SHORT REPORT

Insular lesions, ECG abnormalities, and outcome in acute stroke

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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 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.

Changes in heart rate and blood pressure following insular stimulation or lesions in animal models[1] as well as in humans[2] 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[3]; insular damage may cause activation of the sympathico–adrenal system because of decreased inhibitory insular activity.[4] Intraoperative insular cortex stimulation is suggestive of right sided dominance in mediation of sympathetic cardiovascular effects,[2] and subarachnoid haemorrhage in the right sylvian fissure has been shown to have cardiac consequences.[5] These findings have been supported by animal models,[6] 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.[3]

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.

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).[7] Pre-stroke modified Rankin Scale (mRS)[8] 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.[9]

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.[10] 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

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

Table 1 Characteristics of 179 patients with acute stroke

	All patients n = 179	+ Insular lesion n = 43	– Insular lesion n = 136	p value (+/– insular lesion)
Age	74 (64–81)	72 (64–82)	74 (64–81)	NS
Pre-stroke mRS	1 (0–2)	1 (0–2)	1 (0–2)	NS
Admission SSS	37 (22–47)	24 (12–39)	42 (28–49)	<0.001
3 month SSS	54 (45–58)	44 (29–55)	55 (50–58)	<0.05
3 month mRS	3 (2–4)	4 (2–4)	2 (2–3)	<0.05
3 month mortality (%)	11.2	16.3	9.6	<0.05
History of heart disease (%)*	14.5	11.6	15.4	NS

Data are median (interquartile range) or %.
*History of angina, acute MI or congestive heart disease.
mRs, modified Rankin Scale; SSS, Scandinavian Stroke Scale.

A/S, Denmark) was performed in the first 12–24 hours after admission; the decision to stop telemetry was made by the treating physician, mostly during the morning or evening round. Episodes of pathological activity were automatically registered and kept in the patients' files.

The ECGs were retrospectively analysed by one observer (AFC) as to the occurrence of atrial fibrillation, atrial flutter, tachycardia (heart rate (HR) >120 beats per minute (bpm)), bradycardia (HR <45 bpm), atrioventricular block, ventricular fibrillation >5 seconds, and ST elevation, ST depression, T wave inversion, and corrected Q-T interval ($cQ\text{-}T = Q\text{-}T/\sqrt{R\text{-}R}$) according to guidelines.[11] Ectopic beats >10% of beats were registered. AFC had access to patient number and ECG but no other clinical information.

Statistical analysis

Statistical analysis was performed with SPSS 9.0 for Windows and consisted of the χ^2 test, Mann–Whitney U test, and multiple logistic regression analysis. Variables were chosen based on literature and the tests were performed as a simple enter analyses. Goodness of fit was assessed by the Hosmer–Lemeshow test. The significance level chosen was 0.05 in all tests.

RESULTS

The patients' baseline characteristics are shown in table 1.

In 41 patients (22.9%) acute insular involvement was detected on the day 1 CT scan and in 43 patients (24%) on the day 5–8 scan. In two patients insular lesions were only detected on the second CT scan. Seven patients died before the time of the second scan, however, insular lesions were not visible on the day 1 CT scan of all of these patients. Left insular lesions were detected in 25 patients, right insular lesions were detected in 17 patients, and one patient presented with acute bilateral insular lesions. Sinus tachycardia with HR>120 bpm, ST elevation and ectopic beats >10% were significantly more frequent in patients with stroke lesions involving the insula (table 2). Blood pressure (systolic and diastolic) was not related to presence or laterality of insular involvement, even when stratifying for stroke severity.

When correcting for lesion volume in multiple logistic regression analysis, insular damage (right or left) increased the risk of sinus tachycardia (odds ratio (OR) 3.7, 95% confidence interval (CI) 1.6 to 8.5) and ST elevation (OR 8.3, 95% CI 1.4 to 48.7). In patients with a right insular lesion (table 2), atrial fibrillation, atrioventricular block, ectopic beats, and inverted T wave were significantly more frequent than in patients with left insular lesions. The one patient with bilateral acute insular lesions had an abnormal ECG showing atrial fibrillation, third degree block, ST depression, and inverted T wave.

Right insular involvement independently predicted the three month mortality in a multiple logistic regression model (OR 6.2, 95% CI 1.5 to 25.2), with the three month mortality as dependent variable and right insular involvement versus no radiological involvement of the right insula, stroke severity (SSS) on admission, CT lesion volume on day 5–8, and age as independent variables. The presence of insular involvement when disregarding the side of involvement did not affect the three month mortality in a multivariate logistic regression analysis with three month mortality as the dependent variable and insular involvement versus no insular involvement, stroke severity on admission, CT lesion volume on day 5–8, and age as independent variables.

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

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

	Insular involvement (n = 43)*	No insular involvement (n = 136)	χ^2 p value	Right insula (n = 17)	Left insula (n = 25)	χ^2 p value
Atrial fibrillation	6	15	0.772	4	1	0.009
Sinus tachycardia HR>120 bpm	15	16	0.001	8	6	0.118
Sinus bradycardia HR <45 bpm	7	18	0.802	3	4	0.896
Atrioventricular block	7	21	0.969	4	2	0.029
Ectopic beats >10%	19	35	0.032	12	7	0.016
Prolonged QTc	4	7	0.470	1	3	0.736
ST depression	9	15	0.136	5	3	0.060
ST elevation	5	2	0.011	4	1	0.148
Inverted T wave	10	17	0.144	6	3	0.040
Isoform T wave	0	11	0.067	0	0	–

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

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 role[13] 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 Oppenheimer[14] 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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