Paradoxical Embolism as a Cause of Ischemic Stroke of Uncertain Etiology
A Transcranial Doppler Sonographic Study

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Background and Purpose  This study was designed to test the hypothesis that paradoxical embolization would be a cause of embolic strokes and transient ischemic attacks in patients with stroke of uncertain etiology in all age groups.

Methods  Thirty patients who had stroke of uncertain etiology were studied. They were divided into the following three groups: 13 patients with sudden onset (group A), 11 patients with subacute onset (group B), and 6 asymptomatic stroke patients (group C). Eleven patients with stroke of obvious etiology (group D) and 11 normal healthy volunteers (group E) were also studied as controls. In all patients transcranial Doppler sonography and contrast echocardiography were recorded simultaneously after intravenous injection of the contrast medium. Findings of positive patent foramen ovale in contrast echocardiography or "chirp" sounds in transcranial Doppler sonography were defined as positive for paradoxical contrast embolization. Radioisotope phlethysmography of the lower extremities and pulmonary scintigraphy, using technetium-99 macroaggregated albumin, were performed in all 17 patients who had positive findings of paradoxical contrast embolization and in 12 patients whose findings were negative.

Results  Positive findings of paradoxical contrast embolization were found in 17 subjects by transcranial Doppler sonography but in only 8 on contrast echocardiography. These positive findings were detected more frequently in group A (77%) than in groups B, D, and E (9%, 18%, and 9%, respectively) (P<.05). In group C, 4 of 6 patients (67%) had positive findings. There were positive findings on both phlebography and pulmonary scintigraphy only in 6 group A patients, with positive findings of paradoxical contrast embolization.

Conclusions  Transcranial Doppler sonography is a sensitive detector of right-to-left shunts. Paradoxical cerebral embolization might be frequent in patients with stroke of unknown etiology, especially when the stroke is of sudden onset.

Key Words  • embolism • thrombosis • ultrasonics

Interatrial and/or intrapulmonary communications associated with right-to-left shunts may serve as a route for paradoxical embolic strokes or transient ischemic attacks. Peripheral contrast echocardiography (CE) is now an established method for detecting these right-to-left shunts. In 1988 two case-control studies demonstrated a significantly higher prevalence of right-to-left shunts in young patients with unexplained ischemic stroke (54% and 50%) than in control subjects (10% and 15%, respectively). However, the sensitivity of CE for detecting patent foramen ovale in contrast echocardiography or "chirp" sounds in transcranial Doppler sonography were defined as positive for paradoxical contrast embolization. Radioisotope phlethysmography of the lower extremities and pulmonary scintigraphy, using technetium-99 macroaggregated albumin, were performed in all 17 patients who had positive findings of paradoxical contrast embolization and in 12 patients whose findings were negative.

Features of paradoxical cerebral embolism, we assessed the prevalence of overt or occult deep venous thrombosis and/or varices, pulmonary thromboembolism, and cerebral infarction in cortical or subcortical areas.

Subjects and Methods  We studied 657 consecutive patients who were screened for cerebrovascular disease (CVD) in the First Department of Internal Medicine at Osaka University Medical School between January 1, 1987, and April 30, 1993. This population consisted of 495 males and 162 females ranging in age from 16 to 89 years. Three hundred fifty-six (273 males and 83 females) of the 657 patients had neurological deficits or symptoms or a history of cerebrovascular accidents, including transient ischemic attack (CVD patients). We initially selected 58 of these CVD patients (36 men and 22 women; age range, 21 to 76 years; mean age, 54.9±14.5 years) who had ischemic stroke of uncertain etiology according to the following criteria: (1) normal findings on carotid angiography; (2) no or mild plaque score (ie, not moderate or severe score) on carotid B-mode sonography; (3) negative antinuclear antibody; (4) normal cardiac status according to clinical history, physical examination, electrocardiogram, two-dimensional echocardiography, and chest x-ray film; (5) no obvious risk factors for CVD such as hypertension, diabetes mellitus, and hyperlipidemia; and (6) no abnormal findings on coagulation studies (prothrombin test, activated partial thromboplastin time, and platelet count) at the time of stroke onset.

Thirty of the 58 patients gave informed consent for the study of paradoxical contrast embolization (18 men and 12 women;
age range, 29 to 71 years; mean age, 54.6 ± 13.6 years). We assigned them to the following three groups: those with sudden onset (group A: 9 men and 4 women; mean age, 54.3 ± 12.2 years); those with subacute onset, namely, neurological defects evolving over several hours or days (group B: 6 men and 5 women; mean age, 54.3 ± 14.2 years); and asymptomatic stroke patients (including those exhibiting nonspecific neurological complaints such as headache, lightheadedness, and dizziness) who showed cerebral infarction on x-ray computed tomography (CT) or magnetic resonance imaging (MRI) (group C: 3 men and 3 women; mean age, 55.6 ± 17.6 years). Eleven stroke patients with obvious etiology (group D) and 11 normal healthy volunteers with no history of ischemic CVD and no abnormal neurological signs (group E) were also studied as controls. The 11 group D patients were selected from the 298 CVD patients (with the exception of the 58 patients with ischemic stroke of unknown etiology). We obtained informed consent to the study of paradoxical contrast embolization from these 11 patients (9 men and 2 women; age range, 25 to 82 years; mean age, 54.4 ± 18.1 years) in whom carotid angiography had been performed. We determined that atherothrombotic brain infarction, lacunar infarction, and cardiogenic brain embolism occurred in 6, 2, and 3 patients, respectively, from the results of carotid angiography, electrocardiogram, x-ray CT of the head, and other studies. The 11 volunteers in group E consisted of 10 men and 1 woman aged 25 to 66 years (mean age, 39.3 ± 12.0 years). Either CT (30 patients) or MRI (11 patients) was performed in all patients, and cerebral infarctions were divided into two groups, as in our previous reports: deep subcortical infarction (basal ganglia, internal capsule, thalamus, and cortical or subcortical infarction (excluding deep subcortical infarction).

We used a Medasonics Transpect Doppler instrument with a hand-held transducer operated in the range-gated, pulsed-wave mode at 2 MHz to insonate the right or left middle cerebral artery. All echocardiographic examinations were performed with an imaging system (Toshiba, SSH-160A) that used a 2.5-MHz phased-array transducer. All patients were placed on their backs, and a TCD transducer was fixed firmly between the lateral margin of the orbit and the ear above the zygomatic arch. The middle cerebral artery flow signals were recorded at the depth (45 to 55 mm) that produced the highest Doppler velocity. Microcavitation contrast was generated by agitating a mixture of 0.5 mL of air and 10 mL of physiological saline between two 10-mL syringes connected by a three-port stopcock. The contrast medium was injected rapidly into a 20-gauge cannula that was introduced into the right or left antecubital vein. Two injections were made during normal respiration, and then at least one injection was repeated during the strain phase of a Valsalva maneuver. During each injection an apical four-chamber echocardiographic view was recorded on videotape.

A positive finding of patent foramen ovale was diagnosed if, on echocardiography, the contrast medium crossed the interatrial septum within one to two cardiac cycles after its appearance in the right atrium. Findings of a right-to-left shunt on TCD were considered positive if one or more "chirp" sounds,7 (bubble emboli signals with much higher amplitude than the background Doppler flow signal) were present in the Doppler flow signal after contrast injection. These findings on TCD were reviewed by operators who were unaware of the final diagnosis on contrast echocardiography. A positive finding on either CE or TCD was defined as a positive paradoxical contrast embolization (PE) finding.

Radioisotope phlebography of the lower extremities and pulmonary scintigraphy using technetium-99 macroaggregated albumin (\(^{99m}\)Tc-MAA)\(^{99m}\) was performed in all patients with positive PE findings and in some with negative PE findings. Renal scintigraphy using technetium-99 dimercaptosuccinic acid (\(^{99m}\)Tc-DMSA) was also performed in some patients.

These scintigram findings were reviewed by experienced investigators who were unaware of the final diagnosis. The \(\chi^2\) test was used to compare positive PE findings in each group.

### Results

As shown in the Figure, there were positive PE findings in 1 of the 11 normal volunteers (group E; 9%) and in 17 of the 41 stroke patients (41%) (group A, 10/13; group B, 1/11; group C, 4/6; and group D, 2/11). PE findings were positive in 14 of the 41 patients (34%) and 1 of the 11 normal volunteers (9%) during normal respiration; they occurred in 3 patients for the first time during a Valsalva maneuver. Two injections were given during Valsalva maneuver except for the patients with positive PE findings in the first Valsalva maneuver. Increasing the number of injections during the Valsalva maneuver did not increase the rate of detection. There were positive PE findings on both CE and TCD in 7 patients (6 in group A and 1 in group C), positive PE findings on TCD only in 10 patients (4 in group A, 1 in group B, 3 in group C, 1 in group D, and 1 in group E), and positive PE findings on CE only in 1 patient in group D. Positive PE findings were more frequent in the stroke patients with unknown etiology (15/30, 50%) than in group D (2/11, 18%) and group E (1/11, 9%) (\(P<.05\); multiple comparisons on the \(\chi^2\) test). Furthermore, positive PE findings were more frequent in group A (77%) than in groups B, D, and E (9%, 18%, and 9%, respectively) (\(P<.01\); multiple comparisons on the \(\chi^2\) test).

Deep subcortical infarctions were detected more frequently in group B (9/11, 82%) than in groups A (4/13, 31%) and D (2/11, 18%) (\(P<.01\); multiple comparisons on the \(\chi^2\) test). In group C, 2 of 6 patients (33%) had deep subcortical infarctions.

Radioisotope phlebography of the lower extremities and pulmonary scintigraphy using technetium-99 macroaggregated albumin (\(^{99m}\)Tc-MAA)\(^{99m}\) was performed in all 17 patients who had positive PE findings and in 12 of 24 patients who had negative PE findings (4/9 in group B, 2/2 in group C, and 6/9 in group D) (Table 1). Thrombosis and/or varices of deep veins were detected in their lower extremities on both sides in 13 of 16 patients before examinations: 2 patients had varices on the right side, and 1 had them on the left. Patients with clinical stroke symptoms (groups A, B, and D) had rested quietly for several days while in the acute
TABLE 1. Complications of Either Pulmonary Thromboembolism or Thrombosis and/or Varices of the Deep Veins in 29 Stroke Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>PE</th>
<th>Total</th>
<th>TV+PT</th>
<th>PT Only</th>
<th>TV Only</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Positive</td>
<td>10</td>
<td>6*</td>
<td>0</td>
<td>2*</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>Positive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>Positive</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>Positive</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A-D</td>
<td>Positive</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>6</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

PE indicates paradoxical contrast embolization; TV, thrombosis and/or varices of the deep veins of the lower extremities and pelvis; and PT, pulmonary thromboembolism.

*Thrombosis of the deep veins was found in 6 patients (4 of 6 TV+PT patients in group A, 1 of 2 TV only in group A, and 1 of 2 TV only in group C).

Discussion

Two possible major paradoxical embolic routes appear to be crossing the interatrial septum from the right to left atrium (interatrial shunt) and/or entering the left atrium from the pulmonary artery (intrapulmonary shunt). TCD enables the identification of both inter-atrial and intrapulmonary shunts if the microcavitation contrast can be detected in the middle cerebral artery after intravenous injection of the contrast medium. Nemec et al have reported that TCD may be useful as an alternative to transesophageal study: TCD had an accuracy of 100% (31/31 patients) for prediction of an interatrial right-to-left shunt by transesophageal contrast echocardiography. In this study we aimed to detect right-to-left shunts by a simple and minimally invasive method that most clinicians could put into practice, using both TCD and transthoracic contrast echocardiography. We found that TCD (17/49, 35%) was more sensitive for detecting right-to-left shunts than transthoracic contrast echocardiography (8/49, 16%) because the latter was limited by inadequate imaging, particularly during a Valsalva maneuver. Thus, TCD appears to be a sensitive, unambiguous technique for the detection of positive PE findings in patients suspected of having paradoxical cerebral embolization.

Previously, the diagnosis of paradoxical embolization was generally made at autopsy by visualization of a venous thrombus lodged within a cardiac defect, and very few cases were detected before death. In 1972 Meister et al proposed clinical criteria for diagnosis in vivo, which are (1) an arterial embolism—cerebral or subcortical area; and CA, cortical or subcortical area.

TABLE 2. Transcranial Doppler Findings in 6 Group A Patients With Pulmonary Thromboembolism Using 99mTc Human Serum Albumin Macroaggregates

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Positive PE</th>
<th>Radionuclide Phlebography</th>
<th>Localization of Cerebral Infarction</th>
<th>Renal Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>TCD+CE</td>
<td>Thrombosis</td>
<td>Multiple lacunae in DSA</td>
<td>Yes (left lower area)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>F</td>
<td>TCD+CE</td>
<td>Thrombosis</td>
<td>Multiple lacunae in DSA</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>TCD only</td>
<td>Thrombosis</td>
<td>Left infarction in CA</td>
<td>Yes (multiple lesions)</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>TCD+CE</td>
<td>Thrombosis</td>
<td>Right infarction in CA</td>
<td>Yes (multiple lesions)</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>TCD+CE</td>
<td>Varices</td>
<td>Left thalamic infarction</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>F</td>
<td>TCD only</td>
<td>Varices</td>
<td>Right infarction in CA</td>
<td>No</td>
</tr>
</tbody>
</table>

PE indicates paradoxical contrast embolization; TCD, transcranial Doppler sonography; CE, contrast echocardiography; DSA, deep subcortical area; and CA, cortical or subcortical area.
systemic—with no evidence of a left-sided circulatory origin; (2) the presence of venous thrombosis and/or pulmonary embolism; (3) the existence of an intracardiac defect that would permit right-to-left shunt; and (4) elevation of the right heart pressure—either constant, as during pulmonary hypertension, or transitory, as during cough or a Valsalva maneuver.

Criterion 1 was found to be clinically acceptable and was not controversial. Criterion 2 was also accepted as a very important clinical criterion of paradoxical cerebral embolization. Both thrombosis and/or varices of the deep veins and perfusion scintigraphic defects characteristic of pulmonary thromboembolism were confirmed in 6 patients in group A who had positive PE findings but in none of the patients other than those in group A. Based on the above criteria, we assessed these 6 patients as having paradoxical cerebral embolization. Furthermore, 11 of the 17 patients with positive PE findings did not have pulmonary thromboembolism. Dalen et al.13 reported that resolution of pulmonary vascular obstruction secondary to acute pulmonary embolism might frequently occur within days or weeks, as demonstrated by pulmonary angiography. Therefore, the perfusion scintigraphic defects characteristic of pulmonary thromboembolism might not be found in some patients with pulmonary embolism. Monreal et al.10 reported that only 29 of 116 consecutive patients with confirmed iliofemoral deep venous thrombosis had a high probability of defects suggestive of pulmonary thromboembolism, as demonstrated on lung scans. Thus, it is conceivable that the 11 patients who had positive PE findings but no pulmonary thromboembolism might be true free from paradoxical cerebral embolism. Regarding clinical criterion 3, Nemec et al.11 reported that TCD might be useful for diagnosing a right-to-left shunt and thus might be an alternative to transesophageal study. In regard to clinical criterion 4, a transient inversion of the pressure gradient between the right and left atria often occurs during early systole in normal subjects.14 In our study there were positive PE findings in 14 of 41 patients and in 1 of 11 normal volunteers during normal respiration; such findings occurred in only 3 patients for the first time during a Valsalva maneuver.

Ranoux et al.15 reported that in 68 consecutive patients aged younger than 55 years, although 32 patients had a patent foramen ovale, only 1 had occult venous thrombosis, indicating that paradoxical embolism is not likely to be the primary mechanism of stroke in patients with a patent foramen ovale. In our present study patients who had stroke of uncertain etiology were scattered throughout all age groups (29 to 71 years), and our findings of venous thrombosis were more frequent (6/29 patients; 21%; Table 1) than in the study of Ranoux et al. Before this study was initiated, 10 of 17 patients with positive PE findings and 11 of 28 patients with negative PE findings had been treated with either antiplatelet agents or oral anticoagulants. Antiplatelet drugs or anticoagulants do not necessarily dissolve thrombus but may inhibit further thrombosis. We therefore also examined deep venous varices as abnormal deep venous findings in the lower extremities. There were abnormal deep venous findings in 12 of the 17 patients who had positive PE findings (Table 1). Abnormal deep venous findings might have occurred secondary to immobility caused by stroke. But there was no immobility among the different stroke groups (groups A, B, and D), and all stroke patients could walk without any assistance at least 1 month before the present study. Therefore, we believe that the higher incidence of abnormal deep venous findings in the stroke patients with positive PE findings is not caused by immobility but suggests a close causative relation between abnormal deep venous findings and stroke attack through the mechanism of paradoxical embolism. Using transesophageal contrast echocardiography, de Belder et al.16 also reported that a patent foramen ovale was not related to age. Patients in group E (normal healthy volunteers) were younger than those in the stroke groups, but the rate of positive PE findings in group E was the same as that in group D (stroke of obvious etiology) in this study. Therefore, it appears more likely that the existence of right-to-left shunts is involved in paradoxical cerebral embolization in patients of all age groups.

There were no abnormal findings on coagulation studies (prothrombin time, activated partial thromboplastin time, and platelet count) in any of our patients at the time of stroke onset. However, we were unable to measure protein C and protein S, which are associated with deep venous thrombosis.18

Deep subcortical infarctions were detected more frequently in group B (subacute onset; 82%) than in group A (sudden onset; 31%) (P<.05). Cortical or subcortical infarctions were found in some of the stroke patients with sudden onset, indicating that embolic stroke caused by paradoxical embolism might have occurred. There were positive PE findings in 4 of 6 patients who had asymptomatic infarction of uncertain etiology (including patients with no risk factors such as hypertension, hyperlipidemia, and diabetes mellitus and no abnormal cardiac status). Two of these 4 patients also had cortical or subcortical infarctions on CT, suggesting an embolic mechanism. These results suggested that paradoxical cerebral embolization might be a cause of asymptomatic cerebral infarction of uncertain etiology. In considering the choice of therapy, we believed that the presence of shunt and venous thrombotic episodes required oral anticoagulant therapy rather than antiplatelet agents. However, therapeutic guidelines are not yet usable, and the current approach to therapy is still empirical.17 Prospective studies to define the best treatment should be considered.

In conclusion, paradoxical cerebral embolization should be suspected in patients of all age groups who have ischemic stroke of uncertain etiology, especially in those with sudden onset. The presence of PE should be identified by using both TCD and CE, with TCD being more sensitive than CE for detecting right-to-left shunts. In patients with positive PE findings, the findings of both pulmonary thromboembolism and thrombosis and/or varices of the deep veins were frequent, even in those patients with no suggestive clinical signs.

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