Cardiac Sequelae of Acute Stroke*

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SUMMARY The possibility that acute stroke produces an increase in sympathetic tone with resultant cardiac abnormalities was examined in 100 stroke patients admitted to a stroke ICU and in 50 controls found to have diagnoses other than stroke or TIA after admission to the Unit. Continuous 24 hour Holter ECG tapings were performed and serum cardiac enzymes and plasma norepinephrine concentrations were measured within 48 hours after admission. Significantly, (p < .001) more serious arrhythmias were observed during 24 hour Holter ECG monitoring in stroke patients compared with controls and the difference remained (p < .01) after matching for age and co-existing heart disease. Arrhythmias were more common in older stroke (p < .001) and older control (p = .05) patients and with infarction of the cerebral hemispheres (p < .05) as compared to brainstem lesions. Arrhythmia occurrence was independent of the presence of co-existing heart disease and the level of sympathetic activity. However, the 15 stroke patients with abnormally high CK values (mean 34.3 units) had a higher (p < .02) mean plasma norepinephrine concentration (650.4 pg/ml) than stroke patients with normal CK (427.7 pg/ml). Acute stroke may cause cardiac arrhythmias and myocardial cell damage, the latter through stroke induced increases in sympathetic tone.

Stroke Vol 13, No 6, 1982

ACUTE STROKE has been associated with a variety of cardiac abnormalities. Subarachnoid hemorrhage produces cardiac arrhythmias, changes in the 12 lead electrocardiogram and focal myocardial necrosis. Similar findings have been reported in intracranial hemorrhage in both animals and man. Cerebral infarction has also been reported to increase serum cardiac enzymes and cause repolarization changes on the electrocardiogram suggestive of ischemia.

Two recent studies from our Unit favour a causal relationship between stroke and cardiac abnormalities. Stroke patients at autopsy were found to exhibit focal myocardial myocytolysis comparable to the patchy necrosis observed in the hearts of subarachnoid hemorrhage patients. Also, plasma norepinephrine was significantly elevated in a group of stroke patients compared with non-stroke controls. Additional data derived from oscilloscope ECG monitoring have suggested that cardiac arrhythmias may be more common in stroke patients. These observations led to the hypothesis that acute stroke may increase sympathetic activity with resultant electrocardiographic abnormalities and myocardial cell necrosis.

In order to test this hypothesis, we evaluated 100 stroke patients for several cardiac parameters including arrhythmias detected by 24 hour Holter monitoring, serum cardiac enzyme and plasma norepinephrine values. Similar studies were also performed in 50 control subjects matched with a sub-group of the stroke patients for age and the presence of heart disease to determine if the stroke and not co-existing heart disease was the cause of the anticipated cardiac abnormalities.

Methods

All patients admitted to the Acute Stroke Unit between June, 1977 and May, 1980 were considered for the study. Exclusion criteria included concurrent anti-arrhythmic or beta-blocker therapy, recent initiation of digitalis treatment, poor cooperation of the patient and failure to obtain informed consent from the patient or next of kin.

A single 24 hour Holter electrocardiogram recording was performed on each patient within 48 hours after admission to the Unit. Blood samples were taken for measurement of serum creatine kinase (CK) glutamic oxalo-acetic transaminase (SGOT), lactic acid dehydrogenase and plasma norepinephrine, epinephrine and dopamine. The blood for catecholamine determinations was removed via an indwelling intravenous line at least 30 minutes after the insertion of the needle. Patients were kept recumbent and in quiet surroundings. Blood pressure and heart rate were recorded in duplicate using a Random Zero sphygmomanometer prior to the insertion of the intravenous and after blood sampling. The mean values were calculated for data analysis. All studies were performed between 1300 and 1400 hours after a standard hospital meal at 1200 hours.

Diagnosis of 'stroke' was established on the basis of clinical examination, cerebrospinal fluid analysis, isotope brain scan, computerised axial tomography of the brain and cerebral angiography if clinically indicated. Only patients with cerebral infarction or intracerebral hemorrhage were entered into the study.

The control group was composed of patients admitted to the Unit and found to have diagnoses other than stroke or transient ischemic attacks. They had a variety of conditions including meningioma, peripheral neuropathy, degenerative cervical disc disease, migraine, meningitis and psychogenic illness. All control...
subjects underwent the same procedures as the stroke group.

The Holter electrocardiogram recordings were read using a semi-automated ‘Cardio-Scanner’ (Avionics Ltd) by an observer unaware of the patient’s diagnosis. Each recording was also verified independently by a Cardiologist not involved in the data collection. Each ECG taping was divided into 24 segments of 1 hour. Arrhythmias occurring in any one hour period were noted as ‘one arrhythmia hour.’ For example, if a patient had 5 or more ventricular premature beats per minute during 6 different hour segments, he was noted to have ‘6 arrhythmia hours’ for this category of rhythm disturbance. The 5 ventricular premature beats need only have occurred once during the hour to include this hour as one in which an arrhythmia was observed. For the purpose of analysis, each of the following was designated as a ‘serious arrhythmia’ and the number of hours of serious arrhythmias was tabulated for the stroke and control groups: ventricular tachycardia, couplets, 5 or more VPB’s per minute, second degree or third degree heart block. For example, if episodes of ventricular tachycardia were observed during each of 3 hours in one stroke patient and during 2 hours in another, then the stroke group would have had 5 arrhythmia hours under the ventricular tachycardia category. This number would then be added to the number of hours during which couplets and frequent ventricular premature beats were seen in this group in order to derive the total number of serious arrhythmia hours for the stroke patients. The mean duration of taping in the stroke patients was 19.9 hours and 21.9 hours in the controls.

Plasma catecholamine concentrations were measured according to the method of Sole and Hussain. Standard biochemical assays were used to determine serum CK, SGOT and LDH values. The possible effect of co-existing heart disease in the genesis of cardiac arrhythmias was evaluated by matching the stroke and control groups for this variable. Clinically apparent heart disease was diagnosed on the basis of physical examination, 12 lead electrocardiogram and previous medical records either in hospital or from the family physician. Categories included ischemic heart disease, congestive heart failure, hypertensive and valvular heart disease. Differences between groups were evaluated for statistical significance using the Chi-Square test for proportions and Student’s unpaired t test for mean values.

Results

The stroke group was composed of 100 patients, 64 with hemispheric infarction, 26 with brainstem infarction and 10 with intracerebral hemorrhage. There were 58 males in this group and 25 females among the 50 controls. Stroke patients exhibited more cardiac arrhythmias of all types compared with the control subjects (table 1). Serious ventricular ectopic activity and heart block were more common ($x^2 = 27.92, p < .001$) in the entire stroke group and also in the 50 strokes matched with the controls for age and the presence of heart disease ($x^2 = 6.87, p < .01$). Other electrocardiographic abnormalities were also more common in the stroke group. Atrial premature beats and first degree heart block were observed during 95 and 207 hours in the stroke patients’ recordings compared with 24 and 43 hours respectively in the controls. The excess of serious arrhythmias in the stroke group did not appear to result from the presence of frequent rhythm disturbances in only a few patients. Thirty-five of the 100 stroke patients exhibited at least one episode of serious ventricular ectopic activity or heart block compared with 9 of 50 subjects in the control group ($p < 0.05$).

Data from the stroke patients were further analysed to discover a possible explanation for the observed excess in arrhythmias. Co-existing heart disease did not appear to cause the increase in arrhythmias. The 51 patients with clinically apparent heart disease had a similar incidence of serious arrhythmias compared with those without heart disease (table 2). However, the location of the stroke was a possible factor in the genesis of the rhythm disturbances. Hemispheric infarction caused significantly more serious arrhythmias ($x^2 = 4.89, p < .05$) than brainstem infarction (table 2). The intracerebral hemorrhage sub-group was too small ($n = 10$) to obtain any statistically valid comparisons from the observed data.

Age was also an important factor in the occurrence of cardiac arrhythmias. The stroke group had a significantly higher ($p < .001$) mean age (71.4 $+/1 1.1$ years) than the controls (66.2 $+/1 1.6$ years). Older strokes had more serious arrhythmias ($x^2 = 17.32, p < .001$) than those under age 70 (table 3). A similar preponderance of arrhythmias ($x^2 = 3.71, p = .05$) was observed in the older controls compared with younger subjects (table 3). Fifty-eight of the 100 stroke patients were male and they had about the same number of serious arrhythmia hours (141) as the 42 females (108).

Sympathetic activity as measured by plasma norepinephrine was elevated in the stroke group (table 4). Similar increases were noted for the other catecholamines assayed, epinephrine and dopamine. Blood pressure and heart rate were also raised slightly in the stroke group (table 4) but the differences did not appear to be clinically important. Stroke patients with high plasma norepinephrine did not exhibit an increase in cardiac arrhythmias (table 2). The mean serum CK was higher in the stroke patients and the 15 members of the stroke group with abnormal serum CK values (above 11 units) had a higher ($p < .02$) mean norepinephrine concentration ($650.4 +/1 112.8$ pg/ml) than the remaining stroke patients ($427.7 +/1 37.9$ pg/ml). Serious cardiac arrhythmias were equally common in the high and normal serum CK patients.

Discussion

The findings in this study favour an association between cerebral infarction and abnormalities in cardiac
function. An excess of arrhythmias was seen in the 100 stroke patients compared with controls in all categories including ventricular ectopic beats and heart block. The increased occurrence of arrhythmias could not be accounted for by differences in age or the presence of co-existing heart disease in the stroke group.

Previous investigators have reported an association between increasing age and the frequency of cardiac arrhythmias in apparently healthy subjects free of overt vascular disease. The present data are consistent with these observations. In both the stroke and control groups, individuals over age 70 had significantly more arrhythmias compared with those under age 70. Although the stroke patients were older, they still had more arrhythmias than the controls when age was taken into account by matching.

Underlying heart disease has been suspected as being an important factor in the genesis of cardiac arrhythmias in stroke patients. However, there is little evidence to support this belief. We do know that individuals with coronary artery disease exhibit frequent cardiac arrhythmias during continuous ECG monitoring. In designing the present study, we prospectively evaluated each subject for the presence or absence of cardiac arrhythmias during continuous ECG monitoring. Since most of the centers of cardiovascular control are located in the brainstem, perhaps the cardiac effects of stroke result from factors such as increases in intracranial pressure rather than direct injury to vasomotor or sympathetic efferent neurons.

An increase in sympathetic activity has been proposed as a causative factor in the genesis of cardiac abnormalities following acute stroke. This hypothesis is supported by the presence of high plasma norepinephrine concentrations in the stroke patients with elevated serum CK values. The high serum CK in stroke was also observed in an earlier report from our Unit based upon bedside ECG monitor observations. Since most of the centers of cardiovascular control are located in the brainstem, perhaps the cardiac effects of stroke result from factors such as increases in intracranial pressure rather than direct injury to vasomotor or sympathetic efferent neurons.

Table 1: The Results of 24 Hour Holter ECG Recording are Shown Including the Following Arrhythmias: Ventricular Tachycardia (V. Tach), 2 Consecutive Ventricular Beats (couplet), 5 or more VPB's/min, 1-4 VPB's/min and Heart Block

<table>
<thead>
<tr>
<th>No. arrhythmia hours</th>
<th>n</th>
<th>V. tach*</th>
<th>Couplet*</th>
<th>VPB* 5 +/min</th>
<th>VPB 1-4/min</th>
<th>Heart block</th>
<th>No. Serious arrhythmia hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strokes</td>
<td>100</td>
<td>5</td>
<td>33</td>
<td>167</td>
<td>504</td>
<td>95</td>
<td>3 17 225</td>
</tr>
<tr>
<td>Controls</td>
<td>50</td>
<td>—</td>
<td>4</td>
<td>48</td>
<td>218</td>
<td>24</td>
<td>— — 52</td>
</tr>
<tr>
<td>Matched strokes</td>
<td>50</td>
<td>1</td>
<td>6</td>
<td>72</td>
<td>280</td>
<td>4</td>
<td>1 2 82</td>
</tr>
</tbody>
</table>

*Serious arrhythmias.

The increased occurrence of arrhythmias could not be accounted for by differences in age or the presence of co-existing heart disease in the stroke group. The present data are consistent with the presence of heart disease in more of its members than in the control group. This is possible since we were unable to exclude for certain the presence of heart disease in the stroke patients in the absence of stress test or cardiac catheterization data.

The site of the cerebral infarction appeared to be a factor in the genesis of arrhythmias. Patients with hemispheric infarction had more severe arrhythmias than those with lesions in the brainstem. This observation is consistent with our previous findings based upon bedside ECG monitor observations. Since most of the centers of cardiovascular control are located in the brainstem, perhaps the cardiac effects of stroke result from factors such as increases in intracranial pressure rather than direct injury to vasomotor or sympathetic efferent neurons.

Table 2: The Results of 24 Hour Holter ECG Recording are Shown Including the Following Arrhythmias: Ventricular Tachycardia (V. Tach), 2 Consecutive Ventricular Beats (couplet), 5 or more VPB's/min, 1-4 VPB's/min and Heart Block

<table>
<thead>
<tr>
<th>No. arrhythmia hours</th>
<th>n</th>
<th>V. tach*</th>
<th>Couplet*</th>
<th>VPB* 5 +/min</th>
<th>VPB 1-4/min</th>
<th>Heart block</th>
<th>No. Serious arrhythmia hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>With heart disease</td>
<td>51</td>
<td>5</td>
<td>22</td>
<td>74</td>
<td>290</td>
<td>46</td>
<td>2 15 118</td>
</tr>
<tr>
<td>Without heart disease</td>
<td>49</td>
<td>—</td>
<td>11</td>
<td>93</td>
<td>214</td>
<td>49</td>
<td>1 2 107</td>
</tr>
<tr>
<td>Hemispheric infarction</td>
<td>64</td>
<td>5</td>
<td>32</td>
<td>119</td>
<td>311</td>
<td>50</td>
<td>3 15 174</td>
</tr>
<tr>
<td>Brainstem infarction</td>
<td>26</td>
<td>—</td>
<td>1</td>
<td>47</td>
<td>96</td>
<td>45</td>
<td>— 2 50</td>
</tr>
<tr>
<td>Norepinephrine ≥ 400 pg/ml</td>
<td>39</td>
<td>1</td>
<td>12</td>
<td>39</td>
<td>141</td>
<td>68</td>
<td>— — 52</td>
</tr>
<tr>
<td>Norepinephrine &lt; 400 pg/ml</td>
<td>32</td>
<td>—</td>
<td>12</td>
<td>49</td>
<td>201</td>
<td>36</td>
<td>— — 61</td>
</tr>
</tbody>
</table>

**"Serious" arrhythmias.
possible explanations for this negative result. The sample size may have been inadequate for the frequency of serious cardiac arrhythmias observed in the stroke group. Age could have been a confounding variable since it was an important determinant of arrhythmia occurrence in both the stroke and control populations. The absence of CK-MB data may have reduced the likelihood of detecting an association between myocardial damage and arrhythmia occurrence. It is also possible that peripheral venous norepinephrine concentrations may not reflect sympathetic activity to the heart in all cases since cardiac sympathetic fibres can be stimulated selectively in the absence of a generalised increase in sympathetic tone.22

Most of the earlier reports14–16 that suggested an association between stroke and cardiac arrhythmias may be criticised on the basis of shortcomings in methodology and research design. Examples include the absence of proper control groups for comparison with the stroke patients, arrhythmia detection and interpretation by the ward or Unit nursing staffs with a potentially high interobserver variability and possible observer bias as a result of the diagnoses of the stroke and control groups being available to those documenting the occurrence of arrhythmias. The present study was designed to minimize these potential methodologic problems. Stroke and control patients were prospectively matched for age and the presence of heart disease, ECG recordings were obtained via continuous Holter taping and arrhythmias were interpreted by a "blind observer."

The resulting data affirm a causal relationship between stroke and subsequent cardiac abnormalities. Acute stroke was accompanied by an increase in cardiac arrhythmias and myocardial cell necrosis. The arrhythmias occurred most often in older patients with infarction of the cerebral hemispheres. The myocardial damage may have resulted from increases in sympathetic tone since elevated plasma norepinephrine values were associated with abnormally high CK concentrations. Finally, co-existing heart disease was excluded as a contributing factor to the occurrence of arrhythmias. From these observations, we conclude that the cardiac abnormalities seen in stroke patients may actually be caused by the cerebral event and do not simply reflect co-existing heart disease.

Acknowledgements

Dr. Myers is a Senior Research Fellow and Drs. Hachinski and Sole are Research Associates of the Ontario Heart Foundation. The authors would like to thank Drs. B. Chesnie and C. Pollick for assisting with the interpretation of the Holter tapes and Ms. A. G. McMillan and Ms. E. Roberts for technical and secretarial assistance.

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The Effect of Intravenous Dipyridamole on the Cerebral and Systemic Circulations of the Dog

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SUMMARY In 7 dogs anesthetized with halothane and nitrous oxide, dipyridamole was administered in a loading dose of 1 mg/kg supplemented with 0.5 mg/kg every 30 minutes. Cardiovascular parameters and organ blood flows (using the radioactive microsphere technique) were measured before and at 30 minute intervals after each administration of dipyridamole, for a total of 105 minutes.

The administration of dipyridamole was associated with a 20% reduction in systemic arterial pressure, a 31% reduction in peripheral vascular resistance, and a 13% increase in cardiac index. Cerebrovascular resistance decreased 21%, but regional cerebral blood flow and metabolism were unchanged. Blood flow to the heart increased 355% in the right ventricle and 213% in the left ventricle. Blood flow to the jejunum decreased 52% while blood flow to the kidney and liver decreased slightly.

The circulatory effects of dipyridamole are probably related to its interference with the inactivation of endogenous adenosine. The differential effects of dipyridamole on organ flow are similar to those seen following the IV infusion of adenosine.

DIPYRIDAMOLE is a compound that is best known as an antiplatelet agent.\textsuperscript{8,9,25} It also has vasodilatory actions that are very marked on the coronary vessels, and less pronounced on the cerebral and peripheral circulation.\textsuperscript{5,6,10,15,24,28} These properties suggest that dipyridamole may be a potentially useful agent in the management of patients in whom the cerebral circulation is compromised by thromboembolism or vasospasm following subarachnoid hemorrhage, particularly when the full anticoagulant effects of heparin are contraindicated. The purpose of this study was to document the cerebral and systemic circulatory effects of intravenous dipyridamole.

Materials and Methods

Seven mongrel dogs weighing approximately 17 kilograms (14.5–20 kg) were used for this study. Anesthesia was induced with 1% halothane and maintained with 0.5% halothane and nitrous oxide-oxygen (70:30). Muscular paralysis was achieved with pancuronium 0.5 to 0.7 mg per kilogram total, given in divided doses. Ventilation was controlled with a pump respirator. The animals were hyperventilated and CO\textsubscript{2} added to the inspired gas mixture to maintain arterial PCO\textsubscript{2} at approximately 40 torr. Temperature was maintained at 37°C with a warming blanket.

Blood flow was determined six times in each dog using the radioactive microsphere technique with 15 ± 5 μm spheres labeled with \textsuperscript{141}Ce, \textsuperscript{46}Sc, \textsuperscript{96}Nb, \textsuperscript{88}Sr, \textsuperscript{113}Sn, and \textsuperscript{153}Gd.\textsuperscript{5,16,21} The microspheres were injected into the left ventricle utilizing a pigtail catheter inserted through the femoral artery and positioned manometrically. Blood reference samples were drawn from the right femoral and brachial arteries. At the completion of the experiment the brain was removed and divided into cerebral hemisphere gray matter and mixed gray and white samples, caudate nuclei, corpus callosum, brain stem, and cerebellum. In addition, samples of the
Cardiac sequelae of acute stroke.
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Stroke. 1982;13:838-842
doi: 10.1161/01.STR.13.6.838
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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