

Atrial Fibrillation After Acute Stroke

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Background and Purpose: Atrial fibrillation (AF) is a risk factor for stroke, although it may not always be directly responsible for the stroke. On the other hand, cardiac arrhythmias and electrocardiographic changes have been reported after ischemic stroke and numerous other intracranial pathologies. We tested the hypothesis that some patients with acute stroke may develop transient AF as a consequence of the stroke.

Methods: This study was based on 1,661 patients with first-ever stroke consecutively hospitalized and prospectively included into the Lausanne Stroke Registry. "Recent AF" was defined as AF discovered at or after ("after-admission" AF) admission in patients without any previous history of AF. Populations with recent AF and after-admission AF were compared for AF evolution, risk factors, and lesion type and distribution with patients with previous history of AF (known AF) and with patients with another recognized cardiac source of embolism (cardioembolic).

Results: Twenty-four patients had recent AF on admission, and 17 developed it a few hours to 3 days after stroke. AF disappeared after a few days in 26 (63%; 94% of after-admission AF) patients. Stroke was a primary hematoma in 9.8% of patients with recent AF, 2.8% of patients with known AF, and 0.9% ($p < 0.001$) of patients with cardiac source of embolism. Parietoinsular (32%) and brain stem (11%) involvement were more common in recent AF than in cardioembolic stroke in general (16.7% and 6.7%, respectively; $p < 0.05$).

Conclusions: AF discovered after an acute stroke lasted no more than a few days, suggesting that it may have occurred as a consequence of the stroke. This possibility is emphasized by the significant predominance in patients with recent AF of primary hematoma, which cannot be caused by AF, and of parietoinsular and brain stem involvement, which are experimentally known as arrhythmogenic. This hypothesis should be considered in patients with acute stroke and previously unknown AF before therapeutic decisions are made. (*Stroke* 1993;24:26-30)

KEY WORDS • atrial fibrillation • cerebral infarction • risk factors

Atrial fibrillation (AF) is a well-established risk factor for stroke,¹⁻⁵ although it may not always be directly responsible for the stroke in AF patients who have a stroke.⁶⁻¹⁰ We recently showed that approximately two thirds of ischemic strokes may be secondary to AF itself in patients with nonvalvular AF.¹¹ On the other hand, because cardiac arrhythmias and electrocardiographic (ECG) changes have been reported after ischemic stroke,¹²⁻¹⁷ as well as intracranial hematoma,^{13,15,18-29} brain tumor,^{21,27,30} head injury,³¹⁻³⁴ epilepsy,³⁵⁻⁴⁵ multiple sclerosis,⁴⁶ and basilar artery migraine,⁴⁷⁻⁴⁸ it is not unlikely that AF may sometimes be the consequence instead of the cause of the stroke. In a series of patients with first-ever stroke who were consecutively admitted to a population-based primary care center, we tested the hypothesis that some patients with acute stroke may develop transient AF as a consequence of the stroke.

Subjects and Methods

This study was based on 1,661 patients consecutively included into the Lausanne Stroke Registry,⁴⁹ which is a

computerized prospective registry of patients with first-ever stroke admitted to a population-based primary care center over a 10-year period. Details on the methodology of the registry have been published previously.⁴⁹ All patients have continuous three-lead ECG monitoring beginning at admission and during at least 24 hours after stroke. Other systematic investigations include brain computed tomography (one to four examinations, the first within the first days after stroke), 12-lead ECG, and carotid Doppler ultrasounds with frequency spectral analysis and B-mode echotomography. Transthoracic and transesophageal echocardiography (to look for potential cardiac source of embolism other than AF, such as rheumatic valvular disease, akinetic left ventricular segment after myocardial infarct, cardiac tumor or thrombus, dilated cardiomyopathy, and other rarer diseases previously defined⁴⁹) and intracranial studies (angiography or transcranial Doppler) are done only in selected patients. The results of these investigations, clinical features, risk factors (hypertension, diabetes, smoking, hypercholesterolemia as defined according to the criteria previously reported in the Lausanne Stroke Registry),⁴⁹ and evolution in hospital, are coded into the registry and analyzed.

We assessed the topography of cerebral infarcts on computed tomography following the templates developed by Damasio⁵⁰ and our group.⁵¹

Known AF was defined as chronic or intermittent AF diagnosed at least once by ECG or 24-hour continuous

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TABLE 1. Risk Factors and Lesion Type

| Risk factor | AAAF (n=17) | RAF (n=41) | KAF (n=144) | CE (n=332) |
|------------------------|----------------|---------------|----------------|---------------|
| Mean age (years±SD) | 73.7±8.5 | 73.2±7.7 | 72.3±8.2 | 63.2±14.7 |
| Hypertension | 7 (41.2%) | 17 (41.5%) | 72 (50%) | 116 (35%) |
| Diabetes | 2 (11.8%) | 5 (12.2%) | 21 (15%) | 37 (11%) |
| Smoking | 5 (29.4%) | 12 (29.3%) | 36 (25%) | 132 (40%) |
| Hypercholesterolemia | 1 (5.9%) | 2 (4.9%) | 17 (12%) | 46 (14%) |
| Infarct | 15 (88.24%) | 37 (90.2%) | 140 (97.2%) | 329 (99.1%) |
| Hematoma | 2 (11.76%) | 4 (9.8%) | 4 (2.8%) | 3 (0.9%) |

AAAF, patients with after-admission atrial fibrillation; RAF, patients with recent atrial fibrillation; KAF, patients with known atrial fibrillation; CE, patients with another cardioembolic stroke.

ECG Holter examination before the stroke. Recent AF was defined as AF on admission ECG or on ECG monitoring in patients without any previous past or recent history of AF as reported by themselves and by their general practitioner (all patients and general practitioners were questioned specifically on previous AF). After-admission AF was defined as AF discovered on ECG monitoring in those patients with recent AF who have a sinusual rhythm on ECG at admission. The duration and potential recurrence of transient AF after stroke were also studied by regular ECG during the patient's stay in hospital (23 days on average; range, 3–77 days). The characteristics of patients with recent AF were compared by the Pearson's χ^2 test with Yates' correction⁵² with those in patients with known AF and in patients with cardioembolic stroke (including patients in which known AF was retained as cardioembolic source of stroke) in the absence of recent AF following the registry guidelines.⁴⁹

Results

Of the 1,661 patients studied, 144 (8.7%) had known AF, whereas 41 (2.5%) had recent AF (23 [56%] men and 18 [44%] women; mean age, 73.2±7.7 years). There was no significant difference between recent AF, known AF, and cardioembolic stroke populations for sex ratio (54%/46% [male/female] in known AF and 61%/39% in cardioembolic stroke) and age (Table 1).

Risk Factors

Among patients with recent AF, 17 (41%) had hypertension, five (12%) had diabetes mellitus, 12 (29%) smoked cigarettes regularly, and two (5%) had hypercholesterolemia. There was no significant difference between recent AF, known AF, and cardioembolic stroke populations for these vascular concomitants (Table 1).

Atrial Fibrillation

Among the 41 patients with recent AF, 17 (41.5%) did not have AF on admission, but they developed it, for the great majority asymptotically, a few hours to 3 days after stroke (after-admission AF). The AF lasted no more than 3 days in 26 (63%) patients (16 [94%] with after-admission AF), six (23%) of whom had one to three transient recurrences (two [12%] with after-admission AF). In 15 (37%) patients (one [6%] with after-admission AF), the AF was still present at discharge (average duration of hospitalization of this subgroup: 16 days; range, 3–40 days). There was no signif-

icant difference between patients with persisting and transient recent AF for risk factors, clinical features, and associated heart disease, so we studied them as one group.

When performed, echocardiography showed a potential cardiac source of embolism in two of 18 (11%) patients with recent AF (one with rheumatic valvular disease and one with mitral prolapsus without thrombus), in 26 of 56 (46%) patients with known AF ($p<0.02$) (10 akinetic segments with three visualized thrombi, two mitral stenosis, two mitral prolapsus, and 12 others as previously described,⁴⁹ and in 198 of 233 (85%) patients with cardioembolic stroke ($p<0.001$).

Stroke

Stroke was a primary intracerebral hematoma (Table 1) in four (9.8%) recent AF patients (three striatocapsular hematoma with extension to insula, one large parieto-temporo-occipital hematoma), five (2.8%) known AF patients, and three (0.9%) cardioembolic stroke patients ($p<0.001$).

The topography of cerebral infarcts is summarized in Table 2. In recent AF patients, superficial middle cerebral artery territory infarcts were the most common type of infarcts (59%), especially in the parietoinsular region (32%) (Figure 1). The second most common type of infarct was in the brain stem (11%) (two in tegmentum, two lateral medullary). The distribution of infarcts was significantly different ($p<0.05$) in patients with recent AF and in patients with cardioembolic stroke, this difference being mainly due to a higher prevalence of lower division of middle cerebral artery territory infarcts involving the parietoinsular region in recent AF patients (Figure 1).

The infarcts were left-sided in 25 (61%) recent AF patients, right-sided in 13 (32%) and bilateral in three (7%). In the lower division of middle cerebral artery territory, there were 10 (83%) left-sided and two (17%) right-sided infarcts. This left preponderance was more marked than in cardioembolic stroke (51% left, 38% right, 11% bilateral) or in known AF (46% left, 42% right, 12% bilateral) patients.

When studied separately, patients with after-admission AF presented more markedly this special distribution of stroke: Parietoinsular region was involved in six (40%) and the brain stem in two (13%). Sixty-five percent of the strokes were left-sided.

TABLE 2. Topography of Infarcts

| | AAAF | RAF | KAF | CE |
|----------------------|------------|-------------|-------------|-------------|
| Posterior MCA | 6 (40%) | 12 (32.43%) | 23 (16.43%) | 55 (16.72%) |
| Brain stem | 2 (13.33%) | 4 (10.81%) | 9 (6.43%) | 22 (6.69%) |
| Global MCA | 1 (6.67%) | 5 (13.51%) | 20 (14.29%) | 35 (10.64%) |
| Anterior MCA | 2 (13.33%) | 5 (13.51%) | 21 (15.00%) | 71 (21.58%) |
| MCA+ACA | 1 (6.67%) | 1 (2.70%) | 1 (0.71%) | 1 (0.30%) |
| ACA | 0 (0.00%) | 1 (2.70%) | 4 (2.86%) | 9 (2.74%) |
| PCA | 0 (0.00%) | 1 (2.70%) | 10 (7.14%) | 26 (7.90%) |
| Subcortical | 1 (6.67%) | 3 (8.11%) | 28 (20.00%) | 59 (17.93%) |
| Multiple superficial | 1 (6.67%) | 2 (5.41%) | 7 (5.00%) | 16 (4.86%) |
| Multiple deep | 0 (0.00%) | 1 (2.70%) | 2 (1.43%) | 0 (0.00%) |
| Cerebellum | 1 (6.67%) | 2 (5.41%) | 5 (3.57%) | 11 (3.34%) |
| Other | 0 (0.00%) | 0 (0.00%) | 10 (7.14%) | 24 (7.29%) |

AAAF, patients with after-admission atrial fibrillation; RAF, patients with recent atrial fibrillation; KAF, patients with known atrial fibrillation; CE, patients with another cardioembolic stroke; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Coexisting Causes of Stroke

In two (5%) recent AF patients, AF coexisted with an occlusion of the internal carotid artery ipsilateral to stroke. In two (5%), it coexisted with a >50% stenosis; in 21 (51%), it coexisted with a <50% stenosis; and 16 (39%) patients had no carotid disease. There was no significant difference with known AF patients (6%, 3%, 55%, and 36%, respectively) or with cardioembolic stroke patients (4%, 5%, 40%, and 51%, respectively). It is noteworthy that 17% of patients with after-admission AF presented an occlusion or >50% carotid stenosis (only 9% in other categories).

Discussion

Our study is the first to evaluate systematically a series of patients who developed AF after stroke, in the absence of any previous past or recent history of AF. In

fact, the incidence of AF after an intracranial event appears to be low: 4–7% of patients with subarachnoid hemorrhage,^{25,29} 3–10% of patients with other acute cerebral events,^{12,15,16} and 2.5% of 1,661 first-stroke patients from our registry.⁴⁹

We cannot exclude the possibility that some of our patients with recent AF had a previously undiagnosed chronic or intermittent AF. This is less probable for patients with after-admission AF, because all these patients presented an ECG-proved sinus rhythm at admission and because AF had disappeared during their hospitalization in all but one (94%) patient, without any relapse in all but two (82%). Also, we have studied this subgroup separately, even though their small number excludes statistical significance.

A statistical correlation between stroke and AF is well known,^{1–5} so we did not try to confirm it again (with

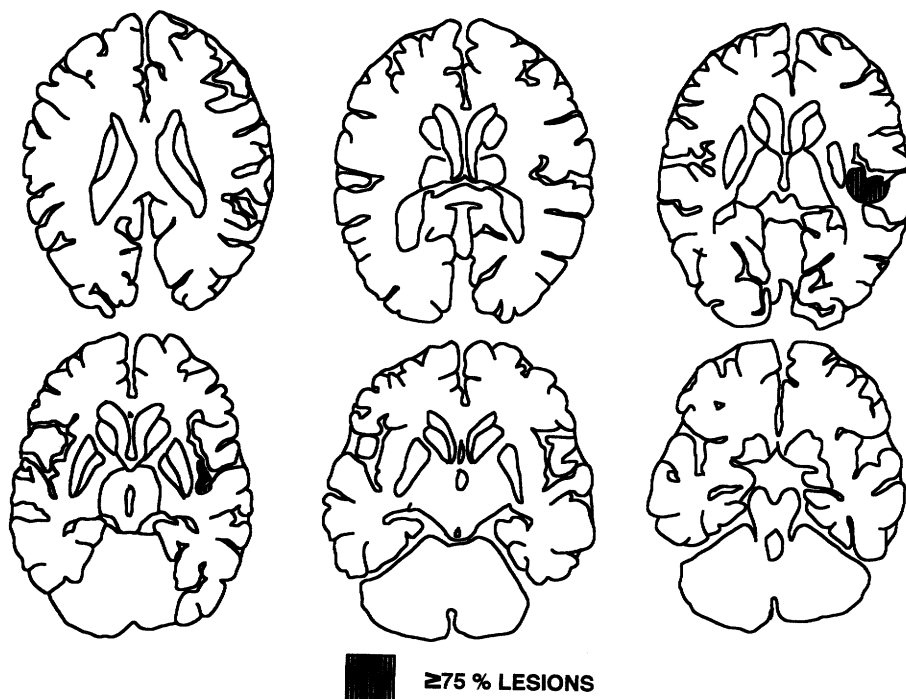


FIGURE 1. Diagrammatic representations of computed tomographic scans. Hatched areas represent the uniformly affected region in more than 75% of patients with recent atrial fibrillation and involvement of the posterior superficial middle cerebral artery territory showing a high prevalence of parietoinsular lesions.

a control group without AF). But, to determine if some AF discovered after stroke may be secondary to the stroke, we compared the recent AF patients with two control groups in which the stroke is recognized as secondary to the pathology: patients with known AF and patients with other cardiac sources of embolism.

Even if ischemic stroke secondary to acute AF is likely in several patients in whom AF is discovered on admission,⁵³ the fact that AF may have been secondary to the stroke in several cases is supported by our findings. First, AF developed clearly after stroke in nearly half of the patients with recent AF and lasted no longer than a few days in more than two thirds of the patients, with uncommon recurrence. Second, there was a preponderance of primary cerebral hematoma, which cannot be caused by AF, in recent AF patients (9.8%) (11.8% in after-admission AF patients) as compared with known AF (2.8%) or cardioembolic stroke (0.9%, $p < 0.001$) populations. As reported recently,⁵⁴ early bleeding in an infarct may lead mistakenly to a diagnosis of primary hematoma. This misdiagnosis seems more frequent in infarct from cardiac origin.⁵⁴ Thus, the number of primary hematoma in both control populations might be overestimated, which might underestimate the real preponderance of primary hematoma in recent AF patients. Furthermore, echocardiography failed to find any associated potential cardiac source of embolism in 89% of the patients with recent AF, whereas 46% of known AF patients ($p < 0.02$) and 85% of cardioembolic stroke patients ($p < 0.001$) had a potential cardiac source of embolism on echocardiography. Moreover, a significant stenosis ($>50\%$) or an occlusion of the ipsilateral internal carotid artery was found in 17% of patients with after-admission AF. This represents nearly twice as much as in known AF and cardioembolic stroke (9% each).

The topographical distribution of infarcts was different among the patients with recent AF, known AF, and cardioembolic stroke, being statistically significant only for cardioembolic stroke, probably because of the small number of patients with known AF. The relative predominance of brain stem lesions in recent AF patients, which is more marked for patients with after-admission AF (twice as many as in patients with known AF or cardioembolic stroke), could be explained by the fact that brain stem lesions may be particularly arrhythmogenic.^{55,56} Actually, the main nuclei directly involved in cardiac regulation, such as the nucleus tractus solitarius (main afferent pathway), the dorsolateral nucleus of the vagus nerve, and the nucleus ambiguus (parasympathetic efferences), are in the caudal brain stem. There are also projections from these nuclei and from the ventral pons, from the rostral ventral medullary epinephrine-containing neurons, and from the serotonergic raphe nuclei to the intermediolateral cell column of the spinal cord (main sympathetic efferent pathway).^{55,56} In humans, the preponderance of brain stem lesions in association with AF has already been reported for hemorrhagic lesions,²⁰ for basilar migraine,⁴⁷ and in multiple sclerosis.⁴⁶

The significant predominance of parietoinsular involvement in recent (32%) and after-admission AF (40%), compared with known AF (16%) and cardioembolic stroke (17%, $p < 0.05$), seems to be more difficult to explain. In humans, hemispheric lesions have already

been associated with arrhythmias,^{12–45} but the association with “secondary” AF is seldom reported.^{13,16,40} We suggest that the involvement of the posterior part of the insula may be associated with a higher risk of developing AF after acute stroke. Actually, the insula has a high number of interconnections with the limbic system, hypothalamus, and other areas involved in autonomic control,^{57,58} and autonomic and cardiovascular changes have been demonstrated after experimental insula damage or stimulation.^{59–61} Recently, cortical stimulation in the rat showed a chronotropic organization of the insular cortex, which seems to act directly on heart, probably through the sympathetic system.^{61–64} In the rat, both tachycardia and bradycardia may be elicited by posterior insula stimulation (by rostral and caudal stimulation, respectively). Therefore, an insula involvement or disinhibition by the stroke may explain the predominance of this lesion in recent and after-admission AF.

Animal experiments have suggested a right-sided predominance for heart rate control in the hemispheres, medulla, spinal cord, and stellate ganglia, and a left-sided predominance of the peripheral sympathetic nerves on arrhythmogenesis.^{55,56} Moreover, a left central lesion in the left middle cerebral artery territory induced major arrhythmias in the cat⁶⁵; in humans, the heart rate increase after amobarbital induced inactivation of the left hemisphere,⁶⁶ and ST-T changes on ECG are more frequent with left-sided lesions.^{19,20,27} Our findings emphasize a particularly marked left predominance of infarcts in patients with recent AF, especially for parietoinsular involvement (83%).

Our findings are compatible with the fact that AF discovered after acute stroke may sometimes be the consequence of it. Further studies should try to identify more accurately the subgroups of patients at risk for AF after stroke (notably with brain stem and posterior insula involvement) to improve stroke and arrhythmia prevention in individual patients.

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