

## Cross-sectional area of the vagus nerve on carotid duplex ultrasound and atrial fibrillation in acute stroke: A retrospective analysis

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### ABSTRACT

**Introduction:** The autonomic nervous system, including the vagus nerve, is associated with the development of atrial fibrillation (AF). However, the association between the cross-sectional area (CSA) of the vagus nerve on ultrasound and the presence of AF has not been fully clarified. This study investigated the association between vagus nerve CSA and the presence of AF in patients with acute stroke.

**Methods:** We retrospectively reviewed 150 consecutive patients with ischemic stroke or transient ischemic attack. Vagus nerve CSA was evaluated by carotid ultrasonography on the axial view at the thyroid gland level. Univariate and multivariable analyses were performed to examine the association between vagus nerve CSA and AF. **Results:** Of 133 patients included in the analysis, 31 (23.3%) were diagnosed with AF before hospital discharge. The median right vagus nerve CSA was significantly smaller in patients with AF than in patients without AF ( $p = 0.03$ ). However, there was no significant difference in median left vagus nerve CSA. Multivariable logistic regression analysis revealed that log transformed and quintiled brain natriuretic peptide level (odds ratio [OR], 5.03; 95% confidence interval [CI], 2.43–10.40) and right vagus nerve CSA (OR, 0.33; 95% CI, 0.12–0.91) were independent predictors of AF.

**Discussion/conclusion:** Smaller right vagus nerve CSA in carotid ultrasonography was an independent predictor of AF in patients with ischemic stroke or transient ischemic attack, suggesting that patients with small right vagus nerve CSA should be closely monitored for development of AF.

### 1. Introduction

Atrial fibrillation (AF) is an important cause of cardioembolic stroke. The autonomic nervous system, including the vagus nerve, is closely involved in AF development [1]; rapid changes in sympathetic–parasympathetic nerve balance promote AF development [1]. Vagus nerve stimulation can induce AF in animal models [2]. Moreover, autonomic nervous function is abnormal in patients with both ischemic stroke and AF [3].

Vagus nerve visualization using computed tomography or magnetic resonance imaging is difficult; there is no established imaging method to evaluate vagus nerve damage. In 1998, the vagus nerve was identified using ultrasonography [4], and the usefulness of ultrasound to visualize the vagus nerve has since been amply reported [5,6]. Tawfik et al. [7] revealed that the cross-sectional area (CSA) of the vagus nerve using

carotid ultrasonography was smaller in patients with diabetes mellitus than in healthy individuals; CSA values had sufficient sensitivity and specificity to predict the presence of diabetes mellitus. Furthermore, autonomic dysfunction in patients with diabetes mellitus was associated with smaller vagus nerve CSA on ultrasound [7]. However, the association between vagus nerve CSA on ultrasound and the presence of AF has not been fully clarified.

This study was performed to investigate the association between vagus nerve CSA, as observed using carotid duplex ultrasonography (CU), and the presence of AF in patients with acute ischemic stroke.

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## 2. Materials and methods

### 2.1. Study population

We retrospectively reviewed 150 consecutive adult patients (aged >20 years) with ischemic stroke or transient ischemic attack (TIA) who were admitted to Iwate Medical University hospital within 14 days after onset between October 2019 and June 2020. This retrospective observational study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Iwate Medical University School of Medicine Institutional Ethics Committee reviewed and approved the protocol (No. MH2020-187), and written informed consent was obtained from all patients or their next of kin before participation. This study was performed in accordance with the STROBE guidelines.

All patients underwent computed tomography or magnetic resonance imaging; a diagnosis of ischemic stroke or TIA was reached based on clinical and brain imaging findings by neurologists experienced in treating patients with stroke. Patients were excluded if they had not undergone CU, electrocardiogram (ECG) on admission, Holter ECG, or > 24 h of ECG monitoring. Diagnosis of stroke subtype was based on the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification [8]. We also investigated the following patient characteristics: age, sex, body mass index (BMI), hypertension (casual blood pressure  $\geq$  140/90 mmHg or medication with regular antihypertensive drugs), diabetes mellitus (fasting blood glucose  $\geq$  7.0 mmol/L, random blood glucose  $\geq$  11.10 mmol/L, hemoglobin A1c  $\geq$  0.065 [6.50%], or use of antidiabetic medication), dyslipidemia (serum total cholesterol  $\geq$  5.70 mmol/L, triglycerides > 1.69 mmol/L, or use of antihyperlipidemic drugs), and current smoking habits. Brain natriuretic peptide (BNP) level was also measured upon admission.

### 2.2. Ultrasound imaging

CU was performed using an Aplio i700 (Canon Medical Systems, Otawara, Japan) and a 12-MHz linear probe. CU examinations were performed by four technologists. Vagus nerve CSA was retrospectively measured by a neurologist (K.O., a registered neurosonographer of the Japan Academy of Neurosonology) who was blinded to each patient's clinical information. Vagus nerve CSA was measured bilaterally at the level of the thyroid gland. Based on Digital Imaging and Communications in Medicine (DICOM) data stored in hospital electronic medical records, the CSA (mm<sup>2</sup>) of the vagus nerve was measured after the periphery of the vagus nerve section had been manually traced using DICOM viewer software (EV Insite; PSP Corporation, Tokyo, Japan) (Fig. 1a, b).

### 2.3. AF detection

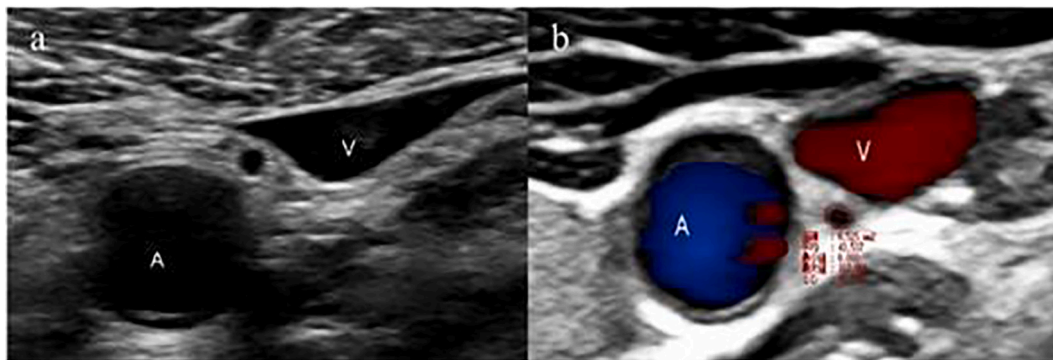
All patients underwent ECG upon admission, as well as ECG monitoring for >24 h or Holter ECG (FM-980; Fukuda Denshi, Tokyo, Japan). The presence of AF was defined as the presence of both irregular RR intervals and the absence of P waves for >30 s in ECG, ECG monitoring, or Holter ECG during the hospital stay; alternatively, it was defined as a history of AF diagnosis.

### 2.4. Statistical analyses

Sample size for this study was determined as follows: AF is reportedly present in approximately 10% of patients with stroke [9]. Thus, based on effect size = 10%,  $\alpha = 0.05$ ,  $\beta = 0.2$ , and standard deviation = 0.1, the required number of patients in each group was 73; to allow for potential dropout or patient exclusion, the target number of patients was 150. We conducted univariate analysis to compare the clinical and radiological characteristics of patients with and without AF. Multivariable logistic regression analysis was performed to identify independent predictors of AF presence during the hospital stay. Based on previous studies, we selected diabetes mellitus, BMI, current smoking habits, and CSA as independent factors for multivariable regression models [10]. For logistic regression analysis, BNP and age were analyzed as continuous variables using the natural logarithm and categorized into quintiles, and BMI was categorized into six levels according to the World Health Organization classification. Receiver operating characteristic curve analysis was performed to determine the optimal CSA cutoff value for predicting AF during the hospital stay; the sensitivity and specificity for predicting AF were calculated. Categorical variables were analyzed using Fisher's exact test. Because not all continuous variables were normally distributed, continuous variables were expressed as medians and interquartile ranges (IQRs), then analyzed using the Mann-Whitney *U* test. All statistical analyses were conducted using SPSS version 26 (IBM Japan, Tokyo, Japan). All reported *p*-values were two-tailed, and *p* < 0.05 was considered statistically significant.

## 3. Results

After review of CU records, two patients who did not undergo CU and 15 patients whose axial images were not recorded on CU were excluded from the study. No patients were excluded because of poor CU image quality or absence of ECG monitoring. Finally, 133 patients were included in this study. Patient characteristics are shown in Table 1. The median age was 74 years (IQR, 68–83.5 years); 81 of 133 patients (60.9%) were male. The median duration of hospitalization was 16 days (IQR, 13–20 days). Thirty-one (23.3%) patients were diagnosed with AF (21 had chronic AF and 10 had paroxysmal AF). Among the 31 patients with AF, five were diagnosed with AF during hospitalization, while 26



**Fig. 1.** Carotid ultrasonography images of the vagus nerve. a: Representative image showing the vagus nerve as a small, rounded, hypoechoic structure between carotid artery and jugular vein. b: Depiction of CSA measurement using image in panel a, showing manually traced regions (red circles). A: common carotid artery; V: jugular vein; CSA: cross-sectional area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**  
Patient characteristics.

Variables	
Age (years), median [IQR]	74 [68–83.5]
Male, no. (%)	81 (54.0)
Duration of hospitalization (days), median [IQR]	16 [13–20]
Initial NIHSS, median [IQR]	3 [1–4]
Current smoker, no. (%)	46 (30.7)
Hypertension, no. (%)	113 (75.3)
Diabetes mellitus, no. (%)	45 (30.0)
Right CSA (mm <sup>2</sup> ), median [IQR]	1.32 [0.88–1.69]
Left CSA (mm <sup>2</sup> ), median [IQR]	1.07 [0.71–1.45]
Subtypes of stroke/TIA	
Small vessel occlusion, no. (%)	39 (29.3)
Large artery atherosclerosis, no. (%)	32 (24.1)
Cardioembolic stroke, no. (%)	23 (17.3)
Others, no. (%)	29 (21.8)
TIA, no. (%)	10 (7.5)

Abbreviations: CSA, cross-sectional area; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; no., number; TIA, transient ischemic attack.

had been diagnosed with AF prior to admission. The median vagus nerve CSA was significantly smaller on the left side than on the right side among all participants (1.07 mm<sup>2</sup> [IQR, 0.71–1.45] vs. 1.32 mm<sup>2</sup> [IQR, 0.88–1.69],  $p < 0.001$ ).

On univariate analysis, patients with AF were significantly older (72.5 vs. 79.0 years,  $p = 0.02$ ) and had significantly higher BNP level (50.1 vs. 240.1 ng/L,  $p < 0.001$ ), compared with patients who did not exhibit AF. Moreover, the proportion of patients with hypertension was significantly higher among patients with AF than among patients without AF (81% vs. 97%,  $p = 0.04$ ). The median right vagus nerve CSA was significantly smaller in patients with AF than in patients without AF (1.33 vs. 1.04 mm<sup>2</sup>,  $p = 0.03$ ), whereas the median left vagus nerve CSA was comparable (Table 2). There was no difference in median CSA between patients with chronic AF and patients with paroxysmal AF (right: 1.43 vs. 1.02 mm<sup>2</sup>,  $p = 0.95$ ; left: 1.15 vs. 1.02 mm<sup>2</sup>,  $p = 0.94$ ), or between patients who were diagnosed with AF during this hospitalization and patients who were diagnosed prior to admission (right: 0.73 vs. 1.16 mm<sup>2</sup>,  $p = 0.24$ ; left: 1.50 vs. 1.09 mm<sup>2</sup>,  $p = 0.39$ ).

Multivariable logistic regression analysis concerning AF detection during hospitalization revealed that log transformed and quintiled BNP level (odds ratio [OR], 3.71; 95% confidence interval [CI], 2.09–6.59) and smaller right vagus nerve CSA (OR, 0.40; 95% CI, 0.16–0.99) were independent predictors of AF. In contrast, age, BMI, hypertension, diabetes mellitus, and current smoking habit were not significantly associated with AF (Table 3).

**Table 2**  
Univariate analysis for atrial fibrillation.

Characteristics	AF (–), $n = 102$	AF (+), $n = 31$	$p$ -Value
Age (years), median [IQR]	72.5 [67–81]	79 [74–85]	0.02
Male, no. (%)	64 (63)	17 (55)	0.53
Initial NIHSS, median [IQR]	3 [1–4]	4 [2–7]	0.28
Hypertension, no. (%)	83 (81)	30 (97)	0.04
Diabetes mellitus, no. (%)	33 (32)	12 (39)	0.52
Dyslipidemia, no. (%)	62 (61)	21 (68)	0.53
Current smoking, no. (%)	37 (36)	9 (29)	0.52
BNP (ng/L), median [IQR]	50.1 [21.8–103.2]	240.1 [121.9–518.9]	< 0.001
BMI (kg/m <sup>2</sup> ), median [IQR]	22.9 [20.4–25.8]	23.0 [20.8–25.3]	0.99
HbA1c (%), median [IQR]	5.9 [5.6–6.8]	6.1 [5.7–6.6]	0.91
Right CSA (mm <sup>2</sup> ), median [IQR]	1.33 [0.92–1.82]	1.04 [0.73–1.56]	0.03
Left CSA (mm <sup>2</sup> ), median [IQR]	1.06 [0.71–1.45]	1.14 [0.77–1.43]	0.99

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CSA, cross-sectional area; HbA1c, hemoglobin A1c; IQR, interquartile range; no., number; NIHSS, National Institutes of Health Stroke Scale.

**Table 3**  
Multivariable regression models for predictors of atrial fibrillation.

Variables	Odds ratio (95% CI)	$p$ -Value
Age	1.65 (0.92–2.98)	0.10
Diabetes mellitus	2.08 (0.53–8.12)	0.29
Hypertension	7.81 (0.48–125.65)	0.15
BMI	1.90 (0.69–5.21)	0.21
Current smoker	3.50 (0.76–16.07)	0.11
BNP	5.03 (2.43–10.40)	< 0.001
Right CSA (mm <sup>2</sup> )	0.33 (0.12–0.91)	0.03

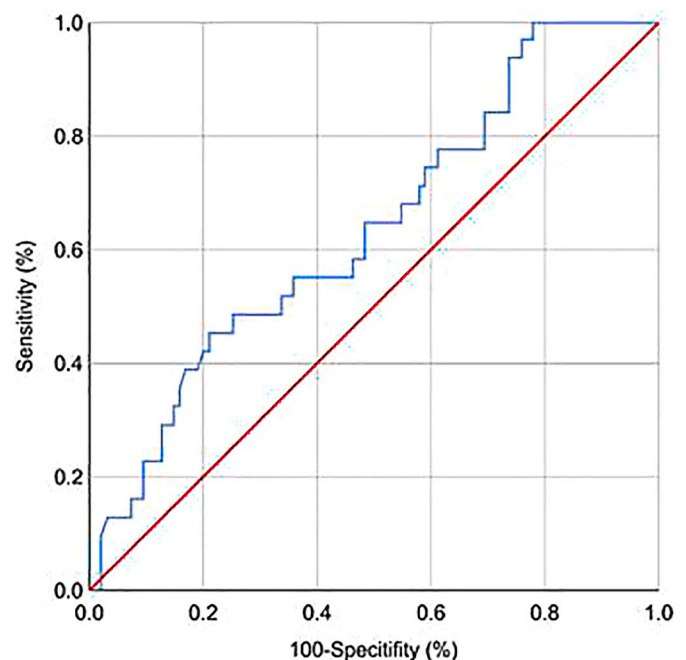
Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CI, confidence interval; CSA, cross-sectional area. The value of BNP and Age were converted to natural logarithm and quintiled for logistic regression analysis. BMI was also classified into six levels according to the WHO classification and used for logistic regression analysis.

Receiver operating characteristic curve analysis was performed to define the optimal CSA cutoff for predicting AF during the hospital stay (area under the curve = 0.64; Fig. 2). Using a cutoff value of 0.91 mm<sup>2</sup>, the sensitivity and specificity for AF were 79% and 45%, respectively.

#### 4. Discussion

Here, we demonstrated that small right vagus nerve CSA on CU evaluation was an independent predictor of AF during the hospital stay in patients with acute ischemic stroke.

Approximately 20%–40% of patients with ischemic stroke do not have a known cause after standard evaluation; this subtype of stroke is classified as a stroke of undetermined etiology [8,11]. With the advent of direct oral anticoagulants for AF treatment, the “embolic stroke of undetermined source” (ESUS) concept has been proposed to aggressively select patients who are eligible for anticoagulation among patients with a stroke of undetermined etiology [12]. There may be patients with ESUS who have undetected paroxysmal AF, which is considered the most important cause of ESUS [13]. Because AF is often paroxysmal and asymptomatic, it is difficult to detect via conventional monitoring techniques [14]. Although various methods (e.g., an external event or loop recorder, long-term outpatient monitoring, or



**Fig. 2.** Receiver operating characteristic curve for the relationship between the presence of atrial fibrillation and the cross-sectional area of the right vagus nerve.

insertion cardiac monitors) can detect AF [15], the detection rate remains low (0%–25%) and these techniques often require a long testing period. Because these monitoring methods cannot readily be implemented in all patients with ESUS, selection of patients with probable undetected paroxysmal AF is a reasonable approach. Frequent premature supraventricular contractions, elevated BNP levels, mechanical thrombectomy, and left atrium dilatation have all been associated with paroxysmal AF detection during long-term examination or monitoring [16]. Additionally, the present findings imply that patients with small right vagus nerve CSA might be favorable candidates for long-term or more invasive examinations to detect paroxysmal AF. Although our data did not demonstrate sufficient sensitivity and specificity for predicting AF, a combination of these previously reported factors and vagus nerve CSA might enhance their effectiveness. Moreover, CSA evaluation by CU can be easily introduced in clinical practice because CU is already widely implemented in carotid artery assessment.

Our results indicated that the left vagus nerve CSA was smaller than right vagus nerve CSA; there was no statistically significant association between left vagus nerve CSA and AF. Similarly, Pelz et al. studied 60 healthy individuals and reported that right vagus nerve CSA was significantly larger than left vagus nerve CSA [17]. Because the vagus nerve provides asymmetrical innervation, nerve fiber distribution may differ between left and right sides; the right vagus nerve plays a greater role in heart rate control.

In the present study, BNP level was also an independent predictor of AF, consistent with previous findings [18,19]. However, in multivariable analysis, we found no statistically significant associations between AF and variables such as age, BMI, diabetes mellitus, and hypertension. Most patients were relatively old (median age, 74 years), had good blood glucose control (median hemoglobin A1c, 0.06 [6.0%]), and exhibited hypertension. There were few obese patients (only two patients had a BMI  $\geq 30$  kg/m<sup>2</sup>). Moreover, this study included patients with ischemic stroke in acute or subacute settings during the hospital stay. Therefore, it may have been inappropriate to use these factors, which were previously reported in a healthy cohort, as explanatory variables in multivariable analysis.

This study had some limitations. First, this was a retrospective and cross-sectional study. We could not examine whether patients with vagal atrophy subsequently developed AF. Second, we could not perform follow-up assessments to evaluate AF development after discharge. Therefore, we did not evaluate the usefulness of vagus nerve CSA for detecting unrecognized subclinical AF in post-discharge settings. The risk of AF development should be further evaluated through prospective and longitudinal studies. Third, the study was conducted at a single center, and the patient population was small; these aspects may limit the generalizability of the results. Fourth, we could not fully determine the duration of ECG monitoring in hospital. Thus, the period of ECG monitoring might have been insufficient for diagnosis of paroxysmal AF during the hospital stay. Fifth, this patient population was not entirely uniform, which may further limit the generalizability of the results. However, when the analysis was limited to patients whose stroke subtypes were “cardioembolic” or “others,” there was no significant difference in vagus nerve CSA according to AF status (right;  $p = 0.22$ , left;  $p = 0.34$ ); this lack of difference may have been caused by the small population included in the analysis.

Overall, we demonstrated that small right vagus nerve CSA on CU was an independent predictor of AF during the hospital stay in patients with acute ischemic stroke. A prospective multicenter study is warranted to elucidate the usefulness of vagus nerve CSA for predicting subclinical AF in patients with ESUS.

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## Data availability statement

The privacy of research patients is protected by the regulations of the Institutional Review Board. Therefore, our data, analytical methods, or research materials are not available to other researchers.

## Declaration of Competing Interest

None.

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