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Difference in autonomic nervous activity in different subtypes of noncardioembolic ischemic stroke

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Arrhythmias, elevated blood pressure (BP), ischemic heart damage, and autonomic dysfunction are cardiovascular complications sometimes seen during the acute phase of stroke [1, 2]. Autonomic nervous activity is most commonly assessed by heart rate variability (HRV) [3], which is reported to be reliable in patients after ischemic stroke [4].

In the acute phase of ischemic stroke, BP changes drastically to maintain cerebral blood flow because of cerebral dis-autoregulation and hemodynamic failure [5]. However, BP fluctuations resulting from autonomic dysfunction are characterized by hyperactive sympathetic nervous activity and hypoactive parasympathetic nervous activity [6]. Few studies have reported how autonomic nervous activity changes from the acute to the sub-acute phase of stroke [2]. Autonomic nervous activity might also differ between different subtypes of non-cardioembolic ischemic stroke [7, 8], but the results obtained so far are controversial.

We hypothesized that autonomic nervous activity would differ between different subtypes of non-cardioembolic stroke and would change between the acute and sub-acute phase. Therefore, we performed a longitudinal study to investigate autonomic nervous activity in different subtypes of non-cardioembolic ischemic stroke.

The present study comprised 341 consecutive patients with acute ischemic stroke who underwent rehabilitation at Itami Kousei Neurosurgical Hospital from July 2013 to

Jun 2014. Patient inclusion criteria included fulfilment of both criteria: computerized tomography or magnetic resonance imaging showed a first-ever acute ischemic stroke and the stroke was classified as non-cardioembolic. Exclusion criteria included brain stem stroke, any clinically relevant arrhythmia on admission including atrial fibrillation, any major concurrent illness including severe cardiac disease and pulmonary disease, diabetes mellitus requiring insulin therapy, and hypertension treated with β -blocker therapy.

Patient characteristics were evaluated by review of medical records and included stroke subtype, age, sex, body mass index, affected side, National Institutes of Health Stroke Scale assessment in the acute and sub-acute phases, days from admission to mobilization, comorbidities, and systolic BP (SBP) and diastolic BP (DBP) on admission. Laboratory data included total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and medications. The present study was approved by the institutional committee of the Graduate School of Health Sciences Kobe University (approval no. 257). Informed consent was obtained from each participant.

HRV and vital signs (including BP) were measured twice, once in the acute phase (within 7 [mean, 4] days from admission) and once in the sub-acute phase (within 14 [mean, 11] days from admission). All measurements were performed after the patient

rested for 10 minutes in the supine position. An electrocardiogram (ECG) was recorded for 3 minutes by an EP-301 portable system (Parama-Tech, Co., Ltd., Fukuoka, Japan) at the same time in both phases, 2 hours after a meal in the daytime, and analyzed on a personal computer.

Power spectral analysis was performed with a Lab Chart Pro Heart Rate Variability Add-On (ADInstruments Pty Ltd, Castle Hill, Australia) using fast Fourier transformation. The power spectra were quantified by measuring the areas in the low frequency (LF; 0.04-0.15 Hz) and high frequency (HF; 0.15-0.40 Hz) bands according to international guidelines [3]. LF and HF were logarithmically transformed to correct for skewness of the distribution [7-10]. We used the natural logarithm of HF power ($\ln\text{HF}$) as the indicator of parasympathetic nervous activity and LF/HF as the indicator of sympathetic nervous activity.

Results are expressed as mean $\pm$ standard deviation. Patients were divided into two groups by stroke subtype: lacunar infarction (LAC) group and large-artery atherosclerotic infarction (LAA) group. Unpaired *t*-test and chi-squared test were used to compare patient characteristics between groups, and a paired *t*-test was used to compare medication within the groups. Two-way analysis of variance was used to compare HRV parameters ($\ln\text{HF}$ and LF/HF) and vital signs between groups. The between-group factor was subtype of stroke, and the within-group factor was time

periods. A *P* value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed with IBM SPSS 20 statistical software (IBM SPSS Japan, Inc., Tokyo, Japan).

Of the 341 patients, 47 were included in the present study. However, 10 patients were excluded because 7 patients were discharged within 1 week, and 3 patients had atrial fibrillation or other arrhythmia during HRV measurements. Thus, 37 patients were divided into the LAC group ($n=16$) and the LAA group ($n=21$). There were no significant between-group differences with the exception of BP on admission and antiplatelet medication (Tables 1, 2).

Use of antiplatelet medication in both groups differed significantly between the time periods and that of a neuroprotective agent in the LAA group differed between the two phases (Table 2). There were no interactions between the groups in terms of HRV parameters and vital signs (Table 2). The LAC group had lower lnHF and higher LF/HF, DBP, and mean arterial pressure (MAP) than those in the LAA group in the acute phase (Table 2). There were no differences in HRV parameters between the groups in the sub-acute phase, however, the LAC group had higher DBP and MAP than those in the LAA group in the sub-acute phase (Table 2). There were no differences in HRV parameters between the time periods in both groups (Table 2). In the LAC group, SBP and MAP were higher in the acute phase than in the sub-acute phase (Table 2).

This is the first study, to our knowledge, to report that autonomic nervous activity differs in different subtypes of non-cardioembolic stroke in the acute phase but not in the sub-acute phase. The main finding was that the LAC group had lower lnHF and higher LF/HF than those in the LAA group in the acute phase. These results are partly compatible with the report by Chen et al. [8] because lnHF in the LAC group was lower than that in the LAA group. A possible mechanism of these different HRV findings in the two groups might be explained in terms of hypertension and etiology. Hypertension is associated with lower parasympathetic nervous activity and a trend towards sympathetic predominance [9, 10]. The proportion of patients with hypertension and antihypertensive medications were not different between the groups. However, BP on admission and DBP and MAP in the acute phase were higher in the LAC group than LAA group.

With regard to the etiology of LAC, Jackson and Sudlow [11] previously reported in a systematic review that the prevalence of hypertension was the only risk factor for LAC. Our patients in the LAC group showed a potential for hypertension. Contrastingly, with regard to the etiology of LAA, carotid stenosis was the risk factor for LAA. Kwon et al. [12] also reported that carotid plaque was associated with depressed HRV, and Xiong et al. [13] reported that patients with carotid stenosis had impaired parasympathetic and sympathetic functions. Our results are partially

compatible with these studies because LF/HF was lower in the LAA group than LAC group. However, HRV parameters did not differ significantly between groups in the sub-acute phase. Further studies might be needed to clarify how long HRV parameters differ between these groups.

Limitations of this study include its small sample size and the exclusion of patients with severe ischemic stroke because of atrial fibrillation or other arrhythmia. We could not investigate many other factors related to autonomic nervous activity such as stroke location, hospital stress, or lifestyle factors such as smoking and physical activity [1, 3].

In conclusion, patients with LAC may be at higher risk of autonomic dysfunction than those with LAA in the acute phase of non-cardioembolic ischemic stroke. HRV parameters may be useful indices for predicting risk management these patients.

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Table 1

Patient characteristics of the LAC and LAA groups.

Characteristic	LAC group n = 16	LAA group n = 21	<i>t</i> or χ^2 value	<i>P</i> value
Age (yrs)	68.4 ± 9.3	74.0 ± 10.7	1.72 ^a	0.094
Male, n (%)	12 (75.0)	12 (57.1)	1.27	0.260
BMI (kg/m ²)	24.7 ± 4.4	25.3 ± 5.0	0.83 ^a	0.414
Right-sided stroke (%)	6 (37.5)	9 (42.9)	0.10	0.742
NIHSS in the acute phase	4.5 ± 3.6	5.4 ± 5.2	0.64 ^a	0.526
NIHSS in the sub-acute phase	2.9 ± 3.4	3.8 ± 4.8	0.65 ^a	0.522
Days from admission to mobilization	1.3 ± 0.6	1.8 ± 1.3	0.10 ^a	0.209
Comorbidity				
Hypertension, n (%)	9 (56.3)	9 (42.9)	0.65	0.419
Diabetes mellitus, n (%)	4 (25.0)	8 (38.1)	0.71	0.400
Dyslipidemia, n (%)	3 (18.8)	1 (4.8)	1.84	0.175
BP on admission				
SBP (mmHg)	170.4 ± 18.0	151.1 ± 19.4	2.36 ^a	0.031
DBP (mmHg)	93.3 ± 16.6	77.6 ± 9.9	2.78 ^a	0.012
Laboratory data				
Total cholesterol (mg/dl)	214.1 ± 37.6	199.0 ± 33.4	1.29 ^a	0.204
HDL cholesterol (mg/dl)	53.8 ± 17.5	47.0 ± 14.7	1.27 ^a	0.211
LDL cholesterol(mg/dl)	132.5 ± 27.7	126.5 ± 31.0	0.60 ^a	0.547
Triglyceride (mg/dl)	157.7 ± 115.9	137.1 ± 80.3	0.64 ^a	0.528

Values are mean ± standard deviation.

BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; BP = blood pressure;

SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein;

LDL = low-density lipoprotein.

^a *t* value.

Table 2

HRV parameters and medication of the LAC and LAA groups in the acute and the sub-acute phases.

	LAC group		LAA group		Interaction	
	n = 16		n = 21		<i>F</i> value	<i>P</i> value
	Acute phase	Sub-acute phase	Acute phase	Sub-acute phase		
lnHF	5.1 ± 1.4 ^a	4.9 ± 1.5	6.1 ± 1.3	5.3 ± 2.3	0.48	0.49
LF/HF	1.6 ± 1.3 ^a	1.3 ± 1.2	0.9 ± 0.7	1.0 ± 1.1	0.93	0.34
SBP (mmHg)	153.9 ± 22.7 ^b	144.3 ± 21.7	139.3 ± 24.1	138.9 ± 21.1	0.76	0.38
DBP (mmHg)	83.6 ± 12.0 ^a	79.7 ± 10.7 ^a	71.0 ± 16.2	68.2 ± 15.0	0.02	0.88
MAP (mmHg)	107.0 ± 12.6 ^{ab}	101.2 ± 11.1 ^a	93.8 ± 17.8	90.8 ± 17.0	0.15	0.70
HR (bpm)	69.2 ± 11.5	69.2 ± 12.5	67.8 ± 11.0	69.9 ± 14.6	0.12	0.73
Medications						
Antiplatelet, n (%)	15 (93.8) ^{ab}	10 (62.5)	14 (66.7) ^b	7 (33.3)		
Neuroprotective agent, n (%)	11 (68.8)	6 (37.5)	18 (85.7) ^b	10 (47.6)		
ARB, n (%)	4 (25.0)	5 (31.3)	2 (9.5)	2 (9.5)		
CCB, n (%)	2 (12.5)	3 (18.8)	1 (4.7)	3 (14.3)		

Values are mean ± standard deviation.

LAC = lacunar infarction; LAA = large-artery atherosclerotic infarction; lnHF = natural logarithm of high-frequency power; LF/HF = ratio of low frequency to high frequency; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

^a *P* < 0.05 between the groups (LAC group vs. LAA group).

^b *P* < 0.05 within the groups (Acute phase vs. Sub-acute phase).