Aspirin Attenuates the Incidence of Silent Brain Lesions in Patients With Nonvalvular Atrial Fibrillation

Hiroshi Sato, MD; Yukihiro Koretsune, MD*; Masatake Fukunami, MD**; Kazuhisa Kodama, MD†; Yoshio Yamada, MD‡‡; Kenshi Fujii, MD§; Kazuo Kitagawa, MD; Masatsugu Hori, MD

**Background** Abnormal findings, including silent cerebral infarction, are frequently observed by magnetic resonance imaging (MRI) in patients with nonvalvular atrial fibrillation (NVAF); however, the prevalence and prevention strategy for these lesions have not been extensively studied. In the present study the preventive effects of aspirin on silent ischemic lesions was investigated.

**Methods and Results** Silent lesions were counted using cranial MRI performed in 78 neurologically normal adults with sinus rhythm and in 212 patients with NVAF without a history of stroke. MRIs were repeated twice in the NVAF patients at 12-month intervals. During the first year, patients received neither antiplatelet agent nor anticoagulant; in the second year, aspirin (330 mg daily) was administered. The prevalence of lesions in the initial MRI was higher in NVAF patients (86.4%) than in sinus rhythm subjects (53.8%; \( p < 0.001 \)). After 12 months without aspirin, new lesions were seen in 20.6% of NVAF patients. The yearly occurrence of new lesions was decreased to 9.6% during the year of treatment with aspirin (\( p = 0.014 \)).

**Conclusions** In patients with NVAF, abnormal lesions are frequently observed by MRI and aspirin treatment may be effective in preventing further small silent lesions. (Circ J 2004; 68: 410–416)

**Key Words:** Aspirin; Atrial fibrillation; Cerebral infarction; Magnetic resonance imaging


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ince the development of highly sensitive techniques for brain imaging by magnetic resonance imaging (MRI), many potentially abnormal findings, including the presence of silent brain infarction (BI), have been recognized in patients without clinically apparent previous cerebrovascular accidents. The reported prevalence of silent lesions observed by MRI varies but there is consensus that it is high in elderly subjects and in patients with risk factors for stroke (eg, hypertension and atrial fibrillation (AF)). The importance of these silent lesions has been emphasized in reports linking them to impaired cognition and depression. Furthermore, silent infarctions are considered a risk factor for symptomatic infarction and brain hemorrhage. Despite their high prevalence and clinical importance, the pathogenesis of silent ischemic lesions is still uncertain, especially in patients with nonvalvular AF (NVAF). If circulating microthrombi cause silent BI, particularly small lesions, in patients with NVAF, oral anticoagulation therapy and antiplatelet therapy may be effective for prevention. Indeed, many clinical trials have shown that these treatments are useful for reducing the risk of stroke and systemic embolism in patients with NVAF. However, a large, well-designed study carried out by the SPINAF group did not show a significant effect of aspirin on the annual event rate of silent BI. That study used computed tomography (CT) to detect the silent lesions, which may explain why the event rate (1.01%/year in the placebo group and 1.57%/year in the warfarin group) was relatively low. We used MRI, which is more sensitive than CT and more accurately detects small ischemic foci, to screen patients with NVAF. The prevalence and locations of lesions were determined, as well as the incidence per year of new lesions and the effects of aspirin on that rate.

**Methods**

**Study Population**

Study subjects were selected from 1,404 patients with NVAF who had been screened in outpatient clinics in 19 hospitals participating in the COOPAT (Co-operative Osaka anti-Platelet Aggregation Trial) study from April 1993 to June 1993. Patients with either continuous AF or intermittent AF were candidates for the study if they had AF documented by 2 electrocardiograms (ECGs) at least 4 weeks apart and had no echocardiographic evidence of rheumatic heart disease. During a 1-year follow-up period to March 1994, attending physicians were encouraged to learn about current published trials by attending at least 1 of 6 educational lectures held by the COOPAT study group. Of the 1,404 patients, 315 were recruited as candidates for the present study from April 1994 to June 1994. Patients over 80 years old, those treated with warfarin or antiplatelet agents, and those with congestive heart failure were excluded. Patients whose attending physician opposed their participation also were excluded. Patients with a self-reported history of stroke or transient ischemic attack (TIA) were excluded whether or not a medical record or physician
confirmation was available. A normal neurologic examination with no focal deficit at the time of entry was required. Of the 315 eligible patients, 212 gave written informed consent to participate in the study according to the requirements of each hospital’s Ethics Review Committee. Control patients with sinus rhythm were neurologically normal adults recruited during routine health check-ups at the cardiology outpatient clinic; 87 consecutive patients with no history of cerebrovascular accidents were enrolled based on their wish to include MRI of the brain in their health screening. All control patients also gave written informed consent.

Study Protocol and MRI

Cranial MRI was performed in all participants at entry to the study. Patients with NVAF then were followed up for 12 months with neither antiplatelet nor warfarin therapy. After a second MRI (first follow-up), eligible patients with NVAF were treated with oral aspirin (330 mg q.d.) and were followed up for another 12 months. The dose of aspirin was determined from previous studies that reported treatment with aspirin 325 mg/day was effective in preventing symptomatic BI in patients with NVAF, but not 75 mg/day.17,18 The third MRI (second follow-up) was performed just before termination of the study. If a patient had a stroke, MRI was also performed, but the patient was subsequently excluded from study together with any patients who suffered from TIA or uncontrollable hypertension, or died from noncardiovascular disease during the follow-up period. MRI scanning was not repeated in the control subjects. The sample size of 130 was estimated on the basis of an anticipated event rate in the control period of 18% per year and in the aspirin periods of 9% per year with 80% power and a two sided Є-level of 5%.

Because this study involved multiple institutions, the MRI instruments differed, but all 3 MRI examinations at 12-month intervals were performed at the same institution for each patient with NVAF. A magnetic field strength of 0.5 T or more was used at each institution.

MRI was performed in the orbitomeatal plane with sections 6 mm thick and obtained at 8-mm intervals. T1-weighted, T2-weighted and proton-weighted images were evaluated independently by a neuroradiologist and a stroke neurologist who were both unaware of the subjects’ clinical data. The final diagnosis of the MRI lesions was made by consensus.

Hypertension, diabetes mellitus, a smoking habit, and ischemic heart disease were evaluated as risk factors. Hypertension was diagnosed when there was either systolic blood pressure >160 mmHg or diastolic pressure >95 mmHg on repeated examination or when the patient had a history of treatment for hypertension. Diabetes was defined as a fasting blood glucose >140 mg/dl or a history of relevant treatment. Ischemic heart disease was judged to be present if there was a history of myocardial infarction or angina pectoris. Valvular regurgitation and hypertrophic cardiomyopathy were diagnosed by echocardiography and/or Doppler echocardiography. Atrial or ventricular premature beats were diagnosed by their appearance on the ECG or Holter ECG.

Statistical Analysis

Comparisons of the baseline characteristics and observations in the NVAF patients and control subjects were performed by univariate analysis with Student’s t-test or Mann-Whitney’s test for continuous variables and the Є2 test with the Fisher exact test for noncontinuous variables. Comparisons of MRI lesions in patients with continuous and intermittent AF used the same tests. The effects of treatment with aspirin were analyzed on an intention-to-treat basis. Multiple logistic regression was used to assess the effect of silent MRI lesions at entry on later occurrence of symptomatic BI, taking into account baseline age, sex and a history of hypertension or diabetes mellitus. All statistical analyses were performed with SPSS software package for Windows version 8.0.1J (SPSS Inc, Chicago, ILL, USA).

Results

Patient Characteristics

A total of 212 patients with NVAF and 78 subjects with sinus rhythm participated in this study (Table 1). Of the NVAF patients, 2 were missing the initial MRI scans and 4 had scans that did not meet the criteria, giving 206 eligible NVAF patients at entry to the study. Because the control subjects were recruited mainly from those undergoing a routine health check-up, the underlying diseases were different from those in the patients with NVAF (Table 2). Univariate comparison of the baseline characteristics indicated that hypertension, diabetes mellitus, and valvular regurgitation were more prevalent in the NVAF patients; mean age did not differ significantly.
Prevalence of Silent Lesions on MRI

More than half of the control subjects (53.8%) had silent lesions on MRI (mean number, 11.8±20.4). In the patients with NVAF, 179 of 206 patients (86.4%) had silent lesions (mean number, 31.8±38.9 (Table 3)). The prevalence of lesions and the mean number of lesions were both significantly higher in NVAF patients than in control subjects. Although the prevalence of MRI lesions ≥3 mm did not differ between the NVAF patients and the control subjects, the mean number of silent lesions ≥3 mm was greater in the NVAF patients. The prevalence and number of silent lesions did not differ between patients with continuous or intermittent AF, so patients with intermittent AF appeared to have a similar risk of silent lesions as patients with continuous AF, irrespective of lesion diameter. Approximately one-quarter of the MRI lesions were ≥3 mm in diameter in the control subjects compared with one-fifth in NVAF patients. Multiple logistic regression analysis showed that NVAF was an independent predictor of silent lesions (odds ratio (OR), 12.5; 95% confidence interval (CI), 5.4–29.6; p<0.0001). Prevalence of silent lesions was associated with age (OR per decade, 1.14; 95% CI, 1.09–1.19, p<0.0001), irrespective of lesion diameter (Fig 1). None of hypertension, diabetes mellitus, valvular regurgitation or ischemic heart disease was an independent risk factor for silent lesions in this model.

Location of the Lesions

The prevalence of silent MRI lesions was particularly high in deep white matter (47%) and the basal ganglia (26%) of control subjects (Table 4) and the patients with NVAF had a similar prevalence pattern (deep white matter...
However, the prevalences of lesions in the brainstem, basal ganglia, deep white matter, and the cortical–subcortical zone were significantly higher than those in the control subjects. The location of lesions ≥3 mm in patients with NVAF was not significantly different from that in the control subjects with sinus rhythm, except in the cortical–subcortical zone. Patients with intermittent AF had a distribution of silent lesion similar to that of patients with continuous AF, irrespective of lesion diameter.

Table 4 Location of Silent Lesions on MRI

<table>
<thead>
<tr>
<th>Location</th>
<th>Control (n=78)</th>
<th>NVAF (n=206)</th>
<th>Continuous (n=129)</th>
<th>Intermittent (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>≥3mm</td>
<td>All</td>
<td>≥3mm</td>
</tr>
<tr>
<td>Cerebellum (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (4)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Brainstem (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>31 (15)**</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Thalamus (%)</td>
<td>9 (12)</td>
<td>2 (4)</td>
<td>38 (18)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Basal ganglia (%)</td>
<td>20 (26)</td>
<td>10 (18)</td>
<td>114 (55)**</td>
<td>36 (18)</td>
</tr>
<tr>
<td>Deep white matter (%)</td>
<td>37 (47)</td>
<td>33 (58)</td>
<td>163 (79)**</td>
<td>106 (52)</td>
</tr>
<tr>
<td>Cortical subcortical (%)</td>
<td>12 (15)</td>
<td>6 (11)</td>
<td>85 (41)**</td>
<td>42 (20)*</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; NVAF, nonvalvular atrial fibrillation; All, all lesions observed on MRI.
*p=0.012 vs control, **p≤0.001 vs control, #p=0.007 vs continuous AF.

Table 5 Annual Incidence of Symptomatic Brain Infarction and Silent Lesions Observed on MRI: Effect of Aspirin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients undergoing MRI</th>
<th>Symptomatic BI</th>
<th>Patients without symptomatic BI</th>
<th>Lesions ≥3 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>%/year</td>
<td>n</td>
</tr>
<tr>
<td>ASP (–)</td>
<td>156</td>
<td>6</td>
<td>3.8</td>
<td>150</td>
</tr>
<tr>
<td>ASP (+)</td>
<td>119</td>
<td>4</td>
<td>3.4</td>
<td>115</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; BI, brain infarction; ASP (–), not treated with aspirin; ASP (+), treated with aspirin.
*p=0.014 vs ASP (–).
Annual Incidence of Symptomatic BI and Silent Lesions: Effects of Aspirin

Of the 206 patients with initial MRI images that could be evaluated, 156 had first follow-up scans available for analysis (Table 1). Six patients had symptomatic BI during the first year without treatment with aspirin (3.8%/year) (Table 5). New silent lesions appeared in 31 of the remaining 150 patients (20.6%/year), and new silent lesions ≥3 mm were observed in 6 patients (4.0%/year).

Of the 150 patients treated with aspirin in the second year, 119 had second follow-up scans available for analysis (Table 1). Four patients had symptomatic BI despite the treatment (3.4%/year; Table 5). No patient had a major bleeding event, but 4 had a minor bleeding event. There were 52 patients who complained of abdominal pain and/or gastrointestinal discomfort and 24 discontinued aspirin treatment. Administration of aspirin did not decrease the annual incidence of symptomatic BI (\( \Delta^2 \) test: \( p=0.825 \)), but the occurrence of silent lesions was significantly reduced (20.2%/year vs 9.6%/year; \( \Delta^2 \) test: \( p=0.014 \)). This alteration in occurrence during aspirin treatment was limited to relatively small lesions because the annual incidence of silent lesions ≥3 mm were not reduced during aspirin treatment (4.0%/year vs 7.8%/year, \( p=0.182 \)).

Fig 2 shows the annual incidence of cerebrovascular events. Symptomatic BI did not occur in patients under 60 years of age, but its incidence exceeded 5%/year in patients with moderate risk (>60 years), and in high risk patients (>75 years old or having a history of hypertension and/or diabetes mellitus). The incidence of the new lesions on MRI was similar, irrespective of the patient’s risk status. However, during the treatment with aspirin the occurrence of new lesions were significantly reduced, although the incidence of new lesions ≥3 mm in diameter was not reduced in any risk group (Fig 2B,C).

Location of New Lesions

The distribution of new lesions with and without aspirin treatment is shown in Table 6. Of the 150 patients observed 1 year after not having had aspirin treatment, 31 had at least one new lesion: 20 had one or more lesions in deep white matter (65%), and 9 had lesions in the basal ganglia (29%). The spatial distribution of the new lesions was similar to that of the initial MRI images. After 1 year of treatment with aspirin, there was a marked reduction in the occurrence of new lesions in both the basal ganglia (0%, \( p=0.005 \)) and deep white matter (27%, \( p=0.002 \)). However, administration of aspirin did not prevent the occurrence of small silent lesions, particularly in the cortical–subcortical zone.

Risk Factors for Stroke and Silent Lesions

During the course of the study, 10 patients (6 in the first year and 4 in the second year) had a symptomatic BI, and 42 patients (31 in the first year and 11 in the second year) developed new silent lesions. Univariate analysis showed that advanced age was associated with symptomatic BI (\( p=0.03 \)). Furthermore, the presence of a silent lesion ≥3 mm was also associated with the appearance of new silent lesions and new lesions ≥3 mm. Multivariate logistic regression analysis was performed using age, sex, history of hypertension, and/or diabetes mellitus, in addition to any of the parameters including presence of lesions, total number of the lesions, presence of lesions ≥3 mm, and total number of lesions ≥3 mm. However, none of these factors contributed significantly to the occurrence of symptomatic BI or silent lesions except advanced age when presence of lesions was included to test the relation to symptomatic BI (OR, 1.13; 95% CI, 1.00–1.28; \( p=0.43 \)). Although this study was not designed to examine the prognostic significance of silent lesions, the results indicate that the presence of silent lesions and their number, irrespective of size, did not significantly increase the likelihood of such an event.

Discussion

The present study demonstrated that the prevalence of silent lesions on brain MRI, especially those <3 mm in diameter, was high in patients with NVAF compared with control subjects with sinus rhythm. These lesions were more prevalent in the basal ganglia, deep white matter, and the cortical–subcortical zone. During treatment with aspirin the appearance of new silent lesions <3 mm in diameter was reduced in the deep white matter and basal ganglia, but not in the cortical zone.

The prevalence of silent lesions in previous CT or MRI studies varies from 10% to 47% in 3,23,24 and population-based studies using MRI report a prevalence of silent lesions ranging from 11% to 28% in 2,25,26. In the present study, the prevalence of silent lesions by MRI, especially those ≥3 mm, was 44.9% in controls, which is relatively high compared with previous reports. It should be noted that this prevalence is related to the particular study subjects rather than true prevalence, because the present study had a possible selection bias inherent in this type of hospital-based study. The prevalence of silent lesions will be affected by the sensitivity of the examination technique and the composition of the study sample with regard to age, sex, race, and vascular risk factors. The frequency of silent lesions in the present study was comparable to the 42–47% reported in other MRI-based studies performed in Japan.\(^{24,27}\)

We used MRI to carefully investigate small brain lesions,
which we defined as hyperintense areas of any size on both the T2-weighted and proton-density images and a corresponding hypodense area on the T1-weighted images. When the lesions were ≥3 mm in diameter, they were considered as silent infarcts, distinguished from perivascular space, gliosis, demyelination, and white matter disease. However, small lesions <3 mm in diameter may be either small infarcts or other white matter lesions such as or and demyelination.38 Despite the limitations of MRI diagnosis, an increased prevalence of these small lesions in patients with AF strongly suggests that embolic episodes involving thrombi of cardiac origin contributed to their formation. A high prevalence of cortical lesions also supports this hypothesis, because an experimental study demonstrated that 87.9% of microspheres injected into the carotid artery were entrapped in the grey matter.39 However, the new lesions in patients with NVAF were observed particularly in deep sites, indicating that the new lesions may not be of embolic origin but instead may reflect ischemic episodes. Because the deep white matter is an arterial border zone already marginally perfused under physiologic circumstances, it is vulnerable to a decrease in cerebral blood flow.39 Reduced cardiac output in patients with AF may induce ischemia of the deep white matter, causing lesions.31 We have already reported that an irregular heart rate blunts nitric oxide (NO) synthesis and increases p-selectin expression on platelets, ultimately increasing the risk for silent BI.32,33 Irregular shear stress upon the vascular endothelium in patients with AF also may cause sclerotic changes related to attenuation of NO synthesis.34,35 This hypothesis is further supported by several reports that the prevalence of lesions in deep white matter and basal ganglia is associated with atherosclerosis-related factors such as aging, hypertension, and diabetes mellitus.3,28,36,37 If the NO attenuation hypothesis is true, the high prevalence of small lesions in the deep white matter and basal ganglia may be explained by ischemic changes in these areas.

The effect of aspirin on the occurrence of the new lesions is another important result of the present study. A preventive effect was clearly seen for lesions in the deep white matter and basal ganglia, but not in the cortico-subcortical zone, indicating that aspirin may prevent these small silent lesions that do not have an embolic origin. This hypothesis is strongly supported by the finding that aspirin in AF patients appears to mainly reduce the noncardioembolic strokes.38 In the present study, during treatment with aspirin, there was a reduction in the appearance of new lesions including those <3 mm in diameter, but symptomatic BI and silent infarcts ≥3 mm in diameter were not reduced. Aspirin inhibits thromboxane B2 production, and may improve perfusion in the arterioles that are responsible for small lesions <3 mm in diameter. Of course, we could not exclude the possibility that these small lesions could reflect small emboli in the arterioles, which could cause further ischemia and synergistically accelerate the ischemic changes. However, aspirin may not attenuate embolic episodes by its anti-platelet action, because the occurrence of both small lesions and silent infarction in the cortical–subcortical zone was not affected by aspirin administration.

In the present study, the prevalence of silent lesions in patients with intermittent AF was not different from that in patients with continuous AF. Although patients with intermittent AF are commonly believed to have a lower risk of stroke than those with continuous AF, subgroup analysis of the SPAF studies demonstrated that patients with intermittent AF had stroke rates similar to patients with continuous AF and similar stroke risk factors.28 Our results are consistent with those findings and may be related to similar mean age and risk factors in the present patients with intermittent AF and continuous AF. Another study also identified hypertension and more advanced age as predictors of stroke in patients with intermittent AF.31

We expected that silent lesions would predict the occurrence of either symptomatic or silent BI because other studies have demonstrated that a previous minor stroke increases the risk for a second episode.42,43 We found that the presence of initial lesions ≥3 mm in diameter was higher in patients who developed a new lesion than in patients without new lesions. However, the presence of a lesion ≥3 mm in diameter was not an independent predictor for symptomatic or asymptomatic BI (lesion ≥3 mm in diameter). Thus, the prognostic significance of small lesions may be limited and this data should be interpreted carefully because the study was not designed to test the predictabilities of silent lesions.

**Study Limitations**

The control subjects and NVAF patients were recruited under substantial bias. Controls were recruited from the outpatient clinic of a cardiology ward, so many subjects particularly concerned about their health would have been included. Furthermore, consecutive NVAF patients were not recruited because the attending physicians had been educated to exclude a patient with risk from this study because of the need for prophylaxis against stroke. Study subjects mainly consisted of patients with no risk or patients who refused prophylactic treatment with warfarin or antiplatelet agents. Although the MRI images were analyzed at one institute, the MRI instruments and the magnetic-field strength differed according to the institution. Moreover, the study design was not randomized. Treatment bias may exist during each year. These drawbacks may limit the applicability of the study results, but the strength of the present study is the performance of serial MRI examinations to obtain annual event rates for silent lesions in patients with NVAF. It is also the first interventional study to examine the effects of aspirin on silent lesions observed on MRI.

In conclusion, small brain lesions observed by MRI in patients with NVAF were common, and increased in number over time. Although the effect of aspirin on both symptomatic and silent BI (lesions ≥3 mm in diameter) may be minimal, it may prevent the occurrence of new smaller lesions, especially in the deep white matter and basal ganglia.

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**References**
