Significant Impairment of Left Atrial Function in Patients with Cardioembolic Stroke Caused by Paroxysmal Atrial Fibrillation

Yoshiharu Taguchi¹, Shuta Takashima¹, Tadakazu Hirai², Nobuyuki Fukuda², Kazumasa Ohara², Keiko Nakagawa², Hiroshi Inoue² and Kortaro Tanaka¹

Abstract

Objective Patients with cardioembolic stroke (CE) caused by paroxysmal atrial fibrillation (Paf) sometimes show normal sinus rhythm on admission, which makes it difficult to diagnose them as having CE. The present study examined the differences in echocardiographic findings between patients with CE caused by Paf (the Paf-CE group) and those with non-cardiogenic embolic ischemic stroke (the Non-CE group).

Methods We examined thirty-two patients with embolic ischemic stroke presenting with a normal sinus rhythm upon admission to our hospital; 13 patients in the Paf-CE group and 19 patients in the Non-CE group. During admission, all patients underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) at a normal sinus rhythm. The left atrial dimension, left ventricular end-diastolic dimension and left ventricular ejection fraction were measured using TTE. The left atrial appendage peak flow velocity (LAAPV), spontaneous echo-contrast in the left atrium (LASEC) and thrombus in the left atrium were evaluated using TEE.

Results Among the clinical background characteristics, hypertension was significantly more frequent in the Non-CE group than in the Paf-CE group (p<0.01). Congestive heart failure was significantly more frequent in the Paf-CE group than in the Non-CE group (p<0.05). LAAPV was significantly lower in the Paf-CE group than in the Non-CE group (34.7 cm/s vs. 64.0 cm/s, p<0.01), and the LASEC grade was significantly higher in the Paf-CE group than in the Non-CE group (p<0.01). A thrombus in the left atrium was detected in two patients in the Paf-CE group, but no thrombi were detected in any of the patients in the Non-CE group.

Conclusion Echocardiographic evaluation is useful, as the above data indicate that the left atrial function is apparently impaired in patients with CE caused by Paf, even in a patient with an apparently normal sinus rhythm.

Key words: cardioembolic stroke, paroxysmal atrial fibrillation, transesophageal echocardiography, left atrial function

(Inter Med 49: 1727-1732, 2010)
(DOI: 10.2169/internalmedicine.49.3580)

Introduction

Cardioembolic stroke (CE) generally results in more severe disability and a higher rate of mortality than other types of ischemic stroke, since it tends to result from a large ischemic lesion (1, 2). The most common cause of CE is atrial fibrillation (AF), especially non-valvular AF (2). The introduction of oral anticoagulation therapy provides an additional 40% risk reduction in recurrent stroke compared with antiplatelet therapy in patients with CE caused by AF (3, 4). Therefore, the precise diagnosis of the subtype of
ischemic stroke and the initiation of the appropriate antithrombotic therapy for secondary stroke prevention is critical. However, patients with CE caused by paroxysmal atrial fibrillation (Paf) sometimes show a normal sinus rhythm on admission (5-9), which makes it difficult to diagnose them as having CE.

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have been recognized as valuable tools for identifying cardiac sources of embolism (10, 11). In particular, since TEE provides high-resolution images of the left atrium (LA), the left atrial appendage peak flow velocity (LAAPV) and spontaneous echo-contrast in the left atrium (LASEC) obtained by TEE have been utilized to assess the severity of blood stasis in the left atrial appendage (LAA), which in turn leads to the risk of CE (10, 12-14). We hypothesized that echocardiographic evaluation, even if performed in a patient with a normal sinus rhythm, might be useful for the diagnosis of patients with CE caused by Paf. Therefore, the present study examined the differences in echocardiographic findings between patients with CE caused by Paf and those with noncardiogenic embolic ischemic stroke (the Non-CE group).

**Methods**

**Study subjects**

From April 1, 2004 to March 31, 2007, 251 patients with ischemic stroke were admitted to the Department of Neurology at Toyama University Hospital, and 40.2% of them (101 patients) were diagnosed as having had an embolic stroke. An embolic stroke was diagnosed if the onset occurred suddenly during the daytime, and involved cortical or hemorrhagic infarctions. Multiple acute lesions in diffusion-weighted images and MRA, TTE within two weeks of stroke onset. These patients were continuously monitored using electrocardiogram for at least two weeks after admission. During admission, on electrocardiograph 13 patients were found electrocardiographically shown to have Paf and were subsequently diagnosed as having CE caused by Paf (Paf-CE group: 9 men and 4 women; mean age, 71.6±10.1 years), and no patients in the Paf-CE group exhibited severe large-artery atherosclerosis. The other 19 patients who did not show any arrhythmia including Paf during admission were diagnosed as having non-cardiogenic embolic stroke (Non-CE group: 13 men and 6 women; mean age, 69.7±12.6 years). Using the TOAST criteria, all patients in the Paf-CE group were classified cardioembolism and all patients in the Non-CE group were classified large-artery atherosclerosis. Paf was defined as AF documented electrocardiographically at least once during the admission period (at least two weeks) and lasting at least one hour.

The baseline clinical characteristics, including hypertension, dyslipidemia, diabetes mellitus, and recent congestive heart failure, were carefully determined from medical records and routine laboratory data. Congestive heart failure was defined as a New York Heart Association (NYHA) functional class of 2 or over. The amount of D-dimer was measured on admission, using the quantitative LPIA-A700 assay system (LPIA-Ace D-dimer; Mitsubishi, Tokyo, Japan).

**Echocardiography**

TTE and TEE were performed during a normal sinus rhythm in all patients. TTE was performed using a 2.5- or 3.5-MHz, phased-array transducer connected to an ultrasound system (SSH-140A; Toshiba; Tokyo, Japan). The left atrial dimension (LAD), left ventricular end-diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF) were determined on M-mode images. TEE was performed using a 5-MHz multiplane transducer connected to the same ultrasound system. Each patient was examined after having fasted, and without premedication except for topical anesthesia of the hypopharynx using lidocaine spray. Multiple standard tomographic planes were imaged to determine the LAAPV, the presence of LA thrombi and the severity of LASEC. All of the images were recorded on a videotape for subsequent analyses. No complication occurred during TEE. LASEC was diagnosed in the presence of dynamic smoke-like echoes within the LA and LAA with a characteristic swirling motion that was distinct from the white noise artifact. The severity of LASEC was defined using the criteria of Fatkin et al (10). Briefly, it was graded from 0 to 4+ according to the following criteria: 0=none (absence of echodensity); 1+=mild (minimal echodensity detectable only transiently during the cardiac cycle with an optimal gain setting); 2+=mild to moderate (transient spontaneous echocardiographic contrast without increased gain settings and more dense pattern than 1+); 3+=moderate (dense swirling pattern during the entire cardiac cycle); and 4+=severe (intense echodensity and very slow swirling patterns in the LAA, usually with a similar density in the main left atrial cavity). The LAA flow velocity profiles were obtained using pulsed-wave Doppler echocardiographic interrogation at the orifice of the appendage. The peak outflow velocity signals within each R-R interval were averaged over a minimum of six cardiac cycles. The presence of LA thrombi and the severity of LASEC were determined by two independent observers. Any differences in the evaluations were resolved by a third independent observer.

**Data analyses**

Variables are presented as the mean±SD. Statistical analyses were performed using SPSS (SPSS version 14.0, Chicago, IL, USA). The significance of any difference in the mean value was tested using an unpaired Student’s t test,
and the difference in proportions between two groups was examined using a χ² test. A Mann-Whitney two-sample rank test was used to evaluate nonparametric distributions. A p value of less than 0.05 was defined as statistically significant.

Results

The clinical characteristics are summarized in Table 1. No significant differences in age, sex, the prevalence of dyslipidemia or the prevalence of diabetes mellitus were observed. Hypertension was significantly more frequent in the Non-CE group than in the Paf-CE group (73.7% vs. 15.4%, respectively, p<0.01). There were no differences in the treatment modality or medications for hypertension between the groups. ARB or ACE was used for 50% of the Paf-CE group and for 57% of the Non-CE group. Congestive heart failure (NYHA ≥2) was significantly more frequent in the Paf-CE group than in the Non-CE group (73.7% vs. 15.4%, respectively, p<0.01). There were no differences in the treatment for dyslipidemia or the prevalence of diabetes mellitus were observed.

Table 1. Clinical Characteristics of Paf-CE Group and Non-CE Group

<table>
<thead>
<tr>
<th></th>
<th>Paf-CE group (N=13)</th>
<th>Non-CE group (N=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.6±10.2</td>
<td>69.7±12.6</td>
<td>0.658</td>
</tr>
<tr>
<td>Men</td>
<td>9 (69.2%)</td>
<td>13 (68.4%)</td>
<td>0.951</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (15.4%)</td>
<td>14 (73.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3 (23.1%)</td>
<td>3 (15.8%)</td>
<td>0.604</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (15.4%)</td>
<td>3 (15.8%)</td>
<td>0.975</td>
</tr>
<tr>
<td>NYHA ≥2</td>
<td>3 (23.1%)</td>
<td>0 (0%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D-dimer (μg/mL)</td>
<td>2.05±1.54</td>
<td>1.22±1.11</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (%) of patients.

Paf-CE group; patients with cardioembolic stroke caused by paroxysmal atrial fibrillation
Non-CE group; patients with non-cardioembolic stroke
NYHA; New York Heart Association functional class

The LAAPV was significantly lower, and the grade of LASEC was significantly higher in patients with CE caused by Paf than in patients with Non-CE, even though the echocardiographic evaluation was performed during a normal sinus rhythm. Patients with CE caused by Paf sometimes show a normal sinus rhythm upon admission, and it is occasionally difficult to detect Paf using electrocardiography during admission. Therefore, the results of our study suggest that TEE findings may be additionally useful for differentiating patients with CE caused by Paf from those with Non-CE.

The major finding of the present study was as follows. TTE was performed at 6±2 days after admission. Regarding the TTE findings, no significant differences in LAD, LVDd or LVEF were observed between the two groups (Table 2).

TEE was performed at 10±3 days after admission. AF was noticed in seven patients within the initial 4 hospital days and in six patients after the 5th to 10th hospital days. Eight patients presented Paf before TEE examination, and five patients presented Paf after TEE examination. The LAAPV was significantly lower in the Paf-CE group than in the Non-CE group (34.7±9.3 cm/s vs. 64.0±12.1 cm/s, respectively, p<0.01) (Table 2, Fig. 1). The LASEC grade was significantly higher in the Paf-CE group than in the Non-CE group (1.9±0.9 vs. 0.6±0.8, respectively, p<0.01) (Table 2, Fig. 1). In the Non-CE group, the LASEC grade was grade 1 or 0 in every patient except for one patient with grade 3. On the other hand, none of the patients had grade 0 LASEC in the Paf-CE group. A left atrial thrombus was detected in two patients (15.4%) in the Paf-CE group, but no thrombi were detected in any of the patients in the Non-CE group (Table 2, Fig. 1).

Discussion

The major finding of the present study was as follows. TEE was performed at 6±2 days after admission. Regarding the TTE findings, no significant differences in LAD, LVDd or LVEF were observed between the two groups (Table 2).
Various causes of embolic stroke in patients with a normal sinus rhythm upon admission are possible, including CE caused by Paf, artery-to-artery embolism, paradoxical embolism, Trousseau syndrome, and so on. A precise differentiation of CE from non-CE is essential for determining which antithrombotic therapy should be started for secondary prevention in patients with embolic stroke with a normal sinus rhythm upon admission. However, CE caused by Paf is often classified into ischemic stroke of undetermined etiology, because Paf is not always detectable on admission. Liao et al (15) reported that new atrial fibrillation or flutter was detected in 5.7 to 7.7% of patients with acute ischemic stroke using 24-hour to 72-hour Holter electrocardiogram monitoring. Thus, short-term monitoring may not be effective for the detection of Paf. Todo et al (9) reported that frequent premature atrial contractions (PAC) in patients with stroke of undetermined etiology should be regarded as a masked type of Paf and should be included in one of the causes of CE. Wallmann et al (16) proposed a supportive diagnostic strategy for identifying Paf in ischemic stroke patients: first, a 24-hour ECG recording is performed to count the number of PAC events, and then serial 7-day ECG recordings are selectively performed in patients with ≥70 PAC events per 24 hours. However, the subjects of the above three reports consisted of patients with acute ischemic stroke including both embolic and non-embolic origins; consequently, the subtypes of stroke in patients with Paf were not always cardioembolic. In the present study, on the other hand, embolic stroke patients were selected, and TEE was indicated for the evaluation of the embolic source. As a result, the present study found that the left atrial function tended to be impaired in patients with CE caused by Paf. Dysfunction of the LAA can be directly connected to LA thrombi formation, which results in cardioembolic stroke. Therefore, we consider that TEE evaluation may be useful for differentiating CE caused by Paf from Non-CE.

Naya et al (17) reported that the plasma brain natriuretic peptide (BNP) level was significantly higher in patients with CE caused by Paf than in patients with Non-CE, and that the LAAPV was significantly lower in patients with CE caused by Paf than in patients with Non-CE. They suggested that BNP and LAAPV measurements might be helpful for differentiating cardioembolic stroke with AF from non-cardioembolic stroke. However, it was not mentioned whether TEE was performed during a normal sinus rhythm in their study. We did not try to evaluate the plasma BNP and appearance of PACs in this study.

Concerning the TTE findings, LA enlargement and cardiac systolic dysfunction have been reported to be useful for identifying the etiology of ischemic embolic stroke with Paf (17). In this study, however, no significant differences in LAD, LVDd or LVEF were observed between the two groups. The number of the subjects in the present study was relatively small, and the TTE measurements may have been imprecise in some patients with obesity or pulmonary emphysema if the ultrasound beam could not penetrate to an adequate depth in these patients.

TEE is currently considered an important method for identifying potential sources of embolism. Since TEE provides a high-resolution image of the left atrium for evaluating the severity of blood stasis in the LAA, dense LASEC and reduced LAAPV on TEE can be a marker of throm-
boembolism in AF patients (14, 18, 19). Therefore, TEE findings are useful for evaluating the risk of cardioembolic stroke in patients with AF. In this study, even though TEE was performed during a normal sinus rhythm, LAA dysfunction was detected in patients with Paf. Left atrial remodeling or atrial stunning may have caused this dysfunction after the cessation of AF.

Congestive heart failure is well known to be associated with CE (20). In the present study, a history of congestive heart failure (NYHA ≥2) was more common in the Paf-CE group than in the Non-CE group. However, cardiac function was maintained, perhaps because the subjects were patients with Paf but not those with chronic AF. Patients with Paf reportedly have less severe heart failure than chronic AF patients (21). Hypertension is known to be associated with atherosclerosis. Only hypertension was significantly more frequent in the Non-CE group than in the Paf-CE group.

The present study has some limitations. First, the number of subjects was small. Only typically embolic stroke patients who presented with a normal sinus rhythm upon admission were enrolled in this study, consequently, TEE was indicated for the evaluation of the embolic source. Indications for TEE might be difficult to rationalize for patients with atherothrombotic or lacunar stroke. Second, as this study was a retrospective study in nature, there may have been a selection bias, and the Non-CE group might have included some CE patients, since not all the patients with Paf may have been detected during admission. Third, we could not identify the duration or the end time of Paf. Documenting the termination of AF is clinically difficult because continuous long-term monitoring is usually limited. Therefore, whether the left atrial dysfunction was caused by left atrial remodeling or atrial stunning, remains unclear. Finally, because of the small number of subjects, we were unable to identify the cut-off levels for the TEE values to differentiate CE caused by Paf from Non-CE. Further prospective studies are needed to clarify these points.

Conclusions

The left atrial function is apparently impaired in patients with cardioembolic stroke caused by paroxysmal atrial fibrillation, even though the echocardiographic examination is performed during a normal sinus rhythm. If the left atrial function is impaired in embolic stroke patients with a normal sinus rhythm, long-term ECG monitoring and anticoagulation should be considered. Transesophageal echocardiographic evaluation may be useful for differentiating cardioembolic stroke from paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. Stroke 38: 2935-2940, 2007.


References


© 2010 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html