemorrhage

The pathophysiology of cerebral ischemia after aneurysmal subarachnoid hemorrhage is multifactorial and complex. Adapted from Loch Macdonald[150] with permission of Springer; all rights reserved.

7.3 Definitions

In medical literature, a variety of terms has been used to describe ischemic complications after aSAH. Definitions are based on clinical, radiographic, angiographic, sonographic, microdialytic or EEG findings. Table 1 list commonly used expressions in literature.

Table 1. Terms used to describe cerebral ischemia after aSAH*
Delayed ischemic (neurological) deficit (DIND)
Delayed cerebral ischemia (DCI)
Secondary cerebral ischemia
Symptomatic ischemia
Vasospasm (VSP)
Clinical vasospasm
Symptomatic vasospasm
Angiographic vasospasm
Sonographic vasospasm
Microdialytic and EEG vasospasm
Permanent neurologic deficit (PND)
Cerebral infarction
Delayed infarction

*aSAH: aneurysmal subarachnoidal hemorrhage

Inconsistencies in definitions complicates research in cerebral ischemia after aSAH, and makes it difficult to compare results between studies, summarize results in metaanalyses, understand the true impact of an intervention, or construct good quality guidelines. Each of the definitions has its strengths and limitations. As long as the precise pathogenesis of ischemia remains unknown, it is challenging to determine

which term is preferable. Consistent use of valid terminology is however essential for collecting useful data about cerebral ischemia after SAH.

In 2009, Frontera and colleagues argued that “delayed cerebral ischemia” (DCI), a definition that incorporates both symptomatic deterioration and cerebral infarction, was the most clinically relevant definition.[151] They compared frequently used definitions, and found that DCI had the strongest associations with overall poor outcome, cognitive impairment and reduced quality of life.

In 2010, a multidisciplinary research group led by Vergouwen proposed uniform definitions for “clinical deterioration caused by DCI” and “cerebral infarction”.[152] They recommended that the term “vasospasm” should be reserved for angiographic arterial narrowing only.

In 2011, a literature review of consensus panel recommendations and original research studies concluded that the use of combined measures with both clinical and radiographic assessment should be limited.[153] Clinical deterioration and angiography results should preferably be reported separately. “Cerebral infarction” (found in neuroimaging studies or autopsy) was considered to be the most appropriate definition for DCI in clinical trials. Cerebral infarction is strongly correlated with functional outcome, neuroimaging can detect ischemia in sedated and comatose patients, and the interobserver agreement rate is high. Furthermore, infarction is an objective quantification of the ultimate consequences of cerebral ischemia.

In 2015, a variation of the terminology for neurological dysfunction after aSAH was proposed.[154] Kapinos argues that the aggregate definitions recommended by consensus panels[152, 153] mixes a heterogenic patient group with neuronal dysfunction caused by different mechanisms and processes. In stead, he advocates for a terminology based on descriping the clinical impairment, physiological disturbance,

or image abnormality, and argues that this is more precise in describing the exact abnormality for each subgroup of patients.

In this thesis, the definitions recommended by the literature reviews and international consensus panel by Vergouwen and colleagues is used.[152, 153]

7.3.1 Delayed cerebral ischemia (DCI)

The term "delayed cerebral ischemia" (DCI) has been used for neurological deterioration or cerebral infarction after SAH, or both.[151] The definition thus includes clinical and/or radiographic (CT/MRI) evidence of ischemia.

7.3.2 Clinical deterioration due to DCI

"Clinical deterioration due to DCI" is defined as a new focal neurological impairment or reduction in level of consciousness.[152, 153] The precise definition is as follows:

- Focal neurological impairment or Glasgow Coma Score reduction ≥2 points
- Duration of the deterioration ≥ 1 hour
- Deterioration should not have been apparent immediately after aneurysm occlusion
- Deterioration should not be attributable to other causes by means of clinical assessment, cerebral CT or MRI scans, and appropriate laboratory studies

Patients with aSAH often have spontaneous mild fluctuations in the level of consciousness. To reduce the number of false-negative events ascribed to DCI, the reduction in the Glasgow Coma Score must be at least 2 points, and the neurological deterioration must last for minimum 1 hour.

Diagnostics of clinical deterioration due to DCI is difficult for several reasons. Firstly, the clinical spectrum of DCI is wide. Clinical features of DCI include neurological

deficits (such as hemiparesis, aphasia, apraxia, hemianopia and neglect) due to focal cerebral ischemia, and reduction in level of consciousness as a result of global cerebral ischemia. The clinical features may be subtle or marked. Symptoms and signs may appear abruptly or gradually, and typically fluctuates over time. Secondly, clinical deterioration due to DCI is a diagnosis *per exclusionem*. Multiple other conditions can cause clinical deterioration after SAH, e.g. rebleeding, hydrocephalus, seizures, hypoxia, hypotension, infections, heart failure, and the effect of sedatives. Because these other factors often are found in mild degrees, it is difficult to know when clinical deteriorations can be truly attributed to DCI. Thirdly, a proportion of patients are comatose or sedated after SAH, making them unavailable for clinical assessment. Using this definition of DCI that is purely based on clinical features will therefore underestimate the true incidence of DCI.

7.3.3 Cerebral infarction from DCI

Clinical features of DCI can be reversible and resolve spontaneously or after treatment. Alternatively, ischemia can progress to cerebral infarction, which can result in long lasting, severe disability or death.

"Cerebral infarction from DCI" is defined as a new infarction, identified on CT or MR scans or autopsy, within six weeks after aSAH.[152, 153] The precise definition is as follows:

- Cerebral infarction should be identified on cerebral CT or MR scan within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks after SAH, or proven at autopsy
- Cerebral infarction should not have been present on CT or MR scan performed between 24 and 48 hours after aneurysm occlusion

- Cerebral infarction should not be attributable to other causes by means of clinical assessment, cerebral CT or MRI scans, and appropriate laboratory studies
- Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI

Neuroimaging to detect cerebral infarction due to DCI is recommended performed within 6 weeks after the bleeding, as this includes the time window in which DCI occurs, and when most patients are in a stable clinical condition. A post-treatment CT or MR scan should be performed 24 to 48 hours after aneurysm occlusion to rule out edema and infarction related to the surgical or endovascular procedure.[155] Other causes of hypodensities or infarctions should also be ruled out.

Two major benefits of using neuroimaging in stead of clinical assessment, is a higher interobserver agreement rate and the ability to detect ischemia in sedated and comatose patients

7.3.4 Vasospasm

The term “vasospasm” (VSP) or “arterial narrowing” is reserved for narrowing of large cerebral arteries as evidenced by angiography (computed tomographic, magnetic resonance or digital subtraction angiography).[152, 153] The term does *not* apply to clinical manifestations of DCI.

Cerebral vasospasm is sometimes already seen in the acute phase after aSAH, but most commonly develops between days 4 and 14 after the hemorrhage, with a peak incidence between day 6 and 10, and resolves spontaneously after 2-3 weeks.[156, 157]

Arterial narrowing can be evaluated directly by angiographic studies, or indirectly by sonographic studies. Cerebral vasospasm is found on angiography in as many as 70% of patients following aSAH,[158] whereas only 30% develops DCI.[159-162]

Transcranial Doppler ultrasound diagnostics was not included in the definition recommended by the multidisciplinary group,[152, 153] due to lower sensitivity and specificity for angiographic arterial narrowing.[163, 164] However, a recent review assessed the impact of TCD vasospasm on DCI, defined as clinical or radiological (CT/MRI) evidence of ischemia.[165] The meta-analysis shows that TCD evidence of vasospasm predicts DCI with high accuracy.[165] The sensitivity and negative predicitive value is high (respectively 90% and 92%), and the specificity is fair (71%).

7.4 Risk factors

The risk of DCI after SAH is primarily related to the severity of the initial hemorrhage. Large amount of subarachnoid blood detected on CT imaging and poor neurological status on admission are established predictors of DCI.[55, 166-169] Several other potential risk factors or predictors have been proposed. A systematic review found strong evidence for increased risk of DCI in smokers (pooled OR 1.2).[170] Data was too sparse to draw conclusions on other suggested predictors. Moderate evidence was found for increased risk in patients with hydrocephalus, history of diabetes mellitus, hyperglycemia on admission, or early systemic inflammatory response syndrome. Moreover, limited evidence was found for increased risk of DCI related to female sex, history of hypertension, initial loss of consciousness, previous use of selective serotonin reuptake inhibitors, hypomagnesemia, history of migraine, low hemoglobin on admission, or high blood flow on early transcranial Doppler. For age, history of cardiovascular disease, previous use of statins, and cocaine, evidence was

inconsistent. Strong evidence was, however found for absence of an association between DCI and the location of the aneurysm.

In addition, there was no significant difference between aneurysm clipping or coiling in the risk of developing cerebral vasospasm or cerebral infarction from DCI.[171, 172]

7.5 Detection and diagnosis

There are three main tools for detection and monitoring of DCI: clinical, radiographical, and physiological.

Clinical monitoring involves frequent neurological assessments to detect new neurological deficits caused by ischemia. Not all ischemic events are, however, detectable on clinical examination. Asymptomatic infarctions are found in 10-20% of patients with aSAH,[173-175] and clinically unrecognized infarctions are more common in comatous patients.[173] Clinical examination is considered adequate in detecting DCI in good grade patients, but less reliable in poor grade patients with reduced level of consciousness. Poor grade patients may thus require advanced multimodal monitoring.

Radiographical monitoring modalities include conventional digital subtraction angiography, CT and MRI with angiography and perfusion techniques.[176, 177]

Physiological monitoring modalities include transcranial Doppler ultrasonography, cerebral microdialysis, brain tissue oxygenation tension, cerebral blood flow, electroencephalography, and near-infrared spectroscopy.[176, 178]

7.6 Treatment

Treatment options can be divided into three groups: preventive measures to avoid the development of DCI, first-line therapy initiated after DCI is established, and rescure therapy for medically-refractory DCI.

7.6.1 Prevention of DCI

The mainstay of DCI prevention in patients with aSAH is treatment with nimodipine and maintenance of normal circulating blood volume.

Nimodipine, a calsium channel antagonist, is the only drug with class 1 evidence of a beneficial effect in the prevention of DCI.[179-181] Administration of Nimodipine is recommended for all patients with aSAH.[54, 56, 176] The drug has has been shown to improve neurological outcomes, but has no proven effect on angiographic vasospasm.[130]

In addition, guidelines from the American Heart Association/ American Stroke Association (AHA/ASA) recommends maintenance of euvolaemia and normal circulating blood volume to prevent DCI (class I, level B).[56]

7.6.2 First-line therapy for new-onset DCI

Hemodynamic therapy with induced hypertension and volume optimization are the foundation in first-line therapy for DCI.[178]

A combination of hypervolemia, induced arterial hypertension, and hemodilution, so called “triple-H therapy”, has long been advocated as standard treatment for DCI after SAH.[182] However, limited data are available regarding the efficacy and safety of such treatment. Based on recent literature, focus has shifted from triple-H therapy towards isolated hypertension and maintenance of euvolemia.[183-186] The hypervolemia-

component offers no definite benefit in DCI-treatment, and expansion of the intravascular volume might even be harmful. Complications associated with induced hypervolemia include hyponatremia, pulmonary edema, cerebral edema, cardiac arrhythmia, and congestive heart failure.[185] Still, hypovolemia is associated with adverse outcome after SAH, and should be avoided in all patients. The goal should thus be to maintain euvolemia, rather than attempting to induce hypervolemia.[176] Hypertension effectively increases cerebral blood flow and is able to reverse ischemic neurological deficits in two-thirds of patients.[187] In the latest AHA/ASA treatment guidelines, induction of hypertension is recommended for patients with DCI as tolerated by cardiac output unless blood pressure is elevated at baseline or cardiac status precludes it.[56]

7.6.3 Rescue therapy for medically-refractory DCI

If ischemia is not adequately reversed in response to first-line therapy, DCI is considered refractory, and second-line "rescue therapy" is indicated. Such rescue therapy primarily consist of endovascular intervention and circulatory optimization.

Endovascular therapy can be divided into mechanical dilation and intra-arterial administration of vasodilating drugs. Both methods have been shown to successfully reduce angiographic vasoconstriction and improve neurological outcome.[188] According to current guidelines, endovascular therapy can be considered in patients with vasospasm-related DCI, particularly those who are not rapidly responding to hypertensive therapy (class IIa, level B evidence).[56, 176] Percutaneous transluminal balloon angioplasty is a procedure where constricted area of cerebral arteries are mechanically stretched and dilated. The technique is limited to proximal vessels, and main drawbacks include risk of thromboembolism, dissection, and vessel rupture. Advantages of intra-arterial vasodilators are better distal penetration, and a favorable

safety profile. Limitations include short-lasting effect, and risk of hypotension and increased ICP.[178, 188]

Augmentation of hemoglobin levels and increasing cardiac output (CO) with fluids and inotropes is also feasible and can improve brain perfusion after SAH.[176, 178, 189]

If a patient still demonstrates neurological worsening despite the above-mentioned measures, the physician is left with the option of engaging nonevidence-based therapies, like induced therapeutic hypothermia, aortic flow diversion, or intrathecal vasodilators.[178]

7.6.4 Ongoing studies and ineffective treatment therapies

There is a lack of high-quality definitive data in several areas regarding treatment of DCI. This has led to a large variability in practice patterns in management of DCI.[190]

Several novel therapies for preventing and treating DCI after aSAH have been assessed, with variable results. Some treatment therapies have failed to show a beneficial effect, whereas others have yielded promising results yet warrant further investigation.

Medications like cilostazol, eicosapentaenoic acid, erythropoietin, heparin, and methylprednisolone all demonstrate promising results in smaller, non-randomized or retrospective studies, yet remain to be tested in larger randomized controlled trials.[191] Topical application of nicardipine implants, a calsium channel antagonist, may also reduce angiographic VSP and clinical deterioration due to DCI, but warrant further investigation.[191-193] In addition, different methods to improve subarachnoid blood clearance have been established, but their effect on outcome remains unclear.[191]

Current evidence does not support prophylactic use of clazosentan, magnesium, or simvastatin.[191] Furthermore, prophylactic angioplasty of the basal cerebral arteries[194], prophylactic hypervolemia[195-197], and antiplatelet prophylaxis[198] is also considered ineffective in reducing morbidity.[178, 188]

7.7 Consequences of DCI

Most case series have reported that 20-35% of patients develop DCI after aSAH.[159, 162, 199-206] Ischemia can be reversible, but may also progress to cerebral infarction, severe disability or death. Next to the initial hemorrhage and rebleeding, DCI is a major causes of morbidity and mortality after aSAH.[81, 159] Patients with DCI incur substantially higher treatment costs and a significantly slower resumption of employment compared to those who do not develop DCI.[199] The cost difference is mainly explained by larger volume of imaging and investigations, longer length of stay, and complications and adverse events that are more serious.[199]

8. NEUROSONOLOGY

Several sonographic methods are used to assess neurological disorders. In this thesis the focus is on carotid ultrasound and transcranial Doppler.

8.1 Ultrasound

Ultrasounds are sound waves that have a frequency above the limit of human hearing (i.e. 20 kHz). In medical ultrasound, also known as ultrasonography, high-frequent sound waves are used to determine size, shape, consistency and movement of tissues, organs and body fluids. Oscillating piezoelectric elements in an ultrasound transducer generates ultrasound by converting electrical pulses to mechanical vibrations. The transducer emits sound waves into the body and receives reflected sound returning from the body. When ultrasound enters the body, it travels through different tissues. Sound waves are reflected back to the transducer (reflection), transmitted to deeper structures (transmission), scattered, or partly absorbed and converted to heat. Returned mechanical vibrations is converted back into electrical energy, and translated into an image on a computer screen. Information about the time interval between when the sound was sent and received, as well as the amplitude and the pitch of the sound, are used to calculate depths and velocities and produce computer images.

Compared to other imaging techniques, ultrasound has several advantages. The method provides real-time information, has low costs, is non-invasive and does not involve harmful ionizing radiation. As many ultrasound devices are portable, examinations can also be performed bedside. The disadvatages of medical ultrasound include limited fields of view due to patient physique or cooperation, and difficulty with imaging structures behind bone and air. Furthermore, a skilled operator is required for optimal examination and interpretation of findings.

The ALARA (As Low As Reasonably Achievable) principle is advocated for all ultrasound examinations. This safety principle instructs that the power setting should be as low as possible and the scanning time as short as possible, to reduce exposure to potentially harmful bioeffects.[207]

There are several ultrasound modes:

A-mode (amplitude mode) is the simplest type of ultrasound imaging. A single transmitter emits an ultrasound pulse, and then switches to receiving mode. Reflected sound waves are displayed on a screen as spikes on the time (x-) axis. The stronger the returned wave, the larger the amplitude of the spike.

B-mode (brightness mode) is the most common form of ultrasound imaging. The strength of the returning wave is recorded as a bright dot instead of a spike. The brightness of the dot indicates the intensity of the returning echo. Multiple ultrasound-emitting crystals are activated sequentially, and a grey-scale image is generated.

M-mode (motion mode) shows movement by displaying echo strenght on a straight line as a function of time.

Doppler mode is used to examine moving elements, for example blood. Ultrasound waves that hit moving structures are reflected with a changed frequency, depending on the direction and velocity of the moving object.

Color Doppler flow imaging combines grey-scale imaging with color codes that indicates direction and velocity. The insonated object is displayed with red color when it is moving towards the ultrasound probe, whereas the color is blue if the direction of movement is away from the probe.

Power Doppler mode visualizes the strength of the Dopplersignal in color (instead of direction and velocity).

Duplex imaging is the combination of B-mode two-dimentional grey-scale image to visualize tissue, and Color Doppler mode to measure velocities. This allows for simultaneous visualization of the anatomy of the area, while assessing blood flow velocities. Furthermore, this method enables measurement of the Doppler angle, making it possible to correct the frequency shift with the use of cosine of the insonation angle.

Triplex imaging is B-mode combined with two displays of the Dopplersignals; within the grey-scale imaging, and graphic flow.

8.2 Carotid ultrasound and intima-media thickness (IMT)

The carotid artery wall lies close to the surface of the skin, and is easily accessible for visualization with ultrasound (Figure 6).

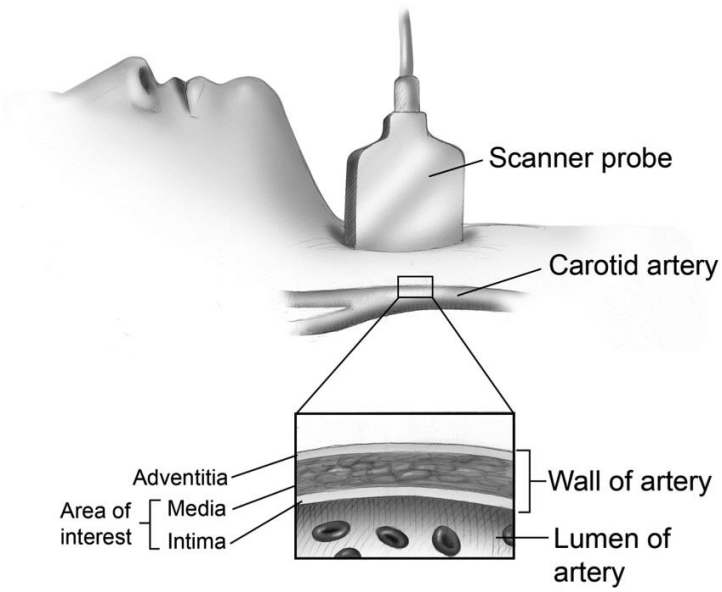

Figure 6. Carotid ultrasound with insonation of the vessel wall
Ultrasound imaging with sagittal view of the carotid artery, showing the three layers of the arterial wall. Reprinted with permission of Stephen W. Parcell, all rights reserved.[208]

The arterial wall is composed of three layers: intima, media, and adventitia. Carotid intima-media thickness (IMT) was first described in 1986 as the combined thickness of the common carotid artery's innermost and middle layer (the tunica intima and tunica media) as measured by ultrasonography.[209] Different tissues have varying echogenicity, and the interfaces are ultrasonographically detectable. Although ultrasound cannot discriminate between the intimal and medial layers because of insufficient axial resolution, B-mode imaging displays a visible transition from the hypoechogenic lumen of the artery into the hyperechogenic intimal layer (lumen-

intima border), and the transition from the hypoechogenic medial layer into the hyperechogenic adventitia (media-adventitia border). Ultrasonography thus depicts the intima-media complex as a double line structure (Figure 7). The ultrasonographic observations of IMT have been verified by histology, and show insignificant difference between sonographic and histological measurements.[210]

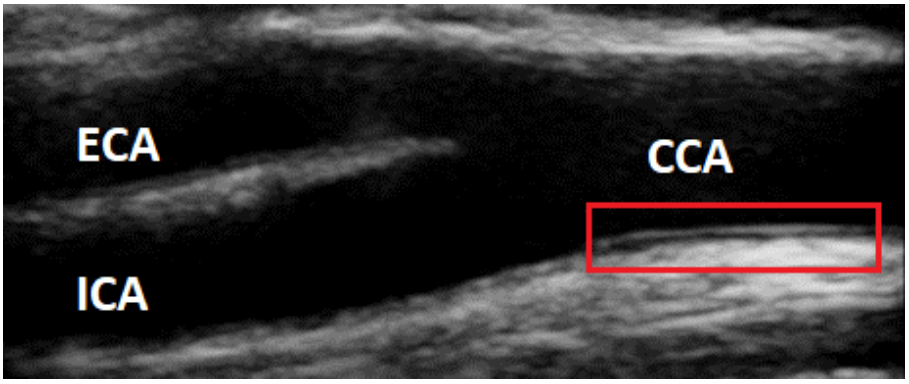

Figure 7. Intima-media thickness visualized by carotid ultrasound
B-mode imaging of the bifurcation of the carotid artery. CCA indicates common carotid artery; ECA, external carotid artery; and ICA, internal caotid artery. The intima-media complex is visible as a double echogenic line within the red box at the far wall of the CCA. Printed with permission of Annette Fromm, Bergen Stroke Research Group, all rights reserved.

IMT provides information about the degree of subclinical atherosclerosis, and is an idependent vascular risk marker.[211] IMT correlates with a number of traditional vascular risk factors such as hypertension, smoking, and hypercholesterolemia.[212, 213] Multiple epidemiological studies have established that increased IMT is associated with elevated risk for ischemic stroke[214, 215] and myocardial infarction.[211, 212, 214-217] IMT is a valuable tool for assessment of atherosclerosis and cardio- and cerebrovascular disease, and is increasingly being used for risk stratification in individuals and as an endpoint in interventional studies.[218]

8.3 IMT and intracranial aneurysms

Persons with atherosclerosis have an increased prevalence of intracranial aneurysms (RR 2.3),[14] and increased carotid IMT is associated with atheroclerosis.[219] Accordingly, it is conceivable that persons harbouring IAs may have increased carotid IMT. However, data available for carotid ultrasound findings in patients with intracranial aneurysms are scarce.[220, 221]

Individual assessment of rupture risk of cerebral aneurysms is challenging, and increased knowledge of predictors for aneurysm rupture sought after. As smoking and hypertension are shared risk factors for aneurysm rupture[34], myocardial infarction[222] and ischemic stroke,[223] IMT may be a shared risk marker. At the start-up time of the observational study, which is the basis for this thesis, no reports had assessed if there is any association between carotid IMT and rupture status of IAs.

8.4 Transcranial ultrasound

Transcranial ultrasound (TCU) is used to evaluate the intracranial vascular system in patients with cerebrovascular disease. TCU enables assessment of cerebral hemodynamics by measuring blood flow velocities in intracranial blood vessels. The technique is based on the Doppler effect which was first described by the Austrian physicist, Christian Doppler, in 1842.[224, 225] The Doppler effect states that if an observer is moving towards or away from the source of sound waves, then a greater or lesser number of waves fronts will pass the observer in a given time interval, and so the observer will measure a higher or lower frequency than that wich was transmitted.

The basic of TCU is that a transducer emits low-frequency sound waves (≤2 MHz) through the cranium, hence the name “transcranial”. When the ultrasound waves hits a moving object, like red blood cells within intracranial blood vessels, they are reflected with a different frequency. The difference in ultrasound frequency provides

information about the velocity and direction of the blood cells, and is called Doppler shift. The mathematical equation and principle of calculating velocitites is illustrated in Figure 8.

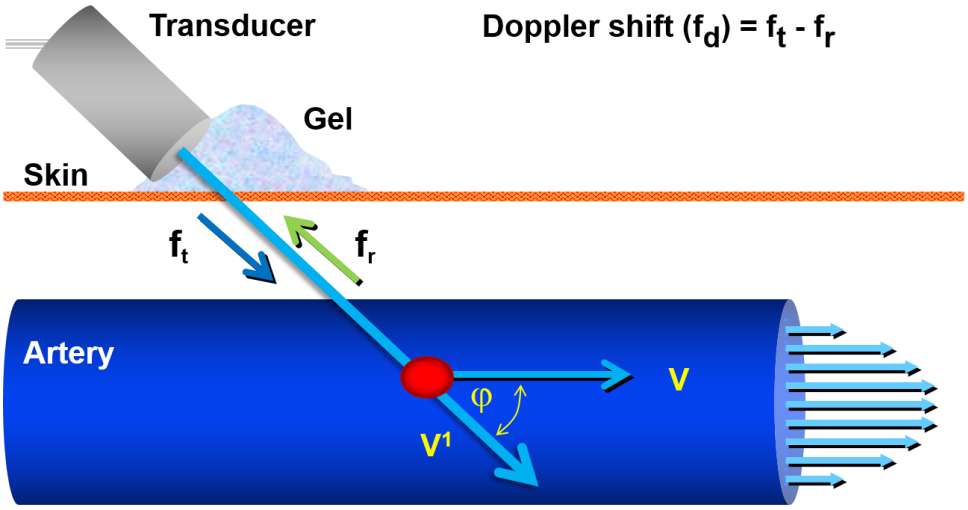

Figure 8. Measurement of blood flow velocitites by means of ultrasonographic Doppler examination.
Blood flow velocity is calculated as $v = f_d\ c\ /\ 2\ f_t \cos\theta$, where v = velocity of blood, c = velocity of sound, f_d = difference in frequency (Doppler shift), f_t = transmitted frequency, f_r = received frequency and θ = insonation angle (angle between sound beam and flow axis). If the Doppler shift is positive (increased frequency) the blood flow direction is towards the probe, and if the Doppler shift is negative (reduced frequency) the blood flow direction is away from the probe. Image by Bergen Stroke Research Group, all rights reserved.

In general, the skull bone is too thick to penetrate with ultrasound, but there are a number of “acoustic windows” such as natural foramina, or where the bone is

sufficiently thin for a significant amount of ultrasound energy to penetrate. Figure 9 illustrates the main bone windows used in transcranial Doppler ultrasound.

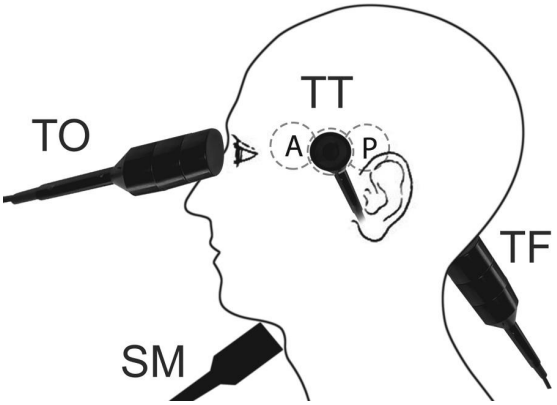

Figure 9. Bone windows and approaches in transcranial Doppler
The main bone windows used in transcranial Doppler ultrasound enables insonation of intracranial vessels through the transtemporal (TT), transorbital (TO), transforaminal (TF) and submandibular (SM) approach.[226] The transtemporal approach is subdivided into three smaller windows: anterior (A), middle (M) and posterior (P). Reprinted from Ttitianova and Vastagh[227] with permission of Cambridge University Press, all rights reserved.

The most commonly used approach is transtemporal, which allows insonation of the middle cerebral arteries, anterior cerebral arteries, posterior cerebral arteries and intracranial internal carotid artery. The transorbital approach is used to insonate the ophthalmic arteries and the carotid siphons. The transforaminal approach allows insonation of the vertebral and basilar arteries through the foramen magnum. The submandibular approach is used to assess the internal carotid artery as it enters the skull. In addition to the four main apporoaches,[226, 228-231] a frontal approach is used to insonate the origins of the A2 segment of the anterior cerebral artery.[232]

The major disadvantage of TCU is that some persons have poor bone windows preventing adequate insonation. The proportion of persons with inadequate bone windows varies from 3% to 35% among studied populations.[233-236] The insonation deficiencies may be bilateral or unilateral. Inadequate or missing bone window is associated with advanced age and female sex,[233, 237-240] African-American[237] and Asian[241] descent, and cranial bone thickness.[234]

Furthermore, it can be difficult to perform TCU examinations in restless or uncooperative patients. This may include children, patients with stroke or head injury, or in a post-operative setting. Patients with aSAH often have reduced cooperation abilities due to confusion and neck stiffness. Additionally, patients often have intracranial air after craniotomy with clipping of IAs or evacuation of hematomas, which prevents adequate insonation the first days after surgery.

There are multiple indications for TCU.[242-246] Table 2 presents major applications for TCU, but is not a complete overview.

Table 2. Indications for transcranial Doppler ultrasound

Detection and monitoring of vasospasm after subarachnoid hemorrhage
Assessment of intra- and extracranial occlusive disease
Intraoperative monitoring of intracranial blood flow
Evaluation of collateral blood flow
Sonothrombolysis and assessment of recanalization in acute ischemic stroke
Detection and monitoring of intracranial vasculopathy in sickle cell disease
Identification of vascular supply of arteriovenous malformations
Assessment of cerebrovascular reactivity
Confirmation of brain death

TCU can be performed using either imaging or non-imaging techniques. The two techniques are presented in the following sections.

8.4.1 Transcranial Doppler (non-imaging)

Conventional transcranial Doppler (TCD) was introduced in 1982 by Rune Aaslid.[247] TCD is performed with small, low frequency sector transducers. The most commonly used frequency is 2 MHz, but transmission can be between 1 MHZ and 3 MHz. Figure 10 illustrates transtemporal insonation of intracranial arteries by TCD.

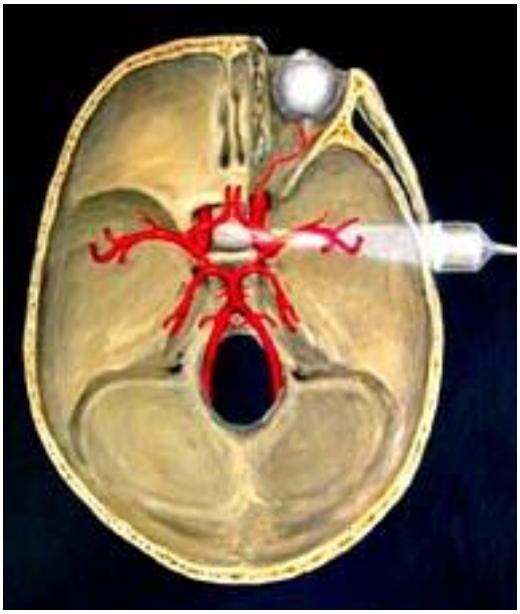

Figure 10. Insonation of intracranial arteries by transcranial Doppler
Image courtesy of Rune Aaslid.

TCD is a non-imaging technique. The insonated blood vessel is not visible, only a spectral Doppler waveform is displayed (Figure 11).

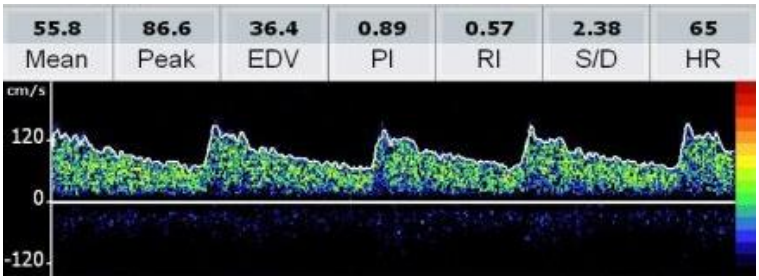

Figure 11. Spectral Doppler waveform of the middle cerebral artery
Spectral Doppler recording with time as the horizontal axis and blood flow velocity on the vertical axis. Mean flow velocity is 55.8 cm/s. Image by Marianne Lundervik Bøthun, all rights reserved.

Acquisition of the Doppler signal from intracranial vessels with this technique requires "blind" manipulation of the probe and adjustment of depth of the sample volume.[226] TCD is therefore often refered to as "blind" Doppler. TCD can be technically challenging, particularly for inexperienced operators.

8.4.2 Transcranial color-coded duplex sonography (imaging)

Transcranial color-coded duplex sonography (TCCS) was introduced in the early 1990s.[248-250] TCCS is performed with a larger sized phased array transducer with Doppler frequency from 2 MHZ to 3.5 MHz, and imaging frequency up to 4 MHz.[229]

Unlike conventional TCD, TCCS allows visualization of anatomic landmarks and spatial course of the blood vessels. In TCCS, brightness-mode and color Doppler flow is combined to obtain grayscale images of cerebral parenchyma and duplex images of intracranial vessels, see Figure 12.

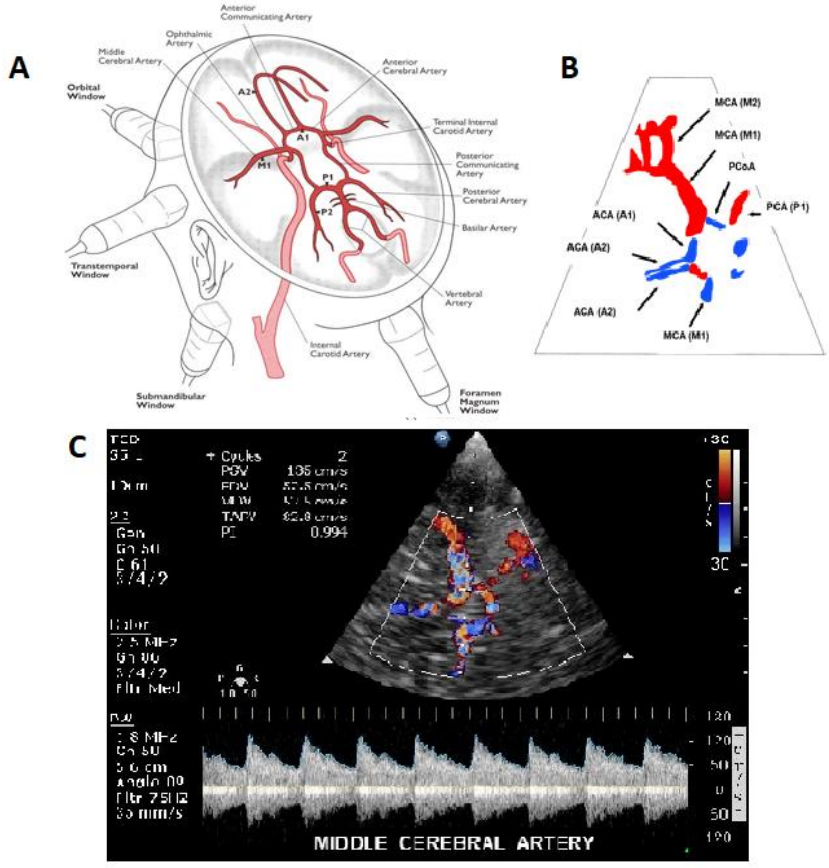

Figure 12. Insonation of intracranial arteries by transcranial color-coded duplex sonography

The upper left panel (A) displays the spatial course of blood vessels. The upper right panel (B) shows a schematic overview over insonated vessels using the transtemporal approach. Red color indicates flow direction towards the probe, and blue color indicates flow direction away from the probe. The lower panel (C) shows combined grey scale image of brain parenchyma, and Color Doppler of intracranial vessels. Time-averaged peak flow velocity (TAPV) in the middle cerebral artery is 82.8 cm/s. Image by Bergen Stroke Research Group and Marianne Lundervik Bøthun, all rights reserved.

TCCS has three major advantages compared with non-imaging transcranial Doppler sonography.[251] Firstly, TCCS facilitates vessel identification and makes it easier to follow tortous vessels and identify arterial branching. Secondly, it offers the opportunity for angle correction, resulting in more accurate measurement of blood flow velocities. Thirdly, imaging of blood vessels and parenchyma enables more precise and detailed diagnostic information. TCCS enables examination of the diameter and position of the third ventricle and a potential midline shift. Intracerebral hemorrhage, aneurysms, and arteriovenous malformations may also be detected by TCCS. Furthermore, both extra- and intracranial vessels can be examined using a single Duplex ultrasound device.

TCCS is less operator-dependent compared with TCD. Still, TCCS have a relative insensitivity for low flow signals, and it is important that TCCS operators use their knowledge of intracranial anatomy and complete a single-gate spectral analysis even if the color visualization is incomplete or suboptimal. Fewer diagnostic criteria for intracranial disease are available for TCCS compared with conventional TCD. Another limitation of TCCS is that imaging transducers are unsuitable for continuous bilateral monitoring by fixation in a headframe; smaller or adabtale transducers are required. There is also a lack of software for a variety of specialized TCD tasks, such as emboli detection and CVR assessment. Lastly, the machine used for TCCS examinations is larger and more expensive compared with conventional TCD machines.

8.5 Transcranial ultrasound and vasospasm

The knowledge that blood flow velocity is increased in a constricted vessel has led to the use of TCU in detection and monitoring of cerebral vasospasm.

Hemodynamic principles states that blood velocity (V) is related to flow (Q) and diameter of a vessel (D) by the following equation: $V = 4Q/\pi D^2$. This relationship indicates that given a constant blood flow, velocity is inversely proportional to the squared diameter of the vessel lumen. An elevated blood flow velocity is thus indicative of vessel lumen reduction.

An example of VSP in the middle cerebral artery (MCA) is shown in Figure 13. For the MCA the commonly used threshold levels for vasospasm are >120 cm/s (mild VSP), and ≥200 cm/s (severe VSP).[163, 165, 244] A rapid increase in velocity (>50 cm/s over two consecutive days) is also strongly predictive of symptomatic vasospasm.[252-254] The use of relative velocity changes have been proposed as an alternative indicator of VSP,[255] but is found inferior in predicting symptomatic VSP compared to established absolute thresholds.[252] For arteries other than MCA, there is no consensus regarding threshold levels.

A variety of factors influence flow velocities, and must be taken into account when interpreting TCU results. Such factors include technical issues, vessel anatomy, patient age, intracranial pressure, arterial blood pressure, hematocrit, arterial CO2 level, collateral flow patterns, and response to therapeutic interventions like triple-H therapy.[244]

Hyperemia will also present with increased flow velocities. Lindegaard and colleagues established a tool to help differentiate hyperemia from vasospasm as a cause of elevated velocities.[256] Lindegaard index (LI) is defined as the ratio between the mean flow velocity in the middle cerebral artery and the mean flow velocity in the ipsilateral extracranial internal carotid artery. Elevated velocities with LI < 3 is indicative of hyperemia, whereas LI 3-6 and LI > 6 indicates mild and severe vasospasm respectively. In published literature, there are several favorable reports for the use of the LI to increase the diagnostic accuracy of TCU.[256-259] However, some

results are less supportive of an added value of using LI compared with uncorrected MCA velocities.[260, 261]

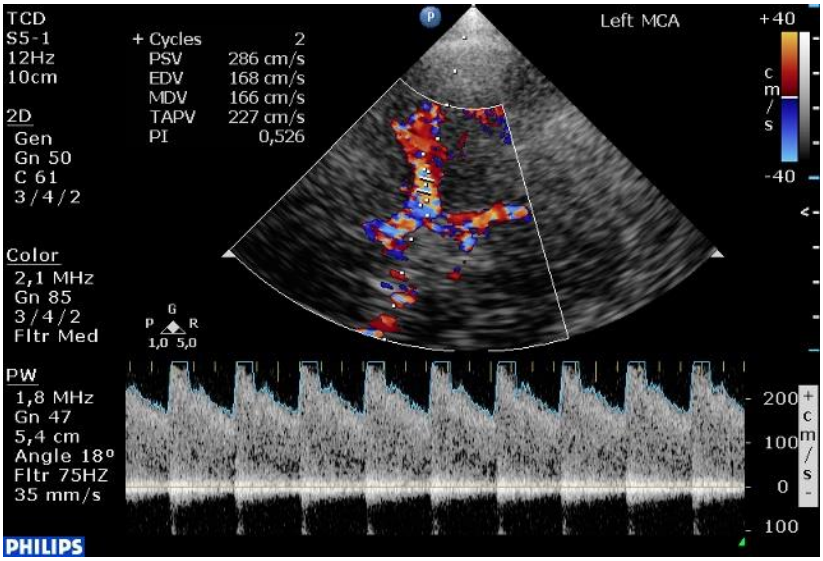

Figure 13. Severe vasospasm in the left middle cerebral artery
TCCS nine days after aneurysmal subarachnoid hemorrhage displays elevated blood flow velocities in the left middle cerebral artery due to severe vasospasm. Time averaged peak velocity is 227 cm/s, and the Lindegaard index 7.7. Image by Marianne Lundervik Bøthun, all rights reserved.

A recent study suggests an alternative approach for diagnosing vasospasm by TCCS.[262] Extracranial ultrasonography of the internal carotid artery (ICA) can be difficult in an intensive care unit setting. Restricted neck movements and central lines in the internal jugular vein can hamper optimal placement of the linear-array probe, making assessment of the extracranial ICA technical challenging. Connolly and collegues proposes a new index, defined as the ratio between blood flow velocities in the MCA and the basal vein of Rosenthal.[262] This intracranial arteriovenous index has

better practicability and a greater reliability compared with the established LI, and is a promising alternative approach.

TCU has several advantages compared with other methods for detection and monitoring of VSP. Firstly, it is non-invasive, and unlike conventional angiography, this method has no risk of complications like thromboembolisms, vessel dissection or rupture. Secondly, repeated measurements and monitoring is feasible, unlike for DSA and CTA, which are restricted due to the use of ionizing radiation and contrast agent. Thirdly, the bedside suitabilty reduces the need to transport unstable patients on ventilators from the ICU to the radiology department. Lastly, the method has low-cost compared with other methods.

The main limitation of TCU in VSP diagnostics is that a proportion of patients cannot be properly insonated due to poor bone window or intracranial air after surgery. Furthermore, the method is operator dependent, and like for CTA, TCD has limited ability to detect distal VSP.

The exact sensitivity and specificity of TCU for detecting vasospasm depends on which parameters and values are used. Different definitions have been used as TCD evidence of vasospasm (absolute thresholds from 120 cm/s to 200 cm/s, or relative changes in blood flow velocity). Furtermore, there is also a variation in the predicted outcome, e.g. angiographic VSP, symptomatic VSP and DCI. A recent review and metaanalysis found that TCD evidence of vasospasm is predictive of DCI with high accuracy (threshold 120 cm/s, sensitivity 90%, specificity 71%, positive predictive value 57%, negative predictive value 92%).[165] The high sensitivity and negative predictive value makes it an ideal method for VSP monitoring. The diagnostic precision is greatest in MCA, which is also the preferred artery to study due to easy accessibility and favorable insonation angle.[163] TCCS has similar, or even better, diagnostic accuracy for VSP assessment, compared with conventional TCD.[259, 263-265]

According to relevant guidelines, TCD is considered reasonable and useful for detection and monitoring of vasospasm after aSAH (Class IIA recommendation/Level B evidence).[56, 176] For VSP in the middle cerebral artery and basilar artery the level of evidence is higher (Class I-II, Level A).[244] Still, there is a lack of knowledge about the effect of TCD monitoring on clinical outcome, and TCD is thus not a mandated standard of care in aSAH. High-quality randomized trials evaluating the impact of TCD monitoring on outcome (disability, quality of life, cerebral infarction, mortality, etc) are warranted.

In conclusion, TCU is recommended for detection and monitoring of VSP after aSAH, yet added evidence for clinical impact is warranted.

8.6 Cerebrovascular reactivity

Cerebrovascular reactivity (CVR) provides information regarding cerebral vasculature control of distribution of blood flow. Cerebral arterioles have the ability to regulate vascular resistance, and play an important role in autoregulation to maintain constant cerebral blood flow throughout variations of cerebral perfusion pressure. Ohm's law states that blood flow (Q) equals difference in pressure (ΔP) divided by resistance (R). Arteriole dilation reduces peripheral resistance and increases blood flow in proximal vessels, whereas arteriole constriction increases resistance and reduces proximal flow. CVR is defined as the change in cerebral blood flow, or blood flow velocity, in response to a stimulus that makes arterioles dilate or contract. Different vasoactive stimuli and measurement methods are listed in Table 3.[266]

Table 3. Different methods used to assess cerebrovascular reactivity[266]
Vasoactive stimuli
CO_2
Hyper-/hypoventilation
Breath-holding
Acetazolamide
Measurement of cerebral blood flow
CT perfusion
MR perfusion
Xenon-enhanced CT
Positron emission tomography
Single Photon Emission Computed Tomography
Near infrared spectroscopy
Transcranial Doppler*

* In transcranial Doppler, cerebral blood flow is not measured directly. Instead, blood flow velocities are used as an indicator of flow.

By reflecting the vasodilating or -constricting capacity of cerebral resistance vessels, CVR provides information about cerebrovascular integrity, hemodynamics and pathophysiology in cerebrovascular diseases. There are several applications for CVR in neurosonology; still the majority of studies have been performed in patients with carotid artery occlusive disease. Impaired CVR is associated with increased risk of stroke and transient ischemic attack.[267] Moreover, several pathological conditions affecting brain microvasculature have a potential association with impaired CVR, including hypertension,[268] diabetes mellitus,[269, 270] and vascular dementia.[271, 272]

CVR tests how cerebral flow responds to exogenic vasoactive stimuli (such as CO_2 or acetazolamide), whereas autoregulation tests investigate how cerebral flow responds to changes in systemic blood pressure. The mechanisms of autoregulation are

multifactorial, and can be affected by a number of physiological parameters such as transmural pressure, CO2, autonomic function, intracranial pressure, etc. CVR on the other hand is solely connected with vasodilation or -constriction. When assessing cerebral autoregulation several vasomotor mechanisms are tested to see if cerebral blood flow levels are maintained at different blood pressure values. In clinical practice, CVR tests are easier to perform compared with the more complex testing of cerebral autoregulation.

8.7 Cerebral vasoreactivity and intracranial aneurysms

Information about CVR can improve the understanding of cerebrovascular integrity in patients harboring intracranial aneurysms. Data on CVR in persons with UIA are sparse. Few reports have been published for this patient group, and all involved small study populations ($n \leq 10$) and used CO_2 as vasoactive stimuli.[273-278] To our knowledge, there are no available data on CVR in persons with UIA assessed with TCD and acetazolamide test.

In contrast to the limited number of CVR studies in persons with UIA, there are several reports on CVR in patients with RIA. CVR is often impaired in the early phase after aSAH,[273-275, 277, 279-281] especially in patients with poor clinical grade.[276, 277, 282, 283]

Impaired CVR may also be associated with VSP and DCI. Proximal artery narrowing in vasospastic vessels causes a poststenotic pressure drop and compensatory arteriolar dilation. The suggested theory is that the when vasospasm develops, pre-existing compensatory arteriolar dilation limits the capacity for further arteriolar dilation in a CVR test. The capacity for arteriolar dilation is impaired or, in severe cases, exhausted. When the peripheral vascular bed reaches its maximum dilating capacities, even a minor reduction of the proximal vessel lumen cannot be further compensated

and leads to ischemia. According to this hypothesis, vasospastic conditions may not become symptomatic in the contrary situation with preserved peripheral vasodilating capacity.

In agreement with this theory, CVR in patients with established cerebral vasospasm after aSAH is reportedly different from CVR in healthy subjects.[284] When CVR was assessed by means of TCD and CO_2, patients with VSP had reduced vasodilating arteriolar capacity under hypercapnia.[284]

If CVR is impaired also prior to ischemic symptoms, it may be able to *predict* the development of VSP and DCI after aSAH. With one exeption,[281] the literature suggests that impaired CVR may be associated with vasospasm and can be a potential predictor for DCI after aSAH.[280, 282, 283, 285-293] However, sample sizes have been limited, methodology has varied and inconsistent and outdated definitions of DCI have been used.

8.8 Transcranial Doppler and acetazolamide challenge

A common method of CVR testing is the TCD and acetazolamide test. Acetazolamide (AZ) has has been used in CVR testing for nearly 30 years.[294, 295] AZ is a pharmaceutical substance that inhibits carbonic anhydrase and causes vasodilation of the cerebral arterioles, yet the exact mechanism of the drug is not fully understood.[296-298] The vasodilator effect of AZ is primarily confined to the arterioles and precapillary sphincters, and AZ has only a minimal effect on the diameter of larger proximal arteries.[299] Velocity measured by TCD is thus approximately proportional to CBF. Reduced arteriolar resistance due to vasodilation causes increased CBF, and increased blood flow velocity, in the major cerebral arteries.

Blood flow velocities (BFV) in an intracranial artery is measured continuously with TCD during the test. Usually the transtemporal approach is applied and the MCA is

insonated, but other intracranial arteries can also be examined. The probe is kept in position with a head strap or a special probe-holding device. BFV is recorded at baseline, and for 15-20 minutes after the injection of AZ in a peripheral vein. The usual dose of AZ is 1000 mg, but it can be adjusted according to body weight for improved standardization. The effect of AZ is apparent after 2 minutes, and velocities reaches maximum level 10-15 minutes after AZ is injected.[300] CVR is reported as absolute change in velocity, or as percentage change. In medical literature, the range of CVR in healthy subjects assessed with TCD and AZ is wide. CVR has been reported to be between 34 and 65%, with velocity increase from 55 to 72 cm/s at baseline, to 76 to 97 cm/s after stimulation with AZ.[269, 294, 300-310] A normal response with elevated MCA velocitites after AZ injection is illustrated in Figure 14.

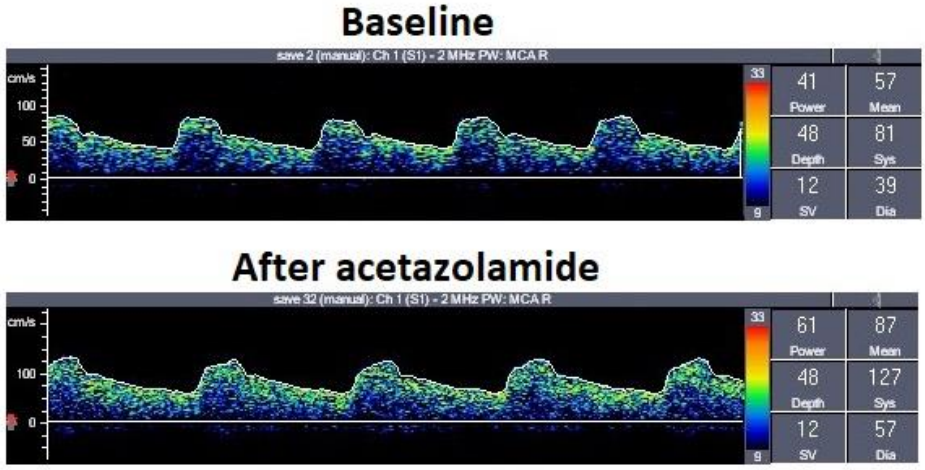

Figure 14. CVR test with transcranial Doppler and acetazolamide

Mean flow velocity (MFV) in the right middle cerebral artery was 57 cm/s at baseline, and 87 cm/s after injection of 1000 mg acetazolamide. Cerebrovascular reactivity (percentage change in MFV after administration of acetazolamide) is thus 52.6%. This result is within the normal range, and indicates an intact vasoregulating capacity. *Note that the y-axis has a different scale for velocities in the two images (upper limit

of 150 and 200 cm/s before and after AZ, respectively). Image by Marianne Lundervik Bøthun, all rights reserved.

In contrast to the normal response with significantly increased velocities after AZ, diminished CVR (lesser velocity increase) or exhausted CVR (no velocity increase), are considered to be pathological responses. In severely pathological cases, AZ can even cause “steal phenomenon”, a paradoxal reduction of blood flow velocitites in severely constricted arteries. Arterioles distal to unaffected arteries have normal dilating capacity, whereas arterioles distal to constricted arteries are already maximally dilated and have exhausted their ability to dilate further. Velocities in the constricted artery will thus be reduced after AZ injection, since blood flow is diverted to (or “stolen” by) unaffected arteries. Such hemodynamic steal phenomenon can lead to clinical deterioration and worsening of cerebral ischemia.[293, 311]

Contraindications for AZ include sulfonamide allergy, severe renal or hepatic disease, adrenal or pituitary insufficiency, and elevated intracranial pressure. Possible side effects are usually transient and well tolerated, and include facial dysesthesias, headache, cranial fullness, flushing, dizziness, and nausea.[295]

9. AIMS

The overall aim of this thesis was to investigate how neurosonological examinations can aid in risk assessment of 1) rupture of intracranial aneurysms and 2) development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Specifically, we wanted to study the two ultrasonographic parameters "carotid intima-media thickness" (IMT) and "cerebrovascular reactivity" (CVR) in patients with intracranial aneurysms. The exact aims of each paper are listed below.

Paper I - Carotid intima-media thickness in patients with intracranial aneurysm

- Investigate carotid IMT and known risk factors for aneurysm rupture in patients treated for ruptured and unruptured intracranial aneurysms
- Compare carotid IMT in patients with aneurysmal subarachnoid hemorrhage with IMT in patients with unruptured intracranial aneurysms, to assess if IMT may be associated with aneurysm rupture risk

Paper II - Cerebrovascular reactivity after treatment for unruptured aneurysms

- Describe CVR in patients after treatment for unruptured intracranial aneurysms, assessed by transcranial Doppler and acetazolamide test
- Assess how characteristics of the patient, aneurysm and treatment modality affect CVR

Paper III - Time-course of cerebrovascular reactivity in patients with unruptured aneurysms

- Compare CVR examined within the first week after aneurysm treatment with CVR re-examined one year later, in order to elucidate the time-course of CVR in patients with unruptured intracranial aneurysms

- Assess whether factors like age, sex, smoking, hypertension, body mass index, treatment side, or treatment modality are associated with the stability of CVR over time

Paper IV - Cerebrovascular reactivity and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

- Investigate if impaired CVR can predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage.
- Determine the relationship between aneurysm rupture status and CVR assessed by transcranial Doppler and acetazolamide test, in order to expand knowledge and improve understanding of CVR in this patient group.

10. METHODS

10.1 Hospital structure and study population

Haukeland University Hospital is a tertitary referral hospital with a catchment area of 1.1 million inhabitants (2017), located on the southwestern coast of Norway. Department of Neurosurgery has 27 beds, including 7 surveillance beds in an intermediate unit (NOVA). Approximately 90 patients with intracranial aneurysms are treated annually.

10.2 Selection of patients

All patients in this thesis are selected from patients treated for saccular intracranial aneurysms at the Department of Neurosurgery, Haukeland University Hospital between February 2011 and May 2013. Patients with non-saccular aneurysms (fusiform, mycotic, blister-like, dissection and traumatic) were not included. The selection process for individual papers is presented below.

Paper I (intima-media thickness) included patients treated for ruptured and unruptured aneurysms between February 2011 and August 2012. The single exclusion criterion for patients in this study was previous aneurysm treatment. Exclusion criteria relevant for CVR-studies (insufficient bone window, contraindications for acetazolamide, and treatment with proximal artery occlusion) did not apply for this paper.

This paper also presents data from healthy control subjects. Controls were spouses and partners of ischemic stroke patients ≤60 years enrolled in the Norwegian Stroke in the Young Study (NOR-SYS) between September 2010 and August 2012.[312] Exclusion criteria for controls were known cardio- and cerebrovascular disease.

The number of patients in the study was 69, of which 41 were treated for ruptured aneurysms and 28 were treated for unruptured aneurysms. The number of controls was 80.

Paper II (**cerebrovascular reactivity**) included patients treated for unruptured intracranial aneurysms at our department between February 2011 and May 2013. Patients not eligible for CVR-testing due to lack of transtemporal bone window or contraindications to acetazolamide (AZ) were excluded from the study. Since CVR-results can be affected by the presence of moderate to severe carotid stenosis and treatment of giant aneurysms with proximal artery occlusion, patients with these conditions were excluded. To reduce possible influence of former aneurysm treatments on CVR, patients with previous treatment of intracranial aneurysms were also excluded. The number of patients in this study was 37.

Paper III (**time-course of cerebrovascular reactivity**) was a follow-up study of patients in Paper II. Inclusion period, inclusion criteria and exclusion criteria were identical to those used in Paper II. The number of patients was reduced from 37 in Paper II to 34 in Paper III due to loss of follow-up of three patients.

In **Paper IV (cerebrovascular reactivity and delayed cerebral ischemia)** patients treated for ruptured and unruptured aneurysms were included. Inclusion period were the same as in Paper II and III (from February 2011 to May 2013). In addition to previously mentioned contraindications for AZ, increased intracranial pressure due to intracerebral hematoma or edema is also relevant for patients with aSAH. Two additional exclusion criteria for patients with aSAH were used in Paper IV. Firstly, moribund patients were excluded for ethical reasons. Secondly, patients with vasospasm or delayed cerebral ischemia present at admission were excluded since injection of AZ can cause steal phenomenon and cerebral ischemia in patients with established vasospasm. The number of patients in this study was 79, of which 42 were treated for ruptured aneurysms and 37 were treated for unruptured aneurysms.

10.3 Patient treatment

Aneurysms were treated with endovascular coiling or surgical clipping. All patients with aSAH were given nimodipine to prevent or treat delayed cerebral ischemia,[54, 180] regardless of presence of ischemic symptoms or not. The standard dose of Nimodipine was 60 mg given orally every four hours, for a minimum of two weeks. In critically ill patients, or in cases with swallowing difficulties, intravenous infusion of 2 mg/h was used. Intraarterial administration was applied in patients with severe and refractory radiographic vasospasm and clinical deterioration due to DCI.[313] Results of ultrasound examinations did not influence DCI management in patients.

10.4 Data collection

The thesis is based on a prospective observational study of patients treated for saccular intracranial aneurysms at the Department of Neurosurgery, Haukeland University Hospital between February 2011 and May 2013. Patients were readmitted for follow-up examinations one year after treatment. Clinical, radiographic and ultrasonographic data were obtained. Details on retrieved data are presented in the following sections.

10.5 Clinical assessment

Information regarding patient demography, aneurysm location, and treatment modality (clipping or coiling) was registered for all patients. Traditional vascular risk factors were also registered: hypertension (previously diagnosed and treated or systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg persistently observed during admission and after the acute phase), smoking status (current, previous or never), diabetes mellitus, dyslipidemia, and body mass index. During hospital stay and follow-up patients underwent neurological examinations to evaluate

neurological status, and to detect and monitor clinical deterioration due to delayed cerebral ischemia. Clinical assessment included thorough neurological examinations and the use of The National Institutes of Health Stroke Scale (NIHSS),[314, 315] a standardized assessment tool for stroke related neurologic deficit. Neurological status was scored routinely three times a day, and more frequent as regarded necessary. The Ph.D. candidate (MLB), medical doctors and nurses at the Department of Neurosurgery, Haukeland University Hospital performed the clinical assessments, and was trained specifically for this purpose.

In patients with aSAH the clinical status upon admission was evaluated with Glasgow Coma Scale (GCS),[316] and World Federation of Neurological Surgeons (WFNS) scale.[317] The doctor on call graded the clinical status upon admission, and the Ph.D. candidate (MLB) reviewed results.

10.6 Radiographic assessment

All patients underwent cerebral computed tomographic (CT) scans and CT angiography prior to aneurysm treatment. Some patients with unruptured aneurysms also had digital subtractions angiography and/or MRI with angiography done as part of their pretreatment assessment. In patients with aSAH, findings in the cerebral CT scan at admission were classified according to the modified CT Fisher scale.[286]

During hospital stay we obtained neuroimaging on admission, postoperatively, at the time of any clinical change, and before discharge. The imaging modality with best suitability according to the clinical situation was used (CT, CTA, MRI, MRA, or DSA).

Angiography (CTA or digital subtraction angiography) was performed upon admission to locate the aneurysm, and during the hospital stay to diagnose or treat vasospasm. An experienced neuroradiologist (GM) assessed all angiograms, CT and

MRI scans retrospectively for the presence of angiographic vasospasm and cerebral infarctions.

In paper III and IV, an experienced neurosurgeon with vascular expertice (CAH) measured aneurysm size using the following parameters: maximal diameter of the dome- independent of angles and directions (maximal diameter, Dmax), maximal diameter of the dome- perpendicular to the aneurysm height (width, W), maximal height from dome tip perpendicular to aneurysm neck (height, H), and diameter of the aneurysm neck (neck, N). Aspect ratio (H/N) and bottleneck ratio (W/N) were calculated.[318, 319]

At follow-up 1 year after aneurysm treatment, patients underwent MRI with time of flight (TOF) angiography.

10.7 Ultrasonographic assessment

In paper I-IV, three ultrasonographic examinations were performed in patients treated for intracranial aneurysms: 1) extracranial duplex sonography with measurement of carotid intima-media thickness; 2) transcranial color-coded duplex sonography to assess blood flow velocities in intracranial arteries; and 3) cerebrovascular reactivity testing using transcranial Doppler and acetazolamide. In paper I, carotid intima-media thickness was also assessed in healthy partners of young patients with ischemic stroke as part of The Norwegian Stroke in the Young Study (NOR-SYS).[312]

10.7.1 Carotid intima-media thickness

In paper I, high resolution B-mode sonography of carotid arteries was performed in patients treated for ruptured and unruptured intracranial aneurysms. Healthy partners of young patients with ischemic stroke were used as controls, since they were already

included in another onoing study (NOR-SYS, The Norwegian Stroke in the Young Study, ClinicalTrials.gov Identifier: NCT01597453).[312]

Patients were examined with a portable Phillips CX50 ultrasound system, and 12-3 MHz linear array transducer. Controls were examined with a non-portable Phillips iU22, and 9-3 MHz linear array transducer (Philips Medical Systems, Bothell, WA, USA).

When examined with carotid ultrasound, subjects were placed in the supine position with the head rotated 45° to the opposite side of the probe. IMT was measured at the longitudinal view of the distal common carotid artery (CCA), carotid bifurcation (BIF) and the proximal internal carotid artery (ICA).

The tip of the flow divider (the dividing point of the internal and external carotid artery) was used for standard positioning and definition of the ICA, BIF and CCA segments. CCA were defined as 20-10 mm proximal to the tip of the flow divider, BIF 10-0 mm proximal to the tip of the flow divider and ICA 0-10 mm distal to the tip of the flow divider. IMT was measured on the far wall, from the interface between blood and tunica intima and the interface between tunica media and tunica adventitia.

We used Q-lab® software (Advanced Ultrasound Quantification, Philips Medical Systems, Bothell, WA, USA) for semiautomated border detection of IMT as the mean value over a 10 mm long segment (Figure 15).

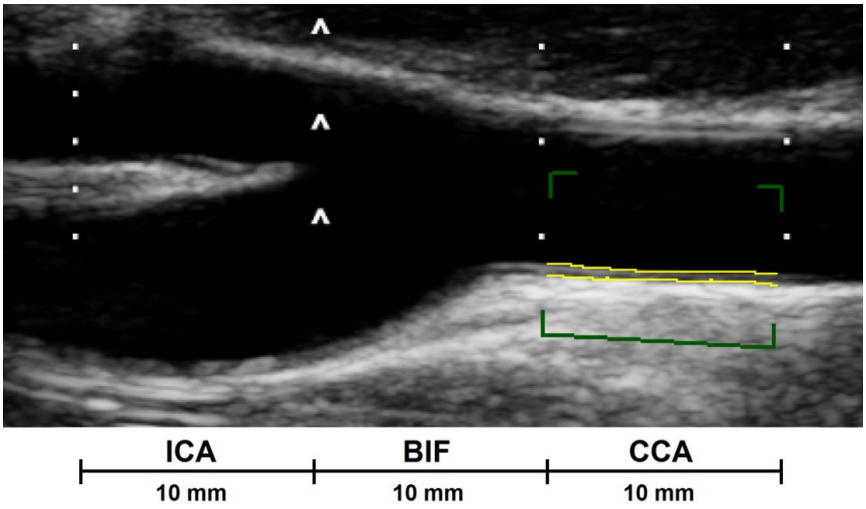

Figure 15. B-mode ultrasound image showing a longitudinal view of the carotid artery

Measurement of carotid intima-media thickness (IMT) on the far wall of a 10 mm long segment of the common carotid artery using semiautomated border detection (yellow outlining). Reprinted with permission of International Journal of Stroke, World Stroke Organization and Blackwell publishing; all rights reserved.[320]

^ Tip of the flow divider
ICA: internal carotid artery
BIF: carotid bifurcation
CCA: common carotid artery

In controls, IMT measurements was obtained at end-diastole to avoid stretching effects during systole resulting in IMT reduction,[321] and Meijer's Carotid Arc® (Bio-Imaging Technologies, B.V., Leiden, the Netherlands)[322] was used for standardization of measurement angles (Figure 16). Images were taken at 90º, 120º, 150º and 180º in the right CCA segment, and at 270º, 240º, 210º, and 180º in the left CCA segment.

IMT-measurements in BIF and ICA segments were performed at the angle representing the site of maximal IMT thickness.

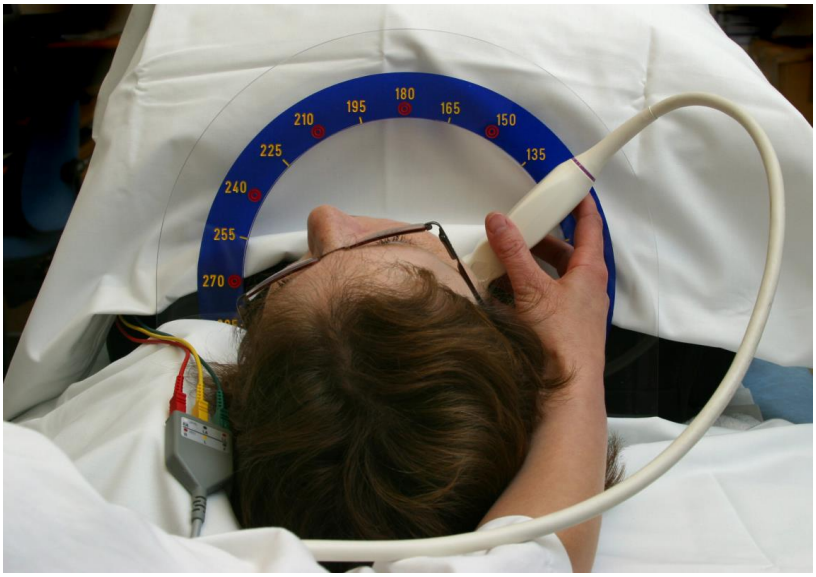

Figure 16. Carotid imaging at prespecified angles

Meijer's Carotid Arc® (Bio-Imaging Technologies, B.V., Leiden, the Netherlands)[322] was used to determine measurement angles when imaging the carotid artery of control persons. Reprinted with permission of International Journal of Stroke, World Stroke Organization and Blackwell publishing; all rights reserved.[320]

In patients with intracranial aneurysms, a simplified scanning protocol was used due to neck stiffness, confusion, reduced patient cooperation abilities, and technical challenges in an intensive care unit setting in patients with aSAH. EKG-monitoring to assess IMT at specific time points during the cardiac cycles was not performed, and images of all segments (CCA, BIF and ICA) were only obtained at the angle representing the most significant pathological IMT, and not at prespecified angles.

10.7.2 Transcranial color-coded sonography

Transcranial color-coded duplex sonography (TCCS) was performed in all patients to assess the transtemporal bone window, visualize intracranial vessels, and perform measurements of blood flow velocities. Patients with aSAH underwent repeated TCCS examinations to detect and monitor sonographic vasospasm. Examinations were performed as often as possible when the sonographer was available, preferably daily and more frequent if neurological deterioration occurred. In patients with UIA, TCCS were performed less frequent, usually once or twice during the hospital stay.

Intracranial cerebral arteries were examined bilaterally through the acoustic windows in the squama of temporal bone. A S5-1 probe (iU22, Phillips Medical Systems, Bothell, WA, USA) was used to measure blood flow velocities in the major cerebral arteries (middle, anterior and posterior cerebral arteries, and internal carotid arteries). Lindegaard Index[256] was calculated. Angle correction was performed when appropriate. For practical reasons, since reduced cooperation skills and neck stiffness is common in the acute phase after aSAH, assessment through the foraminal bone window was not done. Color images with corresponding Doppler curves and velocities were recorded.

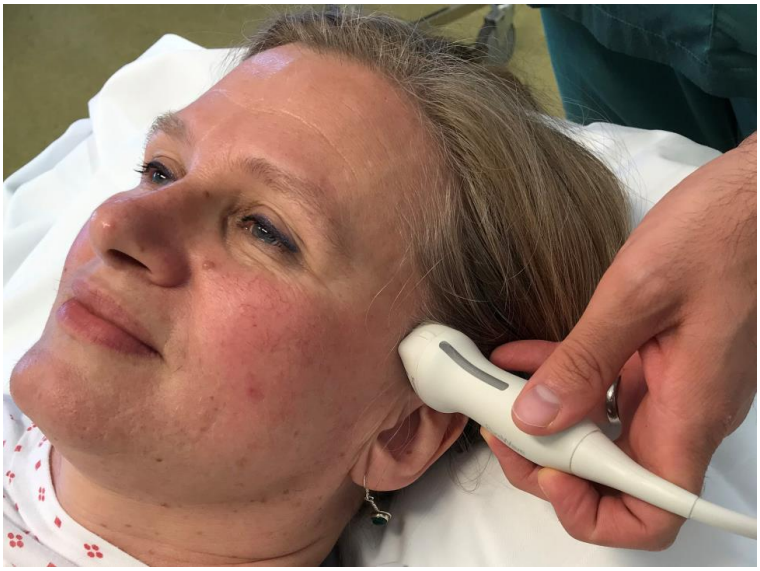

Figure 17. Transcranial color-code duplex sonography examination using transtemporal approach

Image by Bergen Stroke Research Group and Nicola Logallo, all rights reserved.

10.7.3 Cerebrovascular reactivity assessed by transcranial Doppler and acetazolamide

Cerebrovascular reactivity was examined using the transcranial Doppler and acetazolamide test. Patient management was not influenced by CVR results. Patients were examined in the supine position, since posture can affect velocity measurements.[323, 324] Bilateral transtemporal approach and 2 MHz probes (Companion III Nicolet Vascular, Madison, WI, USA) were used to assess mean blood flow velocities (MFV) in the middle cerebral arteries. The site with the best available signal from the MCA was chosen, at an insonation depth between 45 and 60 mm. A headband was used to secure the ultrasound probes to the patient's head (Welder TCD Headband, VIASYS Healthcare, Madison, WI, USA) (Figure 18).

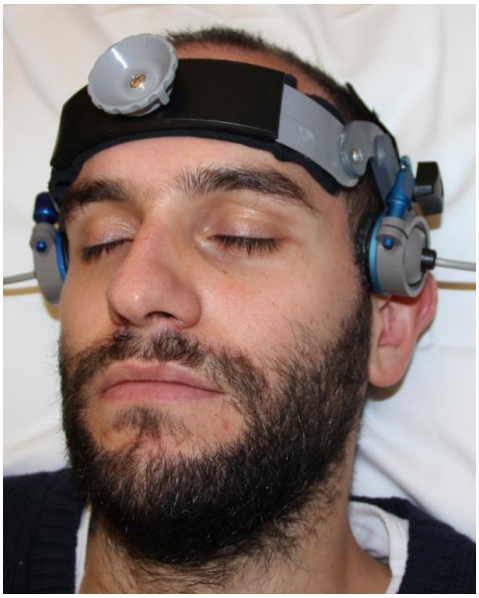

Figure 18. Headband used for cerebrovascular reactivity testing
Probes are applied and fixed over the transtemporal windows bilaterally. Image by Bergen Stroke Research Group and Marianne Lundervik Bøthun, all rights reserved.

First, stable baseline blood velocities in both MCAs were measured. Then acetazolamide (Diamox Goldshield Ltd., Croydon, Surrey, UK; Diamox Sanofi Aventis, Paris, France, or Mercury Pharmaceuticals Ltd., Croydon, Surrey, UK) was injected intravenously over the time-course of one minute. MFV was monitored continuously, and Doppler curve images were saved at baseline and every five minutes after the AZ injection. If velocity plateau phase was established, the examination was concluded after 15 minutes. If not, monitoring was continued for up to 30 minutes. The AZ dose was 1000 mg for patients with body weight <80 kg. For patients weighing ≥80 kg AZ was given in a dose of 15 mg/kg bodyweight, with a maximum dose of 1500 mg.

Cerebrovascular reactivity was calculated as the maximum percentage change in MFV in MCA after administration of acetazolamide: CVR (%) = [(MFV_{AZ} – $MFV_{BASELINE}$) / $MFV_{BASELINE}$] x 100, where CVR is cerebrovascular reactivity, $MFV_{BASELINE}$ is mean blood flow velocity before acetazolamide and MFV_{AZ} is mean blood flow velocity (maximum change) after acetazolamide. In patients with a paradoxical velocity reduction after AZ due to a steal phenomenon, CVR will be a negative value.

Blood flow velocities and CVR for the right and left sides were recorded separately. The set-up is illustrated in Figure 19. The figure shows blood flow velocity changes and Doppler curves during acetazolamide (AZ) test for a single patient treated with clipping of an unruptured right middle cerebral artery (MCA) aneurysm.

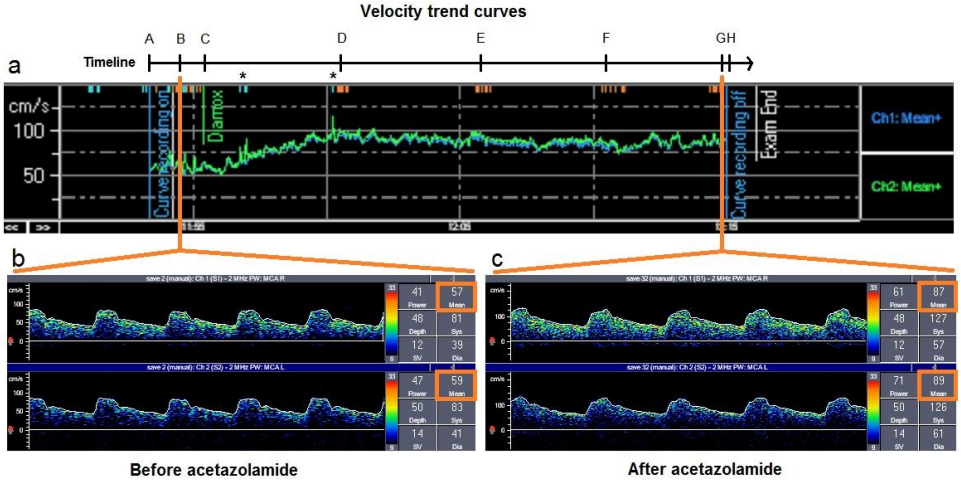

Figure 19. Timeline and changes in blood flow velocities during the transcranial Dopppler and acetazolamide test

The trend window (a) shows mean flow velocities (MFV) in MCA over time on the right (blue line) and left side (green line). MFV was monitored continuously, from the beginning (A) to the end of the recording (H). Doppler curve images were saved at baseline (B) and 5, 10, 15 and 20 minutes after AZ injection (D, E, F, and G). AZ was

given intravenously (C). Shortly after the injection, velocities increased before reaching a maximum level and plateau phase. Velocities were symmetrical in the right and left MCA throughout the test. Brief spikes misleadingly indicating rapid velocity increase approximately two and five minutes after AZ are artefacts caused by change of the display velocity range (*). Doppler curves captured at baseline (B) and 20 minutes after stimulation with AZ (G) are presented in the lower parts of the figure (b and c, respectively). Upper Doppler curves correspond to right MCA, lover curves to left MCA. MFV increased from 57 cm/s in the right MCA in image b, to 87 cm/s in image c. MFV on the left side increased from 59 to 89 cm/s. Note the difference in velocity range in the y-scale in the two images (upper limit of 150 and 200 cm/s before and after AZ, respectively). Image by Marianne Lundervik Bøthun, all rights reserved.

10.8 Assessment of vasospasm and delayed cerebral ischemia

Patients underwent clinical, radiographic and sonographic examinantions as described in previous sections. Results of these examinations were used to determine the presence or absence of vasospasm and delayed cerebral ischemia (DCI). We used the recommended definitions of clinical deterioration and cerebral infarction due to DCI.[152, 153] Detailed describtion of the definitons was presented in section 7.3.

Angiographic vasospasm was defined as arterial narrowing present on CTA, MRA or DSA, not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia. Angiographic vasospasm was classified as none, mild (1-33% reduction in arterial diameter), moderate (34% - 66% reduction) or severe (≥67% reduction). The angiographic grading scale ad modum Nathal was also applied,[325] where grade 0 is no evidence of vasospasm; grade 1 is vasospasm in one vascular axis; grade 2 is vasospasm in two vascular axes; grade 3 is vasospasm in three vascular axes; and

grade 4 is generalized or diffuse vasospasm. The vascular axes were defined as follows: a) internal carotid artery, b) middle cerebral artery, c) anterior cerebral artery (pre- and post-communicating segments), d) vertebral artery, e) basilar artery, f) posterior cerebral artery, and g) any other arterial territory (e.g. posterior cerebellar artery, superior cerebellar artery).

Sonographic vasospasm was defined as increased blood flow velocities on TCCS, with time averaged mean of the peak velocity (TAPV) ≥120 cm/s in any cerebral artery and Lindegaard index ≥3.[256] Severe angiographic vasospasm was defined as TAPV ≥200 cm/s and Lindegaard index ≥6.

10.9 Neurosonographic setting, training and data reliability tests

In **paper I**, one sonographer (MLB) performed carotid ultrasound of patients with IAs, whereas two other sonographers (AF, UWA) examined control subjects. All three sonographers are certified in ultrasound examination of carotid arteries by the Vascular Imaging Center, University Medical Center, Utrecht, The Netherlands.

One sonographer (MLB) performed all transcranial ultrasound examinations and CVR-testing in **paper II-IV**.

In **paper I-IV**, TCCS and carotid ultrasound of patients with intracranial aneurysms were performed with a portable Phillips CX50 ultrasound system and respectively S5-1 sector and 12-3 MHz linear array transducer. **In paper I**, carotid ultrasound of control subjects in was performed with a non-portable Phillips iU22, and 9-3 MHz linear array transducer (Philips Medical Systems, Bothell, WA, USA).

In **paper I**, intra-observer, inter-observer and interequipment reliability for IMT measurements were assessed and found to be satisfactory, with high level of reproducibility (correlations between 0.78 and 0.98).

10.10 Data analysis and statistics

In all papers, we used standard statistical methods, and an α–level of 0.05 as level of significance in all calculations.

In **paper I**, statistical analysis was performed with R version 2.15.1.[326] The main analyses were conducted using both unadjusted and adjusted multinomial logistic regressions, and relative risk ratios with 95% confidence intervals were calculated. A binary logistic regression was also used to analyze the relationship between aSAH and UIA with respect to IMT. Odds ratios with 95% confidence intervals were calculated.

In **paper II**, statistical analysis was performed with R version 3.2.2.[326] A paired t-test did not reveal any significant side-difference, mean CVR across right and left side was thus used as an overall measure of CVR. (Note that the lack of side-difference, and accordingly the use of mean values of both sides, is not consistent with what we found in Papers III and IV. See Section 12.4.3 for thorough discussion.) The relationships between mean CVR and a number of variables were then assessed using simple and multiple linear regression, as well as two-sample t-tests.

In **paper III**, statistical analysis was performed with R version 3.4.3.[326] We used standard and paired t-tests, as well as simple and multiple linear regression.

In **paper IV**, statistical analysis was performed with R version 3.4.3.[326] To examine the relationship between CVR and rupture status, we used standard t-tests and multiple regression analyses. We compared a number of properties of patients with

and without clinical deterioration using the t-test, chi-squared test or Fisher's exact test, as appropriate. Prediction models for clinical deterioration were created using logistic regression. Model discrimination was assessed with area under the receiver operating characteristic (ROC) curve, and model calibration with Hosmer-Lemeshow's C and calibration plots.[327] Results were adjusted for optimism using bootstrapping techniques.[328]

10.11 Ethical considerations

All patients or legal representatives received oral and written information about the study, and signed a written informed consent form. The study was conducted in accordance with the Declaration of Helsinki (2000/2013) of the World Medical Association, and was approved by the local ethics committee (the Regional Committees of Western Norway for Medical and Health Research Ethics, approval number 2011/144).

11. SUMMARY OF PAPERS

In the following, abstracts giving a brief account of the articles included in this thesis are presented.

11.1 Paper I: Carotid intima-media thickness in patients with intracranial aneurysms

Background: Individual assessment of rupture risk of cerebral aneurysms is challenging, and increased knowledge of predictors for aneurysm rupture is needed. Smoking and hypertension are shared risk factors for atherosclerotic disease and cerebral aneurysms, and patients with atherosclerosis have an increased prevalence of intracranial aneurysms.

Carotid ultrasound with evaluation of intima-media thickness (IMT) is a non-invasive, safe, rapid, well-validated and reproducible technique for quantification of subclinical atherosclerosis and assessment of cardio- and cerebrovascular risk. Increased IMT is associated with elevated risk for ischemic stroke and myocardial infarction, but sparse data exist on carotid ultrasound findings in patients with intracranial aneurysms.

Aims: The purpose of this study was to investigate carotid IMT in patients with unruptured intracranial aneurysms (UIA) and aneurysmal subarachnoid hemorrhage (aSAH), and to assess if IMT might be associated with aneurysm rupture risk.

Methods: Patients treated for saccular aneurysms (UIA and aSAH) between February 2011 and August 2012 were included. Standardized high resolution B-mode ultrasound assessment of carotid arteries was done after aneurysm treatment, and traditional vascular risk factors were recorded. Healthy partners of young patients with ischemic stroke were used as controls.

Results: 69 patients treated for UIA (n=28) and aSAH (n=41) were compared with 80 controls. Mean IMT was higher in patients with aSAH (0.79 mm) than patients with UIA (0.65 mm) and controls (0.63 mm). Multiple multinomial regression analysis comparing aSAH, UIA and control groups demonstrated that IMT was the only variable predicative of aSAH compared to UIA. According to the multiple regression model, the probability of having aSAH compared to non-rupture increased by 62% for each 0.10 mm increment of mean IMT (RRR=1.62, p=0.017). Taking into account only patients harboring intracranial aneurysms, simple binary logistic regression was then applied to the UIA and aSAH groups. According to this model the risk of belonging to the aSAH group increased with higher mean IMT values (OR=1.40 per 0.10 mm increase of mean IMT, p=0.024).

Conclusion: There is an association between IMT and intracranial aneurysm rupture status at the time of aneurysm treatment. Carotid IMT can be a potential predictor of aneurysm rupture. IMT may thus be a possible adjunct in the risk assessment of aneurysm rupture, and a helpful tool in patient risk stratification and counseling.

11.2 Paper II: Cerebrovascular reactivity after treatment for unruptured aneurysms

Background: Cerebrovascular reactivity (CVR) is defined as the change in cerebral blood flow, or blood velocity, in response to a vasoactive stimulus. There is a possible association between impaired CVR and vasospasm after aneurysmal subarachnoid hemorrhage. Most studies on CVR and vasospasm have used healthy subjects as reference. However, due to potential different vascular features, CVR in persons with intracranial aneurysms may differ from CVR in healthy subjects. Therefore, our aim was to examine CVR in patients with unruptured intracranial aneurysms (UIA).

Methods: CVR was examined in 37 patients in the first postoperative week after treatment for UIA, using acetazolamide (AZ) test with transcranial Doppler monitoring of blood flow velocities.

Results: Mean blood flow velocity in the middle cerebral arteries was 58.5 (SD 12.8) cm/s at baseline, and 94.3 (SD 19.5) cm/s after stimulation with AZ. Mean CVR was 62.6 (SD 16.8) %. There was no significant difference when comparing right and left sides, and treated and untreated sides. A simple regression analysis suggested that CVR increased with 0.7 percent points for each year a patient aged (p=0.004). However, the significance disappeared in a multiple analysis (increase of 0.6 percent points per year, p=0.055). Other possible influencing factors (gender, smoking, hypertension, body mass index, aneurysm location and treatment modality) were not significantly associated with CVR.

Conclusions: CVR in patients with UIA is not different from normal values reported in healthy subjects, and does not indicate a systemically impaired vascular system in patients with UIA. We suggest that CVR in age and gender matched healthy controls can be used as reference for persons with intracranial aneurysms.

11.3 Paper III: Time-course of cerebrovascular reactivity in patients with unruptured aneurysms

Background: Cerebrovascular reactivity (CVR) is often impaired in the early phase after aneurysmal subarachnoid hemorrhage. There is, however, little knowledge about the time-course of CVR in patients treated for unruptured intracranial aneurysms (UIA).

Methods: CVR, assessed by transcranial Doppler and acetazolamide test, was examined within the first postoperative week after treatment for UIA, and re-examined one year later.

Results: Of 37 patients initially assessed, 34 were re-examined after one year. Bilaterally, baseline and acetazolamide-induced blood flow velocities were higher in the postoperative week compared with one year later ($p<0.001$). CVR on the ipsilateral side of treatment was lower in the initial examination compared with follow-up (58.9% vs. 66.1%, $p=0.041$). There was no difference in CVR over time on the contralateral side (63.4% vs. 65.0%, $p=0.652$). When mean values of right and left sides were considered together, there was no difference in CVR between exams. Aneurysm clipping was associated with 15.5%-points increased change in CVR compared with coiling ($p=0.025$).

Conclusion: Patients with UIA may have a temporary reduction in CVR on the ipsilateral side after aneurysm treatment. The change in CVR appears more pronounced in patients treated with clipping. We recommend that ipsi- and contralateral CVR should be assessed separately, as mean values can conceal side-differences.

11.4 Paper IV: Cerebrovascular reactivity and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

Background: Delayed cerebral ischemia (DCI) is a major cause of disability and death after aneurysmal subarachnoid hemorrhage. The literature suggests that impaired cerebrovascular reactivity (CVR) may be a predictor for DCI; still no CVR based prediction model has been developed. Increased knowledge about possible predictors of DCI can improve patient management in high-risk patients and allow for shorter hospital stay in low-risk patients.

Methods: CVR was examined in 42 patients with aneurysmal subarachnoid hemorrhage and 37 patients treated for unruptured intracranial aneurysm, using acetazolamide test with transcranial Doppler monitoring of blood flow velocities. Patients were followed for development of DCI, separated into clinical deterioration and radiographic infarction.

Results: For all patients, regardless of aneurysm rupture status, CVR was on average 5.5 percentage points lower on the ipsilateral side of aneurysm treatment. Patients with clinical deterioration due to DCI had lower CVR than patients without DCI, and the difference was larger on the contralateral side (33.9% vs. 49.2%). Two prediction models were constructed for clinical deterioration due to DCI. The area under the receiver operating characteristic curve was 0.82 in the model using established predictors, and 0.86 in the model that also included CVR.

Conclusion: Our findings support the hypothesis that impaired CVR may be an independent predictor of clinical deterioration due to DCI, and may assist in identifying patients at risk after aneurysmal subarachnoid hemorrhage. Ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of DCI development, thus highlighting the need to evaluate ipsi- and contralateral CVR separately.

12. DISCUSSION

The results of the research included in this thesis are discussed in the separate articles. This discussion is therefore mainly limited to a discussion of methodological aspects, as well as overall overview of key findings and future perspectives.

12.1 Study population and selection of patients

In our study population, the proportion of endovascular treatment was in the upper range for Western Norway at the time of the study. In **Paper I**, 61% of patients were treated with coiling, and in **Paper II-IV** the endovascular proportion was 60-66%. In 2008-2013, approximately 60% of patients with aSAH admitted in the Department of Neurosurgery, Haukeland University Hospital, were treated with endovascular coiling and 40% with surgical clipping. For elective aneurysm treatment the proportion of patients treated with coiling was somewhat lower (rough estimate 50%). Noteworthy, the overall proportion of endovascular treatment has increased to 70% in recent years (2014-2017), due to increased availability and advances in this treatment modality. A likely explanation for the high proportion of endovascular treatment in CVR studies in **Paper II-IV** is that intracranial air after surgical treatment may hamper ultrasound insonation and CVR-testing. In **Paper IV**, the proportion of endovascular treatment was higher in patients with aSAH compared with patients with UIA (71% vs. 60%). This reflects the higher rate of endovascular treatment in acute settings. Furthermore, patients with hematomas and increased intracranial pressure were excluded from CVR-testing. As larger fractions of these patients undergo open surgery with clip ligation, this also likely contributed to the high proportion of endovascular treatment.

Apart from the high proportion of endovascular treatment, the characteristics of treatment modality and patient demography in the studied populations seems

representative of a typical cohort of patients with IAs. Mean age was 49-55 years and the proportion of females was high (58-68%), as was current smoking (54-60%) and hypertension (44-49%).

Furthermore, our study population included a high proportion of patients with severe aSAH. In **Paper IV** as many as 43% of patients with aSAH had WFNS IV-V and modified CT Fisher 3-4. Similar clinical grades in treatment populations have been described (WFNS grade IV-V: 38%, Hunt and Hess IV-V: 34%),[329, 330] although poor grade patients often are poorly represented in large trials.[331, 332] Our study population is representative for patients treated for aSAH in the Department of Neurosurgery, Haukeland University Hospital. The high proportion of patients with severe aSAH is likely to increase the incidence of DCI, since the strongest predictors of DCI are large amount of subarachnoid blood detected on CT imaging and poor neurological status upon admission.[55, 166-169]

In **Paper I**, we used healthy partners of patients with ischemic stroke as controls, since they were already included in another ongoing study from the Bergen Stroke Research Group: The Norwegian Stroke in the Young Study (NOR-SYS). In NOR-SYS, carotid IMT was examined in spouses and partners of ischemic stroke patients ≤60 years.[312] Ideally, controls should have been selected randomly from a representative sample of the healthy population. We cannot be certain that controls do not harbor intracranial aneurysms, although we do not expect them to have a higher prevalence than the general population. Still, the control group is not ideal, since partners of patients with ischemic stroke may have similar lifestyle and social status, which can affect their risk of developing IAs. However, controls were significantly different from the UIA and aSAH groups regarding prevalence of hypertension and smoking.

Noteworthy, the number of studied patients in all papers is relatively low (34-79 patients with IAs and 80 controls). A larger study population would increase the

statistical power and reduce uncertainties when assessing results. **Paper I** is a pilot study that indicates that IMT is increased in patients with ruptured aneurysms, but the validity of the results needs to be re-tested in a larger population. For **Paper II-IV**, the number of patients is also rather low, but nevertheless as expected in CVR-studies due to the time- and resource demanding method of investigation.

12.2 Clinical assessment

Several scales are used to assess the level of consciousness and clinical status of patients with aSAH. Some of the scales are developed or adapted specifically for patients with SAH, like the Hunt Hess,[333] World Federation of Neurological Surgeons (WFNS) scales,[317] and Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH).[334] Whereas others are not designed specifically for this patient population, e.g. the Glasgow Coma Scale[316] and National Institutes of Health Stroke Scale (NIHSS).[314, 315] The latter scales are widely used to evaluate and document neurological status in patients with cerebral stroke, regardless of stroke etiology. The reliability and validity of the scales have been found to be adequate,[335-344] although improved quality of future reliability studies would be of value, and the choice of appropriate statistical analyses is of great importance.[345] In our study, all of the scales above were applied. All examiners underwent specific training in how to use the scales.

Nonetheless, the diagnosis of clinical deterioration due to DCI is difficult because of the need to exclude other causes of neurological worsening. In practice, many patients have multiple systemic and nervous system dysfunctions that may, or may not, contribute to DCI making it difficult to separate the effects. Clinical assessment of sedated or comatous patients is even more challenging.

12.3 Radiographic assessments

As a pragmatic choice, there were no pre-arranged routine CT or MRI scans during the hospital stay. Imaging was performed whenever clinically indicated, such as after neurological deterioration, new infarction on CT, or increased TCCS blood blow velocities. Among 42 patients with aSAH, 17 were not evaluated with MRI during their primary hospital stay. As CT has lower sensitivity compared with MRI it is possible that we underdiagnose infarctions with this set-up. Still, MRI was performed in the majority of patients during follow-up. Of the 39 patients alive after one year, 36 underwent MRI; two were tourists and lost to follow-up; and one patient declined to take the exam due to claustrophobia and anxiety. More extensive investigations with a preset time-schedule would have been useful, but was not done in our study.

We used a well-known grading system for classification of cerebral infarctions.[174, 346] Still, it is difficult to determine the cause of infarctions after aSAH[347] and one cannot be certain whether infarctions are related to DCI or not. To avoid misclassifying procedure-related infarcts as vasospasm-induced, it is recommended that CT and MRI scans are performed between 24 and 48 hours after aneurysm occlusion.[152, 153] In our study, this recommendation for timing of postoperative imaging was followed in 33 of 42 patients. For the remaining patients, imaging was performed later than 48 hours.

12.4 Ultrasonographic assessments

Assessment of carotid IMT can be performed quickly and does not involve any discomfort or risks. CVR-testing is more time-consuming, especially when performed multiple times, and may cause discomfort for some patients. Still, CVR provides useful information about vascular regulation, which might guide patient treatment.

The methodological aspects of ultrasonographic assessments are discussed below.

12.4.1 Carotid intima-media thickness

Carotid IMT have been studied in numerous populations using several different measurement methods.[212, 348] There are considerable variations with regards to methods used for image acquisition and analysis. Measurements are performed at the near and far wall, or only far wall. IMT is measured in different parts of the carotid segment, and the definitions of segments vary. Investigations are done unilaterally or bilaterally, mean or maximum values are reported, and measurements are determined manually or by the use of automated systems. There are pros and cons for each measurement protocol. A standardized protocol is strongly recommended.[349, 350]

In our study (**Paper I**),[320] IMT was measured at the far wall. Due to ultrasound properties, the far wall can be better visualized compared with the near wall.[351-353] Carotid IMT measurements can be obtained at the common carotid artery (CCA), the carotid bifurcation (BIF), and the internal carotid artery (ICA). Obtaining adequate images of all segments may be difficult. CCA is perpendicular to the ultrasound beam, is thus more easily accessible and the results have higher reliability compared with BIF and ICA.[209, 354] CCA also yields a lower proportion of missing values compared with BIF and ICA which lie at an oblique angle and are more difficult to image.[350, 354] Studies imply that CCA-IMT has better prediction of stroke,[355] whereas ICA-IMT appears to have better prediction for atherosclerotic cardiac events.[356] Due to the focal nature of atherosclerosis, IMT measurements at one site can be very different from those obtained at another site.[357] Hence, measuring IMT at a single site can reduce the sensitivity of detecting atherosclerotic changes. In our study, IMT was measured bilaterally in all carotid segments (CCA, BIF and ICA), and mean values for all sites were used in the regression models. Carotid segments were defined in the identical manner as in the ARIC study.[214, 216] Since this protocol, like many others, uses anatomical landmarks, it is likely that plaques are incorporated in IMT measurements. The Mannheim consensus have recommended measurement of IMT in

plaque free areas.[350, 351] However, carotid plaques and/or IMT incorporating plaques in their measurements provide additional prognostic information to traditional vascular risk factors, whereas IMT measured in plague-free areas does not.[358]

IMT can be determined manually or by an automated system. The former requires thorough quality control to reduce intra- and inter-observer variability. The latter allows repeated measurements in a short time. In our study, IMT analysis was done with semiautomated border detection by Q-lab® software (Advanced Ultrasound Quantification, PhilipsMedical Systems, Bothell,WA, USA). Ideally, IMT measurements should be obtained at end-diastole since stretching effects due to expansion of the lumen diameter of the carotid artery during systole leads to thinning of IMT.[321, 359] In our study, IMT measurements were only synchronized to the cardiac cycle in controls. IMT values in some patients may have been obtained at end-systole, potentially causing a minor reduction of IMT in patients compared with IMT in controls obtained at end-diastole.

Imaging IMT from a single angle does not completely evaluate the carotid artery in all three dimensions. Extensive ultrasound protocols with examination of IMT at multiple prespecified angles allows for improved evaluation of the degree of atherosclerotic burden. In our study, Meijer's Carotid Arc®[360] was used for imaging of IMR at multiple prespecified angles in control subjects. However, such extensive protocols were considered too demanding in patients due to reduced cooperation skills, neck stiffness, confusion and distress. Patients were therefore examined with a simplified protocol were measurements was obtained at the angle representing the visually most significant pathological IMT.

Patient and controls were examined by different equipment and sonographers. One examiner (MLB) investigated all patients using a portable Phillips CX50 ultrasound system, and 12-3 MHz linear array transducer. Two examiners (AF, UWA) investigated controls using a non-portable Phillips iU22, and 9-3 MHz linear array

transducer (Philips Medical Systems, Bothell, WA, USA). CX50 was chosen for patient examinations due to its portability and smaller size, making it suitable for use in the ICU. Controls were examined with the larger iU22 apparatus as part of the pre-established protocol for the NOR-SYS study (The Norwegian Stroke in the Young Study).[312] Still, the same ultrasound algorithm and software was used to measure IMT in patients and controls (Q-lab® software), and all sonographers underwent the same training and certification in ultrasound examination of carotid arteries by the Vascular Imaging Center, University Medical Center, Utrecht, The Netherlands. Intra-observer, inter-observer and interequipment reliability were assessed and found to be satisfactory, with high level of reproducibility (Table 4).

Table 4. Reproducibility of IMT measurements

	Correlation	Mean absolute difference in IMT (mm)
Intra-observer	0.78-0.98	0.02-0.08
Inter-observer	0.83-0.93	0.04-0.11
Inter-equipment	0.94	0.04

Shortly after **Paper I** was accepted for publication, a new report supportive of our findings was published. As in our study, Dusak and colleagues found that IMT was increased in patient with ruptured IAs.[221] They compared mean IMT in the right CCA in patients with unruptured (n=23) and ruptured (n=26) IAs, and found that IMT was increased in patients with RIA (0.61±0.13 cm) compared with UIA (0.52±0.12 cm), p=0.013. We found that mean IMT was higher in patients with aSAH (0.79 mm) than patients with UIA (0.65 mm) and controls (0.63 mm).[320] Regression analysis demonstrated that IMT was predicative of aSAH compared to UIA. The results of Dusak and colleagues[221] strongly supports our hypothesis that carotid IMT is a potential predictor for rupture risk of intracranial aneurysms.[320]

12.4.2 Transcranial ultrasound

We chose to use TCCS for assessment of sonographic vasospasm instead of TCD, since the imaging-method facilitates vessel identification and offers the opportunity for angle-correction, resulting in more accurate measurement of blood flow velocities. The threshold levels for increased veolocity indicating vasospasm is however defined based from results of TCD studies (mean flow velocities), not TCCS (time-averaged peak flow velocities). Angle-corrected velocities obtained from TCCS are approximately 10% to 30% higher than those obtained from TCD,[251, 361] and may lead to overestimation of sonographic vasospasm when using criteria established using conventional TCD. There is a lack of large studies correlating angle corrected velocities to angiographic vasospasm. Acordingly, some sonographers choose not to use angle-correction when performing TCCS, but attempt to obtain as narrow an angle of insonation as possible using image guidance. In our study, we chose to use angle-correction, as we believe this gives a velocity closer to the "true" value.[251] Still, for CVR testing TCD was used due to the possibility for continuous bilateral monitoring of velocities over time with at a fixed position using a headband.

12.4.3 Cerebrovascular reactivity

It is challenging to interpret CVR results for several reasons.

Firstly, the normal range for AZ induced CVR is very wide (see Table 6 in **Paper II**).[269, 294, 300-310] A possible explanation is that AZ may induce moderate hyperventilation in some individuals, which could counteract the vasodilatory effect of the drug. This large variation in velocity response may affect repeatability and accuracy of the test. There is a lack of proper reliability studies for AZ-TCD CVR testing. Nevertheless, reproducibility of TCD measurements of blood flow velocities in MCA have been thouroghly studied and found to be satisfactory,[362-365] and AZ has been used in CVR studies for decades.[295] In our study, one sonographer (MLB)

performed all CVR tests and used the same equipment in all examinations. Intra-observer reliability was however not tested.

Secondly, the data size is often small and reduces the study power. CVR testing with TCD and AZ is time- and resource demanding and it is therefore common with small study populations, as is the case in our study. Technical aspects of the method also limit the number of patients available for testing after aneurysm treatment, since postoperative intracranial air hampers insonation of patients treated with clipping. Our interpretation of collected CVR data developed as more data were acquired. In **Paper II**, we concluded that CVR in patients treated for UIA did not differ from reported values of healthy subjects and that no significant side-difference was found. As mentioned, the normal range of CVR is, however, very wide and the original study size was small. In **Paper III**, we re-tested CVR in the same patients at follow-up one year after aneurysm treatment. Doubling the amount of data, with two exams per patients instead of one, increased statistical power and provided new insight. Supplementary data revealed that there was a side-difference after all, and that CVR was temporarily reduced on the ipsilateral side shortly after aneurysm treatment.

Thirdly, CVR is assessed by multiple measurement methods and vasoactive stimuli, [266] making it difficult to compare results between studies. In our opinion, the AZ-TCD method offers several advantages compared with other methods and is more convenient to use. Instrumentation and set-up is simpler compared with methods measuring cerebral blood flow and/or using CO_2 as vasoactive stimuli. Furthermore, AZ-TCD test can be performed in non-cooperative patients, and allows for studying the time-course of the vascular response. Then again, AZ is contraindicated in patients with known elevation of ICP as AZ may further increase ICP by cerebral vasodilation.[366] We consider this a minor limitations of the method, since patients with increased ICP are high-risk patients and are already closely monitored for development of DCI. However, in less severe cases improved prediction of DCI is very useful, and can support medical and logistic decision making. AZ has potential

side effects, but they are usually mild, short lasting and well-tolerated. Another drawback is that scalp edema in postoperative patient (after aneurysm clipping, hematoma evacuation or drains) makes TCD holding devices like headbands cumbersome and reduces patient tolerability for the procedure.

12.5 Assessment of delayed cerebral ischemia

In previous reports, there have been large inconsistencies in definitions used for delayed cerebral ischemia, making comparison between studies difficult. “Clinical deterioration due to DCI”, “vasospasm”, “angiographic vasospasm”, and “sonographic vasospasm” are some of the various terms used, all with separate definitions. A major strength of our study (**Paper IV**) is that unlike in the majority of previous studies,[280, 281, 283, 285, 287-293, 367] we used the standardized, recommended definitions of DCI, where outcome was separated into clinical and radiographic findings.[152, 153]

Clinical assessment to diagnose $DCI_{clinical}$ included frequent, neurological examinations and the use of The National Institutes of Health Stroke Scale (NIHSS).[314, 315] Clinical assessment has already been addressed in chapter 12.2.

Radiographic assessment to diagnose $DCI_{infarction}$ included CT and MRI examinations. Ideally, MRI should be peformed in all patients since this modality has superior sensitivity for detecting subtle ischemic changes compared with CT. During primary hospital stay, 17 of 42 patients with aSAH were evaluated only with CT. At one-year follow-up, the vast majority of patients (92.3%) were examined with MRI. We used an established classification system for cerebral infarction.[174, 346] Still, is its challenging to accurately assess the etiology of infarctions after aSAH.[347] To avoid misclassifying procedure-related infarcts as DCI-induced, imaging should be performed between 24 and 48 hours after aneurysm treatment. In our study,

imaginging was performed after this recommended time-window in nine of 42 patients (21.4%).

The high proportion of patients with severe aSAH in our study likely affected the incidence of DCI, since the strongest predictors of DCI are large amount of subarachnoid blood detected on CT imaging and poor neurological status on admission.[55, 166-169] Accordingly, the incidence of DCI was also high in our study population: as many as 52.4% of patients developed clinical deterioration due to DCI, and 45.2% had cerebral infarction from DCI. Furthermore, we did not take into account the size or severity of the infarction; minor infarctions were also included, further increasing the incidence of $DCI_{infarction}$.

12.6 Timing of examinations

We did not examine patients after a rigid time schedule. Clinical, radiographical and sonographical examinations as well as CVR testing were performed whenever possible without coming in conflict with patient investigations and treatment. A strict, standardized timeline for CVR-testing and assessments of DCI would have been useful, but is ressource demanding and was not feasible in our study.

For practical and ethical reasons, patients were not examined prior to aneurysm treatment. In theory, this would have been an ideal time point for isolating potential effects of aneurysm treatment itself. Ultrasound examinations prior to aneurysm rupture are possible in a longitudinal study of patients with UIA, with a large number of patients and long observation time. Such studies are time- and cost demanding, and does not provide information about cerebrovascular integrity immediately before aneurysm treatment or rupture. In patients with aSAH, it is crucial with prompt treatment to secure the ruptured aneurysm to avoid rebleeding. Treatment should not be delayed by inessential examinations, such as IMT or CVR. In patients selected for

treatment of UIA, the rupture risk is considered higher than the risk related to prophylactic aneurysm treatment. Although unlikely, discomfort and headache due to CVR testing can potentially trigger aneurysm (re-)rupture if examinations are performed before the aneurysm is secured. All ultrasound examinations were therefore done after aneurysm treatment was concluded.

12.7 Methods of statistical analysis

In all papers, we used standard statistical methods, and a significance level of 0.05. Appropriate methods were chosen according to study aims and sample sizes. The limited number of patients makes subanalyses difficult, and affects statistical power. Still, positive findings in a study with small sample size give a strong indication that observed differences are true.

12.8 Ethical considerations

Relatives gave informed consent on patients' behalf if patients were comatous or confused. If patients regained consciousness and ability to give informed consent, they were thoroughly informed about the study and asked to verify permission already given by relatives. No patients withdrew their consent.

As discussed in section 12.6, ethical considerations affected our choice for the timing of ultrasound examinations in order to avoid harmful consequences for the patients. Patients were not examined prior to treatment due to the potential risk of examinations causing aneurysm (re-)rupture, and to not cause any delay in the acute treatment of a ruptured aneurysm.

12.9 Impact of the presented data and future perspectives

Increased knowledge of potential predictors, both for aneurysm rupture and development of delayed cerebral ischemia after aSAH, can help improve patient care and clinical decision-making.

Paper I provides the new insight that carotid IMT is a potential predictor for rupture risk of intracranial aneurysms. If additional studies[221] confirm that there is an association between increased IMT and aneurysm rupture, carotid IMT may in the future be used for assessment of individual rupture risk and help select patients for prophylactical aneurysm treatment. Prospective cohort studies with larger sample size and long observation time are needed. Carotid IMT is an established vascular risk marker. IMT assessment is quick, inexpensive, and safe to perform, and can easily be incorporated into clinical practice.

Furthermore, the results of the IMT study in **Paper I** is a reminder for clinicians to consider the patient as a whole, not simply treating the aneurysm as an isolated problem. Intracranial aneurysms are not always an isolated focal disease, but can be part of more general blood vessel pathology. The overall vascular status of the patient may be relevant for treatment and follow-up. Hypertension and smoking are shared vascular risk factors for aSAH, and patients with SAH have increased risk of vascular events compared with the general population.[108] Information about IMT in patients with IAs can improve general vascular risk assessment and help avoid future vascular events, like myocardial infarction and ischemic stroke.

Results in **Paper I** also inspired us to initiate a study of lipoprotein metabolism and mitochondrial fatty acid oxidation in patients with intracranial aneurysms. The ongoing study is called “Predictors for rupture risk of intracranial aneurysms - Impact of lipid metabolism and mitochondrial function: RAPID”.

Paper II-IV adds to prior knowledge about CVR in patients with intracranial aneurysms. Previous studies, using various methodology, have shown that CVR is lower in patients with ruptured aneurysms compared with patients with unruptured aneurysms.[273-275, 277, 278] In **Paper IV**, we show that this also applies for CVR testing by means of TCD and AZ. To our knowledge we are the first to us this method to assess CVR in patients with UIA. As in previous CVR reports,[273-275, 277, 278, 368, 369] there is a rather large spread in CVR values between patients, making it challenging to interpret results. Additional reports with CVR data from more patients with IAs will help us better understand cerebrovascular integrity in this patient group, and enable improved interpretation of future results.

Prevention or early intervention of DCI, can improve patient outcome. Measures aimed at identifying high-risk patients can be valuable in patient management. Results in **Paper IV** indicates that CVR may be an independent predictor for clinical deterioration due to DCI after aSAH. To the best of our knowledge, we are the first to include CVR in a prediction model for DCI. If our results are confirmed in validation studies, CVR testing may ble implemented as a useful tool for the clinician to help in early identification of high-risk patients who may benefit from intensive prophylactic treatment, augmented monitoring, or repeat vascular imaging. This can help reduce DCI-related poor outcomes, minimize treatment complications, and titrate duration of stay in an intensive care unit.

Finally, results of **Paper II-IV** draw attention to a previously undescribed side-difference in CVR. Aneurysm treatment seems to cause a temporary reduction in CVR on the ipsilateral side, regardless of development of delayed cerebral ischemia. We accordingly recommend that CVR should be assessed separately on the ipsi- and contralateral sides, and contralateral CVR seems best suited as predictor of DCI.

13. CONCLUSIONS

Neurosonological examinations like carotid IMT and CVR assessed by TCD and AZ seems to be a useful supplementary tool in risk assessment in patients with IAs. Key findings and conclusion for each paper are presented below.

Paper I - Carotid intima-media thickness in patients with intracranial aneurysm

- There is an association between carotid intima-media thickness (IMT) and intracranial aneurysm rupture status at the time of aneurysm treatment.
- Carotid IMT is a potential predictor of aneurysm rupture.
- Carotid IMT may be an adjunct in the assessment of aneurysm rupture risk, and a helpful tool in patient risk stratification and counseling.

Paper II - Cerebrovascular reactivity after treatment for unruptured aneurysms

- Cerebrovascular reactivity (CVR) in patients with unruptured intracranial aneurysms does not differ significantly from reported values of healthy subjects.
- There is a possible association between patient age and increased CVR, whereas sex, smoking, hypertension, body mass index, aneurysm location and treatment modality are not associated with CVR.

Paper III - Time-course of cerebrovascular reactivity in patients with unruptured aneurysms

- There is a temporary reduction in CVR on the ipsilateral side after aneurysm treatment.
- The change in CVR appears to be larger in patients treated with clipping.
- Age and treatment with clipping are positively associated with change in CVR, whereas there is a negative association between CVR at the first exam and change in CVR. Sex, smoking, hypertension, body mass index, treatment side, and body

weight difference between exams are not significantly associated with a difference in CVR.

- CVR from ipsi- and contralateral sides should be assessed separately as mean values of right and left sides can conceal side-differences in CVR.

Paper IV - Cerebrovascular reactivity and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

- In concordance with previous CVR-studies using other vasoactive stimuli and measurements, our study shows that CVR assessed by transcranial Doppler and acetazolamide test is considerably lower in patients with ruptured aneurysms compared with patients with unruptured aneurysms.
- Impaired CVR is a possible independent predictor of clinical deterioration due to delayed cerebral ischemia, and may assist in identifying patients in need of closer observation after aneurysmal subarachnoid hemorrhage.
- An ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of development of delayed cerebral ischemia, highlighting the need to consider ipsilateral and contralateral CVR separately.
- Contralateral CVR seems best suited as predictor of delayed cerebral ischemia.

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15. PAPERS I-IV

II

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Cerebrovascular reactivity after treatment of unruptured intracranial aneurysms — A transcranial Doppler sonography and acetazolamide study

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ABSTRACT

Background: Cerebrovascular reactivity (CVR) is defined as the change in cerebral blood flow, or blood velocity, in response to a vasoactive stimulus. There is a possible association between impaired CVR and vasospasm after aneurysmal subarachnoid hemorrhage. Most studies on CVR and vasospasm have used healthy subjects as reference. However, due to potential different vascular features, CVR in persons with intracranial aneurysms may differ from CVR in healthy subjects. Therefore, our aim was to examine CVR in patients with unruptured intracranial aneurysms (UIA).

Methods: CVR was examined in 37 patients in the first postoperative week after treatment for UIA, using acetazolamide (AZ) test with transcranial Doppler monitoring of blood flow velocities.

Results: Mean blood flow velocity in the middle cerebral arteries was 58.5 (SD 12.8) cm/s at baseline, and 94.3 (SD 19.5) cm/s after stimulation with AZ. Mean CVR was 62.6 (SD 16.8) %. There was no significant difference when comparing right and left sides, and treated and untreated sides. A simple regression analysis suggested that CVR increased with 0.7% points for each year a patient aged ($p = 0.004$). However, the significance disappeared in a multiple analysis (increase of 0.6% points per year, $p = 0.055$). Other possible influencing factors (gender, smoking, hypertension, body mass index, aneurysm location and treatment modality) were not significantly associated with CVR.

Conclusions: CVR in patients with UIA is not different from normal values reported in healthy subjects, and does not indicate a systemically impaired vascular system in patients with UIA. We suggest that CVR in age and gender matched healthy controls can be used as reference for persons with intracranial aneurysms.

1. Introduction

Cerebral arterioles play an essential role in regulating blood flow in the brain. Arteriole dilation causes reduced peripheral resistance and thereby increased blood flow in proximal vessels, whereas arteriole constriction causes increased resistance and reduced proximal flow. Cerebrovascular reactivity (CVR) reflects the vasodilating or -constricting capacity of the cerebral resistance vessels, and is a marker of cerebrovascular integrity. CVR is defined as the change in cerebral blood flow, or blood velocity, in response to a vasoactive stimulus. Acetazolamide (AZ) is a drug that inhibits carbonic anhydrase, an enzyme that converts carbon dioxide (CO_2) and water (H_2O) to carbonic acid (H_2CO_3). AZ is a potent dilator of cerebral arterioles, and has been used for CVR testing for decades [1–7]. Changes in blood flow velocity can be measured using transcranial Doppler (TCD) [7,8].

AZ and TCD have been used to assess CVR in patients with *ruptured* intracranial aneurysms [9,10]. To our knowledge, no studies have used the same method to assess CVR in persons with *unruptured* intracranial aneurysms (UIA).

CVR provides information about the hemodynamics and pathophysiology of cerebrovascular diseases. Previous studies have hypothesized an association between impaired CVR and vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) [11–13]. In these studies patients with and without vasospasm were compared. If additional reference groups were used they consisted of healthy subjects or patients with unrelated disorders [9]. Several CVR studies on healthy subjects exist [3,4,14–22], but these findings might not be directly applicable to aSAH patients as persons with intracranial aneurysms may have

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different vascular features and qualities intracranially compared with the normal population. Smoking and hypertension are known risk factors for development of intracranial aneurysms, and are prevalent among persons with UIA as well as aSAH [23–25]. Smoking promotes atherosclerosis and can affect blood vessel function. Hypertension can cause vascular hypertrophy and may result in rigidity of the cerebrovascular system reducing its autoregulatory capacity [26]. Patients with aSAH and no vasospasm are well-suited as reference group for studies of vasospasm after aSAH. When assessing whether CVR is impaired during the course of vasospasm or not, it can however also be useful to know CVR prior to aneurysm rupture. Data on persons with UIA are sparse [27–31]. Increased knowledge of CVR in patients treated for UIA can improve the understanding of CVR findings in all patients harboring intracranial aneurysms.

The main objective of this study was to describe CVR in patients treated for UIA, assessed by TCD and AZ. We also aimed to assess how aspects regarding the patient, aneurysm and treatment modality affect CVR.

2. Methods

2.1. Participants

From February 2011 to May 2013 we prospectively included consecutive patients treated for unruptured intracranial saccular aneurysms in the Department of Neurosurgery, Haukeland University Hospital. Exclusion criteria were: previous treatment of intracranial aneurysms (ruptured or unruptured); non-saccular aneurysms (fusiform, mycotic, blister-like, dissection and traumatic); giant aneurysms treated with proximal artery occlusion; carotid stenosis (>50%) or occlusion; lack of transtemporal bone window in transcranial Doppler examination; and contraindications to acetazolamide (e.g. sulfonamide allergy, adrenal or pituitary insufficiency, kidney or liver failure).

Information regarding patient demography, aneurysm location, and treatment modality (clipping or coiling) was registered. Body mass index, smoking status (current, previous, or never), and hypertension (previously diagnosed and treated or systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg persistently observed during admission) were also recorded.

The study was conducted in accordance with the Declaration of Helsinki (2013) of the World Medical Association, and was approved by the local ethics committee. Written informed consent was obtained from all patients.

2.2. Cerebrovascular reactivity

Cerebrovascular reactivity (CVR) testing was performed within a week after aneurysm treatment, before the patient was discharged from the hospital. All examinations were performed by the same sonographer (MLB). Patients were examined in a supine position.

Before the CVR test, a transcranial color-coded duplex sonography (TCCS) examination was done to assess the transtemporal bone window, visualize the circle of Willis, and find a suited insonation depth for the middle cerebral arteries (MCA). This investigation was done with a portable Philips CX50 TCCS system, using a 5–1 MHz sector array probe (Philips Medical Systems, Bothell, WA, USA).

CVR testing was then performed using acetazolamide (AZ) and transcranial Doppler (TCD) monitoring of blood flow velocities. Mean blood flow velocities (MFV) in both MCAs were measured using a portable TCD system (Companion III Nicolet Vascular, VIASYS Healthcare, Madison, WI, USA) with 2 MHz probes applied over the transtemporal window. The site with the best available signal from the MCA was selected, at an insonation depth between 45 and 60 mm. Doppler monitoring probes were secured to the patient's head using a head band (Welder TCD Headband, VIASYS Healthcare, Madison, WI, USA).

After establishing stable baseline blood velocities, acetazolamide (Diamox Goldshield Ltd., Croydon, Surrey, UK; or Diamox Sanofi Aventis, Paris, France) was administered intravenously over one minute. MFV in both MCAs was monitored continuously, and Doppler curve images were saved at baseline and every five minutes after the AZ injection. If velocity plateau phase was established after 15 min, the examination was concluded, if not, monitoring was continued for up to 30 min. The AZ dose was 1000 mg for patients with body weight up to 79 kg. For patients weighing 80 kg or more AZ was given in a dose of 15 mg/kg bodyweight, with a maximum dose of 1500 mg.

Cerebrovascular reactivity was calculated as the percentage change in MFV after administration of acetazolamide: $CVR\ (\%) = [(MFV_{AZ} - MFV_{BASELINE}) / MFV_{BASELINE}] \times 100$; where CVR is cerebrovascular reactivity, $MFV_{BASELINE}$ is baseline mean blood flow velocity (before acetazolamide), and MFV_{AZ} is maximal mean blood flow velocity after acetazolamide.

2.3. Statistical analysis

All variables were assessed for symmetry around the mean by considering the range and quartiles. Symmetric variables were summarized with mean and standard deviation (SD), and non-symmetric with median and interquartile range (IQR). A paired t-test suggested that there was no difference in CVR on the right and left side ($p = 0.643$). Therefore, the average of the two sides (mean CVR) was used as outcome variable in regression analyses. Two categories for treatment side were applied in the regression analysis; right and left. Patients with midline aneurysms were allocated according to chosen side of approach. First, simple linear regression was applied to assess the relationships between mean CVR and age, gender, BMI, hypertension, smoking, treatment modality and treatment side. Then, a multiple regression analysis was run with the same outcome and covariates. The following relationships were examined using standard t-tests:

- CVR ipsilateral to aneurysm treatment (treated side) vs. CVR contralateral to aneurysm treatment (untreated side)
- CVR for patients treated for MCA aneurysms vs. CVR for patients treated for aneurysms in other locations
- CVR for patients with a history of stroke vs. CVR for patients with no history of stroke
- CVR for patients examined using Diamox Goldshield vs. CVR for patients examined using Diamox Sanofi Aventis

Statistical analysis was performed with R version 3.2.2.

3. Results

3.1. Patients, aneurysm and treatment

Of the 53 patients consecutively recruited during the study period, 16 were excluded; 5 with previous aneurysm treatment, 3 with proximal artery occlusion treatment; 3 with contraindications to AZ (sulfonamide allergy, adrenal and pituitary insufficiency); 4 due to lack of temporal bone window; and 1 because the hospital pharmacy could not provide AZ in time. This left us with a study population of 37 patients.

Table 1 shows patient characteristics, and Table 2 shows aneurysm and treatment characteristics. MCA aneurysms were most common (45.9%), followed by ACOM (16.2%). Multiple aneurysms were identified in 12 of 37 patients (32.4%). Treatment of a single aneurysm was performed in 33 of 37 patients (89.2%). The remaining four patients underwent treatment for two aneurysms each. Of 37 patients, 22 (59.5%) were treated with coiling, and 15 (40.5%) with clipping.

Table 1
Patients characteristics.

Age, years[a]	50.5 (10.6)
Height, cm[a]	169.4 (8.5)
Weight, kg[a]	77.2 (15.8)
BMI, kg/m^2[a]	26.8 (4.9)
Female[b]	24 (64.9)
Hypertension[b]	18 (48.6)
Smoking[b]	
Current	20 (54.1)
Previous	13 (35.1)
Never	4 (10.8)
	n = 37

BMI: Body mass index.
SD: Standard deviation.
[a] Mean (SD).
[b] n (%).

Table 3
Blood flow velocities and cerebrovascular reactivity.

	$MFV_{BASELINE}$ (cm/s)	MFV_{AZ} (cm/s)	ΔMFV (cm/s)	CVR (%)	MV (n)
Right	60.2 (12.8)	97.1 (19.7)	36.9 (11.3)	62.8 (18.6)	2
Left	57.2 (15.0)	89.6 (21.6)	32.4 (8.9)	59.7 (17.5)	9
Mean	58.8 (12.5)	94.5 (19.4)	35.7 (10.1)	62.6 (16.8)	
Ipsilateral	59.6 (13.6)	93.6 (17.7)	34.0 (9.1)	59.4 (19.1)	9
Contralateral	57.8 (14.4)	93.4 (22.9)	35.6 (11.1)	63.0 (17.2)	2
Mean	58.5 (12.8)	94.3 (19.5)	35.7 (10.1)	62.6 (16.8)	

Mean flow velocities and CVR are reported as mean (SD).
SD: standard deviation.
$MFV_{BASELINE}$: Baseline mean blood flow velocity (before acetazolamide).
MFV_{AZ}: Maximal mean blood flow velocity after acetazolamide.
ΔMFV: Absolute change in mean flow velocity after acetazolamide.
CVR: Cerebrovascular reactivity (relative change in mean flow velocity after acetazolamide).
MV: Missing value.

3.2. Cerebrovascular reactivity

Median time between aneurysm treatment and CVR testing was 51.8 (IQR 28.4) hours (range 27.2–146.5). Of 37 patients, 26 successfully underwent bilateral CVR testing. In 11 patients CVR testing was unilateral due to insufficient temporal bone window or postoperative intracranial air. Of 37 patients, 23 (62.2%) weighed <80 kg and therefore received 1000 mg AZ. The remaining 14 patients (37.8%) weighed ≥80 kg, and were given 15 mg AZ per kg bodyweight. Mean bodyweight was 77.2 (SD 15.8) kg (range 40–106), and mean AZ dose per bodyweight was 15.0 (SD 2.2) mg/kg. There was no correlation between AZ dose per kg and CVR (Pearson's R = 0.08, p = 0.657).

Table 3 shows blood flow velocities and CVR results. Data is presented according to laterality relative to hemisphere and treatment. Mean blood flow velocity (MFV) in the MCA ipsilateral to the treated aneurysm was 59.6 (SD 13.6) cm/s at baseline and 93.6 (SD 17.7) cm/s after stimulation with AZ. Mean CVR on the ipsilateral side was 59.4 (SD 19.1) %. On the contralateral side MFV was 57.8 (SD 14.4) cm/s at baseline and 93.4 (SD 22.9) cm/s after AZ, giving a CVR of 63.0 (SD 17.2) %. There was no significant difference in CVR between the right and left sides (p = 0.643), or between treated and untreated sides (p = 0.160). Data seemed to be symmetrically distributed, and mean and median values for CVR were very similar.

Fig. 1 shows the timeline with MCA velocity changes during the AZ test. The highest absolute velocity after AZ injection was 90.7 cm/s [95% confidence interval (CI) 83.9–97.4] and 91.3 cm/s (95% CI 83.4–99.2) in the ipsi- and contralateral MCA respectively. The highest percentage velocity increase compared with baseline was 54% (95% CI 47–62) and 59% (95% CI 53–65) on the ipsi- and contralateral side respectively. Velocity plateau phase was established in all patients within 20 min after AZ injection.

Table 4 shows the results of the simple and multiple regression analyses, assessing possible relationships between mean CVR and age, gender, BMI, hypertension, smoking, treatment modality and treatment side. Only CVR and age were significantly associated in the simple analysis (CVR increased with 0.7% points per year, p = 0.004). In the multiple model, no covariates were significant, including age (CVR increased with 0.6% points per year, p = 0.055). Still, females had a tendency for higher CVR than males (6.5% points with p = 0.266 in the simple model, and 9.1% points with p = 0.147 in the multiple model). Regression analyses were repeated after stratification for gender, age (≤50 years vs. >50 years), and treatment modality (coiling vs. clipping), this did not change results notably. Still, in the simple analyses of male patients and patients treated with coiling, hypertension was negatively associated with CVR. In males the reduction in CVR was 27.4% points (p = 0.001), and in patients treated with coiling the reduction was 20.1% points (p = 0.004). The significances disappeared in the multiple analyses; the reductions were 21.9% points (p = 0.316) and 4.2% points (p = 0.526) in the male subgroup and in patients treated with coil, respectively.

A t-test showed no significant difference in CVR between MCA aneurysms and aneurysms located in other arteries (p = 0.201).Three patients had a history of stroke prior to the aneurysm treatment; one pontine infarction, one basal ganglia hemorrhage and one minor MCA infarction. Mean CVR were 66.2%, 64.3% and 95.4% in these patients, respectively. A t-test showed no significant difference between CVR in patients with and without history of stroke (p = 0.302). Diamox Goldshield was used for CVR testing in 23 patients (62.2%), and Diamox Sanofi Aventis was used in 14 patients (37.8%). There was no significant difference in mean CVR for the two AZ manufacturers (p = 0.943).

Table 2
Aneurysm and treatment characteristics.

Multiple aneurysm	12 (32.4)
Location treated aneurysms	
MCA	17 (45.9)
ACOM and anterior complex	6 (16.2)
Pericallosa	1 (2.7)
Carotid top	2 (5.4)
Intradural ICA	1 (2.7)
Extradural ICA	3 (8.1)
Ophthalmic	3 (8.1)
PCOM	1 (2.7)
Basilar top and cerebelli superior	2 (5.4)
PICA, VB, distal posterior	1 (2.7)
Treatment modality	
Coil	22 (59.5)
Clip	15 (40.5)
Treatment side[a]	
Left	19 (51.4)
Right	18 (48.6)
	n = 37

All variables are reported as n (%).
MCA: Middle cerebral artery.
ACOM: Anterior communicating artery.
ICA: Internal carotid artery.
PCOM: Posterior communicating artery.
PICA: Posterior inferior cerebellar artery.
VB: Vertebrobasilar arteries.
[a] One patient treated with combined clipping of an ACOM aneurysm and a right MCA aneurysm in one procedure was allocated to the right side. Eight patients with midline aneurysms (ACOM and basilar top) were allocated to the chosen side of approach.

3.3. Side effects using acetazolamide

The majority of patients, 34 of 37 (91.9%), experienced one or several side effects of AZ. Facial and extremity paresthesia, flushing, cranial fullness and headache were most common (see Table 5 for details). Side effects were mild, short lasting and self-limiting.

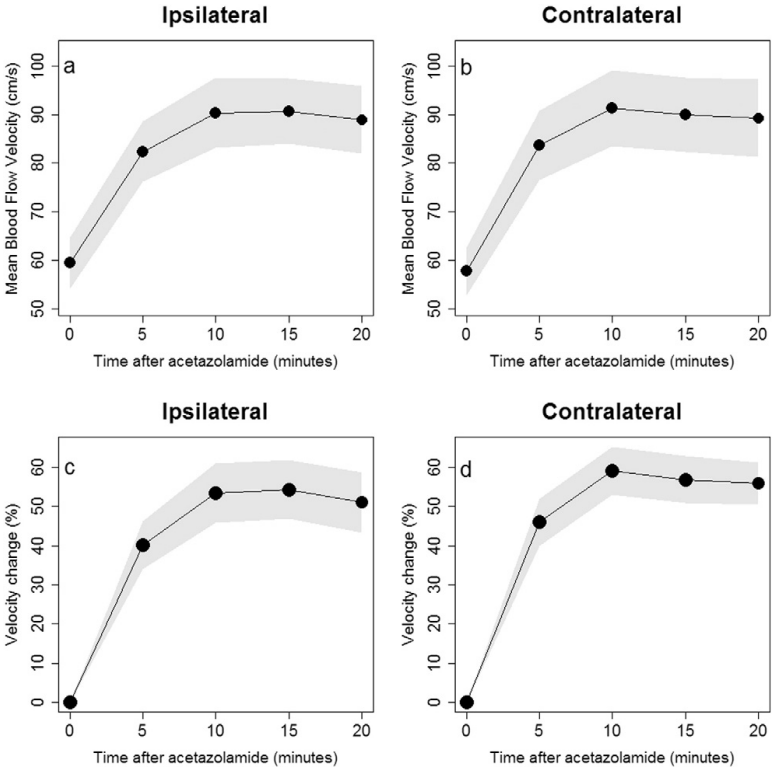

Fig. 1. Absolute and relative changes in blood flow velocity after acetazolamide (AZ) injection Upper part of the figure shows timeline with absolute mean flow velocities in middle cerebral arteries ipsilateral (a) and contralateral (b) to the treated aneurysm at baseline and after AZ injection. Lower part of the figure shows percent change in velocity on the ipsilateral (c) and contralateral (d) side compared with baseline. 95% confidence intervals are indicated by the shadowed area.

4. Discussion

4.1. Main findings

Mean CVR, evaluated by AZ test with TCD, was 62.6 (SD 16.8) %. There was no significant difference in CVR when comparing right and left sides ($p = 0.643$), and treated and untreated sides ($p = 0.160$).

Table 4
Regression results.

	Simple		Multiple	
	Estimate	p	Estimate	p
Age, years	0.7	0.004	0.6	0.055
Female	6.5	0.266	9.1	0.147
BMI, kg/m^2	0.4	0.501	0.3	0.634
Hypertension	−9.0	0.105	−4.2	0.526
Smoking				
Current	ref	–	ref	–
Previous	−2.1	0.737	−3.1	0.597
Never	−10.5	0.266	−11.3	0.219
Treatment modality				
Coil	ref	–	ref	–
Clip	3.9	0.499	0.7	0.910
Treatment side				
Left	ref	–	ref	–
Right	−3.2	0.566	−7.9	0.165

BMI: Body mass index.
ref.: Reference.

The simple regression for CVR vs. age suggested an increase in CVR of 0.7% points per year ($p = 0.004$), but the significance disappeared in the multiple regression (increase of 0.6% points per year, $p = 0.055$). Other possible influencing factors like gender, smoking, hypertension, body mass index, aneurysm location and treatment modality were not significantly associated with CVR.

4.2. Strengths

To the best of our knowledge, no previous studies have used AZ test and TCD to assess CVR in patients with UIA. Our sample size is moderate to high compared with previous CVR studies in healthy subjects. All examinations were performed by the same sonographer (MLB).

Table 5
Side effects of acetazolamide, n (%).

Facial and extremity paresthesia	24 (64.9)
Warm/flushing	22 (59.5)
Cranial fullness	21 (56.8)
Headache	13 (35.1)
Nausea	4 (10.8)
Tinnitus/fullness of the ear	4 (10.8)
Dizziness	3 (8.1)
Altered taste	0 (0)
Acidosis	0 (0)

4.3. Limitations

Gender and age matched case-controls would be useful when interpreting results, but it was not part of our study design. Although the sample size is large compared with previous CVR studies, the limited number of patients makes it difficult to draw definite conclusions regarding regression and subgroup effects. Results must thus be interpreted with caution, especially for the smallest subgroups concerning aneurysm location and history of stroke.

The aneurysm treatment itself may affect CVR. Patients were examined after treatment, not before. The study does thus not provide absolute information regarding the potential effects of aneurysm treatment on CVR. However, the post-treatment timing makes results better suited for comparison with aSAH patients as they also undergo aneurysm treatment. An additional reason for no pre-treatment CVR testing was to avoid test-induced aneurysm rupture, a highly unlikely yet feared complication.

For CVR testing an AZ dose of 13 to 18 mg/kg is recommended [15,32]. For a simple and practical setup 1 g AZ is commonly used. We used 1 g AZ for the majority (59.5%) of patients. To avoid submaximal vasodilation, an increased dose was given to patients with high bodyweight. Patients weighing ≥80 kg received 15 mg/kg, since this dose is considered sufficient for causing maximum vasodilatory effect [15]. Mean AZ dose in our study was 15.0 (SD 2.2) mg/kg. The recommended AZ dose was achieved for the vast majority of patients. Of 37 patients, 34 (91.9%) received an AZ dose between 12.7 and 17.2 mg/kg. The doses for the remaining three patients were 10.6, 11.0 and 25 mg/kg. There was no correlation between AZ dose per kg and CVR (Pearson's $R = 0.08$, $p = 0.657$). This did not change when removing individuals who had received doses lower than 12.7 mg/kg or higher than 17.2 mg/kg. Our choice of AZ dosage is not ideal, but has the advantage of better suited doses than the commonly used setup of 1 g AZ regardless of bodyweight, and a simpler setup compared with a rigorous bodyweight-based dosage.

CVR studies are done using various methods. CO_2 inhalation or intravenous AZ are commonly used as vasodilatory stimuli [1,3,5,15,33], and cerebral blood velocities or flow are measured with brain perfusion imaging, using Doppler, CT, MRI or nuclear medicine techniques. In our study CVR was examined using AZ and TCD. The benefits of AZ are the simpler instrumentation setup compared with CO_2, and its suitability for non-cooperative patients. Main drawbacks are side effects, and the chance of hyperventilation counteracting the vasodilatory effect of AZ. Furthermore, CO_2 is a more physiologic stimulus and adverse effects are more easily terminated. Although application can be dangerous for prolonged periods and in critical ill patients, it has been suggested that CO_2 may be safer compared with AZ [34]. The benefits of TCD are low-cost, bedside applicability, no use of ionizing radiation or contrast agent, and the possibility of continuous monitoring. The main drawback is that 10–15% of the population lack bone window. Velocity measurements with TCD are an indirect measure of blood flow changes. According to the law of Hagen-Poiseuille, blood flow velocity will be proportional with flow if the vessel diameter is constant. AZ predominantly affects arterioles and precapillary sphincters, whereas basal cerebral arteries seemingly are not much affected [35]. It is therefore accepted that changes in MCA velocity can be used as an indirect measure for relative changes in blood flow.

4.4. Healthy subjects

Persons without intracranial aneurysms were not examined in our study, but previous reports in healthy subjects can be used for comparison. The use of different methods to examine CVR makes it challenging to compare results between studies. Direct comparison is feasible between our study and previous studies using the same method to assess CVR, i.e. TCD and AZ. A well-known TCD manual is commonly referred to when interpreting CVR results [36]. The authors of the book state that the normal value for CVR assessed with TCD and AZ is 38 ± 15%, yet point out that a single report with CVR of 62% differs from other available literature at the time [37]. An updated literature search identifies additional studies on CVR in healthy subjects assessed using TCD and AZ. Table 6 summarizes major findings of all studies [3,4,14,15,18–22,37–40]. CVR is reported to be between 34 and 65%, with velocity increase from 55 to 72 cm/s at baseline, to 76 to 97 cm/s after stimulation with AZ. We found a mean CVR of 62.6 (SD 16.8) %, with velocity increase from 58.5 (SD 12.8) cm/s to 94.3 (SD 19.5) cm/s. Our data for patients treated for UIA are thus within the normal range compared with previous results for healthy subjects, specifically in the upper part of the spectrum. This indicates that CVR is not worse in patients with UIA than the reported normal values in healthy subjects. The reported wide range of CVR in the normal population can be explained by shortcomings in the reliability of the assessment method, or a genuine large variation between individuals. Case–control studies with age- and gender matching are advisable for interpreting patients' CVR results, but were not done in our study. A possible explanation for CVR being in the high normal range in our study is a temporary increase of reactivity due to vessel manipulation during the clipping or coiling procedure. Alternatively, it is conceivable that patients with UIA may have different vessel features and qualities compared with healthy subjects.

A prospective cohort study of 1695 individuals belonging to the general population in Rotterdam, The Netherlands, demonstrated that a lower CVR was associated with higher risk of death. The association was independent of cardiovascular risk factors and incidence of stroke. This suggests that a lower CVR reflects a systemically impaired vascular system [41]. One might expect a lower CVR in patients with UIA because of the high prevalence of general vascular risk factors like hypertension and smoking. Surprisingly we found the opposite. Our results of CVR in the upper high normal range do thus not indicate a systemically impaired vascular system in patients with UIA.

4.5. Unruptured intracranial aneurysms

Our study is one of few studies on CVR in patients with UIA, and is to our knowledge the first to use AZ test and TCD to assess CVR in this patient group. In previous studies using CO_2 as vasoactive stimuli no more than ten patients with UIA has been examined [27–31]. Abe et al. examined the effects of prostaglandin E1 induced hypotension on local cerebral blood flow and CO_2 reactivity in patients during surgery of intracranial aneurysms [27,28]. They studied 34 patients with ruptured and nine patients with unruptured aneurysms, and found lower intraoperative CVR in patients with ruptured aneurysms compared with unruptured ones. Dernbach et al. used intraoperative measurement of local CBF to evaluate pressure autoregulation and CO_2 reactivity in patients who underwent aneurysm clipping [29]. They examined 14 patients with aSAH and 10 patients with UIA. They found significant reduction in CO_2 reactivity in aSAH patients after early surgery, compared with patients treated for UIA and patients treated more than a week after aSAH. In their study of the effect of nimodipine on CVR, Seiler et al. used TCD and CO_2 to examine nine patients with aSAH, two patients with UIA, and five patients with unruptured arteriovenous malformations (AVM) [30]. They found a significant reduction of CVR in the second week after aSAH. When reexamined six to eight weeks after aSAH, CVR values were equal to preoperative values found in patients with UIA and AVM. Schmieder et al. used TCD with CO_2 as vasodilatory stimuli to compare CVR in 27 patients 10 months after aSAH, 5 patients treated for incidental aneurysms, and 20 volunteers without cerebrovascular disease [31]. They found normal CO_2 reactivity and no right to left differences in all three groups, with no significant differences between the groups. This is in accordance with our findings of CVR of patients treated for UIA being within the normal range.

4.6. Aneurysm location and treatment

Only one other study has looked at CVR in relation to aneurysm localization and treatment modality. Jarus-Dziedzic et al. found that aneurysm

Table 6
Cerebrovascular reactivity studies in healthy subjects, evaluated by acetazolamide test and transcranial Doppler.

	Subjects (n)	Female (%)	Age (years)	AZ dose	$MFV_{BASELINE}$ (cm/s)	MFV_{AZ} (cm/s)	ΔMFV (cm/s)	CVR (%)
Sorteberg 1989	8	25.0	46 (30–67)	1 g	65 ± 6 (56–78)	88 ± 10 (74–106)	~23[a]	36 ± 9 (21–48)
Piepgras 1990	33	30.3	43 ± 13 and 47 ± 15 (21–78)	1 g	60.9 ± 10.7 (38–84)	~85[a]	24.4 ± 9.2 (6–48)	~40[a]
Mancini 1996	10	40.0	MV (26–82)	1 g	95.3 ± 14[b] systolic	MV	MV	35[c] systolic
					41.3 ± 7.1[b] diastolic	MV	MV	50[c] diastolic
Dahl 1994	36	63.9	36 (24–64)	1 g	71.7 ± 13.6 right	95.4 ± 19.9 right	~24[a]	34.2 ± 9.7 right
					71.2 ± 14.9 left	97.0 ± 21.1 left	~26[a]	35.5 ± 8.7 left
Dahl 1995	48	52.1	41.8 (23–74)	1 to 1.6 g	63.5 ± 13.5	~91[a]	~28[a]	43.4 ± 10.5
Ulrich 1995	32	31.3	48 ± 16 (18–73)	1 g	62.38 ± 16.07	84.91 ± 24.54	~23[a]	36.1
Hamann 1996	18	MV	60 ± 10.9	1 g	MV	MV	29.7 ± 8.3	62.0 ± 17.3
Karnik 1996	36	50.0	MV	14.3 mg/kg	60.2 ± 12.5 f	89.9 ± 14.4 f	~30[a]	~49[a]
					54.5 ± 18.8 m	75.7 ± 24.5 m	~21[a]	~39[a]
Patrick 1996	7	42.9	37 (30–52)	1 g	61 ± 10	85 ± 15	~24[a]	39 ± 14
Valikovics 1996a	19	100.0	38 ± 11	1 g	61 ± 13	~97[a]	~36[a]	59 ± 33
Fülesdi 1997	40	50.0	39.3 ± 11.4	1 g	57.1 ± 14.4	87.9 ± 21.0	~31[a]	64.6 ± 24.7
Oláh 2000	56	51.8	41.5 ± 12.7 f	1 g	63 ± 4 f	93 ± 5 f	34.9 ± 11.6 f	57.9 ± 23.9 f
			43.9 ± 14.5 m		57 ± 4 m	76 ± 5 m	24.2 ± 9.5 m	43.7 ± 17.8 m
Schwertfeger 2006	33	30.3	42	15 mg/kg	54.6 ± 14.4	81.4 ± 18.9	26.78 ± 7.66	~49[a]
					56.7 ± 11.6 f–up	82.2 ± 14.1 f-up	25.48 ± 7.73	~44[a]

Numbers are presented as mean ± standard deviation, range in parenthesis if available.
f: Female.
m: Male.
f-up: Follow-up.
AZ: Acetazolamide.
$MFV_{BASELINE}$: Baseline mean blood flow velocity (before acetazolamide).
MFV_{AZ}: Maximal mean blood flow velocity after acetazolamide.
ΔMFV: Absolute change in mean flow velocity after acetazolamide.
CVR: Cerebrovascular reactivity (relative change in mean flow velocity after acetazolamide).
MV: Missing value.
[a] Rough estimates based on published data.
[b] Systolic and diastolic velocities — not mean flow velocities.
[c] Relative change in systolic and diastolic velocity after acetazolamide — not mean flow velocity.

localization and treatment method (surgical or endovascular) did not affect CVR after aSAH [10], which is in accordance with our findings.

4.7. Other possible influencing factors

It has been suggested that age, gender, smoking and hypertension may affect CVR. Studies that have addressed this issue have produced varied results; both positive and negative correlations as well as no significant association are reported [19,21,42–57]. In our study the only factors significantly associated with CVR were age (in all patients) and hypertension (in males and coiled patients). The correlations were however only significant in the simple regression model and can be explained by confounding or random variation.

The wide range of CVR in healthy subjects (Table 6) makes it difficult to use reported normal values as reference material. The studied normal populations have different demographic compositions [3,4,14,15,18–22,37–40], and difference in possible influencing factors like age and gender may explain variations between studies. Although no significant association was found between CVR and gender in our study, age- and gender matching is strongly advisable in CVR studies as this can help eliminate potential confounding factors, and may make studies more accurate.

5. Conclusions

Our study provides novel information about CVR after treatment for UIA. To the best of our knowledge, this is the first study that uses TCD and AZ test to assess CVR in this patient group. CVR was in the upper high normal range, and does not indicate a systemically impaired vascular system in patients with UIA. We suggest that CVR in age and gender matched healthy subjects can be used as reference for persons with intracranial aneurysms.

Conflict of interest

None.

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Corrigendum

Corrigendum to "Cerebrovascular reactivity after treatment of unruptured intracranial aneurysms - A transcranial Doppler sonography and acetazolamide study" [Journal of the Neurological Sciences 363 (2016) 97–103]

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The authors regret that there were three errors in the published version of this paper. These errors and their corrections are detailed below:

1) The interquartile range (IQR) for the median time between aneurysm treatment and cerebrovascular reactivity (CVR) testing was incorrectly reported as 28.4 h. The correct value is 43.7 h. (Page 99, Chapter 3.2.)

2) A typing error for a single patient caused minor inaccuracies in reported velocities. Data were corrected before statistical analysis was performed, but unfortunately Table 3 contained five uncorrected velocity values.

Published velocities (cm/s):

	$MFV_{BASELINE}$	MFV_{AZ}	ΔMFV
Right	60.2 (12.8)	97.1 (19.7)	36.9 (11.3)
Left	57.2 (15.0)	89.6 (21.6)	32.4 (8.9)

Corrected velocities (cm/s):

	$MFV_{BASELINE}$	MFV_{AZ}	ΔMFV
Right	59.7 (13.2)	96.2 (19.9)	36.5 (11.1)
Left	57.2 (15.0)	90.1 (21.3)	32.9 (8.9)

The revised version of Table 3 is presented below. (Page 99, Table 3.)

Table 3 Blood flow velocities and cerebrovascular reactivity.

	$MFV_{BASELINE}$ (cm/s)	MFV_{AZ} (cm/s)	ΔMFV (cm/s)	CVR (%)	MV (n)
Right	59.7 (13.2)	96.2 (19.9)	36.5 (11.1)	62.8 (18.6)	2
Left	57.2 (15.0)	90.1 (21.3)	32.9 (8.9)	59.7 (17.5)	9
Ipsilateral	59.6 (13.6)	93.6 (17.7)	34.0 (9.1)	59.4 (19.1)	9
Contralateral	57.8 (14.4)	93.4 (22.9)	35.6 (11.1)	63.0 (17.2)	2
Mean	58.5 (12.8)	94.3 (19.5)	35.7 (10.1)	62.6 (16.8)	

Mean flow velocities and CVR are reported as mean (SD).
SD: standard deviation.
$MFV_{BASELINE}$: Baseline mean blood flow velocity (before acetazolamide).
MFV_{AZ}: Maximal mean blood flow velocity after acetazolamide.
ΔMFV: Absolute change in mean flow velocity after acetazolamide.
CVR: Cerebrovascular reactivity (relative change in mean flow velocity after acetazolamide).
MV: Missing value.

3) Table 6 incorrectly states that the report of Mancini and colleagues was published in 1996. The correct year of publication is 1993. (Mancini M, De Chiara S, Postiglione A, Ferrara LA. Transcranial doppler evaluation of cerebrovascular reactivity to acetazolamide in normal subjects. Artery. 1993;20:231–241) (Page 102, Table 6.)

The authors would like to apologise for any inconvenience the above errors may have caused.

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Research Article

Time Course of Cerebrovascular Reactivity in Patients Treated for Unruptured Intracranial Aneurysms: A One-Year Transcranial Doppler and Acetazolamide Follow-Up Study

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Background. Cerebrovascular reactivity (CVR) is often impaired in the early phase after aneurysmal subarachnoid hemorrhage. There is, however, little knowledge about the time course of CVR in patients treated for unruptured intracranial aneurysms (UIA). *Methods*. CVR, assessed by transcranial Doppler and acetazolamide test, was examined within the first postoperative week after treatment for UIA and reexamined one year later. *Results*. Of 37 patients initially assessed, 34 were reexamined after one year. Bilaterally, baseline and acetazolamide-induced blood flow velocities were higher in the postoperative week compared with one year later ($p < 0.001$). CVR on the ipsilateral side of treatment was lower in the initial examination compared with follow-up (58.9% versus 66.1%, $p = 0.04$). There was no difference in CVR over time on the contralateral side (63.4% versus 65.0%, $p = 0.65$). When mean values of right and left sides were considered there was no difference in CVR between exams. Larger aneurysm size was associated with increased change in CVR ($p = 0.04$), and treatment with clipping was associated with 13.8%-point increased change in CVR compared with coiling ($p = 0.03$). *Conclusion*. Patients with UIA may have a temporary reduction in CVR on the ipsilateral side after aneurysm treatment. The change in CVR appears more pronounced for larger-sized aneurysms and in patients treated with clipping. We recommend that ipsilateral and contralateral CVR should be assessed separately, as mean values can conceal side-differences.

1. Introduction

Constriction and dilation of cerebral arterioles regulate cerebral blood flow. Cerebrovascular reactivity (CVR) reflects this regulating capacity and is a marker of cerebrovascular integrity. Impaired CVR is associated with increased risk of cerebro- and cardiovascular disease and death [1]. The temporal development of CVR has been studied in healthy subjects and in patients with cerebrovascular disease. In healthy persons, CVR is stable over time [2]. In the early phase after aneurysmal subarachnoid hemorrhage (aSAH), CVR is often impaired [3–8], especially in patients with massive hemorrhage, poor neurological status at admission, and vasospasm [9–15]. It has been suggested that transient reduction of CVR after aSAH may be associated with development of delayed cerebral ischemia and poor outcome [9, 16, 17]. There is, however, little knowledge regarding the time course of CVR in patients with unruptured intracranial aneurysms (UIA). It is unknown whether, and how, aneurysm treatment affects CVR. Information on the time course of CVR in patients treated for UIA may help in differentiating between potential effects of aneurysm treatment and the impact of an aneurysm bleeding.

The main objective of this study was to evaluate the time course of CVR in patients treated for an UIA by comparing

CVR within the first week after aneurysm treatment with CVR one year later. We further wanted to assess whether other factors like age, sex, smoking, hypertension, body mass index, aneurysm size, treatment side, or treatment modality were associated with the stability of CVR over time.

2. Methods

2.1. Participants and Time Scheme. In a previous study, we analyzed early postoperative CVR data from patients treated for UIA in the Department of Neurosurgery, Haukeland University Hospital, between February 2011 and May 2013 [18]. The patients were treated with either endovascular coiling or surgical clipping, and they were examined within the first week after aneurysm treatment. In the present study, CVR was reevaluated in the same patients one year after aneurysm treatment. Exclusion criteria were identical to those used in the previous study: former treatment of intracranial aneurysms; nonsaccular aneurysms; giant aneurysms treated with proximal artery occlusion; carotid stenosis (>50%) or occlusion; lack of transtemporal bone window in transcranial Doppler examination; and contraindications to acetazolamide (e.g., sulfonamide allergy, adrenal or pituitary insufficiency, and kidney or liver failure).

Demographics, aneurysm location, and treatment were recorded, as well as body mass index, smoking status, and hypertension (previously diagnosed and treated or systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg persistently observed during admission). Aneurysm size was measured using the following parameters: maximum diameter of the dome, independent of angles and directions (maximum diameter, Dmax), maximum diameter of the dome, perpendicular to the aneurysm height (width, W), maximum height from dome tip perpendicular to aneurysm neck (height, H), and diameter of the aneurysm neck (neck, N). Aspect ratio (H/N) and bottleneck ratio (W/N) were calculated [19, 20].

The study was conducted in accordance with the Declaration of Helsinki (2013) of the World Medical Association and was approved by the local ethics committee. All patients gave written informed consent.

2.2. Cerebrovascular Reactivity. CVR testing was performed using transcranial Doppler (TCD) monitoring of blood flow velocities in the middle cerebral arteries (MCA) before, during, and after intravenous injection of acetazolamide (AZ). The method has previously been described in detail [18]. Except for an additional manufacturer of AZ, the method of CVR testing was identical to the initial study [18]. The AZ manufacturers used in this study were Goldshield Ltd., Croydon, Surrey, UK; Sanofi Aventis, Paris, France; and Mercury Pharmaceuticals Ltd., Croydon, Surrey, UK. The AZ dose was 1000 mg for patients weighing < 80 kg, and 15 mg/kg for patients weighing ≥ 80 kg. The maximum dose was 1500 mg. All examinations in the initial and follow-up study were performed by the same sonographer (MLB).

Cerebrovascular reactivity was defined as the maximum percentage change in mean blood flow velocity (MFV) after administration of AZ: $\text{CVR}\,(\%) = [(\text{MFV}_{\text{AZ}} - \text{MFV}_{\text{BASELINE}})/\text{MFV}_{\text{BASELINE}}] \times 100$, where CVR is cerebrovascular reactivity, $\text{MFV}_{\text{BASELINE}}$ is baseline mean blood flow velocity (before AZ), and MFV_{AZ} is maximum mean blood flow velocity after AZ.

2.3. Statistical Analysis. Two measures of central tendency and dispersion were used: mean and standard deviation (SD) for variables that were symmetric around the mean, and median and interquartile range (IQR) for those that were nonsymmetric. In cases where patients underwent treatment for multiple aneurysms during the same procedure, averaged aneurysm size was used in the analyses. The relationships between blood flow velocities and CVR at the time of initial examination and one year later were studied using paired t-tests. Paired t-test was also used to assess possible differences in velocities and CVR related to side (right/left and ipsilateral/contralateral to the aneurysm treatment). Regarding treatment modality (clipping or coiling), two-sample t-tests were used. To simplify analyses, patients with midline aneurysms were allocated to the side chosen for endovascular or surgical approach. As in the previous study [18], mean CVR of the two sides (right and left) was calculated for all individuals. If the measurement on one side was missing, the mean CVR was set to the nonmissing value. Simple linear regressions, stratified on treatment modality, were conducted on mean CVR at follow-up versus mean CVR at first examination. Also, difference in mean CVR between first exam and follow-up was the outcome in a multiple regression and a set of simple linear regressions. Covariates were age, sex, hypertension, smoking, body mass index, weight difference from initial exam to follow-up, treatment modality, maximum aneurysm diameter (Dmax), mean CVR at the time of initial examination, and difference in mean AZ dose per kg from initial exam to follow-up. Lastly, maximum aneurysm diameter was included as covariate in a simple linear and multiple regression with CVR at the time of the initial examination as outcome, in addition to the covariates tested in a previous report (age, sex, hypertension, smoking, body mass index, and treatment modality) [18]. The regression analyses were repeated with ipsilateral CVR as outcome variable instead of mean CVR, and with stratification for age, sex, and treatment modality.

All statistical analyses were performed with R version 3.4.3 [21].

3. Results

3.1. Patients, Aneurysm, and Treatment. Of 37 patients examined in the initial study, two patients chose to abstain from the follow-up test due to side effects of AZ at the initial examination, and one patient did not meet for follow-up due to long travel to the hospital. This left us with a study population of 34 patients.

Table 1 shows patient characteristics. Weight difference is the difference in body weight from the first examination to follow-up. All other variables listed in the table were recorded at the time of aneurysm treatment. Mean age was 49.0 (SD 9.6, range 27–65) years. In 20 of the 34 patients (58.8%) the body

Table 1: Patients characteristics.

	($n = 34$)
Age, years[a]	49.0 (9.6)
Height, cm[a]	169.2 (8.6)
Weight, kg[a]	76.1 (15.5)
BMI, kg/m^2[a]	26.5 (4.8)
Weight difference, kg[a]	0.4 (4.7)
Female[b]	22 (64.7)
Hypertension[b]	15 (44.1)
Smoking[b]	
Current	19 (55.9)
Previous	11 (32.4)
Never	4 (11.8)

[a]mean (SD); [b]n (%); BMI: body mass index; SD: standard deviation.

weight was different at the time of follow-up compared with the first examination (range 10 kg reduction–13 kg increase). In 11 patients (32.4%) the weight difference was >2 kg. Table 2 shows aneurysm and treatment characteristics.

3.2. Cerebrovascular Reactivity. In total, 56 bilateral and 12 unilateral examinations were performed in the 34 patients. Unilateral examinations were more common in the initial exams (23.5%) compared with follow-up (11.8%), presumably because postoperative intracranial air can cause insufficient insonation. Median time between treatment and initial exam was 51.0 (IQR 39.5) hours. Median time between treatment and follow-up exam was 376.5 (IQR 31.8) days. Median time between initial examination and follow-up was 374.5 (IQR 29.3) days.

Of 68 examinations, 42 (61.8%) were performed using 1000 mg AZ. The remaining 26 examinations (38.2%) were done with 15 mg AZ per kg because of high bodyweight. Mean bodyweight was 76.1 (SD 15.5, range 40 to 110) kg at the time of the first examination and 76.6 (SD 17.2, range 40 to 118) kg at follow-up. Mean AZ dose was 15.1 (SD 2.3) mg/kg in the first examination and 15.1 (SD 2.4) mg/kg at follow-up. There was no correlation between AZ dose per kg and CVR (Pearson's $R = 0.08$, $p = 0.66$ in the first examination, and $R = -0.11$, $p = 0.52$ at follow-up).

Table 3 shows blood flow velocities and CVR results. In the initial examination MFV in the middle cerebral arteries was 58.6 cm/s before stimulation with AZ and 94.3 cm/s after, giving a mean CVR of 62.7%. Follow-up testing showed MFV 51.4 cm/s before AZ, 84.4 cm/s after, and mean CVR of 65.6%. Bilaterally, baseline and AZ-induced blood flow velocities were higher in the postoperative week compared with 1 year after aneurysm treatment ($p \leq 0.009$ in all situations). When assessing mean values of the right and left sides, no difference between CVR at first examination and follow-up was found ($p = 0.31$). When assessing CVR according to treatment laterality, there was no difference over time on the contralateral side (65.0% at follow-up versus 63.4% at the initial examination, $p = 0.65$). However, on the ipsilateral side of aneurysm treatment there was an apparent change in CVR over time. Ipsilateral CVR was 58.9% (SD 19.3) in the initial examination versus 66.1% (SD 18.5) at follow-up ($p = 0.04$), corresponding to an absolute increase of 7.2% and relative increase of 12%. Subgroup analyses for treatment modalities had lower sample sizes, and the significance disappeared ($p = 0.16$). CVR change on the ipsilateral side seemed larger in patients treated with clipping compared with patients treated with coiling (absolute increase 10.5 versus 4.7%, and relative increase 17 versus 8%), yet the number of patients in each subgroup is low ($n = 12$ for clipping and $n = 22$ for coiling) and results are inconclusive ($p = 0.42$). The same trend was found for mean CVR values of the right and left side, with an absolute and relative increase of 8.7% and 13% in patients treated with clipping versus 0.2% absolute reduction and 0% relative change in patients treated with coiling ($p = 0.18$). The tendency of larger CVR difference between exams was present for all patients treated with aneurysm clipping, regardless of whether temporal clipping of a parent artery was performed or not. However, despite similar values for CVR difference between exams, patients treated with temporal clipping appeared to have higher CVR values compared with patients treated with "standard" clipping (without the need for temporary clipping), at both the initial exam and follow-up. Due to few observations, statistical power is however insufficient to evaluate potential differences within the clipping subgroup.

Table 4 shows the results of the regression analyses regarding the relationship between difference in mean CVR from the first examination to follow-up and several different variables. In the simple analysis, maximum aneurysm diameter and CVR in the first examination were associated with a change in CVR. An 1 mm increase in the maximum diameter of the aneurysm dome was associated with an increase in CVR difference by 3.2 and 2.5 percentage points in the simple and multiple regressions, respectively ($p = 0.005$ and $p = 0.04$). For every percentage point increase in CVR in the first examination, the change in CVR from initial exam to follow-up was reduced with 0.3 percentage points ($p = 0.05$). The association was stronger in the multiple model, where the reduction in CVR change was 0.5 percentage points for every percentage point increase in CVR in the first examination ($p = 0.01$). In the multiple analyses age and treatment modality were also associated with change in CVR. For age, the change in CVR increased with 0.8 percentage points per year ($p = 0.03$). For treatment modality, the multiple model showed that patients treated with clipping had 13.8 percentage points increased change in CVR compared with patients treated with coiling ($p = 0.03$). There were no associations between change in CVR and sex, body mass index, body weight difference between exams, hypertension, and smoking. There were no major changes in the results when regression analyses were repeated after stratification for sex, age (≤50 years versus >50 years), and treatment modality (coiling versus clipping).

Regression analyses were also repeated with ipsilateral CVR as outcome variable instead of mean CVR. Patients with missing CVR values on the ipsilateral side, at the time of either the first exam or follow-up, were excluded. This applied to 7 of 34 (20.6%) patients: 2 of 22 (9.1%) patients treated with coiling and 5 of 12 (41.7%) patients treated with clipping.

Table 2: Aneurysm and treatment characteristics.

	$n = 34$
Multiple aneurysms, *n* (%)	12 (35.3)
Treatment modality, *n* (%)	
Coil	22 (64.7)
Clip[a]	12 (35.3)
Treatment side, *n* (%)[b]	
Left	18 (52.9)
Right	16 (47.1)
Location of treated aneurysms, *n* (%)	
MCA	14 (41.2)
ICA, incl. ophthalmic artery and PCOM	10 (29.4)
ACOM, anterior complex, and pericallosal artery	7 (20.6)
Basilar top, cerebelli superior, PICA, VB, and distal posterior	3 (8.8)
Size of treated aneurysms, mean (SD)[c]	
Maximum diameter (*D*max), mm	6.3 (2.4)
Height (*H*), mm	6.4 (2.8)
Neck (*N*), mm	4.1 (1.8)
Width (*W*), mm	5.4 (2.2)
Aspect ratio (*H*/*N*)	1.6 (0.5)
Bottleneck ratio (*W*/*N*)	1.4 (0.5)

[a]In four of twelve patients temporal clipping of a parent artery was performed; [b]one patient treated with combined clipping of an ACOM aneurysm and a right MCA aneurysm in one procedure was allocated to the right side. Eight patients with midline aneurysms (ACOM and basilar top) were allocated to the chosen side of approach; [c]the majority of patients received treatment for a single aneurysm. For the 4 of 34 patients (11.8%) that underwent treatment for two aneurysms during the same procedure, aneurysm size was averaged; ACOM: anterior communicating artery; ICA: internal carotid artery; MCA: middle cerebral artery; PCOM: posterior communicating artery; PICA: posterior inferior cerebellar artery; VB: vertebrobasilar artery; maximum diameter (*D*max): maximum diameter of the dome (independent of angles and directions); height (*H*): maximum height from dome tip perpendicular to aneurysm neck; neck (*N*): diameter of the aneurysm neck; width (*W*): maximum diameter of the dome, perpendicular to the aneurysm height (*H*).

The lower sample size in the analyses with ipsilateral CVR as outcome yielded more uncertainty. Apart from higher p values, findings were primarily consistent with the results of the original regressions using mean CVR as outcome. Maximum aneurysm diameter and CVR at first exam were still associated with change in ipsilateral CVR between exams in the simple analysis ($p = 0.05$), whereas the multiple analysis provided weaker evidence for such associations ($p = 0.22$ for aneurysm diameter and $p = 0.10$ for first CVR). The positive association between change in CVR and age and clipping found in the regression with mean CVR was less obvious in the regression with ipsilateral CVR. The estimate for age was 0.7 ($p = 0.10$) versus 0.8 ($p = 0.03$) in the regression with mean values. The estimate for clipping was 9.8 ($p = 0.19$) in the regression with ipsilateral values versus 13.8 ($p = 0.03$) in the regression with mean values.

Finally, regression analyses were performed to assess if larger aneurysm diameter was correlated with lower initial CVR. When only results from the initial exam were included in the statistical analyses, fewer observations yielded high p values. Maximum aneurysm diameter had an estimate of −0.6 in the simple analysis ($p = 0.61$) and −1.7 in the multiple analysis ($p = 0.15$). Few observations hamper the assessment of a possible association between larger aneurysm size and reduced CVR in the first week after aneurysm treatment.

Figure 1 shows a scatter plot of mean CVR at first exam and follow-up. The regression lines for the two treatment modalities are almost parallel, with the line for patients treated with clipping shifting up about 8 to 15 percentage points. This is in accordance with Table 4.

Figure 2 shows box plots comparing change in mean CVR from first exam to follow-up in patients treated with coiling and clipping. Although there was little evidence for difference in mean CVR change in patients treated with coiling compared with clipping ($p = 0.14$), Figure 2 hints that patients treated with clipping had a greater difference between the initial examination and follow-up. Still, the evidence is inconclusive.

Diamox Goldshield Ltd. was used in 44 CVR tests (64.7%), Sanofi Aventis in 20 tests (29.4%), and Mercury Pharmaceuticals Ltd. in 4 tests (5.9%). There did not seem to be any important differences in CVR between the three manufacturers (Mercury versus Goldshield: $p = 0.07$; Mercury versus Sanofi Aventis: $p = 0.84$; Goldshield versus Sanofi Aventis: $p = 0.46$).

4. Discussion

4.1. Main Findings. In this study, we found a lower CVR on the ipsilateral side of aneurysm treatment in the post-operative week compared with one-year follow-up. There was no evidence of any difference in CVR over time when mean values of the right and left sides were assessed. Larger aneurysm size is associated with increased change in CVR.

Table 3: Blood flow velocities and cerebrovascular reactivity at baseline and follow-up.

	First exam mean (SD)	Follow-up mean (SD)	Absolute difference	Relative difference	p
$MFV_{BASELINE}$ (cm/s)					
Ipsilateral	59.8 (13.8)	51.2 (13.3)	−8.6	0.86	<0.001
Contralateral	57.7 (14.7)	52.0 (12.1)	−5.7	0.90	0.003
Mean	58.6 (13.2)	51.4 (11.7)	−7.2	0.88	<0.001
MFV_{AZ} (cm/s)					
Ipsilateral	93.6 (18.0)	84.4 (20.2)	−9.2	0.90	0.001
Contralateral	93.4 (23.3)	85.0 (20.1)	−8.4	0.91	0.009
Mean	94.3 (20.0)	84.4 (18.5)	−9.9	0.90	<0.001
ΔMFV (cm/s)					
Ipsilateral	33.8 (9.2)	33.1 (9.8)	−0.7	0.98	0.43
Contralateral	35.7 (11.2)	33.0 (11.8)	−2.7	0.93	0.15
Mean	35.7 (10.2)	33.1 (9.9)	−2.7	0.93	0.09
CVR (%)					
Ipsilateral	58.9 (19.3)	66.1 (18.5)	7.2	1.12	0.04
Contralateral	63.4 (17.5)	65.0 (23.6)	1.7	1.03	0.65
Mean	62.7 (17.2)	65.6 (19.4)	2.9	1.05	0.31
MV (n)					
Ipsilateral	7	3			
Contralateral	1	1			

CVR: cerebrovascular reactivity; $MFV_{BASELINE}$: baseline mean blood flow velocity (before acetazolamide); MFV_{AZ}: maximum mean blood flow velocity after acetazolamide; ΔMFV: absolute change in mean flow velocity after acetazolamide; MV: missing value; p: p value from paired t-test (follow-up–first); SD: standard deviation. Note that if one side had a missing value, the mean is just the remaining value. This is why the mean is not simply the mean of ipsilateral and contralateral values. Patients with MV were excluded from the paired t-test. The sample size was therefore reduced in the analyses of ipsilateral and contralateral values (ipsilateral $n = 27$, contralateral $n = 33$, mean $n = 34$).

Table 4: Regression results: difference in mean CVR between exams versus a number of variables.

	Simple		Multiple	
	Estimate	p	Estimate	p
Age, years	0.1	0.68	0.8	0.03
Female	−4.9	0.42	−4.5	0.46
BMI, kg/m^2	−0.2	0.78	−0.1	0.84
Weight difference, kg	0.3	0.63	0.3	0.81
Hypertension	1.7	0.78	3.3	0.58
Smoking				
Current	ref	-	ref	-
Previous	−2.8	0.67	−2.8	0.62
Never	−5.2	0.59	−0.7	0.94
Treatment modality				
Coil	ref	-	ref	-
Clip	9.0	0.14	13.8	0.03
Maximum aneurysm diameter (Dmax)	3.2	0.005	2.5	0.04
Mean CVR at first exam, %	−0.3	0.04	−0.5	0.01
Difference in AZ dose per kg	−2.4	0.49	−1.9	0.81

AZ: acetazolamide; BMI: body mass index; CVR: cerebrovascular reactivity; Dmax: maximum diameter of the aneurysm dome (independent of angles and directions); ref: reference.

In addition, results suggest that the difference in CVR may be greater in patients treated with clipping compared with coiling, but evidence is inconclusive.

In a previous study, where CVR was examined in the first week after aneurysm treatment, we did not find any difference when comparing treated and untreated sides (59.4% versus 63.0%, $p = 0.16$) [18]. We concluded that CVR in patients with UIA did not differ from normal values reported in healthy subjects and that findings did not indicate a systemically impaired vascular system in patients with UIA. New

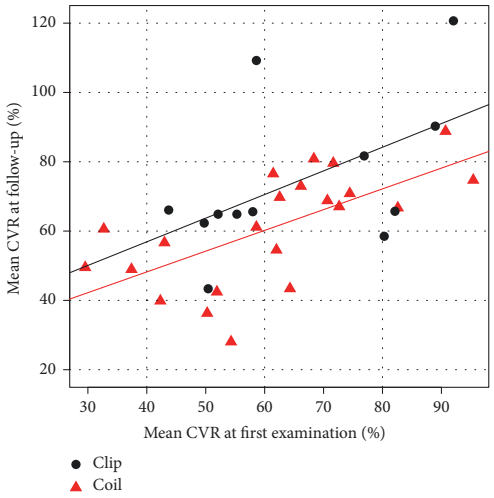

Figure 1: Scatter plot of mean cerebrovascular reactivity (CVR) at the time of initial examination and follow-up, together with regression lines. Results for patients treated with coiling are marked with red triangles, and results for patients treated with clipping are marked with black dots.

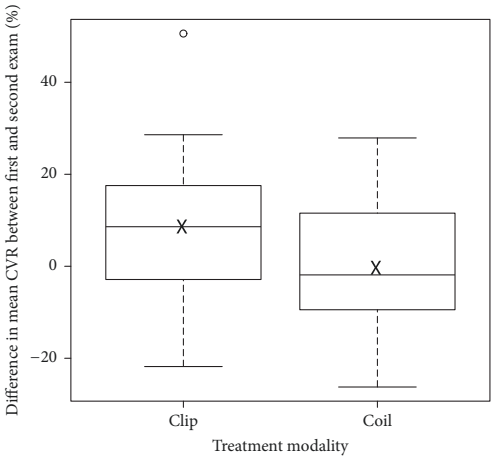

Figure 2: Box plots comparing change in mean cerebrovascular reactivity (CVR) from the first examination to follow-up in patients treated with coiling and clipping. Boxes extend from the 25th to the 75th percentile. Horizontal bars represent the median, and whiskers extend to the most extreme point that is less than 1.5 times the interquartile range from the box. Mean values are marked with crosses, and a single outlier is depicted as a circle.

information based on results from follow-up testing one year later now indicates that there may be a side difference in CVR after aneurysm treatment after all. Ipsilateral CVR was 58.9% after treatment versus 66.1% one year later, and contralateral CVR was 63.4% after treatment versus 65.0% one year later. The postoperative CVR of 58.9% seems to stand out as lower than the other CVR values, indicating a temporary reduction in CVR on the treated side. Even though we could not rule out the fact that the trend with lower CVR on the ipsilateral side was due to chance when only postoperative results were assessed ($p = 0.16$) the difference was more pronounced when follow-up results were included (difference in ipsilateral CVR over time, $p = 0.04$). Still, the sample size is limited and results must be interpreted with caution.

Furthermore, this study showed higher baseline and AZ-induced blood flow velocities in the postoperative week compared with one year after aneurysm treatment. The increased velocities can be explained by postoperative hyperemia. Transient hyperemia is common after craniotomy [22]. However, hyperemia has previously only been found in the first postoperative hour [22], and the median time for the first CVR testing in our study was 51.0 (IQR 39.5) hours after treatment. To our knowledge, there have been no reports about transient hyperemia after endovascular aneurysm treatment. Alternatively, posttreatment spasm could be the cause of elevated blood flow velocities at the initial exam. Moreover, comparison of absolute blood flow velocities is problematic as the probe positioning and insonation angle probably were different at the time of the initial and follow-up exam. Still, there is no reason why altered insonation angle and probe positioning should only cause increased velocities. In theory, changes in technical insonation aspects could just as well cause a reduction of measured velocities.

Our finding of reduced CVR on the ipsilateral side after aneurysm treatment may be related to postoperative hyperemia. It is possible that a transient hyperemia in response to aneurysm clipping or coiling affects the arteriolar vasodilating capacity and thus influences CVR. Baseline velocities ($MFV_{BASELINE}$) were higher at first exam compared with one-year follow-up (59.8 cm/s versus 51.2 cm/s, $p < 0.001$), whereas the absolute change in velocity (ΔMFV) was the same at the two examination times (33.8 cm/s versus 33.1 cm/s, $p = 0.43$). Since CVR is defined as percentage change in velocity after AZ compared with baseline, the same ΔMFV yields lower CVR values when baseline velocities are increased (unchanged numerator and higher denominator of the fraction). An alternative explanation for decreased CVR after aneurysm treatment may be that harboring an aneurysm in itself impairs CVR. This effect may still be present in the first postoperative days, while vasodilating capacity can be restored after aneurysm treatment and CVR normalized one-year later. Since TCD and AZ testing were not performed prior to aneurysm treatment it is difficult to say if the reduction in CVR is caused by the aneurysm itself or by aneurysm treatment.

4.2. Time Course of CVR in Healthy Subjects. Schwertfeger et al. (2006) assessed the time course of CVR in healthy subjects [2]. TCD and AZ were used to investigate CVR in 33 healthy subjects at baseline and after 1 to 3 years (mean 21.6 months). They performed unilateral testing and found no changes in CVR over time. Like in our study, they did not find any association between sex and smoking and CVR

change. Unlike their findings, we found a positive association between age and change in CVR from first examination to follow-up ($p = 0.03$ in the multiple regression model). The possible influence by age on CVR is unclear, and studies in healthy subjects have shown varying effects [23–30].

4.3. Time Course of CVR in Patients with Intracranial Aneurysms. Several studies have assessed the time course of CVR in patients with ruptured intracranial aneurysms. CVR is often impaired in the early phase after aSAH [3–6], especially in patients with massive hemorrhage, poor neurological status at admission, and vasospasm [9–15]. There is a possible association between progressive impairment in CVR in the early phase after aSAH and subsequent development of delayed cerebral ischemia [9, 16]. Transient reduction of CVR may also be associated with poor outcome [17]. Follow-up studies months and years after aSAH have shown normalization of CVR, regardless of the severity of hemorrhage and presence of vasospasm in the acute phase [31–33]. In contrast to the numerous studies on CVR in patients with aSAH there are few studies addressing CVR in patients with UIA. To our knowledge only one study has used AZ test and TCD to assess CVR in this patient group [18], and six reports have used CO_2 as vasoactive stimuli [3, 4, 7, 14, 15, 33]. In these studies, CVR testing was performed either at a single time-point after aneurysm treatment [18, 33] or at multiple time-points within 24 hours in close relation to the time of aneurysm surgery [3, 4, 7, 14, 15]. To our knowledge, this is the first study to investigate within-subject differences over time in patients treated for UIA. We found evidence in favor of a transient reduction of CVR on the ipsilateral side of aneurysm treatment, and recommend separate assessment of ipsilateral and contralateral CVR as mean values of right and left sides can conceal side-differences. Our finding of possible transient reduction of CVR also after treatment for *unruptured* aneurysms provides valuable insight and may enable better interpretation of CVR results after aneurysm treatment.

Studies with measurement of CVR at a single time-point have not shown any association between CVR and aneurysm treatment modality [18, 31], whereas in this follow-up study a possible association between treatment modality and change in CVR was found. Patients treated with aneurysm clipping appeared to have a larger difference in CVR between exams. This tendency was present for all patients treated with aneurysm clipping, regardless of whether temporal clipping of a parent artery was performed or not. Still, the number of patients in the subgroups for treatment modality is low. In particular, the number of observations in patients treated with clipping is reduced due to missing values, presumably related to postoperatively intracranial air. Results should thus be interpreted with caution.

4.4. Technical Considerations. Blood flow velocities demonstrate diurnal variations [34]. The follow-up examination was not performed at the identical time of day as the initial CVR test, but the time differences between exams were small (median 2.25 hours, IQR 2.56 hours) and we consider their influence as negligible. Mean AZ dose was the same in the first examination and follow-up (mean 15.1 mg/kg, SD 2.3 and 2.4 mg/kg, respectively). A third of the patients had a weight difference of >2 kg from first exam to follow-up. Nonetheless, the weight difference was small (mean 0.4 kg, SD 4.7 kg) and there was no association between weight difference and change in CVR ($p = 0.93$). We used different brands of AZ, but there was no differences in CVR between the three manufacturers. As expected, insufficient insonation due to postoperative intracranial air was more common on the ipsilateral side of aneurysm clipping compared with the contralateral side, or compared with patients treated with coiling.

4.5. Strengths and Limitations. To our knowledge, this is the first study to investigate within-subject differences in CVR over time in patients treated for UIA. The sample size is in the upper range compared with CVR studies in healthy subjects [2, 35–46]. The method of testing was identical at initial examination and follow-up. We used the same sonographer (MLB) in all examinations to reduce operator variability, as the intrarater reproducibility for TCD examinations has been found superior to interrater [47, 48].

The AZ dose should ideally have been bodyweight-based in all patients in the study, not only in patients weighing ≥80 kg. Still, the recommended AZ dose of 13 to 18 mg/kg [39, 49] was achieved for the vast majority of patients (91.2%). Blood flow velocities are affected by physiological factors such as hematocrit, arterial CO_2 tension, heart rate, and mean arterial pressure [50], and hyperventilation can theoretically counteract the vasodilatory effect of AZ. We did not routinely monitor these parameters in our study.

Even though the sample size is rather large compared with other CVR studies, the limited number of patients makes it difficult to draw definite conclusions regarding regression results and subgroup effects, especially for treatment modality. The regression analyses based on ipsilateral CVR were hampered by missing values in several patients, especially in patients treated with clipping. Subgroup analysis based on laterality and treatment modality should be considered when planning the sample size of future studies.

To best assess the effect of aneurysm treatment on CVR it would have been preferable to examine patients before and after the procedure. Patients were not examined before aneurysm treatment in our study, partly because this study was part of a larger study where the set-up was designed for comparison of CVR in patients treated for ruptured and unruptured aneurysms, and partly because we wanted to avoid test-induced aneurysm rupture, a highly unlikely yet serious complication.

5. Conclusions

This study implies that patients with UIA may have a temporary reduction in CVR on the ipsilateral side after aneurysm treatment. The change in CVR is associated with larger aneurysm size and is possibly more pronounced in patients treated with clipping. We recommend that results from ipsilateral and contralateral sides should be assessed separately as mean values can conceal side-differences in CVR.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Impaired cerebrovascular reactivity may predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Introduction: Delayed cerebral ischemia (DCI) is a major cause of disability and death after aneurysmal subarachnoid hemorrhage. The literature suggests that impaired cerebrovascular reactivity (CVR) may be a predictor for DCI; still no CVR based prediction model has been developed. Increased knowledge about possible predictors of DCI can improve patient management in high-risk patients and allow for shorter hospital stay in low-risk patients.

Method: CVR was examined in 42 patients with aneurysmal subarachnoid hemorrhage and 37 patients treated for unruptured intracranial aneurysm, using acetazolamide test with transcranial Doppler monitoring of blood flow velocities. Patients were followed for development of DCI, separated into clinical deterioration and radiographic infarction.

Results: For all patients, regardless of aneurysm rupture status, CVR was on average 5.5 percentage points lower on the ipsilateral side of aneurysm treatment. Patients with clinical deterioration due to DCI had lower CVR than patients without DCI, and the difference was larger on the contralateral side (33.9% vs. 49.2%). Two prediction models were constructed for clinical deterioration due to DCI. The area under the receiver operating characteristic curve was 0.82 in the model using established predictors, and 0.86 in the model that also included CVR.

Conclusion: Our findings support the hypothesis that impaired CVR may be an independent predictor of clinical deterioration due to DCI, and may assist in identifying patients at risk after aneurysmal subarachnoid hemorrhage. Ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of DCI development, thus highlighting the need to evaluate ipsi- and contralateral CVR separately.

1. Introduction

Delayed cerebral ischemia (DCI) is a major cause of disability and death after aneurysmal subarachnoid hemorrhage (aSAH) [1,2]. Identification of patients at high risk of developing DCI can improve patient management, and valid predictors of DCI could allow for shorter hospital stay in patients at low risk. Large amount of subarachnoid blood and poor clinical admission status are known predictors for DCI [3–7]. Other predictors, like smoking and hydrocephalus have been suggested [8]. Still, additional information is needed to make prediction more accurate.

Cerebrovascular reactivity (CVR) is often impaired in the early phase after aSAH [9–15], especially in patients with poor clinical grade [12,16–18]. Several test methods have shown reduced CVR in patients with aSAH compared with unruptured intracranial aneurysms (UIAs) [9–12,19], but this has not been confirmed for the transcranial Doppler (TCD) and acetazolamide (AZ) test (TCD-AZ test) [20]. With one exception [14], the literature suggests that impaired CVR may be associated with vasospasm and can be a potential predictor for DCI after aSAH [15–17,21–30]. However, sample sizes have been limited, methodology has varied and inconsistent and outdated definitions of DCI have been used. To our knowledge, no CVR based prediction model has yet been developed.

The main objective of this study was to assess if impaired CVR can

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be a predictor for DCI after aSAH. In adjunct, we wanted to assess the relationship between aneurysm rupture status and CVR assessed by TCD-AZ test, in order to improve understanding of CVR in this patient group.

2. Methods

2.1. Participants

Patients treated at the Department of Neurosurgery, Haukeland University Hospital between February 2011 and May 2013 were prospectively included. Inclusion criteria were: age ≥ 18 years and treatment for saccular intracranial aneurysms with endovascular coiling or surgical clipping. Exclusion criteria were: previous treatment of intracranial aneurysms, giant aneurysms treated with proximal artery occlusion, carotid stenosis (> 50%) or occlusion, lack of transtemporal bone window in TCD examination, DCI present at admission, moribund patients, and contraindications to acetazolamide.

2.1.1. Clinical, sonographic and radiographic assessment

In all patients demographics, body weight, smoking status, hypertension, aneurysm location, and treatment modality was recorded. In patients with ruptured aneurysms, the clinical status upon admission was evaluated with Glasgow Coma Scale (GCS) [31] and World Federation of Neurological Surgeons (WFNS) scale [32]. Admission computed tomographic (CT) scan was classified according to the modified CT Fisher scale [33].

Patients were monitored clinically, sonographically and radiographically for development of DCI, vasospasm and cerebral infarction. Neurological status was scored routinely three times a day, and more frequent as regarded necessary. As a pragmatic choice, sonographic examinations were performed whenever possible, in order to avoid conflicts with patient investigations or treatment. Blood flow velocities in major intracranial arteries were assessed with transcranial color-coded sonography (TCCS) using a portable Philips CX50 system (5–1 MHz sector array probe) and Lindegaard Index was calculated [34]. TCCS was performed daily and more frequent if neurological deterioration occurred. Neuroimaging, i.e. CT or magnetic resonance imaging (MRI) with or without angiography and digital subtraction angiography (DSA) was performed tailored to the clinical situation. An experienced neuroradiologist (GM) assessed all angiograms, CT and MRI scans retrospectively for vasospasm and cerebral infarctions.

2.1.2. Cerebrovascular reactivity

CVR testing was performed with acetazolamide (AZ). The AZ dose was 1000 mg for patients weighing < 80 kg, and 15 mg/kg for patients weighing ≥80 kg. The maximum dose was 1500 mg. CVR testing was performed after aneurysm treatment to avoid risk of (re-)rupture. Patients treated for unruptured intracranial aneurysms (UIA) were examined once, whereas patients treated for aSAH underwent serial testing during the hospital stay. The time interval between examinations was minimum 24 h. To avoid steal phenomenon and neurological deterioration, CVR testing was not performed after a patient was diagnosed with DCI. TCD was used to monitor blood flow velocities in the middle cerebral arteries (MCA) after intravenous injection of acetazolamide (AZ) [20]. Cerebrovascular reactivity was calculated as the maximum percentage change in MFV in MCA after administration of acetazolamide: CVR (%) = $[(MFV_{AZ} - MFV_{BASELINE}) / MFV_{BASELINE}] \times 100$, where $MFV_{BASELINE}$ is mean blood flow velocity before acetazolamide and MFV_{AZ} is mean blood flow velocity (maximum change) after acetazolamide. In patients with a paradoxical velocity reduction after AZ due to a steal phenomenon, CVR will be a negative value.

2.1.3. Clinical deterioration and cerebral infarction due to delayed cerebral ischemia

All patients with aSAH, regardless of presence of ischemic symptoms or not, were given 60 mg nimodipine orally every four hours to prevent DCI [35,36]. Critically ill patients and patients with swallowing difficulties were given nimodipine as intravenous infusion 2 mg/h. Patients with severe and refractory radiographic vasospasm and clinical deterioration due to DCI were given intraarterial nimodipine [37]. Patient management was not influenced by CVR results.

We distinguished between clinical deterioration and radiographic infarction due to DCI [38,39].

Clinical deterioration ($DCI_{clinical}$) was defined as a new focal neurological impairment or ≥ 2 points reduction in Glasgow Coma Score, lasting for minimum 1 h, and not appearing immediately after aneurysm occlusion. Other causes of deterioration were excluded by clinical assessment, cerebral CT or MRI, and laboratory analyses.

Radiographic infarction ($DCI_{infarction}$) was defined as a new infarction identified on CT or MR scans during the hospital stay, within six weeks after aSAH. Infarctions present on the admission or immediate postoperative CT, and hypodensities resulting from the clipping or coiling procedure, ventricular catheter placement or intraparenchymal hematoma were not regarded as cerebral infarctions from DCI.

Angiographic vasospasm was defined as arterial narrowing present on CTA, MRA or DSA, not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia. Angiographic vasospasm was classified as none, mild (< 33% reduction in arterial diameter), moderate (34–66%) or severe (≥67%), and was also categorized with the Nathal grading scale [40].

Sonographic vasospasm was defined as time-averaged peak velocity (TAPV) ≥120 cm/s in any cerebral artery and Lindegaard index ≥3

Table 1
Patient, aneurysm and treatment characteristics.

	aSAH (n = 42)	UIA (n = 37)
Age, years[a]	53 ± 13	50 ± 11
Height, cm[a]	171 ± 9	169 ± 8
Weight, kg[a]	76 ± 18	77 ± 16
BMI, kg/m^2[a]	26 ± 5	27 ± 5
Female	24 (57.1)	24 (64.9)
Hypertension	19 (45.2)	18 (48.6)
Smoking		
Current	27 (64.3)	20 (54.1)
Previous	8 (19.0)	13 (35.1)
Never	7 (16.7)	4 (10.8)
Multiple aneurysm	9 (21.4)	12 (32.4)
Aneurysm diameter[a,b]	7 ± 3	7 ± 3
Location treated aneurysms		
Middle cerebral artery	12 (28.6)	17 (45.9)
ACOM, anterior complex and pericallosa	17 (40.5)	7 (18.9)
ICA, incl. ophthalmic artery and PCOM	6 (14.3)	10 (27.0)
Basilar top, cerebelli superior, PICA, VB, distal posterior	7 (16.7)	3 (8.1)
Treatment modality		
Coil	30 (71.4)	22 (59.5)
Clip	12 (28.6)	15 (40.5)
Treatment side[c]		
Left	21 (50.0)	19 (51.4)
Right	21 (50.0)	18 (48.6)

ACOM: anterior communicating artery; aSAH: aneurysmal subarachnoid hemorrhage; BMI: body mass index; ICA: internal carotid artery; PCOM: posterior communicating artery; PICA: posterior inferior cerebellar artery; UIA: unruptured intracranial aneurysms; VB: vertebrobasilar arteries.

[a] Mean ± standard deviation. All other variables are reported as n (%).

[b] Maximum diameter of the aneurysm dome. For patients with aSAH the size of the ruptured aneurysm is reported. For patients that underwent treatment for multiple UIA during the same procedure, aneurysm size was averaged.

[c] Twenty-four patients with midline aneurysms (ACOM and basilar top) were allocated to the chosen side of approach. One patient treated with combined clipping of an ACOM aneurysm and a right middle cerebral artery aneurysm in one procedure was allocated to the right side. The coiling procedure failed to adequately secure the aneurysm in one patient, so clipping was performed instead.

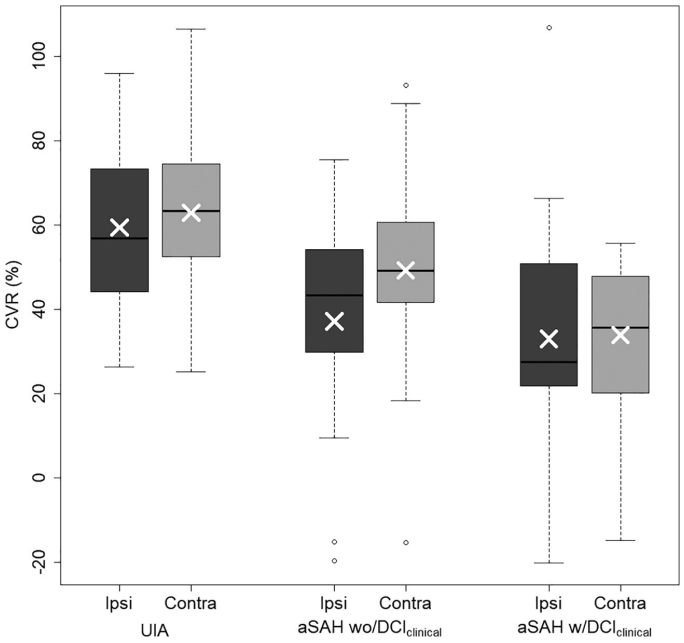

Fig. 1. Box plots comparing cerebrovascular reactivity (CVR) in patients with unruptured intracranial aneurysms (UIA), aneurysmal subarachnoid hemorrhage (aSAH) without clinical deterioration due to delayed cerebral ischemia (DCI), and aSAH with clinical deterioration due to DCI. For patients with aSAH serial measurements of CVR were performed, and the lowest measured value is presented. Ipsilateral CVR are shown in dark grey boxes, and contralateral CVR in light grey boxes. Boxes extend from the 25th to the 75th percentile. Horizontal bars represent the median, and whiskers extend to the most extreme point that is < 1.5 times the interquartile range from the box. Mean values are marked with white crosses, and outliers are depicted as points.

Table 2
Blood flow velocities and cerebrovascular reactivity in patients with ruptured vs. unruptured aneurysms.

	UIA (n = 37)	aSAH (n = 42)			
	Singel exam	First exam	Lowest value	Average of all exams	*p*-values UIA vs. aSAH
$MFV_{BASELINE}$ (cm/s)					
Ipsi	60 ± 14	57 ± 20	55 ± 19	61 ± 18	0.54, 0.25, 0.79
Contra	58 ± 14	59 ± 18	53 ± 18	60 ± 19	0.79, 0.18, 0.59
MFV_{AZ} (cm/s)					
Ipsi	94 ± 18	80 ± 28	76 ± 27	86 ± 25	0.02, 0.003, 0.15
Contra	93 ± 23	86 ± 29	79 ± 29	89 ± 29	0.25, 0.02, 0.42
ΔMFV_{AZ} (cm/s)					
Ipsi	34 ± 9	23 ± 21	18 ± 17	25 ± 17	0.004, < 0.001, 0.01
Contra	36 ± 11	28 ± 19	22 ± 15	29 ± 16	0.03, < 0.001, 0.03
CVR (%)					
Ipsi	59 ± 19	43 ± 35	33 ± 28	45 ± 30	0.02, < 0.001, 0.02
Contra	63 ± 17	48 ± 27	40 ± 23	51 ± 25	0.008, < 0.001, 0.01

[34]. Severe sonographic vasospasm was defined as TAPV ≥200 cm/s and Lindegaard index ≥6.

2.1.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki (2013) of the World Medical Association, and was approved by the local ethics committee (the Regional Committees of Western Norway for Medical and Health Research Ethics, approval number 2011/144). Written informed consent was obtained from all patients or a legal representative.

2.2. Statistical analysis

We reported CVR separately as ipsilateral and contralateral values to avoid that mean values could obscure side differences [41]. Due to the wide range of reported CVR measured by TCD and AZ in healthy subjects [42–54] and patients with UIA [20], we studied CVR as a continuous variable. Effects are reported per percentage point change in CVR. Midline aneurysms were allocated according to chosen side of approach for treatment. Standard *t*-tests and multiple regression analyses (adjusted for age, sex, hypertension, smoking, aneurysm diameter and treatment modality) were carried out to examine the relationship between CVR and rupture status.

We then compared clinical, radiographical and sonographical variables of patients with and without $DCI_{clinical}$, with chi-squared or Fisher's exact test, as appropriate. Next, we assessed the predictive potential of both contralateral and ipsilateral CVR for $DCI_{clinical}$ and $DCI_{infarction}$, to decide which measure of CVR was most appropriate to use in patients with multiple measurement (first, lowest, or within-patient average of all exams). A priori, we chose the lowest or first measured CVR as the exposure (more convenient in clinical use). *t*-test was used to compare CVR in aSAH patients with and without $DCI_{clinical}$ or $DCI_{infarction}$, and to assess side differences. Simple logistic regression analyses were conducted for both $DCI_{clinical}$ and $DCI_{infarction}$ versus both within-patient average CVR and lowest measured contralateral CVR. Further, box plots were constructed, based on the lowest measured

Table 3
Characteristics of patients with aneurysmal subarachnoid hemorrhage.

	Total (n = 42[a])	Clinical DCI (*n* = 22)	No clinical DCI (*n* = 19)	p-Value
GCS on admission[b]	11 ± 4	11 ± 4	12 ± 4	0.44
WFNS				
I GCS 15	8 (19.0)	1 (4.5)	7 (36.8)	0.02[c]
II GCS 13–14, without neurological deficit	14 (33.3)	9 (40.9)	5 (26.3)	0.51
III GCS 13–14, with neurological deficit	2 (4.8)	1 (4.5)	1 (5.3)	1.00[c]
IV GCS 7–12	10 (23.8)	7 (31.8)	3 (15.8)	0.29[c]
V GCS 3–6	8 (19.0)	4 (18.2)	3 (15.8)	1.00[c]
Modified CT Fisher				
1 Thin SAH without IVH	6 (14.3)	1 (4.5)	5 (26.3)	0.08[c]
2 Thin SAH with IVH	8 (19.0)	4 (18.2)	3 (15.8)	1.00[c]
3 Thick SAH without IVH	15 (35.7)	7 (31.8)	8 (42.1)	0.72
4 Thick SAH with IVH	13 (31.0)	10 (45.5)	3 (15.8)	0.09
Hydrocephalus (during primary stay)	30 (71.4)	20 (90.9)	9 (47.4)	0.007
Cerebral infarction due to DCI	19 (45.2)	13 (59.1)	5 (26.3)	0.07
Angiographic vasospasm				
None	22 (52.4)	6 (27.3)	16 (84.2)	< 0.001
Mild	3 (7.1)	2 (9.1)	1 (5.3)	1.00[c]
Moderate	12 (28.6)	9 (40.9)	2 (10.5)	0.07
Severe	5 (11.9)	5 (22.7)	0 (0.0)	0.05[c]
Angiographic scale ad modum Nathal[d]				
No vasospasm	22 (52.4)	6 (27.3)	16 (84.2)	< 0.001
One axis	5 (11.9)	2 (9.1)	2 (10.5)	1.00[c]
Two axes	1 (2.4)	1 (4.5)	0 (0.0)	1.00[c]
Three axes	6 (14.3)	5 (22.7)	1 (5.3)	0.19[c]
Generalized/diffuse vasospasm	8 (19.0)	8 (36.4)	0 (0.0)	0.004[c]
Sonographic vasospasm[e]				
None	20 (48.8)	1 (4.8)	18 (94.7)	< 0.001
Mild to moderate	14 (34.1)	13 (61.9)	1 (5.3)	< 0.001
Severe	7 (17.1)	7 (33.3)	0 (0.0)	0.009[c]

aSAH: aneurysmal subarachnoid hemorrhage; CT: Computer Tomography; DCI: Delayed cerebral ischemia; GCS: Glasgow Coma Score; IVH: intraventricular hemorrhage; SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurosurgical Societies score.

[a] Missing information regarding presence or absence of clinical DCI in one patient due to sedation

[b] Mean ± standard deviation. All other variables are reported as n (%)

[c] Due to few observations Fishers exact is used instead of chi-squared test

[d] The vascular axes were defined as follows: a) internal carotid artery, b) middle cerebral artery, c) anterior cerebral artery, d) vertebral artery, e) basilar artery, f) posterior cerebral artery, and g) any other arterial territory.

[e] Missing sonographic information in one patient.

iCVR and cCVR for UIA, aSAH without $DCI_{clinical}$, and aSAH with $DCI_{clinical}$.

From this, two prediction models for $DCI_{clinical}$ were created. Model I included WFNS, modified CT Fisher scale, age, sex, smoking, and hydrocephalus, all variables suspected to affect risk of $DCI_{clinical}$. Model II included all variables from Model I plus contralateral CVR. Model discrimination was assessed with area under the ROC curve (AUC), and model calibration with Hosmer-Lemeshow's C and calibration plots [55]. Results were adjusted for optimism using the bootstrapping techniques [56]. Uniformity of fit was evaluated across clinical grade (WFNS I-III vs. IV-V).

Statistical analysis was performed with R version 3.4.3 [57]. The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. Results

3.1. Patients, aneurysm and treatment

An overview of the source population is available in the online supplement (Table S1). Of 136 patients consecutively recruited during the study period, 57 were excluded, leaving a study population of 79 patients. In total, 37 patients were treated for UIA and 42 patients had aSAH (Table 1).

3.2. Cerebrovascular reactivity

In total, 101 bilateral and 20 unilateral examinations were performed. In patients with aSAH, 84 examinations were done. Median time for first exam was 3.2 (IQR 3.2; range: 1.3–15.0) days after ictus and 2.3 (IQR 2.9; range: 0.8–10.8) days after aneurysm treatment. Median time for the exam with the lowest CVR value was 5.3 (IQR 4.5; range: 1.8–20.2) days after ictus and 4.7 (IQR 3.9; range: 0.8–19.8) days after aneurysm treatment. In patients with UIA, a single examination was performed a median of 2.2 (IQR: 1.8; range: 1.1–6.2) days after aneurysm treatment.

3.3. Ruptured versus unruptured aneurysms

Patients with aSAH had lower CVR compared with patients with UIA (Fig. 1). There was no difference in baseline velocities ($MFV_{BASELINE}$) between aSAH and UIA patients (Table 2). Increase in velocity after AZ (ΔMFV_{AZ}) was however smaller in patients with aSAH, yielding lower both ipsilateral and contralateral CVR. For all patients, regardless of aneurysm rupture status, CVR was on average 5.5 percentage points lower on the ipsilateral side ($p = .04$). Regression analyses (adjustment for age, sex, hypertension, smoking, aneurysm diameter and treatment modality) confirmed that CVR was lower in patients with aSAH. Patients with UIA had a single CVR measurement, whereas aSAH patients were subject to several measurements. There are thus several approaches to calculate individual CVR: the first exam, the lowest value across exams, or the within-patient average for all exams, on both the ipsilateral and contralateral side. Using the first exam, the adjusted ipsilateral CVR was 19.6 percentage points lower in patients with aSAH ($p = .005$), and the contralateral CVR was 16.6 percentage points lower ($p = .002$). Using the lowest value across exams, the adjusted difference between the aSAH and UIA groups was 31.1 percentage points on the ipsilateral side ($p < .001$), and 23.6 percentage points on the contralateral side ($p < .001$). Using the within-patient average, CVR was 19.6 percentage points lower among patients with aSAH on the ipsilateral side ($p = .002$) and 14.7 percentage points lower on the contralateral side ($p = .004$).

3.4. Delayed cerebral ischemia and cerebral infarctions

Of 42 aSAH patients, 22 (52.4%) developed $DCI_{clinical}$. Median time from ictus to diagnosis of $DCI_{clinical}$ was 9 days (IQR 4.8, range 5–19). Furthermore, 19 patients (45.2%) developed $DCI_{infarction}$, and five patients (11.9%) developed infarctions from other causes (Table 3). Four patients with severe, refractory radiographic vasospasm and $DCI_{clinical}$ were given nimodipine intrarterially as rescue therapy and survived with $DCI_{infarction}$. In all patients, angiographic vasospasm and $DCI_{infarction}$ were located bilaterally or on the same side as the ruptured aneurysm. No patients had isolated vasospasm or infarctions on the contralateral side of the ruptured aneurysm. The overall prevalence of poor grade patients and thick bleedings was high; with WFNS grade IV-V in 42.9% of all patients with aSAH, and modified Fisher grade 3–4 in 66.7%. The proportion of patients with excellent clinical admission status (WFNS grade I) was lower ($p = .02$) and hydrocephalus was more prevalent ($p = .007$) in patients with $DCI_{clinical}$.

The different approaches to CVR (first exam, lowest value and

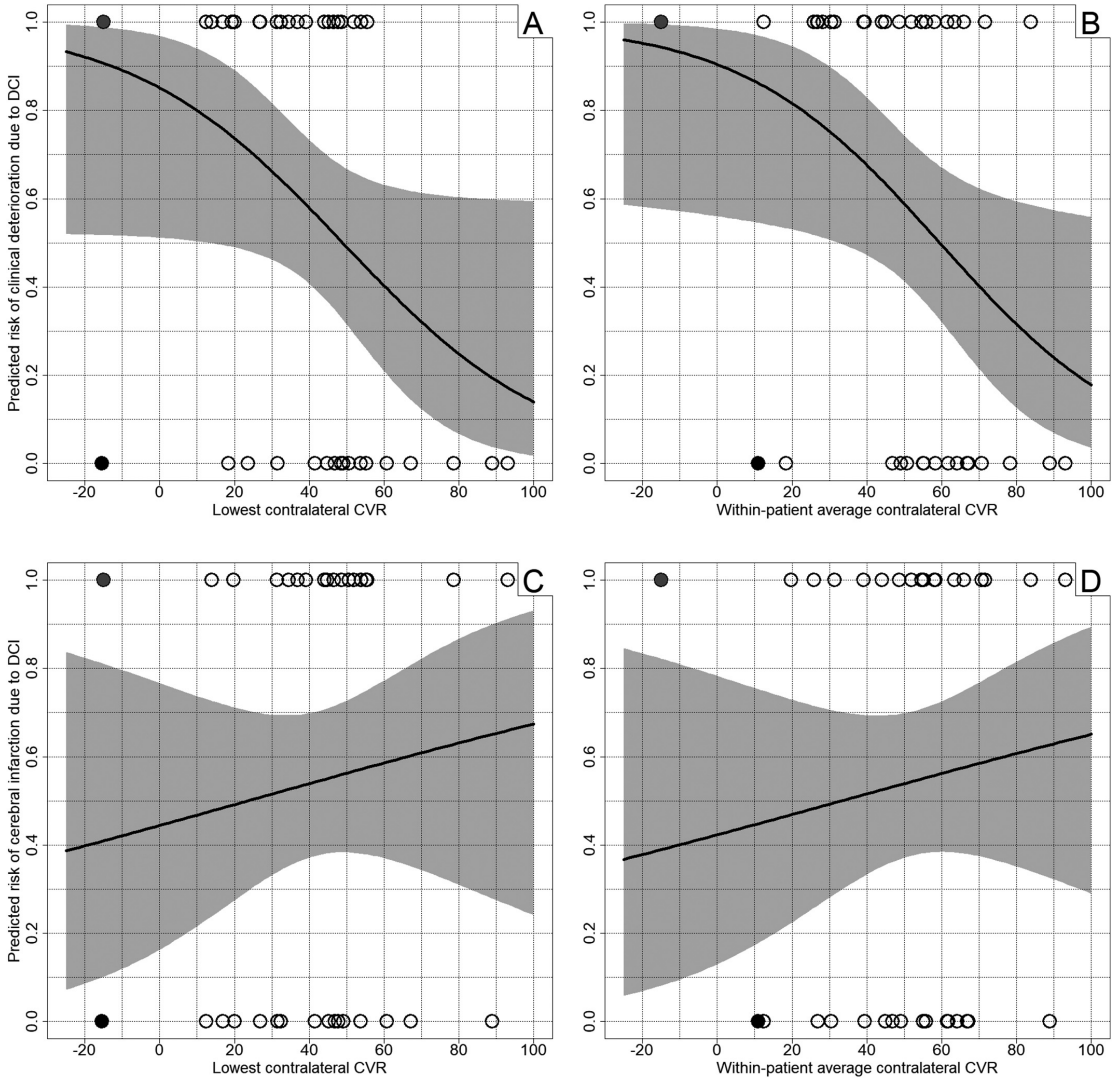

Fig. 2. Probabilities of developing clinical deterioration (A, B) and cerebral infarction (C, D) due to DCI for different CVR values, as predicted by logistic regression. CVR on the contralateral side of aneurysm treatment is used in the models, and the lowest measured CVR (A, C) and within-patient-average CVR of all exams is presented (B, D). The solid black line shows the estimated regression line. Uncertainty is indicated by the shadowed area (95% confidence band). Two patients, marked with a solid grey and black dot, had a paradoxical velocity reduction after AZ.

within-patient average) were compared for patients with and without $DCI_{clinical}$ or $DCI_{infarction}$ (Tables S2-S3). For $DCI_{infarction}$, there was no difference in ipsilateral or contralateral CVR between groups across all approaches (Table S2). For $DCI_{clinical}$ (Table S3), there was no difference in ipsilateral CVR between groups. However, the lowest contralateral CVR was lower in patients with $DCI_{clinical}$ than without (33.9% vs. 49.2%, $p = .05$) and the difference in within-patient average CVR was even larger (43.2% vs. 61.9%, $p = .02$). Differences in first-exam CVR were less apparent (44.0% vs. 56.2%, $p = .19$). Mean combined values of the right and left side masked side-differences between the groups. Fig. 1 shows box plots illustrating the difference between ipsi- and contralateral sides.

Because CVR on the ipsilateral side was similar between patients with and without $DCI_{clinical}$ and $DCI_{infarction}$, contralateral CVR was selected as the exposure variable in logistic regressions (Fig. 2). CVR did not predict $DCI_{infarction}$, but did predict $DCI_{clinical}$. For $DCI_{clinical}$, OR was 0.96 for both the lowest value (95% CI 0.93–1.00, $p = .05$) and within-patient average (95% CI 0.93–1.00, $p = .03$). This corresponds to a 4% reduction in the odds of developing $DCI_{clinical}$ per percentage point increase in CVR. Hence, $DCI_{clinical}$ risk increased with lower contralateral CVR. The risk of developing $DCI_{clinical}$ is 28.3% when the lowest CVR on the contralateral side is 75%, whereas the risk is 49.0% with CVR 50% and 70.1% with CVR 25%.

The prediction models using lowest value and within-patient

Table 4
Multivariable predictors of clinical deterioration due to delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage.

	Odds ratio (95% Confidence Interval)	
	Model I (without CVR)	Model II (with CVR)
Candicate predictors		
CVR	–	0.94 (0.89, 1.00)
Smoking (current vs. former/never)	0.33 (0.04, 2.63)	0.20 (0.01, 3.2)
Hydrocephalus	0.30 (0.02, 4.40)	0.06 (0.00, 4.0)
Established predictors		
Modified CT Fisher I-II	ref	ref
Modified CT Fisher III-IV	3.1 (0.40, 23)	2.1 (0.13, 31)
WFNS I	ref	ref
WFNS II-III	24 (0.71, 836)	3.2 (0.03, 303)
WFNS IV	69 (1.07, 4450)	31 (0.16, 5892)
WFNS V	5.9 (0.14, 251)	1.0 (0.01, 162)
Demographic characteristics		
Male sex	13 (1.14, 150)	37 (2.0, 666)
Age	0.90 (0.82, 0.99)	0.95 (0.85, 1.05)
AUC, crude	0.90 (0.80, 1.00)	0.96 (0.90, 1.00)
AUC, adjusted for optimism[a]	0.82 (0.69, 0.90)	0.86 (0.70, 0.94)

AUC: area under the receiver operating curve; CT: computed tomography; CVR: cerebrovascular reactivity; ref.: reference; WFNS: World Federation of Neurological Surgeons Scale.
[a] Adjusted for optimism with bootstrapping techniques

average were similar for $DCI_{clinical}$, even though the *p*-value for the OR was slightly lower in the second model. Still, the lowest measured CVR is more convenient to use in clinical practice, and the time of the lowest CVR reflects the typical time period for onset of DCI. The lowest value on the contralateral side was therefore chosen as the CVR predictor for $DCI_{clinical}$ in the following analyses.

In prediction Model I the area under the receiver operating characteristic curve (AUC) after correction for optimism was 0.82, and in Model II the corresponding AUC was 0.86 (Table 4). Confidence intervals for AUC for the two models were overlapping. Receiver operating characteristic curves and calibration plots are shown in Fig. 3. Hosmer and Lemeshow's C statistics were C = 15.33 (Model I), and C = 9.41 (Model II). Stratification for clinical grade (WFNS I-III vs. IV-V) did not cause any major changes in the prediction models.

Two patients had a paradoxical velocity reduction after AZ. One patient with a single contralateral CVR of −14.9% (grey dot, Fig. 2) developed both $DCI_{clinical}$ and $DCI_{infarction}$. Another patient with a negative CVR recovered without ischemic symptoms or infarction (black dot, Fig. 2). Notably, the CVR reduction was transient, with CVR of −15.4% in the first exam and 37.4% when re-tested a week later, making the within-patient average CVR 11.0%.

4. Discussion

To our knowledge, this is the first study that has used TCD and AZ to compare CVR in patients with aSAH and UIA. The study indicates that contralateral CVR may be an independent predictor for clinical deterioration due to DCI after aSAH, but CVR is not able to predict radiographic infarction due to DCI.

Various methods are used to assess CVR [58]. It is unclear if CVR results are consistent for different methodologies. Comparing results by multiple methods could elucidate potential differences, but has not been done. The TCD-AZ test is widely applied for CVR testing. The method has some advantages compared with other methods (easier set-up, reduced need for patient co-operation, high safety profile), but also some disadvantages (potential side effects, dose-dependent effects, and contraindications for AZ) [58]. We found that CVR was considerably lower in patients with ruptured aneurysms compared with patients with unruptured aneurysms and this difference appeared to be bigger on the ipsilateral side of aneurysm treatment. This is in concordance with previous CVR-studies using other vasoactive stimuli and measurement methods [9–12,19].

Since the 1970s, literature has suggested that impaired CVR may be associated with DCI after aSAH [14–17,21–30]. With the exception of one study [14], these findings are consistent across different methodologies, study designs, sample sizes, and definitions of DCI. Study sizes have however been small, and CVR has not been integrated as standard assessment after aSAH [35,59–61]. In clinical work, a CVR based prediction model of DCI would be valuable.

In our prediction models, the confidence intervals for the coefficients of the established predictors all included the value 1 by quite some margin, whereas the confidence interval for the coefficient of CVR was 0.89 to 1.00 (Table 4). Note also that 0.94 is the OR per unit change in CVR, which corresponds to an OR of about 0.54 per change of 10, and an OR of 0.05 per change of 50. Among patients in our study, CVR ranges from less than zero to > 90. Hence, contralateral CVR appears to be the strongest predictor of DCI in the model. The confidence intervals of the AUCs were overlapping, which indicates that CVR did not have additional value in the prediction of DCI after aSAH. Still, including CVR in the model caused a substantial increase of optimism adjusted AUC from 0.82 to 0.86. This warrants further investigation, especially as a more accurate prediction model for DCI is needed.

Practical considerations such as ease-of-use and patient comfort are arguments in favor of single CVR testing. Serial testing is time consuming and can be challenging due to reduced patient co-operation, postoperative intracranial air, drains and monitoring equipment in the intensive care unit. Still, DCI has a dynamic nature, the first measured CVR had very low predictive power, and serial CVR-measurements provided added information regarding the dynamic changes in CVR throughout the acute phase after aSAH.

Overall, 52.4% of patients with aSAH in this study developed DCI. In comparison, the reported incidence of DCI is 20–35% in larger case series [1,62–70]. The high frequency of DCI may reflect the high proportion of poor grade patients in our cohort, as poor clinical grade upon admission is associated with higher risk of developing DCI. Given the high proportion of patients with large bleedings and poor clinical conditions in our study, results may not be fully valid for other populations. Still, stratification for clinical grade (WFNS I-III vs. IV-V) did not cause any major changes in the prediction model.

In a previous report we argued that ipsi- and contralateral CVR should be assessed separately, as mean values can conceal side-differences [41]. One-year follow-up study indicated that patients with unruptured aneurysms had a temporary reduction in ipsilateral CVR. The present study indicates that ipsilateral CVR is reduced also after treatment for *ruptured* aneurysms. Ipsilateral CVR reduction thus seem to occur in all patients after aneurysm treatment, regardless of $DCI_{clinical}$ status. Acknowledging this side-difference enables improved interpretation of CVR after aneurysm treatment. Aneurysm treatment in itself does not induce a substantial CVR reduction on the contralateral side, making the contralateral CVR more suitable as a predictor since any DCI-related CVR reduction will be more pronounced on this side compared with the already reduced CVR on the ipsilateral side.

In concordance with the pre-existing hypothesis that CVR can predict DCI, we found impaired CVR in patients with $DCI_{clinical}$. Surprisingly, we did not find an equivalent reduction in CVR in patients with $DCI_{infarction}$. This is quite a conundrum as one would expect impaired CVR for both categories of DCI, assuming clinical symptoms and infarctions are two time-points in a continuum of the same disease. The statistical power in our study may be insufficient to detect CVR impairment in patients with $DCI_{infarction}$. Still, as $DCI_{infarction}$ is presumably associated with more advanced ischemia one would also expect CVR impairment to be more advanced in patients with $DCI_{infarction}$ compared with $DCI_{clinical}$. However, the pathophysiology of cerebral ischemia after aSAH is multifactorial and complex [71], and it is possible that there are differences in the pathogenesis for clinical and radiographical presentations. Furthermore, we used $DCI_{infarction}$ as a dichotomous

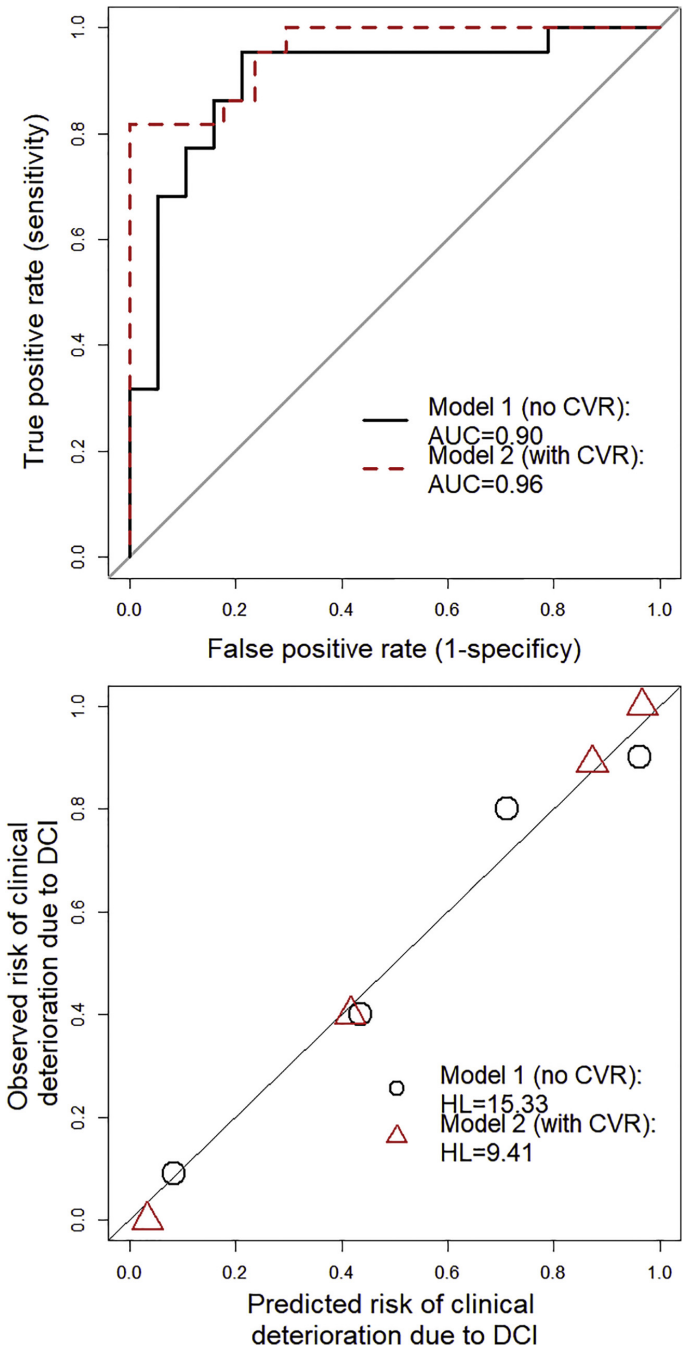

Fig. 3. Discrimination and calibration plots for predictive models with and without CVR. A, The crude receiver operating characteristic (ROC) show the discrimination of the predictive model with and without CVR, not adjusted for optimism. See Table 4. B, The plot shows the calibration (actual outcome versus predicted outcome) analyzed in four equal groups for both predictive models.

variable, not taking into account the size or severity of the infarction. For ethical reasons, moribund patients and patients with increased ICP were excluded (Table S1), this probably reduced the number of patients with severe infarctions that was tested and left a higher proportion of minor infarctions in the studied population. Additional studies with larger study sample and more comprehensive radiographical examinations including assessment of infarction size could help clarify if impaired CVR is associated with $DCI_{infarction}$ or not.

There are limitations to our study. The study population is small, although the number of patients ($n = 42$) is higher than in other neurosonological studies (median $n = 27$, range 18–34) [14,16,19,22,30,72,73]. Further limitations are the lack of external validation of the prediction model. We did not examine patients according to a rigid time schedule. To better compare the aSAH and UIA groups, and overcome the dynamic nature of CVR over time, CVR should ideally have been examined in all patients at the same time intervals after treatment. All patients underwent cerebral imaging with CT and/or MRI after aneurysm treatment. Among 42 patients with aSAH, 17 were only evaluated with CT/CTA during their primary hospital stay. Still, MRI was performed in the majority of patients during follow-up. Of the 39 patients alive after one year, 36 underwent MRI; two were tourists and lost to follow-up; and one patient declined to take the exam due to claustrophobia. We used a well-known classification system for cerebral infarction [74,75]. Still, the attribution of infarction etiology after aSAH is difficult and not easily validated [76], and one cannot be certain whether infarctions are related to DCI or not. To avoid misclassifying procedure-related infarcts as vasospasm-induced, CT and MRI scans should be performed between 24 and 48 h after aneurysm occlusion. This was only done in 33 of 42 patients. The diagnosis of sonographic vasospasm and clinical deterioration due to DCI was set without blinding of CVR-results. Ideally, the AZ doses should have been bodyweight-based in all patients in the study, not only in patients weighing ≥80 kg. Still, the recommended AZ dose of 13 to 18 mg/kg [46,77] was achieved in 91.7% of CVR tests. We used different brands of AZ, yet no difference in CVR has been found when the three manufacturers were compared [41].

A strength of our study is the methodology. Unlike the majority of previous studies [14,15,17,21–29], we used standardized definitions of DCI separated into clinical and radiographic findings [38,39]. We performed serial testing, which is better adjusted to the dynamic nature of vasospasm and DCI. We also tested CVR in patients treated for UIA to increase our general understanding of CVR in patients with intracranial aneurysms. One sonographer (MLB) performed all ultrasound examinations and CVR-tests to reduce operator variability. One neuroradiologist (GM) diagnosed angiographic vasospasm and cerebral infarction, unaware of the patient's clinical and sonographic status.

Central drawbacks with regards to clinical use is that CVR testing is time consuming and that a number of patients experience side effects related to AZ, like headache, flushing, nausea or paresthesia [20]. Still, potential side effects are usually transient and well tolerated [78]. Results are promising, but does not provide firm confirmation that impaired CVR predicts DCI. There are still unresolved issues, and it is too soon to recommend routine use of CVR in clinical practice. Results needs to be externally validated, and the conundrum regarding CVRs relation to $DCI_{infarction}$ needs to be investigated. If validation studies confirm our findings, CVR testing may assist clinicians in early identification of patients who may benefit from aggressive prophylactic treatment, closer monitoring, or repeat vascular imaging. Determining those at greatest risk can help reduce DCI-related poor outcomes while minimizing treatment complications and titrate length of stay in an intensive care unit.

Pretreatment CVR testing could assess potential effects on CVR caused by aneurysm treatment itself. Still, patients were not examined prior to treatment because of the potential risk of causing aneurysm (re-)rupture, and to avoid delay in the acute treatment of a ruptured aneurysm. CVR can be assessed at an earlier time in patients with UIA with assumed low rupture risk and no planned treatment, but this will not give any information about the status of cerebrovascular integrity immediately before aneurysm treatment or rupture. We did not take into account variations of intracranial pressure (ICP) or systemic blood pressure in patients with aSAH. AZ does not cause major changes in systemic blood pressure [43,79], but may lower ICP by reducing cerebrospinal fluid secretion [80]. AZ may also *increase* ICP by cerebral vasodilation [81] and may not be well suited for patients with increased ICP. These high-risk patients are closely monitored for development of DCI and AZ testing might be of less importance. In less severe cases, however, improved prediction of DCI is highly useful, and can assist medical and logistic decision making.

5. Conclusions

Impaired CVR on the contralateral side may be an independent predictor of $DCI_{clinical}$, and may assist in identifying patients in need of closer observation after aSAH. An ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of $DCI_{clinical}$ status, highlighting the need to consider ipsilateral and contralateral CVR separately. This study underscores the value of serial CVR measurements, and future studies aiming to investigate the relationship between CVR and DCI after aSAH should take this into account. Our prediction model can be useful in clinical practice, but needs to be validated.

Author contribution statement

Study conception and design: Bøthun, Helland, Thomassen. Acquisition of data: Bøthun, Helland, Moen. Analysis and interpretation of data: All. Drafting of manuscript: Bøthun, Haaland. Critically revising the article: All. Reviewed submitted version of manuscript: All. Statistical analysis: Haaland. Study supervision: Bøthun, Helland, Thomassen.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116539.

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