Serum Cardiac Enzymes in Stroke

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SUMMARY Serum cardiac enzyme levels (CK, LDH, SGOT) were estimated and the ECG recorded for 4 days following admission of 288 patients (Group I) to a stroke intensive care unit. Sixty-four of these patients, subsequently found not to have strokes, served as controls. Mean serum levels of all 3 cardiac enzymes were elevated in 8% of the 224 patients with stroke. The mean serum enzyme levels in patients with transient ischemic attacks (TIA) did not differ from controls.

In a second group of 230 patients with stroke (Group II) serum CK levels were measured and the iso-enzymes were fractionated to determine the tissue source of the enzymes. One hundred and one patients had raised total CK values and 25 of these (11%) had raised CK-MB (heart) iso-enzyme, the remainder having CK-MM (skeletal muscle) fraction. No serum CK-BB (brain) iso-enzyme was detected in any patient. Patients with positive serum levels of CK-MB had more evidence of acute myocardial ischemia on ECG (p < 0.05), and more cardiac arrhythmias (p < 0.001) than those with normal CK levels. Scattered areas of myocytolysis were found in the myocardium at autopsy in one patient.

The acute rise in serum cardiac enzymes which we have recorded in the initial stages of stroke suggest that acute myocardial involvement is a commoner complication than is generally recognized. Also, since the CK-MB rises were modest and progressive, it is more likely that this acute myocardial dysfunction is a consequence, rather than a cause, of the acute cerebrovascular lesion.

SUBARACHNOID hemorrhage produces a variety of cardiac disturbances in both animals and man.1-4 These include electrocardiogram (ECG) changes,1 disturbances of cardiac function,4 focal myocardial necrosis,8 and an increase in circulating catecholamines.3 Although similar cardiac changes occur in other forms of intracranial hemorrhage,4 the occurrence of similar cardiac changes in non-hemorrhagic forms of stroke is less certain.

Raised levels of serum cardiac enzymes — serum glutamic oxalo-acetic transaminase (SGOT), lactate dehydrogenase (LDH) and creatine phosphokinase (CK) — have been reported in the initial phase of stroke5-6 but without iso-enzyme fractionation, the tissue source of these enzymes has not been proven. Twenty-nine percent of patients with stroke investigated by Dimant and Grob1 had raised serum enzyme levels and those with elevated CK levels had a higher incidence of ECG abnormalities, as well as a higher mortality than those with normal CK levels.

The high incidence of cardiac arrhythmias in patients with acute stroke7-10 may simply reflect underlying vascular disease common to both the heart and brain. However, the association of the cardiac arrhythmia with an acute rise in serum cardiac enzyme levels at the onset of the stroke may indicate the presence of an acute myocardial lesion.

In the present study, daily serum enzyme determinations, 12-lead ECG's and continuous cardiac monitoring were performed to elucidate a possible association between stroke and abnormalities of cardiac function.

Materials and Methods

All patients, initially admitted to the emergency room of a general hospital, were transferred to the stroke intensive care unit (Unit) when an acute cerebrovascular lesion was suspected. The Unit consists of 5 beds with facilities for continuous nursing and medical care, including cardiac monitoring. Details of this facility and classification of the types of strokes are described elsewhere.11 Diagnosis of the type of stroke was based on clinical examination, cerebral spinal fluid analysis, isotope brain scan, computerized axial tomography of the brain and, where indicated, cerebral angiography.

Serum enzyme levels were determined daily for the first 4 days following admission. CK was estimated by the method of Rosalki,12 LDH was assayed by the method of Wroblewski,13 and SGOT was estimated by the Henry modification of the Karmen method.14 Serum cardiac enzyme levels were said to be raised when at least 2 of these 3 enzyme levels were elevated.

When CK was found to be greater than 9 Okinaka units, the CK iso-enzymes were fractionated by the method of agar electrophoresis (Corning ACI). The 3 bands which can be identified by this method are CK-MM (skeletal muscle), CK-MB (cardiac muscle), and CK-BB (brain). Significant MB iso-enzyme was reported present if more than a trace was detected.

Both quantitative and qualitative values of CK can be obtained by the Corning ACI method. Quantitation is achieved by photographing the fluorescence caused by the iso-enzymes acting on a fluorescent substrate. The negative is scanned using a Beckman densitometer. The data have been verified in our laboratory using tissue extracts and commercial control sera and found to be quantitative.

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Drs. Hachinski and Myers are Senior Research Fellows of the Ontario Heart Foundation.
We estimated the total CK units and proportion of CK in each of the fractions on electrophoresis. Our normal range for CK-MB is less than one (values usually undetectable). The specificity of this method has been tested against various tissue extracts including the heart, skeletal muscle, brain, liver and others.

Results

Group I

In an initial series of 288 patients admitted to the Unit, serum CK (without iso-enzyme fractionation), SGOT and LDH were estimated daily for the initial 4 days following admission. Sixty-four patients subsequently found not to have stroke served as a control group and they had a variety of illnesses including Ménière's disease and cerebral tumors. The numbers of the different types of strokes are shown in table 1. When the total numbers of patients in the stroke and control groups were compared, there was no significant difference in the incidence of raised CK, SGOT and LDH levels (table 1). However, the mean values of all 3 enzymes were raised in the sub-group with cerebral hemorrhage (table 2). Significantly elevated CK values were found in all stroke sub-groups except for TIA.

Control Group with Raised Enzyme Levels

Eight of the 64 control cases had a rise in 2 or more serum cardiac enzyme levels (table 1). Two had acute myocardial infarction and one had acute coronary insufficiency. These patients were admitted to the Unit because of syncope but no neurological lesion was found subsequently. The raised enzyme levels in the remaining 5 cases in this group could be accounted for due to non-cardiac effects such as trauma or intramuscular injections. A second group of patients involving one patient with subarachnoid hemorrhage.

Table 1 Comparison of Stroke and Control Groups of Patients with Elevated Serum Levels of at Least 2 Cardiac Enzymes (Group I) or with Elevated CK-MB iso-enzymes (Group II)

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>Hemispheric infaracts</td>
<td>137</td>
<td>148</td>
</tr>
<tr>
<td>Brain stem infaracts</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Transient ischaemia attacks (TIA)</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>Total Strokes</td>
<td>224</td>
<td>230</td>
</tr>
<tr>
<td>Control Group</td>
<td>64</td>
<td>53</td>
</tr>
</tbody>
</table>

† Includes one patient with subarachnoid hemorrhage.

Stroke Group with Raised Enzyme Levels

Eighteen of 224 patients with stroke had raised enzyme levels (table 1) including 11 in whom the ECG showed changes compatible with myocardial damage. Four of these 11 had evidence of acute transmural myocardial infarction, 3 had evolving ST-T wave changes consistent with subendocardial ischemia or infarction (fig. 1), while 4 showed left ventricular hypertrophy with marked ST depression and T-wave inversion.

Two of the 7 patients without ECG changes had other reasons for enzyme elevation, one having polymyositis and the other fulminating septicemia.

All 5 of the remaining cases had cardiac arrhythmias and 4 of these died shortly after discharge from the Unit. Therefore, 16 of the 18 patients in the stroke group with raised enzyme levels had evidence of possible cardiac dysfunction.

Group II

After initiation of this study, it became apparent that many of the raised enzyme levels observed were due to non-cardiac effects such as trauma or intramuscular injections. A second group of patients were, therefore, examined for the cardio-specific CK-MB iso-enzyme levels.

Two hundred and thirty patients with stroke and 53 controls were admitted to the Unit. One hundred and one patients with stroke and 35 controls were found to have raised total CK values (table 1). After iso-enzyme fractionation of the sera, 25 of the patients with stroke and 3 of the controls had raised CK-MB levels. CK-BB iso-enzyme was not detected in any patient and the remainder of the raised CK levels were due to elevated CK-MM.

Controls with Raised CK-MB Levels

All three patients without stroke were admitted in a stuporous state to the Unit with an initial diagnosis of acute cerebrovascular lesion. One patient had a transmural myocardial infarction, another had massive pulmonary embolism and the third had terminal hepatic coma. Cardiac arrhythmias were not detected in any.

Table 2 Incidence of Mean Serum Cardiac Enzyme Levels (± SEM) in Each Type of Stroke (Group I)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>CK (±SEM)</th>
<th>LDH (±SEM)</th>
<th>SGOT (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infaracts</td>
<td>7.2 ± 0.7†</td>
<td>206 ± 5.1</td>
<td>17.0 ± 0.5</td>
</tr>
<tr>
<td>Brain stem infaracts</td>
<td>7.4 ± 1.3†</td>
<td>176 ± 8.7</td>
<td>17.1 ± 1.4</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>11.0 ± 2.2***</td>
<td>245 ± 17.8**</td>
<td>20.7 ± 1.6**</td>
</tr>
<tr>
<td>TIAs</td>
<td>4.9 ± 0.7</td>
<td>192 ± 8.3</td>
<td>18.2 ± 1.2</td>
</tr>
</tbody>
</table>

Controls | 4.7 ± 0.6  | 188 ± 7.2  | 15.7 ± 7.3  |

| Difference from controls *p = 0.05, **p > 0.005, ***p > 0.001. |

1 Includes one patient with subarachnoid hemorrhage.

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A 64-year-old woman collapsed with a right hemiparesis and died 5 days after admission. Lumbar puncture 6 hours after admission revealed an opening pressure of 140 mm water (clear CSF with no cells). Day 1 $\text{CK} = 25$ (MB present), $\text{LDH} = 137$, $\text{SGOT} = 23$. Day 2 $\text{CK} = 26$ (MB present), $\text{LDH} = 174$, $\text{SGOT} = 30$. ECG showed acute myocardial infarction.
Stroke Patients with Raised CK-MB Levels

Seventeen of the 25 patients with stroke with elevated cardiac iso-enzyme levels had ECG findings consistent with myocardial damage. Three showed transmural myocardial infarction and 5 had evolving repolarization abnormalities compatible with subendocardial infarction. Nine had ECG evidence of left ventricular hypertrophy and strain. During the period of observation there were evolutionary changes showing progressively more ST depression and T-wave inversion.

In the remaining 8 patients in this group, no ECG abnormalities were seen, but 6 of them had cardiac arrhythmias and one had polymyositis.

The mean daily values of serum enzymes in these 25 patients with elevated CK-MB levels showed a gradual rise over the 4 days following admission (table 3). This is quite unlike the acute rise (within 24–28 hs) seen in acute myocardial infarction and suggests a process of continuing low-grade myocardial necrosis.

Incidence of Cardiac Arrhythmias

Twenty-three (92%) of 25 patients in the CK-MB+ group had cardiac arrhythmias compared to 102 (50%) of 205 patients in the CK-MB− group (chronic arrhythmias excluded). This difference is significant at \( p < 0.001 \) level, \( \chi^2 \) test). There was also a significant difference \( p < 0.02 \) in the total number of arrhythmias (table 4).

The 25 patients in the CK-MB+ group were then matched for age and sex with 25 patients in the CK-MB− group. Seventeen patients had ECG changes of evolving ST depression and T-wave inversion in the CK-MB+ group compared to 10 patients without detectable cardiac iso-enzyme levels \( p < 0.05, \chi^2 \) test).

Pathological Correlation

A 70-year-old man with a fatal brain stem infarction had raised CK-MB levels and evolving ST-T-wave changes on ECG. The patient had no previous heart disease and was admitted in a decerebrate and comatose state, dying on the fourth day. On the day of admission, CK = 40.0 O.U. (MB present), LDH = 222 I.U. and SGOT = 68 I.U. On the second day, CK = 16 O.U. (MB present), LDH = 263 I.U. and SGOT = 30 I.U. Serial daily ECG’s showed widespread and progressive depression of ST-T segments in the inferolateral chest leads with prominent U waves.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Stroke day</th>
</tr>
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<tbody>
<tr>
<td>CK-MB</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>LDH</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>SGOT</td>
<td>1 2 3 4</td>
</tr>
</tbody>
</table>

Superventricular ectopies | CK-MB+  Group | CK-MB− Group |
---------------------------|----------------|--------------|
Ventricular ectopies  | 10  20        | 47           |
Paroxysmal atrial fibrillation | 4  20        | 9            |
Ventricular tachycardia | 1  1          | 0            |
Nodal rhythm | 1  1          | 0            |
Total | 30* | 138 |

At autopsy there was extensive atherosclerosis of the coronary arteries and a recent subendocardial infarction of the left ventricle. No mural thrombus was present but there were multiple scattered areas of acute myocytolysis seen in the myocardium (fig. 2). Death was due to medullary compression from a swollen infarcted cerebellar hemisphere, associated with basilar artery thrombosis. There was no evidence of embolism to either the brain or any other organ.

Discussion

Myocardial dysfunction with intracranial hemorrhage is well documented, and includes evolving "ischemic" changes on ECG, a rise in serum cardiac enzymes and elevated serum catecholamine levels. Although autopsy examination of the heart in such patients may be surprisingly normal, subendocardial lesions are sometimes found. These myocardial changes have been attributed to increased sympathetic activity and can be produced experimentally in animals by infusion of catecholamines, and by stimulation of certain areas of the brain.

Although cerebral infarction is a more common form of stroke than cerebral hemorrhage, similar acute cardiac dysfunction has seldom been described. In 231 neurosurgical autopsies, 18 had focal myocytolysis but only one had cerebral infarction. However, raised serum CK levels with ischemic changes on ECG were associated with significantly increased mortality in 78 patients with ischemic strokes. Meyer et al. found an increase in serum and CSF catecholamines in a relatively small number of patients with acute cerebral infarction only when hypertension was also present. They concluded that the catecholamine increase resulted from the non-specific effect of stress and hypertension rather than the cerebral lesions themselves. We also found significantly higher levels of plasma catecholamines in patients with acute cerebral infarction compared to control (non-stroke) patients. Further, plasma catecholamine levels were significantly elevated in both normotensive and hypertensive stroke groups.

The significant elevations of serum SGOT, LDH and CK found in 8% of our patients with stroke, suggests a much higher myocardial involvement in...
ischemic or hemorrhagic stroke, than hitherto believed. The progressive ischemic changes on ECG and the timing of elevated cardio-specific CK isoenzyme are further evidence that these cardiac changes follow closely upon the heels of the acute cerebrovascular lesion. Also, the increased incidence of cardiac arrhythmias found in Group II is consistent with our previous finding of increased arrhythmias in a group of patients with acute stroke matched for age, sex and duration of stay in the Unit against a control group. The cerebral lesions themselves, however, do not appear to elevate serum cardiac enzyme levels in the absence of cardiac lesions or other causes known to affect these enzymes.

The incidence of raised cardiac enzyme levels was the same whether the lesion was ischemic or hemorrhagic so that embolism of a mural thrombus to the brain is unlikely to be the explanation. In any case, the massive cerebral ischemic lesions encountered can scarcely be attributed to the small subendocardial lesions as indicated by the minor serum enzyme elevations, since the degree of serum CK-MB rise is proportional to the volume of infarcted cardiac muscle. Although the specificity of the MB isoenzyme for cardiac muscle is controversial, it still remains the most sensitive indicator of acute myocardial necrosis. Circulating levels of serum CK-BB could not be detected by earlier workers but increasingly sensitive fluorometric and radioimmunoassay techniques have shown that trace amounts do exist and may rise following a variety of cerebral lesions. The early peak (within a few hours) and transient nature of the brain iso-enzyme in the blood may explain our inability to detect it in our patients.

The present findings indicate that acute ischemic
and hemorrhagic strokes may be accompanied by acute myocardial ischemia or infarction with raised serum cardiac enzyme levels and associated with cardiac arrhythmias. These coincidental findings raise the possibility that the acute cardiac abnormalities sometimes seen in stroke patients are a direct consequence of the neurological lesion.

Acknowledgment

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References

Serum cardiac enzymes in stroke.
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