Cortical Spreading Ischaemia and Delayed Ischaemic Neurological Deficits after Subarachnoid Haemorrhage

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CONTENTS Volume 1

PART I

DELAYED ISCHAEMIC NEUROLOGICAL DEFICITS (DIND) AFTER ANEURYSMAL SUBARACHNOID HAEMORRHAGE

I 1
Epidemiology

Although cerebral haemorrhage represents only 10%-15% of all strokes, it has been estimated to cause more than 50% of the overall stroke mortality (Bamford et al. 1990). The 30-day mortality rate at around 45% is similar for intracranial and subarachnoid haemorrhage (SAH) (Broderick et al. 1993). SAH represents one quarter to one third of all cerebral haemorrhages (Nilsson et al. 2000). The more recent studies have estimated an annual rate of SAH between 6 in North America and 10 in Europe per 100,000 population (Broderick et al. 1993; Nilsson et al. 2000). Women are affected about twice as often compared with men (Broderick et al. 1993; Nilsson et al. 2000). Approximately 75% of spontaneous SAHs are caused by intracranial aneurysms (Nilsson et al. 2000).

In a recent population-based European study, 16% of the patients with SAH died before reaching the hospital. Another 5% deceased at the day of haemorrhage after admission (Pobereskin 2001). Among patients surviving the initial haemorrhage treated without surgery, rebleeding is the major cause of morbidity and mortality. The risk is between 15% and 20% within the first two weeks. The goal of early surgery is to reduce this risk. Of those reaching neurosurgical care, secondary deterioration caused by delayed ischaemic neurological deficits (DINDs) is assumed to be the predominant complication after SAH. In the international cooperative study on the timing of aneurysm surgery, DINDs were responsible for disability in 6.3% and mortality in 7.2% among patients with SAH (Kassell et al. 1990a). The recent randomised, double-blind, vehicle-controlled trials of tirilazad mesylate found a rate of 33% to 38% for DINDs in all patients of the vehicle group. Cerebral infarctions occurred in 10% to 13% (Haley et al. 1997; Lanzino and Kassell 1999; Lanzino et al. 1999).

I 2
Clinical presentation

DINDs are clinically characterised by confusion or decreased level of consciousness with a focal neurological deficit. The diagnosis is one of exclusion. In contrast to the usual clinical presentation of stroke, symptoms typically develop gradually, waxing and waning over several hours. Increased headache and meningismus, low-grade fever, seizures, and a disturbance of consciousness are usually followed by the appearance of focal neurological symptoms that typically reflect ischaemia in the anterior circulation. Characteristic signs include mental status changes, abulia, akinesia, anosagnosia, Witzelsucht, aphasia, hemiparesis, paraparesis or urinary incontinence (Adams and Love 1992).

I 3
Risk factors

It has been hypothesised that intracellular products of red blood cells induce DINDs (MacDonald and Weir 1991). This hypothesis has been based on: (a) the temporal correlation between the occurrence of DINDs (day 4 - 12 after the haemorrhage, maximum at day 7) and haemolysis in the subarachnoid space (Pluta et al. 1998), and (b) the correlation between the amount of subarachnoid blood in the initial computed tomogram (CT) and the risk to develop a DIND (Fisher et al. 1980; Kistler et al. 1983; Brouwers et al. 1993). Up to 70% of patients develop angiographically visible delayed arterial spasm after SAH (Brouwers et al. 1993). While the absence of angiographic spasm has a high negative predictive value, the positive predictive value of moderate/severe angiographic spasm for the development of a DIND is only between 33% and 50% (Vora et al. 1999; Unterberg et al. 2001). This positive predictive value is less than that of a coin toss suggesting additional pathogenetic factors.

Most “classical” vascular risk factors seem to increase the likelihood for a DIND.

Thus, in cigarette smokers, a slightly higher risk for the development of DINDs has been observed. Weir et al. (1998) analysed 3500 patients from five multi-centre trials and found an odds ratio of 1.2 (95% confidence interval 1.1-1.4). A higher prevalence of hypertension in patients developing a DIND was suggested in case-control studies (Brandt et al. 1991; Öhman et al. 1991). Even though age was negatively correlated with angiographic spasm, the incidence of DINDs was either similar to that observed in younger patients (Fortuny et al. 1980) or increased with advancing age (Lanzino et al. 1996). This is possibly related to the finding that the subarachnoid clot is thicker in elderly patients due to parenchymal atrophy allowing for a larger quantity of blood to collect (Inagawa et al. 1988; Sakaki et al. 1989). In addition, the prevalence of hypertension is higher in the elderly. As another risk factor for the evolution of a DIND, cocaine use was identified (Conway and Tamargo et al. 2001). To my knowledge, a particular study related to diabetes and DIND has not been performed, yet. A causal link between hyperglycaemia and outcome after DIND was not established in the Cooperative Aneurysm Study (Lanzino et al. 1993).

Only the gender relation for DINDs is clearly different from that of most other variants of ischaemic stroke, which show a significant male preponderance. In contrast, the incidence of DINDs was either similar in men and women with SAH (North American Study) (Kongable et al. 1996) or significantly higher in women (European Studies) (George et al. 1989; Rosenorn et al. 1993). DINDs share this epidemiological feature with migraine-related stroke (Tzourio et al. 2000). However, although migraine, particularly migraine with aura, has been established as a risk factor for ischaemic stroke in all recent population- and hospital-based studies (reviewed by Tzourio et al. 2000), it has not been investigated so far whether the coexistence of migraine is linked to an increased risk for DINDs. To my knowledge, there are also no epidemiological studies regarding female hormones and incidence of DINDs.

I 4
Differential diagnosis

I 4.1
Re-bleeding

Maximal frequency of re-bleeding after aneurysmal SAH is in the first day (4% on the first day, then 1.5% daily for 13 days). Fifteen to 20% re-bleed within the first two weeks (Winn et al. 1977). The risk was neither altered by blood pressure on admission nor site of the aneurysm (Inagawa et al. 1987). Early surgery prevents re-bleeding.

I 4.2
Hydrocephalus

Acute hydrocephalus was observed on admission CT in 15% of SAH patients with 40% of these being symptomatic (Graff-Radford et al. 1989). Factors assumed to contribute to acute hydrocephalus include: blood interfering with cerebrospinal fluid circulation through the Sylvian aqueduct, fourth ventricle outlet, subarachnoid space, and/or with re-absorption at the arachnoid granulations. Chronic hydrocephalus is due to pia-arachnoid adhesions or permanent impairment of the arachnoid granulations. Acute hydrocephalus does not inevitably lead to chronic hydrocephalus. Cerebral lesions typically associated with hydrocephalus are located at the ventricle poles.

I 4.3
Hyponatraemia

Hyponatraemia commonly occurs following SAH. Although it had been attributed to a rise in antidiuretic hormone (ADH) producing hypervolaemic hyponatraemia, the ADH increment is usually transient, lasting for only about 4 days. Another theory was based on the fact that there is often a delayed peak in atrial natriuretic factor (ANF), a 28-amino acid

polypeptide, after an initial smaller rise (Wijdicks et al. 1991). Increased ANF secretion leads to a urinary loss of sodium (cerebral salt wasting syndrome) resulting in hypovolaemic hyponatraemia. Although cerebral salt wasting syndrome has clearly been shown to be the cause of hyponatraemia in the majority of these patients (Harrigan 1996), it has remained unclear whether ANF is the operative natriuretic factor in SAH (Kröll et al. 1992). The neurological effects of hyponatraemia can mimic DINDs.

I 4.4
Peri- and intra-operative complications associated with aneurysm clipping

A particular problem in studying DINDs is the differentiation from peri- or intra-operative complications associated with aneurysm clipping. Direct or indirect surgical complications have a different pathogenesis from DINDs and, hence, are likely to be different in pathoanatomy of the cerebral lesions, age and gender distribution, risk factor profile and response to medical treatment. In other words, surgically related ischaemic infarcts represent an important confounding factor in studies on DINDs. Unfortunately, in many studies on DINDs, surgical complications were not adequately controlled. E.g., Millikan, in 1975, expatiated upon his experience from a series of 198 patients that “any diffuse or focal brain damage, which occurs after the first few hours following the bleed or particularly following a neurosurgical procedure, is automatically explained as being due to vasospasm”. This clinical problem is further complicated by the interaction between delayed vasospasm with parenchyma partially damaged during the surgical procedure since partial damage may result in increased vulnerability. That interaction might also result in delayed neurological deficits although the pathogenesis would be different from that of DINDs in non-operated patients. Serial magnetic resonance imaging (MRI) could help to differentiate between surgically related and unrelated lesions when images taken at the second post-operative day are

compared with those at, e.g., day 12 after the haemorrhage. Unfortunately, the serial MRI study of Shimoda et al. (2001) is inconclusive in this respect. Concerning aneurysm closure and its ischaemic consequences in MR images, the recent, comparative study of aneurysm coiling or clipping by Hohlrieder et al. (2002) is interesting. Of the 112 patients treated after aneurysm rupture, 57% suffered from ischaemic infarcts. However, also the 32 patients in whom the aneurysm was electively coiled or clipped showed secondary cerebral infarcts in 41%.

Direct intra-operative complications resulting in ischaemia are, e.g., spatula pressure, stenosis of the aneurysm-bearing vessel by the surgical clip around the aneurysm neck, generalised brain swelling or aneurysm rupture. The most important surgical complication is probably thrombosis occurring post-operatively and requiring post-operative control angiography to be distinguished from a DIND. E.g., Proust et al. (1995) investigated 230 consecutive patients with ruptured aneurysm. Whereas post-operative thrombosis occurred in 25 cases (11%), DINDs caused only 15 secondary complications in this study (7%). Similar percentages for post-operative thrombosis were reported in other studies with systematic control angiography (11% in a series of 100 subjects [Creissard et al. 1990], 12% in a series of 66 subjects [MacDonald et al. 1993] and 11% of 63 patients who died after aneurysm surgery [Karhunen et al. 1991]), whereas the incidence was considerably lower in studies without systematic control angiography (3% in the International Cooperative Study on Aneurysm Surgery [3521 patients, Kassell et al. 1990b] and 4% in a series of 150 patients [Gilsbach et al. 1988]). That comparison suggests that post-operative thrombosis is the most important confounding factor for DINDs in studies without systematic control angiography.

In summary, the differentiation between DINDs and surgically related ischaemic infarcts is difficult and controversial. Only for ischaemic lesions in the cortex associated with

DINDs, it was shown that surgery was not a confounding factor (Neil-Dwyer et al. 1994). Most surgically related complications including post-operative thrombosis will produce territorial infarcts.

I 4.5
Ischaemic stroke unrelated to surgical complications or DIND in the post-operative course

The incidence of different variants of ischaemic stroke is significantly increased for any kind of surgery during the post-operative period from the hospitalisation until 30 days after surgery. This may be related to changes in coagulation, bed rest, medication, diagnostic tests etc. (Wong et al. 2000). In addition, it is likely that the rate of stroke caused by cardiac embolism is particularly increased after SAH since SAH is well known to produce cardiac arrhythmias (reviewed by Sakr et al. 2002). However, the role of cardiac embolism, atherosclerosis or other frequent aetiologies of ischaemia for ischaemic deficits after SAH has never been adequately studied to my knowledge. These aetiologies may particularly contribute to ischaemic complications after SAH in the elderly. The majority of these aetiologies, in particular cardiac embolism, will produce territorial infarcts.

I 5
Pathoanatomy

Robertson performed the first pathoanatomical study on DINDs in 1949. A microscopically detected infarct of motor cortex in case number 8 of the original publication laid the foundation of the hypothesis that ischaemic changes can occur remote from the territory of the artery bearing the aneurysm. From a large autopsy series, Falconer reported similar findings in 1954. As a typical example, he presented a case of a non-operated patient with a left anterior cerebral artery aneurysm in whom a cortical necrosis was detected in the territory of the left middle cerebral artery. Birse and Tom, in 1960, presented a detailed

histological analysis of these widespread ischaemic lesions after SAH in 8 selected autopsy cases of non-operated patients. They provided clear diagrams emphasizing the characteristic focal cortical distribution of the infarcts, which were often arranged around a fissure or a sulcus (*Fig. 1A and B*). Deeper structures of the brain showed small ischaemic patches. Stoltenburg-Didinger and Schwarz published a large autopsy study of operated and non-operated patients in 1987. They analysed 207 cases after aneurysmal SAH collected from 1969 to 1985. In 106 of 139 patients properly examined microscopically, either bell-shaped or laminar infarcts in the cortex were a constant finding. The large majority of these cortical infarcts occurred in areas covered with a subarachnoid clot. Of the 156 patients not undergoing surgery, only 9 demonstrated a larger infarct in the territory of one of the three major cerebral arteries (6%). In contrast, 13 of the 51 patients in whom a clipping of the ruptured aneurysm was performed, showed a territorial infarct (26%) (Chi-Square-Independence-test, $p < 0.0001$). This indicated some pathogenetic role of the surgical intervention for a considerable number of territorial infarcts. Neil-Dwyer and colleagues, in 1994, performed a prospective autopsy study including 53 cases. This study aimed to differentiate between the lesions induced by the initial haemorrhage and that by delayed ischaemia. A significant correlation was confirmed between delayed ischaemia and cortical ischaemic lesions. Interestingly, moderate to severe cortical ischaemic lesions were also detected in 56% of patients without evidence of vasospasm in the angiogram.

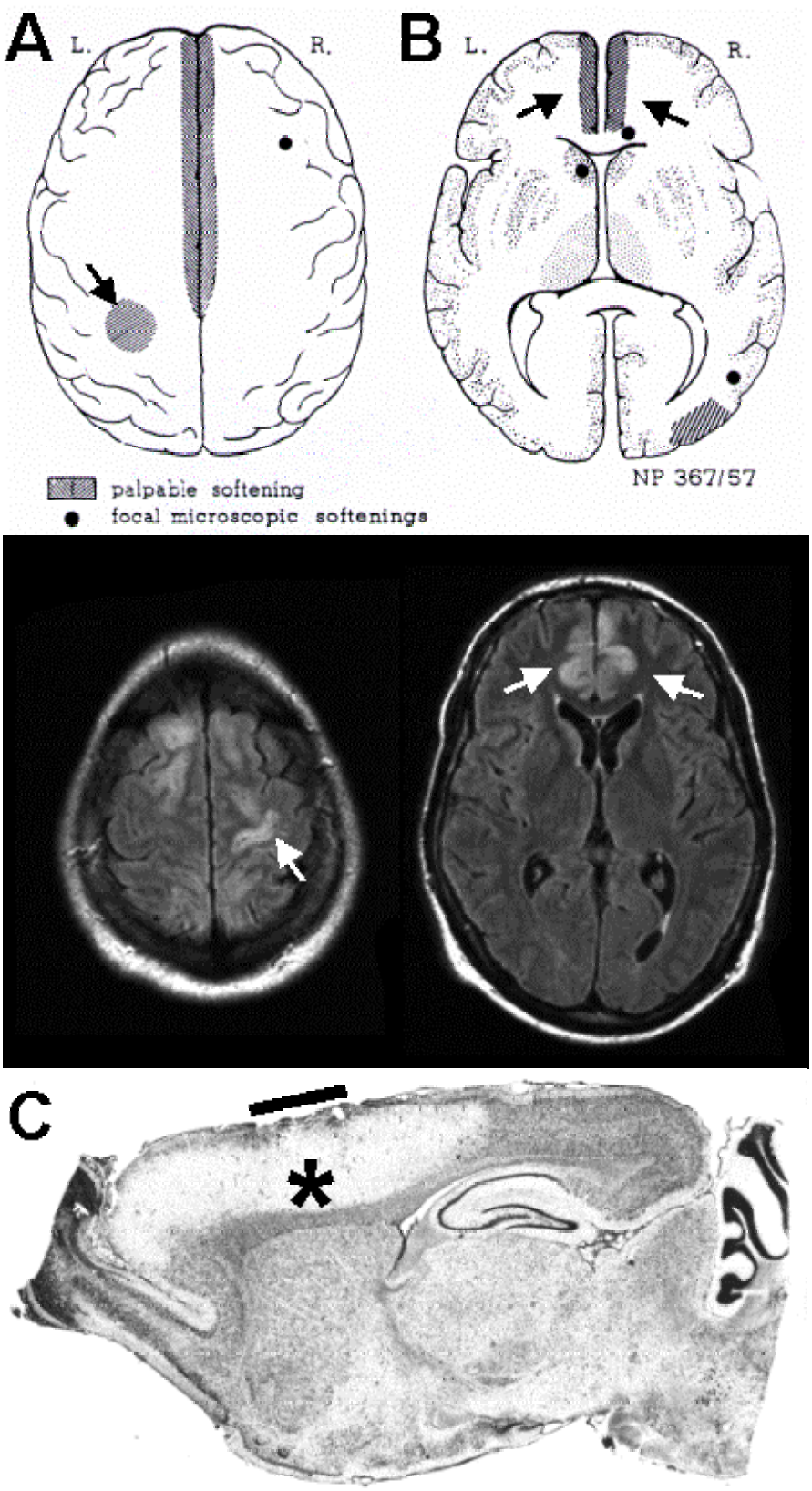

Figure 1
A and B
The upper two pictures are diagrammatic representations of macroscopic and microscopic cerebral infarction in a 37-year old man with DIND at day 8 after subarachnoid haemorrhage. The DIND was characterised by a rapid deterioration with development of paraplegia. The patient died 4 days later. The pictures are taken from a paper of 8 cases selected from a larger autosy series by Sheila Birse and Mary Tom published in Neurology in 1960.
The lower two pictures are turbo inversion recovery magnitude magnetic resonance images from a 33-year old man who developed a DIND with mental status changes and right-sided hemiparesis about 6 days after subarachnoid haemorrhage (Dreier et al. 2002b). The patient was treated in the intensive care unit with a good recovery. In both patients, the aneurysm was un-operated at the time point when the pictures were made so that the lesions represent the typical pattern occurring in the natural course of the disease. The most characteristic feature of the lesions is their distribution in the cortex band around a sulcus (arrows in A) or a fissure (arrows in B). In both patients, the aneurysm was located at the anterior communicating artery in which case the blood is typically pushed upwards along the interhemispheric fissure.
C *A similar focal laminar cortical necrosis is observed after cortical spreading ischaemia in response to the red blood cell products haemoglobin and increased subarachnoid K^+ in the rat (*). The bar illustrates size and position of the cranial window. It is unclear why the lesion can extend beyond the borders of the window. Likely, haemoglobin and K^+ have diffused to areas neighbouring the window (Dreier et al. 2000).*

I 6
Treatment

I 6.1
Relative risk reduction of poor outcome after SAH by nimodipine

A recent systematic review of all randomised controlled clinical trials on Ca^{2+}-antagonists in patients with SAH (2756 patients in total) confirmed a significant reduction in frequency of poor outcome by nimodipine. This resulted from a reduction in the occurrence of DINDs (Feigin et al. 1998). Nimodipine prevents 1 of 3 bad outcomes due to a DIND. One of 7 patients develops a bad outcome due to a DIND after SAH (Kassell et al. 1990a). Hence, about 21 patients have to be treated with nimodipine to prevent one bad outcome after SAH. This beneficial effect was shown for oral nimodipine. It is unclear why the more expensive intravenous nimodipine is routinely used in many centers.

At the cellular level, nimodipine directly inhibits slowly inactivating voltage-sensitive Ca^{2+} channels (L-type). Blockade of Ca^{2+} entry from the extracellular space into vascular smooth muscle leads to cerebral vasodilatation and increases cerebral perfusion (Kazda and Towart 1982; Andersson et al. 1983; Haws et al. 1983). It was proposed that Ca^{2+} antagonists may reverse chronic vasospasm of the major cerebral arteries (Allen and Bahr 1979). However, no significant effect on cerebral vasospasm was angiographically detected following nimodipine treatment in several randomised clinical trials (Feigin et al. 1998). In addition, chronic vasospasm induced by autologous blood in the subarachnoid space did not resolve in response to high doses of nimodipine in primates (Espinosa et al. 1984; Nosko et al. 1985; Lewis et al. 1988). Haemoglobin is assumed to play a major role in the pathogenesis of the large artery spasm (MacDonald and Weir 1991; Pluta et al. 1998). However, nimodipine poorly antagonised haemoglobin-induced arterial constriction in different species such as monkey, dog and man (Nosko et al. 1986).

These clinical and experimental findings suggested that the anti-ischaemic effect of

nimodipine may be related to a direct protection of neurons through blockade of excitotoxic Ca^{2+} entry (Brandt et al. 1988; Pisani et al. 1998). However, if a cytoprotective effect on neurons was the key function of nimodipine, the drug would also act on other types of ischaemia than DINDs. In several animal studies of focal cerebral ischaemia, nimodipine was not consistently effective (Langley and Sorkin 1989; Scriabine et al. 1989). In a recent meta-analysis, no evidence was available to justify the use of nimodipine in patients with ischaemic stroke unrelated to SAH (Horn and Limburg 2001).

I 6.2
Systemic blood volume and DINDs

The risk reduction over the last 20 years to develop delayed ischaemia has not only been related to the prophylactic use of nimodipine but also to an improved fluid management. In approximately one-third of the patients after SAH, excessive natriuresis and intravascular volume contraction occurs (van Gijn and Rinkel 2001). In the past, hyponatraemia was erroneously attributed to water retention. Therefore, fluid restriction was applied which was later found to increase the risk for DIND. Two non-randomised studies with historical controls suggested that a daily fluid intake > 3 l of saline (against 1.5 – 2 l in the past) was associated with a lower rate of DINDs (Hasan et al. 1989; Vermeij et al. 1998). In addition, a randomised study was performed comparing controls and patients treated with volume expansion using albumin and crystalloid to obtain a haematocrit of 45% (Rosenwasser et al. 1983). In this small trial, moderate hypervolaemic haemodilution resulted in a significant reduction of DINDs. A more intense prophylactic volume expansion with elevated cardiac filling pressures was not superior to a moderate volume expansion (Lennihan et al. 2000; Egge et al. 2001). Hyponatraemia per se does not increase the risk of a DIND (Qureshi et al. 2002).

In patients with ischaemic stroke unrelated to SAH, haematocrit levels were significantly higher than in matched controls (Toghi et al. 1978; Harrison et al. 1981). However, in contrast to the benefit of patients with DIND, a meta-analysis did not find any evidence that moderate volume expansion improved outcome (Asplund et al. 2001).

I 7
Animal models

Megyesi et al. (2000) counted 57 different SAH models in animals to study the arterial spasm. All known models share the feature that DINDs or ischaemic lesions are essentially never observed despite the presence of significant arterial spasm (Megyesi et al. 2000). This, once again, suggests that the arterial spasm alone is probably not sufficient to induce DINDs. That DINDs do not occur in animal SAH models in contrast to SAH in man may be due to the better collateralisation in smaller mammals. However, the main reason is probably related to the clinical observation that the amount of blood in fissures and cisterns in the initial CT after SAH is well correlated with the incidence of DINDs (Fisher et al. 1980; Kistler et al. 1983; Brouwers et al. 1993). This suggests that a considerable quantity of blood has to collect to induce a DIND. It is obvious that the subarachnoid space of man can accommodate a significantly larger volume of blood than that of the species used for SAH models (rat, rabbit, cat, pig, dog, smaller primates). The observation by Stoltenburg-Didinger and Schwarz (1987) that the lesions typically occurred in areas covered with subarachnoid clot indicated a direct effect of the red blood cell products on the underlying cortex in addition to inducing arterial spasm at the base of the brain. A possibility to circumvent the problem of the limited subarachnoid space in the rat and to model the accumulation of red blood cell products at the cortical surface is to directly superfuse these products. With aid of this approach, we have demonstrated that red blood cell products are indeed able to produce ischaemia and ischaemic

cortical lesions (*Fig. 1C*) (Dreier et al. 1998; 2000). Relevance of this model for the clinical condition was supported by the therapeutic effect of nimodipine and increase of the systemic volume, respectively (Dreier et al. 2002a).

PART II

SUMMARY OF OUR OWN RESULTS

II 1

Dreier JP, Körner K, Görner A, Lindauer U, Weih M, Villringer A, Dirnagl U. Nitric oxide modulates the CBF response to increased extracellular potassium. J Cereb Blood Flow Metab. 1995 15:914-919.

The response of the regional cerebral blood flow (CBF) to brain topical superfusion of an increased K^+ concentration in the artificial cerebrospinal fluid (ACSF) ($[K^+]_{ACSF}$) at 20 mM was characterised in a closed cranial window preparation in barbiturate anaesthetised and ventilated rats. It was concluded that the vasodilator nitric oxide (NO) is a modulator of the rise in CBF following increased $[K^+]_{ACSF}$.

As a by-product of this study, we accidentally discovered spontaneous ischaemic responses of an unknown mechanism in response to the co-application of an inhibitor of the NO-synthase (NOS) with increased $[K^+]_{ACSF}$. These spontaneous ischaemic responses were characterised in the next study.

II 2

Dreier JP, Körner K, Ebert N, Görner A, Rubin I, Back T, Lindauer U, Wolf T, Villringer A, Einhäupl KM, Lauritzen M, Dirnagl U. Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K^+ is increased in the subarachnoid space. J Cereb Blood Flow Metab. 1998 18:978-990.

It turned out that the spontaneous ischaemic responses to the co-application of a NOS inhibitor with increased $[K^+]_{ACSF}$ were caused by an inverted coupling between neuronal/astroglial metabolism and CBF: The increased $[K^+]_{ACSF}$ triggered a neuronal/astroglial depolarisation wave which, under physiological conditions, leads to a cortical spreading hyperaemia. However, under the conditon of NOS inhibitor with increased $[K^+]_{ACSF}$, the coupling was inverted so that vasoconstriction was induced instead of vasodilatation resulting in energy compromise. Under this condition, the neuronal/astroglial

network was unable to repolarise since the process of repolarisation requires energy. Because the vasoconstrictive stimulus was coupled to the neuronal/astroglial depolarisation, a vicious circle of prolonged ischaemia was established. That neuronal activation can induce ischaemia, was an unexpected finding. The most characteristic feature of this new ischaemic variant was its propagation in the cerebral cortex together with the neuronal/astroglial depolarisation wave. This caused us to name it 'cortical spreading ischaemia'.

The most potent natural NO-lowering agent is haemoglobin when it is released into the extracellular space. Haemoglobin binds NO with an affinity 1500 times higher than its affinity for oxygen at its haeme iron and reactive sulfhydril groups at cysteine$^{\beta}$93. Therefore, we investigated whether cortical spreading ischaemia also occurred in response to haemoglobin and increased $[K^+]_{ACSF}$. We showed that this protocol was at least similarly effective as NOS inhibition with increased $[K^+]_{ACSF}$ (*Fig. 2*).

Haemoglobin (21.03 ± 0.75 mM) and K^+ (102.4 ± 3.9 mM) are the protein and ion, respectively, with the highest concentration in the red blood cell. As described in PART I, DINDs occur in a close temporal correlation with haemolysis of the subarachnoid blood. The subarachnoid level of haemoglobin reaches its maximum on the seventh day after SAH (Pluta et al. 1998). Values of up to 500 μM have been reported from intracranial haematomas in humans (Ohta et al. 1980). Similarly, extracellular K^+ concentrations of up to 50 mM were measured in intracranial haematomas in neurosurgical patients (Ohta et al. 1983). This led to the hypothesis that DINDs may be caused by a mechanism related to cortical spreading ischaemia.

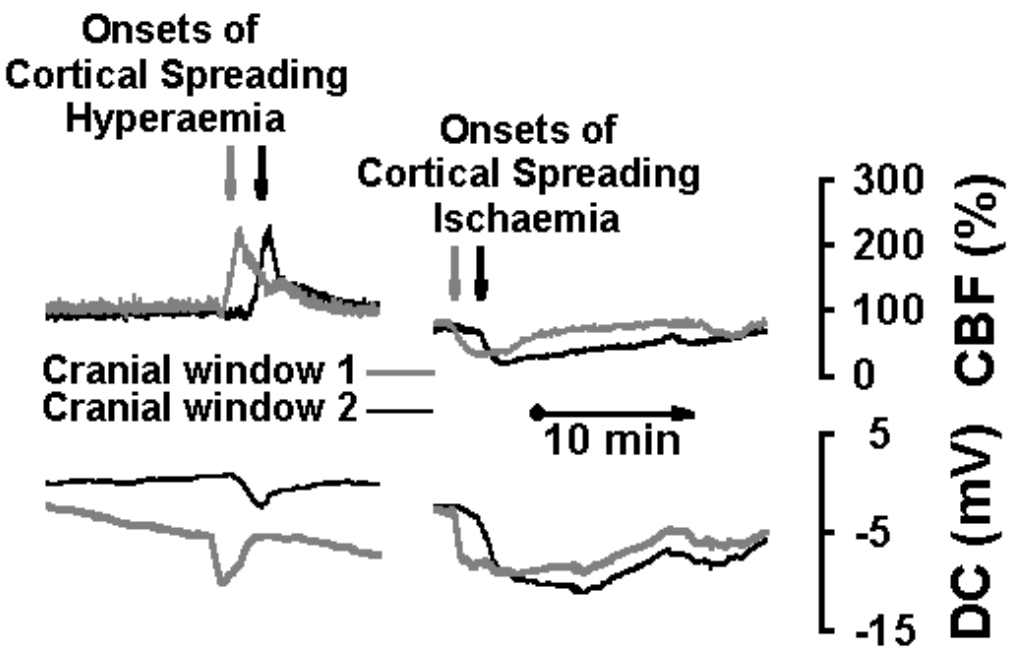

Figure 2
Under physiological conditions, a cortical spreading hyperaemia (upper trace, left part) (CBF = cerebral blood flow) is coupled to a spreading neuronal depolarisation wave (lower trace, left part) (DC = slow direct current potential) propagating from cranial window 1 to cranial window 2. However, when red blood cell products, haemoglobin and increased K^+, are in the subarachnoid space, the coupling between neuronal activation and cerebral blood flow is inverted so that a cortical spreading ischaemia (upper trace, right part) is coupled to the spreading neuronal depolarisation wave (lower trace, right part). Due to a vicious circle, both depolarisation wave and its CBF response are prolonged under this condition (see text).

II 3

Dreier JP, Ebert N, Priller J, Megow D, Lindauer U, Klee R, Reuter U, Imai Y, Einhäupl KM, Victorov I, Dirnagl U. Products of hemolysis in the subarachnoid space inducing spreading ischemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? J Neurosurg. 2000 93:658-666.

In this study, we showed that cortical spreading ischaemia induced by haemoglobin and increased $[K^+]_{ACSF}$ in the rat led to bell-shaped or laminar infarcts in the cortex very similar to the pathoanatomical pattern of DINDs in man (*Fig. 1*). That the lesions are essentially restricted to the brain cortex is explained by the fact that spreading neuronal depolarisation waves do not run in the white matter. Deeper structures may only be damaged

by the waves when long penetrating arteries are constricted at the cortical level.

II 4

Dreier JP, Petzold G, Tille K, Lindauer U, Arnold G, Heinemann U, Einhäupl KM, Dirnagl U. Ischaemia triggered by spreading neuronal activation is inhibited by vasodilators in rats. J Physiol (Lond). 2001 531(Pt 2):515-526.

In this study, we investigated the effect of an NO-dependent and NO-independent vasodilator, *S*-nitroso-*N*-acetylpenicillamine and papaverine, respectively, on cortical spreading ischaemia produced by NOS inhibition with increased $[K^+]_{ACSF}$. We found that particularly the NO-donor but also papaverine was able to convert cortical spreading ischaemia to cortical spreading hyperaemia.

II 5

Dreier JP, Sakowitz OW, Unterberg AW, Benndorf G, Einhäupl KM, Valdueza JM. Migrainous aura starting several minutes after the onset of subarachnoid hemorrhage. Neurology. 2001 57:1344-1345.

The Brazilian physiologist Leão first described neuronal/astroglial depolarisation waves. He coined the name ‘cortical spreading depression’ in 1944. One year later, together with his colleague Morison, he came up with the hypothesis that cortical spreading depression may be the correlate of migrainous aura based on the striking resemblance of its electrophysiological features and the clinical presentation of migrainous aura. Cortical spreading depression is a short, regenerative depression of spontaneous neuronal activity in the grey matter that propagates at a rate of approximately 3 mm/min (Lauritzen 1994). The neuronal/astroglial depolarisation wave underlying cortical spreading ischaemia is not the same as but closely related to cortical spreading depression. Therefore, it was obvious to investigate whether migrainous aura-like symptoms may occur during the clinical course after SAH. Interestingly, within a short period of time, we found two patients with migraine who

experienced migrainous-aura like symptoms several minutes after the onset of acute headache induced by SAH. Both patients developed a DIND later on. Unfortunately, at the time of DIND, the patients were unable to adequately describe their symptoms because of a profoundly altered mental status. However, also the initially gained information on a migrainous aura-like attack as a symptom of SAH was remarkable since literature suggests the occurrence of spreading depression-like depolarisations at the acute stage of SAH in animal models (Hubschmann and Kornhauser 1980; Busch et al. 1998). Our findings were also of clinical value since migraine is the most important misdiagnosis of SAH, which can lead to a delay of aneurysm surgery (Edlow and Caplan 2000).

II 6

Dreier JP, Kleeberg J, Petzold G, Priller J, Windmuller O, Orzechowski HD, Lindauer U, Heinemann U, Einhaupl KM, Dirnagl U. Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain. 2002 125:102-112.

The 21-residue peptide endothelin-1 has gained much attention in neurological and neurosurgical research being both a powerful vasoconstrictor and a neuronal and astroglial modulator. Numerous studies have investigated whether endothelin-1 is involved in the pathogenesis of arterial spasm after SAH (reviewed by Zimmermann and Seifert 1998). Endothelin-1 was also suggested to play a role in stroke and migraine. In our animal study, we demonstrated that this endothelium-derived factor is the most potent inductor of cortical spreading depression currently known. This may have implications particularly for migraine research since clinical observations strongly suggest that endothelial irritation may somehow initiate one of the pathways leading to cortical spreading depression. In addition, it may be of significance for DINDs since preliminary results indicate that endothelin-1 can replace increased $[K^+]_{ACSF}$ in the protocol used to initiate cortical spreading ischaemia.

II 7

Dreier JP, Windmüller O, Petzold G, Lindauer U, Einhäupl KM, Dirnagl U. Ischemia triggered by red blood cell products in the subarachnoid space is inhibited by nimodipine administration or moderate volume expansion/hemodilution in rats. Neurosurgery. 2002 51:1457-1467.

Over the last 20 years, the risk to develop a DIND has significantly decreased. This has been related, at least partially, to the prophylactic use of nimodipine and improved fluid management (see above). In this study, we investigated whether nimodipine or moderate hypervolaemic haemodilution convert cortical spreading ischaemia produced by haemoglobin with increased $[K^+]_{ACSF}$ to cortical spreading hyperaemia (compare II 4). The positive result of our study supported a link between DINDs and cortical spreading ischaemia (*Fig. 3*).

II 8

Dreier JP, Sakowitz OW, Harder A, Zimmer C, Dirnagl U, Valdueza JM, Unterberg AW. Focal laminar cortical MR-signal abnormalities after subarachnoid hemorrhage. Ann Neurol. 2002 52:825-829.

It is often erroneously believed that the typical substrate of DINDs after SAH are territorial infarcts. This is not supported by the autopsy studies, which showed a large predominance of triangular, round or laminar cortical ischaemic lesions and, in addition, ischaemic patches in deeper cerebral structures (Robertson 1949; Falconer 1954; Birse and Tom 1960; Crompton 1964; Stoltenburg-Didinger and Schwarz 1987; Neil-Dwyer et al. 1994). In non-operated patients, the relation between autopsy cases with cortical to those with territorial infarcts was 13:1, while in operated patients, it was 3:1 due to a relative increase in the frequency of territorial infarcts (Stoltenburg-Didinger and Schwarz 1987). The significance of the cortical lesions is clinically underestimated because they are typically undetected by CT (Stoltenburg-Didinger and Schwarz 1987; Neil-Dwyer et al. 1994). We presented two cases demonstrating the suitability of magnetic resonance (MR) imaging to visualize such cortical lesions (*Fig. 1*).

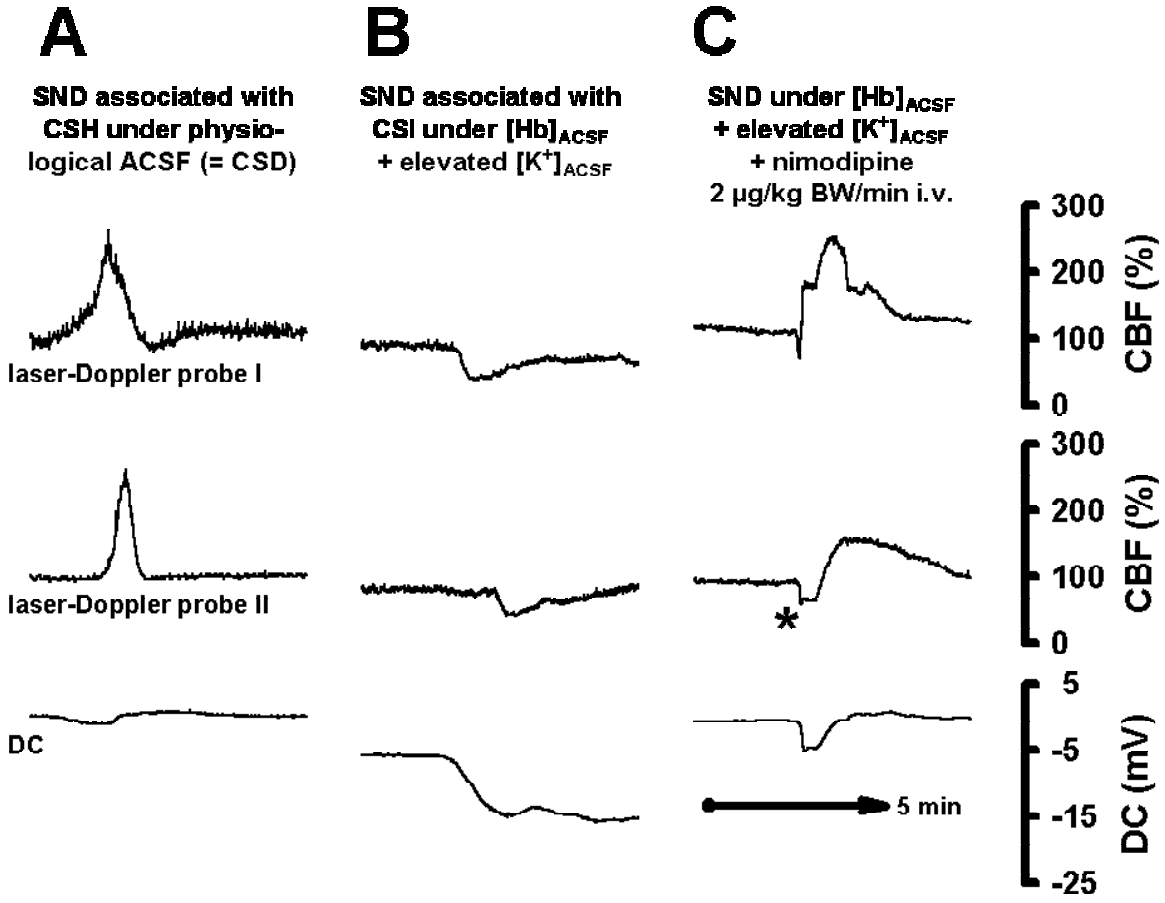

Figure 3

Comparison of cerebral blood flow (CBF)- and direct current (DC)-responses to the spreading neuronal/astroglial depolarisation wave (SND). While the upper two traces represent CBF at two different laser-Doppler positions, the lower trace gives the DC-potential at one cranial window.

A *Physiological artificial cerebrospinal fluid (ACSF) topically, 0.9% saline intravenously (control): The depolarisation wave is associated with a cortical spreading hyperaemia (CSH) under physiological conditions (= cortical spreading depression (CSD) of Leão).*

B *ACSF containing haemoglobin ($[Hb]_{ACSF}$) and elevated K^+ ($[K^+]_{ACSF}$) topically, 0.9% saline intravenously: Cortical spreading ischaemia (CSI) in response to the depolarisation wave.*

C *ACSF containing the red blood cell products topically, nimodipine is given intravenously at a dose of 2 µg/kg bodyweight/min (i.v.): Cortical spreading ischaemia reverts to a cortical spreading hyperaemia in presence of nimodipine. Only a short initial hypoperfusion (*) preceding cortical spreading hyperaemia indicates the presence of the red blood cell products in the subarachnoid space. The effect of moderate hypervolaemic haemodilution was similar to that of nimodipine.*

PART III

ASSESSMENT

The occurrence of DINDs was first described five decades ago by Robertson (1949). This year of discovery fell into the era of cerebral angiography, which had been introduced by Moniz in 1927. When Ecker and Riemenschneider (1951) first demonstrated delayed arterial spasm after subarachnoid hemorrhage with cerebral angiography, it was believed that, in principal, the pathogenesis of delayed ischaemic neurological deficits was explained, i.e., arterial spasm of the Circle of Willis arteries causing cerebral infarction. Today, the key words "vasospasm subarachnoid hemorrhage" yield more than 2000 references in the medline. However, several findings have challenged the simplistic link between DINDs and vasospasm: (a) The clinical match between cerebral angiography findings and DINDs is low as briefly reviewed in the present paper. (b) Neil-Dwyer et al. (1994), in their prospective autoptic study, not even detected a significant difference regarding the occurrence of DIND-induced lesions between patients with and without angiographically demonstrated vasospasm. (c) Also, the pathoanatomical pattern, the widespread distribution of DIND-induced lesions in the cortex, suggests that the key pathophysiological problem is not related to the proximal segments of the cerebral arteries. (d) Animal studies of subarachnoid haemorrhage essentially failed to demonstrate DINDs or delayed lesions despite angiographically demonstrated arterial spasm.

As an alternative, we have proposed that direct action of RBC products on the microcirculation and neuronal/astroglial network may be responsible for the cortical lesions associated with DINDs. However, there are also limitations of our approach. The main limitation is related to the high concentrations of haemoglobin and $[K^+]_{ACSF}$ used for the induction of cortical spreading ischaemia. The haemoglobin concentration applied in our

experiments was five times higher than that measured in human cerebral haematomas. The necessity of relatively high haemoglobin concentrations is possibly due to: (a) The higher ischaemic threshold and better collateralisation in small mammals compared with man. An influence of the species is supported by the fact that DINDs are not observed in animal SAH models (Megyesi et al. 2000). (b) The incubation time with haemoglobin is shorter in our experiments compared with that after SAH. (c) The site of haemoglobin application spares the base of the brain, so that spasm of basal arteries would not contribute to the energy compromise. However, in future studies, it will be interesting to investigate whether lower haemoglobin concentrations are sufficient for the induction of cortical spreading ischaemia if NO producing sources are disturbed in a similar way as it is probably the case after SAH (Pluta et al. 1996).

The level of $[K^+]_{ACSF}$ was also relatively high in our studies. Extracellular K^+-levels of this magnitude were in fact measured in human cerebral haematomas (Ohta et al. 1983). However, the effect of the rise in baseline $[K^+]_{ACSF}$ is probably mediated by a gradual rise in extracellular K^+ in the cortex ($[K^+]_o$), a concomitant down-regulation of the (Na^+)-(K^+)-ATPase activity and disturbance of the neuronal/astroglial repolarisation (Dreier et al. 2001). All these changes can probably also be achieved by other factors than elevated $[K^+]_{ACSF}$, which have been implicated in the pathogenesis of DINDs such as energy compromise (due to the arterial spasm) (Jamme et al. 1997; Nedergaard et al. 1993; Müller and Somjen 2000), a decline in intracerebral glucose concentration (Dreier et al. 2000; Unterberg et al. 2001), or a rise in endogenous ouabain-like factors (Dreier et al. 1997; Lusic et al. 1999).

Our results call for future studies analysing whether spreading depression-like depolarisations occur in patients after SAH using monitoring tools like DC-EEG, near-infrared spectroscopy, microdialysis or functional MRI. In addition, it will be necessary to

investigate whether the coupling between neuronal metabolism and CBF is fundamentally altered after experimental SAH in animals.

CONCLUSION

The coupling between neuronal activity and cerebral blood flow is a fundamental process, which underpins all cerebral functions. The topic of my Habilitation is the discovery of a new variant of ischaemia in which neuronal activation triggers a cerebral ischaemic event through the inversion of the coupling between neuronal activation and cerebral blood flow. This inversion occurs when red blood cell products are present in the subarachnoid space. The most distinct feature of this variant of ischaemia is its propagation in the cerebral cortex together with the wave of neuronal activation. Therefore, we named the phenomenon 'cortical spreading ischaemia'.

The presented animal model may have implications for the delayed ischaemic neurological deficits after subarachnoid haemorrhage. The link with this clinical syndrome has been based: (a) on the induction of cortical spreading ischaemia by red blood cell products in the subarachnoid space, (b) the correspondence between the characteristic patterns of the cortical ischaemic lesions, (c) and the therapeutic effects of nimodipine and moderate hypervolaemic haemodilution in clinical syndrome and animal model. With the aid of this model, it was possible to experimentally confirm the hypothesis that red blood cell products can induce cerebral ischaemia. We hope that the model will contribute to develop new strategies for the treatment of patients with subarachnoid haemorrhage.

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