Sympathetic Nervous System Activity in Patients with Subarachnoid Hemorrhage


SUMMARY  In patients with subarachnoid hemorrhage there were increased concentrations of plasma epinephrine and norepinephrine when compared with those concentrations in a group of patients admitted to hospital with other illness.

Reassessment after a variable period showed that in patients whose eventual clinical result was poor the plasma epinephrine and norepinephrine concentrations increased further while in those with a good result those concentrations showed a decline. No such changes were evident in plasma dopamine-β-hydroxylase activities which were within normal range.

In a sub-group of patients who had neurosurgery after admission for clipping an aneurysm, the post-operative changes of plasma epinephrine and norepinephrine concentrations were related to the clinical condition of the patients.

An increase in sympathetic nervous system and adrenal medullary activity results in increases in plasma norepinephrine and epinephrine concentrations. Similarly, changes in plasma dopamine-β-hydroxylase (DβH) activity have been suggested as a useful index of sympathetic nervous system activity.

The purpose of this study was 3-fold. Firstly, to record plasma epinephrine and norepinephrine concentrations and DβH activities in patients with SAH and to compare the values with those in a group of patients admitted with other illnesses. Secondly, to measure the changes in epinephrine and norepinephrine concentrations and DβH activities in patients with SAH who had neurosurgery (clipping of the aneurysm) and to compare the values with those in a group of patients who had other neurosurgical operations. Thirdly, to determine the significance of the increased plasma catecholamine concentrations in relation to the severity and outcome of SAH.

Patients

Patients with Subarachnoid Hemorrhage

Twenty-one patients, who had been referred to the neurosurgical department, were investigated. All had had a SAH confirmed by obtaining blood-stained cerebrospinal fluid on lumbar puncture and the subsequent radiographic demonstration of one or more intracranial aneurysms. On initial assessment all were considered suitable for eventual neurosurgery (Botterell grade 1, 2 or 3). Five of the 21 patients bled again one or more times from the aneurysm while in hospital awaiting neurosurgery; as a result they became more disorientated and drowsy and were returned to the referring hospital without neurosurgical intervention. The other 16 had a craniotomy and clipping of a ruptured intracranial aneurysm. Of the 16, 5 patients received β-blockers might have altered their plasma catecholamine concentrations. Within 24 hours of admission informed consent was obtained from the patients and a venous blood sample was collected for plasma epinephrine, norepinephrine and DβH measurements after 30 min of supine bed rest. In 14 patients a further sample (re-evaluation sample) was collected 2–12 hours either before they underwent neurosurgery or when
they were deferred as unfit for surgery due to poor neurosurgical condition. The clinical details of the patients are given in table 1.

**Anesthesia, Postoperative Monitoring and Drug Therapy**

For those patients who had neurosurgery, the anesthetic procedure was similar in each; induction of anesthesia was with thiopentone and pancuronium, the trachea was intubated and automatic ventilation of the lungs carried out with a mixture of oxygen 30% and nitrous oxide 70%. Anesthesia was maintained with increments of pancuronium and analgesic supplements of fentanyl. Hypotension during the operation was reestablished before the patient was transferred to the intensive therapy unit for postoperative monitoring. For each patient the surgical procedure was craniotomy and obliteration of the ruptured aneurysm using an occlusive metal clip across the aneurysm neck. After 32 to 64 hours in the unit the patients were transferred to the neurosurgical ward, their clinical condition having been assessed as suitable by the attending neurosurgeon.

In the immediate postoperative period the following variables were monitored continuously: systolic and diastolic blood pressures using an indwelling arterial cannula, the pressure being recorded by an external transducer and connected to a similar pressure transducer. Pressure measurements were taken with reference to the level of the external auditory meatus.

When systolic arterial pressure exceeded 200 mm Hg it was reduced using 10 mg hydralazine intravenously. When intracranial pressure exceeded 30 mm Hg it was reduced by withdrawing cerebrospinal fluid via the ventricular catheter or by giving an intravenous infusion of mannitol (20%). All patients received diphenylhydantoin intramuscularly every 8 hours as an anticonvulsant and ampicillin intravenously every 6 hours as prophylaxis against infection.

**Postoperative Neuroradiological Assessment**

In the postoperative period all patients had carotid angiography to determine the presence or absence of radiologically demonstrable vasospasm. When the spasm was confined to one intracranial vessel close to the original site of
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TABLE 2 Clinical Details of Control Neurosurgery Group of Patients

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Preoperative blood pressure</th>
<th>Type of surgery</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 66</td>
<td>F</td>
<td>160/90</td>
<td>Removal of frontal meningioma</td>
<td>No postoperative complications; clinical outcome good.</td>
</tr>
<tr>
<td>2 34</td>
<td>F</td>
<td>130/70</td>
<td>Removal of posterior fossa meningioma</td>
<td>No postoperative problems except occasional episodes of convulsions. Controlled with diphenylhydantoin. Clinical outcome good.</td>
</tr>
<tr>
<td>3 41</td>
<td>F</td>
<td>120/80</td>
<td>Elective clipping of a L. MCA aneurysm</td>
<td>Previous history of SAH and clipping of aneurysm 4 months ago. Clinical outcome after neurosurgery good.</td>
</tr>
<tr>
<td>4 56</td>
<td>M</td>
<td>130/90</td>
<td>Elective clipping of a R. PCA aneurysm</td>
<td>Previous history of SAH and clipping of aneurysm 18 months ago. Clinical outcome after neurosurgery good.</td>
</tr>
</tbody>
</table>

MCA = middle cerebral artery; PCA = posterior cerebral artery; SAH = subarachnoid hemorrhage.

the ruptured aneurysm it was called local vasospasm. When the vasospasm involved more than 1 intracranial vessel it was termed generalized vasospasm.

Postoperative Assessment of Patients

Short-term Postoperative Assessment

This was based on the presence or absence of postoperative intracranial vasospasm and the postoperative level of consciousness during the first week after neurosurgery.

Patients Without Complications

These patients did not develop postoperative intracranial vasospasm and the level of consciousness was normal.

Patients With Complications

After an initial period, when their level of consciousness was normal, these patients became drowsy, sometimes developed neurological signs and angiographic evidence of local or generalized vasospasm developed. Clinical improvement began after about 48 hours and continued steadily.

Patients Who Died

These patients died within 60 hours of completion of the operation. All had evidence of severe generalized cerebral vasospasm.

Long-term Postoperative Assessment

Six weeks after neurosurgery the clinical state of all the 21 patients with SAH was reassessed and patients were divided into 2 groups.

Good Result Group

This group consisted of patients whose clinical result either enabled the patient to resume normal daily activity or to become independent, but not go to work because of a neurological deficit.

Poor Result Group

This group consisted of patients whose clinical state was such that they still needed help in daily life or patients who had died after surgery. Five patients for whom neurosurgery was deferred because of a deteriorating neurological state were included in this group.

Control Groups

Control Group Patients Admitted to Hospital Other than for Neurosurgery

This group consisted of 7 patients who were admitted with one of the following acute clinical problems: (1) lobar pneumonia, (2) acute appendicitis (3 patients), (3) urinary tract infection and cystitis, (4) systemic lupus erythematosus accompanied by fever, and (5) pleurisy. A venous blood sample was collected from those patients within 2 hours of admission and on the fifth day after admission when their acute symptoms were subsiding (re-evaluation sample).

Control Neurosurgery Patients

Two patients who had elective clipping of intracranial aneurysms without a preceding SAH and 2 patients who had removal of intracranial meningiomas formed this group. The relevant clinical details are given in table 2. None of the patients had any preoperative complicating disease and preoperative angiograms in the 2 patients admitted for aneurysm clipping showed no spasm. The anesthetic procedure was the same as for the patients with SAH who had neurosurgery. In the postoperative period the same variables were monitored as in the patients with SAH. None of the patients required antihypertensive drug therapy in the postoperative period and the intracranial pressure did not exceed 30 mm Hg. The clinical outcome of these patients was good.

Methods

In patients with SAH and in control neurosurgery patients, preoperative venous blood samples were collected just before premedication and the postoperative blood samples were collected every 6 hours beginning immediately after surgery. Plasma epinephrine and norepinephrine concentrations were measured by a previously described radioenzymatic method and D/3H activities by a photometric method. The data were analysed using Student’s 2-tailed paired or unpaired t-test. All results are stated as mean ± SEM.
TABLE 3  Plasma Epinephrine and Norepinephrine Concentrations in Subarachnoid Hemorrhage and Control Group of Patients at Admission and on Re-evaluation (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Subarachnoid hemorrhage</th>
<th>Control group patients with other illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All the patients (N = 21)</td>
<td>Good result group (N = 10)</td>
</tr>
<tr>
<td>Plasma Epinephrine (A)</td>
<td>ng/ml</td>
<td>ng/ml</td>
</tr>
<tr>
<td>On admission</td>
<td>0.65 ± 0.11</td>
<td>0.41 ± 0.08</td>
</tr>
<tr>
<td>On re-evaluation</td>
<td>0.30 ± 0.06</td>
<td>0.92 ± 0.24</td>
</tr>
<tr>
<td>Plasma Norepinephrine (NA)</td>
<td>ng/ml</td>
<td>ng/ml</td>
</tr>
<tr>
<td>On admission</td>
<td>0.94 ± 0.10</td>
<td>0.68 ± 0.12</td>
</tr>
<tr>
<td>On re-evaluation</td>
<td>0.46 ± 0.07</td>
<td>1.25 ± 0.16</td>
</tr>
<tr>
<td>Plasma dopamine-β-hydroxylase (DβH)</td>
<td>IU/L</td>
<td>IU/L</td>
</tr>
<tr>
<td>On admission</td>
<td>31.59 ± 4.32</td>
<td>35.18 ± 7.08</td>
</tr>
<tr>
<td>On re-evaluation</td>
<td>35.63 ± 8.15</td>
<td>20.3 ± 8.15</td>
</tr>
</tbody>
</table>

The *P* values indicate the degree of significance of the difference between adjacent pair of values.

The normal range for this laboratory

- A = 0.02 - 0.26 ng/ml
- NA = 0.23 - 0.72 ng/ml
- DβH = 2.5 - 30.6 IU/L

Results

All the groups were matched for age and sex.

Plasma Epinephrine and Norepinephrine Concentrations and DβH Activity on Admission in Patients with SAH; Comparison with Values in Patients Admitted for Other Disease

Although the plasma epinephrine concentrations in the patients with SAH were above the normal range they were not significantly greater than the raised concentrations in patients admitted with other illnesses (table 3). Plasma norepinephrine concentrations in patients with SAH were above the normal range and were significantly higher than the concentrations in patients with other illnesses (*P* < 0.01). Plasma DβH activities in patients with SAH were not significantly different from the normal range.

When the patients with SAH are subdivided into good result and poor result groups, further differences are apparent in the plasma norepinephrine concentrations at the time of admission. In patients with a good result norepinephrine concentrations were not significantly different from those of patients with other illnesses. However, in patients with a poor result norepinephrine concentrations were significantly elevated when compared with the concentrations in: (1) patients with other illnesses (*P* < 0.001) and (2) patients with SAH with good result (*P* < 0.01) (fig. 1).

There was no significant difference between the plasma DβH activities in patients with a good or poor result (table 3).

Changes in Plasma Epinephrine and Norepinephrine Concentrations and DβH on Re-evaluation of Patients with SAH

Blood samples for re-evaluation of plasma epinephrine and norepinephrine concentrations and DβH activities were collected from patients with SAH at least 24 hours after admission (see table 1).

On re-evaluation the plasma epinephrine concentrations in the poor result group had increased and become significantly different from all other groups (*P* < 0.05). In contrast, plasma epinephrine concentrations in the patients with a good result showed a decline. Similarly, plasma norepinephrine concentrations showed a further rise in patients with a poor result from the already significantly elevated initial concentrations. However, in patients with a good result there was a reduction in plasma norepinephrine.
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Plasma Epinephrine and Norepinephrine Concentrations and DβH Activity in Patients after Neurosurgery

Patients with SAH Who Had Neurosurgery

In analyzing the results the patients were divided into 3 groups as described above.

(1) Patients Without Complications

None of the patients in this group had angiographic evidence of postoperative vasospasm and the level of consciousness after neurosurgery was normal. In this group the mean plasma norepinephrine concentrations were within the normal range and in 1 patient whose values were elevated they returned to within normal range very rapidly (4-6 hours) (fig. 2). The plasma epinephrine concentrations, which were increased after surgery, showed a gradual decline toward normal values within 6-12 hours. The changes in plasma DβH activities were not consistent though they showed a decline (fig. 3).

(2) Patients with Complications

These patients in the immediate postoperative period had angiographic evidence of vasospasm, either localized or generalized, and were unable to respond to verbal commands due to alterations in level of consciousness. In all 5 cases the vasospasm was associated with an increase in intracranial pressure requiring treatment. Subsequently, all these patients showed symptomatic improvement and the eventual clinical outcome was good except for 1 patient who died of myocardial infarction (confirmed at post-mortem) 4 days postoperatively.

The plasma epinephrine and norepinephrine concentrations changes were not significantly different from those in patients who did not develop complications although the mean plasma norepinephrine concentrations were considerably higher (fig. 4). However, by the time the patients were ready to be transferred back to the neurosurgical ward, the plasma epinephrine and norepinephrine concentrations had returned toward normal.

The changes in plasma DβH activity were inconsistent in these patients and the mean values were lower than those in patients without complications (fig. 3).

(3) Patients who Died

These patients developed angiographic evidence of severe generalized vasospasm and all died within 30 to 64 hours after neurosurgery. In this group plasma epinephrine and norepinephrine concentrations were significantly elevated and remained so until a few hours before death (fig. 5).

In all 3 patients several postoperative angiograms showed...
that radiologically demonstrable vasospasm increased slowly, reaching a maximum at 24–36 hours after surgery, and gradually regressing thereafter. Immediately after surgery all 3 patients responded to verbal commands. However, within 6–8 hours their level of consciousness began to deteriorate. They no longer responded to verbal command and finally even to painful stimuli. The plasma norepinephrine concentrations in these patients reached a peak within 8–10 hours after neurosurgery and then declined. The change in mean plasma DβH activity after neurosurgery was not significant (fig. 3).

(4) Patients who Underwent Control Neurosurgery

In order to assess the effects of anesthesia and neurosurgery on postoperative plasma epinephrine and norepinephrine concentrations and DβH activity changes, this group of patients was investigated. Preoperative catecholamine and DβH levels were 0.15 ± 0.06 ng/ml, 0.25 ± 0.06 ng/ml and 55.17 ± 2.18 IU/L respectively. Immediately after surgery plasma epinephrine and norepinephrine concentrations were 0.28 ± 0.06 ng/ml and 0.51 ± 0.07 ng/ml. Thereafter, these concentrations returned to within the normal range within 12 hours. The concentrations of the catecholamines in the postoperative period are comparable with those in patients who did not have any postoperative complications and were significantly lower than the values in the other 2 operated groups of patients with SAH. The plasma DβH activity did not show any significant variation during or after surgery and postoperative values were similar to those in the patients with SAH who had neurosurgery.

Discussion

Plasma catecholamine concentrations were increased in most patients with SAH at admission. The increase in plasma epinephrine concentrations was similar to that found in patients admitted with other illnesses. The increased levels are not specific to patients who have SAH but are probably due to the stress of the illness. In this study, the increased plasma norepinephrine concentrations were significantly different from the concentrations in the control group of patients admitted to hospital for other reasons suggesting...
that in patients with SAH there is increased sympathetic nervous system activity.

The changes in plasma catecholamine concentrations in patients with SAH have previously not been evaluated using radioenzymatic methods. However, in one study using a fluorometric method\textsuperscript{27} it was found that plasma epinephrine and norepinephrine concentrations were elevated and high concentrations were found in association with increased systolic and diastolic pressures, S-T segment changes and a poor clinical outcome. Meyer et al.\textsuperscript{18} using a fluorometric technique, also found that plasma catecholamine concentrations were increased after SAH but did not attempt to correlate these values with the clinical findings.

In the present study the patients with a poor eventual clinical result had significantly higher plasma catecholamine concentrations than those with a good eventual result. It may be argued that patients whose clinical condition is poor are likely to be referred to a neurosurgical unit more quickly than those whose clinical condition is better. Since plasma norepinephrine and epinephrine concentrations may decline after the initial episode of hemorrhage this difference in time interval may account for the differences present on admission between the good and poor result groups. The mean time interval between the onset of symptoms and collection of the first sample was 9.5 ± 8.8 days (mean ± SD) for the good result group and 7.0 ± 4.3 days for the poor result group. These times are not significantly different indicating that differences in time interval are unlikely to have contributed to the differences in catecholamine concentrations between the two groups.

Plasma D/3H activities in patients with good result were not significantly different from the values present in patients with poor result indicating again that unlike plasma catecholamines D/3H activities are not a good index of sympathetic nervous system activity.

The mechanisms of sympathetic nervous system and adrenal medullary activation after SAH are obscure. Although these findings can be at least partially attributed to a normal stress reaction, the prolonged elevation, when compared with patients with other illnesses, especially on re-evaluation, suggests that there may be other causative factors for this sympatho-adrenal medullary over-activity. A more feasible explanation may be hypothalamic dysfunction induced by arterial spasm or disruption of small vessels supplying the hypothalamus. This hypothesis is supported by the following observations: the blood supply of the hypothalamus is through fine perforating vessels arising from anterior cerebral, internal carotid and posterior communicating arteries\textsuperscript{36-38} — all common sites for intracranial aneurysms. Rupture of an aneurysm, by disrupting these fine vessels or by causing vasospasm of the main trunk, could diminish hypothalamic blood supply leading to damage, consequent alteration in hypothalamic function and increase in sympatho-adrenal medullary activity; ischemic lesions have been found at autopsy in the hypothalamus of patients who died following SAH (61% of 106 consecutive cases)\textsuperscript{39} and in experimental animals after SAH.\textsuperscript{40} Melville et al.\textsuperscript{18} employed electrical hypothalamic stimulation (posterior and lateral) in cats and noted increases in blood pressure and ECG changes similar to those seen after SAH in man. This was interpreted to be a sympathetic effect because the changes were not influenced by vagotomy but could be abolished by high spinal section at the level of C.2. Similar findings have been reported by other workers.\textsuperscript{30, 44} Stimulation of the posterior hypothalamus in dogs has been reported to increase epinephrine and norepinephrine release from adrenal medulla.\textsuperscript{46}

After admission, patients with a good result had lower catecholamine concentrations while in patients with a poor result they increased. This may be due to the fact that in the latter group of patients there is persistent or even further enhancement of sympatho-adrenal medullary over-activity. Therefore, the detection of such changes in plasma epinephrine and norepinephrine concentrations may help in assessing prognosis and may assist in the selection of patients for neurosurgery.

The plasma catecholamine concentrations did not increase above the upper limit of normal in the control group of neurosurgery patients, indicating that anesthesia and surgical procedure per se do not cause an increase.

Plasma epinephrine concentrations were persistently increased in patients who died after neurosurgery, declining only a few hours before death. This is in contrast to the concentrations in patients who did not develop complications or in patients who recovered after developing complications. This suggests that in patients who die there is an agonal adrenal medullary over-activity which may be non-specific.

Plasma norepinephrine concentrations were different in all 3 groups of patients who underwent neurosurgery, suggesting that the degree of postoperative sympathetic nervous activity is related to the clinical outcome of the patient.

In patients who developed vasospasm in the postoperative period the vasospasm was preceded by an increase in plasma norepinephrine concentrations which suggests that sympathetic nervous over-activity is followed by vasospasm and deterioration in level of consciousness.

Previous workers have indicated that a progressively increasing intracranial pressure can cause a deterioration in level of consciousness.\textsuperscript{36, 37} In this study the intracranial pressure was kept below 25–30 mm Hg and thus the changes in level of consciousness cannot be attributed to an increase in intracranial pressure. Furthermore, in the postoperative period the PaO\textsubscript{2} and PaCO\textsubscript{2} concentrations were kept within normal range. Therefore, in the postoperative period, sympathetic nervous system and adrenal medullary over-activity is associated with the clinical deterioration of the patient's condition.

The lack of change in plasma D/3H activities indicates that, unlike plasma norepinephrine concentrations, a change in circulating D/3H activities is a poor index of sympathetic nervous system activity.

References

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C R Benedict and A B Loach

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