Insular lesions, ECG abnormalities, and outcome in acute stroke

H Christensen, G Boysen, A F Christensen, H H Johannesen


PATIENTS AND METHODS

Patients

Between 1999 and 2001 patients were recruited from an acute stroke unit receiving all stroke patients (<6 hours after onset) from a well defined urban region of a population of 600 000. Patients with acute stroke were included in the study after obtaining informed consent, within 24 hours of symptom onset. Patients with other acute life-threatening diseases, pregnant women, children, and patients who were not evaluable—for example, due to severe dementia—were excluded. The Scientific-Ethics Committee of Copenhagen approved the study (file nr (KF)01-358/98).

The study population consisted of 179 patients (162 patients with cerebral infarction and 17 patients with intracerebral haemorrhage). None of the patients were treated with thrombolysis. Five of the patients were also included in trials with neuroprotectants or low molecular weight heparin. However, none of these trials have shown any effect. Acute myocardial infarction was not diagnosed during the first seven days in any patient.

Clinical observation

The severity of the stroke was assessed on admission with the Scandinavian Stroke Scale (SSS). Pre-stroke modified Rankin Scale (mRS) was assessed on admission, and functional outcome rated as mRS at three months. In case of death, the time and the cause were registered. The diagnosis of cerebral infarction or intracerebral haemorrhage was based on clinical findings and computed tomography (CT) scans in all patients. Vital signs were observed as previously described.

Neuroimaging

CT scans were done on day 1 and day 5–8 (follow up scan). The scans were read by one neuroradiologist (HHJ), blinded to all clinical data apart from the expected lesion side. Lesion volume was calculated as the sum of the computer assisted manually traced perimeter of each slice multiplied by the thickness of the slice. The presence and side of insular involvement was assessed on both scans. The insula is a well defined structure; it is the cerebral cortex beneath the sylvian fissure. The boundaries are the temporal, frontal, and parietal opercula. The underlying white matter—the extreme capsule—forms the internal boundary. Insular lesions were diagnosed if the grey matter outline of the insula was blurred or/and had a hypodense attenuation.

Electrocardiography

On admission, 12 lead electrocardiograms (ECGs) were obtained (Cardiovit AT-60; Schiller, Switzerland). Continuous ECG telemetry (Teleguard 3200; Danica Biomedical) was recorded on the first day after admission and ECG telemetry was done in the first 12–24 hours after admission. Information regarding mortality at three months was obtained.

Insular lesions were related to sinus tachycardia with heart rate >120 bpm (p = 0.001), ectopic beats >10% (p = 0.032), and ST elevation (p = 0.011). Right insular lesions were related to atrial fibrillation (p = 0.009), atrioventricular block (p = 0.029), ectopic beats >10% (p = 0.016), and inverted T wave (p = 0.040). Right insular lesions, compared with left or no insular lesions, increased the odds of death within three months (OR 6.2, 95% CI 1.5 to 25.2) independent of stroke severity, lesion volume, and age. As the number of patients in the present study is relatively small, our findings need to be confirmed in studies on other populations of stroke patients.

Abbreviations: CT, computed tomography; ECG, electrocardiogram; mRS, modified Rankin Scale; SSS, Scandinavian Stroke Scale

H changes in heart rate and blood pressure following insular stimulation or lesions in animal models as well as in humans are well documented. Electrocardiographic (ECG) abnormalities are frequent in acute stroke. The mechanism by which these abnormalities occur is not well understood but may involve the insular cortex; insular damage may cause activation of the sympathetic-adrenal system because of decreased inhibitory insular activity. Intraoperative insular cortex stimulation is suggestive of right sided dominance in mediation of sympathetic cardiovascular effects, and subarachnoid haemorrhage in the right sylvian fissure has been shown to have cardiac consequences. These findings have been supported by animal models, leading to the hypothesis that insults to the right insula in a direct or indirect manner affect cardiac function; a possible consequence may be sudden cardiac death after stroke.

In this study we tested the hypothesis that insular damage, especially right insular damage, is related to ECG abnormalities and to mortality in acute stroke by investigating the relation between the presence and laterality of insular involvement in acute stroke and (a) ECG abnormalities as recorded on the first day after admission and (b) mortality at three months.

It has been suggested that lesions in the insula may result in abnormal electrocardiographic (ECG) findings and increase the risk of sudden death. We investigated if computed tomography (CT) detected insular lesions due to acute stroke were related to ECG abnormalities and mortality at three months. Acute insular lesions were diagnosed in 43/179 patients (left insular = 25; right insular = 17; bilateral = 1) with acute stroke (cerebral infarcts = 62 and intracerebral haemorrhage = 17) based on CT scans from 5–8 days after stroke onset; 12 lead ECGs were recorded on admission and ECG telemetry was in the first 12–24 hours after admission. Information regarding mortality at three months was obtained.

Insular lesions were related to sinus tachycardia with heart rate >120 bpm (p = 0.001), ectopic beats >10% (p = 0.032), and ST elevation (p = 0.011). Right insular lesions were related to atrial fibrillation (p = 0.009), atrioventricular block (p = 0.029), ectopic beats >10% (p = 0.016), and inverted T wave (p = 0.040). Right insular lesions, compared with left or no insular lesions, increased the odds of death within three months (OR 6.2, 95% CI 1.5 to 25.2) independent of stroke severity, lesion volume, and age. As the number of patients in the present study is relatively small, our findings need to be confirmed in studies on other populations of stroke patients.
Table 1 Characteristics of 179 patients with acute stroke

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>+ Insular lesion n = 43</th>
<th>- Insular lesion n = 136</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 (64–81)</td>
<td>72 (64–82)</td>
<td>74 (64–81)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-stroke mRS</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>NS</td>
</tr>
<tr>
<td>Admission SSS</td>
<td>37 (22–47)</td>
<td>24 (12–39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 month SSS</td>
<td>54 (45–58)</td>
<td>44 (29–55)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>3 month mRS</td>
<td>3 (2–4)</td>
<td>4 (2–4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3 month mortality (%)</td>
<td>11.2</td>
<td>16.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

History of heart disease (%)*
- Atrial fibrillation 6 (15) 4 (7) 0.009
- Atrioventricular block 2 (4) 2 (3) 0.772
- Ectopic beats >10% 19 (41) 35 (26) 0.001
- ST elevation 7 (16) 3 (2) 0.001
- ST depression 7 (16) 3 (2) 0.001
- Inverted T wave 10 (23) 17 (13) 0.001

Table 2 ECG abnormalities and insular involvement in 179 patients with acute stroke, and ECG abnormalities and side of insular lesion in 42 patients with acute stroke and a unilateral insular lesion

<table>
<thead>
<tr>
<th>Insular involvement (n = 43)*</th>
<th>No insular involvement (n = 136)</th>
<th>Right insula (n = 17)</th>
<th>Left insula (n = 25)</th>
<th>χ² p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation 15%</td>
<td>15</td>
<td>4</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Sinus tachycardia HR &gt;120 bpm</td>
<td>15</td>
<td>4</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Sinus bradycardia HR &lt;45 bpm</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Atrioventricular block 7%</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Ectopic beats &gt;10%</td>
<td>19</td>
<td>35</td>
<td>7</td>
<td>0.001</td>
</tr>
<tr>
<td>Prolonged QTc 4%</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>ST depression 9%</td>
<td>9</td>
<td>15</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>ST elevation 5%</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Inverted T wave 16%</td>
<td>10</td>
<td>17</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>Isoform T wave 0%</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of patients.
*Including one patient with bilateral lesions.

The causes of death in patients with right insular involvement as estimated by the attending physician did not differ from those of patients with strokes in other locations.

DISCUSSION

In the present study, insular damage, especially right sided insular damage was related to ECG changes in patients with
acute stroke. Right insular lesion predicted death within three months of stroke independent of age, severity of stroke, and infarction volume. Patients with insular involvement significantly more often presented with ECG abnormalities.

A drawback of this study is that we lacked ECGs from before stroke onset and therefore cannot conclude that the observed abnormalities result from the stroke incident. Another weakness is that CT scans do not allow discrimination between lesions in different insular regions as magnetic resonance imaging might have done. Large numbers of ECG findings were compared and multiple comparisons may increase the risk of a chance finding. The strength of this study is that it included the most common ECG abnormalities in more patients than in previous studies and therefore provides a broader approach to the subject. In agreement with other studies we found higher rates of arrhythmias in patients with insular lesions but could not confirm any relation with prolonged QTc interval.12

Based on this study, we cannot determine how right insular involvement predicted three month mortality, as the causes of death in these patients did not seem to differ from those in patients without insular lesions. Whether cardiac arrhythmias played a decisive role13 in any death in the present study is uncertain. The given causes of death are based on best clinical judgement since autopsy was obtained in only one case. The importance of the insular regions for cardiac rhythm was demonstrated by Oppenheimer14 and our finding that a right insular location of the stroke lesion significantly increases risk of death within three months supports the hypothesis that damage to the right insula directly or indirectly affects cardiac function. If these results were reproduced in subsequent studies on different patient populations, further investigations—for example, Holter monitoring of patients with right insular lesions, might reveal conditions that can be modified by therapeutic intervention and thereby improve outcome.

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