Right-to-left shunts may be not uncommon cause of TIA in Japan

Yohei Tateishi[a, b], Yasuyuki Iguchi[a], Kazumi Kimura[a], Kazuto Kobayashi[a],

Kensaku Shibazaki[a], Katsumi Eguchi[b]

Address correspondence to:

Dr. Y Tateishi

[a] Department of Stroke Medicine, Kawasaki Medical School

577 Matsushima, Kurashiki City, Okayama 701-0192, Japan

Tel.: +81-86-462-1111   Fax: +81-86-464-1027

[b] First Department of Internal Medicine, Nagasaki University Graduate School of

Biomedical Sciences

1-7-1 Sakamoto, Nagasaki City, Nagasaki 852-8102, Japan

Tel.: +81-95-819-7200 Fax: +81-95-819-7215 E-mail: ytate@nagasaki-u.ac.jp

Abstract

Background and purpose   Although 30% to 60% of transient ischemic

attacks (TIAs) have embolic sources, the etiology of the remaining TIAs is

unknown. Right-to-left shunt (RLS) is one of the most important etiologies of

cryptogenic stroke. The aim of this study was to determine whether RLS is

related to transient ischemic attack (TIA) of unknown etiology.

Methods   We performed transesophageal echocardiography (TEE) and/or

transcranial Doppler (TCD) studies for consecutive TIA patients in order to detect

RLS from April 2004 to December 2006. TIA patients were divided into three

groups, as follows: 1) Cardioembolic TIA, with a patent cardioembolic source, 2)

thrombotic TIA, with an atherothrombotic and/or lacunar mechanism, and 3)

undetermined TIA, without identified cause of TIA. We compared the

characteristics and presence of RLS among these three groups.

Results   We enrolled 124 TIA patients (age: 67 ± 13 y, 80 men). There

were 13 patients with Cardioembolic TIA, 25 with Thrombotic TIA, and 86 with

Undetermined TIA. TEE and/or TCD were able to detect RLS in 61 of the 124

(49%) patients. RLS was frequent in patients with Undetermined TIA compared

with those in the other TIA groups (60% in the Undetermined TIA group, 28% in

the Thrombotic TIA group, and 15% in the Cardioembolic TIA group; p < 0.001).

Smoking and previous history of TIA were frequent in the Thrombotic TIA group

(p = 0.030 and p = 0.016, respectively).

Conclusion RLS may play an important role in the etiology of TIA of

undetermined cause.

Introduction

Transient ischemic attack (TIA) is associated with the risk of early stroke, death, and disability.[1] Indeed, the appropriate strategy of treatment of patients with TIA is needed to prevent subsequent cerebral infarction.[2, 3] Although 30 – 64 % of cases of TIA have apparent embolic sources, such as carotid arterial disease or cardiac disease,[4, 5] there are many patients with TIA of unknown etiology.[6]

Paradoxical embolism is associated with cryptogenic stroke and may be a cause of stroke in a large number of patients.[7] We suspect that patients with TIA of unknown or undetermined causes frequently have right-to-left shunt (RLS). The aim of this study was to determine the frequency of RLS in consecutive TIA patients, and to investigate whether TIA of undetermined cause is related to RLS.

Methods

From April 2004 to December 2006, we enrolled consecutive patients with TIA who were admitted to our hospital within 14 days of onset. TIA was defined as a sudden onset of a focal neurological deficit or amaurosis fugax, suspected

to be of cerebrovascular origin, lasting less than 24 hours. We excluded patients who did not consent to transesophageal echocardiography (TEE) or transcranial Doppler sonography (TCD).

On admission, information on the symptoms and duration of TIA was obtained from patients or their families. We also obtained the following information about patient history and medication: 1) gender and age; 2) vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking); 3) potential cardiac sources of emboli; 4) arterial lesions (occlusive lesions of the carotid or vertebrobasilar artery able to cause neurological symptoms); and 5) previous illnesses (TIA, cerebral infarction, and ischemic heart disease). Vascular risk factors were identified as follows: 1) hypertension, use of antihypertensive agents, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; 2) diabetes mellitus, use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥ 6.4%; 3) hyperlipidemia, use of antihyperlipidemic agents, or serum cholesterol level > 220 mg/dL; and 4) smoking or any lifetime experience with cigarette use.

All patients were examined by 12-lead ECG, 24-hour ECG Holter monitoring, and transthoracic echocardiography to detect potential cardiac

sources of emboli, which included atrial fibrillation, dilated cardiomyopathy, acute myocardial infarction, intraventricular thrombus, mitral valve disease, prosthetic cardiac valves, and atrial septal defect. We performed carotid duplex sonography for all patients to evaluate significant arterial lesions in the ipsilateral carotid system.

Brain magnetic resonance (MR) studies including diffusion-weighted imaging (DWI) and MR angiography were performed for all patients to investigate cerebral and cerebral arterial lesions. TCD and TEE were performed to test for the presence of RLS. Evaluation of extra- and intracranial vascular lesions was performed by carotid duplex sonography, MR angiography, CT angiography, and/or digital subtraction angiography. Diagnosis of deep venous thrombosis (DVT) and pulmonary embolism was performed using duplex sonography, scintigraphy, and/or contrast CT. Laboratory studies, including complete blood cell count, blood biochemistry, and coagulation system tests, were performed. In this study, the interpretations of all studies were blinded to the patient's clinical status. Patients and their families gave written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

MR imaging

MR imaging studies were performed using a commercially available echo planar instrument on a 1.5-T MR unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI). The neuroimaging protocol for acute stroke in our hospital included a fluid-attenuation inversion recovery (FLAIR) sequence (repetition time [TR]/echo time [TE], 8002 ms/109 ms; TI, 2000 ms; field-of-view, 24 cm; acquisition matrix, 256 x224; and section thickness, 6.0 mm with a 1.0-mm intersection gap), diffusion-weighted trace sequence (TR/TE, 8000 ms/78 ms; b values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 128 x192 matrix; and 6.0 mm with a 1.0 mm intersection gap), and time-of flight MR angiography covering the circle of Willis (TR/TE, 28 ms/6.9 ms; 20° flip angle). The acquisition time for all DWI examinations was <1 min. MRI findings were reviewed by experienced radiologist blinded to clinical status.

TCD study

Bilateral middle cerebral arteries were insonated from the temporal window at a depth of 50-55 mm using a 2 MHz handheld transducer (MultiDop T; DWL, Lindau, Germany / Pioneer TC 8080; Nicolet Vascular, Madison, WI) when both middle cerebral arteries were detectable. When we could not detect middle

cerebral artery flow from the temporal window, we detected it in the siphon of the

internal carotid artery through transorbital access. A contrast study was

performed to detect RLS. Contrast material was prepared by agitating 9mL

saline and 1mL air with two syringes over a 3-way stopcock. The agitated saline

was rapidly injected into a right antecubital vein during provocative maneuvers

(Valsalva maneuver and coughing). Bolus injection was repeated 3 times.

Doppler audio signals on TCD examination were recorded onto digital audiotape

and/or hard disc. Microembolic signals were identified by typical visual

appearance on the spectral display and characteristic sounds, according to

standard consensus criteria.[8] We validated suspected microembolic signals by

"off-line" assessment without patient's clinical information.

TEE study

We performed TEE using an ultrasound unit (HDI-5000; Philips Medical

System, Bothell, WA) with a 4- to 7-MHz wideband multiplane transducer for

transesophageal imaging. TEE was performed in awake patients using lidocaine

gel for local pharyngeal anesthesia. TEE studies included imaging of all valves

and cardiac chambers. Gain settings were adjusted to distinguish background

noise and spontaneous echocardiographic contrast. We circumferentially

assessed the left atrial cavity and left atrial appendage to locate fixed or mobile

echo-dense masses that could be clearly differentiated from the cardiac wall. A

contrast study was performed to detect patent foramen ovale (PFO). PFO was

diagnosed when at least 3 microbubbles were identified in the left atrium within 3

cardiac cycles from the right atrium.[9] Atrial septal aneurysm was diagnosed

when the atrial septum protruded into the left or right atrium or both for at least

15 mm. We observed all segments of the thoracic aorta, including the

descending aorta, aortic arch, and ascending aorta, to detect aortic plaque.

Complicated aortic lesions were defined as those having increased intimal

thickness for at least 4 mm in the ascending aorta or the arch of the aorta. The

examinations were recorded on super VHS videotapes and reviewed by three

experienced sonographers blind to clinical data.

Analysis

First, we divided the patients with TIA into three groups: Cardioembolic

TIA, Thrombotic TIA, and Undetermined TIA. If TIA patients had an obvious

source of emboli, such as atrial fibrillation, a mechanical prosthetic valve, dilated

cardiomyopathy, left ventricular thrombus, or an akinetic left ventricular segment,

they were included in the Cardioembolic TIA group. Those in the thrombotic TIA

group had a stenotic lesion ($\geq$ 50%) in the relevant carotid or cerebral artery (atherothrombotic TIA), or ischemic lesions with a diameter of less than 1.5 cm in the territory of the basal ganglia, thalamus, or brainstem on MRI without any embolic source (lacunar TIA). The remaining patients were defined as those with TIA of "undetermined etiology", and formed the Undetermined TIA group. Patients who had two or more embolic sources were categorized in the Undetermined TIA group. We compared the background, duration of symptoms, D-dimer level, presence of source of emboli, such as RLS, atrial septal aneurysm, and complicated aortic lesion, and DVT among the three groups. We then divided the TIA patients with Undetermined TIA into two subgroups: 1) a HDM subgroup of patients with hypertension and/or diabetes mellitus, and a 2) non-HDM subgroup of patients without hypertension and diabetes mellitus. We compared clinical background and the presence of RLS between the non-HDM and HDM subgroups.

All values are the mean $\pm$ standard deviation (SD) or proportions of each group. Statistical comparison of characteristics among the three groups was performed using one-way factorial analysis of variance, such as the chi-square test, Fisher's exact test, Mann-Whitney's U test, and Kruskal-Wallis test, with

probability values (p) < 0.05 considered significant.

Results

One hundred twenty-nine patients with TIA were admitted to our hospital from April 2004 to December 2006. We excluded five patients who did not consent to undergo TEE or TCD. Thus, 124 patients (age: 67 $\pm$ 13 y, 80 men) were enrolled in the present study. They were divided into three groups: the Cardioembolic TIA group of 13 patients, the Thrombotic TIA group of 25 patients, and the Undetermined TIA group of 86 patients. We performed TCD in 101 patients (81%) and TEE in 103 patients (83%). Eighty-one patients (65%) underwent both TCD and TEE.

Table 1 shows the clinical background of the subjects of the three groups, and Figure 1 the prevalence of RLS. Cardioembolic TIA occurred in 10 patients with atrial fibrillation, one with a prosthetic aortic valve, one with a left ventricular thrombus, and one with dilated cardiomyopathy. Thrombotic TIA occurred in 16 patients with atherothrombotic TIA and 9 patients with lacunar TIA.

RLS was detected in 61 of 124 (49%) patients. Fifty-two patients (60%) in the Undetermined TIA group had RLS, along with 2 of 13 (15%) patients in the

Cardioembolic TIA group and 7 of 25 (28%) patients in the Thrombotic TIA group (p < 0.001). A total of 72% of patients in the Thrombotic TIA group smoked. Recurrent TIA was found in 7 of 25 (28%) patients in the Thrombotic TIA group. Overall, smoking and prior history of TIA were frequently observed in the Thrombotic TIA group compared with the two other groups (p = 0.030 and p = 0.016, respectively). However, there were no significant differences in other clinical characteristics among the three groups. DWI demonstrated ischemic lesions in 32 of 124 patients (26%). The mean time from onset to MRI study was 3.3 ± 4.3 days. DWI revealed lesions in 3 of 13 patients (23%) in the Cardioembolic TIA group, 15 of 25 patients (60%) in the Thrombotic TIA group, and 14 of 86 patients (16%) in the Undetermined TIA group (p < 0.001).

Table 2 shows clinical characteristics of the non-HDM and HDM subgroups. Patients in the non-HDM subgroup were younger and less likely to have vascular risk factors than those in the HDM subgroup. RLS was more frequently observed in the non-HDM subgroup than in the HDM subgroup (76% vs 53%, p = 0.038) (Figure 2). The previous stroke was less in the non-HDM subgroup than in the HDM subgroup (p = 0.046).

Discussion

In our study, about half of patients with TIA had RLS, and RLS was particularly frequent in patients with TIA of undetermined cause. In addition, TIA patients with neither hypertension nor diabetes mellitus frequently had RLS.

The frequency of PFO ranged from 10% to 44% for all subtypes of ischemic stroke, 31% to 77% for cryptogenic stroke, 4% to 25% for stroke of known cause, and 3% to 22% for control subjects.[10] A retrospective Western study found that TEE could detect PFO in 12 of 59 (20%) TIA patients.[11] The frequency of RLS in our series was higher than in that study because most TIAs in the Western study has been caused by atherothrombotic carotid lesions.[12]

In our study, patients in the Undetermined TIA group frequently had RLS. This finding is consistent with the reports of Yeung et al. and Cerrato et al., which noted that RLS was prevalent in all subtypes of stroke.[13, 14] Some causes of undetermined TIA may include paradoxical brain ischemia detectable on DWI. When patients in the Undetermined TIA group were divided into two subgroups, the non-HDM subgroup with neither hypertension nor diabetes mellitus and the HDM subgroup with hypertension and/or diabetes mellitus, RLS was frequently observed in the non-HDM subgroup. We previously reported that RLS was

strongly associated with lacunar stroke in patients without hypertension and diabetes mellitus.[15] We therefore believe that RLS may be one of the causes of TIA in patients with neither hypertension nor diabetes mellitus.

There are some limitations to the present study. First, TEE was performed on selected patients. The rate of detection of RLS in TCD study might be inferior to that on TEE study, because the sensitivity of TCD study in detecting RLS is less than that of TEE study.[16] Second, we were unable to perform peripheral venous ultrasound to detect DVT in all patients.

In conclusion, the prevalence of RLS was remarkably high in patients of the Undetermined TIA group, and RLS was particularly common in patients with Undetermined TIA with neither hypertension nor diabetes mellitus. RLS may thus be one of the mechanisms of TIA of undetermined cause.

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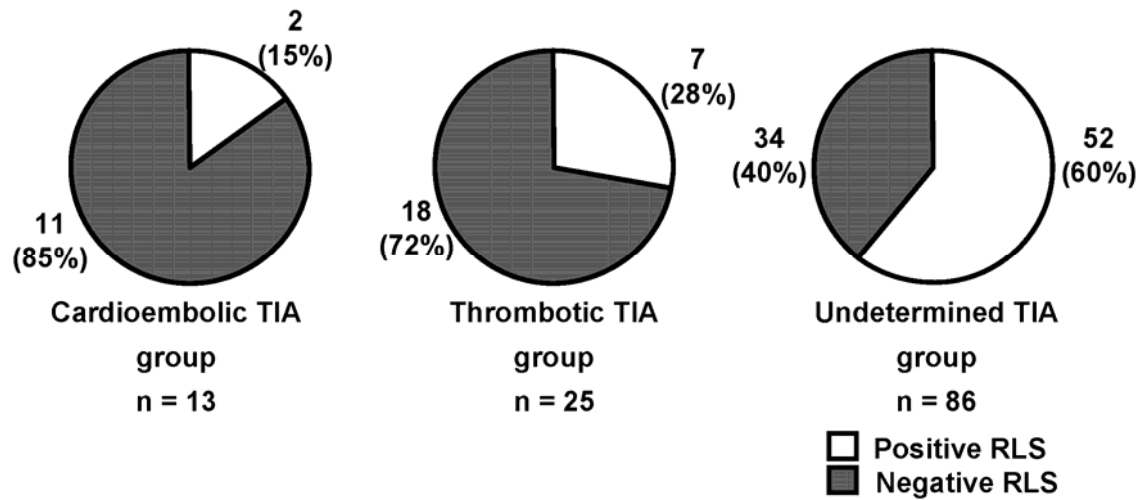
Legends

Figure1. Proportion of RLS in patients with Cardioembolic TIA, Thrombotic TIA

and Undetermined TIA. RLS is found in 2 of 13 (15%) patients with

Cardioembolic TIA, 7 of 25 (28%) in Thrombotic TIA and 52 of 86 (60%)

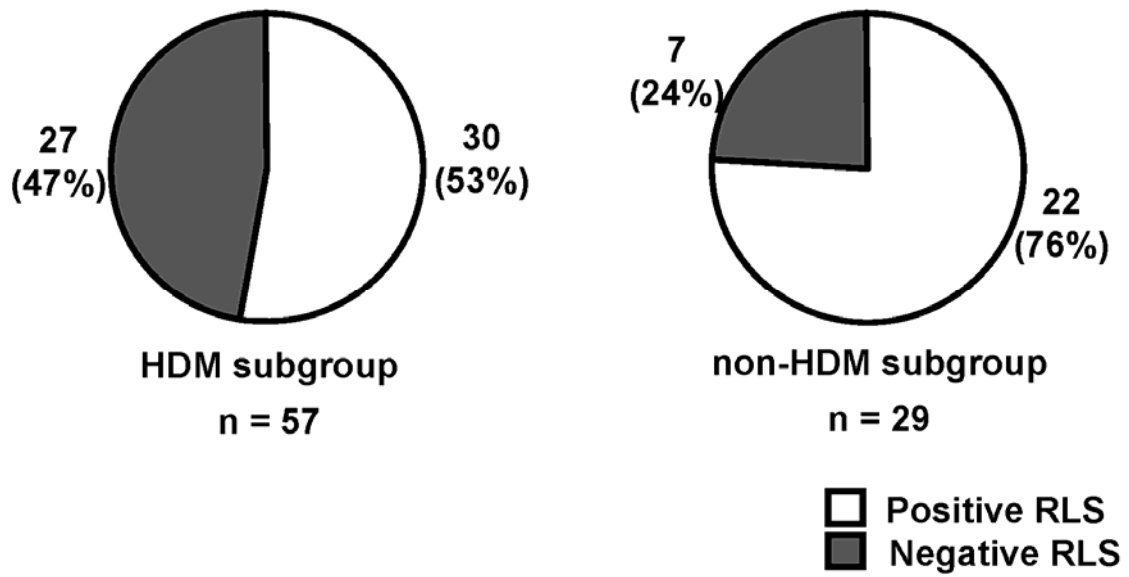with Undetermined TIA, respectively (p < 0.001).

Figure 2. Proportion of RLS between HDM group (patients with hypertension

and/or diabetes mellitus) and non-HDM group (patients without

hypertension and diabetes mellitus). RLS is observed in 30 of 57 patients

of HDM group and in 22 of 29 patients of non-HDM group (53% vs 76%, p

= 0.038).

Table 1.

Clinical backgrounds of TIA patients

Variables	Cardioembolic TIA group n=13		Thrombotic TIA group n=25		Undetermined TIA group n=86		P
Age, y, mean (SD)	69	(13)	63	(13)	68	(12)	0.071
Male, n (%)	9	(69)	20	(80)	51	(59)	0.155
Duration of symptom, min, mean (SD)	508	(617)	152	(323)	204	(373)	0.063
Vascular risk factors, n (%)							
Hypertension	8	(62)	19	(76)	51	(59)	0.316
Diabetes Mellitus	2	(15)	10	(40)	19	(22)	0.136
Hyperlipidemia	4	(31)	16	(64)	39	(45)	0.116
Smoking	6	(46)	18	(72)	36	(42)	0.030
Past history, n (%)							
TIA	0	(0)	7	(28)	8	(9)	0.016
Stroke	1	(8)	2	(8)	12	(14)	0.813
Ischemic heart disease	1	(8)	4	(16)	7	(8)	0.491
Atrial fibrillation, n (%)	10	(77)	0	(0)	2	(2)	<0.001
Arterial lesion*, n (%)	0	(0)	16	(64)	5	(6)	<0.001
Right-to-left shunt, n (%)	2	(15)	7	(28)	52	(60)	<0.001
Atrial septal aneurysm[†], n (%)	1/12	(8)	1/19	(5)	11/72	(15)	0.454
Aortic complicated lesion[†], n (%)	3/12	(25)	8/19	(42)	24/72	(33)	0.608
Ischemic lesion on DWI, n (%)	3	(23)	15	(60)	14	(16)	<0.001
Deep venous thrombosis[‡], n (%)	1/7	(14)	0/10	(0)	5/58	(9)	0.533
D-dimer, μg/dl, mean (SD)	1.2	(1.1)	1.0	(1.3)	1.5	(5.2)	0.736

SD; standard deviation, TIA; transient ischemic attack, DWI; diffusion weighted image

* "Arterial lesion" is the occlusive lesion of carotid or vertebrobasilar artery which is able to cause the neurological symptom.

[†] TEEs were performed in 12 patients of Cardioembolic TIA, 19 of Thrombotic TIA and 72 of Undetermined TIA.

[‡] In order to detect the deep venous thrombosis, duplex sonography, scintigraphy, and/or contrast CT were studied in 7 patients of Cardioembolic TIA, 10 of Thrombotic TIA and 58 of Undetermined TIA.

Table 2.

Clinical backgrounds of TIA patients with the non-HDM subgroup and HDM subgroup

Variables	HDM subgroup n=57		non-HDM subgroup n=29		P
Age, y, mean (SD)	71	(10)	64	(15)	0.062
Male, n (%)	34	(60)	17	(59)	0.927
Duration of symptom, min, mean (SD)	202	(379)	206	(369)	0.364
Vascular risk factors, n (%)					
Hypertension	51	(89)	0	(0)	
Diabetes Mellitus	19	(33)	0	(0)	
Hyperlipidemia	31	(54)	8	(28)	0.019
Smoking	24	(42)	12	(41)	0.949
Past history, n (%)					
TIA	5	(9)	3	(10)	0.813
Stroke	11	(19)	1	(3)	0.046
Ischemic heart disease	7	(12)	0	(0)	0.050
Atrial fibrillation, n (%)	2	(4)	0	(0)	0.310
Arterial lesion, n (%)	4	(7)	1	(3)	0.506
Right-to-left shunt, n (%)	30	(53)	22	(76)	0.038
Atrial septal aneurysm[†], n (%)	7/45	(16)	4/27	(15)	0.528
Aortic complicated lesion[†], n (%)	19/45	(42)	5/27	(19)	0.082
Ischemic lesion on DWI, n (%)	12	(21)	2	(7)	0.095
Deep venous thrombosis[‡], n (%)	4/34	(12)	1/24	(4)	0.314
D-dimer, μg/dl, mean (SD)	1.9	(6.4)	0.7	(0.3)	0.843

SD; standard deviation, TIA; transient ischemic attack

* "Arterial lesion" is the occlusive lesion of carotid or vertebrobasilar artery which is able to cause the neurological symptom.

[†] TEEs were performed in 45 patients of HDM subgroup and 27 of non-HDM subgroup.

[‡] In order to detect the deep venous thrombosis, duplex sonography, scintigraphy, and/or contrast CT were studied in 34 of HDM subgroup and 24 of non-HDM subgroup.