Aus der Klinik für Anästhesie und Intensivtherapie des Fachbereichs
Medizin der Philipps-Universität Marburg
Direktor: Prof. Dr. med. Hinnerk Wulf
in Zusammenarbeit mit der Pauls Stradiņš Universitätsklinik für
Anästhesie und Intensivtherapie; Riga, Lettland

Initial 24 Hour ICU Glucose Levels are Associated with the Development of Cerebral Vasospasm after Subarachnoid Haemorrhage

Inaugural-Dissertation zur Erlangung des Doktorgrades der gesamten Humanmedizin dem Fachbereich Medizin der Philipps-Universität Marburg

vorgelegt von

Philipe Sebastian Breiding
aus Worms (Rheinland-Pfalz)

Marburg 2017

Angenommen vom Fachbereich Medizin der Philipps-Universität Marburg am 20.12.2017.
Gedruckt mit Genehmigung des Fachbereichs.

Dekan: Herr Prof. Dr. H. Schäfer
Referent: Herr Prof. Dr. G. Geldner
1. Koreferent: Herr Prof. Dr. J. Bartsch

ABSTRACT

Cerebral vasospasm (CVS) is a well-known cause of morbidity and mortality amongst patients who have suffered from subarachnoid haemorrhage (SAH). Its presence is associated with reduced cerebral perfusion and potential further development of neurological deficit. The aetiology of CVS has been proven to be multifactorial and several risk factors have been associated with its development. Since CVS has been linked to signalling changes in vascular endothelium, serum glucose was chosen as a potential prognostic indicator and risk factor due to its relation with endothelial dysfunction.

The objective of this study was to evaluate the association between serum glucose levels in ICU patients admitted with SAH and the development of CVS. The study is a retrospective observational study in which data was collected on patients admitted to the ICU of Pauls Stradiņš Clinical University Hospital with the primary diagnosis of SAH. We compared serum glucose levels on ICU admission and average glucose levels for the first 5 days in the ICU in patients with and without subsequent development of CVS.

Twenty-four patients diagnosed with SAH were included in the study. CVS was confirmed in 25% *(n=6)*. There was no significant difference in age and gender distribution between groups. Patients with subsequent development of CVS had higher WFNS score values *(4.80 and 3.56; p=0.008)*. We found lower mean glucose levels on admission for patients that developed CVS compared to those that did not develop CVS *(7.32 and 9.28 mmol/L; p=0.05)*. The average glucose levels on first 24h of ICU stay were also lower in patients who developed CVS *(7.26 and 9.29 mmol/L; p=0.03)*. There were no significant differences in average glucose levels between groups from day 2 to day 5 of ICU stay. Overall mortality was not affected by ICU glucose levels and average glucose levels of first 24h were negatively correlated to the duration of ICU stay *(r_s = -0.408, p<0.05)*.

The study shows that admission and initial average 24h glucose levels may prove to be a prognostic indicator for the potential development of CVS after SAH. Glucose averages of the first day of ICU stay were significantly related to the development of CVS and may demonstrate importance after further investigation, possibly with a larger patient group.

Table of Contents

I. Abbreviations

AA – *Arachidonic acid*

COX – *Cyclooxygenase*

CSF – *Cerebrospinal fluid*

CT – *Computed tomography*

CTA – *Computed tomography angiography*

CTP – *Computed tomography perfusion*

CVS – *Cerebral vasospasm*

DCI – *Delayed cerebral ischemia*

DIND – *Delayed ischaemic neurologic deficit*

DSA – *Digital subtraction angiography*

EVD – *External ventricular drain*

GCS – *Glasgow coma scale*

IIT – *Intensive insulin therapy*

ICP – *Intracranial pressure*

ICU – *Intensive care unit*

LOS – *Length of stay (total duration of hospital stay)*

LOS-ICU – *Length of ICU stay (total duration of ICU stay)*

MRA – *Magnetic resonance angiography*

MTT – *Mean transit time*

NIHSS – *National institutes of health stroke scale*

NO – *Nitric oxide*

OxyHb – *Oxyhaemoglobin*

PDGF – *Platelet derived growth factor*

p.o. – *Per os*

PWI – *Perfusion weighted imaging*

ROS – *Reactive oxygen species*

SAH – *Subarachnoid haemorrhage*

SCV – *Symptomatic cerebral vasospasm*

TCD – *Transcranial doppler*

TCCS – *Transcranial color coded sonography*

TGC – *Tight glycaemic control*

VSM – *Vascular smooth muscle*

WFNSS – *World federation of neurological surgeons scale*

1. INTRODUCTION

Despite recent advances in surgery and neurocritical care, the mortality of subarachoid haemorrhage (SAH) remains at about 50% with 25% of deaths occurring during the first 24 hours after the event [1]. Although a large amount of deaths are attributed to neurological damage resulting from a remarkable build up of intracranial pressure (ICP) after for example aneurysmal rupture, the majority of morbidity and mortality is still associated with progressive cerebral infarctions that occur as a result of cerebral vasospasm (CVS). Approximately 70% of patients who experience aneurysmal SAH will demonstrate angiographic evidence of arterial narrowing [2] and about 46% will develop CVS with peak onset between days four and fourteen after SAH [1]. Several observational studies have demonstrated a variety of factors that may play a role in the potential development of CVS after SAH [3-6] however, most of these factors are not clinically modifiable once haemorrhage has occurred.

Diagnosis of this reversible vasculopathy is made by a combination of clinical, angiographic and transcranial Doppler ultrasonographic methods [21]. Thus far, the calcium channel blocker nimlodipine is the only available pharmacological therapy, which has shown to grant some prophylactic benefit in terms of neurological outcome [22]. In patients with CVS, hemodynamic therapy (known as “triple H therapy”: haemodilution, hypertension, hypervolemia) is usually initiated and refractory vasospasm can be treated with endovascular balloon angioplasty in some cases [21].

Since the pathophysiology of CVS has been linked to signalling changes in vascular endothelium [10], serum glucose was chosen as a potential prognostic indicator and risk factor due its relation with endothelial dysfunction. Serum glucose has shown to be a relevant predictor of outcome after acute brain injury and tight glycaemic control (TGC) in the ICU has become standard practice in order to reduce the complications associated with it [7]. In SAH, hyperglycaemia on admission has been shown to be a good indicator of severity of the ictus and has correlated with functional outcome of the patient [11].

Although a relationship between elevated serum glucose levels and the development of CVS has already been established [8, 9, 13], there is limited information about the importance of glucose values on ICU admission and initial 24-hour glucose levels in patients with SAH and the influence that these parameters have on patient outcome as well as

morbidity and mortality. Given its predictable onset between day four and fourteen after bleeding, CVS is a potentially modifiable complication.

The purpose of this study was to examine how admission and dynamic serum glucose levels during hospitalization are related to the development of CVS and clinical outcomes after SAH. The objective was to evaluate the prognostic significance of serum glucose levels in the ICU and the subsequent development of CVS.

2. THEORETICAL BACKGROUND

2.1. Vasospasm in General

The earliest description of a patient with delayed cerebral ischemia was perhaps by Sir William Gull in 1859 [51]. In his research entitled "cases of aneurysm of the cerebral vessels" he described the case of a 30-year-old female who whilst walking suddenly called out, "Oh my head," vomited and fainted shortly afterwards. She was admitted to the hospital at noon the following day. Upon examination, her right arm and leg were fairly paralyzed, the muscles flaccid. Her condition improved, and she was able to eat 3 days after the ictus. On the 4th day, she spoke some words, but on the 5th day, her condition worsened. Her pupils became fixed, dilated, and she died. The subsequent autopsy showed SAH in the left Sylvian fissure with massive softening of the left cerebral hemisphere and two aneurysms of the middle cerebral artery, one of which had ruptured.

In 1949, Australian Physiologist Graeme Robertson described the post mortem findings of 27 Patients who suffered from aneurysm rupture and subsequent SAH. He found infarctions in brain parenchyma supplied by patent arteries and concluded: "Hence, it seems possible that the ischaemic changes were due to temporary spasm of the supplying vessels." [52]. As medical technology progressed, Robertson's hypothesis was proven correct in 1951 when Ecker and Reichmeider at Syracuse Memorial Hospital, New York were able to visualise alterations in the diameter of cerebral arteries by comparing angiograms taken on consecutive days in 350 different patients [71]. A marked reduction in vessel calibre was noted in 11 of the cases with aneurysmal SAH, which returned to normal over the course of several days. These findings firmly established the concept of CVS in the field of neurology.

In 1964, Stonelli and French found vasospasms confirmed by angiogram less frequently in patients who went on to make a good postoperative recovery [72]. The findings led to improvement in the management of patients with SAH. Increasing blood pressure to 150-170/90-100 mmHg using vasopressors was found to reduce neurological deficits. This marked the beginning of the modern triple H therapy (haemodilution, hypertension and hypervolaemia) together with the findings of Kosnick and Hunt in 1976 [73]. The researchers demonstrated improvement of neurological deficits in six out of seven patients with aneurysmal SAH using norepinephrine, hypertonic saline and albumin.

Fischer was the first to describe the clinical characteristics of delayed cerebral ischemia (DCI) in 1975 as an onset about 3-13 days after a single SAH, in about one third of patients. These criteria have remained true until present day. The general time course of angiographic vasospasm was further evaluated by Weir et. al. by measuring the diameters of cerebral arteries on 627 angiograms from 293 patients with ruptured aneurysms [52]. The research showed that angiographic CVS usually portrayed an onset at 3 days, was maximal at 6-8 days and resolved by 12 days. The invention of computed tomography (CT) eventually aided in predicting the onset, location and potential severity of CVS, leading to Fischer et. al. classifying CT-hyperdense subarachnoid blood into four grades, which could be used to predict whether angiographic vasospasm would occur and how severe it would be [53].

2.2. Pathophysiology of Cerebral Vasospasm

The pathophysiology behind delayed vasospasm after SAH has been the subject of multiple studies, continuing controversies and on-going search for the substance or substances that may cause this clinically frustrating complication. Effective therapeutic development has been largely hindered by the fact that the underlying pathogenic mechanisms still remain poorly understood. Nevertheless, intensive research over the past three decades has identified certain mechanisms that may play a role in its development.

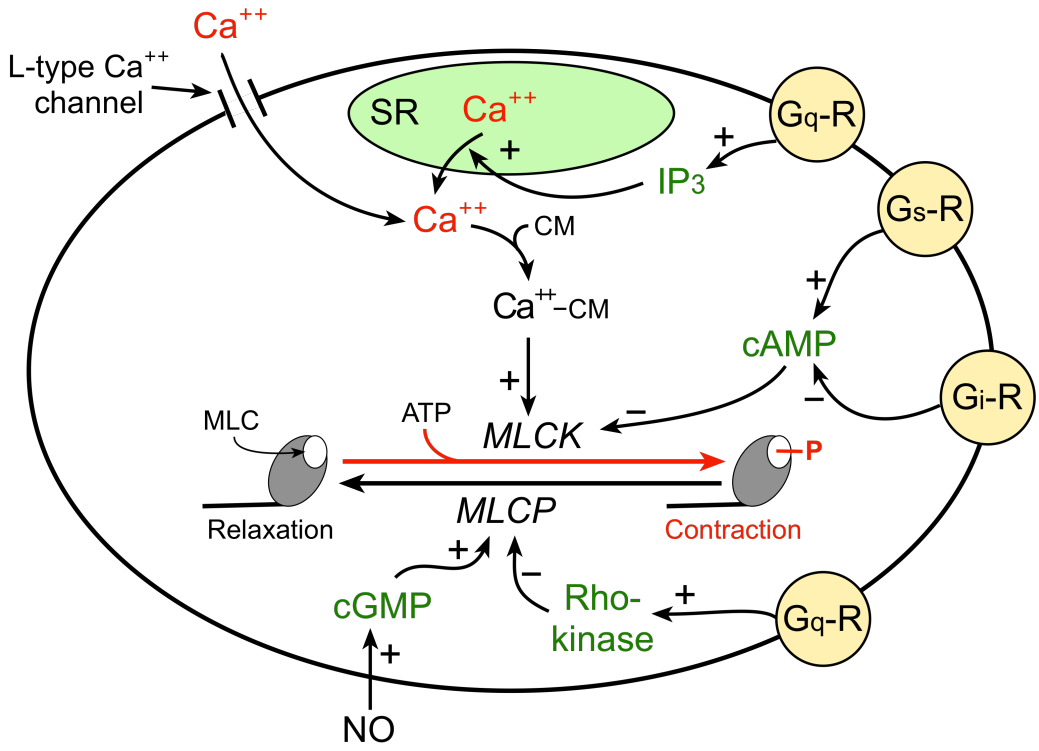
Experimental data suggests that the causative agents of CVS can generally be divided into two main categories: (1) compounds found in blood or metabolites of compounds found in blood and (2) compounds that are regulated or induced as a consequence of blood around the vessels. Reactions involving free radicals, an imbalance between vasoconstrictor and vasodilator substances, inflammatory processes, neurogenic factors that regulate vascular tone, membrane pathology and endothelial apoptosis have all been postulated as causative

agents. Since CVS tends to occur more frequently and intensively in vessels surrounding large blood clots [23], the rationale that blood itself or metabolites of components of blood cause vasospasm remains compelling.

2.2.1. Smooth Muscle Contraction and Spasmogens

The essence of CVS can be defined as a prolonged and abnormal contraction of vascular smooth muscle cells (VSM). It is well known that VSM contraction and relaxation is fundamentally maintained by the presence of free intracellular calcium either through calcium channels or by release of calcium from internal stores (e.g. sarcoplasmic reticulum). Blood products and/or metabolites released after SAH are believed to stimulate cell membrane receptors, such as G-protein-coupled receptors and receptor tyrosine kinases, which may stimulate calcium influx from the extracellular space or release of calcium from the intracellular pool ultimately leading smooth muscle cell contraction (Fig. 2.2.1) [24].

Figure 2.2.1 Mechanisms involved in vascular smooth muscle contraction. (Source: Klabunde, R.E. *Cardiovascular Physiology Concepts*. Lippincott Williams & Wilkins, 2011)



Experimental studies have shown that breakdown products of blood in the subarachnoid space are involved, directly or indirectly, in the development of CVS after SAH. The most prominent spasmogenic agent responsible for the development of CVS is believed to be oxyhaemoglobin (OxyHb) [25, 26, 27] with its ability to:

- Induce direct vasoconstriction
- Release arachidonic acid (AA) metabolites and endothelin from the arterial wall
- Inhibit vasodilation through nitric oxide (NO) scavenging
- Damage perivascular nerves
- Promote free radical reactions through generation of reactive oxygen species (ROS)

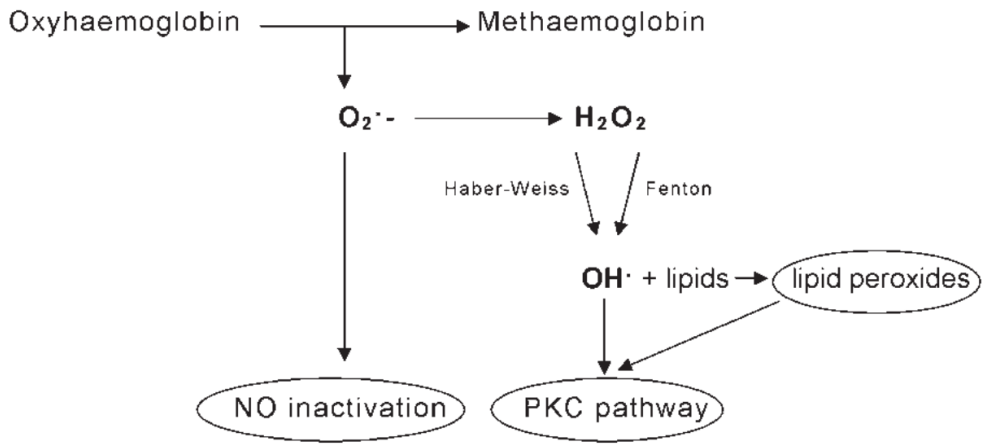
Furthermore, OxyHb is present in high concentrations in the cerebrospinal fluid (CSF) during the time of CVS and changes in OxyHb concentrations tend to mirror the evolution of CVS [26].

2.2.2. Free Radicals

A free radical is an uncharged molecule (typically highly reactive and short-lived) having an unpaired valency electron [28]. The term reactive oxygen species (ROS) is used to describe radicals such as superoxide ($O_2\bullet^-$) and hydroxyl ($OH\bullet$) and non-radical derivatives of oxygen such as hydrogen peroxide (H_2O_2) [29].

The formation of ROS after SAH is thought to be due to the autoxidation of OxyHb into methemoglobin. This leads to the production of $O_2\bullet^-$, which is converted to H_2O_2 by superoxide dismutase. H_2O_2 can then be converted to OH through the Fenton reaction or together with $O_2\bullet^-$ may undergo the iron-catalyzed Haber-Weiss reaction, also generating OH. OH can combine with lipids to form lipid peroxides which themselves are capable of spasm and damaging the structure of arteries as well as directly or indirectly activating the protein kinase C pathway leading to CVS [30]. $O_2\bullet^-$ itself could also contribute to CVS by inactivating the powerful vasodilator nitric oxide, however, the principal free radical source in vasospasm remains $OH\bullet$ with its ability to produce lipid peroxides (Fig. 2.2.2).

Figure 2.2.2 Free radicals after SAH. (Source: Kolias, A.G. et. al. *Pathogenesis of Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage: Putative Mechanisms and Novel Approaches.* Journal of Neuroscience Research, 2009)



Polidori et. al. has shown that patients with CVS displayed elevated levels of lipid peroxides in their CSF [31] and the fact that antioxidant agents such as 1,2-bis(nicotinamide)-propane, tirilazad, and ebselen have improved experimental vasospasm and reduced lipid peroxidation in animal models provides evidence in support of the role of free radicals in the pathogenesis of CVS [32].

2.2.3. Endothelial Factors – Nitric Oxide and Endothelins

It is well known that endothelial factors such as nitric oxide (NO) and endothelins play a large role in maintaining vascular smooth muscle tone with the former generally responsible for smooth muscle relaxation and the latter responsible for smooth muscle contraction. In physiological states, a delicate balance exists between endothelium-derived vasoconstrictor and vasodilator substances. NO released from l-arginine in vivo activates soluble guanylyl cyclase, which catalyzes the conversion of guanosine triphosphate to cGMP ultimately leading to smooth muscle relaxation [33]. The role of NO in the development of CVS can be attributed to several influencing factors:

- OxyHb scavenges readily available NO [34].
- Neuronal death due to ischemia leads to a decrease in neuronal nitric oxide synthase (nNOS) and subsequently decreased NO production [34].
- Asymmetric dimethylarginine (ADMA), which is synthesized during the methylation of l-arginine residues, inhibits endothelial nitric oxide synthase (eNOS) [35].

- Increases in inducible nitric oxide synthase (iNOS) leads to the generation of free radicals such as OH• [36].

Evidence in support of the role of NO in the pathogenesis of CVS is provided by the fact that a variety of NO donors, delivered in different ways, have been shown to reverse or prevent vasospasm in animal models [37] and Simvastatin, which is capable of increasing eNOS activity has ameliorated vasospasm in mice [38].

Among the four different isoforms of ET in humans, ET-1 plays the largest role in vasoconstriction after SAH [39]. It is primarily produced by the endothelium itself, but can also originate from astrocytes and neurons [39]. Apart from causing vasoconstriction, ET possesses the ability to remodel and induce structural and inflammatory changes within the blood vessels themselves. Studies have shown that cerebral blood vessels may be sensitized to ET-1 after SAH and that an up-regulation of ET_A receptors occurs following the ictus [40]. The ET-1–ET receptor interaction results in the activation of phospholipase C, which ultimately leads to an increase in intracellular calcium and activation of phosphokinase C [40].

2.2.4. Arachidonic Acid and its Metabolites

Arachidonic acid, as a structural component of cell membrane phospholipids, can be metabolised into a wide variety of biologically active substances by enzymes such as cyclooxygenase (COX). The COX pathway ultimately results in the formation of Prostacyclin (PGI_2) (powerful vasodilator), Thromboxane (TXA_2), and Prostaglandins such as PGE_2 and PGF_{2a}, which are capable of vasoconstriction [50]. In 1979, Boullin et. al described an imbalance between vasoconstricting PGs, TXA_2 and the vasodilating PGI_2 as a possible mechanism for CVS.

2.2.5. Neurogenic Factors

Cerebral arteries have sensory, sympathetic and parasympathetic innervation. Direct vascular contact with surrounding subarachnoid blood is postulated to cause an impairment in vascular innervation, a phenomenon described as denervation by Sercombe et. al. in 2002 [41]. Unfortunately not much information has been attained in this area and in fact studies have shown that sympathetic denervation appears to ameliorate CVS in experimental models

[42]. Studies have also shown that lesions in pathways of brainstem reflexes responsible for controlling cerebrovascular tone have prevented the establishment of vasospasm in experimental models [43]. This may prove the hypothesis that SAH activates local reflexes that act over brainstem nuclei to constrict cerebral arteries. Despite scientific evidence, it is still widely believed that neurogenic factors perhaps only play an ancillary and not central role in the pathogenesis of CVS [44].

2.2.6. Structural Factors

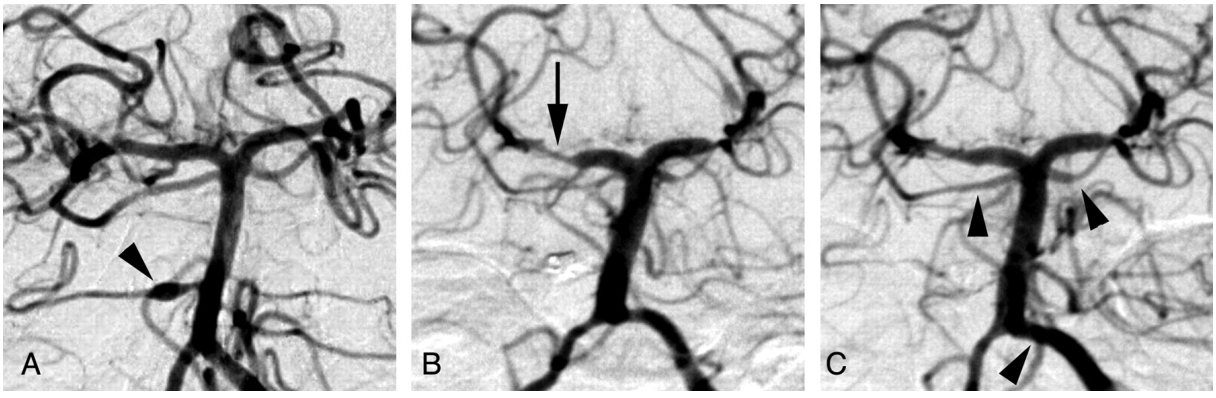
The structural factors relating to the development of CVS are mainly based on the fact that experimental studies have demonstrated that the presence of blood in the subarachnoid space leads to increased proliferative activity across all layers of the arterial wall, mainly involving the adventitia and endothelium [45]. The hypothesis remains that substances such as platelet-derived growth factor (PDGF) released from aggregated platelets at the subarachnoid clot may contribute to CVS by thickening the arterial wall [46]. Endothelial apoptosis, leading to impairment of endothelium-dependent vasorelaxation and increased exposure to spasmogens, has also been observed after CVS [47] and recently p53, a transcription factor that acts as a tumour suppressor, has been implicated in both apoptosis and cellular proliferation in relation to CVS [48, 49]. Although the evidence of cell proliferation and consequent arterial wall thickening after SAH is existent, the role of this phenomenon in the pathogenesis of CVS remains controversial as proliferation is limited and there appears to be no significant wall thickening during the period of maximal intensity of the vasospasm [42].

2.3. Diagnostic Principles of Cerebral Vasospasm

The initial suspicion of CVS is generally raised after sudden onset of new focal / cognitive neurologic deterioration roughly four to fourteen days after SAH, more widely known as delayed ischaemic neurologic deficit (DIND) which may encompass typical stroke symptoms such as newly acquired muscle weakness, aphasia or confusion manifested as a sudden drop in Glasgow Coma Scale (GCS) rating / rise in National Institutes of Health Stroke Scale (NIHSS). The fact that many SAH patients will initially be treated in an ICU setting and often kept sedated makes an accurate neurologic status evaluation difficult.

The current gold standard for effectively diagnosing CVS remains cerebral angiography (DSA) with accurate depiction of the vessels of the brain by intra-arterial contrast agent application and subsequent digital subtraction x-ray imaging. This procedure is invasive, requires the availability of significant resources and may lead to complications in up to 2.63% of cases ranging from benign conditions such as access-site haematoma (4.2%) to stroke with permanent disability (0.14%) or even death (0.06%) [55].

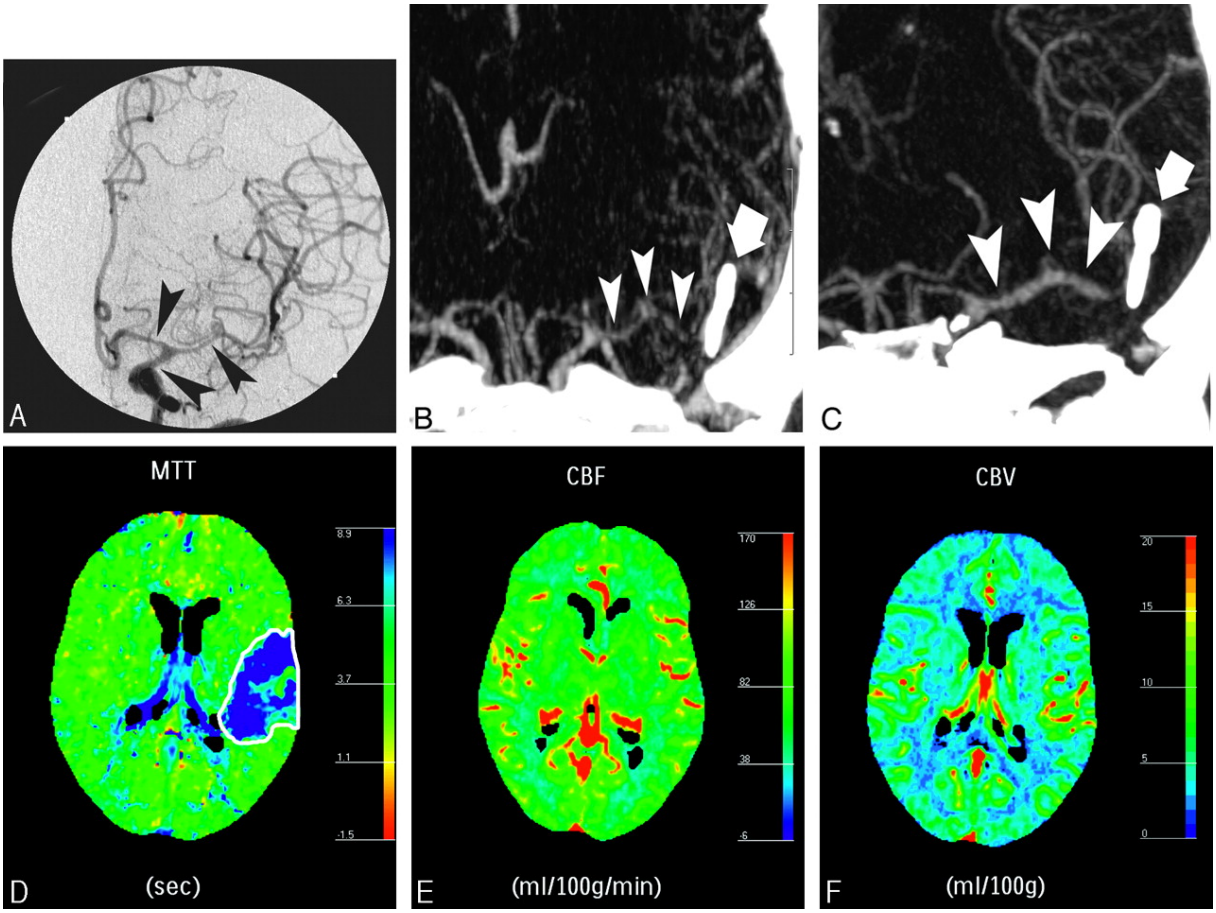
Figure 2.3.1 Vertebrobasilar angiograms obtained from a patient with SAH after right AICA aneurysm rupture (A). Image (B) represents a 50% right P2 PCA segment stenosis 12 days after coil-embolization of the aneurysm. The arrowheads in (C) indicate improved angiographic vasospasm in the left distal vertebral artery, superior cerebellar arteries and posterior circulation following treatment with 10-mg intra-arterial Verapamil. (Source: Sehy, J.V., et.al. *Improvement in Angiographic Cerebral Vasospasm after Intra-Arterial Verapamil Administration.* AJNR, 2010.)



CT-Angiography (CTA) is a less invasive alternative that in conjunction with CT-Perfsuion (CTP) has gained popularity for diagnosing CVS and evaluating whether endovascular therapy will be required. It too uses x-ray imaging technology and derives images of vessels in 3 dimensions with the ability to quantitatively depict cerebral blood flow

and cerebral blood volumes by means of CTP. In a study performed by Wintermark et. al. in 2006, CTA and CTP represented an accurate screening test in patients with suspected CVS. Post-contrast vessel narrowing and a CTP-derived mean transit time (MTT) with a threshold of 6.4 seconds represented the most accurate combination for the definite diagnosis of CVS [56]. MR-Angiography (MRA) with perfusion-weighted imaging (PWI) is another alternative that eliminates the CT drawbacks of radiation exposure, however adds the disadvantage of extended examination times and inferior vessel resolution compared to both DSA and CTA.

Figure 2.3.2. DSA (A), CTA (B, C) and CTP (D, E, F) images of a 44-year-old patient 6 days after rupture and clipping of a left MCA bifurcation aneurysm. DSA showed moderate vasospasm of the distal left ICA and severe vasospasm of the left ACA A1 segment and left MCA M1 / proximal M2 segments (arrowheads, A). Correlating CTA image with increased MTT / CBV (D / F) and normal CBF (E) in the respective left MCA territory. Image (C) represents resolution of the vasospasm following intra-arterial Nimlodipine therapy. (Source: Binaghi, S., et. al. *CT Angiography and Perfusion CT in Cerebral Vasospasm after Subarachnoid Hemorrhage.* AJNR, 2007.)



Transcranial Doppler ultrasonography or contrast-enhanced / non-contrast-enhanced transcranial color-coded sonography is another potentially non-invasive method, primarily used to measure blood flow in large proximal intracranial vessels. The flexible nature of

ultrasonography allows this procedure to be performed at the patient's bedside without the hazards of radiation exposure. Unfortunately these modalities are heavily operator dependent and provide limited feedback in patients with hyperostosis of the temporal bones. In 2004 the American Academy of Neurology recognized TCCS as an effective method in diagnosing CVS but recommended its use only for the middle cerebral artery (MCA) where the diagnostic applicability was seen in 67% of patients with a sensitivity of 100% and specificity of 93%. These percentages decreased with regard to other vessels in the brain, especially those of the posterior circulation [57].

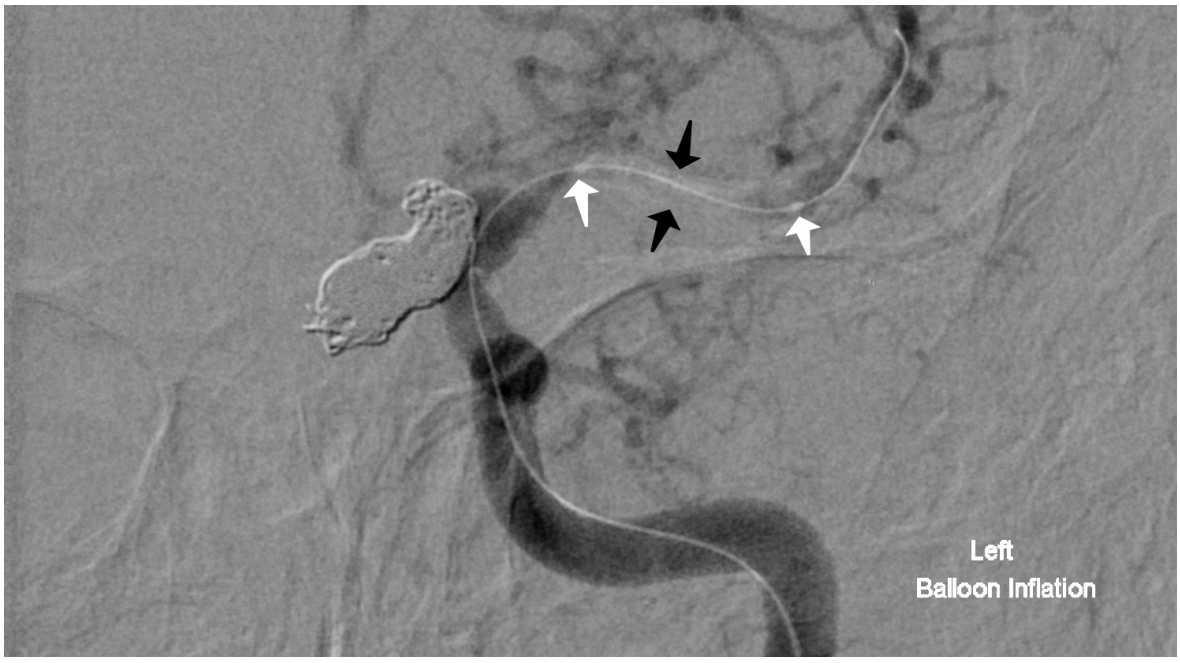
2.4. Treatment Principles of Cerebral Vasospasm

Although therapeutic approaches and the availability of therapeutic resources vary from clinic to clinic, the evidence based principles in the treatment of CVS after SAH remain similar around the globe. The therapeutic approach of CVS already commences once SAH is diagnosed and is usually based on three vital components: (1) prompt reduction of ICP, (2) optimization of the rate of cerebral oxygen demand and (3) improving cerebral blood flow. A prompt ICP reduction may be achieved by surgical means of early ventriculostomy and external ventricular drainage (EVD) in conjunction with endovascular / open surgical treatment of the bleeding source if visible on routine imaging. Early ICP reduction and bleeding source treatment allows for more aggressive further potential CVS treatment over the course of care.

The improvement of cerebral blood flow remains the most important aspect of CVS therapy. Alongside calcium channel blockers, triple H therapy has gained widespread acceptance over the past 20 years and encompasses three main physiologic components, namely: hypertension, haemodilution and hypervolemia. The rationale behind this treatment is that maintenance of high circulating blood volume, increased perfusion pressures, and decreased blood viscosity will enhance CBF in the setting of vasoconstriction [69]. Volume expanding fluids increase cardiac output which in turn increases blood pressure resulting in increased CBF in hypo perfused cerebral territories. Hypertension may be achieved by volume expanding fluid therapy alone but can also be realized by vasoactive drugs such as dopamine or phenylephrine. Haemodilution with a target haematocrit of 30-35% is implemented as a reasonable balance between reduced blood viscosity and oxygen-carrying capacity.

Despite being in use for well over 30 years, the therapeutic approach with Triple-H has undergone scrutiny within the past decade to determine whether each of the three individual therapeutic components share similar therapeutic value. Hypervolaemia and haemodilution remain the most controversial components of haemodynamic therapy to this day. A randomized controlled trial with 82 patients performed in 2000 by Lennihan et. al. showed that hypervolaemic therapy did not increase CBF or blood volume compared with normovolaemic therapy [58]. Another study performed in 2001 showed neither early nor late outcome measure differences (in particular no differences in CBF) between patients treated with Hypervolaemic fluid therapy and those treated with normovolaemia [59]. With regards to haemodilution, issues are seen as to whether an increased CBF due to reduced blood viscosity can outweigh the expense of severe decreases in oxygen delivering capacities [60].
In 2010, Dankbaar et. al. performed a widespread literature review to evaluate the effects of the individual triple H components on the cerebral blood flow (CBF) of patients following CVS. Although none of the 11 studies included in the review contained a control group, it became evident that hypertension appears to be more effective in increasing CBF than haemodilution or hypervolaemia [54].

Figure 2.4.1. Balloon angioplasty of the left MCA M1 segment due to vasospasm following left PCOM aneurysm rupture. Depicted: proximal and distal ends of the balloon (white arrows) and inflated balloon (black arrows). (Source: Prof. Alan Coulthard. *From the case: Balloon angioplasty for cerebral vasospasm.* Radiopedia.org, 2016.)



Although there is still much controversy today as to which techniques are best, which patients are the best candidates and which is the best time to intervene, more invasive techniques such as endovascular balloon angioplasty and intra-arterial administration of vasodilators have proven to be effective methods in increasing CBF and improving patient outcome [70]. If little angiographic spasm presents in the proximal intracranial vessels, then intra-arterial administration of vasodilators such as Nimlodipine may suffice. In the larger cerebral vessels, balloon angioplasty has shown to be very effective, even as a prophylactic measure for CVS as Zwienenberg-Lee et. al. described in 2008 [61]. The overall competence in regards to radiographic resolution of CVS is similar between both methods and one study comparing their effectiveness showed no difference in clinical patient outcomes [62].

2.5. Current State of Research

2.5.1. Factors Associated with the Development of Cerebral Vasospasm

The current state of research regarding patient-specific or clinical factors which may increase / reduce the likelihood of developing SCV after SAH is broad. The statistical significance of independent risk factors often varies between individual studies and contradicts each other respectively. In order to gain a complete understanding of potential risk factors, Inagawa, T. performed an extensive literature review in 2016 including Twenty-one clinical studies in which 23 multivariate analyses were performed on factors predictive of CVS after SAH. He concluded that severe SAH evident on CT-imaging appeared to be the only definite consistent risk factor for CVS after SAH, followed by cigarette smoking, hypertension, and left ventricular hypertrophy on electrocardiogram [63]. The effects of various other risk factors such as age, clinical grade, hydrocephalus, etc. appeared to be related to the severity of SAH rather than being independent risk factors for the development CSV [63].

2.5.2. Serum Glucose and the Development of Cerebral Vasospasm

With regards to serum glucose, there is as well a large discrepancy between individual studies in its potential contribution to the development of CVS. Several studies have suggested that hyperglycaemia is associated with an increased incidence of CVS [9, 13]. Other studies found no relationship between hyperglycaemia and SCV [4, 64] whereas a single study performed by Naidech et. al. showed that moderate hypoglycaemia was associated with CVS and worse functional outcome in multivariate models with focus being

placed on the nadir blood glucose values throughout hospital stay [14]. The above-mentioned studies will further be examined and contrasted in the *discussion* and *conclusion* parts of this dissertation.

3. MATERIALS AND METHODS

3.1. Hypothesis and Aim

Over the course of the past decade, several studies have been performed to assess potential risk factors in the development of CVS (see 3.5). A great majority of these risk factors are patient specific and represent conditions / characteristics, often chronic, which may not be altered in an ICU setting. Other factors represent dynamic features that can be controlled and adapted artificially with little delay. Serum glucose represents an entity that can easily be obtained from a patient's blood sample, analysed and artificially raised / lowered. With this in mind, the objective of this study was to further evaluate the association between serum glucose levels in ICU patients admitted with SAH and the development of CVS with emphasis being placed on the dynamic inpatient blood glucose levels. The aim was to gain a better understanding about the role of glycaemic control in ICU patients diagnosed with SAH.

3.2. Study Design

The study is a retrospective observational study in which data was collected on all patients admitted to the ICU of Pauls Stradiņš Clinical University Hospital with the primary diagnosis of SAH (International Classification of Diseases, tenth revision, diagnostic codes I60 and S06.6). The study included patient data gathered from January 2015 to January 2016 with a proven diagnosis of either traumatic or aneurysmal SAH after detailed case history review. Patients were included regardless of age or gender. Only patients admitted within 48 hours of ictus and surviving the first seven days of hospitalisation were considered. The remaining patients were excluded from the study. The study gained institutional approval by the ethical committee of Rīgas Stradiņa universitāte on 29.10.2015 (Nr. 0003), signed by the committee chairman Prof. Olafs Brūvers.

3.3. Patient Variables

3.3.1 Clinical and Baseline Characteristics

Various patient-specific information was extracted from the data at hand in order to gain an overview about potential factors in conjunction with blood glucose itself that could contribute towards the development of CVS. Clinical and baseline characteristics including age, sex, Fischer grade, World Federation of Neurological Surgeons Scale (WFNSS) and medical history of chronic hypertension, diabetes and cardiovascular disease were extracted. SAH related conditions such as the presence of cerebral oedema on initial radiographic examination, AVM and hydrocephalus were also recorded.

3.3.2. Glycaemic Characteristics

The admission blood glucose (first blood glucose value [mmol/L] documented in the patient's ICU medical record), daily blood glucose and discharge blood glucose (last blood glucose value [mmol/L] documented in the patient's ICU medical record) were recorded. All patients had multiple blood glucose measurements taken each day throughout their ICU stay and insulin use as well as glucose administration were recorded. The average of all blood glucose values from one day was considered the mean daily blood glucose value. The mean daily blood glucose values for the first fourteen days after SAH as well as for the entire ICU stay were averaged to represent a mean inpatient blood glucose value. Additionally, a median blood glucose value for the first fourteen days after SAH as well as for the entire ICU stay was noted. The most frequent blood glucose value was considered the mode blood glucose value. The highest blood glucose value recorded was considered the maximum blood glucose value and the lowest blood glucose value recorded was considered the minimum blood glucose value. The glycaemic range was measured as the difference between the maximum blood glucose value and the minimum blood glucose value of the first fourteen days after SAH as well as for the entire ICU stay.

3.3.3. Hyperglycaemia Cut-off Value

Hyperglycaemia was defined as an admission blood glucose value, mean 24-hour blood glucose value and mean inpatient blood glucose value of $\geq$ 7.8 mmol/L. This cut-off value was based on the American Association of Clinical Endocrinologists and American

Diabetes Association guidelines that suggest a glycaemic target of 140 – 180 mg/dL (7.8 – 10 mmol/L) [21].

3.4. Outcome Measures

3.4.1 Diagnostic Criteria of CVS

The presence of vasospasm was established via the results of CT-Angiography (CTA). The decision for performing CTA was based upon worsening of neurologic symptoms such as a drop in GCS / rise in NIHSS or new onset of focal neurologic deficits which were identified by an ICU nurse during routine neurologic status evaluation and confirmed by a medical doctor. Diagnostic criteria involved a comparison of the lumen of the suspected vessel (s) with a normal segment of artery both proximal and distal to the narrowing as well as comparison to CTA images before the onset of the newly discovered neurologic deterioration. Bedside ultrasonography was not regularly performed in the ICU setting and digital subtraction angiography (DSA) was only performed if CVS could not be ruled out or if endovascular balloon angioplasty / intra-arterial administration of vasodilators was planned.

3.4.2. ICU Treatment regimen for CVS

As standard practice, all patients diagnosed with SAH in the ICU received nimlodipine prophylactically (intravenous 5 ml/h for two days, then converted to p.o. 60 mg every 4 hours for 14-21 days after SAH). Intensive care management for patients that either displayed an onset of clinical symptoms / neurologic deterioration or CTA evidence of vasospasm included triple-H therapy (hypertension, haemodilution and hypervolemia).

In the ICU of Pauls Stradiņš Clinical University Hospital, patients are generally maintained with sedation following SAH, especially if they are artificially ventilated. When sedation is necessary, midazolam ± fentanyl is used. Per protocol, the sedative dose was reduced every day to allow the nursing staff to conduct accurate neurologic assessments of the patient. Clinical outcome measures were comprised of the total duration of hospital stay (LOS), the total duration of ICU stay (LOS-ICU) and mortality.

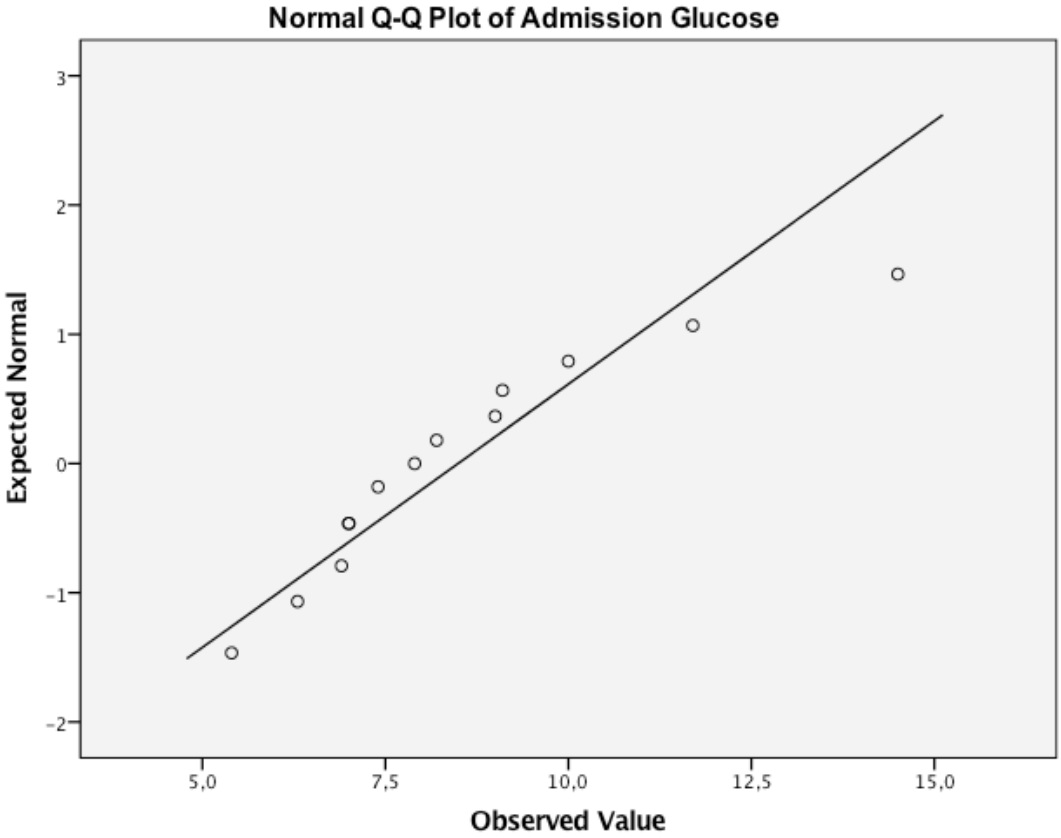
3.5 Statistical Analysis

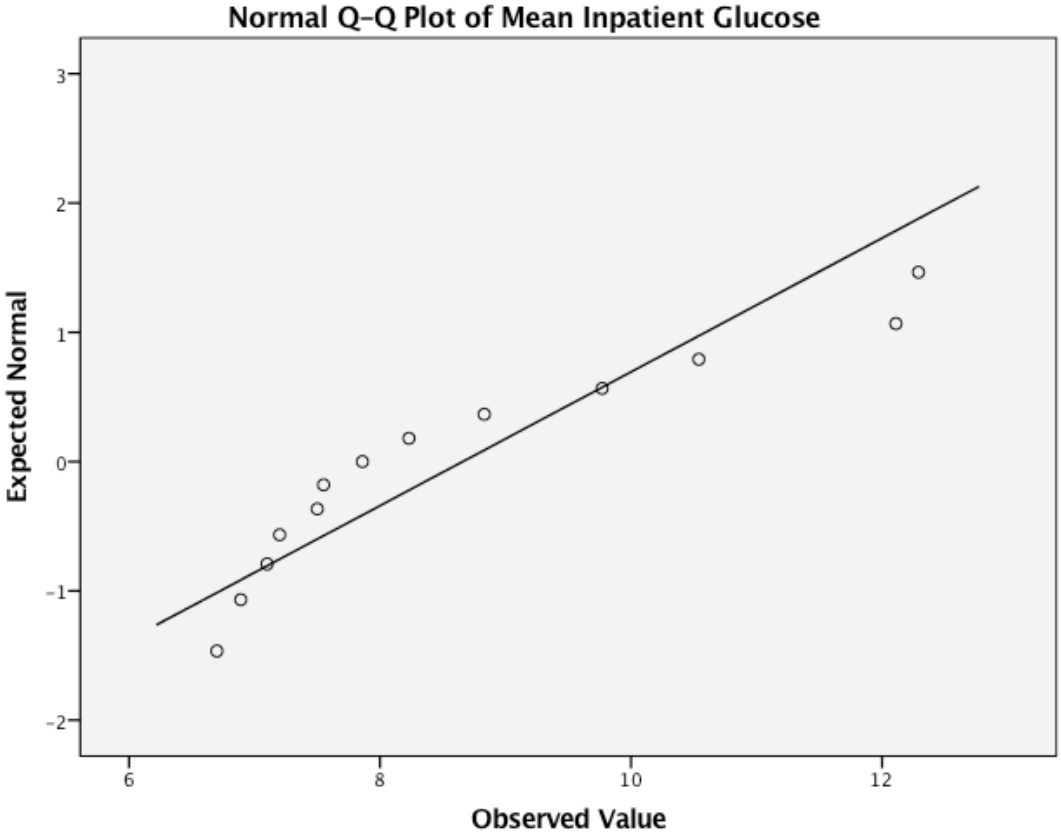
All data was gathered using Microsoft Excel for Mac (2011, v.14.5.7:151005) and analysed using IBM SPSS Statistics (2015, v.23.0.0.0). Statistical analysis succeeded independently after consultation with the statistics department of Riga Stradiņš University, Faculty of Medicine. Nominal data was reported as true / false or present / absent and analysed with a chi-square test where appropriate. Continuous (scale) and ordinal data were reported as mean ± SD and their differences were analysed using independent samples t-test after the data showed normal distribution using the Kolmogorov-Smirnov test (Figures 3.5.1 and 3.5.2). Correlation between continuous (scale) data was also analysed using Spearman correlation. Descriptive statistics were implemented for baseline and clinical characteristics of the patient groups.

Blood glucose values for each patient group (presence of CVS or no presence of CVS) were reported as mean ± SD and median values. The analysis of the two groups involved interpretation of the means and application of independent samples t-test. Independent samples t-test was also applied for blood glucose values using mortality as a grouping variable and clinical characteristics such as cerebral oedema, hydrocephalus, hypertension, cardiovascular disease and diabetic status were analysed using chi-square test.

Hyperglycaemia on admission, hyperglycaemia after 24 hours and hyperglycaemia after 14 days were treated as nominal data with a cut-off value of 7.8 mmol/L [21] and analysed using a chi-square test. A Spearman's rank correlation coefficient (r) was utilised to analyse the relationship between blood glucose values and clinical outcome measures such as length of hospital stay (LOS), length of ICU stay (LOS-ICU) and LOS until exitus.

Figures 3.5.1. and 3.5.2. Normal distribution of Admission ICU blood glucose values and mean inpatient blood glucose values demonstrated by Normal Q-Q Plots.





4. RESULTS

4.1. Descriptive Statistics

A total of twenty-four patients diagnosed with SAH were included in the study. Their baseline and clinical characteristics are shown in Table 4.1.1. A comparison between patients who developed CVS and those who did not develop CVS is shown in Table 4.1.2.

Table 4.1.1 Baseline and clinical characteristics of twenty-four patients with SAH

Characteristic	No. (%) of Patients
Age *(years)* [a]	56.88 ± 15.46
Female	12 (50)
CVS	6 (25)
WFNSS *(points)* [a]	4.00 ± 1.04
Fischer scale *(points)* [a]	4.00 ± 0.00
Medical history	
Diabetes mellitus	3 (12.5)
Hypertension	13 (54.2)
Cardiovascular disease	5 (20.8)
SAH-related conditions	
Aneurysm rupture	20 (83.3)
Cerebral oedema	9 (37.5)
Hydrocephalus	8 (33.3)
Blood glucose values *(mmol/L)* [a]	
Admission	8.79 ± 2.76
24-hour	8.78 ± 2.81
Inpatient	8.83 ± 2.38
Hyperglycaemia [b]	
Admission	14 (58.3)
24-hour	11 (45.8)
Inpatient	13 (54.2)
Duration of stay *(days)* [a]	
ICU	12.08 ± 7.02
Total	19.21 ± 13.08
Mortality	12 (50)

[a] Values presented as mean ± SD, [b] Blood glucose values ≥ 7.8 mmol/L.

Table 4.1.2. Comparison of baseline and clinical characteristics in patients with and without CVS

	CVS: No. (%)		
Variable	**No (n = 18) [e]**	**Yes (n = 6)**	***p* Value [f]**
Age *(years)* [a]	57.94 ± 15.65	53.67 ± 15.83	NS
Female	11 (61.1)	1 (16.7)	NS
Male	7 (38.9)	5 (83.3)	NS
WFNSS *(points)* [a]	3.56 ± 1.01	4.8 ± 0.45	< 0.05
Fischer scale *(points)* [a]	4.00 ± 0.00	4.00 ± 0.00	NS
Medical history			
Diabetes mellitus	1 (5.6)	2 (33.3)	NS
Hypertension	9 (50)	4 (66.7)	NS
Cardiovascular disease	4 (22.2)	1 (16.7)	NS
SAH-related conditions			
Aneurysm rupture	14 (77.8)	6 (100)	NS
Cerebral oedema	4 (22.2)	5 (83.3)	<0.05
Hydrocephalus	4 (22.2)	4 (66.7)	NS
Blood glucose *(mmol/L)* [a]			
Admission	9.28 ± 2.93	7.32 ± 1.58	< 0.05
24-hour [c]	9.29 ± 3.04	7.26 ± 1.17	< 0.05
Inpatient [d]	8.95 ± 2.54	8.44 ± 1.98	NS
Hyperglycaemia [b]			
Admission	12 (66.7)	2 (33.3)	NS
24-hour	10 (55.6)	1 (16.7)	NS
Inpatient	10 (55.6)	3 (50)	NS
Duration of stay *(days)* [a]			
ICU	12.11 ± 7.90	12.00 ± 3.69	NS
Total	21.33 ± 14.49	12.83 ± 2.86	< 0.05
Mortality	7 (38.9)	5 (83.3)	NS

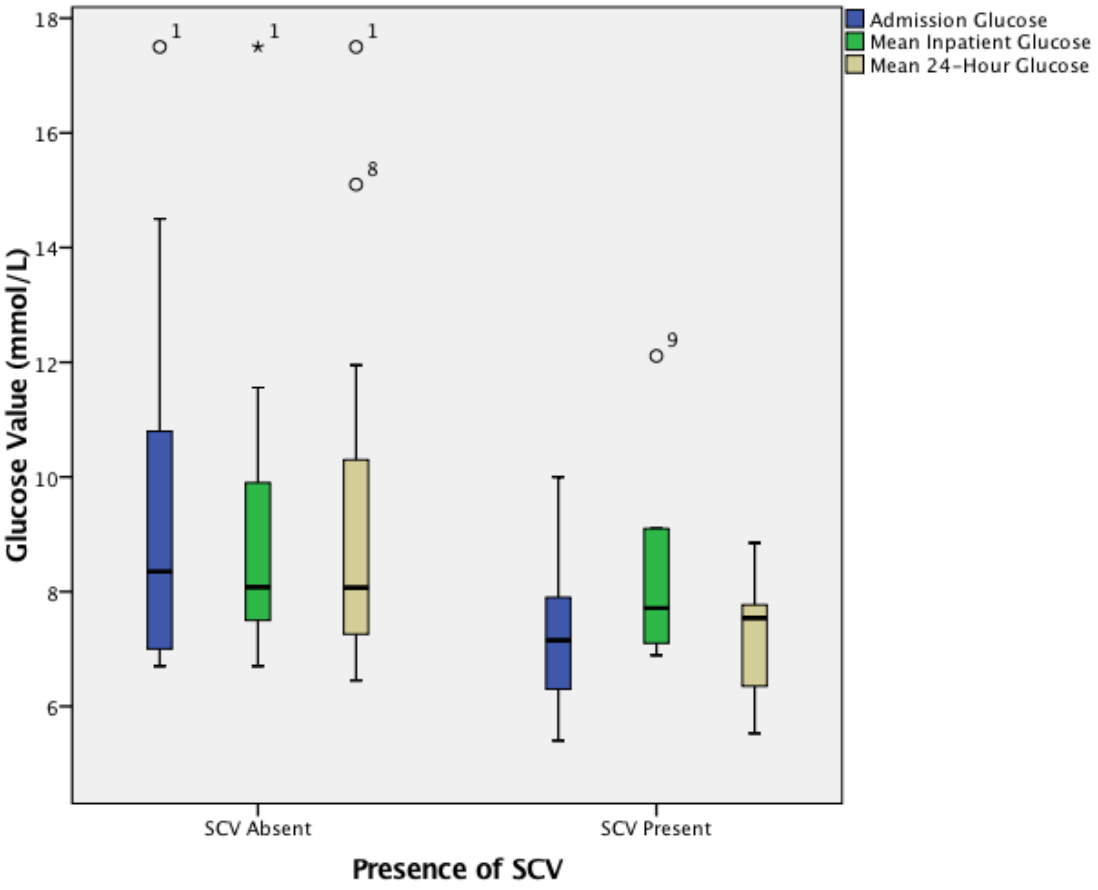
[a] Values presented as mean ± SD, [b] Blood glucose values ≥ 7.8mmol/L, [c] Average of mean glucose values of the first day in ICU, [d] Average of mean daily blood glucose values for the first fourteen days, [e] All patients without CVS, [f] NS = Non-significant.

4.2. Analysis of Data

As expected, patients that developed CVS displayed a higher clinical severity on admission *(WFNSS 4.8* ± 1.01 *vs. 3.56* ± 0.45*, p < 0.05).* A finding of cerebral oedema on initial radiologic examination was more frequently seen in patients who developed CVS *(83.3% vs. 22.2%, p < 0.05).*

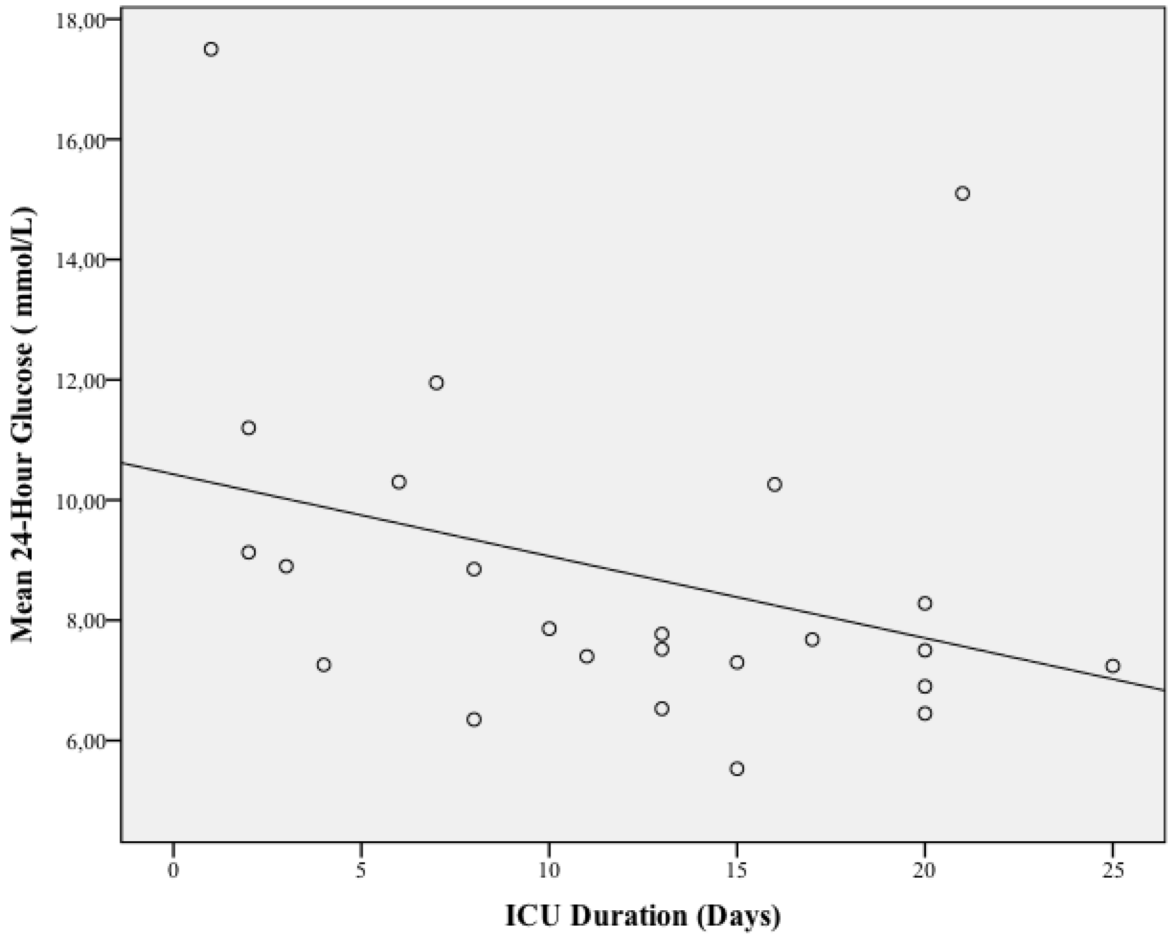
The mean inpatient blood glucose values *(8.44 ± 1.98 mmol/L vs. 8.95 ± 2.54 mmol/L, p = 0.62)* did not show a significant difference in mean in the development of CVS. However, contrary to expectations, a lower blood glucose value on admission *(7.32 ± 1.58 mmol/L vs. 9.28 ± 2.93 mmol/L, p < 0.05)* and during the first 24 hours of ICU stay *(7.26 ± 1.17 mmol/L vs. 9.29 ± 3.04 mmol/L, p < 0.05)* was seen in patients with subsequent development of CVS (Figure 5.2.1.). Hyperglycaemia on admission *(33.3% vs. 66.7%, p = 0.17)* and during the first 24 hours of ICU stay *(16.7% vs. 55.6%, p = 0.12)* was less frequently seen in patients who developed CVS than patients who did not develop CVS.

Figure 4.2.1 Comparison between mean admission, mean inpatient and mean 24-hour glucose value (mmol/L) and development of CVS



People developing CVS had a shorter mean length of hospitalisation *(12.83 ± 2.86 days vs. 21.33 ± 14.49 days, $p < 0.05$)* and we found that duration of ICU stay was negatively correlated to glucose averages of the first 24 hours of ICU stay *($r_s = -0.408$, $p < 0.05$)* (Figure 4.2.2.) and almost significantly negatively correlated to mean inpatient glucose levels *($r_s = -0.377$, $p = 0.07$).*

Figure 4.2.2 Correlation between mean 24-hour glucose values and duration of ICU stay



CVS *(83.3% vs. 38.9%, $p = 0.07$)* and signs of cerebral oedema on initial radiological examination *(66.7% vs. 8.3% $p < 0.05$)* were more frequently seen in patients that suffered from a fatal outcome. Differences in admission *(9.18 ± 3.17 mmol/L vs. 8.4 ± 2.35 mmol/L, $p = 0.5$),* mean 24-hour *(8.87 ± 3.16 mmol/L vs. 8.7 ± 2.57 mmol/L, $p = 0.89$)* and mean inpatient *(9.44 ± 2.95 mmol/L vs. 8.21 ± 1.54 mmol/L, $p = 0.21$)* blood glucose values did not show statistical significance to mortality. However, patients that suffered from a fatal outcome showed a negative correlation between duration of hospitalisation and glucose levels

on ICU admission (r_s=*-0.714, p < 0.05*), mean 24-hour glucose levels (r_s=*-0.670, p < 0.05*) and mean inpatient glucose levels (r_s=*-0.621, p < 0.05*).

4.2.1 Clinical predictors of CVS

Cerebral oedema *(RR, 8.29; 95% CI, 0.01 – 0.87; p = 0.01)* and hydrocephalus *(RR, 4; 95% CI, 0.06 – 1.01; p = 0.05)* were found to significantly increase the risk for CVS. Admission blood glucose *(RR, 2.8; 95% CI, 0.8 – 1.59; p = 0.15)*, mean 24-hour blood glucose *(RR, 4.23; 95% CI, 0.32 – 1.73; p = 0.1)* and mean inpatient blood glucose *(RR, 1.18; 95% CI, 0.21 – 3.38; p = 0.6)* were not found to be significant predictors of CVS (Table 4.2.1.1.). The relative risk (RR) for the blood glucose values takes into account the adjusted RR for every 1 mmol/L decrease in blood glucose value below 7.8 mmol/L (since lower blood glucose values were associated with the development of CVS).

Table 4.2.1.1 Multivariate analysis of factors associated with CVS after SAH

Predictor	Relative Risk	95% CI	*p* Value [a]
Cerebral Oedema	8.29	0.01 – 0.87	0.01
Hydrocephalus	4	0.06 – 1.01	0.05
Admission Glucose [b]	2.8	0.8 – 1.59	0.15
Mean 24h Glucose [b]	4.23	0.32 – 1.73	0.1
Mean Inpatient Glucose [b]	1.18	0.21 – 3.38	0.6

CI = confidence interval, [a] Determined with chi-square test, [b] RR for every 1 mmol/L decrease in blood glucose value below 7.8 mmol/L

5. DISCUSSION

5.1. Discussion of Results

According to the results obtained from our study, we discovered that the development of CVS seems to be associated with lower blood glucose values on ICU admission and lower mean blood glucose values after 24 hours of ICU stay. Mean inpatient blood glucose levels did not show significant difference in groups to the development of CVS. Patients with lower blood glucose values on ICU admission also had a longer duration of ICU stay (possibly connected to the higher incidence of CVS development). A higher WFNSS and the presence of cerebral oedema on initial radiological examination also seem to be related to the development of CVS and patient mortality. This contrasts well with the findings of Ingawa, T., further endorsing the theory that severe SAH evident on CT-imaging appears to be a consistent risk factor for CVS [63].

An association between hypoglycaemia and neurologic deficit, in particular hemiparesis has been described in various studies and case reports dating all the way back to 1928 [65 ,66]. A detailed literature review performed by Tetsuhiru et. al. in 2012 summarised articles from January 1950 to December 2010 that described cases of newly discovered hemiplegia in hypoglycaemic patients [67]. Although the exact mechanism of hemiparesis in hypoglycaemic patients remains unclear, several studies included in the review associated a state of hypoglycaemia with the development of vasospasm.

Several more recent preceding studies have determined the importance of TGC of SAH patients in an ICU setting and have linked the development of CVS and worse patient outcome to episodes of hyperglycaemia throughout the entire ICU stay [8, 9, 13]. Hyperglycaemia on admission has also been investigated, however has thus far only been linked to changes in neurological grade [18] and increased incidence of morbidity and mortality [19]. The relationship to the development of CVS remains unclear. Two studies have focused on the effects of (mild) hypoglycaemia and patient outcome after SAH [7, 14], with emphasis being placed on the nadir (minimum) glucose value throughout ICU stay. After prospectively examining 172 patients with SAH, Naidech et. al. determined that a nadir glucose of $\leq$ 4.4 mmol/L is associated with cerebral infarction, vasospasm and worse functional outcome at 3 months after SAH [14]. The data in this study represented admission blood glucose values comparable to ours *(8.93 vs. 8.79)*. Similar to our study, no differences

in mean inpatient blood glucose values were observed between patients who developed CVS and those that did not. Nevertheless, since only a single patient in our study presented with nadir glucose of ≤ 4.4 mmol/l throughout the entire ICU stay, it remains difficult to compare our results.

Brain injury including aneurysmal SAH has already been linked to the initiation of metabolic derangements that indicate distress such as increased glutamate, glycerol, and lactate/pyruvate ratio [16, 17]. Two studies performed in 2006 and 2008 demonstrated that low levels of blood glucose following intensive insulin therapy (IIT) in the ICU were associated with increased prevalence of cerebral metabolic distress due to subsequently reduced cerebral glucose availability [16, 17]. In one study performed by Oddo et. al. [16], tight glycaemic control (blood glucose 4.4 – 6.7 mmol/L) was associated with a greater prevalence of low cerebral glucose and subsequent development of brain energy crisis compared to intermediate glycaemic control (6.8 – 10 mmol/L). The study determined that lower systemic glucose values independently predicted brain energy crisis, which in turn correlates with an increased mortality. Keeping the relationship between mild hypoglycaemia and the development of brain energy crisis in mind, one can postulate that the presence of a brain energy crisis due to lower blood glucose values on admission and after the first 24-hours of ICU stay may further contribute to the initial development of CVS and worse patient outcome.

If lower blood glucose values on admission and within 24h of ICU stay are potentially hazardous after SAH, ICU protocols that define target glucose values may need to be refined for different ICU settings. Instead of immediate implementation of TGC with a target glucose range of 4.4 to 6.1 mmol/L as proposed by the Leuven Surgical Trials in 2001 [68], a delayed onset of aggressive insulin therapy could lead to improved clinical outcomes.

5.2. Discussion of Limitations

Certain limitations of this retrospective study were noted and deserve to be mentioned. First, it was not possible to accurately include all nutritional intake retrospectively, and this factor was not taken into account as a possible contribution to elevated / reduced blood glucose levels in the included patients. Nonetheless, all patients received standardised and appropriate nutritional support, therefore we do not believe that differences in nutritional

intake would have been significant enough to lead to changes in mean inpatient blood glucose levels.

Second, the use of sedatives may have biased the clinical definition of CVS, especially in mechanically ventilated patients. It is well known that the use of sedatives may limit the detection of changes in neurologic status. However, using our methodology, we found 25% of SAH patients to develop CVS, which compares to similar findings from preceding studies [2, 3].

Third, we did not have access to data from invasive monitors such as brain oxygen tension or microdialysis parameters, so the mechanism of neuronal energy failure related to blood glucose values is speculative. Finally, in a great majority of the cases we relied on CTA for the initial diagnosis of CVS instead of the current DSA gold standard. This was mainly due to a lack of resources and requirement for rapid and early diagnosis. Nevertheless, CTA has proven to be a highly sensitive, specific and accurate diagnostic method with proof of good correlation to DSA [12].

6. SUMMARY AND CONCLUSIONS

In summary, we found that lower blood glucose values on ICU admission and after 24h of ICU stay were associated with the development of CVS after SAH. Mean inpatient blood glucose values were not related to the development of CVS. While controlling blood glucose levels in an ICU setting remains an important factor in critical care, patients with SAH may benefit from protocols that aim for a wider target glucose range in order to avoid a state of hypoglycaemia, especially within the early stages of disease. The study cannot definitely establish causality, although it might spark refinement of standard glucose control protocols, especially in the early stages of ICU presentation.

II. List of Tables

III. List of Figures

IV. References and Bibliography

I Books

[21] Abhinav, K., Edwards, R., Whone, A. *Rapid Neurology and Neurosurgery.* West Sussex: John Wiley & Sons, 2012. 73p

[22] Hayden, G. M. *Tarascon Neurosurgery Pocketbook*. Burlington: Jones & Bartlett, 2014. 166p

[28] International Union of Pure and Applied Chemistry – The Compendium of Chemical Terminology. 596p

[42] Mathiesen, T. *Vasospasm and delayed ischaemic deficit. Manual of neurosurgery.* 1996 Edinburgh: Churchill Livingstone. 428–432p

II Journals and Publications

[1] Suarez, J.I., Tarr, R.W., Selman, W.R. *Aneurysmal subarachnoid haemorrhage*. N Engl J Med, 2006. 354(4):387-96

[2] Biller, J., Godersky, J.C., Adams, H.P. *Management of aneurysmal subarachnoid hemorrhage*. Stroke. 1988. 19:1300 –1305

[3] Keyrouz, S., Diringer, M. *Clinical review: Prevention and therapy of vasospasm in subarachnoid haemorrhage.* Critical Care, 2007. 11:220

[4] Inagawa, T., Yahara, K., Ohbayashi, N. *Risk factors associated with cerebral vasospasm following aneurysmal subarachnoid hemorrhage.* Neurol Med Chir (Tokyo), 2014. 17;54(6):465-73

[5] Hunt, W.E. *Clinical assessment of SAH.* J Neurosurg. 1983. 59:550–551

[6] Kistler, J.P., Crowell, R.M., Davis, K.R., et al. *The relation of cerebral vasospasm to the extent and location of subarachnoid blood visualized by CT scan*: *A prospective study*. Neurology. 1983. 33:424 – 436

[7] Schmutzhard, E., Rabinstein, A.A. *Spontaneous subarachnoid hemorrhage and glucose management.* Neurocrit Care. 2011. 15(2):281-6

[8] Weir, C.J., Murray, G.D., Dyker, A.G., et al. *Is hyperglycemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study.* BMJ. 1997. 314: 1303–1306

[9] Badjatia, N., et al. *Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage.* Crit Care Med. 2005. 33(7):1603-9

[10] Keyrouz, S.G., Diringer, M.N. *Clinical review: Prevention and therapy of vasospasm in subarachnoid haemorrhage.* Crit Care, 2007. 11(4): 220

[11] Alberti, O., Becker, R., Benes, L., et al. *Initial hyperglycemia as an indicator of severity*

of the ictus in poor-grade patients with spontaneous subarachnoid hemorrhage. Clin Neurol Neurosurg. 2000. 102:78 – 83

[12] Anderson, G.B., et. al. *CT angiography for the detection of cerebral vasospasm in patients with acute subarachnoid hemorrhage.* AJNR Am J Neuroradiol. 2000. 21(6):1011-5.

[13] Charpentier, C. *Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage.* Stroke*,* 1999. 30:1402–1408

[14] Naidech, A.M., et.al. *Moderate Hypoglycemia is associated with vasospasm, cerebral infarction, and 3-month disability after subarachnoid hemorrhage.* Neurocrit Care, 2010. 12(2):181-7

[15] McCowen, K.C., Malhotra, A., Bistrian, B.R. *Stress-induced hyperglycaemia.* Crit Care Clin. 2001. 17:107–124

[16] Oddo, M., et. al. *Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study.* Crit Care Med. 2008. 36(12):3233-8

[17] Vespa, P. et. al. *Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury*. Crit Care Med, 2006. 34(3):850-6

[18] Sato, M. et. al. *Admission blood glucose levels and early change of neurological grade in poor-grade patients with aneurysmal subarachnoid haemorrhage.* Acta Neurochir (Wien). 2006. 148(6):623-6

[19] Cagiran, E. et. al. *Admission Blood Glucose and Morbidity-Mortality in Subarachnoid Hemorrhage Patient.* Journal of Neurological Sciences (Turkish). 2013. V.30N.1P.168-177

[20] Moghissi, E.S., et al. *American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control.* Endocr Pract. 2009. 15(4):353-69

[23] Kistler, J.P. et. al. *The relation of cerebral vasospasm to the extent and location of subarachnoid blood visualized by CT scan: a prospective study.* Neurology. 1983. 33(4):424-36

[24] Tani, E. *Molecular mechanisms involved in development of cerebral vasospasm.* Neurosurg Focus. 2002. 12(3):ECP1

[25] Macdonald, R.L., Weir, B.K. A review of hemoglobin and the pathogenesis of cerebral vasospasm. Stroke. 1991. 22:971–982

[26] Nishizawa, S., Laher, I. *Signaling mechanisms in cerebral vasospasm.* Trends Cardiovasc Med. 2005. 15:24–34

[27] Pluta, R.M. *Delayed cerebral vasospasm and nitric oxide: review, new hypothesis, and proposed treatment.* Pharmacol Ther. 2005. 105:23–56

[29] Halliwell B, Gutteridge, M.C. *Free radicals in biology and medicine.* New York: Oxford University Press. 1999. p 27

[30] Cook, D.A., Vollrath, B. *Free radicals and intracellular events associated with cerebrovascular spasm.* Cardiovasc Res. 1995. 30:493–500

[31] Polidori, M.C., et. al. *Increased levels of plasma cholesteryl ester hydroperoxides in patients with subarachnoid hemorrhage.* Free Radic Biol Med. 1997. 23:762– 767

[32] Asano, T. et. al. *Experimental evaluation of the beneficial effect of an antioxidant on cerebral vasospasm.* Neurol Res. 1984. 6:49–53

[33] Marin, J., Rodriguez-Martinez, M.A. *Role of vascular nitric oxide in physiological and pathological conditions.* Pharmacol Ther. 1997. 75:111–134

[34] Pluta, R.M., et.al. *Loss of nitric oxide synthase immunoreactivity in cerebral vasospasm.* J Neurosurg. 1996. 84:648–654

[35] Jung, C.S., et. al. *Association between cerebrospinal fluid levels of asymmetric dimethyl-L-arginine, an endogenous inhibitor of endothelial nitric oxide synthase, and cerebral vasospasm in a primate model of subarachnoid hemorrhage.* J Neurosurg. 2004. 101:836–842

[36] Widenka, D.C., et. al. *Inducible nitric oxide synthase: a possible key factor in the pathogenesis of chronic vasospasm after experimental subarachnoid hemorrhage.* J Neurosurg. 1999. 90:1098–1104

[37] Pluta, R.M., *Reversal and prevention of cerebral vasospasm by intracarotid infusions of nitric oxide donors in a primate model of subarachnoid hemorrhage.* J Neurosurg. 1997. 87:746–751

[38] McGirt, M.J., et. al. *Simvastatin increases endothelial nitric oxide synthase and ameliorates cerebral vasospasm resulting from subarachnoid hemorrhage.* Stroke. 2002. 33:2950–2956

[39] Chow, M., Dumont, A.S., Kassell, N.F. *Endothelin receptor antagonists and cerebral vasospasm: an update.* Neurosurgery. 2002. 51:1333–1341

[40] Miyauchi, T., Masaki, T. *Pathophysiology of endothelin in the cardiovascular system.* Annu Rev Physiol. 1999. 61:391–415

[41] Sercombe, R., Dinh, Y.R., Gomis, P. *Cerebrovascular inflammation following subarachnoid haemorrhage.* Jpn J Pharmacol. 2002. 88:227–249

[43] Shiokawa Y, gado-Zygmunt TJ, Arbab MA, Svendgaard NA. *Effect of unilateral pre- and postganglionic lesioning of the trigeminal nerve on the development of cerebral vasospasm in the squirrel monkey: angiographic findings.* Br J Neurosurg. 1992. 6:445–455

[44] Weir, B., Macdonald, R.L., Stoodley, M. *Etiology of cerebral vasospasm.* Acta Neurochir Suppl. 1999. 72:27–46

[45] Pluta, R.M., Zauner, A., Morgan, J.K., Muraszko, K.M., Oldfield, E.H. *Is vasospasm related to proliferative arteriopathy?* J Neurosurg. 1992. 77:740– 748

[46] Borel ,C.O., et. al. *Possible role for vascular cell proliferation in cerebral vasospasm after subarachnoid hemorrhage.* Stroke. 2003. 34:427–433

[47] Zubkov, A.Y., Ogihara, K., Bernanke, D.H., Parent, A.D., Zhang, J. *Apoptosis of endothelial cells in vessels affected by cerebral vasospasm.* Surg Neurol. 2000. 53:260–266

[48] Zhou, C., Yamaguchi, M., Colohan, A.R., Zhang, J.H. *Role of p53 and apoptosis in cerebral vasospasm after experimental subarachnoid hemorrhage.* J Cereb Blood Flow Metab. 2005. 25:572–582

[49] Cahill, J., Calvert, J.W., Solaroglu, I., Zhang, J.H. *Vasospasm and p53- induced apoptosis in an experimental model of subarachnoid hemorrhage.* Stroke. 2006. 37:1868–1874

[50] Leslie, J.B., Watkins, W.D. *Eicosanoids in the Central Nervous System.* J Neurosurg. 1985. 63:659–668.

[51] Gull, W.M. *Cases of aneurism of the cerebral vessels.* Guys Hosp Rep. 1859. 5:281–304

[52] Weir, B., Grace, M., Hansen, J., Rothberg, C. *Time course of vasospasm in man.* J Neurosurg. 1978 48:173–178

[53] Fisher, C.M., Kistler, J.P., Davis, J.M. *Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning.* Neurosurgery. 1980. 6:1–9

[54] Daankbar, J.W., et. al. *Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review.* Crit Care. 2010. 14(1):R23

[55] Kaufmann, T.J., et. al. *Complications of Diagnostic Cerebral Angiography: Evaluation of 19 826 Consecutive Patients.* Radiology. 2007. 243:812-9

[56] Wintermark, M. et.al. *Vasospasm after subarachnoid hemorrhage: utility of perfusion CT and CT angiography on diagnosis and management.* AJNR Am J Neuroradiol. 2006. 27(1):26-34

[57] Sloan, M.A., et. al. *Assessment: Transcranial Doppler ultrasonography. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.* Neurology. 2004. 62(9):1468-81

[58] Lennihan, L. et. al. *Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage : a randomized controlled trial.* Stroke. 2000. 31(2):383-91

[59] Egge, A. et. al. *Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study.* Neurosurgery. 2001. 49(3):593-605

[60] Hino, A. et. al. *Effect of hemodilution on cerebral hemodynamics and oxygen metabolism.* Stroke. 1992. 23:423-426

[61] Zwienenberg-Lee, M. et. al. *Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial.* Stroke. 2008 39(6):1759

[62] Aburto-Murrieta, Y. et. al. *Endovascular treatment: balloon angioplasty versus nimodipine intra-arterial for medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage.* Vasc Endovascular Surg. 2012. 46(6):460

[63] Inagawa, T. *Risk Factors for Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage: A Review of the Literature.* World Neurosurg. 2016. 85:56-76

[64] Dumont, T., Rughani, A., Silver, J., Tranmer, B. *Diabetes mellitus increases risk of vasospasm following aneurysmal subarachnoid hemorrhage independent of glycemic control.* Neurocrit Care. 2009. 11:183-189

[65] Diecke, O. *Angiospastic hemiplegia as hypoglycemic reaction.* Dtsch Med Wochenschr. 1928. 54:1375–80

[66] Ravid, J.M. *Transient insulin hypoglycemic hemiplegias.* Am J Med Sci.1928. 175:756-69

[67] Yoshino, T. et. al. *A case of hypoglycemic hemiparesis and literature review.* Ups J Med Sci. 2012. 117(3):347-51

[68] Van den Gerghe, G. et. al. *Intensive Insulin Therapy in Critically Ill Patients.* N Engl J Med. 2001. 345:1359-1367

[69] Kassell, et. al. *Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension.* Neurosurgery. 1982. 11(3):337-43

[70] Kerz, T. et. al. *Endovascular therapy for vasospasm after aneurysmatic subarachnoid haemorrhage.* Br. J. Neurosurg. 2016. 30(5):549-53

[71] Ecker, A., Riemenschneider, P.A. *Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms.* J Neurosurg. 1951. 8:660-667

[72] Stornelli, S.A., French, J.D. *Subarachnoid hemorrhage-factors in prognosis and management.* J Neurosurg. 1964. 21:769-780

[73] Kosnik, E.J., Hunt, W.E. *Postoperative hypertension in the management of patients with intracranial arterial aneurysms.* J Neurosurg. 1976. 45:148–54

V. Curriculum Vitae

Breiding, Philipe Sebastian, born 02.04.1992 in Worms, Germany

Primary and Secondary Education

1998 – 2005	John F. Kennedy International School Saanen, Switzerland
2005 – 2009	Woodridge College and Preparatory School Thornhill, South Africa

Military Service

01.2010 – 09.2010	Gebirgsjägerbrigade 23 - Gebirgsjägerbataillon 232 Bischofswiesen, Germany

Tertiary Education

2010 – 2016	Riga Stradiņš University - Faculty of Medicine Riga, Latvia

Work Experience

08.2016 – 10.2016	Assistenzarzt, Universitätsklinik für Neurochirurgie - Inselspital Bern, Switzerland
12.2016 – Today	Assistenzarzt, Universitätsinstitut für Diagnostische und Interventionelle Neuroradiologie - Inselspital Bern, Switzerland

VII. Directory of Academic Teachers

My academic teachers in Rīga and Marburg were:

Zane Ābola, Edgars Bodnieks, Sarmīte Boka, Jānis Dundurs, Renārs Erst, Dace Gardovska, Götz Geldner, Rolands Gibners, Valērija Groma, Simona Gurbo, Ilona Hartmane, Andris Jumtiņš, Āris Kaksis, Oskars Kalējs, Regīna Kleina, Ralfs Kolitis, Jeļena Krasiļņikova, Juta Kroiča, Angelika Krumina, Gaida Krūmiņa, Iveta Kudaba, Guna Laganovska, Juris Leja, Viesturs Liguts, Jevgēnija Livdāne, Inguna Lubaua, L. Lugovskojs, Inese Mihailova, Edvīns Miklaševičs, Erika Nagle, Ivars Neiders, Georgi Orlikov, Daina Pastare, Māra Pilmane, Aldis Puķītis, Guntars Pupelis, Santa Purviņa, Juris Pokrotnieks, Elmārs Rancāns, Dace Rezeberga, Maija Rumaka, Oļegs Sabeļņikovs, Juris Salaks, Jānis Sokolovs, Peteris Studers, Ojārs Teteris, Signe Tomsone, Ilze Umalas, Indulis Vanags, Ludmila Vīksna, Ņina Zazerska, Smuidra Žermanos, Dace Žibala, Jana Žodžika.

VIII. Note of Thanks

At this point I would like to thank all those who supported me in the making of this dissertation.

My thanks go to Prof. Götz Geldner and Assist. Prof. Oļegs Sabeļņikovs for enabling me to pursue the topic at hand, for their continuous constructive feedback and for sparking a great amount of interest in the nature of research, which I will most definitely carry with me into the future.

Furthermore, I would like to thank the staff of Pauls Stradiņš Clinical University Hospital, in particular the Department of Anaesthesiology and Reanimatology for providing me with the resources and support to carry out the given research.

Finally, I would like to thank my father Ernst Michael, my mother Heidi and my cat Ninja whom each in their own way contributed to the accomplishment of this dissertation.

IX. Zusammenfassung in deutscher Sprache

Der zerebrale Vasospasmus (ZVS) ist eine bekannte Ursache für Morbidität und Mortalität bei Patienten, die an einer Subarachnoidalblutung (SAB) gelitten haben. Seine Entstehung ist mit einer reduzierten zerebralen Perfusion und einer möglichen Entwicklung des neurologischen Defizits verbunden. Die Ätiologie von ZVS hat sich als multifaktoriell erwiesen und es wurden bereits mehrere Risikofaktoren mit seiner Entwicklung verbunden. Da ZVS mit Signalisierungsveränderungen im vaskulären Endothel bereits verknüpft wurde, haben wir die Serumglukose als potentiellen prognostischen Indikator und Risikofaktor, aufgrund ihrer Beziehung zur Endothel-Funktionsstörung gewählt.

Ziel dieser Studie war es, die Assoziation zwischen Serum-Glukosespiegel bei SAB-Patienten und der Entwicklung von ZVS zu bewerten. Die retrospektive Studie beinhaltete Daten von Intensivpatienten der Pauls Stradiņš Universitätsklinik mit der primären Diagnose SAB. Wir verglichen die Aufnahme Serum-Glukosespiegel und die Glukosespiegel-Mittelwerte für die ersten 5 Tage auf der Intensivstation bei Patienten mit und ohne anschließende Entwicklung von ZVS.

Insgesamt vierundzwanzig Patienten wurden in die Studie aufgenommen. ZVS wurde in 25% *(n = 6)* bestätigt. Es gab keinen signifikanten Unterschied in der Alters- und Geschlechterverteilung zwischen den Gruppen. Patienten mit ZVS hatten höhere WFNS-Scores *(4.80 und 3.56; p=0.008)*. Wir entdeckten niedrigere Aufnahme-Glukosewerte bei Patienten, die ZVS entwickelten *(7.32 und 9.28 mmol/L; p=0.05)*. Die Glukose-Mittelwerte in den ersten 24 Stunden des Aufenthalts zeigten sich auch niedriger bei Patienten, die ZVS entwickelten *(7.26 und 9.29 mmol/L; p=0.03)*. Es zeigten sich keine signifikanten Unterschiede im durchschnittlichen Glukosespiegel vom 2. bis zum 5. Tag des Aufenthalts. Mortalität wurde durch die Glukosespiegel nicht beeinflusst und die Glukose-Mittelwerte der ersten 24 Stunden korrelierten negativ mit der Dauer des Aufenthalts auf der Intensivstation *(rs = -0.408, p<0,05)*.

Die Studie zeigt, dass Aufnahme- und Initiale 24 Stunden Glukosespiegel prognostische Indikatoren für die potenzielle Entwicklung von ZVS nach SAB sein könnten. Glukose-Mittelwerte am ersten Tag des Intensivaufenthalts waren mit der Entwicklung von ZVS signifikant verknüpft und könnten, nach weiterer Analyse, möglicherweise mit einer größeren Patientengruppe, eine bedeutende Geltung erzielen.

X. Ehrenwörtliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin Marburg zur Promotionsprüfung eingereichte Arbeit mit dem Titel „Initial 24 Hour ICU Glucose Levels are Associated with the Development of Cerebral Vasospasm after Subarachnoid Haemorrhage" in der Klinik für Anästhesiologie und Intensivtherapie, unter der Leitung von Prof. Götz Geldner, mit Unterstützung von Assist. Prof. Oļegs Sabeļņikovs, ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation aufgeführten Hilfsmittel benutzt habe. Ich habe bisher an keinem in- oder ausländischen medizinischen Fachbereich ein Gesuch um Zulassung zur Promotion eingereicht, noch die vorliegende oder eine andere Arbeit als Dissertation vorgelegt. Ich versichere, dass ich sämtliche wörtlichen oder sinngemäßen Übernahmen und Zitate kenntlich gemacht habe. Mit dem Einsatz von Software zur Erkennung von Plagiaten bin ich einverstanden.

Ort, Datum: **Unterschrift:**

Philipe Sebastian Breiding

Die Hinweise zur Erkennung von Plagiaten habe ich zur Kenntnis genommen.

Ort, Datum: **Unterschrift Betreuer:**

Prof. Dr. med. Götz Geldner