# Silent Brain Infarction in Patients with Rheumatic Mitral Stenosis

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**SUMMARY**

Silent brain infarction (SBI) is defined as asymptomatic infarction areas detected in computerized tomography (CT) scans in patients without a history of stroke. The incidence of SBI is increased in CT or magnetic resonance imaging in patients with carotid stenosis and with atrial fibrillation (AF), but its relation with rheumatic mitral stenosis (MS), another major source of emboli, is uncertain. The aim of this study was to investigate the incidence of SBI in patients with MS.

Fifty-three patients with MS (44 females and 9 males; range 25-52 years; mean age 38±7 years) diagnosed by transthoracic echocardiography (TTE) were enrolled in the study. Mitral valve calcification, left atrium (LA) dimension, and the presence of associating mitral regurgitation on TTE were recorded. Electrocardiographic evaluation was done for rhythm analysis and neurologic examination was performed prior to cerebral CT. Carotid artery Doppler examination was carried out in patients with SBI to exclude carotid artery lesions. Patients with a history of hypertension, diabetes mellitus, anticoagulant drug usage, presence of thrombus in LA, left ventricular segmental or systolic dysfunction, or other valve diseases were excluded from the study.

The incidence of SBI was found to be 24.5% in patients with MS (47% cortical, 53% lacunar). SBI was observed to be significantly high in patients with LA dimension >4 cm or in patients with AF ($p<0.05$). The SBI incidence was markedly higher if AF was found with enlarged LA when compared with patients having sinus rhythm and small LA ($p<0.01$). When moderate to severe mitral regurgitation was associated with MS, the SBI incidence was found to be lower ($p<0.05$). Although SBI was higher in patients with MVA<1.5 $cm^2$, it was not statistically significant ($p>0.05$). No significant correlation was found between calcific and noncalcific valves for SBI ($p>0.05$).

Our data suggest that SBI may be expected in about 1/4 of patients with MS. The presence of LA enlargement and AF increase the incidence of SBI in patients with MS, whereas the presence of moderate to severe mitral regurgitation decreases the incidence of SBI. (Jpn Heart J 2002; 43: 137-144)

**Key words:** Silent brain infarction, Rheumatic mitral stenosis

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SILENT brain infarction (SBI) is defined as an asymptomatic infarct detected on computerized tomography (CT) or magnetic resonance imaging (MRI) in patients with no history of stroke and unrelated to the symptoms and signs of the index stroke.[1-8] These kinds of asymptomatic infarct areas have also been shown in an autopsy series.[9] The silent character of these lesions relates either to their small size and location in truly silent brain areas or to their production of a minor deficit that may have gone unreported and unrecognized as a stroke.[1]

Several studies have examined and observed a significant relationship between the frequency of asymptomatic CT/MRI lesions and cerebrovascular risk factors including hypertension, carotid artery lesions, atrial fibrillation (AF), and diabetes mellitus (DM).[5,10-12] It was also reported that cardiogenic microemboli might also cause similar cerebral lesions.[12] In patients with rheumatic mitral stenosis (MS), the annual incidence rate of all symptomatic emboli is about 4%; more than half of which are cerebral, but many asymptomatic systemic emboli and occasional asymptomatic cerebral emboli are found postmortem. In patients with SBI, the importance of the presence or absence of MS as a major source of emboli is uncertain. In the English literature, it has not yet been studied whether rheumatic MS is related with SBI. Therefore, in this study, we have investigated the relation between rheumatic MS and SBI.

## MATERIALS AND METHODS

One hundred and eighty-six patients with rheumatic MS admitted to cardiology clinics between September, 1998 and March, 1999 were included in the study. Among these 186 patients, 53 patients (44 females and 9 males; range 25-52 years; mean age 38±7 years) fulfilled the study criteria and were accepted for enrollment in the study which was carried out in both cardiology and neurology clinics. Age, sex, history of hypertension, DM, and stroke were recorded. Electrocardiograms were evaluated for rhythm analysis (sinus rhythm or AF).

All patients underwent transthoracic echocardiography (TTE) in the echocardiography unit using a Wing Med CFM 800 echocardiograph. Mitral stenosis was defined as a decrease in mitral valve area (MVA$< 2.5$ cm$^2$), the presence of a diastolic gradient in the mitral valve, a decrease in the mobility of the posterior mitral valve, and a thickening of the subvalvular apparatus. Presence of calcification on the mitral valve, MVA, anteroposterior dimension of LA, and associating mitral regurgitation (MR) were recorded. MVA was calculated by planimetry and pressure half time methods. LA enlargement is defined as an anteroposterior dimension of LA $>4$ cm measured in the parasternal long axis view. Patients with a history of hypertension, diabetes mellitus, or anticoagulant drug usage, the presence of aortic valve disease, left ventricle (LV) segmental or

global systolic dysfunction, the presence of a thrombus in LA or in LV, a prosthetic valve, or other valve diseases on TTE were excluded from the study.

Following the cardiologic examinations, the patients underwent a detailed neurologic examination at a neurology clinic. Patients with hemiparesy, aphasia, hemianopsy, facial paralysis, motor, sensory, verbal, sight area and cranial neurons dysfunctions, and transient ischemic attack (TIA) were also excluded.

Cerebral CT scans were performed in all patients. General Electric Prospeed Plus and Hitachi 510 systems were used for brain scanning. Contrast agent was not given. In the supine position, axial slices of 10 mm in thickness were obtained from the skull base to the top of the dome. All scans were described by the same neuroradiologist with no knowledge of the patient's clinical data. All patchy, low density areas that were sharply demarcated from the surrounding tissue in whole slices were designated as silent infarctions. The size and localization of each lesion were also recorded. Lesions were named as cortical infarcts (lesion included in a part of the cerebral cortex), lacunar infarcts (small-deep lesions between 5-15 mm localized at basal ganglions, thalamus, internal and external capsules, and brain stem), and watershed infarcts (border zone hypodensities between arterial territories).

Patients with detected SBI on their CT also underwent carotid artery Doppler examination to exclude carotid artery lesions.

**Statistical Analysis:** All values are expressed as the mean±standard deviation. The Mann Whitney-U test was used for age comparisons and chi-square test was used for rate comparisons between the groups. Pearson's chi-square scores were defined. SPSS for Windows program was used for statistical analysis. A $p$ value $<0.05$ was considered statistically significant.

## RESULTS

Eighty-one patients among 186 MS patients were enrolled in the study. Of these 81, 14 had an aortic valve disease, 7 had left atrial thrombus, 2 had LV segmental systolic dysfunction, and 5 had TIA, so a total of 28 patients were excluded. Of the 53 patients who fulfilled the study criteria (44 females and 9 males; range 25-52 years; mean age 38±7 years). ECG revealed AF in 25 (47%) and sinus rhythm in 28 (53%).

Transthoracic echocardiography revealed noncalcific MS in 33 (62%) and calcific MS in 20 (38%) patients. Besides MS, 7 (13%) had associated mild MR and 15 (28%) had associated moderate to severe MR, while MR was not detected in 31. MVA was $<1.5$ cm$^2$ in 21 (40%) patients and $>1.5$ cm$^2$ in 32 (60%) patients. LA dimension was <4 cm in 29 (55%) patients and >4 cm in 24 (45%).

Apart from 5 patients with TIA (excluded from the study), the results of the neurologic examinations were normal. Cerebral CT revealed SBI in 13 (24.5%) of the 53 patients, while 40 (75.5%) had no SBI. Two of the patients with SBI had more than one SBI (both had 2 SBIs). Of the total of 15 SBI, 7 (47%) were cortical and 8 (53%) were lacunar type infarction. Three of the 7 cortically located lesions also extended to the subcortical watershed area (border zone hypodensities between arterial territories). All cortical SBI were <20 mm in dimension, except one (20-23 mm). Two of the lacunar SBI were 15 mm and six were between 5-10 mm. Of the 8 lacunar lesions, 3 were in basal ganglions, 2 in capsula externa, and one each in the thalamus, corona radiata and frontosubcortical white matter. The results of the carotid artery Doppler examinations of all patients with SBI were normal.

When the patients were evaluated for their echocardiographic features; 8 of the 33 (24%) patients with noncalcific MS had SBI and 5 of the 20 (25%) patients with calcific MS had SBI. No significant difference was found between the calcific and noncalcific groups for SBI ($p>0.05$). SBI was detected in 7 (33%) of the 21 patients with MVA <1.5 $cm^2$ and 6 (19%) of the 32 patients with MVA >1.5 $cm^2$ with no statistically significant difference ($p>0.05$). Among the 15 patients associated with moderate-severe MR to MS, 1 (6.7%) had SBI, while 12 (31%) of the 38 patients without MR or with mild MR associated with MS had SBI. A significant difference was found between the two groups for SBI ($\chi^2=5.24$, $p<0.05$).

The incidences of SBI in events with LA dimension >4 cm and with LA dimension <4 cm were 9/24 (37.5%) and 4/29 (14%), respectively. A significant difference was found between the two groups for SBI ($\chi^2=3.64$, $p<0.05$).

Ten of the 25 (40%) patients with AF had SBI, while 3 of the 28 (10.7%) patients with sinus rhythm had SBI. SBI was found to be significantly high in patients with AF ($\chi^2=4.42$, $p<0.05$).

Among the 18 patients who had AF accompanied by an enlarged LA, the SBI incidence was 44% (8/18), while it was 5% (1/20) in patients with sinus rhythm accompanied by a small LA ($\chi^2=7.71$, $p<0.01$). The data are summarized in the Table.

**Table.** Incidences of Silent Brain Infarction According to Event Characteristics

| Characteristic | Yes | No | *p* |
|---|---|---|---|
| Calcific MS | 8/33 (24%) | 5/20 (25%) | NS |
| MVA <1.5 $cm^2$ | 7/21 (33%) | 6/32 (19%) | NS |
| Moderate-Severe MR | 1/15 (6.7%) | 12/38 (31%) | <0.05 |
| LA >4 cm | 9/24 (37.5%) | 4/29 (14%) | <0.05 |
| AF | 10/25 (40%) | 3/28 (10.7%) | <0.05 |
| AF + LA >4 cm | 8/18 (44%) | 1/20 (5%) | <0.01 |

MS=mitral stenosis; MVA=mitral valve area; MR=mitral regurgitation; LA=left atrium; AF=atrial fibrillation; NS=nonsignificant.

## DISCUSSION

Silent brain infarction incidences in population based studies of normal adults with MRI are reported to be between 10.6% and 40%.[4,5,12] In these studies, age significantly influenced the SBI incidence. Two of them reported that the SBI incidence was significantly increased with older age (over 55 years or 65 years). The incidences of SBI in previous CT studies of first-ever stroke or TIA patients vary from 10% to 38%.[1,2,6-8,13,14] This wide range of rates is partly explained by variations in patient age and improvements in CT technology. We have found the SBI incidence in 24.5% of patients with MS. Our study is the first to explore SBI in patients with rheumatic MS. Cortical and lacunar localizations of these well demarcated hypodense infarcts had similar rates (8 (53%):7(47%)).

It was also reported that the detection of SBI was expected to be more common in patients with stroke than in the normal population. In our study group, the mean ages of patients with SBI and patients without SBI were 41±4 years and 39 ±7 years, respectively ($z=0.09$, $p>0.05$). Our findings suggest that age is not an independent risk factor for SBI in our study group. This may be related to the relatively young age of our patient population for SBI risk. One of the major limitations of our study was the lack of MRI, which is more sensitive for SBI detection. We may have found the SBI incidence was higher if MRI was performed instead of CT.

When the patients were evaluated for their echocardiographic features, we found that LA enlargement on TTE is an independent risk factor for SBI (37%: 13.7%, $p<0.05$). In a prior study, SBI in patients with ischemic stroke were related to age and size of the LA.[15] In another study that investigated the epidemiologic features of SBI in patients with nonvalvular AF, it was reported that age and increased LA dimensions were additional risk factors for SBI.[16] Although our study found a strong relation between LA enlargement and SBI, we did not find any correlation between SBI and age. The presence of MS as a cause of LA enlargement and the younger patient population are the two important contributions of our study to the literature.

When moderate to severe MR was associated with MS, the SBI incidence was found to be significantly lower (6.7%: 31%, $\chi^2=5.24$, $p<0.05$). Clinical embolic events occur in about 20% of patients with rheumatic heart disease. Embolism usually complicates MS or mixed stenosis-regurgitation, whereas pure MR less frequently results in embolism.[17] Contradictory findings exist concerning MR for SBI. Some studies have reported that significant MR is protective against LA spontaneous echo contrast and LA thrombus formation and therefore decreases the risk of thromboemboli.[18-20] However, in one study, significant MR was found to be protective against LA thrombus formation but not against sys-

temic embolism.[21] Our findings suggest that MR is protective against SBI.

Although the SBI incidence was found to be higher in patients with MVA <1.5 $cm^2$, no statistically significant difference was observed (33%: 18.5%, $p>0.05$). It was reported that a decrease in MVA increased the risk of thrombus formation, however, no influence on the systemic emboli was observed.[22] Although we did not a find significant relation between MVA and SBI, it may be another independent risk factor in a greater number of patients.

We found more SBI in patients with AF than in patients with sinus rhythm (40%: 10.7%, $\chi^2=4.42$, $p<0.05$). Likewise in another study, the incidence of SBI was greater in patients with AF than in patients with sinus rhythm.[3] It was reported that the risk of stroke in patients with non-rheumatic chronic AF is increased more than 5-fold over that in controls with sinus rhythm, corresponding to a 4-5% annual incidence of stroke. The risk of stroke increased 17-fold when the etiology of AF was rheumatic valve disease.[23] Our findings suggest that AF increases the risk of SBI in patients with MS.

We found the SBI incidence was markedly higher in patients with AF associated with enlarged LA than in patients with sinus rhythm associated with small LA (44%: 5%, $p<0.01$). In a previous study, although a strong relation between LA enlargement and SBI was observed, they did not find any relation between SBI and AF or other sources of embolism in the heart as potential causes of index stroke.[15] In patients with nonvalvular AF, age and increased LA dimension were associated with an additional risk for SBI.[16] The above-mentioned studies were conducted either in patients with nonvalvular AF or in patients with ischemic stroke. Our study is the first to suggest that the presence of AF and an enlarged LA were associated with additional risk for SBI in patients with MS.

Although cortical localization is more commonly seen in cardioembolic cerebrovascular events, we have found cortical and lacunar localizations in similar ratios. Hypertension is the main cause of silent deep infarcts but less frequently, microemboli originated from cardiac sources might also cause similar type lesions.[24] The presence of potential cardiac sources of emboli such as rheumatic valve disease, AF, and enlarged LA, is thought to indicate that microemboli which originated from the heart are responsible for SBI on CT. Our findings also suggest that microemboli originating from the heart may cause lacunar infarcts other than cortical infarcts. Hypertension was not encountered in our patient group. Interestingly, most of our patients were hypotensive. It has been reported that hypotension (by causing cerebral hypoperfusion) might be responsible for SBI, especially at the watershed area.[25] Other than cardiac microemboli, the same mechanism may also be responsible in our patients.

One of the major limitations of our study is the lack of MRI which is more sensitive for SBI detection. Although the CT scan is less sensitive than MRI in

demonstrating very small lesions and unremarkable diffuse perivascular lesions, it is still clinically useful for diagnosing hypodense areas that are sharply demarcated from the surrounding tissue that suggests infarction. Another limitation is the lack of transesophageal echocardiography, which has significant superiority for the detection of thrombus in LA and LA appendages. Among 186 patients with MS, only 53 patients were studied and this might have been affected the randomly selection property of the events.

In conclusion, our data suggest that SBI may be expected in about 1/4 of patients with MS. The presence of LA enlargement and AF increase the SBI incidence in MS patients, whereas moderate to severe mitral regurgitation decreases the SBI incidence. SBI detected on CT may be the first sign that indicates a cardiac source of embolism, especially in countries with a high prevalance of rheumatic heart disease. SBI originating from the heart may be a predictor of further symptomatic cerebrovascular events. This emphasizes the importance of active tracing and subsequent anticoagulant treatment of patients with MS and SBI.

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