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ORIGINAL ARTICLE

Right-side propensity of cardiogenic emboli in acute ischemic stroke with atrial fibrillation*

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Abstract

Objectives. We attempted to determine the propensity for sidedness of cardiogenic emboli associated with atrial fibrillation (AF) by comparing the sides on which microembolic signals (MES) were detected via transcranial Doppler (TCD) monitoring and the location of infarcts on magnetic resonance imaging. *Design.* Patients with AF on Holter monitoring and MES on TCD monitoring were selected from an ischemic stroke registry. Patients with prosthetic valves or cerebral/carotid artery stenosis were excluded. *Results.* By TCD monitoring of 30 patients, 78 MES were detected: 47 on the right and 31 on the left side (60.3% vs. 39.7%, $p < 0.01$, chi-square test). Among 21 patients who had middle or anterior cerebral artery (MCA/ACA) territory infarcts, 16 had right-side-dominant infarcts and 5 patients had left-side-dominant infarcts (76.2% vs. 23.8%, $p < 0.01$, chi-square test). The median infarct volume on the right side was 16.2 (3.18–75.4) ml, while that of left side was 1.2 (0.25–5.05) ml ($p < 0.01$, Mann–Whitney *U* test). *Conclusion.* This study demonstrated the existence of a right-side propensity of cardiogenic emboli and the larger infarct volume of right-side MCA/ACA stroke in patients with AF. These results can be attributed to anatomical differences between the innominate and the left common carotid artery.

Key words *atrial fibrillation, acute ischemic stroke, cardiogenic embolism, microembolic signals, right-side propensity*

Introduction

Cardiogenic embolism is one of the major causes of ischemic stroke, comprising up to 40–80% of cases (1), the majority of which are associated with atrial fibrillation (AF), particularly in the elderly population (2). It seems reasonable that the diameter and angulation of the branches of the aortic arch, for example, of the innominate and left common carotid artery, could be important determinants for the destination of cardiogenic emboli, to either the right or left side of the brain. Relatively little data exist for addressing this hypothesis (3,4).

Transcranial Doppler ultrasound (TCD) was introduced in 1990s (5) and has proven useful in detecting microembolic signals (MES) of the intracranial cerebral arteries (6). MES in patients with AF were detected by TCD monitoring in 22% of symptomatic subjects, while fewer were detected in asymptomatic subjects (7).

A recent study demonstrated that cardiogenic ischemic stroke tends to consist of a large cortico-subcortical infarct and to have a right-side propensity (3) relative to aortogenic ischemic stroke. However, this comparison seems inconclusive in terms of right-side propensity because it compared cardiogenic with aortogenic ischemic stroke. Thus, we attempted to measure right-side propensity in cardiogenic ischemic stroke patients associated with AF by comparing the numbers of MES on TCD monitoring, and the location and volume of infarct on magnetic resonance imaging (MRI).

*This paper has not been presented at an international meeting yet.

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Materials and methods

Between January 2011 and April 2014, patients were selected from a tertiary university hospital stroke registry who met the following inclusion criteria: 1) patients with acute ischemic stroke (AIS) within 14 days of onset of symptom, 2) patients with either paroxysmal or persistent AF on 24-h Holter monitoring, and 3) patients who had an adequate temporal acoustic bone window on both sides and showed MES on TCD monitoring. Patients who had occlusion or any degree of stenosis of the cerebral/carotid arteries recognizable on time-of-flight MR angiography (TOFMRA) or who had anomalous aortic arch variations on contrast-enhanced MR angiography (CEMRA) were excluded. Patients with prosthetic valves were also excluded, because it has been reported that emboli from patients with prosthetic valves are more gaseous and have different characteristics on TCD monitoring (8).

We evaluated the presence of diabetes mellitus (DM), hypertension (HT), and the presence of anticoagulation effects (prothrombin time (PT) international normalized ratio (INR) >1.7 for warfarin, and activated partial thromboplastin time (aPTT) >1.5 times the upper limit of normal (ULN) for heparin) from medical records.

TCD monitoring

TCD monitoring was performed between day 3 and 21 after onset of stroke symptoms, to detect MES in both MCAs. A 2-MHz pulse-wave TCD device (Companion III Nicolet Vascular, Madison, WI, USA) was used for 30-min insonation of both MCAs at depths of 45 and 55 mm. All sonic signals were automatically saved in computer hard disk and were analyzed by an experienced observer (YB Kim), who was blinded to clinical and laboratory data. The MES were determined according to the following criteria presented at the Ninth International Cerebral Hemodynamics Consensus Conference (9): (1) short duration (usually 0.01–0.02 s); (2) high intensity (higher than the intensity of background); (3) unidirectional embolus signal; (4) signals which occurred randomly during the cardiac cycle; and (5) the presence of an associated harmonious whistle that may change with blood flow.

MRI acquisition

MRI and MR angiography (MRA) were performed using a 1.5T scanner (Intera; Philips Medical Systems, Best, The Netherlands). Axial and sagittal T1-weighted spin-echo (repetition time [TR], 420 ms; echo time [TE], 11 ms), axial T2-weighted fast spin-echo (TR, 4000 ms; TE, 100 ms), axial fluid attenuation inversion recovery (FLAIR) (TR, 6,000 ms; TE, 120 ms), and diffusion-weighted imaging (DWI) (b-values, 0 and 1,000 s/mm2; TR, 6,000 ms; TE, 74 ms) were included in the routine MRI protocol. MRIcron was used to measure infarct volume on DWI–MRI from each patient (10).

TOFMRA was acquired using a standard protocol of three-dimensional TOF sequences. CEMRA was taken in a coronal orientation with 4.4 ms/1.55 ms (repetition time/echo time), flip angle of 40°, 0.6-mm slice thickness, no gap, slab thickness of 78 mm, a rectangular field of view of 50%, and an image matrix of 358×358, with sequential k-space ordering. The angiographic MR sequence was performed employing a contrast-enhanced timing-robust angiography (CENTRA) technique. Imaging was initiated during a bolus tracking MR fluoroscopic sequence when contrast medium was detected at the carotid artery. The contrast-enhanced scan was acquired after intravenous injection of 20 mL of Magnevist (0.5 M gadopentetate dimeglumine, Bayer Schering Pharma, Berlin, Germany) at a rate of 2 mL/s.

The right and left side MES numbers from the patients were compared. The ratio of right versus left lesion sidedness on MRI was compared in patients with middle cerebral and/or anterior cerebral artery (MCA/ACA) territory infarct. In cases with bilateral MCA/ACA territory infarct, lesion side dominance was determined by infarct volume. Infarct volumes in the MCA/ACA territory were compared as well. Categorical and continuous variables were compared by chi-square, and Mann–Whitney *U* test. Analyses were performed with IBM SPSS statistics (IBM, Armonk, NY, USA). This retrospective review was approved by institutional review board in 2014.

Results

From the registry, 235 AIS patients were identified to have an electrocardiographic record of AF. Among them, 36 consecutive patients had AF on Holter monitoring and MES on TCD monitoring. Six of them were excluded because 5 patients had stenosis of a cerebral/carotid artery and one patient had a prosthetic valve. Thus, 30 patients remained for analysis. The percentage of male patients was 82.1% and the mean age was 70.5 ± 10.3. The prevalences of DM and HT were

Table I. Distribution of MES between right and left MCA on TCD monitoring.

	Right MCA		Left MCA		*P*-value
Number of MES (%)	47	(60.3%)	31	(39.7%)	0.01*

*Chi-square test.

Table II. Lesion side of patients† (n = 21) with ischemic stroke in MCA/ACA territory on diffusion-weighted MRI.

	Right MCA/ACA dominant‡		Left MCA/ACA dominant‡		*P*-value
Number of patients	16	(76.2%)	5	(23.8%)	<0.01*

ACA, indicates anterior cerebral artery; MCA, indicates middle cerebral artery.
*Chi-square test.
†Confined to patients with MCA/ACA territory infarct.
‡Dominant infract sides were assigned according to lesion volume on diffusion-weighted MRI.

25.0% and 64.3%, respectively. Eighteen patients had persistent AF and 12 had paroxysmal AF. Nineteen patients (63.3%) were within the effective anticoagulation range (PT INR >1.7 or aPTT >1.5 times ULN) at the time of TCD monitoring.

Via TCD monitoring of 30 patients, 78 MES were detected. 47 MES were on the right MCA, while 31 were on the left MCA (60.3% vs. 39.7%, $p = 0.01$, chi-square test, Table I). Two patients had equal numbers of MES on each side. Among the 28 patients with unequal MES distribution, 17 patients had right–side-dominant MES while 11 patients had left-side-dominant MES (60.7% vs. 39.3%, $p > 0.1$, chi-square test).

Among 21 patients with MCA/ACA territory ischemic stroke, 16 patients had right-side-dominant infarcts (4 of which were right dominant bilateral) and 5 patients had left-side infarcts (76.2% vs. 23.8%, $p < 0.01$, chi-square test, Table II).

In the same 21 patients with MCA/ACA infarct, the median infarct volume on the right side was 16.2 (interquartile range: 3.18–75.4) ml, while that on the left side was 1.2 (interquartile range: 0.25–5.05) ml ($p < 0.01$, Mann–Whitney *U* test, Table III).

Discussion

This study revealed that microemboli from patients with AIS and AF had a greater tendency to be detected in the right MCA (60.3%) than in the left MCA (39.7%), and that the location of AIS is likely to be on the right side (76.2%). Furthermore, the volumes of AIS on the right side were larger than those on the left. To select more homogeneous cardiogenic embolisms, we included only AIS patients who had AF along with MES on TCD monitoring and excluded those who had cerebral/carotid artery stenosis. To our knowledge, this is the first report to demonstrate a right-side propensity of microemboli of cardiac origin by TCD monitoring.

Why should the innominate artery, which supplies the right side of the brain, capture more emboli than the left common carotid artery? Recent reports that addressed this question attributed the right-side propensity to the large diameter of the innominate artery (3,4). Further studies are required, but it is conceivable that its larger inner diameter may accommodate a greater number of emboli.

Carr et al. reported that the curvature of the aorta and pulsatile aortic flow, combined with inertial effects of emboli, can also contribute to right-side predilection (4). They argued that the inertial and drag forces on medium-sized particles (>1-mm diameter) carry sufficient magnitude to cause them to be pushed along the upper aspect of the arch, which positions them to continue up the branch arteries. The larger infarct volume of right-side MCA/ACA infarct in this study can be explained by the proposition that they were pushed by inertia toward the outer curvature as the blood flows along the aortic arch. Subsequently, they would then be likely to be trapped by the large orifice of the innominate artery, which is the first branch of the aortic arch.

Other researchers with different points of view may argue that AF can be the result of ischemic stroke, especially on the right side, which involves the insular region rather than a preexisting condition. There have also been some reports on AF following stroke (11), particularly when they affected the right insular region, which might disturb the balance of autonomic control of the heart, leading to arrhythmia or myocardial injury (12,13). However, the right-sided tendency of MES in this study represents strong counterevidence that can hardly be explained as a consequence of ischemic stroke, which may or may not involve the right insular area.

Because the data were analyzed retrospectively, we could not assess all determinants of aortic arch anatomy so as to exclude all possibilities of aortogenic emboli. Aortogenic emboli, which reportedly tend to

Table III. Comparison of infarct volume between right and left side in patients† ($n = 21$) with MCA/ACA territory infarct on diffusion-weighted MRI.

	Right-sided MCA/ACA		Left-sided MCA/ACA		*P*-value
Median volume, ml (IQR)	16.2	(3.18–75.4)	1.2	(0.25–5.05)	<0.01*

ACA, indicates anterior cerebral artery; MCA, middle cerebral artery; IQR, interquartile range.
*Mann–Whitney U test.
†Confined to patients with MCA/ACA territory infarct.

go to the left hemisphere, if any were included, would not affect the result of this study that indicated a right-side propensity (3). Poor temporal windows among elderly women prevented equal enrollment of both genders, which is an inherent limitation of TCD. To include more homogeneous cardiogenic embolisms and to exclude any possible arterial origin of ischemic stroke, we selected patients who had AIS with MES from AF without any recognizable arterial narrowing of cerebral vessels. This created a unique cardiogenic AIS group, but resulted in a group with a low number of patients.

Despite these acknowledged limitations, this study is valuable for its contribution in delineating an important characteristic of cerebral embolisms originating from the heart with AF. The tendency suggested from our study does not seem profound, but it is important for understanding cardiogenic cerebral embolisms which account for a major part of ischemic stroke, and possibly provides a clue in analyzing cryptogenic ischemic strokes, a significant proportion of which are suspected, if controversially, to be cardiogenic.

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