The development of delayed ischemic neurological deficits (DIND) resulting from posthemorrhagic arterial narrowing is responsible for a considerable percentage of the morbidity and mortality associated with aneurysmal subarachnoid hemorrhage (SAH).\textsuperscript{1,16,44} Despite extensive experimental and clinical investigation, the etiology and pathophysiology of cerebral vasospasm (CVS) are only poorly understood. However, a number of previous studies have shown that high concentrations of vasoactive compounds, acting as highly potent spasmodic metabolites, can be identified in the cerebrospinal fluid (CSF) of patients with SAH,\textsuperscript{9,12,31,32,43} and that the concentration of these substances in the CSF correlates closely to the clinical presentation of the patients,\textsuperscript{13} the volume of hematoma,\textsuperscript{7,45} and the incidence of vasospasm.\textsuperscript{16,31,44}

A novel family of extremely potent, endothelium-derived vasoconstrictor peptides, named endothelins (ETs), have been isolated, originally from porcine endothelial cells.\textsuperscript{15,41} These peptides were also found to be expressed by a number of cell types in the brain, including neurons,\textsuperscript{10,18,37} glial cells,\textsuperscript{5,21} choroid plexus cells,\textsuperscript{4} and macrophages invading the brain under pathophysiological conditions.\textsuperscript{4} When applied to the adventitial side of blood vessels, ETs exert an extremely potent and long-lasting constrictive effect on cerebral vessels.\textsuperscript{26,33} Recently, Clozel and Watanabe\textsuperscript{3} showed that BQ123, an antagonist to the endothelin ET\textsubscript{A} receptors, when administered locally prevents early CVS in a rat model of acute SAH, and Nirei, \textit{et al}.\textsuperscript{27} provided evidence that the ET\textsubscript{A} receptor antagonist FR 139317 ameliorates CVS in a two-hemorrhage canine model of SAH. These observations have prompted the hypothesis that ETs might play a role in SAH-associated CVS. Both ET-1 and ET-3 are present in human CSF and plasma.

Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage

Correlation with cerebral vasospasm, delayed ischemic neurological deficits, and volume of hematoma

\textbf{Volker Seifert, M.D., Ph.D., Bernd-Michael Löffler, M.D., Ph.D., Michael Zimmermann, M.D., Sébastien Roux, M.D., and Dietmar Stolke, M.D., Ph.D.}

Neurosurgical Clinic, University of Essen, Essen, Germany; Pharma Division, Preclinical Research, F. Hoffmann-La Roche Ltd., Basel, Switzerland

\begin{itemize}
  \item Plasma and cerebrospinal fluid (CSF) concentrations of endothelin (ET)-1, ET-3, and big ET-1 in patients with aneurysmal rupture were measured serially for 2 weeks after the onset of aneurysmal subarachnoid hemorrhage (SAH) and compared with levels of ETs in patients without SAH and the plasma concentrations of ETs in normal volunteers. Big ET-1 was the predominant peptide present in the CSF of SAH patients. The CSF concentrations of big ET-1, ET-1, and ET-3 were significantly higher in older patients than in younger patients. In SAH patients with cerebral vasospasm (CVS) documented by transcranial Doppler sonography and clinical signs, postoperative concentrations of ETs in the CSF remained at or were increased above levels measured before surgery. In SAH patients without CVS, the concentrations of ETs in the CSF decreased with time, whereas the time course of CVS coincided with the increase in concentrations of big ET-1 and ET-1. The temporal dependence of concentrations of big ET-1 and ET-1 in SAH patients with and without CVS were significantly different. The volume of hematoma in the basal cisternas as detected by computerized tomography was predictive of the concentrations of ETs in the CSF. Plasma concentrations of ETs were not correlated with CVS. The possible role of ETs in the pathogenesis of CVS associated with SAH and the controversial data reported to date are discussed.
\end{itemize}

\textbf{Key Words} • endothelin • endothelial cells • subarachnoid hemorrhage • cerebral vasospasm • delayed ischemic neurological deficits
sured ET concentrations only in plasma or CSF\textsuperscript{25,35} or have determined ETs only in a single patient.\textsuperscript{26} In this study, big ET-1, ET-1, and ET-3 were measured serially for the first time in the plasma and CSF of SAH and non-SAH patients and in the plasma of healthy volunteers. This study was designed to elucidate the potential role of ETs in the pathogenesis of SAH-associated CVS and DIND, and their effect on the volume of hematoma.

**Clinical Material and Methods**

**Study Groups**

**Patients With SAH.** Twenty-two consecutive patients admitted within 24 hours after their initial SAH were included in this study. There were nine women and 13 men, with a mean age of 41 years (range 17 to 76 years). The SAH was verified by cranial computerized tomography (CT); all patients underwent cerebral angiography. In all cases, at least one aneurysm was revealed as the cause of the bleeding. All patients underwent neurosurgical intervention with microsurgical aneurysm clipping within 4 days after admission, and an intraventricular catheter was placed either after admission or at the time of craniotomy. No patient exhibited signs of severe cardiac insufficiency, cardiac ischemia, concomitant infection, or acute or chronic renal failure.

Neurological condition on admission was evaluated using the Hunt and Hess\textsuperscript{13} grading scale, and the CT findings of degree of SAH were categorized according to Fisher, \textit{et al}.\textsuperscript{7} Flow velocities in the cerebral basal arteries were measured daily by means of transcranial Doppler sonography (TCD). The mean cerebral blood velocity (CBV), as determined by TCD, was graded according to the following scale: Grade 1, CBV 80 cm/sec or less; Grade 2, CBV 81 to 120 cm/sec; Grade 3, CBV 121 to 160 cm/sec; and Grade 4, CBV 161 cm/sec or more. Grade 3 was defined as moderate vasospasm and Grade 4 as severe vasospasm. Daily neurological evaluation was performed and categorized in all patients using the Glasgow Coma Scale (GCS).\textsuperscript{19} The occurrence of CVS and resulting DIND was diagnosed by the TCD characteristics described above and from clinical signs of postoperative neurological worsening after a CT scan had excluded other possible causes of deterioration such as edema, hemorrhage, and/or ventricular enlargement.

**Patients Without SAH.** Concentrations of ETs in the plasma and CSF in the absence of SAH were determined in 15 consecutive patients with diagnosed spinal stenosis or lumbar disc herniation who underwent lumbar myelography. There were four women and 11 men, with a mean age of 58 years (range 26 to 73 years).

**Normal Volunteers.** Concentrations of ETs in the plasma of a second control group were determined in a group of 18 apparently healthy individuals. There were eight women and 10 men, with a mean age of 42 years (range 29 to 60 years).

**Sample Collection**

In all patients with SAH, a ventricular catheter was placed, and 3 to 5 ml CSF was drawn into tubes containing ethylenediaminetetraacetic acid (EDTA) from the catheter, which was usually left in place during the patients’ stay on the intensive care unit. Thereafter, the CSF was collected by serial lumbar puncture. Plasma samples (5 to 8 ml in tubes containing EDTA) were collected from SAH patients via intravenous lines. Plasma samples (5 to 10 ml, in tubes containing EDTA) were drawn from the cubital vein of non-SAH patients and normal volunteers. In non-SAH patients, 3 to 5 ml CSF was collected into EDTA tubes via lumbar puncture. All samples were stored at ~70°C until assayed.

**Sample Extraction and Radioimmunoassay**

Big ET-1, ET-1, and ET-3 were measured as described elsewhere.\textsuperscript{19,20} Briefly, plasma or CSF (500 μl in triplicate samples) was extracted on commercial cartridges\textsuperscript{19} after conditioning with 3.0 ml methanol followed by 3.0 ml of 0.2 mol phosphate/citric acid, pH 7.0. The cartridges were washed with 3.0 ml water and eluted with 2.0 ml methanol/water (90:10, v/v). The eluates were dried in an evaporator\textsuperscript{19} and reconstituted in an assay buffer containing 20 mM borate HCl, 0.1% (w/v) bovine serum albumin, and 0.1% (w/v) NaNO\textsubscript{3}, pH 7.4. Radioimmunoassays were performed as previously described.\textsuperscript{20} Measurement of ET-1 was performed with the specific rabbit anti-ET-1 antisera RAS 6901 at a final dilution of 1:15000, ET-3 with the specific rabbit anti-ET-3 antisera RAS 6911\textsuperscript{19} at a final dilution of 1:15000, and big ET-1 with the specific rabbit anti-big–ET-1 antisier RAS 5313.\textsuperscript{19} Free and bound tracer was separated by adsorption at 25°C for 15 minutes on 250 μl magnetobeads\textsuperscript{19} supplemented with 0.1% (w/v) Tween-20. Standard curves were constructed by serial dilution of ET (0.1 to 300 pg/tube for ET-1 and ET-3, and 1 to 600 pg/tube for big ET-1 in triplicate tests). Data were transformed to logit/log curves. The median inhibiting concentrations for ET-1, ET-3, and big ET-1 were 20.8 ± 1.3, 13.7 ± 0.8, and 59.3 ± 2.3 pg/ml, respectively, in six samples. The regression coefficients of standard curves (r\textsuperscript{2}) were 0.998 or greater, and the inter- and intraassay variability was less than 10%. The extraction recovery as measured in plasma was 95% or greater for ET-1 and big ET-1 and 90% or greater for ET-3. The detection limit (at B/B\textsubscript{0} = 0.95) was 0.25 pg/tube for ET-1, 3.0 pg/tube for big ET-1, and 0.25 pg/tube for ET-3, where B/B\textsubscript{0} represented the maximum binding of the respective tracer by the antisier corrected for the non-specific binding.

**Data Calculation and Statistical Analysis**

The ET immunoreactivity of patients with and without SAH, and of normal volunteers was expressed as picograms of ET per milliliter of plasma or CSF. Data were not corrected for extraction recovery. Blood and CSF samples from SAH patients were taken up to 3 days before...
and 2 weeks after surgery; however, only ET measurements taken before surgery and in the 1st week after surgery were used for this study. To reduce the number of missing individual values and the number of time periods, data were grouped according to the day of measurement relative to the day of surgery: −3 to −1 (days before surgery), 0 (day of surgery), and 1 to 3 and 4 to 7 (days after surgery). An analysis of variance was performed for each parameter using the following factors: CVS group (SAH with and without CVS); day of measurement; the interaction between the two, and patients nested in CVS. The logarithms of the concentrations were used. While the CVS group factor describes the overall concentration-to-time change, the interaction of these factors describes differences in concentration changes over time between the two CVS groups. Because each patient contributed to several measurement day groups, the patient factor was used as a random factor. This random factor was taken into account for the calculation of the F tests. The dependency of the concentrations of ETs on the volume of hematoma was analyzed by the Spearman rank-order correlation test.

For the graphic representation, the individual arithmetic means were calculated per measurement day group. Based on this, the overall mean for Day −3 to −1 groups was calculated for both CVS groups. The individual means were divided by the overall means to standardize the mean values in the Day −3 to −1 groups to 100%. The means and their standard errors of these normalized values are given in Figs. 1 to 4.

Results

The clinical presentation of the patients with SAH is summarized in Table 1. The mean day of surgical intervention was Day 3 (range Days 1 to 4) after admission. Of the 22 patients in this group, 14 (63.6%) developed increased CBV indicative of CVS, as detected by TCD, and 10 (45.5%) showed clinical signs of vasospasm-induced DIND. Only one (12.5%) of the eight patients without CVS but nine (64.3%) of the 14 patients with CVS developed DIND. Based on Spearman correlation coefficients, an association was shown of DIND with CVS (p < 0.003) and with the Fisher hematoma volume grade (p < 0.05). The mean day on which CVS appeared, as detected by TCD, was Day 2 (range Days 0 to 5) after surgery (Table 1). The TCD profiles of SAH patients with and without CVS are given in Fig. 1 left. The GCS profiles of both groups were similar (Fig. 1 right).

Basal Plasma ET Concentrations

The mean plasma concentrations of ETs are summarized in Table 2. The plasma concentrations (means and ranges) of big ET-1 and ET-3 in normal volunteers and non-SAH patients were similar, whereas plasma ET-1 levels were higher in the non-SAH patients than in the normal volunteers (p < 0.001). Concentrations (on a molar base) of big ET-1 in plasma of normal volunteers and non-SAH patients were 45% and 58% lower, respectively, than the ET-1 concentrations (p < 0.001). In contrast, concentrations of big ET-1 in the plasma of SAH patients with and without CVS were similar, but 44% higher than the respective ET-1 concentrations. Thus, the concentrations of big ET-1 in the plasma of patients with or without CVS rose 2.4- to 3.7-fold as compared to the concentrations in normal volunteers or non-SAH patients (p < 0.001 for both). The mean plasma concentrations of ET-1 in SAH patients with or without CVS were 1.4-fold (p < 0.001) and 1.3-fold (p < 0.05) higher than those of normal volunteers.

Correlation Between Age and ET Concentrations

The mean concentrations of ET-1 and ET-3 in the plasma and CSF of SAH patients at Days −3 to −1 and those of non-SAH patients were not significantly different from those measured in the non-SAH patients, but were 1.4-fold (p < 0.001) and 1.3-fold (p < 0.05) higher than those of normal volunteers.
mean concentrations of ETs measured in the CSF of SAH patients at Days -3 to -1 showed a significant age dependency (p < 0.05 for each). The concentrations of ETs in CSF seemed to increase substantially in patients above 50 years of age. Because the age groups were unmatched, the non-SAH patients (mean age 58 years) and the SAH patients without CVS (mean age 52 years) represented older patients with higher concentrations of ETs in the CSF, whereas the SAH patients with CVS (mean age 38 years) showed lower concentrations of ETs in the CSF at Days -3 to -1. No significant age dependency of the concentrations of ETs before surgery was observed in plasma (Fig. 2).

**Correlation Between Vasospasm and ET Concentrations**

The time courses of the concentrations of ETs in SAH patients with and without CVS are summarized in Fig. 3. Concentrations of ETs in the CSF of SAH patients with CVS showed a different time course from those without CVS. The levels of big ET-1 over time in the presence and absence of CVS were significantly different (p < 0.001, Fig. 3 upper): whereas big ET-1 remained at high concentrations over the observation period in the presence of CVS, it declined with time in the absence of CVS. The presence of CVS was predictive of high concentrations of big ET-1 (p < 0.001). Cerebral vasospasm was also predictive for high concentrations of ET-1 in the CSF (p < 0.05, Fig. 3 center), but the effect on concentrations of ET-3 was only borderline (p < 0.058, Fig. 3 lower). None of the ET levels measured in plasma showed a significant correlation with CVS.

**Correlation Between ET Levels and Fisher Classification**

The classification of hematoma volume according to the grading of Fisher, et al.,7 showed that concentrations of ET-1 and ET-3 in the CSF increased with the Fisher
Endothelin concentrations in patients with aneurysmal SAH

The current concept of the complex etiology of CVS is based on the presumption of a multifactorial origin, including the liberation of spasmodic metabolites during posthemorrhagic clot lysis in the basal cisterns and the impairment of cerebral vasodilatation related to endothelial dysfunction and posthemorrhagic structural changes in the arterial wall.1,9,12,22,31,32,44 This study, to the best of our knowledge, provides for the first time parallel measurements of big ET-1, ET-1, and ET-3 in the CSF and plasma and demonstrates the correlation of temporal endothelin changes to the occurrence of vasospasm, DIND, and the Fisher grade of hematoma volume.

Our data demonstrate that concentrations of ET-1 in the CSF increase over time in SAH patients with CVS and that this increase coincides with the appearance of CVS as documented by TCD and clinical symptoms. Our findings are in agreement with those of other authors6,35,36 who reported elevated ET-1 levels in the CSF of patients with CVS related to SAH. As Ehrenreich, et al.,6 demonstrated, the present study also showed distinct temporal patterns of ET levels in the CSF of individual patients. We therefore clustered ET data from single days into groups of days. This interindividual variability of ET profiles in CSF may explain why some authors who analyzed only one or a few samples per patient could not confirm increased concentrations of ET-1 in SAH.8,11,17,36 In addition, we provide evidence for the first time that the analysis of ET concentrations in CSF is influenced by patient age. Despite the effect of different antisera and extraction techniques30 used to measure concentrations of ETs in different groups, the age dependency of ET levels may explain the reported differences in these concentrations.

In agreement with Suzuki, et al.,36 we also observed increased plasma concentrations of ET-1 in SAH patients compared to those of normal volunteers. In contrast to these authors, the increase was much lower in our study owing to the fact that ET-1 was much higher in the plasma of the normal volunteers than previously reported and, therefore, no significant difference in SAH patients with and without CVS was observed. Furthermore, this difference in concentration was even lower than in non-SAH patients. It is noteworthy that a younger group of normal individuals (age 25 to 35 years) was used as a control in the study by Suzuki, et al., as compared both to our normal individuals (mean age 42 years) and to our non-SAH patients (mean age 58 years). Thus, differences in plasma ET-1 concentrations observed in this study and that reported by Suzuki, et al., may be due to an age-dependent increase in basal ET-1 plasma concentrations.

Whereas concentrations of big ET-1 in SAH associated with CVS remained at the high levels identified before surgical intervention, these levels substantially decreased over time in the absence of CVS. However, it remains difficult to compare absolute concentrations of big ET-1 determined in SAH with normal basal concentrations because of the lack of age-matched normal control values, and we await further studies. Interestingly, concentrations of big ET-1 in the CSF of SAH and non-SAH patients was several-fold higher than in plasma.

Our data are in agreement with those reported previously,11 in which concentrations of big ET-1 in the CSF of SAH patients with CVS were only slightly increased over levels measured before surgery. In contrast to the report of Hamann, et al.,11 in our study SAH patients with and without CVS showed significantly different temporal development of concentrations of big ET-1 in CSF. The maintenance of high concentrations of big ET-1 in CSF in the presence of CVS could be indicative of an increased production of ET-1 under this pathophysiological condition. This assumption would be in agreement with our finding of increased ET-1 concentrations in the CSF of patients with CVS. The concentrations of big ET-1 determined in the present study are different from those reported by Hamann, et al. This difference may be due to the use of different antisera in the two studies: whereas we used an antiserum that is highly specific for mature big ET-1,19 Hamann, et al., used an antiserum that recognized the C-terminal peptide 22–38 of big ET-1.30 Therefore, the latter antiserum might underestimate big ET-1 because of cross reaction with breakdown products.

Fig. 2. Graphs showing the age dependency of preoperative concentrations of endothelin (ET) in the plasma and cerebrospinal fluid (CSF) of subarachnoid hemorrhage patients. The mean preoperative concentrations of ETs measured in younger patients (open bars, mean age 36.6 ± 2.7 years) and older patients (hatched bars, mean age 59.4 ± 4.5 years) are plotted. The groups do not differ significantly with regard to average grading on the Hess and Hunt13 and Fisher, et al., grading scales. * = p < 0.05; ** = p < 0.005; *** = p < 0.001; n = number of patients.
The ET-3 levels in CSF were also slightly increased in SAH patients with CVS as compared to those without CVS but, in contrast to Kraus, et al.,17 in our study this increase was of only borderline significance. This discrepancy may be due to differences in the detection techniques used (CSF was extracted in our study) as well as to the different time points evaluated. Interestingly, we could demonstrate that the concentrations of ET-1 and ET-3 in CSF measured within the first 3 days after the occurrence of SAH are significantly correlated with the volume of hematoma.

Our results, in combination with those of other investigators,6,17,35,36 contribute further to the hypothesis concerning the role of ETs in the CSF compartment as a key factor in the pathophysiology of CVS. However, the question remains: are ETs mediators or markers of the disease? A number of points favor a role for ETs as mediators of CVS, namely: 1) ETs are extremely potent constrictors of human cerebral vessels;23,28 2) the ET_A receptor antagonist FR 139317 has been able to reduce CVS in a two-hemorrhage model of SAH;27 3) ETs are able to elicit chronic CVS upon application into the cisterna magna of dogs;2,14,26 4) threshold concentrations of ET-1 potentiate contractions to norepinephrine and serotonin in human arteries;42 5) thrombin and oxyhemoglobin, which are present in high concentrations in SAH,9,22,25,38 are known to induce ET-1 release;29 6) as substantiated for the first time in the present report, the temporal increase of ET-1 in CSF in the presence of CVS parallels that of CBV as measured by TCD; 7) significant increases of ET-1 in the CSF of SAH with CVS coincides with the appearance of clinically relevant vasospasm; and 8) big ET-1, the precursor of mature ET-1, in the CSF of SAH patients with CVS remained at high levels, whereas it decreased with time in

Fig. 3. Graphs showing the temporal changes in concentrations of endothelin (ET) in the cerebrospinal fluid (CSF) and plasma of patients with subarachnoid hemorrhage with (square) and without (circles) cerebral vasospasm. Concentrations of ET are expressed as a percentage of the basal concentrations measured before surgery and are grouped according to the day of measurement relative to the day of surgery. Normalization was performed, as described in detail in Clinical Material and Methods. Data are presented as means ± standard error of the means. P values given in the graphs for individual day groups were calculated by the two-tailed Student t-test for unpaired samples (95% interval of confidence). Numbers presented in the graphs = numbers of patients evaluated.
patients without CVS. It should be mentioned that after intracisternal injection, big ET-1 has been shown to increase cisternal ET-1 concentrations and induce CVS.14

According to our results and those of Hamann, et al.,11 and Fujimori, et al.,3 plasma ETs seem not to be involved in the pathogenesis of SAH-related CVS. These findings support the view that ETs act as paracrine rather than as endocrine factors. Whether the increased concentrations of ETs measured in the CSF are of pathophysiological relevance or whether they just reflect even higher increases of ET concentrations in the altered tissues (that is, in the spastic vessel wall) are questions that need to be investigated further.

In conclusion, our data strongly support an involvement of ETs in SAH-related CVS. In concert with a number of other vasoactive factors, ETs may substantially contribute to the disturbed equilibrium of vasoconstriction and vasorelaxation in this pathophysiological situation. Plasma ETs seem not to contribute to the development of CVS; however, definite proof of the role of ETs in SAH-related CVS awaits the use of ET antagonists in man.

Acknowledgments

The authors thank Dr. Luder Banken for help with the statistical analyses and Jean-Paule Maire for excellent technical assistance.

References


Manuscript received October 20, 1993. Accepted in final form May 5, 1994.
Address reprint requests to: Volker Seifert, M.D., Ph.D., Neurosurgical Clinic, University of Essen, Hüfelandstrasse 55, Essen 45122, Germany.

V. Seifert, et al.
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*H&H = clinical grading score according to Hunt and Hess\textsuperscript{13} scale; DIND = delayed ischemic neurological deficits; MCA = middle cerebral artery; ACoA = anterior communicating artery; ICA = internal carotid artery; BA = basilar artery.

\textsuperscript{†}Volume of hematoma graded according to Fisher, \textit{et al.},\textsuperscript{7} based on the computerized tomography appearance.

\textsuperscript{‡}Transcranial Doppler sonography (TCD) score: 1 = cerebral blood velocity (CBV) \(\leq 80\) cm/sec; 2 = CBV 81 to 120 cm/sec; 3 (defined as moderate CBV) = CBV 121 to 160 cm/sec; 4 (defined as severe CBV) = CBV \(\geq 161\) cm/sec.

\textsuperscript{§}Day of appearance of cerebral vasospasm (CVS) after surgery, according to results of transcranial Doppler sonography. Day 0 = day of surgery; — = no CVS.
### TABLE 2

**Basal plasma concentrations of endothelin***

<table>
<thead>
<tr>
<th>Study Group</th>
<th>No. of Cases</th>
<th>Big ET-1 (pg/ml) CSF</th>
<th>Big ET-1 (pg/ml) Plasma</th>
<th>ET-1 (pg/ml) CSF</th>
<th>ET-1 (pg/ml) Plasma</th>
<th>ET-3 (pg/ml) CSF</th>
<th>ET-3 (pg/ml) Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>18</td>
<td>12.4 ± 0.9 (5.6–20.1)</td>
<td>13.2 ± 0.4 (9.7–18.4)</td>
<td>13.5 ± 0.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>non-SAH</td>
<td>15</td>
<td>105.4 ± 9.3 (26.1–150)</td>
<td>13.6 ± 1.2 (8.6–19.6)</td>
<td>15.9 ± 2.5</td>
<td>18.7 ± 1.1</td>
<td>18.3 ± 0.9</td>
<td>11.5 ± 1.0</td>
</tr>
<tr>
<td>SAH</td>
<td>20</td>
<td>85.6 ± 9.7 (30.3–201)</td>
<td>36.4 ± 3.2 (18.7–72.0)</td>
<td>9.7 ± 7.5</td>
<td>18.1 ± 1.3</td>
<td>18.7 ± 2.9</td>
<td>13.5 ± 0.9</td>
</tr>
<tr>
<td>SAH-CVS</td>
<td>6</td>
<td>121.2 ± 24.3 (11.0–32.2)</td>
<td>46.2 ± 9.1 (6.8–32.4)</td>
<td>6.6 ± 9.0</td>
<td>18.6 ± 1.5</td>
<td>27.7 ± 8.4</td>
<td>11.9 ± 3.0</td>
</tr>
<tr>
<td>SAH+CVS</td>
<td>14</td>
<td>70.2 ± 7.6 (32.4 ± 2.4)</td>
<td>32.4 ± 2.4 (18.6 ± 1.5)</td>
<td></td>
<td></td>
<td>13.6 ± 1.4</td>
<td>13.1 ± 0.6</td>
</tr>
</tbody>
</table>

*Concentrations of big endothelin (ET)-1, ET-1, and ET-3 measured in the plasma of normal volunteers and plasma and cerebrospinal fluid (CSF) of patients with and without subarachnoid hemorrhage (SAH), as described in detail in Clinical Material and Methods. Concentrations of ET in SAH patients are presented as the mean basal concentrations at Days −3 to −1, subdivided into values with and without cerebral vasospasm (CVS). Two patients without CVS have been excluded because surgery was performed on the day of admittance. The mean age of normal volunteers was 42.3 ± 4.1 years, of non-SAH patients 57.9 ± 3.1 years, of SAH patients with CVS 38.4 ± 2.8 years, and of SAH patients without CVS 51.5 ± 7.4 years. Data are presented as the means ± standard error of the means. For Cases 8 and 21 (see also Table 1), no preoperative concentrations of ET’s could be measured.