Effect of Elevated Plasma Norepinephrine on Electrocardiographic Changes in Subarachnoid Hemorrhage

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We compared electrocardiographic abnormalities and plasma norepinephrine concentrations in 40 patients with subarachnoid hemorrhage within the first 24 hours, at 72 hours, and after 1 week. In 20 patients with high plasma norepinephrine concentrations within the first 24 hours, sinus tachycardia ($p<0.02$) and negative T waves ($p<0.01$) were more frequent than in the 20 patients with normal plasma norepinephrine concentrations. After 72 hours, only sinus tachycardia ($p<0.03$) was found with increased frequency in the 26 patients with high plasma norepinephrine concentrations. Although 24 patients had high plasma norepinephrine concentrations after 1 week, we found no differences in the frequency of electrocardiographic abnormalities compared to patients with normal plasma norepinephrine. However, QTc prolongation, U waves, ST depression, and arrhythmias were found with similar frequency in patients with both high and normal plasma norepinephrine concentrations. We conclude that, with the exception of sinus tachycardia and negative T waves, electrocardiographic changes in patients with subarachnoid hemorrhage do not depend on elevated plasma norepinephrine concentrations. (Stroke 1991;22:746–749)

Subarachnoid hemorrhage (SAH) may be associated with cardiac abnormalities, including a high prevalence of arrhythmias and other electrocardiographic (ECG) changes.1 Although the appearance of changes in ECG during the acute phase of stroke — typically consisting of inversion of T wave, ST segment elevation or depression, prolongation of the corrected QT (QTc) interval, and the presence of U waves2-4 — has been a well-recognized phenomenon for four decades,5 clinical significance of cardiac arrhythmias in patients with SAH has been recognized only recently.6 The mechanism of ECG abnormalities remains obscure. It has been suggested that cardiac arrhythmias, myocardial necrosis, and ECG abnormalities may result from abnormally increased sympathetic activity.1 Elevated plasma norepinephrine concentration, an indicator of peripheral sympathetic activity, has been suggested as the causal link between the cerebral event and ECG abnormalities.1 Although the use of β-adrenergic blocking agents has been suggested,7-8 no clinical reports confirm the dependence of ECG changes on high plasma norepinephrine levels in patients with SAH.

The purpose of our study was to investigate the frequency of ECG abnormalities in the first week after SAH in patients with high plasma norepinephrine levels and to compare them to ECG changes in SAH patients with normal plasma norepinephrine levels.

Subjects and Methods

We prospectively studied 40 patients (14 men, 26 women) with SAH admitted to the Department of Neurology of the University Medical Center, Ljubljana, from January 1987 to May 1989 within the first 24 hours after sudden onset of headache. Patients were 27-75 years old (mean, 48±11 years).

Subarachnoid hemorrhage was diagnosed if the patients suffered a sudden onset of headache and stiff neck, with or without lateralizing neurologic signs, and had a grossly bloody cerebrospinal fluid. The diagnosis was confirmed by computerized axial tomographic scan, and then an angiographic study of the carotid and vertebral arteries by femoral catheterization or direct puncture was performed in all patients. The neurologic status was graded according to the Hunt-Hess scale.9

Within the first 24 hours after onset of headache, each patient underwent a clinical cardiologic examination, ECG recording, chest radiograph, and serum
electrolyte determination. Patients with hypokalemia (<3.5 mmol/l) and patients receiving medication (e.g., β-blockers) that might interfere with norepinephrine assay were not included. The ECG was monitored (Eti-Hellige Servomed, Niš, Yugoslavia) for 72 hours, and each arrhythmic event on the scope was interpreted by a cardiologist. The ECGs were recorded within the first 24 hours, after 72 hours, and 1 week after SAH. A heart rate exceeding 100 beats/min was defined as tachycardia and less than 60 beats/min as bradycardia. The P wave was measured in lead II and was considered abnormal if it exceeded 2.5 mm (1 mV=10 mm) or 0.10 second. A PR interval shorter than 0.12 second or longer than 0.20 second was considered abnormal, as was prolongation of QRS complex exceeding 0.10 second. S1+Rv was regarded as normal when it was less than 35 mm. ST segment elevation or depression of 1 mm were defined as abnormal. When U wave was more than 1 mm in height, it was considered abnormal. T wave abnormalities were observed in the I+II, V3, V3+V4, V5+V6, and aVL leads. QTc interval was measured using the Bazett formula from an average of 10 complexes.

At the same time as the ECGs were recorded, all blood samples were collected in prechilled plastic tubes containing heparin and glutathione (5 mmol/l final concentration) that were placed on ice immediately and centrifuged at 4°C (15 minutes, 900g). Plasma was separated from the erythrocytes immediately and stored at −20°C. The assay was performed as described by Peuler and Johnson.10 Plasma was incubated directly with catechol-O-methyltransferase, which was prepared as previously described11 in the presence of trinitiated 3-adenosyl-l-methionine-methyl to produce a labeled 3-methyl derivative of norepinephrine. Reference values for plasma norepinephrine were 0.53–2.51 nmol/l.

Frequency of ECG abnormalities in records of patients with high plasma catecholamines were compared to those in records of patients with catecholamines within normal limits using Yates-corrected x² analysis.

**Results**

According to the Hunt-Hess scale, 32 patients were grade 1 or 2 (asymptomatic or meningism, no neurologic deficits); six were grade 3 (drowsiness, confusion, or mild focal deficit); and two were grade 4 to 5 (stupor to deep coma) on admission. The two patients in the last group died on the 12th and 16th days, respectively. Angiographic study of the carotid and vertebral arteries showed a cerebral aneurysm in 15 patients, and clipping was performed in all of them within the first 72 hours after the onset of sudden headache. Five patients had a history of systemic arterial hypertension and one of diabetes mellitus, but no prior heart disease was reported in any of the patients.

Plasma norepinephrine was elevated in 20 patients within the first 24 hours: range, 2.81–8.10 nmol/l; mean, 4.61±1.55 nmol/l. On the third day, plasma norepinephrine was elevated in 26 patients: range, 2.57–8.10 nmol/l; mean, 4.68±1.51 nmol/l. After 1 week, 24 patients had high plasma norepinephrine levels: range, 3.05–12.4 nmol/l; mean, 6.14±2.85 nmol/l.

We found no abnormalities of the P waves, PR intervals, or QRS complexes in our patients, either with high or normal plasma norepinephrine. Tables 1 and 2 show T wave, ST segment, U wave, QT; interval changes, heart rate, and arrhythmias in patients with high and normal plasma norepinephrine levels within the first 24 and 72 hours after the onset of sudden headache.

After 1 week, we found no significant (p>0.05) differences in the incidence of negative T wave changes (four versus two), prolongation of QTc (four versus two), atrial fibrillation (two versus one), and ventricular (four versus three) or supraventricular premature complexes (one versus two) in patients with high plasma norepinephrine versus those with normal plasma norepinephrine, respectively. No ST segment and U wave changes or unsustained ventricular tachycardia were observed in either group after 1 week.

**Discussion**

Cardiac abnormalities are present in more than 50% of patients suffering from SAH,2 including serious arrhythmias.4 In our study, only 25% of patients in the first 24 hours after SAH had normal ECG, but 70% of them had normal ECG after 1 week, despite the fact that plasma norepinephrine levels were

| TABLE 1. Number of Patients With High and Normal Plasma Norepinephrine Concentrations Demonstrating Electrocardiographic Changes or Abnormalities Within 24 Hours After Subarachnoid Hemorrhage |
|-----------------|-----------------|-----------------|
|                | High NE (n=20)  | Normal NE (n=20) | p    |
| T wave (lead)  |                 |                 |      |
| I, II          | 10              | 3               | <0.04|
| V2             | 9               | 6               | NS   |
| V3, V4         | 12              | 4               | <0.02|
| V3, V4         | 12              | 3               | <0.01|
| aVL            | 14              | 3               | <0.01|
| ST segment     |                 |                 |      |
| <−1 mm         | 7               | 3               | NS   |
| >+1 mm         | 4               | 2               | NS   |
| U wave         | 12              | 14              | NS   |
| QT, >0.425     | 12              | 14              | NS   |
| Heart rate >101 beats/min | 12 | 4 | <0.02 |
| AF             | 2               | 1               | NS   |
| VPC            | 7               | 6               | NS   |
| SVPC           | 2               | 1               | NS   |
| VT             | 1               | 1               | NS   |

NE, plasma norepinephrine; NS, not significant (p>0.05); AF, atrial fibrillation; VPC, ventricular premature complex; SVPC, supraventricular premature complex; VT, ventricular tachycardia.
Within the first 24 hours invariably had similar levels and were highly improbable. Consistent time course of norepinephrine levels in 3 and 7 days later as well. We feel that with such a possibility to be rather remote, however, because patients with high norepinephrine levels for only a short time would not be detected by our present results. Hypokalemia was associated invariably with malignant ventricular arrhythmias in patients with SAH. We excluded all patients with low serum potassium concentrations and therefore observed unsustained ventricular tachycardia in only six of our patients. This arrhythmia, as well as all others observed in our patients (atrial fibrillation, premature supraventricular and ventricular complexes), were not related to elevated plasma norepinephrine levels.

We conclude that ECG abnormalities and elevated plasma norepinephrine levels are simultaneous reflections of the neurologic event in patients with SAH, possibly via a hypothalamic mechanism or an abnormally increased sympathetic activity triggered by insula, as recently proposed. The increased sympathetic activity, reflected by a high plasma norepinephrine concentration, does not seem to be the causal link between the cerebral event and ECG abnormalities, contrary to prior suggestions. The suggested preventive use of β-adrenergic blocking agents therefore does not seem to be warranted by our present results.

References


**KEY WORDS** • electrocardiography • norepinephrine • subarachnoid hemorrhage
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