European Journal of Neurology 2002, **9:** 389–399

Cerebral vasospasm and ischaemic infarction in clipped and coiled intracranial aneurysm patients

M. Hohlrieder[a,b], M. Spiegel[b], J. Hinterhoelzl[b], K. Engelhardt[b], B. Pfausler[b], A. Kampfl[b], H. Ulmer[c], P. Waldenberger[d], I. Mohsenipour[e] and E. Schmutzhard[b]

[a]*Department of Anaesthesiology and General Intensive Care Medicine,* [b]*Department of Neurology,* [c]*Department of Biostatistics,* [d]*Department of Radiology,* [e]*Department of Neurosurgery, University Hospital, Innsbruck, Austria*

Keywords:
brain infarction,
intracranial aneurysm,
intracranial vasospasm

Received 9 November 2001
Accepted 28 February 2002

The influence of the treatment modalities (clipping/coiling) on the incidence of vasospasm and ischaemic infarction in aneurysm patients is still judged controversially. The purpose of this study was to analyse and compare retrospectively cerebral vasospasm and ischaemic infarction, as well as neurological deficits and outcome within a large population of clipped and coiled patients with ruptured and unruptured aneurysms. Within a 2-year period, a total of 144 interventions (53 clipping/91 coiling) entered the study. Daily bilateral transcranial Doppler sonographic monitoring was performed to observe vasospasm development. All cerebral computed tomography (cCT) and magnetic resonance imaging (MRI) scans were reviewed with respect to occurrence and localization of ischaemic infarctions. Focal neurological deficits were recorded and clinical outcome was evaluated using the Glasgow Outcome Scale. Statistical analysis included the use of multivariate logistic regression models to find determinants of vasospasm, ischaemic infarction and neurological deficits. Altogether, vasospasm was detected after 77 (53.5%) interventions, 61.8% in females ($P < 0.01$). Clipped patients significantly more often exhibited vasospasms (69.8 vs. 44.0%, $P < 0.005$) and were treated 1 week longer at the intensive care unit ($P < 0.005$). Seventy-seven patients (53.5%) developed ischaemic infarctions, 62.3% after clipping and 48.4% after coiling ($P > 0.05$). In the multivariate analysis, aneurysm-rupture was the strongest predictor for vasospasm and vasospasm was the strongest predictor for infarction. Neurological deficits at discharge (46.5%) were independent of treatment modality, the same applied for the mean Glasgow Outcome Scores. There was no significant difference in mortality between surgical and endovascular treatment (9.4 vs. 12.1%). Whilst the vasospasm incidence was significantly higher after surgical treatment, ischaemic infarctions were only slightly more frequent. The incidence of neurological deficits and clinical outcome was similar in both treatment groups.

Background

The main causes for poor outcome in patients with ruptured intracranial aneurysms are vasospasm and rehaemorrhage. Today, early neurosurgical or endovascular interventions are possible and significantly diminish the risk of rehaemorrhage. Thus, vasospasm remains the single leading cause of fatal courses and/or poor neurological outcome (Kassell *et al*., 1990a; Zabramski and Hamilton, 1994; Yalamanchili *et al*., 1998). Although arterial narrowing can be seen in up to 70% of the subarachnoid haemorrhage (SAH) patients, only 20–40% develop focal neurological deficits as a result of vasospasm-induced ischaemia (Zabramski and Hamilton, 1994; Adams *et al*., 1987; Solomon *et al*., 1991; Inagawa, 1992; Haley *et al*., 1994; Rabb *et al*., 1994).

In experimental studies, the presence of erythrocytes in the cerebrospinal fluid has been shown to be essential in causing vasospasm (Duff *et al*., 1988; Macdonald *et al*., 1991). Moreover, the amount of subarachnoid blood detected on the initial cerebral computed tomography (cCT) is highly predictive for delayed ischaemia and infarction (Fisher *et al*., 1980; Kistler *et al*., 1983). Therefore, it has been suggested that vasospasm may not exist in the case of unruptured aneurysms or after rupture when subarachnoid blood is removed surgically within 48–72 h of SAH (Handa *et al*., 1987; Nosko *et al*., 1987; Inagawa *et al*., 1990). In contrast to neurosurgical clipping, endovascular techniques do not allow the removal of subarachnoid blood-clots.

Correspondence: Erich Schmutzhard, Department of Neurology, University Hospital, Anichstraße 35, 6020 Innsbruck, Austria.
Fax: +43 512 504 4243; e-mail: erich.schmutzhard@uibk.ac.at

Obliteration of the aneurysmal sac can now be safely achieved by the introduction of Guglielmi Detachable Coils (GDC). But yet, the influence of this treatment modality on the incidence of vasospasm and ischaemic infarction has not been firmly established in direct comparison within a large population of clipped and coiled patients with ruptured and unruptured aneurysms. Whilst Gruber *et al.* (1998) found a higher infarction rate with endovascular treatment, Yalamanchili *et al.* (1998) reported a higher frequency of clinically relevant vasospasm in neurosurgically treated patients. In a recently published multivariate analysis (Charpentier *et al.*, 1999), the treatment modality was not associated with an increased risk for cerebral vasospasm.

The purpose of this study was to analyse retrospectively the frequency and characteristics of cerebral vasospasm and ischaemic infarction, as well as neurological deficits and outcome in a population of clipped and coiled patients with ruptured and unruptured cerebral aneurysms, treated at the University Hospital Innsbruck within the 2-year period (1997–98). In uni- and multivariate analysis, beside other factors, the influence of the treatment modality (neurosurgical versus endovascular therapy) was determined. By means of logistic regression analysis we assessed prognostic factors for vasospasm, ischaemic infarction and focal neurological deficits.

Table 1 Description of the sample (144 interventions)

Mean age ± SD	51.2 ± 12.3
Median age	51.0
Male : female	1 : 1.62
Aneurysms	
Ruptured	112 (77.8%)
Symptomatic	19 (13.2%)
Incidental	13 (9.0%)
Aneurysm diameter	
Mean ± SD	7.6 ± 5.4 mm
Minimum	2 mm
Maximum	25 mm
Initial H & H grade	
0	32 (22.2%)
I	24 (16.7%)
II	43 (29.9%)
III	13 (9.0%)
IV	17 (11.8%)
V	15 (10.4%)
Mean ± SD	2.03 ± 1.60
Treatment	
Surgical	53 (36.8%)
Endovascular	91 (63.2%)
Stay NICU/SU	
Mean	23.3 ± 26.1 days
Minimum	1 day
Maximum	122 days

NICU = neuro-intensive care unit; SU = stroke unit.
A symptomatic aneurysm denotes neurological signs, but no SAH.

Patients and methods

Patient population

In a 2-year period, 150 consecutive patients underwent treatment for cerebral aneurysms at the University Hospital of Innsbruck, Austria. In principle, all coiled or clipped patients were eligible for this study. Nevertheless, patients were excluded if they were treated by both surgery and GDC occlusion within 4 weeks, or if cerebral vasospasm was already present at admission. Patients with impenetrable temporal ultrasound windows were excluded. Out of the remaining 115 patients, 90 were treated once, 22 twice, two of them thrice and one woman was even treated four times within this 2-year period. Repeated operations were mainly performed because of insufficient occlusion of the aneurysm. The medical records of all these patients were reviewed retrospectively. Thus, a total of 144 interventions (Table 1) form the basis for this study. About 36.8% (53) of the interventions were performed (in 51 patients) with standard craniotomy for aneurysmal clipping and 63.2% (91) of the interventions were performed (in 78 patients) with endovascular placement of GDCs. Consequently, 14 patients were coiled and clipped (but not within 4 weeks).

The patients ranged in age from 25 to 84 years (mean 51.2 ± 12.3). Eighty-nine of 144 interventions (61.8%) were performed in female patients. In 112 cases (77.8%), patients had presented with aneurysm rupture, whilst in the others the aneurysms were symptomatic in some other way (cranial nerve palsies, headache, vegetative symptoms, transient neurological deficits, etc.) or detected incidentally by imaging techniques. At admission, the patients were graded according to the Hunt and Hess Scale (Hunt and Hess, 1968); patients with non-ruptured aneurysms were graded as zero.

Diagnostics and treatment

Subarachnoid haemorrhage was diagnosed by clinical presentation and confirmed by cCT. Cerebral angiography to determine the exact location and morphology of the aneurysms was performed by the transfemoral route using Seldinger's technique. The diagnostic work-up was regularly completed within 24 h after admission.

All patients were admitted and treated in the neurological intensive care unit (NICU), in the neurosurgical intensive care unit, or in the stroke unit (SU) until

clinical recovery and improvement of vasospasm. For each patient, the best possible treatment modality (surgical or endovascular) to use was discussed by a team of neurologists, neurosurgeons and neuroradiologists and a joint decision was reached. Patients in advanced age and candidates for surgery with high-risk aneurysms in the posterior circulation or with difficult surgical anatomy were more likely to be treated by endovascular GDCs. Angiographic evidence of an unfavourable aneurysm morphology was rather considered to be an indication for surgical treatment.

During 10 of 144 interventions (6.9%) two aneurysmal sacs were treated simultaneously, once (0.7%) even three aneurysmal sacs were clipped in one session. Thus, in summary 156 *aneurysmal sacs* were clipped or coiled. More than 9 of 10 aneurysms (142, 91.0%) were located in the anterior circulation, the anterior communicating artery (50) and the middle cerebral artery (MCA) (48) being most frequently affected. In the posterior circulation, the basilar artery (eight) and the posterior inferior cerebellar artery (five) were most commonly affected.

In most of the craniotomy patients the pterional approach was used. The aneurysm was clipped using standard microsurgical techniques and subarachnoid blood was removed in the surgical bed to the extent possible. For endovascular treatment a transfemoral approach was used to place the GDCs. In all the cases treatment was performed under general anaesthesia. Intra-operative complications including aneurysm perforation and ischaemic complications were registered as well as the success of the intervention, which was classified as 'full' or 'partly/none.' This classification was based on control angiography immediately after the intervention. External drainage was instituted for any patient in whom hydrocephalus was seen by cCT.

Post-operatively, the patients received colloid and crystalloid solutions for prophylactic volume expansion and haemodilution to maintain a mean systolic blood pressure greater than 120 mmHg. If necessary, catecholamine support was added to the therapy in order to raise the blood pressure. At the intensive care units or stroke unit, where all patients were admitted immediately after the intervention, nimodipine was administered. Intravenous infusion (15–30 μg/kg/h) was continued as long as vasospasm was present on bilateral transcranial Doppler (TCD) examinations. Subsequently, nimodipine was continued orally (180–360 mg/day) for 7 days. All timings depended on the clinical and TCD findings. The endovascular patients were heparinized for 2 days to prevent thromboembolic phenomena because of GDCs. On average patients were treated for 23.3 ($\pm$26.1) days at the NICU/SU.

Diagnosis of vasospasm, infarction, and neurological deficits

Using the transtemporal approach in all patients, daily TCD sonographic monitoring was done. Insonating the main trunk of the MCA, the segment with the highest mean cerebral blood flow was used for analysis. Besides, the intradural internal carotid artery (ICA) as well as the A1 segment of the anterior cerebral artery (ACA) were insonated. Vasospasm was diagnosed if the mean TCD velocities exceeded 120 cm/s (Proust *et al.*, 1999). The highest mean flow velocities and their temporal appearance were recorded in all patients. Diagnosis of generalized vasospasm was based on visual interpretation of angiographic examinations.

Cerebral computed tomography and magnetic resonance imaging (MRI) scans were taken several times post-operatively in all patients. All of them were reviewed by blinded neuroradiologists with respect to occurrence of hypodense (cCT) or hyperintense (MRI) areas, their localization and the point of time of their first appearance. Cerebral infarction was defined by the development of a hypodensity/hyperintensity on cCT/MRI scans with or without focal neurological deficits, not attributable to other pathologies (Yoshimoto *et al.*, 1999). The localization was classified according to the main cerebral blood vessels (ACA, MCA, posterior cerebral artery, anterior border zone and posterior border zone, choroid artery, cerebellar arteries, pontine arteries).

By daily neurological examination – when applicable – focal neurological deficits were recorded throughout each patient's entire stay at the NICU/SU. The main deficits were motor dysfunctions like hemiparesis or cranial nerve palsies, but also aphasia and dysphasia, frontal release signs and other neurological deficits. In addition, pre- and post-interventional brain oedema, cerebrospinal fluid infection, installation of ventricular drainage and bleeding during hospital admission were registered. Clinical outcome was evaluated on the day of discharge from the NICU/SU using the Glasgow Outcome Scale (Jennett and Bond, 1975).

Statistical analysis

Univariate analysis of continuous data was performed with Student's *t*-test and one-way ANOVA. Non-normally distributed data were analysed using the Mann–Whitney *U*-test and the Kruskal–Wallis *H*-test. Categorical data were tested by Pearson's chi-square test or Fisher's exact test. Descriptive continuous data were reported as mean $\pm$ SD, as categorical data percentages were calculated. Following univariate analysis, determinants of vasospasm, ischaemic infarction and

neurological deficits were analysed with the use of multivariate logistic regression models. Therefore, all variables univariately associated or correlated according to theoretical considerations or clinical experience were entered into the multiple-regression models. Adjusted odds ratios and 95% confidence intervals were calculated to represent the relative risk of the predictive variables. Statistical significance was considered at a *P*-value of less than 0.05. Data analysis was performed using SPSS statistical software for Windows (version 8.0.0).

Results

Characteristics of treatment groups

Neurosurgical treatment was performed in 20 male and 33 female patients, whilst 35 male and 56 female patients underwent endovascular coiling. Table 2 shows the details of both groups. The average Hunt & Hess grades on the day of admission as well as the mean ages did not differ. Overall, endovascular treatment was significantly more often performed in posterior circulation aneurysms ($P < 0.05$).

The comparison of the two groups with respect to the duration of hospitalization showed a significant difference. On average, clipped patients were treated 1 week longer at the NICU/SU ($P < 0.005$). Intra-operative complications occurred in eight (8.8%) of the coiled patients but in none of the clipped patients ($P < 0.05$). Whilst 32 (37.4%) of the endovascular operations were partly or not successful, only two cases (3.8%) of incomplete aneurysm occlusion were recorded amongst the surgical group ($P < 0.0001$). Brain oedema was significantly more frequently seen in clipped patients ($P < 0.05$). More detailed analysis revealed that preoperative brain oedema did not differ between the treatment groups. However, post-operative brain oedema occurred in 43.4% (23) after craniotomy and in 28.6% (26) after endovascular coiling. No significant difference was noticed regarding the incidence of pre-interventional re-bleeding and cerebrospinal fluid infection, as well as necessity of ventricular drainage because of obstructive hydrocephalus. There was no case of post-interventional re-bleeding during admission at the NICU/SU.

Cerebral vasospasm

Altogether, vasospasm, diagnosed by TCD ultrasonography, was detected after 77 (53.5%) interventions. Females (55, 61.8%) were significantly more often affected than males (22, 40.0%, $P < 0.01$). Compared with non-vasospasm patients, the average age of vasospasm patients was slightly lower, but the difference did not reach statistical significance (49.4 ± 12.8 vs. 53.3 ± 11.5 years). Vasospasm was diagnosed in MCA (54), ACA (21) and ICA (6). Generalized vasospasm, diagnosed by cerebral angiography, was noticed in 19 (13.2%) patients. On average, flow velocities peaked between the fifth and the sixth day (5.87 ± 9.78 days) after treatment and ranged from 120 to 330 cm/s (mean in vasospasm patients: 199.8 ± 56.9 cm/s).

Compared with unruptured aneurysm-patients, vasospasm occurred significantly more frequently in patients with ruptured aneurysms. Only seven (21.9%) patients without subarachnoid blood suffered from vasospasm, but 70 (62.5%) of the SAH group ($P < 0.001$) suffered. Clipped patients significantly more often developed vasospasm (69.8% vs. 44.0%, $P < 0.005$). Thus, the highest mean flow velocities were 210.5 ± 54.8 cm/s in clipped and 189.9 ± 57.6 cm/s in coiled patients ($P > 0.05$).

Patients with Hunt & Hess grades IV and V more often developed vasospasms ($P < 0.001$), the highest

Table 2 Characteristics of treatment groups

	Neurosurgical ($n = 53$, 36.8%)	Endovascular ($n = 91$, 63.2%)	Significance
M : F ratio	1 : 1.65	1 : 1.60	n.s.
Age (years)	51.1 ± 12.4	51.3 ± 12.3	n.s.
Unruptured aneurysm	10 (18.9%)	22 (24.2%)	n.s.
Initial H & H Grade	1.98 ± 1.51	2.05 ± 1.66	n.s.
Posterior aneurysm site	1 (1.9%)	13 (14.3%)	$P < 0.05$
NICU/SU days	27.5 ± 25.0	20.8 ± 26.5	$P < 0.005$
Full interventional success	51 (96.2%)	57 (62.6%)	$P < 0.0001$
Intra-OP complication	0 (0%)	8 (8.8%)	$P < 0.05$
Ventricular drainage	16 (30.2%)	27 (29.7%)	n.s.
Brain oedema	38 (71.7%)	46 (50.5%)	$P < 0.05$
CSF infection	8 (15.1%)	12 (13.2%)	n.s.
Rehaemorrhage*	5 (9.4%)	9 (9.9%)	n.s.

*All of them pre-interventional; n.s. = not significant.

incidence of vasospasm having being seen in Hunt & Hess group IV patients (82.4%). Cerebral computed tomography revealed a significantly higher rate of brain oedema in vasospasm patients (77.9 vs. 35.8%, $P < 0.001$). The presence of vasospasm significantly prolonged the period of hospitalization at NICU/SU (34.8 ± 28.6 vs. 10.0 ± 14.0 days).

By means of multiple logistic regression analysis, five independent prognostic factors for vasospasm development were found. As Table 3 shows, the rupture of an aneurysms was the strongest predictor for vasospasm. Nevertheless, with the exception of the patients' age, the other factors were also associated with a more than threefold increase of risk, their *P*-values being well within a significant range.

Cerebral infarction

In total 77 patients (53.5%) developed ischaemic infarctions as documented on cCT and MRI scans. In five patients the ischaemic lesion was already found preoperatively. Compared with females (43, 48.3%) the incidence was higher in males (34, 61.8%), but the difference did not reach statistical significance. Infarction patients were slightly younger than the rest (49.9 ± 12.8 vs. 52.7 ± 11.7 years). On average, the diagnosis was established on the third post-operative day (3.26 ± 11.3). Infarctions occurred most frequently in the area of MCA and ACA. Details are listed in Table 4. Twenty-nine patients (20.1%) presented infarctions involving only one vascular territory, multiple infarctions could be demonstrated in 48 patients (33.3%).

Compared with the coiling group, clipped patients developed cerebral infarctions more often (62.3 vs. 48.4%); however, the difference was not statistically significant. Patients with ruptured aneurysms suffered from infarction in 57.1% (64), but also non-bleeding patients showed a remarkable incidence of 40.6% (13). Brain oedema (72.7 vs. 41.8%, $P < 0.001$) as well as the necessity of ventricular drainage (37.7 vs. 20.9%, $P < 0.05$) were found to be significantly associated with ischaemic infarction, as was cerebral vasospasm: 50 patients (64.9%) out of the vasospasm group developed infarctions, but only 40.3% (27) of the non-vasospasm group ($P < 0.005$) developed infarctions. Generalized vasospasms caused an infarction in 84.2%. In contrast, vasospasm of single arteries were rather rarely followed by an infarction in the corresponding territory: ICA in 50.0%, ACA in 40.9%, MCA in 36.9%. The stay at the NICU/SU was significantly longer in infarction patients (31.4 ± 30.4 vs. 13.9 ± 15.6 days).

Multiple logistic regression analysis (Table 5) revealed vasospasm to be the strongest predictor for cerebral infarction. Male sex was associated with a 2.28-fold increase of risk. Treatment modality and aneurysm rupture were shown to have less impact on the infarction incidence.

Neurological deficits and outcome

Transitory neurological deficits during the stay at the NICU/SU were seen in 38 (26.4%) patients, mainly hemiparesis (10), facial palsy (6), aphasia (5) and hemineglect (4). Persisting sequelae, still present at discharge from the NICU/SU, were more frequent: 67 patients (46.5%) were discharged with neurological deficits including hemiparesis (15), 'frontal signs' (11), facial palsy (11), abducens and/or oculomotor nerve palsy (9), tetraparesis (6), ptosis (5) and aphasia (5). Temporary and persisting neurological deficits were both independent of treatment modalities. Whilst the

Table 3 Independent risk factors associated with cerebral vasospasm

Parameter	OR	95% CI	*P*-value
Female sex	3.58	1.56–8.24	0.0027
Lower age	1.03	1.00–1.06	0.0835
Ruptured aneurysm	4.83	1.70–13.69	0.0031
Surgical treatment	3.52	1.53–8.09	0.0030
Pre-operative brain oedema	3.40	1.23–9.41	0.0186

Table 4 Distribution of ischaemic infarctions

Territory	Infarctions
MCA	44 (30.6%)
ACA	35 (24.3%)
PCA	20 (13.9%)
ABZ	17 (11.8%)
PBZ	12 (8.3%)
Cerebellum	10 (6.9%)
Pons	6 (4.2%)
CA	5 (3.5%)

MCA = middle cerebral artery; ACA = anterior cerebral artery, PCA = posterior cerebral artery; ABZ = anterior border zone, PBZ = posterior border zone; CA = choroid artery.

Table 5 Independent risk factors associated with ischaemic infarctions

Parameter	OR	95% CI	*P*-value
Male sex	2.28	1.05–4.91	0.0361
Lower age	1.01	0.98–1.04	0.5729
Vasospasm	2.89	1.30–6.41	0.0092
Surgical treatment	1.40	0.67–2.94	0.3749
Ruptured aneurysm	1.25	0.52–3.03	0.6211

former were slightly more frequent in clipped patients (28.3 vs. 25.3%), the latter were more frequent in coiled patients (47.3 vs. 43.4%). Persisting neurological deficits were significantly associated with female sex (53.9 vs. 32.7%, $P < 0.01$), ruptured aneurysm (53.6 vs. 18.8%, $P < 0.001$), higher Hunt & Hess grades ($P < 0.001$), brain oedema (58.3 vs. 28.3%, $P < 0.001$), vasospasm (64.9 vs. 23.9%, $P < 0.001$) and ischaemic infarction (58.4 vs. 31.3%, $P < 0.005$).

The results of multiple logistic regression analysis are presented in Table 6. The treatment modality was not significantly associated with higher incidence of neurological deficits in univariate analysis and was, therefore, not considered in the regression analysis. Vasospasm, causing a 3.60-fold risk, was the strongest predictor in this analysis.

Besides, the Glasgow Outcome Scale was used to measure the clinical outcome. The mean overall Glasgow Outcome Score of this series was 3.62 ± 1.51 (Table 7). About 43.8% of the patients could resume their previous job and daily activities (GOS 5), 11.1% (16 patients) died, mostly as a consequence of devastating vasospasm (GOS 1). There was no significant difference in mortality between surgical and endovascular treatment (9.4 vs. 12.1%). The mean Glasgow Outcome Scales were very similar in clipped (3.64) and coiled (3.60) patients. Patients with unruptured aneurysms showed significantly better scores than SAH patients (4.72 ± 0.81 vs. 3.30 ± 1.40, $P < 0.001$). Poorer Glasgow Outcome Scores were positively correlated with higher Hunt & Hess grades ($P < 0.001$). Whilst the treatment modality did not cause a noteworthy difference in the mean Glasgow Outcome Scores, vasospasms (3.25 ± 1.26 vs. 4.04 ± 1.48, $P < 0.001$) as well as ischaemic infarctions (4.19 ± 1.23 vs. 3.12 ± 1.39, $P < 0.001$) were significantly associated with lower scores.

Table 6 Independent risk factors associated with neurological deficits at discharge

Parameter	OR	95% CI	*P*-value
Female sex	2.43	1.05–5.65	0.038
Higher age	1.02	0.99–1.05	0.270
Ischaemic infarction	2.97	1.33–6.67	0.008
Ruptured aneurysm	3.53	1.20–10.42	0.022
Vasospasm	3.60	1.57–8.23	0.002

Table 7 Glasgow Outcome Scores at discharge

	Overall	Clipped patients	Coiled patients
GOS I	16 (11.1%)	5 (9.4%)	11 (12.1%)
GOS II	16 (11.1%)	6 (11.3%)	10 (11.0%)
GOS III	38 (26.4%)	16 (30.2%)	22 (24.2%)
GOS IV	11 (7.6%)	2 (3.8%)	9 (9.9%)
GOS V	63 (43.8%)	24 (45.3%)	39 (42.9%)
Total	144 (100%)	53 (100%)	91 (100%)

Discussion

Vasospasm resulting from aneurysmal SAH is a complicated multifactorial and multistage process. The time course and severity of vasospasm are important determinants for post-operative therapies and clinical outcome for these patients (Okada *et al.*, 1999).

Many studies deal with 'symptomatic vasospasms', mostly defined as delayed neurological deterioration that cannot be attributed to re-bleeding, hydrocephalus, intracerebral haematoma or other known complications of SAH. But especially in patients with poor clinical grade, who are often under analgesia and sedation, the detection of neurological deterioration can be very difficult. The objective measurement of flow velocities by TCD sonography is the most common method for the detection and monitoring of vasospasm. This technique makes it possible to detect non-invasively stenotic changes in cerebral arteries on the basis of relationship between blood-flow velocity and vessel lumen.

The horizontal portion (M1) of MCA is the easiest to locate and the most suited for TCD recording in vasospasm patients (Creissard and Proust, 1994). Hence, most of the results published about the usefulness of TCD in vasospasm diagnosis rely upon the sole M1 mean flow velocity recording. Distal ICA can be located easily as well and TCD data from ICA recordings are reliable (Creissard and Proust, 1994; Proust *et al.*, 1999). For ACA, different reports of angiographic diameter and TCD velocity have shown no or low significant correlations (Proust *et al.*, 1999). Creissard and Proust (1994) found TCD to be an almost perfect tool in vasospasm diagnosis, but only if A1 was constantly and reliable insonated. However, in our sample only two patients presented with sole ACA vasospasm. Besides, all patients were handled equally and so there should be no problem in comparing the two treatment modalities regarding the incidence of vasospasm.

Vasospasm was diagnosed on the basis of an increase in mean TCD velocities of ≥120 cm/s. Aaslid *et al.* (1984) have already suggested that mean flow velocities of the MCA greater than 120 cm/s indicate vasospasm. Only a part of these 'vasospasm patients' show neurological deterioration with the meaning of a 'symptomatic vasospasm.' Therefore, our incidence of vasospasm (53.5%) is not comparable with other studies dealing with 'symptomatic vasospasm.'

Post-interventional cerebral angiography to confirm a diagnosis of vasospasm was not performed in all patients, its clinical utility in patients with vasospasm remaining controversial, because the procedure is associated with complications. Several reports suggest that the risk/benefit ratio does not warrant serial angiography (Shehadi 1975; Mani *et al*., 1978; Earnest *et al*., 1984; Dion *et al*., 1987; Gruber *et al*., 1998). For detecting angiographic vasospasm, Sloan *et al*. (1989) reported that TCD ultrasonography had a sensitivity of 84% and a specificity of 89%. Referring to this, Lindegaard *et al*. (1988) found a sensitivity of 85% and a specificity of 98%. Because of the high specificity, the possibility is low that patients who do not have vasospasm will be classified as having vasospasm.

The early excluding of the aneurysm from the blood circulation is the prerequisite for aggressive management of vasospasm. Since its introduction in 1991, coil embolization, an endovascular technique for treating cerebral aneurysms, has been used frequently. It is performed by neuro-interventional radiologists and provides an alternative to neurosurgical aneurysm clipping. The influence of these two therapeutic modalities on the incidence of vasospasm and infarction is still judged controversially. Whilst Gruber *et al*. (1998) found a higher infarction rate amongst coiled patients, Yalamanchili *et al*. (1998) reported a greater frequency of clinical vasospasm in clipped patients. In a recently published multivariate analysis (Charpentier *et al*., 1999), no difference in risk of symptomatic vasospasm could be identified between surgical and endovascular treatment.

For studies of ruptured aneurysm treatment, selection bias may be a particularly difficult problem. Prognosis after rupture is largely determined by the pre-procedural neurological condition, as demonstrated by Hunt & Hess. This may be an important factor in determining how an aneurysm is treated, resulting in selection bias (Johnston, 2000). The fact that patients were not matched for presenting Hunt & Hess grade was one of the problems of Gruber's study (Gruber *et al*., 1998). Fifty-eight per cent of the patients in the endovascular group were Hunt & Hess grade IV or V and only 32% of the patients in the surgery group were in the same grades. Beyond that only 29% of the whole sample were coiled, all the remaining patients underwent surgery.

Although our study is not a prospectively randomized clinical trial, we have two well-balanced treatment groups: The mean initial Hunt & Hess grade was only 0.07 points lower in the surgical treatment group. We found vasospasm occurring significantly less often after coiling than after clipping. This confirms the observations of Debrun *et al*. (1998) including 324 patients, who found the same significant difference. Rosenwasser (1998), in their experience with 80 patients treated with GDC occlusion, also found the incidence of symptomatic vasospasm to be markedly less than in surgically treated patients. In a rather small study, Yalamanchili *et al*. (1998) concluded that the frequency and severity of cerebral vasospasm may be reduced in those treated by endovascular occlusion as compared with those treated by direct surgical clipping.

In our study, the rates of SAH are somewhat unbalanced between both treatment groups. Ruptured aneurysms were seen in 81.1% of the clipped patients and in 75.8% of the coiled patients. This is a very small and non-significant difference and can, therefore, not be decisively responsible for the higher incidence of vasospasm in the clipped group.

It has been frequently suggested that early surgical evacuation of the cisternal blood-clot may reduce the incidence of vasospasm (Handa *et al*., 1987; Nosko *et al*., 1987; Inagawa *et al*., 1990). In contrast to surgery, the endovascular treatment of aneurysms does not allow removal of subarachnoid blood-clots. Despite this, the largest clinical series report that vasospasm remains the most significant cause of death and disability, even in patients undergoing early surgery (Kassell *et al*., 1990b). Moreover, several studies comparing clipping and coiling (including ours) reveal higher incidences of vasospasm in surgically treated patients. Charpentier *et al*. (1999) suggested that early evacuation of the cisternal blood-clot cannot be the crucial determinant of the occurrence of cerebral vasospasm, because they found no relationship between the type of treatment and vasospasm occurrence. The failure may be because of the difficulty in removing subarachnoid blood-clots (Taneda, 1982; Kassell *et al*., 1990a,b). There is no clear evidence that early surgery significantly reduces the severity of vasospasm (Chyatte *et al*., 1988; Miyaoka *et al*., 1993). On the contrary, results of several laboratory and clinical studies have suggested that craniotomy results in exacerbation of vasospasm (Sundt, 1977; Suzuki *et al*., 1979; Kassell and Drake, 1982; Kassell *et al*., 1990a,b; Mayberg and Winn, 1990; Solomon *et al*., 1991). Stornelli and French (1964), Sundt and Whisnant (1978) and Allcock and Drake (1965) have cautioned that early surgery with or without preoperative spasm is more likely to precipitate postoperative vasospasm. In the majority of cases, open surgery with microdissection of the cerebral vasculature causes higher stress in the acute phase after SAH than does endovascular treatment (Miyaoka *et al*., 1993; Öhman *et al*., 1991; Murayama *et al*., 1997).

Surgery might affect vasospasm because of extensive retraction of the brain or over-manipulation of the main arteries. It has been demonstrated that the regional cerebral blood flow (rCBF) tends to fall progressively during the first 2–4 weeks (Ikeda and Yamashita, 1992; Meyer *et al.*, 1983; Mickey *et al.*, 1984; Jakobsen *et al.*, 1990; Kawamura *et al.*, 1992). Focal vasospasm might not explain such a global reduction of CBF, possibly surgical manipulations such as brain retraction could cause a more reduced rCBF. Previous studies (Tomita *et al.*, 1990) have reported that CBF was significantly lower post-operatively in the vicinity of the surgical route, and delayed ischaemic neurological deficits are more likely to occur. In summary, vasospasm seems to result from both exposure to blood products and cerebral manipulation. But obviously, in combination these two factors are very potent in producing vasospasm (Landau and Ransohoff, 1968; Wilkins, 1980; Mayberg and Winn, 1990).

Beside vasospasm, ischaemic injury is a major cause of morbidity and mortality after SAH (Qureshi *et al.* 2000). Various mechanisms have been proposed; namely, spasm alone or in combination with intracerebral haematomas, the mass effect of some aneurysms, extension of aneurysm thrombus into the parent vessel, or extracranial vascular occlusion might give rise to cerebral infarction after aneurysm rupture (Graham *et al.*, 1983). Cerebral computed tomography is valuable in detecting cerebral ischaemia after aneurysmal SAH. But not every hypodensity on cCT may be termed an infarct. Some such hypodensities may be gone after 3 months, some are even reversible earlier and do not constitute an infarction. We defined an infarction by the development of a hypodensity on cCT scans during NICU/SU stay. As some such hypodensities are reversible after discharge, our 53.5% incidence of 'infarctions' may be distinctly higher than incidences found for persistent infarctions. Öhman *et al.* (1991) found an 49.3% incidence of hypodense areas consistent with infarction. Petruk *et al.* (1988) reported an incidence of 42.4% of infarcts from vasospasm in nimodipine-treated patients compared with 53.3% of placebo-treated patients. We found coiled patients to develop less cerebral infarctions than clipped patients. Koivisto *et al.* (2000) also found significantly more ischaemic lesions in surgical patients and suggested that surgical manipulation of the arteries cause local vasospasm that leads to ischaemic deficits. As our multivariate analysis revealed, vasospasm indeed seems to be the most important cause for higher infarction rates in clipped patients.

The correlation between vasospasm and cCT evidence of cerebral infarction is well documented. Seiler *et al.* (1986), Grosset *et al.* (1992, 1993a, 1994) and Gruber *et al.* (1998) showed a positive correlation between maximal CBF velocity and the incidence of delayed ischaemic infarctions. Graham *et al.* (1983) clearly demonstrated a significant relationship between presence and degree of vasospasm and ischaemic brain damage, particularly when arterial territory infarction was considered. But there was no correlation between boundary zone infarction and the presence of vasospasm (Graham *et al.*, 1983). Öhman *et al.* (1991) showed moderate to severe diffuse vasospasm to be highly prognostic for the development of cerebral infarction: more than 65% of patients exhibiting vasospasm had infarction on follow-up cCT ($P = 0.0007$).

Hence, most patients show a close relationship between increasing blood-flow velocity and development of infarction (Lindegaard *et al.*, 1989; Grosset *et al.*, 1993b; Okada *et al.*, 1999). However, some patients with high blood-flow velocities do not develop ischaemic neurological deficits or infarctions, whereas others with low blood-flow velocities do (Okada *et al.*, 1999). We found 40.3% infarctions in the non-vasospasm group, and in contrast to this, an incidence of 35.1% vasospasm patients who did not develop ischaemic lesions. Obviously, there is a high quota of infarction patients exhibiting vasospasms of peripheral branches not detectable by TCD (Okada *et al.*, 1999). The mean flow velocity at the M1 segment seems to be inadequate to estimate the severity of vasospasm extending to vessels more peripheral. It has already been shown that severe vasospasm extending to more peripheral sites can produce more serious ischaemic insults, compared with that localized to basal vessels (Okada *et al.*, 1999). On the other hand, cerebral blood-flow velocities may increase independent of vasospasm caused by post-operative hyperaemia or an induced hyperdynamic state. This could partly explain the 35.1% vasospasm patients without infarctions.

However, recently when considered in terms of physical survival, management results have improved significantly with the use of new microsurgical techniques as well as the use of GDCs (Öhman *et al.*, 1991). Nevertheless, vasospasm and ischaemic infarctions remain as risk factors for unfavourable outcome (Rabb *et al.*, 1994; Enblad and Persson, 1997). In our study, vasospasm was associated with a 3.6-fold risk of neurological deficits at discharge. This is well comparable with a review considering more than 1000 reports, in which a common OR of 3.05 has been calculated (Dorsch and King, 1994). In a recent study, Koivisto *et al.* (2000) found post-operative vasospasm to be associated with poorer clinical outcome (OR 2.47).

It has been shown that those institutions that used coil embolization more frequently had better overall outcome for unruptured aneurysms (Johnston, 2000). This supports the conclusion that coil embolization might be safer for treatment of unruptured aneurysms. For ruptured aneurysms, institutional use of coil embolization was also associated with better outcomes (Johnston, 2000). Although we found a higher risk of vasospasm and cerebral infarction in clipped patients, there was no significant relationship between type of treatment and outcome. The early technique-related mortality was similar in both groups. This is in accordance with the results of a recent prospective randomized study (Koivisto *et al*. 2000).

Acknowledgements

We thank Dr A.K. Pallua and Dr M. Wagner for providing their diagnostic expertise in cCT.

References

Aaslid R, Huber P, Nomes H (1984). Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg* **60:**37–41.

Adams HP, Kassell NF, Torner JC, Haley EC (1987). Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: influences of clinical condition, CT results, and antifibrinolytic therapy. A report of the Cooperative Aneurysm Study. *Neurology* **37:**1586–1591.

Allcock JM, Drake CG (1965). Ruptured intracranial aneurysms – the role of arterial spasm. *J Neurosurg* **22:**21–29.

Charpentier C, Audibert G, Guillemin F *et al*. (1999). Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. *Stroke* **30:**1402–1408.

Chyatte D, Fode NC, Sundt TM (1988). Early versus late intracranial aneurysm surgery in subarachnoid hemorrhage. *J Neurosurg* **69:**326–331.

Creissard P, Proust F (1994). Vasospasm diagnosis: theoretical sensitivity of transcranial Doppler evaluated using 135 angiograms demonstrating vasospasm. Practical consequences. *Acta Neurochir (Wien)* **131:**12–18.

Debrun GM, Aletich VA, Kehrli P *et al*. (1998). Evaluation of cerebral vasospasm after early surgical and endovascular treatment of ruptured intracranial aneurysms. *Neurosurgery* **43:**646–647 (correspondence).

Dion JE, Gates PC, Fox AJ, Barnett HJ, Blom RJ (1987). Clinical events following neuroangiography: a prospective study. *Stroke* **18:**997–1004.

Dorsch NWC, King MT (1994). A review of cerebral vasospasm in aneurysmal subarachnoid hemorrhage, part 1: incidence and effects. *J Clin Neurosci* **1:**19–26.

Duff TA, Louie J, Feilbach JA, Scott G (1988). Erythrocytes are essential for development of cerebral vasculopathy resulting from subarachnoid hemorrhage in cats. *Stroke* **19:**68–72.

Earnest F, Forbes G, Sandok BA *et al*. (1984). Complications of cerebral angiography: prospective assessment of risk. *Am J Roentgenol* **142:**247–253.

Enblad P, Persson L (1997). Impact on clinical outcome of secondary brain insults during the neurointensive care of patients with subarachnoid hemorrhage: a pilot study. *J Neurol Neurosurg Psychiatry* **62:**512–516.

Fisher CM, Kistler JP, Davis JM (1980). Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomography scanning. *Neurosurgery* **6:**1–9.

Graham DI, Macpherson P, Pitts LH (1983). Correlation between angiographic vasospasm, hematoma, and ischemic brain damage following SAH. *J Neurosurg* **59:**223–230.

Grosset DG, Straiton J, du Trevou M, Bullock R (1992). Prediction of symptomatic vasospasm after subarachnoid hemorrhage by rapidly increasing transcranial Doppler velocity and cerebral blood flow changes. *Stroke* **23:**674–679.

Grosset DG, Straiton J, McDonald I, Cockburn M, Bullock R (1993a). Use of transcranial Doppler sonography to predict development of a delayed ischemic deficit after subarachnoid hemorrhage. *J Neurosurg* **78:**183–187.

Grosset DG, Straiton J, McDonald I, Bullock R (1993b). Angiographic and Doppler diagnosis of cerebral artery vasospasm following subarachnoid hemorrhage. *Br J Neusurg* **7:**291–298.

Grosset DG, McDonald I, Cockburn M, Straiton J, Bullock R (1994). Prediction of delayed neurological deficit after subarachnoid hemorrhage: a CT blood load and Doppler velocity approach. *Neuroradiology* **36:**418–421.

Gruber A, Ungersbock K, Reinprecht A *et al*. (1998). Evaluation of cerebral vasospasm after early surgical and endovascular treatment of ruptured intracranial aneurysms. *Neurosurgery* **42:**258–267.

Haley EC, Kassell NF, Torner JC, Truskowski LL, Germanson TP (1994). A randomized trial of two doses nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg* **80:**788–796.

Handa Y, Weir BK, Nosko M, Mosewich R, Tsuji T, Grace M (1987). The effect of timing of clot removal on chronic vasospasm in a primate model. *J Neurosurg* **67:**558–564.

Hunt WE, Hess RM (1968). Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* **28:**14–20.

Ikeda K, Yamashita J (1992). Postoperative central conduction time and cerebral blood flow in patients with aneurysmal subarachnoid hemorrhage. relationship with prognosis and ischemic conditions. *Surg Neurol* **38:**445–453.

Inagawa T (1992). Cerebral vasospasm in elderly patients treated by early operation for ruptured intracranial aneurysms. *Acta Neurochir (Wien)* **115:**79–85.

Inagawa T, Yamamoto M, Kamiya K (1990). Effect of clot removal on cerebral vasospasm. *J Neurosurg* **72:**224–230.

Jakobsen M, Enevoldsen E, Bjerre P (1990). Cerebral blood flow and metabolism following subarachnoid hemorrhage. cerebral oxygen uptake and global blood flow during the acute period in patients with SAH. *Acta Neurol Scand* **82:**174–182.

Jennett B, Bond M (1975). Assessment of outcome after severe brain damage. *Lancet* **1:**480–484.

Johnston SC (2000). Effect of endovacular services and hospital volume in cerebral aneurysm treatment outcomes. *Stroke* **31:**111–117.

Kassell NF, Drake CG (1982). Timing of aneurysm surgery. *Neurosurgery* **10:**514–519.

Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP, Kongable GL (1990a). The International Cooperative

Study on the Timing of Aneurysm Surgery. Part 1: overall management results. *J Neurosurg* **73:**18–36.

Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP (1990b). The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: surgical results. *J Neurosurg* **73:**37–47.

Kawamura S, Sayama I, Yasui N, Uemura K (1992). Sequential changes in cerebral blood flow and metabolism in patients with subarachnoid hemorrhage. *Acta Neurchir (Wien)* **114:**12–15.

Kistler JP, Crowell RM, Davis KR *et al.* (1983). The relation of cerebral vasospasm to the extent and location of subarachnoid blood visualized by CT scan: a prospective Study. *Neurology* **33:**424–436.

Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M (2000). Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. *Stroke* **31:**2369–2377.

Landau B, Ransohoff J (1968). Prolonged cerebral vasospasm in experimental subarachnoid hemorrhage. *Neurology* **18:**1056–1065.

Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P (1988). Cerebral vasospasm after subarachnoid hemorrhage investigated by means of transcranial Doppler ultrasound. *Acta Neurochir Suppl (Wien)* **42:**81–84.

Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P (1989). Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. *Acta Neurochir* **100:**12–24.

Macdonald RL, Weir BK, Runzer TD *et al.* (1991). Etiology of cerebral vasospasm in primate. *J Neurosurg* **75:**415–424.

Mani RL, Eisenberg RL, McDonald EJ, Pollock JA, Mani JR (1978). Complications of catheter cerebral angiography: analysis of 5000 procedures. I: criteria and incidence. *Am J Roentgenol* **131:**861–865.

Mayberg MR, Winn HR (1990). *Neurosurgery Clinics of North America: Cerebral Vasospasm*. Saunders, Philadelphia, PA, **1:**265–463.

Meyer CHA, Lowe D, Meyer M, Richardson PL, Neil-Dwyer G (1983). Progressive change in cerebral blood flow during the first three weeks after subarachnoid hemorrhage. *Neurosurgery* **12:**58–76.

Mickey B, Vorstrup S, Voldby B, Lindewald H, Harmsen A, Lassen NA (1984). Serial measurement of regional cerebral blood flow in patients with SAH using 133Xe inhalation and emission computerized tomography. *J Neurosurg* **60:**916–922.

Miyaoka M, Sato K, Ishii S (1993). A clinical Study of the relationship of timing of outcome of surgery for ruptured cerebral aneurysms. A retrospective analysis of 1622 cases. *J Neurosurg* **79:**373–378.

Murayama Y, Malisch T, Guglielmi G *et al.* (1997). Incidence of cerebral vasospasm after endovascular treatment of acutely ruptured aneurysms: report of 69 cases. *J Neurosurg* **87:**830–835.

Nosko M, Weir BK, Lunt A, Grace M, Allen P, Mielke B (1987). Effect of clot removal at 24 hours on chronic vasospasm after SAH in the primate model. *J Neurosurg* **66:**416–422.

Öhman J, Servo A, Heiskanen O (1991). Risk factors for cerebral infarction in good-grade patients after aneurysmal subarachnoid hemorrhage and surgery: a prospective Study. *J Neurosurg* **74:**14–20.

Okada Y, Shima T, Nishida M *et al.* (1999). Comparison of transcranial Doppler investigation of aneurysmal vasospasm with digital subtraction angiographic and clinical findings. *Neurosurgery* **45:**443–449.

Petruk KC, West M, Mohr G *et al.* (1988). Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg* **68:**505–517.

Proust F, Callonec F, Clavier E *et al.* (1999). Usefulness of transcranial color-coded sonography in the diagnosis of cerebral vasospasm. *Stroke* **30:**1091–1098.

Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN, Ulatowski JA (2000). Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. *Crit Care Med* **28:**984–990.

Rabb CH, Tang G, Chin LS, Gianotta SL (1994). A statistical analysis of factors related to symptomatic cerebral vasospasm. *Acta Neurochir (Wien)* **127:**27–31.

Rosenwasser RH (1998). Evaluation of cerebral vasospasm after early surgical and endovascular treatment of ruptured intracranial aneurysms. *Neurosurgery* **42:**267 (comment).

Seiler RW, Grolimund P, Aaslid R, Huber P, Nornes H (1986). Cerebral vasospasm evalueted by transcranial ultrasound correlated with clinical grade and CT-visualized subarachnoid hemorrhage. *J Neurosurg* **64:**594–600.

Shehadi WH, (1975). Adverse reactions to intravasculary administered contrast media. A comprehensive Study based on a prospective survey. *Am J Roentgenol Radium Ther Nucl Med* **124:**145–152.

Sloan MA, Harley EC, Kassell NF *et al.* (1989). Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology* **39:**1514–1518.

Solomon RA, Onesti ST, Klebanoff L (1991). Relationship between the timing of aneurysm surgery and the development of delayed cerebral ischemia. *J Neurosurg* **75:**56–61.

Stornelli SA, French JD (1964). Subarachnoid hemorrhage – factors in prognosis and management. *J Neurosurg* **21:**769–780.

Sundt TM (1977). Cerebral vasospasm following subarachnoid hemorrhage: evolution, management, and relationship to timing of surgery. *Clin Neurosurg* **24:**228–239.

Sundt TM, Whisnant JP (1978). Subarachnoid hemorrhage from intracranial aneurysms. Surgical management and natural history of disease. *N Engl J Med* **299:**116–122.

Suzuki J, Onuma T, Yoshimoto T (1979). Results of early operations in cerebral aneurysms. *Surg Neurol* **11:**407–412.

Taneda M (1982). Effect of early operation for ruptured aneurysms on prevention of delayed ischemic symptoms. *J Neurosurg* **57:**622–628.

Tomita H, Ito U, Tone O, Hayashi H, Shishido T, Momma S (1990). Laterality of symptomatic vasospasm following early aneurysm surgery. In: Sano, K, Takakura, K, Kassell, NF, Sasaki, T, eds. *Cerebral Vasospasm*. University of Tokyo Press, Tokyo, pp. 33–34.

Wilkins RH (1980). *Cerebral Arterial Spasm*. Williams & Wilkins, Baltimore, MD, pp. 158–201.

Yalamanchili K, Rosenwasser RH, Thomas JE, Liebmann K, McMorrow C, Gannon P (1998). Frequency of cerebral vasospasm in patients treated with endovascular occlusion of intracranial aneurysms. *Am J Neuroradiol* **19:**553–558.

Yoshimoto Y, Wakai S, Satoh A, Tejima T, Hamano M (1999). A prospective Study on the effects of early surgery on vasospasm after subarachnoid hemorrhage. *Surg Neurol* **51:**392–398.

Zabramski JM, Hamilton MG (1994). Cerebral vasospasm. In: Carter LP, Spetzler RF, eds. *Neurovascular Surgery*. McGraw-Hill, New York, pp. 583–601.