Utility of Plain Chest Computed Tomography in Diagnosing Cardioembolic Stroke due to Paroxysmal Atrial Fibrillation

Short title: Chest CT for the diagnosis of PAF

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Abstract

Background

Diagnosing cardioembolic stroke due to paroxysmal atrial fibrillation (PAF) is difficult, mainly due to a low detection rate. We evaluated whether left atrial volume, which can be simply measured using non-contrast chest computed tomography (CT-LAV), can contribute to the diagnosis of cardioembolic stroke due to PAF (PAF-CE).

Methods

Fifty-one consecutive patients with acute ischemic stroke within 24 h of onset were included in this study. Upon admission, we measured the left atrial diameter using transthoracic echocardiography (TTE-LAD) and CT-LAV. Patient background factors such as sex, age, and stroke risk factors; brain natriuretic peptide (BNP) value; and QTc interval were evaluated on admission. Utilities of BNP value, CT-LAV, and TTE-LAD in PAF-CE diagnosis were compared.

Results

Patients were classified into three groups: cerebral thrombosis (CTB) group including large-artery atherosclerosis and small-vessel occlusion (n=16), cardioembolic stroke due to non-valvular atrial fibrillation (AF-CE) group (n=20), and cardioembolic stroke due to paroxysmal atrial fibrillation (PAF-CE) group (n= 15). BNP value was highest in the AF-CE group (240.5 pg/mL), followed by the PAF-CE (187.9 pg/mL) and CTB groups (35.0 pg/mL) ($p<0.001$). There was a significant difference in TTE-LAD among the groups (AF-CE group, 43.8 mm;

PAF-CE group, 38.3 mm; CTB group, 34.1 mm) ($p<0.001$). CT-LAV was higher in the AF-CE group (142 mm^3) than in the PAF-CE (95.8 mm^3) and CTB groups (95.8 mm^3) ($p<0.001$). In differentiating PAF-CE, the area under the receiver operating characteristic curve was 0.867, 0.742, and 0.845 for BNP value, TTE-LAD, and CT-LAV, respectively. A cut-off CT-LAV value of ≥ 69.6 mm^3 had a high diagnostic rate (>80% of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy).

Conclusion

CT-LAV can be useful in PAF-CE diagnosis. Further studies with larger sample sizes are required to confirm our findings and determine better cut-off value for CT-LAV.

TEXT

Introduction

Cardioembolic stroke resulting from non-valvular atrial fibrillation (NVAF) (AF-CE) is known to result in poor outcomes, with many cases of in-hospital death[1]. There are also some cases of cerebral embolism in which the embolic source cannot be detected. These cases are described as embolic strokes of undetermined source (ESUS)[2]. When treating ESUS, the efficacy of antithrombotic agents for secondary prevention is unclear, and aspirin is currently recommended as the better choice[3]. However, in terms of causes of cardioembolic stroke, paroxysmal atrial fibrillation (PAF) is also known to be associated with a high primary risk for ischemic stroke[4]. Approximately 30% of cases of ESUS are thought to be caused by PAF[5], and some patients require treatment with an anticoagulant agent as secondary prevention.

Patients who do not exhibit NVAF at the time of ischemic stroke onset require long-term electrocardiography (ECG) monitoring. As the PAF detection rate for 24-h observation is only 2.9%, ECG monitoring must be performed for at least 72 h[1]. Therefore, various tests are performed to differentiate cardioembolic stroke due to PAF[6][7]. Transthoracic echocardiography (TTE) can be used to simply and noninvasively measure left atrial diameter (LAD). TTE-LAD dilatation is a finding that is suggestive of the presence of PAF[8][9][10]. However, there is a risk of measurement error resulting from difference in body position during testing or technical skill of the tester.

As aortic arch calcification detected via chest computed tomography (CT) is also known to be a risk factor for ischemic stroke[11], many patients are assessed for ischemic stroke upon admission.

Therefore, we measured simple left atrial volume (CT-LAV) with non-contrast chest CT in patients with acute ischemic stroke and investigated whether these values were useful in diagnosing cardioembolic stroke due to PAF (PAF-CE).

Materials and methods

We retrospectively observed a total of 238 patients, including 158 with large-artery atherosclerosis and small-vessel occlusion and 80 with cardioembolic stroke due to NVAF or PAF who were hospitalized between April 2014 and March 2018 at the Department of Neurology, Dokkyo Medical University Hospital, and whose condition developed within 24 h after admission. Ischemic stroke was classified using the Stop Stroke Study TOAST (SSS-TOAST)[4] by Ay et al. Definitive diagnosis of PAF-CE was defined as meeting the ESUS diagnostic criteria[2] upon admission and NVAF being noted during hospitalization.

Brain natriuretic peptide (BNP) levels were observed with blood testing during admission as well as QTc interval on ECG testing. Smoking, daily alcohol consumption, hypertension, dyslipidemia, and diabetes mellitus were evaluated as risk factors for cerebrovascular disease. We also investigated duration of hospitalization.

We excluded patients who did not undergo BNP or QTc interval evaluation while being hospitalized, patients who did not undergo non-contrast chest CT or TTE within 24 h after hospitalization, and those with cryptogenic stroke and stroke of other determined etiologies including ESUS.

Evaluation of TTE-LAD and CT-LAV

TTE was performed using Vivid7 (GE Healthcare Japan), Vivid E9 (GE Healthcare Japan), Sonos-7500 (Philips, Japan), and iE33 (Philips, Japan). We used a sector-array probe in the parasternal long-axis view to measure TTE-LAD.

In non-contrast chest CT, we used Aquilion CXL (Canon Medical Systems, Japan), Aquilion One Vision edition (Canon Medical Systems, Japan), Sensation 40 (Siemens Healthineers, Japan), and Sensation 64 (Siemens Healthineers, Japan) with the horizontal sectional view. Imaging conditions were mediastinal window (window level 50, window width 400) with slice thickness of 5 mm or 8 mm. CT-LAV was calculated with the following formula.

CT-LAV (mm^3)= longitudinal diameter (mm) × lateral diameter (mm)× number of slice × slice width (5 or 8) / 2

Statistical analysis

Subjects were divided into a cerebral thrombosis (CTB) group (large-artery atherosclerosis and small-vessel occlusion), AF-CE group, and PAF-CE group. We analyzed sex, risk factors, duration of hospitalization, QTc interval, BNP level, TTE-LAD, and CT-LAV differences in each group. The statistical software used was SPSS Statistics version 25 (IBM). We used Pearson's chi-square test to analyze categorical variables. When analyzing continuous variables, we used the Mann-Whitney U test for comparisons between two groups and the Kruskal-Wallis test for comparisons between three groups. A P-value <0.05 indicated a statistically significant difference.

We used the receiver operating characteristic (ROC) curve to investigate PAF-CE diagnosis sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. In addition, we used univariate logistic regression to calculate odds ratios.

Ethical standard

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the 1975 Declaration of Helsinki, as revised in 2008. The institutional review board of Dokkyo Medical University Hospital approved the study (IRB approved number, R-8-8). All patients provided written informed consent to participate.

Results

Investigation of three groups

Of the total 238 patients, 16 were classified in the CTB group, 20 in the AF-CE group, and 15 in the PAF-CE group, and 187 patients were excluded. Male patients accounted for 68.8% of the CTB group, 40.0% of the AF-CE group, and 80.0% of the PAF-CE group, indicating that there were few men in the AF-CE group ($p<0.05$).

However, there were no differences noted for age, smoking, daily alcohol drinking, and duration of hospitalization, and no significant differences were observed for the prevalence of hypertension, dyslipidemia, or diabetes mellitus **(Table 1)**.

The QTc interval was 0.434 s (median) in the CTB group, 0.446 s in the AF-CE group, and 0.451 s in the PAF-CE group, indicating no significant differences (p=0.109). The BNP level was highest in the AF-CE group, at 240.5 pg/mL (median). It was elevated in the PAF-CE group, at 187.9 pg/mL, but within the normal range in the CTB group, at 35.0 pg/mL (p<0.001). TTE-LAD was 43.8 mm in the AF-CE group, 38.3 mm in the PAF-CE group, and 34.1 mm in the CTB group, indicating an intergroup difference (p<0.001). CT-LAV was highest in the AF-CE group, at 142 mm^3. It was 95.8 mm^3 in the PAF-CE group and 53.7 mm^3 in the CTB group (p<0.001) **(Table 2)**.

Post hoc analysis

No significant differences were noted between the CTB group and the AF-CE group (p=0.474) and PAF-CE group (p=0.0860) in terms of sex (Pearson's chi-square test). However, a difference was noted between the AF-CE and PAF-CE groups (p=0.0180).

Significant differences were noted in the BNP levels between the CTB group with the AF-CE group and PAF-CE group. However, no difference was noted between the AF-CE and PAF-CE groups (p=0.298, Mann-Whitney U test). Meanwhile, significant differences were noted between all groups for TTE-LAD and CT-LAV

(Mann-Whitney U test) **(Fig.1 A,B,C)**.

Comparison of CTB group and PAF-CE group

When diagnosing PAF-CE, ROC area under the curve was 0.867 for BNP level, 0.742 for TTE-LAD, and 0.845 for CT-LAV, indicating that BNP level and CT-LAV were particularly useful **(Fig.2)**.

When the BNP cutoff value was set at 79.5 pg/mL or above, PAF-CE diagnosis could be made with a sensitivity of 86.7%, specificity of 81.3%, and accuracy of 80.7%. Investigation of the diagnostic rate when the CT-LAV cutoff value was set at 69.6 mm^3 or higher indicated that sensitivity, specificity, PPV, and NPV were all 80% or higher, with a higher level of 80.6% also achieved for accuracy. However, accuracy was low, at just 61.3% when the TTE-LAD cutoff value was set at 37.2 mm or greater **(Table 3)**.

The results of univariate logistic regression for each of these cutoff values indicated that BNP level (p=0.00185, odds ratio 19.5, 95% confidence interval 3.01–127) and CT-LAV (p=0.00171, odds ratio 17.3, 95% confidence interval 2.92–103) were useful in diagnosing PAF-CE. However, TTE-LAD was not found to be useful (p=0.214).

Discussion

We investigated whether QTc interval, BNP level, TTE-LAD, and CT-LAV differed between the CTB, AF-CE, and PAF-CE groups and found that, while BNP level was low in the CTB group, no differences were noted in the AF-CE and PAF-CE groups. We were also able to prove that TTE-LAD and CT-LAV were highest for the AF-CE group and high in the PAF-CE group, with a difference noted with the CTB group. BNP level and CT-LAV were found to be useful in the differential diagnosis of CTB and PAF-CE, which is important when selecting the method of secondary prevention[12].

Although our investigation did not reveal any differences in QTc interval. QTc interval prolongation is known to be a risk factor for NVAF[13][14][15]. Hoshino et al.[7] measured QTc interval upon hospital admission in 744 ischemic stroke patients and found that PAF was likely to be detected in patients with a prolonged QTc interval. The cutoff value for this was reportedly 0.438 s. While we did not detect any statistically significant difference, we measured the QTc interval in the CTB group as being 0.434 s (median), while the QTc interval in the PAF-CE group was prolonged, at 0.451 s. Therefore, if the sample size was increased, it might be possible to show that QTc interval is useful in diagnosing PAF-CE.

As BNP level reflects remodeling of the left atrium, it is known to become elevated prior to AF onset and associated with left atrial overload[16]. Furthermore, in cases of ischemic stroke in the acute stage, elevated BNP level is useful for predicting PAF-CE. Fujii et al.[8] consider a BNP level of 144 pg/mL or higher to be of critical importance. However, Yoshioka et al.[9] reported that a level of 90 pg/mL or higher is optimal for predicting PAF, and they have constructed PAF prediction scores using cutoff values of 50 pg/mL, 90 pg/mL, and 150 pg/mL or higher. Thus, there is no optimal cutoff value for elevated BNP level in cases of acute ischemic stroke caused by PAF. A meta-analysis of approximately 2,800 patients indicated that BNP levels are more elevated in cases of AF-CE and PAF-CE than in cases of CTB even 72 h after onset[6]. In our study, which targeted cases of ischemic stroke within 24 h after onset, BNP measurement was also performed within 24 h after onset. Therefore, although median BNP levels in cases of CTB were somewhat elevated, at 35.0 pg/mL, they were markedly elevated in cases of AF-CE (240.5 pg/mL) and PAF-CE (187.9 pg/mL). Moreover, in the differential diagnosis of CTB and PAF-CE, we found that PAF-CE could be diagnosed at a higher rate with a BNP level of 79.5 pg/mL or higher. While this BNP cutoff value is lower than that reported in previous studies, it is similar to the value reported by Yoshioka et al.[9].

In cases of NVAF, structural remodeling causes left atrial enlargement, dilatation, cell death, and fibrosis on weekly basis[17]. However, left atrial dilatation might not only be the result of atrial remodeling related to permanent arrhythmia. In fact, left atrial dilatation can arise as a result of thromboembolic cardiologic factors of the fibrillation unrelated to permanent or paroxysmal arrhythmia[18][19]. In addition, it has been reported that TTE-LAD can also become dilatated in cases of PAF-CE, and PAF-CE diagnosis scores using TTE-LAD have been proposed[8][9][10]. Fujii et al.[8] have suggested that the cutoff value for TTE-LAD should be 38.0 mm while Yoshioka et al.[9] suggested 40.0 mm. Suissa et al.[10] proposed that a TTE-LAD value larger than the normal range should be considered to be a finding suggestive of PAF-CE. The results of our investigation indicated that TTE-LAD in the CTB group was within the normal range, at 34.1 mm. However, the result was 43.8 mm for the AF-CE group and 38.3 mm for the PAF-CE group. When differentiating CTB and PAF-CE, TTE-LAD of 37.2 mm or larger is considered to be a finding suggestive of PAF-CE, and it is similar to the figure reported by Fujii et al. [8]. However, accuracy was not overly high, at just 61.3%. Some patients with ischemic stroke cannot maintain a set position during testing, while others cannot follow the directions of the tester. Measurement errors may also arise as a result of the tester's level of skill. These factors may have been the reason why a high TTE-LAD diagnostic rate was unable to be achieved.

CT-LAV was 53.7mm^3 in the CTB group, 142mm^3 in the AF-CE group, and 95.8 mm^3 in the PAF-CE group. Like TTE-LAD, it was high in patients with NVAF and PAF. These results suggest that in patients in whom it is difficult to measure TTE-LAD, CT-LAV could be useful in diagnosing PAF-CE. We also demonstrated that at 69.3 mm^3 or higher, PAF-CE could be diagnosed with a high accuracy of 80.6%, which has almost the same diagnostic rate as that for BNP. To more accurately calculate CT-LAV with chest CT imaging, respiration and heart rate need to be synchronized. However, as no reports have attempted to perform PAF-CE diagnosis using normal chest CT, which is used to diagnose conditions such as aortic arch calcification and pneumonia, we believe that the fact that we were able to obtain findings suggestive of PAF-CE with CT-LAV could be very useful in clinical settings.

Patients determined to have PAF while hospitalized were diagnosed as PAF-CE in this study. However, the possibility that some patients exhibited PAF after being discharged cannot be ruled out. Moreover, in cases of insular infarctions, imbalance of sympathetic and parasympathetic activities can cause NVAF to develop[20]. Therefore, limitations of this study include the possibility that patients with PAF were included in the CTB group, possibility that cases of NVAF due to ischemic stroke were included in the AF-CE group and PAF-CE group, and small sample size.

Conclusions

Like BNP level, CT-LAV might be useful in diagnosing PAF-CE. Furthermore, appropriate cutoff values need to be determined based on further investigation on a larger sample size.

Conflicts of interest

There are no financial or other relations that could lead to a conflict of interest.

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Figure legend

Figure 1 Post hoc analysis of BNP, TTE-LAD and CT-LAV

A: BNP, B: TTE-LAD, C: CT-LAV

BNP value was significantly lower in CTB group, but there was no difference between PAF-CE group and AF-CE group (Mann–Whitney U test). TTE-LAD and CT-LAV values were lowest in CTB group and highest in AF-CE group (Mann–Whitney U test).

* p<0.05 ** p<0.01 *** p<0.001

CTB, cerebral thrombosis; AF, non-valvular atrial fibrillation; PAF, paroxysmal atrial fibrillation; CE, cardioembolic stroke; BNP, brain natriuretic peptide; TTE, transthoracic echocardiography; LAD, left atrial diameter

CT, computed tomography; LAV, left atrial volume

Figure 2 ROC curve of BNP, TTE-LAD and CT-LAV in diagnosis of PAF-CE

Area under the ROC curve was 0.867, 0.742 and 0.845 for BNP, TEE-LAD and CT-LAV, respectively.

CTB, cerebral thrombosis; AF, non-valvular atrial fibrillation; PAF, paroxysmal atrial fibrillation; CE, cardioembolic stroke; BNP, brain natriuretic peptide; TTE, transthoracic echocardiography; LAD, left atrial diameter; CT, computed tomography; LAV, left atrial volume; ROC curve, receiver operating characteristic curve

Table 1　Clinical background factors among CTB, AF-CE and PAF-CE groups

	Groups			
	CTB (n=16)	AF-CE (n=20)	PAF-CE (n=15)	*p* value
Male (n, %)	11 (68.8)	8 (40.0)	12 (80.0)	0.0413*
Age (years, median; range)	74 (43-89)	74.5 (66-92)	83 (64-93)	0.224
Smoking (n, %)	2 (12.5)	3 (15.0)	1 (6.67)	0.746*
Daily alcohol consumption (n, %)	2 (12.5)	4 (20.0)	3 (20.0)	0.809*
Hypertension (n, %)	13 (81.3)	14 (70.0)	13 (86.7)	0.468*
Dyslipidemia (n, %)	8 (50.0)	7 (35.0)	4 (26.7)	0.392*
Diabetes mellitus (n, %)	3 (18.8)	5 (25.0)	3 (20.0)	0.889*
Days of hospitalization (median; range)	15 (7-45)	19.5 (2-50)	16 (10-39)	0.231

Kruskal-Wallis Test,　*Pearson's chi-square test

CTB, cerebral thrombosis; AF, non-valvular atrial fibrillation; PAF, paroxysmal atrial fibrillation; CE, cardioembolic stroke

Table 2　Comparison of four diagnostic markers among CTB, AF-CE and PAF-CE groups

	Group			
	CTB (n=16)	AF-CE (n=20)	PAF-CE (n=15)	*p* value
QTc interval	0.434	0.446	0.451	0.109
(sec, median; range)	(0.400-0.479)	(0.384-0.556)	(0.374-0.505)	
BNP	35.0	240.5	187.9	<0.001
(pg/ml, median; range)	(6.6-406.2)	(84.1-609.3)	(41.7-687.8)	
TTE-LAD	34.1	43.8	38.3	<0.001
(mm, median; range)	(28.1-45.1)	(36.7-64.7)	(33.9-51.3)	
CT-LAV	53.7	142	95.8	<0.001
(mm^3, median; range)	(19.9-106)	(90.1-411)	(35.2-138)	

Kruskal-Wallis Test

CTB, cerebral thrombosis; AF, non-valvular atrial fibrillation; PAF, paroxysmal atrial fibrillation;
CE, cardioembolic stroke;
BNP, brain natriuretic peptide; TTE, transthoracic echocardiography; LAD, left atrial diameter;
CT, computed tomography; LAV, left atrial volume

Table 3 Diagnostic rate of PAF-CE using BNP, TTE-LAD and CT-LAV

	Sensitivity	Specificity	PPV	NPV	Accuracy
BNP ≥ 79.5 pg/ml	86.7%	81.3%	76.5%	85.7%	80.7%
TTE-LAD ≥ 37.2 mm	60.0%	62.5%	60.0%	62.5%	61.3%
CT-LAV ≥ 69.6 mm^3	80.0%	81.3%	80.0%	81.3%	80.6%

AF, non-valvular atrial fibrillation; PAF, paroxysmal atrial fibrillation; CE, cardioembolic stroke; BNP, brain natriuretic peptide; TTE, transthoracic echocardiography; LAD, left atrial diameter; CT, computed tomography; LAV, left atrial volume; PPV, positive predictive value; NPV, negative predictive value