Is Occult Atrial Disorder a Frequent Cause of Non-Hemorrhagic Stroke? Long-Term ECG in 86 Patients

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SUMMARY To assess the importance of occult atrial disorder with possible embolization as a cause of non-hemorrhagic stroke, 68 patients with neurologic symptoms lasting 24 hours or more and 18 patients with transient ischemic attacks were examined by long-term electrocardiographic recording (LTER). Lacking matched controls we used a reference population of 103 elderly subjects selected at random from the general population for a previous LTER study. Permanent or episodic atrial arrhythmias of types known to cause cerebral embolization were detected by LTER in 32 (47%) of the 68 patients with a clinical diagnosis of cerebral embolization or thrombosis and in 6 (33%) of the 18 patients with transient ischemic attacks. Of the 38 patients with atrial arrhythmia during LTER 17 had such arrhythmias in their standard ECGs. This frequency of atrial arrhythmias during LTER differs from that of the reference population (p < 0.025). Thirteen of 16 patients with multiple cerebral lesions had signs of atrial arrhythmia during LTER.

Patients having occult atrial disorder with episodic atrial arrhythmia may be an important and common risk group for non-hemorrhagic stroke in addition to the previously recognized group of patients with atrial arrhythmia detectable in the standard ECG. LTER may be important in the evaluation of patients with unexplained stroke.

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ATRIAL DISORDER may cause stroke by two potential mechanisms: by arrhythmias causing decreased cardiac output, i.e., hemodynamic stroke, or by left atrial thrombus formation with subsequent systemic embolization. There is little evidence that sudden hemodynamic changes are of clinical importance. Brain infarcts are rare among survivors of cardiac arrest and although focal neurological signs may be observed in connection with cardiac arrhythmias only few patients paced for bradycardia have such a history. On the other hand, atrial fibrillation with or without mitral valve disease causes cerebral embolization from left atrial thrombus formation. In the Framingham study the risk for developing stroke showed an almost sixfold increase after the onset of atrial fibrillation in ischemic heart disease. Recently collected of the mitral valve has been associated with stroke in young patients and with atrial arrhythmias.

Patients with atrial dysfunction in form of the sick sinus syndrome have also been found to develop cerebral embolization. During a 4.5 year period 254 cases of mainly episodic and mild sick sinus syndrome were diagnosed in Malmö. During an average follow-up time of two years after the diagnosis of their arrhythmia they had annual incidences of cerebral and non-cerebral arterial embolization of 7.2 and 2.8% per patient, respectively, despite only mild or drug-induced arrhythmia among the 230 not subjected to car-

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ing most cases of acute myocardial infarction or obvious and/or threatening arrhythmias. As one of the wards almost exclusively admits men there is a male overrepresentation.

All patients and/or their relatives were subjected to a standardized interview on arrival to the wards. A detailed cardiac and neurologic history was obtained and a physical examination was performed. A special protocol was used and later evaluated by the senior staff physician. Using these data all strokes were classified mainly according to the principles of Millikan et al\(^\text{18}\) and were given the following designations: **Transient ischemic attacks** (TIA) in cases of two or more completely reversible attacks of short duration and never exceeding 24 hours with the same neurological signs or symptoms; **Embolization** in cases where a neurological defect developed within seconds and was not preceeded by prodromal signs, irrespective of past or present cardiac arrhythmia; **Thrombosis** in cases with a gradual onset of neurological signs or having prodromal signs. All patients with an unknown mode of onset including those developing stroke during sleep were arbitrarily referred to the thrombotic group. The classification used relies heavily on the medical history and the correlation to underlying pathology is certainly sometimes problematic. Especially the differential diagnosis of embolic and thrombotic brain infarcts may be uncertain.

Patients with a diagnosis of intracranial hemorrhage were not included.

Lumbar punctures, brain scans, EEGs and angiographic studies were performed according to the clinical situation. Computerized tomography was not available for routine use at the time of the study.

**LTER and Classification of Arrhythmias**

On days 2–6 after arrival the patients were examined by LTER for approximately 24 hours using portable ECG tape recorders type SRA/HRB-3 (Helcomed Nord-Hellige). This period of monitoring was chosen since the prolongation of LTER up to 48 hours in patients with suspected Adams-Stokes syndrome had been shown to detect only 7% more cases of atrio-pathic arrhythmia (Abdon et al\(^\text{18}\)). In order to avoid bias all tapes were coded. Tapes from ward patients with suspected Adams-Stokes syndrome and patients free from cardiac and neurological signs were also coded, mixed with those from arrhythmic patients and analyzed. No information regarding age, sex, or clinical data was available to the ECG interpreter.

All ECG-tapes were analyzed using a semi-automatic processing as described elsewhere.\(^\text{17}\) Heart rates were calculated from three or more cardiac cycles and given as beats per minute (bpm). Frequent ventricular premature contractions (i.e. one in 5 or less regular beats) and their potentially dangerous forms\(^\text{20}\) were also protocolled.

In cases with the fulfillment of one or more of the following criteria the designation sick sinus syndrome was given irrespective of drug effects:

1) Sinus bradyarrhythmia with a difference in consecutive sinus cycles of 20% or more and \(\leq 50\) bpm,
2) regular sinus bradycardia \(\leq 45\) bpm when awake,
3) sino-atrial block and 4) sinus arrestes of \(\geq 1.5\) seconds. (However, no patients in the present series and no subject of the reference population was classified as having the sick sinus syndrome only by fulfilling criterion No. 4). Patients with the sick sinus syndrome and episodes of atrial fibrillation or tachycardia were considered to have the bradycardia-tachycardia syndrome.

Lacking matched controls we compared the LTERs from stroke patients with those from a reference group of 103 elderly individuals randomly selected from the population of Malmö and described in a previous report.\(^\text{17}\) They had been examined using the same equipment and classification as in the present study. Nine of the 103 individuals had a probable history of stroke.

**Statistical Analysis**

Statistical analysis was performed using the chi-square test including Yates’ correction. Data were cast in 2x2 contingency tables and the null hypothesis of independence of row and column variables was tested. When multiple comparisons were made Fisher’s exact test was used and the total significance at the 5% level was obtained by the product \( (1 - p_1)(1 - p_2)(1 - p_3) \ldots (1 - p_n) > 0.95 \) where \( p_1 \ldots p_n \) designate the p-values of each comparison.

**Results**

TIAs were diagnosed in 18 patients, 14 men and 4 women aged 51–85 years (mean 68 ± sp 8 years). Two of them had the sick sinus syndrome, both with a moderate sinus bradycardia induced by betablockers. Three TIA-patients had permanent atrial fibrillation and one had paroxysmal atrial tachycardia. Thus 6 (33%) of the TIA patients had atrio-pathic arrhythmia. Cerebral thrombosis was diagnosed in 33 patients, 20 men and 13 women, aged 51–88 years (mean 74 ± 10). In 8 of these patients a sick sinus syndrome was found, being of the bradycardia-tachycardia type in 4. Six patients had permanent and one had paroxysmal atrial fibrillation. Thus 15 (45%) of the patients with cerebral thrombosis had atrio-pathic arrhythmia. Cerebral embolization was designated in 35 patients, 26 men and 9 women, aged 48–89 years (mean 69 ± 10). During LTER 11 had the sick sinus syndrome which was of the bradycardia-tachycardia type in 8. Atrial fibrillation was permanently present in 3 patients while 3 had episodes of this arrhythmia. Accordingly atrio-pathic arrhythmias were found in 17 (49%) of the patients with cerebral embolism.

Among the total of 21 patients having the sick sinus syndrome, 15 were on drugs known to provoke or aggravate sinus bradycardia, 13 of them being on maintenance digitalis. In 9 patients, digitalis was discontinued due to severe bradycardia. In 6 of these patients, reexamination was performed which showed a normal rhythm in 4 while 2 had persisting bradycardia. Among the 103 reference individuals 9 had the sick sinus syndrome, 4 of them being triggered by drugs.
Standard Admission ECG

The standard admission ECG showed atrio-pathic arrhythmia in 17 (20%) as compared with the 38 (44%) having it during LTER.

Previous Strokes and Atriopathic Arrhythmia

Among the 18 TIA-patients 3 had suffered a previous stroke from another focus. One of them had the sick sinus syndrome. Among the 15 remaining TIA-patients 5 had atrio-pathic arrhythmia. Among the 68 patients with cerebral embolization or thrombosis 52 had no previous stroke in other vascular regions. Nineteen of these 52 had atrio-pathic arrhythmias as compared to 13 of the 16 patients with previous strokes in other vascular areas. In cerebral embolism and thrombosis this difference in atrio-pathic arrhythmias between patients with and without stroke in other areas is significant (p < 0.05). (See table 1.)

Aorto-Cervical Angiograms

Aorto-cervical angiograms were performed in 28 patients considered for possible endarterectomy. Twelve had TIAs and in 16 a first TIA could not be excluded. Twenty of the 28 patients had atheromatous lesions corresponding to the neurological deficit. In 17 of these 20 patients there were no atrio-pathic arrhythmias while one had sick sinus syndrome and 2 had atrial fibrillation and/or tachycardia. Two of the remaining 8 patients had severe atheromatous lesions not corresponding to the site of the neurological lesion, both without atrio-pathic arrhythmias. Finally, 6 patients had essentially normal vessels with the finding of atrio-pathic arrhythmias in 3 of them.

Carotid artery surgery was uneventfully performed in 15 of the patients with appropriately located lesions. All were found to have ulcerated plaques at surgery. (See table 2.)

The age-related prevalence of atrio-pathic arrhythmias in patients with embolic or thrombotic stroke and the 103 elderly individuals selected at random and subjected to LTER during a previous study are shown in figure 1. Within the respective age brackets the prevalence of atrio-pathic arrhythmias was always increased among patients with embolic or thrombotic stroke compared to the reference population. Beginning with a 13% prevalence in stroke patients 59 years of age or younger there was a steady increase to as much as 71% for those aged 80 years or more. The corresponding increase in atrio-pathic arrhythmias in the reference population was from 0 to 40%.

Table 3 illustrates the same reference and stroke population with respect to atrio-pathic arrhythmia, sex and age. For statistical analyses some age groups have been pooled. The groups of male and female stroke patients differed significantly (chi square 9.91, d.f. 3, < 0.025), the age-related prevalence being uniformly higher among females. For the statistical comparison of reference and stroke populations, data for males and females were summed in the respective age classes. Reference and stroke populations were clearly different (chi square 10.14, d.f. 3, p < 0.025). In each age group the combined male and female prevalence of atrio-pathic arrhythmia in stroke patients exceeded that of reference individuals. There were proportionally more males in the stroke than in the reference population. As even female stroke patients had a higher prevalence of atrio-pathic arrhythmia the relatively high prevalence of arrhythmia in the stroke population seems to be related to stroke itself rather than to the differences in the age and sex distributions among reference individuals and patients.

Factors Predisposing for Stroke — Comparison With the Reference Population

Factors predisposing for stroke among the stroke

**Table 1** Previous Stroke in Other Vascular Areas and Atriopathic Arrhythmia in Patients with Transient Ischemic Attacks and Thrombotic or Embolic Stroke

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Previous stroke</th>
<th>No previous stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atro-pathic arrhythmia</td>
<td>Total</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Thrombotic or embolic</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 2** Correlation of Roentgenological Findings with Neurological Symptoms and Arrhythmia in the 28 Patients Studied with Angiography

<table>
<thead>
<tr>
<th>Angiographic lesion</th>
<th>Arrhythmia</th>
<th>No</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No atrio-pathic arrhythmia</td>
<td>17</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*Atheromatous plaque corresponding to localization of the current neurological symptoms.
patients and the reference population are given in Table 4. Patients with a systolic blood pressure of \( \geq 175 \) or a diastolic of \( \geq 115 \) mm of mercury were classified as hypertensive. Myocardial infarction was diagnosed according to ECG-changes or typical enzyme patterns following cardiac symptoms.

Hypertension was significantly more common in patients with stroke than in the reference population, both for patients aged 70 years or more and those below 70 years of age. The increased fraction of patients with previous myocardial infarction was significant only for patients aged 70 years or more. Diabetes mellitus was as a whole about equally common in stroke patients and reference subjects but when age was considered, it was found to be significantly more common in younger patients. Significant differences were also found for both age groups as regards previously recorded atrio-pathic arrhythmias and digitalis therapy.

Valvular disease of the heart was diagnosed in 4 stroke patients and in 2 subjects of the reference population, respectively.

### Factors Predisposing for Stroke in Patients with and without Atriopathic Arrhythmias

Stroke disposing factors among patients with and without atrio-pathic arrhythmia are presented in Table 5. Hypertension, previous myocardial infarction and diabetes mellitus was equally common among stroke patients with and without atrio-pathic arrhythmia. A previously recorded atrio-pathic arrhythmia or maintenance digitalis therapy was significantly more common among patients with atrio-pathic arrhythmia during LTER.

**Discussion**

In the present study three main observations associating episodic or permanent atrio-pathic arrhythmia with non-hemorrhagic stroke were made:

1) The prevalence of atrio-pathic arrhythmias among patients with non-hemorrhagic stroke was 44%, being twice that found in the reference population. This difference is significant and not explained by differences in age and sex distribution between reference individuals and patients. The number of patients with atrial fibrillation or tachycardia is higher than or agrees with the results of other investigators. In addition, we find a large number of patients with the sick sinus syndrome, possibly due to the sensitivity of the diagnostic technique.

2) ECG-documentation of previous atrio-pathic arrhythmia was available in 15 of 38 patients (39%) with atrio-pathic arrhythmias during LTER. This differs significantly from the reference population.

3) A history of multiple neurological foci suggesting systemic embolization was present in 16 cases, 13 of whom had atrio-pathic arrhythmias during LTER. When the current neurological lesion could be explained by an angiographically demonstrable lesion at an appropriate location, atrio-pathic arrhythmias were infrequent. These observations are consistent with the hypot-
A triopathic arrhythmia in the stroke patients may, or may not, be related to the prevalence of risk factors did not differ significantly between the arrhythmic and nonarrhythmic groups. Abildskov et al.27 pointed out that stroke patients are easily falsely considered to have primary cardiac disease. However, in young patients with non-hemorrhagic stroke the routine ECG only infrequently shows atrioopathic arrhythmia.28 In the present study the prevalence of atrioopathic arrhythmia increased by age both among stroke patients and the reference population. Together these and our results are consistent with the conclusion that atrioopathic arrhythmias in stroke patients represent in intrinsic age-related atrial disorder rather than atrial dysfunction due to the current cerebral lesion. This is substantiated by the occurrence of stroke in the Malmö series of patients during follow-up for established sick sinus syndrome. Norris et al.29 observed sinus bradycardia during coning. None of our patients, however, was in the stage of coning during LTER and only two patients expired as a direct consequence of the cerebral damage, the remaining five having secondary causes. Lavy et al.29 monitored stroke patients immediately following arrival at hospital and compared the arrhythmias detected by monitoring with prior routine ECGs when available. They arrived at the ‘impression’ that most of the arrhythmias were caused by the stroke. However, their most important finding may be that no less than 11 of 43 patients with non-hemorrhagic stroke had documented preexisting arrhythmia. Goldstein21 compared the ECG in stroke with prior recordings and found that atrial fibrillation was overrepresented in stroke patients as compared with reference individuals and that it was frequently observed prior to the stroke. The importance of preexisting arrhythmia was also demonstrated by Friedman et al.30 They compared previous ECGs of stroke patients with those from age and sex matched reference individuals with the same blood pressure. The major difference between stroke patients and reference individuals then was arrhythmia and digitalis therapy.

Compared with the reference population the stroke patients had increased prevalences of cardiovascular risk factors such as previous myocardial infarctions, hypertension, and diabetes. In the stroke population the prevalence of risk factors did not differ significantly between the arrhythmic and nonarrhythmic groups. The increased prevalence of atrioopathic arrhythmia in the stroke patients may, or may not, be related to the accumulation of risk factors. The atrial disorder, if related to risk factors, may or may not cause systemic embolization. Thus we could not decide from these data only, if risk factors in stroke are also risk factors for systemic embolization.

The criteria used for the diagnosis of an episodic sick sinus syndrome may appear to be too permissive but several facts support them. The majority of our patients with the sick sinus syndrome had the bradycardic type, i.e. more than one type of arrhythmic evidence of atrial disorder. However, in the Malmö series of patients with episodic sick sinus syndrome patients with purely bradycardic arrhythmia still had an annual risk for embolization of 5.3% per patient. Furthermore, the risk for developing stroke was unrelated to the severity of the bradycardia.10 Also, despite normalization of the rhythm following digitalis withdrawal, patients with digitalis-induced sick sinus syndrome had the same rate of embolization as patients with spontaneous and persisting sick sinus syndrome. This view that even mild — spontaneous or drug-induced sinus bradycardia — may have serious implications is supported by the report of Hinkle et al.31 which revealed that this arrhythmia is associated with an increased risk of death.

In the Malmö series of episodic sick sinus syndrome 30 autopsies were performed: Nine patients had single and 5 had multiple encephalomalacias and 11 patients had non-cerebral arterial embolizations. A left atrial thrombus was found in 6 of 30 patients. These results are similar to those found in patients with atrial fibrillation.5-8 As chronic atrial fibrillation may be the end stage of the sick sinus syndrome it seems possible that some patients with atrial fibrillation and embolization belong to the sick sinus syndrome-entity rather than being ‘atherosclerotic’ or ‘idiopathic.’

In conclusion, we find that 44% of the patients in this series of non-hemorrhagic stroke had atrioopathic arrhythmia during LTER. Sufficient evidence was obtained to warrant the conclusion that atrial disease or dysfunction as reflected by atrioopathic arrhythmia may have caused a substantial proportion of non-hemorrhagic stroke in the present series. It is suggested that the sick sinus syndrome and atrial fibrillation and tachycardia are to be considered as a common group of atrioopathic arrhythmias reflecting atrial disorder predisposing for left atrial thrombus formation and subsequent systemic embolization.

In common clinical practice the sick sinus syndrome is diagnosed when severe sinus node dysfunction capable of causing the Adams-Stokes syndrome is found. The present and previous studies from Malmö indicate that sinus node dysfunction should also be evaluated from another aspect. As even mild sinus node dysfunction is associated with a risk for systemic embolization, the criteria for the sick sinus syndrome should probably be wider than usually applied.

In agreement with the recent suggestion by Easton and Sherman33 the LTER has proven its value in providing etiological information and deserves widespread application for this purpose. If the concept of episodic atrioopathic arrhythmia reflecting atrial disorder can be confirmed as a frequent cause of systemic embolization this should have implications for future efforts in the primary and secondary prevention of non-hemorrhagic stroke.
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