Cerebral blood flow changes in acute subarachnoid hemorrhage

Gerrit Alexander Schubert, Claudius Thome

Department of Neurosurgery, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany

TABLE OF CONTENTS

1. ABSTRACT

Delayed vasospasm and secondary injury due to ischemia occur frequently in the setting of subarachnoid hemorrhage (SAH), and these changes have been well characterized within the last decades. Considerable effort has also been put into the development of therapeutic strategies and appropriate monitoring modalities. However, although in particular acute injury is known to contribute significantly to overall outcome in SAH, these immediate alterations still remain largely neglected in current research. Few studies exist to date which mainly describe rapid alterations in perfusion and metabolism. As the main characteristic of the very first minutes and hours after SAH, an immediate phase of CPP-independent hypoperfusion has been observed repeatedly both experimentally and clinically, and it has mostly been attributed to the development of acute vasospasm. Endothelin and nitric oxide, prime suspect in the pathogenesis of chronic vasospasm, may play a pivotal role in this early scenario, possibly being promoted by the drastic ICP increase and extravasation of blood compounds. The much disputed concept of inflammation in chronic vasospasm may not be applicable this early after the ictus, but mechanisms of cellular and structural changes causing microvascular platelet aggregation and immediate disruption of the basal lamina, however, are thought to contribute significantly to the imminent cascade of disturbances in perfusion and metabolism. This review is intended to summarize current insights and illustrate recent efforts to better understand alterations in cerebral perfusion in these very first minutes and hours after SAH which – at some point – may also be amenable to early therapeutic intervention.

2. INTRODUCTION

Subarachnoid hemorrhage (SAH) remains one of the foremost neurosurgical challenges due to its relatively high incidence (10-15/100.000), still associated with high morbidity and mortality despite considerable improvement in microneurosurgery, interventional treatment and neurointensive care units (1).

Several specific phases after SAH have been identified, and each phase contributes significantly to the overall outcome of this disease, which reaches up to 50% of cumulative mortality: the severity of the initial hemorrhage (early phase), the intervention to treat the ruptured aneurysm (perioperative phase) and the development of deficits during the chronic phase of vasospasm (chronic phase).

A plethora of experimental and clinical investigations concerning the perioperative phase has been undertaken to optimize securing the injured vessel, be it by endovascular coiling or surgical clipping of the aneurysm (2, 3, 4). An equal number of studies and reviews have been concerned with the prognosis, identification, treatment or prevention of vasospasm during the chronic phase between days 5-14 after the bleed (5, 6, 7).

Although the theory of biphasic development of vasospasm has been postulated in the Mid-60´s already, only very limited further data is available looking into the first part, the early phase after SAH (8, 9). The
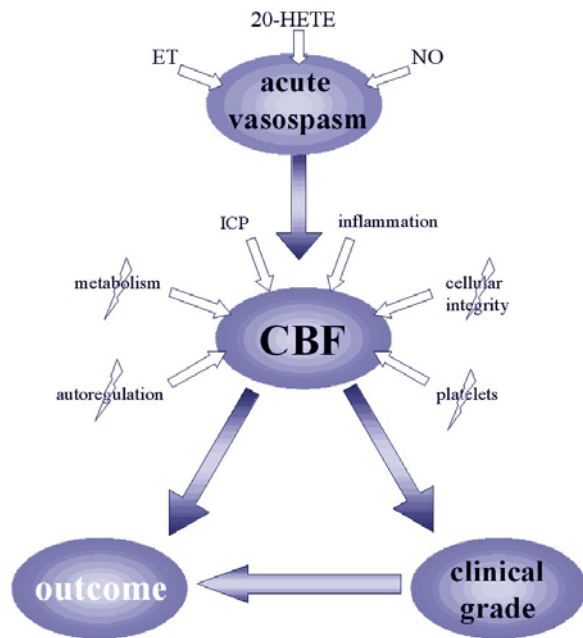
Figure 1. Illustration of the complexity of acute changes in SAH as well as their clinical relevance. Acute reduction of CBF is caused by a variety of cellular and structural changes, but the theory of acute vasospasm as a major factor has gained widespread acceptance. Acute hypoperfusion is known to correlate with the clinical grade at presentation, which in turn determines overall outcome. Thus, a correlation of CBF decrease and ultimate clinical recovery seems plausible.

initial severity of the hemorrhage and cerebral blood flow (CBF) reduction during the very first moments after an insult are major determinants for imminent morbidity and mortality (10, 11. 12). Neurological grading such as the World Federation of Neurological Surgeons (WFNS) or Hunt and Hess grading scales are universally accepted. The scales are defined by the initial and acute neurological deficit of a patient and are known to correlate well with the patient´s outcome (13, 14).

Thus, it is all the more surprising, that only limited effort has been put into the characterization of this acute pathophysiology and those changes in perfusion in particular, as it may very well be a crucial trigger in an oftentimes detrimental cascade, which is potentially amenable to favourable, early manipulation.

In this review we will summarize results and conclusions of selected experimental, but most importantly also recent clinical efforts highlighting the importance of early CBF changes after subarachnoid hemorrhage (Figure 1).

3. EXPERIMENTAL DATA

3.1. Perfusion and metabolism

As the extent of CBF reduction was found to correlate with a worsening in clinical outcome,

hemodynamic changes have been of interest to several research groups. In animal models, the occurrence of subarachnoid hemorrhage is usually approximated by either endovascular filament perforation or direct injection of blood into the cisterna magna or the chiasmatic cistern (15, 16, 17). Experimentally, a rapid increase in intracranial pressure (ICP) and a consecutive dramatic fall in cerebral perfusion pressure (CPP) immediately after the insult have been reliably reproduced[4,36,84,117], while Laser-Doppler flow (LDF) remains decreased at 20% of baseline values even after recovery of CPP (1, 15, 18, 19). This phase of prolonged hypoperfusion which is independent from perfusion pressure has been confirmed by studies from our own group and others, as well as a generalized loss of CO_2-reactivity after SAH (1, 15, 20, 21, 22). Furuichi *et al.* were able to show that slow and rapid injection of autologous blood into the cisterna magna, as well as rapid, but not slow injection of saline leads to an increase in sympathetic nerve activity and consequently to a dramatic and prolonged decrease in CBF (23). The underlying narrowing within the microvasculature was observed together with a suppression of metabolism, as estimated by a reduction in tissue oxygenation, and it was correlated with the severity of the hemorrhage (18, 24). Metabolic disturbances, as appreciated by microdialysis and magnetic resonance spectroscopy, include a depletion of glucose and concomitant increase in lactate and excitatory amino acids, supporting the theory of relative substrate depletion (25).

3.2. Cellular changes

CBF reduction is thought to precede complex cellular changes[3], which include rapidly developing cytotoxic edema on diffusion-weighted imaging (DWI) (25, 27). A wave-like propagation of cell depolarization, failure of energy-dependent Na^+/K^+ pumps and neuronal cell death may lead to cellular swelling (27). Generalized edema has been frequently observed after SAH, and as the extent of hypoperfusion seems to correlate with the extent of neuronal cell death, a recent capacious review explores the emerging role of apoptosis in caspase-dependent and -independent as well as mitochondrial pathways, mechanisms that may be influenced favourably by application of caspase inhibitors among others (28, 29, 30).

3.3. Structural changes

The exhaustion of autoregulation as mentioned above has been hypothesized to contribute to changes of vascular integrity; both the disruption of the blood-brain barrier and endothelial injury have been observed consistently within minutes to hours after the injury (31, 32, 33, 34). Adhesion molecules are expressed rapidly within the vasculature, promoting inflammation and consecutive luminal changes (35, 36). Other mechanisms include induction of vascular endothelial growth factor, luminal proteases and the above mentioned rise in ICP to increase permeability (37, 38, 39, 40). Loss of vascular integrity has also been attributed to an immediate loss of collagen IV in conjunction with an activation of MMP-9, leading to cerebral edema and vasoconstriction (39, 41). Platelet aggregation within minutes after SAH is followed

by a release of vasoactive compounds and mechanical blockage of vessels, also causing Hypoperfusion (42).

Ostrowski *et al.* have expertly summarized current insights into the cascades of molecular signaling pathways that are initiated early after a bleed, and in another recent overview, Sehba *et al.* have recapitulated oxidative injury by free radicals among other mechanisms (43, 44).

We will therefore limit our synopsis to few most pertinent explanatory principles in view of acute vasospasm, which as its own entity is well documented both historically and in current experimental setups (8, 19, 30, 45, 46).

3.4. Acute vasospasm
3.4.1. Endothelin
Endothelin (ET) is considered a prime causative suspect in the setting of delayed vasospasm, but acute liberation of ET-1 and the rapid development of vasoconstriction has also been investigated and is thought to be caused by the rapid increase in ICP itself throughout the brain, a hypothesis that is supported by the fact that early hypoperfusion is also a generalized phenomenon (7, 47, 48, 49, 50, 51). Other factors such as vascular shear stress, oxyhemoglobin and hypoxia can also induce the transcription of ET-1 mRNA with consequent synthesis of ET-1 within minutes (52). Consequently, additional investigations are already concerned with the prevention of acute vasospasm on the basis of endothelin A receptor antagonists (53, 54).

3.4.2. 20-HETE
20-hydroxyeicosatetraenoic acid (20-HETE) is another mediator of cerebral vasospasm; it activates protein kinase C and rho kinase and thereby sensitizes the vasculature to calcium, but it is also known to modulate the response to vasodilators and vasoconstrictors alike (55). An increase in 20-HETE within the CSF after SAH has been demonstrated both in animal experiments and clinically, and it has been associated with an acute decrease in CBF (56, 57, 58, 59). Interestingly, it has also been shown, that the inhibition of 20-HETE synthesis may have a beneficial influence on both acute Hypoperfusion and chronic vasospasm (60, 61, 62). Similar effects have been observed with the application of hypothermia and lipid-peroxidase inhibitors (1, 63).

3.4.3. Nitric oxide
Nitric oxide (NO) has been vigorously studied due to its well known vasodilatory effects and its maintenance of cerebral blood flow by demand (64, 65). Oxyhaemoglobin within the subarachnoid space after SAH scavenges NO and triggers ischemia on the basis of spreading depolarization (66); decreased availability of NO after SAH can cause relative, unopposed vasoconstriction (67, 68). Administration of a NO-donor can influence this acute vasoconstriction favourably, and it also reduces the release of excitatory amino acids (39, 69, 70). The effect of NO has been lend further indirect support by an animal model where treatment with 3-hydroxy-3-methylglutaryl

coenzyme A reductase inhibitors (statins) helped to augment cerebral blood flow by induction of enhancing nitric oxide synthase (eNOS) (71).

4. CLINICAL DATA

4.1. Clinical grade, perfusion and metabolism
A recent analysis of a very large cohort of SAH patients again showed that both cerebral infarction and the initial WFNS grade on admission are the most important predictors of overall outcome after SAH (72); also, WFNS grade itself and the length of the initial loss of consciousness are significantly correlated with the development of infarction (73). Investigations from Jakobsen *et al.* have been able to correlate the severity of this acute neurological deficit with the extent of initial hypoperfusion, and those observations have been confirmed by several other groups (74). Using Xenon-enhanced computed tomography (CT) among other techniques, a more pronounced initial decrease in CBF was found in those patients with a higher Hunt and Hess grade (12, 75, 76, 77). If the initial change in CBF parallels the neurological presentation of a patient, a correlation of CBF and outcome is plausible, necessitating more efforts to determine changes in CBF within the very first hours after the bleed (78). It remains a logistic challenge to examine patients with regard to crucial physiological parameters such as ICP, CPP and CBF within the first minutes and hours after SAH. High initial mortality and delayed presentation to a dedicated neurovascular center usually limit the number of patients eligible to be investigated, and those few studies successfully enrolling patients very early after the bleed usually preclude a generalized conclusion due to the small sample size.

Interpretation of an acute decrease in cerebral blood flow, though, is certainly limited without the knowledge of changes in cerebral metabolism, and – while experimental data suggest a scenario of severe depletion of energy substrates - ambivalent clinical results exist when investigating the correlation of CBF and metabolism (74). After SAH, oxygen uptake – measured by the cerebral metabolic rate for oxygen ($CMRO_2$) – decreases, and it also seems to correlate with clinical grade, being more severely diminished in unconscious than in conscious patients (12, 79, 80, 81). Some debate has been concerned with the occurrence of luxury perfusion immediately after SAH, usually defined as a more pronounced decrease in $CMRO_2$ than in CBF, paralleled by an ubiquitous decrease in arterio-venous difference for oxygen ($AVDO_2$) (12, 43). However, concomitant normal and increased oxygen extraction fraction have also been described within the first two days contradicting this hypothesis (79, 82).

Admission plasma glucose levels are oftentimes elevated after SAH as a catecholamine-driven stress response, providing ample amount of substrate in a predominantly anaerobic glycolysis, which in turn leads to severe lactate-acidosis with a worse prognosis (83, 84, 85, 86). Also, lactate was found to be elevated in both CSF and within the parenchyma (87, 88, 89). It indicates a pronounced disruption in metabolism on the basis of

impending cerebral ischemia with considerable accumulation of excitatory amino acids such as glutamate as verified by bed-side microdialysis (90, 91). These monitoring findings also support the concept of early detrimental hypoperfusion after SAH.

4.2. Intracranial pressure

On rare occasions, a dramatic rise of ICP to diastolic levels immediately after an aneurysmal bleed could be observed directly, a stage of the disease that is paralleled clinically by the typical initial syncopal episode (92, 93, 94). Before CSF can be displaced into the spinal canal, this massive increase in ICP has been postulated to culminate in a cerebral circulatory arrest of several minutes when simultaneous transcranial doppler sonography documented oscillating flow velocities of systolic input and diastolic output flow on the basis of massively increased peripheral resistance (95, 96, 97). According to Nornes, patients with a pressure peak and consecutive perfusion arrest of only a few minutes (Nornes Type I) had a considerably better chance of survival than those patients with continuous ICP elevation (Nornes Type II), possibly due to the extent of the initial ischemic compromise (93, 94). Hypothetically, this classification may be reflected somewhat by the general observation that patients with a classic non-aneurysmal perimesencephalic hemorrhage do suffer a distinctly less pronounced increase in ICP, and therefore experience a less severe reduction of CBF. This would explain the generally more benign outcome. The immense rise in ICP in aneurysmal SAH – initially ensuring hemostasis and thereby the patient´s survival – has been considered to be caused by the volume of acutely extravasated blood in the subarachnoid space, but also by acute vasoparalysis leading to direct transmission of arterial pressure to the parenchyma.

4.3. Autoregulation

Disruption of autoregulation has been observed not only in the experimental but also in the clinical setting. On the basis of both experimentally proven increase of CBF and a preservation of CO_2-vasoreactivity due to modification of the NO pathways, recent clinical analyses were looking into the effect of prior therapy with cholesterol-lowering agents such as statins in SAH patients (98, 99): a match-controlled cohort study which showed an improvement in early outcome and a retrospective analysis demonstrating a significant decrease in the incidence of symptomatic vasospasm (100, 101). Also in a prospective fashion, if treatment with statins was initiated early after SAH, improvement in autoregulation, amelioration of vasospasm and delayed neurological deficits could be observed (102, 103). However, the implications of these findings have to be examined cautiously, even more so on the basis that another study has correlated the use of selective serotonin reuptake inhibitors (SSRIs) and statins with a greater risk of developing vasospasm (104, 105).

4.4. Acute vasospasm

The hypothesis of immediate, reflectory vasodilation as well as luxury post-insult hyperperfusion seen with transcranial doppler has been supported by few selected clinical observations (106, 107, 108). Contrarily, authors have published angiographic case studies demonstrating a phase of hyperacute spastic narrowing after SAH (109). Angiography during aneurysmal rupture could not provide definite proof for acute constriction in this ultra-early phase of SAH, as more than one third of the patients had to be excluded due to obscuration of the vessels in question (110). Although these selected contradictory observations do not allow to draw a reliable conclusion, a retrospective analysis of a large multicenter trial has also demonstrated acute vasospasm to occur angiographically in up to 10% of patients admitted for the treatment of SAH within the first 48 hours (110, 111, 112). It was associated with poor admission grade, risk of further deterioration, infarction and also poor neurological outcome, though it did not correlated with the occurrence of late vasospasm. Since detection of proximal angiographic vasospasm becomes more and more feasible on CT angiography – which probably is a suitable and more readily available early diagnostic tool in SAH –, further data on the presence of acute vasospasm may be acquired in the near future (113). However, the incidence of peripheral vasospasm – currently appreciated on neither conventional nor CT angiography due to technically limited resolution – may certainly be even higher than 10% (114). Experimental and clinical evidence of distal microvasospasm may in part explain the initial decrease in CBF (39, 115, 116). Interestingly, prolonged hypoperfusion during the acute phase has been observed clinically in small case series within the first three days, and this perfusion compromise is independent of CPP, as ICP rapidly regains prebleeding levels (117, 118). Recently, preliminary observations from our own group within the first 6 hours after SAH were in excellent accordance with those findings (Figure 2, unpublished data), and may correspond to early focal lesions found acutely in high-grade SAH by magnetic resonance imaging (119).

It is believed by some groups that inflammatory cell infiltration of the aneurysm wall as well as progressive degradation of the endothelial layer may herald the rupture of an aneurysm, followed by disruption of the basal membrane and consequently culminating in an aneurysmal tear (120). In a time course that has to be characterized in more detail, mononuclear leukocytes then secrete ET-1 and proinflammatory cytokines such as IL-1β, IL-6 and TNF-α (121, 122). ET-1 is considerably more elevated in the parenchyma than in the CSF or plasma, which is in good aggreement with the fact that endothelin mostly acts in a paracrine fashion from the adventitial, not the luminal side of the vessel (123, 124, 125). The importance of these responses in the acute phase after SAH is supported by the fact, that only the early intrathecal concentration of proinflammatory cytokines has been associated with poor clinical outcome (126). Correspondingly, but not addressing the acute phase, selective endothelin-A receptor antagonists have been found to ameliorate delayed vasospasm (7).
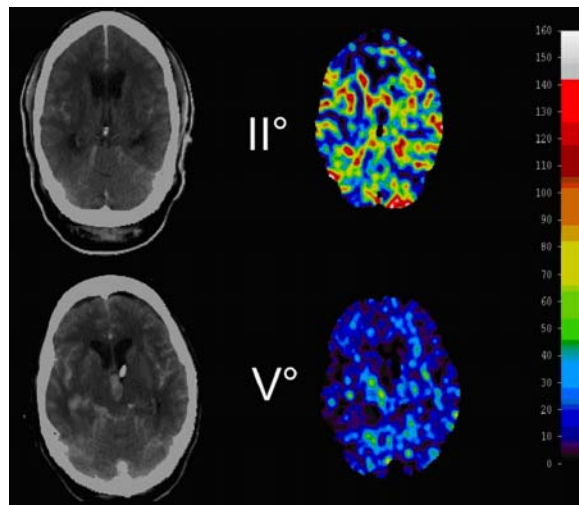
Figure 2. Illustration of exemplatory cerebral blood flow changes measured by Xenon-enhanced CT early after SAH. The first patient presented three hours after SAH (upper left: symmetrical hemorrhage on CT) to our department with moderate headache and mild confusion, GCS 14, being graded HH II°. Except for the right frontal area close to normal perfusion levels were present (upper right). The second patient also presented three hours after SAH, but was comatous upon admission with a GCS of 4 being graded HH V°. CT scanning (lower left; external ventricular drain in place) showed severe SAH and Xenon-enhanced CT demonstrated profound and ubiquitous reduction in perfusion averaging approximately 15ml/100g x min (lower right).

Cell adhesion molecules (CAMs) and E-selectin in particular have also been advocated to participate in the development of vasospasm through very early steps of an inflammatory response, as they increase rapidly after SAH in both CSF and plasma (127, 128). It has been argued, however, that most inflammatory changes are less likely to occur during the very acute phase due to their time-consuming nature of initiation as expertly outlined in a overview by Sercombe *et al.* (129).

5. CONCLUSION

Acute hypoperfusion is a characteristic feature early after SAH. As a multifactorial event it precedes a preliminary recovery and secondary deterioration due to delayed vasospasm. The combination of this early and profound change in perfusion is thought to reflect the impact of primary injury, thereby causing a specific vulnerability to secondary insults.

6. PERSPECTIVE

A multitude of contributing factors has been described in acute brain injury after SAH so far, but understanding of the underlying mechanisms and the ultimate relevance of these early changes still is incomplete. It will be crucial for future research efforts to shed more light into this cascade, since although primary

neuronal loss cannot be prevented, amelioration of the extent of acute injury might prove useful to minimize potentially deleterious sequelae.

Acute hypoperfusion constitutes one major factor in the pathophysiological cascade of SAH. Strategies to counteract these early CBF changes may well be beneficial for our SAH patients, but this requires thinking about early interventions rather than waiting for chronic vasospasm to occur later on.

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Abbreviations: 20-HETE; 20-hydroxyeicosatetraenoic acid; CBF: cerebral blood flow; CPP: cerebral perfusion pressure; CT: computed tomography; DWI: diffusion-weighted imaging; ET: endothelin; GCS: Glasgow coma scale; HH: Hunt and Hess; ICP: intracranial pressure; LDF: Laser-Doppler flow; NO: nitric oxide; SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurological Surgeons

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Send correspondence to: Dr Gerrit A. Schubert, Dept. of Neurosurgery, University Hospital Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Tel: 49-621-383-2360, Fax: 49-621-383-2004, E-mail: gerrit.schubert@nch.ma.uni-heidelberg.de