Increased Sympathetic Nervous Activity in Patients With Nontraumatic Subarachnoid Hemorrhage

S. Naredi, MD; G. Lambert, PhD; E. Edén, MD, PhD; S. Zäll, MD, PhD; M. Runnerstam, MD; B. Rydenhag, MD, PhD; P. Friberg, MD, PhD

Background and Purpose—Activation of the sympathetic nervous system, which leads to elevation of circulating catecholamines, is implicated in the genesis of cerebral vasospasm and cardiac aberrations after subarachnoid hemorrhage. To this juncture, sympathetic nervous testing has relied on indirect methods only.

Methods—We used an isotope dilution technique to estimate the magnitude and time course of sympathoadrenal activation in 18 subarachnoid patients.

Results—Compared with 2 different control groups, the patients with subarachnoid hemorrhage exhibited an approximately 3-fold increase in total-body norepinephrine spillover into plasma within 48 hours after insult (3.2±0.3 and 4.2±0.7 versus 10.2±1.4 nmol/L; P<0.05 versus both). This sympathetic activation persisted throughout the 7- to 10-day examination period and was normalized at the 6-month follow-up visit.

Conclusions—The present study has established that massive sympathetic nervous activation occurs in patients after subarachnoid hemorrhage. This overactivation may relate to the well-known cardiac complications described in subarachnoid hemorrhage. (Stroke. 2000;31:901-906.)

Key Words: norepinephrine ■ subarachnoid hemorrhage ■ sympathetic nervous system

Increased concentrations of plasma and urine norepinephrine (NE) and its metabolites have been found in patients after subarachnoid hemorrhage (SAH).1–4 These increased levels of NE have been associated with cardiac complications.3–6 ECG abnormalities, such as depressed or elevated ST segments, QT prolongation, T-wave abnormalities, and arrhythmias, similar to those seen in patients with myocardial ischemia, are frequently observed in patients after SAH.7,8 Evidence has accumulated that suggests that these ECG abnormalities reflect underlying cardiac pathology and dysfunction,3,5,5 possibly because of elevated catecholamines (CAT; vide supra), although other results indicate no relation between ECG changes and high levels of NE.2,10,11 Given previous observations in patients with congestive heart failure, increased central nervous system catecholaminergic neuronal activity, which results in peripheral sympathetic activation, would be consistent with the presence of cardiac anomalies in these patients.12,13

Although reports exist that attempt to delineate sympathetic nervous system involvement after SAH, the techniques used (which usually measure antecubital venous plasma or urinary catecholamines) lack the precision of isotope dilution methodologies. Hitherto, NE and epinephrine (EPI) kinetic studies have not been performed in patients after acute nontraumatic SAH. Estimation of NE spillover into the circulation by use of dilution of intravenously infused [3H]-NE with endogenous NE in plasma (ie, specific activity of plasma [3H]-NE) provides a useful index of NE release from sympathetic nerves.14 However, most NE released is efficiently removed by neuronal and extraneuronal uptake, so that only a small portion escapes into the circulation.15 Plasma concentrations of NE are the net result of bidirectional flux of the transmitter. Both removal and release processes must be considered to adequately assess the release of NE into plasma, because changes in the former may alter plasma concentrations of NE, irrespective of any change in NE release from sympathetic nerves. The radiotracer technique is based on steady-state infusion of tracer amounts of radiolabeled NE to establish rates of entry and removal of NE to and from the plasma compartment.16

In the present study, measurements of total-body NE and EPI spillover and clearance were performed on 3 separate occasions within the first 10 days after SAH insult and in 5 patients at an outpatient follow-up visit approximately 6 months subsequent. Findings in the SAH patient group were compared with data obtained in 2 control groups: (1) healthy subjects and (2) patients investigated invasively in the intensive care unit for refractory pain.

Subjects and Methods
The present study was performed at Sahlgrenska University Hospital. Local ethical and isotope committees at Sahlgrenska University...
Hospital approved all study protocols, and all subjects (or next of kin) gave informed consent to participate in the study.

Subjects
Eighteen patients, including 8 men and 10 women (median age, 51 years; range, 36 to 66), with acute SAH were included in the study. Fifteen healthy, age-matched volunteers of median age 52 years (range, 38 to 64) with no history of neurological or cardiovascular disease and with ECG and routine serum chemistry within the normal range, served as 1 control group. Eleven patients with no evidence of cardiovascular disease and without demonstrable ECG changes17 were undergoing clinical investigation for refractory pain were included as a second control group (median age, 68 years; range, 37 to 81). The latter group underwent a catheterization procedure in the intensive care unit. Thus, the “environmental milieu” for these patients was similar to that of the SAH patients.

All SAH patients were treated at the neurointensive care unit of Sahlgrenska University Hospital. All patients were admitted to the neurointensive care unit within 24 hours after onset of bleeding. Median Hunt/Hess classification of patients with intracranial aneurysms17 was 3.5 (range, I through V; see Table). None of the patients had a history of myocardial disease. Two patients were on antihypertensive β-blocker treatment.

Methods
Diagnosis of SAH was made by CT scan. Estimation of the amount of blood in the subarachnoid space was determined according to the criteria proposed by Fisher et al18 (Table).

Monitoring
All patients had central venous and arterial lines for continuous monitoring of central venous and systemic arterial blood pressures, respectively. Oxygen saturation was determined by pulsoximetry (Datex Cardiocap 2). In 7 patients, an intraventricular catheter was inserted as a result of hydrocephalus (Stille EDN v-kat 20-cm set; Datex Cardiocap 2). In 7 patients, an intraventricular catheter was inserted as a result of hydrocephalus (Stille EDN v-kat 20-cm set; Datex Cardiocap 2). Monitoring of central venous and systemic arterial blood pressures, monitoring of intracranial pressure, and to drain cerebrospinal fluid.

The limit for drainage of cerebral spinal fluid was normally set at 20 cm H2O above forehead level. Zero baseline for intracranial pressure was set at the forehead level and for systemic pressure at heart level (pressure monitor, Datex Cardiocap 2). The drainage system was closed every hour to measure actual intracranial pressure and calculate cerebral perfusion pressure. The value for mean arterial pressure was given on the pressure monitor, and the cerebral perfusion pressure was calculated as mean arterial pressure minus intracranial pressure. The nursing staff recorded these variables at least hourly. Myocardial function was evaluated with serial ECGs, ICP). The catheter was used to monitor intracranial pressure and to drain cerebrospinal fluid.

Localization of aneurysm and outcome in relation to total-body NE spillover

<table>
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<th>Patient No.</th>
<th>Total-Body NE Spillover, nmol/min</th>
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<th>CT Fischer</th>
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Experimental Protocol and Blood Sampling

Catecholamine kinetic determinations were made within 48 hours after SAH, and follow-up studies were performed 24 hours subsequent and 7 to 10 days after SAH. Measurements of total-body NE and EPI spillover were performed on admittance in all 18 patients (within 48 hours). Six patients were thereafter excluded because they received a drug that interferes with catecholamine release. Twelve patients were measured at 72 hours after insult. Two of these died before the end of the first week. The sympathoadrenal function of the remaining 10 patients was examined on 3 occasions (ie, within 48 hours, after 72 hours, and 7 to 10 days after the insult). In addition, in 5 of 10 patients, a further study was performed approximately 6 months after SAH.

Baseline arterial blood samples were taken at least 30 minutes after tritium-labeled catecholamine infusion was begun. This procedure is based on the fact that steady-state conditions of tritiated NE prevail approximately 13 minutes after infusion begins. Blood samples (10 mL) were collected into ice-chilled tubes containing...
EGTA and glutathione. Plasma was separated by centrifugation and stored at −80°C until it was assayed.

**Assays**

Catecholamines were extracted from plasma (1 mL) and samples of infusate (10 µL) with alumina adsorption, separated, and quantified by high-performance liquid chromatography with coulometric detection. Timed collection of [3H]-eluate that left the electrochemical cell permitted separation of the [3H]-labeled NE and EPI for subsequent counting by liquid scintillation spectroscopy. Interassay coefficients of variation were 4.6% and 10% for endogenous NE and EPI, respectively, and 3.2% and 7% for [3H]-NE and [3H]-EPI, respectively. Intraassay coefficients of variation were 2% and 10% for endogenous NE and EPI, respectively, and 3% for both [3H]-NE and [3H]-EPI.

**Calculations**

Separate total-body NE and EPI spillover (S_{TB}), respectively, were ascertained by use of the isotope dilution method proposed by Esler et al and calculated according to the following formula (in pmol/min):

\[ S_{TB} = I/SA_A \]

where \( I \) is the infusion rate of tritium-labeled catecholamine (NE and EPI, respectively, in dpm/min) and \( SA_A \) is the specific activity of the catecholamine (CAT) in arterial plasma (in dpm/pmol), calculated to be the following:

\[ SA_{CAT} = [3H] CAT/SA_A \]

where \([3H]-CAT_A\) is the arterial plasma concentrations of the tritium-labeled NE and EPI (in dpm), and \( CAT_A \) is the arterial plasma concentration of NE and EPI (in pmol/mL). Total-body CAT clearance (CL_{TB}) was calculated to be the following (in mL/min):

\[ CL_{TB} = I/[3H]CAT \]

**Statistics**

All results, unless otherwise specified, are expressed as mean ± SEM. Comparisons between groups were evaluated by use of Kruskal-Wallis nonparametric ANOVA. Mann-Whitney nonparametric test was used for comparison of NE and EPI plasma concentrations and total-body catecholamine spillover between healthy subjects and SAH patients. The null hypothesis was rejected if the 2-tailed \( P \) value was <0.05. The possible relation between total-body NE spillover and intracranial and cerebral perfusion pressures was assessed with the Spearman rank correlation.

**Results**

**Catecholamine Kinetics**

On admission to the neurointensive care unit, SAH patients exhibited elevated arterial plasma NE concentrations, regardless of whether they were sedated. Given the normality of NE clearance in the SAH patients (approximately 2.6 L/min) and control groups (approximately 2.3 L/min), the elevated plasma NE concentrations in the SAH group translated into a >3-fold increase in the rate of spillover of NE to plasma (\( P<0.05 \); Figure 1) compared with both control groups. This enhanced total-body NE spillover persisted throughout the course of the experimental period. The elevation in NE spillover was not accompanied by a statistically significant increase compared with healthy subjects in the rate of total EPI spillover, which was 1.9±0.4 nmol/min on admission and 1.7±0.3 nmol/min 24 hours subsequent to and 1.5±0.4 nmol/min 7 days after initial trauma. Total-body NE spillover was normalized in patients on follow-up approximately 6 months after the SAH (Figure 1). All 5 follow-up patients demonstrated high levels of NE spillover during the week after insult, whereas 2 showed a low degree of sympathetic activation within the first 48 hours (Figure 2, same patients examined at all time points). Examination of the clinical data on admission revealed no association between the marked elevation in NE spillover and the Hunt/Hess score, Fisher score, or the localization of the aneurysm (Table). For an adequate validation of such possible relationships, a larger study is required. No relation was seen between the rate of total-body NE spillover to plasma and intracranial pressure or between total-body NE spillover and cerebral perfusion pressure. The time of measurement (ie, before or after surgery or embolization) did not affect the magnitude of NE spillover (measurements were made in 4 of 12 and 7 of 12 patients before and after intervention, respectively). The 1 patient who did not receive intervention demonstrated a high total-body NE spillover (8.6 nmol/min).

**Clinical Results**

Ten of 12 patients studied throughout the week-long study period presented abnormal ECG recordings, including QT
prolongation, depressed or elevated S segments, T-wave abnormalities, and arrhythmias. The 2 patients who displayed normal rates of NE spillover to plasma presented normal ECGs throughout the entire study period. In the patients examined approximately six months after SAH, abnormalities in the previous ECG had normalized completely. Three patients exhibited CK-MB and troponin plasma levels above the diagnostic level for myocardial infarction, and 1 displayed a pathological echocardiography with 2 areas of hypokinesia and reduced ejection fraction. In this patient, the echocardiogram was normal on examination 6 months after insult.

Five patients exhibited signs of cerebral vasospasm detected clinically or by transcranial Doppler, angiography, or signs of ischemia on CT scan. Mean arterial and central venous pressures for the 12 patients throughout the study period were 97 ± 2 and 8 ± 0.5 mm Hg, respectively. These pressures were stable throughout the intensive-care study period. Moreover, heart rate remained stable during the same period at 75 ± 3 bpm. In the 7 patients with intracranial pressure monitoring, mean pressure was 18 ± 2 mm Hg. If the 2 patients who died were excluded, this value was reduced to 11 ± 2 mm Hg; mean cerebral perfusion pressure for the 7 patients with intracranial pressure monitoring was 77 ± 4 mm Hg. All patients had normal serum electrolyte levels.

Overall outcome for the 18 patients according to the Glasgow outcome score (GOS) 3 months after the bleeding was as follows: 13 patients survived with good outcome or were moderately disabled, 1 was severely disabled, and 4 had died (Table).

**Discussion**

In the present study we have identified, and thus firmly established, the presence of a dramatic elevation in sympathetic nervous activity, evidenced as high rates of total-body spillover of NE to plasma in patients after SAH. This increase persists for at least 7 to 10 days. This augmented activity of the sympathetic nervous system may contribute to the cardiac disturbances that prevail in this serious condition. Furthermore, a differentiated activation of the sympathoadrenal system occurs, inasmuch that a roughly normal adrenal activity occurs in addition to marked sympathetic activation.

The idea that sympathoexcitation with associated elevations in systemic blood pressure after nontraumatic SAH arises secondary to the accompanying elevation in intracranial pressure stems from the experiments conducted by Harvey Cushing early in the 20th century. Although these experiments are not necessarily directly applicable to the setting of SAH, Cushing noted that increments in intracranial pressure resulted in a marked blood pressure elevation. In an animal model of SAH, a marked elevation in systemic arterial pressure occurred only when the rise in intracranial pressure approached systemic blood pressure. The degree of vasoconstriction elicited by the different volumes of blood did not vary considerably, but the intracisternally injected of the larger volume elicited a marked blood pressure elevation. The rise in systemic pressure as a result of the Cushing response can be prevented by prior α-adrenergic blockade and is believed to be mediated by means of alterations in neuronal activity in the brain stem in response to local ischemia, or more particularly, hypoxia. Taken together, the sympathoexcitation that we observe in the clinical setting after nontraumatic SAH would appear to originate in local constriction of small vessels that supply the brain stem.

The pathophysiology behind cerebral vasospasm is not completely understood. Some studies suggest the possibility that elevated levels of circulating catecholamines, coupled with an abnormal sensitivity of the cerebral vasculature to these catecholamines, may be involved in the genesis of vasospasm. Development of delayed cerebral ischemia is a serious problem despite the prophylactic use of the calcium antagonist nimodipine. In the present study, the 3 patients with the highest rates of total-body NE spillover also experienced cerebral vasospasm. This supports the idea that catecholamines are involved in but are probably not the only factor in the pathogenesis of vasospasm.

A variety of other vasoactive substances, such as serotonin, endothelin, oxyhemoglobin, and nitric oxide, have also been proposed to play a role in the genesis of vasospasm. Catecholamines potentiate the action of endothelin. Hemoglobin and oxyhemoglobin are particularly efficient at producing spasm of cerebral vessels in vitro and in vivo. Part of this effect may relate to the ability of hemoglobin to bind the vasodilator nitric oxide, but oxyhemoglobin also produces free radicals, which could induce vasospasm by means of several mechanisms. The demonstration of the effectiveness of endothelin antagonists and nitric oxide donors in the management of vasospasm after experimental SAH holds further promise in the treatment of the condition. Furthermore, activation of the renin-angiotensin system seems to be of importance in the SAH condition, although no firm relationship could be found with regard to vasospasm and ECG changes in a small patient study. Interestingly, Fassot and collaborators found in experimental SAH that an intact renin-angiotensin system was a prerequisite for maintaining adequate blood pressure control. It is reasonable to assume that a high degree of sympathetic nervous system activation also gives rise to a secondary increase in renin release from the kidney.

One pertinent question is whether the blood-brain barrier is intact or disrupted in the presently investigated SAH patients. However, we are convinced that it is still intact, for the following reasons. First, brain NE at rest contributes only marginally to total-body NE spillover (on the order of approximately 3% if the principal central nervous system metabolite to NE, 3-methoxy-4-hydroxyphenylglycol (MHPG), is considered. In the present study, which shows such a dramatic increase in total-body NE spillover in the SAH patient group, central nervous system NE spillover would have to be unbelievably increased, which is highly unlikely. Second, we also measured MHPG concentrations in the cerebrospinal fluid in both SAH and refractory-pain patients. MHPG concentrations in the SAH patients were only half those found in the pain patients (who then are very
likely to have an intact blood-brain barrier), 0.52 ± 0.06 and 1.07 ± 0.18 nmol/L for the former and latter groups, respectively. If the blood-brain barrier had been disrupted, the MHPG concentrations in the cerebrospinal fluid would have been much higher in the SAH patients, not lower. Third, other preliminary experiments that we performed have demonstrated that clonidine, a sympatholytic centrally acting drug, clearly reduced sympathetic activity short term, which indicates an augmented sympathetic nerve firing that can be reduced (unpublished data, 1999). Thus, we believe that we have a true elevation in sympathetic nerve traffic to a major part of the body.

Findings are controversial as to the connection between elevated levels of plasma catecholamines and ECG abnormalities.2–6,10,11 In the present study, the 2 patients with normal total-body NE spillover to plasma were the only subjects who did not develop ECG abnormalities. Although the number of observations was limited, these data support the contention of a link between increased sympathetic activity and cardiac abnormalities after SAH. Although equivocal in SAH, the linkage between sympathetic activation and cardiac consequences is not without precedent. For example, in patients with congestive heart failure, not only is sympathetic nervous activity increased, but the degree of cardiac sympathetic activation is the most reliable index of mortality.13 One may envisage that with the high prevailing rates of total-body NE spillover in the presently studied SAH patients, it is reasonable to assume that cardiac NE spillover is grossly elevated. Hence, it is tempting to speculate that high NE levels in the heart are associated with the observed ECG changes after SAH, in line with important evidence that high cardiac NE levels in the heart are associated with the observed ECG changes after SAH, in line with important evidence that high cardiac NE spillover in patients investigated for malignant arrhythmias.42 Moreover, high catecholamine concentrations both in man and pigs have been linked to myocardial damage.43–45 Consequently, reduction of the high degree of sympathetic activation present in the SAH patients should be considered favorable.

In response to the hypotension that accompanies the use of vasodilator drugs, the sympathetic nervous system is reflexly stimulated. Hypotension associated with calcium channel–blocking drugs such as nimodipine could elicit activation of the sympathetic nervous system. However, the patients in the present study were not hypotensive, but were instead the reverse, with a mean arterial pressure close to 100 mm Hg. Therefore, it seems unlikely that the observed elevation in sympathetic nervous activity was due to a reflex response to hypotension.

**Methodological Considerations**

The bulk of circulating NE represents transmitter release from sympathetic nerve varicosities and <10% originates from adrenal medullary secretion.15 The released NE is mainly recaptured into the axoplasm by an active transport mechanism (uptake 1) and transferred back to storage vesicles. Most studies that investigate sympathetic nervous activation after SAH patients have analyzed NE concentrations in plasma obtained from antecubital venous blood. This procedure does not correctly describe the magnitude of sympathetic activity. Research has clearly shown that the forearm effectively extracts approximately 50% of inflowing NE.46 Thus, the forearm is not representative of total-body sympathetic activity. Instead, arterial sampling should be performed to determine endogenous NE. At least, this procedure avoids any organ-extraction procedures.

Several studies have also tried to estimate sympathetic activity in SAH patients from measurements of NE and metanephrines, as well as vanillylmandelic acid, in urine. However, NE in urine has a complex source. Only ±10% of circulating NE appears unchanged in the urine, which thereby renders urinary measurements of NE for interpretation of the degree of sympathetic activity extremely difficult and hazardous.

The metanephrines are extraneuronal O-methylated metabolites of NE and EPI. Thus, their plasma concentrations enable examination of the extraneuronal uptake and metabolism of catecholamines. The adrenals are the major source of circulating metanephrines,15 and consequently metanephrines either in plasma or urine are not a good index of sympathetic activity. Considered collectively, estimation of NE spillover into the circulation as performed in the present study, with the dilution of intravenous, infused, and tritiated NE with endogenous NE in plasma (ie, the specific activity of plasma-tritiated NE), provides a well-documented, robust, and useful index of NE release from sympathetic nerves.14

We conclude that nontraumatic SAH is associated with an extreme elevation in sympathetic nervous system activity that persists at least during the first week after insult. This increased sympathetic nervous activity may, at least in part, be related to the observed ECG aberrations, perhaps due to elevated cardiac sympathetic drive, which, in turn, may cause myocardial structural alterations.

**Acknowledgments**

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**References**


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