Plasma Norepinephrine in Stroke

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SUMMARY Cardiac arrhythmias, myocardial necrosis and ECG abnormalities in stroke may result from abnormally high levels of sympathetic activity. To examine this possibility, plasma norepinephrine, epinephrine and dopamine were measured in 74 patients with cerebral infarction, 18 with transient ischemic attacks and 33 non-stroke controls.

Mean norepinephrine, epinephrine and dopamine values (pg/ml) in cerebral infarction (433.2, 81.6, 57.6) were higher \( p < 0.01 \) than in controls (281.1, 60.1, 40.5, respectively). Transient ischemic attacks produced values intermediate to these two groups (319.3, 80.9, 54.9). The elevated catecholamine concentrations in cerebral infarction could not be explained by differences in age, blood pressure, heart rate, stress, type or severity of stroke. The high plasma norepinephrine in the stroke group is consistent with an increase in peripheral sympathetic activity which could produce the cardiac abnormalities of cerebral infarction.

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ACUTE STROKE may be associated with a number of cardiac abnormalities including a high prevalence of arrhythmias and electrocardiographic changes. Elevated cardiac enzymes have also been found in patients with stroke compared with a variety of control populations. In a recent study, Norris et al. observed that 44 percent of 230 patients admitted to a Stroke Intensive Care Unit had elevated total CK levels and 11 percent had the cardiac isoenzyme CK-MB present when the CK was fractionated. These findings suggest that stroke is associated with myocardial cell necrosis. The possibility of cardiac damage in some patients with stroke has also been raised in a report of focal myocytolytic lesions in patients dying of cerebral infarction in the absence of coronary artery disease.

Similar observations have been reported in both human and experimental subarachnoid hemorrhage. In this condition, plasma norepinephrine values are elevated, suggesting that the causal link between the cerebral event and cardiac sequelae may be an abnormal elevation in sympathetic activity. Acute stroke may affect the heart similarly, and to evaluate this a group of patients with cerebral infarction was studied to determine if high levels of sympathetic activity exist. Accordingly, plasma catecholamines — norepinephrine, an indicator of peripheral sympathetic activity, epinephrine, an indicator of adrenal activity, and dopamine have been measured in both patients with stroke and control subjects and correlated with other variables which may affect sympathetic function.

Methods

Consecutive admissions to the Stroke Intensive Care Unit were entered in the study if they satisfied the inclusion criteria. The Unit consists of 5 beds with facilities for continuous nursing and medical care including ECG monitoring. Further details have been described elsewhere. Three groups of patients were included in the study: 1) patients with acute cerebral infarction including lesions in the brainstem or hemispheres, 2) those experiencing transient ischemic attacks, 3) "control" patients initially admitted to the Unit erroneously suspected of having a stroke. The non-stroke controls were selected for comparison with the stroke patients because all admissions to the Unit received similar care and were subject to the same type of stress associated with an intensive care setting. Potential subjects were excluded from the study if they were receiving anti-arrhythmic drugs, anti-hypertensive therapy except diuretics, nocturnal sedation, tranquilizers or other agents known to affect the sympathetic nervous system. Failure to obtain informed consent also resulted in exclusion.

Preliminary assays were performed to determine if the levels of plasma catecholamines changed during the first 3 days after admission. Samples taken from 10 patients showed similar mean values on days #1, 2 and 3 for norepinephrine and epinephrine but there was a 32.5% reduction \( p < 0.01 \) in dopamine between days #1 (48.0 pg/ml) and #3 (32.4 pg/ml). The samples for catecholamine estimation were taken within 24 hours after admission in over 90 percent of the patients; the blood samples in the remainder were drawn on the second or third hospital day.

Thirty minutes prior to the removal of blood samples for plasma catecholamines, an indwelling heparin lock device was inserted into a forearm vein and the patients were maintained supine and in quiet surroundings. A rest hour was established for the Unit between 1300 and 1400 hours to provide standardized conditions for the sampling. The blood sample was also taken for serum cortisol estimation. Heart rate and blood pressure were recorded in duplicate before and after the blood sampling procedure and the mean values were computed. A previously described stroke scoring system in routine operation in the Unit was used to assess the degree of functional disability within 48 hours after admission. Final diagnoses were established for each individual on the basis of clinical examination, cerebrospinal fluid analysis, isotope brain scan, computerized axial tomography of the brain and, where indicated, cerebral angiography. Plasma
TABLE 1. Mean (± SEM) Values for Plasma Catecholamines (pg/ml) in the 3 Patient Groups. Significant Differences Indicated By: *p < 0.02, **p < 0.01, ***p < 0.001

<table>
<thead>
<tr>
<th>Patient</th>
<th>n</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td>74</td>
<td>433.2 ± 33.9*</td>
<td>81.6 ± 4.5**</td>
<td>57.6 ± 4.6***</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>18</td>
<td>319.3 ± 32.6</td>
<td>80.9 ± 8.5</td>
<td>54.9 ± 5.6</td>
</tr>
<tr>
<td>Control</td>
<td>33</td>
<td>282.1 ± 19.8</td>
<td>60.1 ± 3.5</td>
<td>40.5 ± 3.1</td>
</tr>
</tbody>
</table>

norepinephrine, epinephrine and dopamine were measured according to the method of Sole and Hussain.\(^{13}\)

Differences in various parameters between the cerebral infarction and control groups were evaluated using Student’s unpaired \(t\)-test (2 tail). Coefficients of correlation \((r)\) were computed for various parameters which possibly could affect the plasma norepinephrine concentration. The mean plasma norepinephrine values were adjusted for age and blood pressure using multivariate analysis.

**Results**

Catecholamine Data

Mean plasma catecholamine levels were significantly higher in the patients with acute cerebral infarction compared to the control group (table 1). Norepinephrine had the greatest elevation (54%) while epinephrine and dopamine increased by lesser amounts (36, 42%, respectively). Transient ischemic attacks produced catecholamine concentrations intermediate between those in the cerebral infarction and control groups. However, not all differences were significant, possibly because of the smaller number \((n = 18)\) of patients with transient ischemic attacks.

Patient Characteristics in Stroke and Control Groups

Various characteristics of the patients entered into the stroke and control groups are summarized in table 2. Both blood pressure and age are possible factors which could affect the plasma norepinephrine concentrations. Serum cortisol has been used as a non-specific measurement of stress although cortisol production may also rise with increases in sympathetic activity.

The patients with cerebral infarction were older \((p < 0.001)\) and had slightly higher blood pressure levels. There were 56 patients with infarction in a cerebral hemisphere and 18 with brainstem infarction. The control group had a variety of diagnoses including brain tumor (meningioma and glioma), peripheral neuropathy, hysteria, hepatic encephalopathy and Guillain-Barré syndrome.

Possible Factors Affecting Plasma Norepinephrine Levels

Age

A comparison of the catecholamine levels between the stroke and control groups was made using multivariate analysis, adjusting for age and blood pressure (table 3). The mean adjusted norepinephrine concentration among patients with stroke remained significantly higher than control values. Since the older patients with cerebral infarction had more severe strokes (see below) age may not be a totally independent variable in the analysis. Accordingly, the effect of age on the plasma norepinephrine was examined further.

If age were an important determinant of plasma norepinephrine concentration, one would expect correlation between these variables. However, there was no significant correlation between age and norepinephrine in either the stroke or control groups (table 4). The 15 members of the control group over age 65 (mean 73.1 years) also had a lower \((p < 0.001)\) mean plasma norepinephrine concentration \((301.5 ± 22.4 \text{ pg/ml})\) than the patients with cerebral infarction.

Blood Pressure

Unlike age, blood pressure exhibited a weak but significant positive relationship to the norepinephrine values in the control subjects (table 4). This

TABLE 2. Mean (± SEM) Values for Characteristics of Cerebral Infarction (n = 74) and Control (n = 33) Patients. Significant Differences from Control are Indicated (**p < 0.001, *p < 0.02)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cerebral Infarction</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm/Hg)</td>
<td>139.9 ± 3.7</td>
<td>132.7 ± 2.6</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm/Hg)</td>
<td>82.4 ± 1.4</td>
<td>78.2 ± 2.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79.6 ± 1.5</td>
<td>77.8 ± 1.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.7 ± 1.4**</td>
<td>57.3 ± 3.1</td>
</tr>
<tr>
<td>Serum cortisol (mcg/ml)</td>
<td>16.4 ± 1.1*</td>
<td>11.9 ± 1.1</td>
</tr>
</tbody>
</table>

TABLE 3. Comparison of Catecholamine Levels in Patients with Cerebral Infarction and Controls with Adjustment for Age and Blood Pressure

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>Adjusted mean concentration (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>360.9</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>75.1</td>
</tr>
<tr>
<td>Dopamine</td>
<td>48.3</td>
</tr>
</tbody>
</table>

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Severity of Stroke

The patients with stroke were evaluated using the stroke index weighted for such factors as level of consciousness and degree of disability. The index was available in all but 2 of the patients in the cerebral infarction group and ranged from 0 (normal) to 170 (maximal severity). The median index for this population was 15 with a skewed distribution of data between 1 and 132. Patients below the median level had a mean norepinephrine value of 374.6 ± 27.8 compared with 501.9 ± 62.1 pg/ml for those more severely disabled (p = 0.07). Younger patients had less severe strokes. Of those persons 65 years or less, 13 of 19 had a stroke index under the median value compared with 23 of 53 in the older age group (χ² = 3.5, p = 0.06).

Discussion

The plasma norepinephrine concentration has been accepted as an index of peripheral sympathetic activity in previous studies of cardiovascular and neurologic disorders. Norepinephrine is a neurotransmitter in the sympathetic nervous system both in the brainstem and the periphery. Increases in sympathetic tone are accompanied by the release of norepinephrine into the synaptic cleft of the nerve terminal-receptor site. Some "spill over" into the plasma seems to occur upon stimulation so that the norepinephrine concentration in the plasma is usually elevated if the sympathetic activity is high.

Subarachnoid hemorrhage has been associated with raised plasma norepinephrine and sympathetic activity. A similar phenomenon has been suspected in cerebral infarction. In 1964 Tomomatsu et al. reported elevated urinary catecholamines in 7 patients with prolonged cerebral ischemia or infarction. More recently, Meyer et al. found plasma norepinephrine values to be high in cerebral infarction. However, this report included only 5 control subjects and the majority of the 23 patients with infarct were studied more than 3 days after the acute event. In 10 patients with acute cerebral infarction, Kanda et al. noted a significant increase in serum dopamine beta-hydroxylase, another putative index of sympathetic activity, but the study did not include any control subjects. High urinary norepinephrine excretion has also been correlated with mortality in cerebral infarction and the authors proposed norepinephrine as a possible predictor of subsequent mortality.

In the present study, elevated plasma norepinephrine values were found in patients with cerebral infarction. This increase may be independent of blood pressure, age and stress, factors which could affect plasma norepinephrine concentration. The increase in norepinephrine could not be explained by hospitalization since it was not found in the control group. Some of the control subjects had conditions which previously have been associated with high norepinephrine levels (brain tumor and Guillain Barré syndrome) and yet the mean values of the stroke group were still over 50 percent higher.

The effect of age on plasma norepinephrine concentration remains controversial. Most of the studies reported to date have involved hypertensive populations with or without control groups. Although some workers have reported a significant positive correlation between age and norepinephrine, others have found this to be present only in younger subjects.

### Table 4. Coefficient of Correlation (r) for the Plasma Norepinephrine Value Compared with Blood Pressure, Heart Rate and Age for Stroke and Control Groups

<table>
<thead>
<tr>
<th>Systolic blood pressure</th>
<th>Stroke Correlation coefficient (r) vs</th>
<th>Control Correlation coefficient (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic blood pressure</td>
<td>r = 0.2184</td>
<td>r = 0.3641**</td>
</tr>
<tr>
<td>Heart rate</td>
<td>r = 0.1813</td>
<td>r = 0.4134***</td>
</tr>
<tr>
<td>Age</td>
<td>r = 0.2305*</td>
<td>r = 0.4257***</td>
</tr>
<tr>
<td></td>
<td>r = 0.1674</td>
<td>r = 0.0770</td>
</tr>
</tbody>
</table>

Relationship was not seen in the group with stroke suggesting that higher norepinephrine values were not likely affected by blood pressure. Furthermore, the 61 "normotensive" (WHO criteria less than 160/95 mm Hg) stroke victims who had a mean blood pressure (133.9 ± 2.2/78.7 ± 1.3 mm Hg) similar to the control group (table 2) had a significantly higher (p < 0.01) mean plasma norepinephrine concentration (413.7 ± 38.5 pg/ml) compared to the controls.
In some instances there was no correlation detected. There is generally more agreement that blood pressure correlated positively with norepinephrine in both hypertensive patients and normotensive controls. However, the correlation is not a strong one and could be missed in any single population, especially if numbers are relatively small.

Blood pressure correlated significantly with norepinephrine in the control group but not in the patients with cerebral infarction, suggesting that the neurologic event in some way altered the weak relationship between blood pressure and norepinephrine. This observation is consistent with the belief that high blood pressure itself was not the cause of the elevated norepinephrine in the stroke group. Also, the plasma norepinephrine remained significantly increased in the stroke group after adjustment for blood pressure and age using multivariate analysis.

Stress is another factor which may raise the plasma norepinephrine concentration so serum cortisol was measured simultaneously with the norepinephrine to see if there was any significant relationship. The low coefficient of correlation suggests that stress, as measured by serum cortisol levels, was not an important determinant of the elevated plasma norepinephrine. The mean cortisol concentration in patients with cerebral infarction was significantly higher than in controls, although both values were within the normal range. These findings parallel the results of studies in subarachnoid hemorrhage where both plasma catecholamines and cortisol have been reported to be high. The data in subarachnoid hemorrhage suggest that the neurologic event is responsible for the increased values, possibly via hypothalamic mechanisms. The same phenomenon could explain the elevated cortisol in our study although stress could not completely be excluded.

It is conceivable that the increased circulating norepinephrine detected in patients with cerebral infarction originated primarily from the destruction of brain tissue and not from the synaptic clefts of the sympathetic nerve terminals. Although this possibility cannot be excluded, a stronger correlation between the severity of the stroke and the norepinephrine level might have been expected than was found in this study. Also, the plasma epinephrine concentration was significantly elevated in the patients with acute cerebral infarction. This hormone is primarily secreted from the adrenal glands and is not found in high concentrations in the cerebral hemisphere tissue.

In studies on plasma norepinephrine in cerebral infarction, it seems advisable to exclude those individuals with either concurrent seizure activity or a hemorrhagic component when identifiable. Among the patients not included in the present series, 7 with a grand mal seizure occurring within the previous 24 hours had a mean plasma norepinephrine concentration of 533.0 pg/ml and in 4 with intracerebral hemorrhage the value was 698.0 pg/ml. The addition of these latter 4 individuals to the stroke group would have made the difference from the controls more striking. The catecholamine values for the patient with transient ischemic attacks were intermediate between the stroke and control groups. Because of relatively small numbers, it is difficult to draw any conclusions from these data.

The norepinephrine concentration in cerebral infarction is elevated in comparison with non-stroke control subjects and the increase is not fully explained by factors such as age, blood pressure or stress. The presence of high plasma norepinephrine in stroke could explain the cardiac arrhythmias, ECG abnormalities and raised the serum cardiac enzymes. In subarachnoid hemorrhage, there is considerable evidence that increases in sympathetic activity following the acute event result in the adverse cardiac effects associated with this condition. It now appears that the same mechanism is possible in cerebral infarction.

Acknowledgment

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References

In Vivo and In Vitro Studies on the Cerebrovascular Dilatation Induced by Diazoxide in Normotensive And Renal Hypertensive Goats

C. Estrada, M.D., G. Dieguez, M.D., M.V. Conde, Ph.D., B. Gomez, M.D., and S. Lluch, M.D.

SUMMARY We studied the in vivo and in vitro effects of diazoxide on the cerebral circulation of 8 normotensive (mean arterial pressure = 100 mm Hg) and 5 renal hypertensive (mean arterial pressure = 146 mm Hg) goats. Intravenous injection of 5 mg/kg of diazoxide into normotensive goats increased cerebral blood flow 40 ml/min/100 g and mean arterial pressure dropped 22 mm Hg whereas in hypertensive goats cerebral blood flow was unchanged and mean arterial pressure decreased 50 mm Hg. The increase in heart rate due to intravenous diazoxide was similar in normotensive and hypertensive goats (35 beats/min). Cumulative applications of diazoxide (10^{-4} to 10^{-2}M) on isolated middle cerebral arteries produced dilatory responses both under resting conditions and after previous tonic contraction by serotonin. This relaxation was significantly greater in arterial segments from hypertensive goats. The results indicate that diazoxide exerts powerful dilatatory effects on cerebral vessels, both in vivo and in vitro, and that these effects are particularly evident in hypertensive animals.

EMERGENCY TREATMENT in a hypertensive crisis still raises many questions regarding the consequences on cerebral circulation. Hypotensive drugs devoid of effect on cerebral vessels risk decreasing cerebral blood flow and inducing cerebral ischemia, since hypertensive patients' tolerance to blood pressure reductions is impaired.1,2 On the other hand, hypotensive drugs inducing cerebral vasodilatation may be harmful by increasing intracranial pressure5 or in producing arteriolar dilatation in elderly patients with arteriosclerotic stenosis, so that perfusion pressure reduces. It is important to know the direct effect of antihypertensive drugs on cerebral circulation in order to select proper treatment.

Diazoxide is a benzothiadiazine derivative devoid of diuretic action that is widely used in the treatment of hypertensive crisis. Data obtained from animal and human studies indicate that the mechanism of hypotensive action is direct relaxation of vascular smooth muscle.4 With regard to the cerebral vessels there are clinical observations indicating that cerebral blood flow is maintained within normal levels during the hypotensive action of diazoxide.7 Previous results from this laboratory5 indicated that diazoxide has a direct dilatatory effect on cerebral vessels when it is administered through the internal maxillary artery of the unanesthetized goat. When the drug is injected intravenously, as a bolus, in doses of 5-7 mg/kg it produces hypotension while cerebral blood flow is increased, thus indicating a drop in cerebrovascular resistance.

This paper describes an investigation into the effects of diazoxide on the cerebral circulation of normotensive and renal hypertensive goats. The experiments in vivo were carried out in the unanesthetized animal, using an experimental preparation that permits the effects on cerebral blood flow of various interventions to be assessed in normal states.8,9 In addition, the
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