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Cerebral vasospasm: results of a structured multimodal treatment

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Summary

Symptomatic cerebral vasospasm (CVS) with delayed ischemic neurologic deficits affects about one third of the patients after aneurysmal subarachnoid hemorrhage (SAH). In spite of the lack of definite evidence of large clinical trials, the devastating outcome of the natural history of symptomatic CVS demands an aggressive CVS treatment in a practically oriented, structured multimodal treatment regimen. With our treatment protocol good functional outcome could be reached in 66% of the patients with symptomatic CVS. This policy requires close and fast multidisciplinary collaboration between neurosurgeons, neuroradiologists, competent in endovascular interventions, and specialists for neurointensive care. We report on our experience with 79 cases with symptomatic CVS and delayed ischemic neurologic deficit (DIND) after aneurysmal SAH. The different treatment options with CVS are reviewed and practical guidelines for a step by step treatment are given.

Keywords: Cerebral vasospasm; triple h therapy; ischemia; spasmolysis; hypothermia; barbiturate coma.

Introduction

With early aneurysm clipping delayed ischemic neurologic deficit (DIND) due to cerebral vasospasm (CVS) became the most common cause of death and disability due to aneurysmal subarachnoid hemorrhage (SAH) [30]. Symptomatic CVS with DIND affects about one third of the patients and, without specific treatment, the outcome of DIND is devastating, causing death (30%) and permanent disability (34%) [14, 16].

We report on our experience with 79 cases with symptomatic CVS after aneurysmal SAH. The different treatment options with CVS are reviewed and practical guidelines for a structured step by step multimodal treatment protocol are given.

Materials and methods

Patient population

The study was approved as a part of the project E-015/99 by the Ethics Committee of the University of Zurich. Between January 1999 and December 2003 198 patients with SAH were admitted within three days after symptoms onset into the Department of Neurosurgery, University Hospital Zurich and were treated with aneurysm clipping. In 1999 a standardized protocol for detection and treatment of CVS was established. Patients data, imaging studies and characteristics of treatment were prospectively analyzed. Neurological outcome was assessed after 3 and 12 months in the outpatient clinic by an independent neurologist using the Glasgow Outcome Scale (GOS) [24]. Those patients who did not show up at control were contacted and asked about their functional status.

Structured treatment

Aneurysm clipping was performed with the standard microsurgical technique described by Yasargil [64]. Only patients having undergone aneurysm clipping within three days after SAH were included. All patients were treated with nimodipine for 21 days. Patients were kept flat in bed as long as cerebral autoregulation, examined with transcranial Doppler (TCD), was defect. Before the patients developed signs of CVS daily fluid balance was aimed to be positive, adjusting fluid intake by intravenous infusion of crystalloids and hydroxylethyl-starch solution (HES) 1000 ml per day. No prophylactic triple h (hypertensive hypervolemic hemodilution) therapy was initiated. Dexamethasone was given perioperative. Prophylactic antiepileptic treatment with phenytoine or valproate was initiated in SAH patients with Hunt and Hess grade 3 and higher. In patients with SAH Hunt and Hess grade 1 to 3, sedation was stopped immediately after surgery. In patients with severe SAH Hunt and Hess grade 4 to 5, a ventricular catheter (NMT Neuroscience, Frankfurt, Germany or Raumedic, Rehau, Germany) was inserted to provide continuous intracranial pressure (ICP) monitoring and drainage of cerebrospinal fluid (CSF) if necessary. If a ventricular catheter could not be placed within the ventricular system because of massive brain edema, a subdural (NMT Neuroscience, Frankfurt, Germany) or an intraparenchymatous (Raumedic, Rehau, Germany) ICP probe was inserted. With elevated ICP (>15 mmHg) treatment with intermittent CSF drainage, osmotherapy (Mannitol 20% and hypertonic NaCl-hydroxyethyl-starch solution), mild hyperventilation (target $PaCO_2$ values adapted to jugular bulb oximetry) and tris-hydroxymethyl-aminomethane (THAM) buffer was initiated. Patients with persistant ICP-values > 15 mmHg were eligible for treatment with barbiturate coma combined with mild hypothermia. Medical therapy, barbiturate coma and hypothermia treatment were performed according to a standardized algorithm for treatment of elevated ICP [31].

Detection of cerebral vasospasm

TCD blood flow measurements were performed daily. "Symptomatic CVS" was defined in the absence of sedation and poor neurological grade by the occurrence of DIND (decrease in consciousness, new focal neurological deficits). Before "symptomatic CVS" was suspected, hypoxia, electrolyte imbalance and hydrocephalus were excluded by a further CT scan. CVS in all patients were confirmed by digital subtraction angiography. If the neurological state could not be properly assessed (e.g. sedation or poor neurological grade), patients were additionally monitored with jugular bulb oxymetry, lactate measurements from the jugular bulb [20], daily cerebral blood flow (CBF) measurements [33] and/or perfusion CT examinations. If jugular bulb O_2-desaturation occurred, arteriovenous differences of lactate (avDL) were – 0.2 umol/dl or less, CBF-values decreased by more than 20% and/or differences in territorial or hemispheric transit times occurred in perfusion CT, "symptomatic CVS" was suspected and digital subtraction angiography was performed. All patients with new ischemic infarctions – in comparison with the postoperative CT examination – were classified likewise to have "symptomatic CVS".

Treatment of cerebral vasospasm

If signs of CVS occurred, patients were treated according to a multimodal structured treatment protocol (Table 1).

Hypertensive hypervolemic hemodilution (triple h) therapy was induced if TCD mean blood flow velocities increased (mean middle cerebral artery (MCA) blood flow velocities > 140 cm/sec or increase up to >50 cm/sec within 24 hours) and/or the patient developed symptomatic CVS. Contraindications to initiate triple h therapy were heart failure, valvular heart disease, symptomatic coronary heart disease, cardiac arrhythmias and aortic aneurysms. Triple h therapy was guided with a new system to monitor systemic hemodynamics [36]. A 13 cm long 4-F arterial thermistor catheter (PV-2015L13, Pulsion Medical Systems, Munich) was inserted into the femoral artery and connected to the pulse contour analysis computer (PICCO Pulsion Medical Systems, Munich). Thermodilution measurements with calibration of cardiac index (CI) and determination of global enddiastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI) and extravascular lung water index (EVLWI) were performed every six hours. In addition to the conventional parameters (mean arterial pressure (MAP) > 105 mmHg, central venous pressure (CVP) 8–12 mmHg and hematocrit 28–32%) triple h therapy was adapted to the following target values: CI > 4l/min/m^2, ITBVI 900–1000 ml/m^2 and EVLWI < 10 ml/kg. Triple h therapy was induced by administration of crystalloid and colloid infusions. Dobutamine and norepinephrine were adjusted to maximize cardiac function. Excessive natriuresis and diuresis (osmolarity in urine > osmolarity in serum, sodium in serum < 140 mmol/l) was inhibited with fludrocortisone 0.2 mg/day, excessive water diuresis (osmolarity in urine < osmolarity in serum, sodium in serum > 140 mmol/l) with desmopressine 1–4 × 2 ug i.v. per day.

Endovascular treatment: If patients with DIND did not improve or worsened despite triple h therapy digital subtraction angiography and endovascular treatment with percutaneous balloon angioplasty and/or superselective papaverine infusion (totale dose of 300 mg) into the vasospastic vessels were performed [17, 25]. Contraindications for endovascular treatment were the presence of incompletely clipped aneurysms, ischemic infarctions or space-occupying brain edema in CT.

Barbiturate coma, hypothermia: Symptomatic CVS, resistant to the above treatment or reoccurring after two to three spasmolysis sessions were treated with barbiturate coma and/or hypothermia, if ever possible, as a combined treatment. Barbiturate coma with thiopental (loading dose of 10 mg/kgBW, followed by continuous infusion) was induced at the same time as induction of hypothermia and was adapted to a burst suppression pattern in continuous EEG-monitoring. Cooling of the patients (target brain temperature 33 °C) was accomplished by using cooling blankets (Bair Hugger, Augustine Medical, Saint Prarie; MN, USA and Blanketrol, CSZ, Cincinnatti; OH, USA) or endovascular cooling catheters (Cool Line Catheter and Coolgard System; Alsius Corporation, Irvine, CA, USA) [31]. Patients were excluded if they initially suffered from congestive heart failure, neurogenic pulmonary edema, severe aspiration pneumonia, other infections or Raynaud's phenomenon. Hypothermia only was performed if specific contraindications for thiopental were present such as liver failure, hyperkaliemia or hypernatriemia. Barbiturate coma and hypothermia were continued until signs of CVS decreased. Barbiturate coma and hypothermia were terminated earlier if signs of severe infection, cardiovascular instability, liver failure (barbiturate coma), severe electrolyte disturbances (barbiturate coma) or coagulation disorders (hypothermia) were observed.

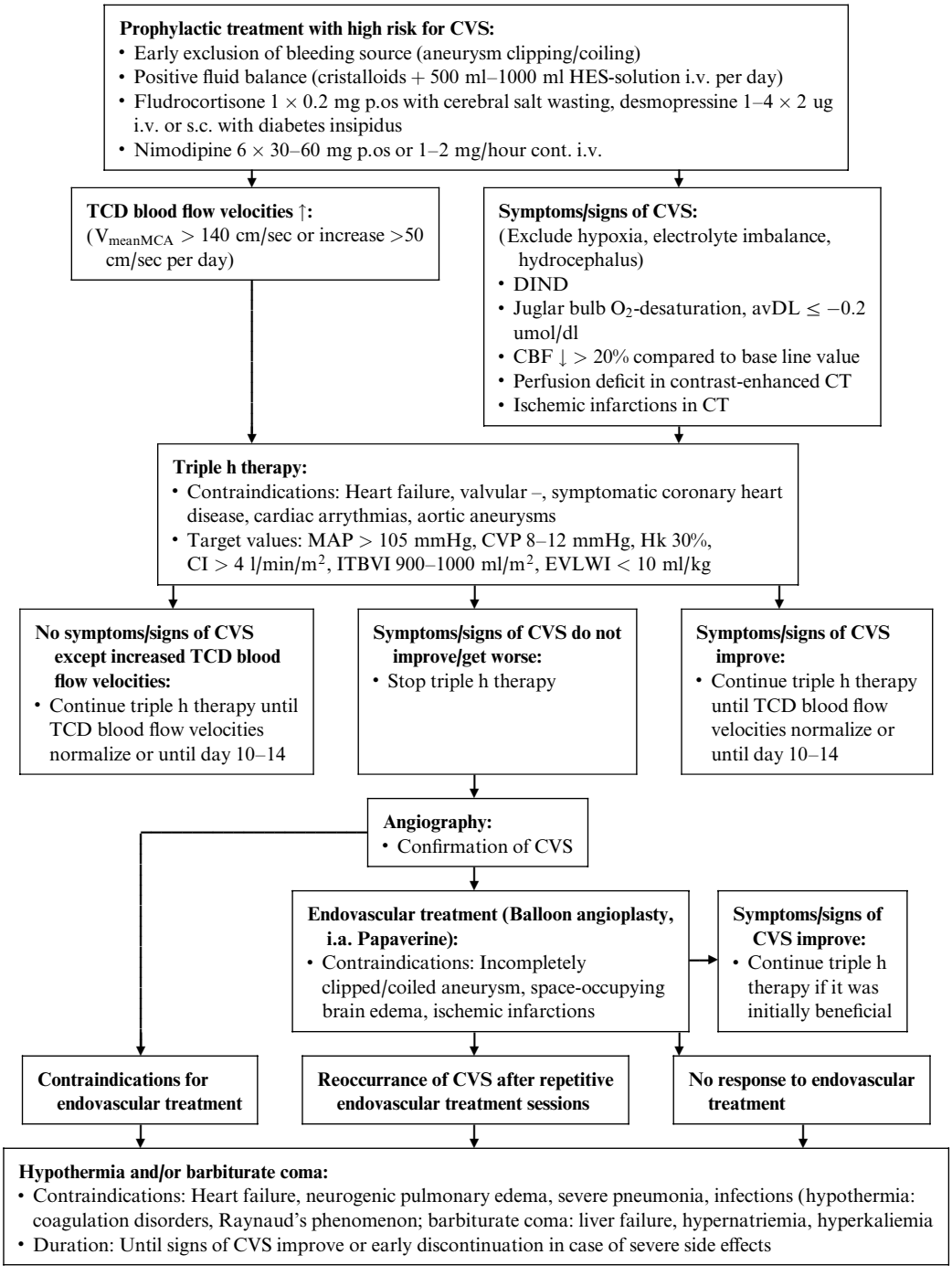
Outcome measurements

Neurological outcome was assessed after three and 12 months in the outpatient clinic by a neurologist using the Glasgow Outcome Score (GOS) [24], GOS 1 denominating death, GOS 2 vegetative state (unable to interact with the environment), GOS 3 severe disability (unable to live independently but able to follow commands), GOS 4 moderate disability (capable of living independently but unable to return to work or school) and GOS 5 mild or no disability (able to return to work or school). Those patients who did not show up at control were contacted and asked about their functional status.

Results

From 198 patients treated with aneurysm clipping within three days after SAH, TCD mean blood flow velocities increased in 105 patients (52.5%). 79 patients developed symptomatic CVS (39.9%). Characteristics of patients with symptomatic CVS are given in Table 2. The majority of patients with symptomatic CVS suffered from severe SAH. 50 patients (63.3%) had Hunt and Hess grades 3 to 5 and 69 patients (87.4%) belonged to the Fisher grades 3 and 4. Treatment characteristics are given in Table 3. 78 patients (98.7%) were treated with triple h therapy. In one patient with symptomatic CVS triple h therapy was not initiated because of heart failure. In 45 (57.7%) of the 78 patients triple h therapy had a sustained positive effect and symptoms of CVS decreased, making further therapy steps such as spasmolysis, barbiturate coma and hypothermia unnecessary. 33 patients (41.8%), despite of therapeutic triple h therapy, did not improve or worsened. These patients were subjected to digital subtraction angiography and percutaneous angioplasty and/or superselective papaverine infusion. Due to reoccurrence of CVS five patients were treated twice and two patients three times with spasmolysis. 13

Table 1. *Structured treatment protocol Department of Neurosurgery, University Hospital Zurich*



CVS Cerebral vasospasm; *TCD* transcranial Doppler; $V_{meanMCA}$ mean blood flow velocity in the middle cerebral artery; *AvDL* arteriovenous difference of lactate; *DIND* delayed ischemic neurologic deficit; *CBF* cerebral blood flow; *MAP* mean arterial pressure; *CVP* central venous pressure; *Hk* hematocrit; *CI* cardiac index; *ITBVI* intrathoracic blood volume index; *EVLWI* extravascular lung water index.

patients had contraindications for endovascular treatment (eight patients with space-occupying brain edema and five with ischemic infarctions in CT scans) and 13 patients suffered from resistant or reoccurring CVS to repetitive spasmolysis. These patients were treated with barbiturate coma and/or hypothermia, 23 with combined treatment and three patients with hypothermia only. From these patients with refractory

Table 2. *Patient characteristics*

	Number of patients with symptomatic CVS (n = 79; 100%)
Age; mean (SD)	50.9 (11.9)
Gender	
– Male	17 (21.5%)
– Female	62 (78.5%)
GCS before surgery; mean (SD)	10.0 (4.6)
Grading	
– H & H grade 5	10 (12.7%)
– H & H grade 4	25 (31.6%)
– H & H grade 3	15 (19.0%)
– H & H grade 2	27 (34.2%)
– H & H grade 1	2 (2.5%)
– Fisher grade 4	42 (53.2%)
– Fisher grade 3	27 (34.2%)
– Fisher grade 2	8 (10.1%)
– Fisher grade 1	2 (2.5%)

n Number; *GCS* Glasgow Coma Scale; *H & H* Hunt and Hess grade.

Table 3. *Treatment characteristics*

	Number of patients with symptomatic CVS (n = 79; 100%)
Triple h therapy	78 (98.7%)
Spasmolysis	33 (41.8%)
– Once	26 (32.9%)
– Twice	5 (6.3%)
– Three times	2 (2.6%)
Hypothermia combined with barbiturate coma	23 (29.1%)
Hypothermia only	3 (3.8%)

n Number; *Triple h* hypertensive hypervolemic hemodilution.

CVS 13 patients (50%) survived with good functional outcome (GOS 4 and 5), 6 patients (23.1%) survived severely disabled and 7 patients (26.9%) died.

Of the total of 198 patients having suffered from aneurysmal SAH, six patients (3%) died from CVS and 16 patients (8.1%) suffered from permanent additional deficits from CVS (Table 4). 13 patients survived severely disabled or in a vegetative state (GOS 3 and 2 in 6.5%). In patients with symptomatic CVS good functional outcome (GOS 4 and 5) could be achieved in 52 of 79 patients (65.8%). 13 of the patients (16.5%) survived severely disabled and 14 (17.7%) died, six due to multiple infarctions, due to rebleeding and seven due to severe infections with acute respiratory distress syndrome or sepsis.

Table 4. *Patient outcome*

	Number of patients with symptomatic CVS (n = 79; 100%)
Died of CVS	6 (7.6%)
Permanent additional deficits because of CVS	16 (20.3%)
GOS	
– 5	36 (45.6%)
– 4	16 (20.2%)
– 3	13 (16.5%)
– 2	0 (0%)
– 1	14 (17.7%)

n Number; *cvs* cerebral vasospasm; *GOS* Glasgow Outcome Scale.

Discussion

In the cooperative aneurysm study 7.2% of the patients died from CVS and 6.3% survived with severe disability from CVS [30]. It is difficult to compare reports of management results because of different patient populations regarding the prognostic factors for poor outcome, in addition to variations in timing and methods for quantification of outcome. In our series, applying a step by step multimodal treatment protocol in 198 patients with aneurysmal SAH, 3% died from CVS and 6.5% survived severely disabled or in a vegetative state from CVS. From 79 patients with symptomatic CVS, good functional outcome could be obtained in 66% of the cases.

Recommendations for a structured treatment protocol

Prediction of CVS

In clinical practice not only treatment, but the accuracy of prediction and detection of symptomatic CVS, most difficult in patients under sedation and with poor neurological grade, is a very most important aspect influencing the outcome of patients after SAH. Recently, Claassen *et al.* revised the Fisher scale according to the risk to develop CVS [12]. The highest risk of developing DIND occurs in patients with thick basal cistern blood and the presence of blood in the lateral ventricles. After SAH, the complex changes of cerebral hemodynamics and oxygenation pattern with the development of DIND are underestimated if TCD-monitoring and angiography are considered singularly [1]. The role of TCD in predicting symptomatic CVS is limited to the cases where very high mean blood flow

velocities are detected [61]. Moreover, to control the treatment of CVS, TCD values are influenced by triple h therapy [40]. Discrepancies between radiographic findings and DIND may depend on the relationship between local cerebral oxygen-requirement and -delivery, which only can be determined if CBF and cerebral oxygen extraction can be estimated. Jugular bulb oximetry reflects the balance between CBF and the cerebral metabolic rate of oxygen ($CMRO_2$). It represents, nevertheless, only global cerebral perfusion. The sensitivity of $SjvO_2$ to detect smaller ischemic areas secondary to CVS of single vessels is limited [33]. In cases of distal arterial narrowing, new techniques applying near infrared spectroscopy (NIRS) with a indocyanine green (ICG) dye dilution mode measuring regional values of local cortical perfusion may be more sensitive, especially in detecting microvascular or "distal" vasospasm [32, 35]. Daily TCD blood flow velocities-checks during the highest vasospasm risk period (between 4 and 10 days postbleed), however, may warn of spasm development [1, 38] and allow more aggressive prophylactic treatment of threatening CVS with triple h therapy. Cerebral angiography with direct visualization of proximal CVS and prolonged transit time of the contrast flow remains the golden standard procedure to diagnose CVS. Angiography should be routinely performed after aneurysm clipping within 14 days after ictus and in case of occurrence of symptomatic CVS at an earlier date. Shortcomings of angiography include the lack in detecting micovascular vasospasm and the risks of the procedure including catheter-induced vasospasm or vessel dissection. Advantages lie in the potential for endovascular intervention.

Pharmacologic approaches

Nimodipine, a specific blocker of the L-type voltage-gated calcium channels, has been tested in several controlled trials [2, 46]. But not the originally anticipated direct effects on vascular smooth muscle cells, but the neuroprotective effects may be of some clinical benefit in patients who never experience vasospasm, macroscopically visible in angiography [42]. Barker and Ogilvie showed in a later metanalysis improvements in good and fair outcomes, as well as reductions of death rate and CT detected infarcts with nimodipine [6]. The modified steroid free radical scavenger tirilazad mesylate, inhibiting iron-dependendent lipid perxidation and scavering free radicals, has been investigated in four large controlled trials [28]. After first promising results later metanalysis showed only post hoc positive effects in patients with poor grades [15]. Many other medical treatment options are under investigation and can not be discussed in detail within this limited context. First pilot studies with high dose magnesium sulphate, with its vascular protection properties, showed promising results [10, 60]. After randomization of 60 patients in a controlled clinical study our own results showed that with magnesium sulfate infusion (dosage of 16 mmol in 15 mins. i.v., thereafter 64 mmol/24 h continuously i.v., adapted to a target magnesium level in serum of 2× baseline value for 14 days) had to be interrupted because of severe hypotension in 40% of the patients (unpublished data). The complex regulatory mechanisms of vascular smooth vessel tone after SAH are under extensive research and may lead to further promising treatment options like nitric oxide donors or selective endothelin-1 antagonists [14, 49, 65].

Triple h therapy

Benefits of triple h therapy have never been unequivocally demonstrated by randomized controlled trials [52]. In early studies patients with volume expansion showed less DIND and better outcome compared to control patients who were kept dehydrated [51], whereas in more recent studies no effect of hypervolemia on either CBF or DIND was found if control patients already receiving over 3000 ml fluids per day [37]. Dorsch therefore concludes that adequate fluid loading might be the most important aspect of early treatment and CVS prophylaxis and that it is reasonable to reserve the more vigorous loading and induced hypertension for when DIND occurs [14]. Therefore, as a prophylactic treatment in patients with high risk for CVS, fluid balance has to be carefully observed and kept positive within 1000–1500 ml per day and hematocrit is aimed to be 30%, providing the optimal level of reduced blood viscosity and improving CBF while still maintaining adequate serum oxygen carrying capacity [23]. The usefulness of triple h therapy, however, reversing secondary neurological deficits in 59% of our patients, is obvious in our daily clinical practice. Therefore, according to our treatment protocol, if TCD blood flow velocities increase and/or the patients develop symptoms of CVS triple h therapy is aggressively initiated. If triple h therapy fails to improve DIND or if the patients worsen during triple h ther-

apy, other treatment options have to be applied and, avoiding harmful side effects, triple h therapy can be reset. In order to guide triple h therapy and achieve as high efficiency as possible and to avoid volume overload with consecutive pulmonary edema as the most severe complication [5, 29, 57] extended monitoring of systemic hemodynamics is needed. Target values have to be defined, aimed at consequently and documented for quality control. Monitoring of mean arterial pressure (MAP), central venous pressure (CVP) and pulmonary artery occlusive wedge pressure (PAOP) are conventionally used to control triple h therapy [29], although their limitations to estimate intravascular volume state are well recognized [50]. Moreover, pulmonary artery catheterization as an invasive method is controversially discussed in the literature [13]. Recently an alternative method based on transpulmonary double-indicator dilution for assessment of intravascular volume has been established [22]. Global enddiastolic volume (GEDV) and intrathoracic blood volume (ITBV) have been reported to reflect the intravascular volume status more adequately than CVP or PAOP. Further, extravascular lung water (EVLW) is a reliable predictor for early pulmonary edema [22]. Own experiences showed that the new monitoring system might be the optimal instrument to guide triple h therapy [36]. Excessive natriuresis and diueresis may occur in the context of "cerebral salt wasting" most often in patients with ruptured aneurysms of the anterior communicating artery [63] and may be aggravated by fluid and volume load with triple h therapy. Polyuria may anticipate effective intravascular volume expansion. Mori *et al.* showed that the inhibition of natriuresis with fludrocortisone reduces the sodium and water intake required for hypervolemia and prevents hyponatriema. Therefore, with a high osmolarity in urine and a normal to low sodium in serum, fludrocortisone 0.2 mg/day may be supplemented with triple h therapy. In our institution, on the other hand, excessive water diuresis (low osmolarity in urine, high sodium in serum), similar to a constellation of diabetes insipidus, is treated with desmopressine $1–4 \times 2$ ug i.v. per day to avoid hypernatriemia [43].

Endovascular treatment

Indications, technology and side effects of endovascular treatment are described in detail in the subsequent article. For the neurointensivist the following aspects are to be emphasized. Balloon angioplasty and papaverine spasmolysis are performed in general anaesthesia. Symptomatic CVS leads to reduced O_2 delivery in the affected vascular territories with acute ischemia. General anaesthesia, reducing metabolic requirements of the brain, may counteract this O_2 imbalance until blood flow in vasospastic vessels is restored by a successful endovascular intervention. Respiratory arrest with vertebral artery injections and seizures are described during spasmolysis. Furthermore, in a patient with CVS, most often being confused and agitated, anaesthesia ensures that the patient does not move during the intervention. As a side effect of papaverine, with its vasodilatatory capacity, systemic hypotension may occur, which has to be treated aggressively with volume expansion, dobutamine and norepinephrine. According to our experience, maintenance of induced hypertension, high cardiac output and hypervolemia during and after the procedure are most important issues, in order to increase the efficiency of the endovascular intervention and to reduce the reoccurrence rate of CVS. Development of elevated ICP is described after papaverine instillation in patients with bilateral diffuse vasospasm [3]. Therefore brain edema and elevated ICP are considered as contraindications for papaverine treatment and ICP monitoring is recommended in patients at risk.

Other vasodilators for intra-arterial and systemic treatment are under examination. Arakawa *et al.* published a small case series treated with the cardiac inotrope milrinone, a phosphodiesterase inhibitor like papaverine [4]. Its use is limited by the side effect of severe systemic hypotension. In our clinical practice, we apply low dosages of milrinone through continuous intravenous infusion to augment hyperdynamic therapy by enhancing cardiac performance if cardiac output is diminished because of high systemic vascular arterial resistance in combination with catecholamines. Fasudil hydrochloride, a enzyme protein kinase C inhibitor, intraarterialy infused, has been shown to reduce symptomatic CVS [55]. Its use, at present, is limited to Japan.

Barbiturate coma, hypothermia

Animal and clinical studies have shown that hypothermia has the potential to limit the extent of secondary brain damage [7, 11, 39, 47]. Several positive effects relevant in SAH have been demonstrated, e.g. temperature dependent reduction of cerebral oxygen metabolism [20, 34], stabilization of the blood-brain barrier

[56], decreased release of neurotransmitters [26], attenuation of free radical production, and decreased postischemic edema formation [47].

Numerous neuroprotective mechanisms, partly similar to hypothermia, could be shown for barbiturates [9, 62]. The application of thiopental boli with temporary clipping is wide spread in neuroanesthesia [53]. In 1980 Kassell applied barbiturate coma in 12 patients with refractory CVS [27]. With limited resources in intensive care the results were disappointing. 11 patients died from uncontrollable intracranial hypertension, cardiac arrythmias or infections. In three patients, treated with combined barbiturate coma and hypothermia severe acid base and electrolyte disturbances occurred. With improved supportive intensive care, Finfer *et al.* in 1999 published the results of 11 patients with angioplasty resistant CVS treated with barbiturate coma, 10 of them surviving with good functional outcome [18]. Hypothermia has been applied with temporary clipping during aneurysm surgery [21] and in patients after severe SAH, brain edema and elevated ICP [19, 44]. Only a small case series treated with hypothermia (32 °C–34 °C) because of refractory CVS is described by Nagao [45]. Among eight patients five survived with good functional outcome and two patients survived moderately disabled.

In the present series 26 patients were treated with barbiturate coma and/or hypothermia. 13 patients had contraindications for endovascular treatment (space-occupying brain edema or ischemic infarctions) and 13 patients suffered from resistant or reoccurring CVS after repetitive spasmolysis. From these 23 patients, with most resistant CVS, 50% survived with a good functional outcome.

However, one has to be aware of the potentially hazardous side effects of hypothermia and barbiturate coma. From 21 patients with high grade SAH and refractory intracranial hypertension, treated with long term hypothermia/barbiturate coma up to 16 days, all patients developed severe infections [19]. It is known from animal and clinical studies, that hypothermia, as well as barbiturates, predispose to bacterial infections [8, 58]. Biggar *et al.* showed in pigs, that hypothermia impairs neutrophil circulation and their release from the bone marrow. Hypothermia may also cause bone marrow suppression and platelet sequestration in the spleen [41, 48, 54]. In addition, it has been shown in trauma patients, that leukocytes and neutrophils are reversibly and significantly decreased in thiopental coma [8]. Furthermore, patients treated with long term hypothermia develop thrombocytopenia, defects in the platelet's ability to produce thromboxane B2 with possible bleeding complications [59]. Platelets have to transfused early and amply. Because of acid base and electrolyte disturbances (hypernatriemia and hyperkaliemia) as well as negative cardiac inotropic effects barbiturate coma have to be discontinued often. In fact, without hypothermia/barbiturate coma patients with refractory CVS might exhibit poor outcome and death. In this context, the application of aggressive treatment regimen with severe side effects and elaborate intensive care treatment are justifiable.

Conclusions

With a structured step by step treatment protocol for symptomatic CVS good functional outcome can be reached in 66% of the patients. Dorsch in a recent review concluded that with CVS as a multifactorial problem, it is likely that detection, prevention and treatment will continue to require application along several different lines [14]. In spite of the lack of definite evidence of large clinical trials, the devastating outcome of natural history of symptomatic CVS demands an aggressive CVS treatment in a structured, practically oriented multimodal treatment protocol. This policy requires close and fast multidisciplinary collaboration between neurosurgeons, neuroradiologists, competent in endovascular interventions, and specialists for neurointensive care.

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Management of unruptured intracranial aneurysms