学位論文

Left Atrial Volume Index as a Predictor for Large-Vessel Occlusion in Cardiogenic Cerebral Infarction: A Single Cohort Study
（心原性脳主幹動脈閉塞の予測因子としての左房容積係数に関する単施設後方視的研究）

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Left Atrial Volume Index as a Predictor for Large-Vessel Occlusion in Cardiogenic Cerebral Infarction: A Single-Center Cohort Study

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■ OBJECTIVE: **The left atrial volume index (LAVI) is considered to be the most accurate index to estimate the size of the left atrium (LA). In this study, we investigated the relationship between LA size measured by LAVI and the occurrence of large-vessel occlusion (LVO) in patients with cardiogenic cerebral infarction (CCI).**

■ METHODS: **This retrospective single-center cohort study involved 118 patients with CCI within the internal carotid artery (ICA) or middle cerebral artery regions seen between January 2015 and July 2020. In all patients, the type of CCI was determined according to the Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Scores (TOAST) subtype diagnosis criteria. LVO was defined as positive when magnetic resonance imaging and computed tomography angiography showed ICA, M1, or M2 occlusion, with all others defined as non-LVO. Clinical characteristics, including LAVI, were evaluated in the records of several patients to investigate if they were risk factors for developing LVO.**

■ RESULTS: **Seventy patients (59%) were diagnosed as having LVO infarction (ICA occlusion, $n = 19$ [16%]; M1 occlusion, $n = 26$ [22%]; and M2 occlusion, $n = 25$ [21%]). Echocardiography showed no difference between LVO and non-LVO in terms of the ejection fraction ($P = 0.64$), LA dimension ($P = 0.93$), and LA volume ($P = 0.06$). However, LAVI significantly differed between the LVO and non-LVO groups ($P = 0.02$). Multivariate logistic regression analysis showed larger LAVI as a significant risk factor for LVO ($P = 0.01$).**

■ CONCLUSIONS: **Our findings suggest that a larger LAVI is a predictor of developing LVO in patients with CCI.**

INTRODUCTION

Although direct oral anticoagulants (DOAC) have dramatically improved the prevention of cardiogenic cerebral infarction (CCI) in recent years,[1] severe neurologic deficits from cardiogenic emboli-induced large-territory cerebral infarction are still commonly observed occurrences. There are 2 types of CCI: small-vessel occlusion caused by relatively small cardiogenic emboli, and large-vessel occlusion (LVO) caused by large cardiogenic emboli. Because cardiogenic emboli generally form in the left atrium (LA), anatomic differences of the LA can lead to variations in emboli formation, which further leads to differences in the specific type of cerebral infarction. Thus, LA enlargement is one of the anatomic characteristics that is emerging as a risk factor for CCI.[2]

Key words
- Echocardiography
- Large-vessel occlusion
- Left atrial volume index
- Left atrium

Abbreviations and Acronyms
AF: Atrial fibrillation
CCI: Cardiogenic cerebral infarction
DM: Diabetes mellitus
DOAC: Direct oral anticoagulants
EF: Ejection fraction
ICA: Internal carotid artery
IQR: Interquartile range
LA: Left atrium
LAD: Left atrial dimension
LAV: Left atrial volume
LAVI: Left atrial volume index
LVO: Large-vessel occlusion
MCA: Middle cerebral artery
MRI: Magnetic resonance imaging
NIHSS: National Institutes of Health Stroke Scale

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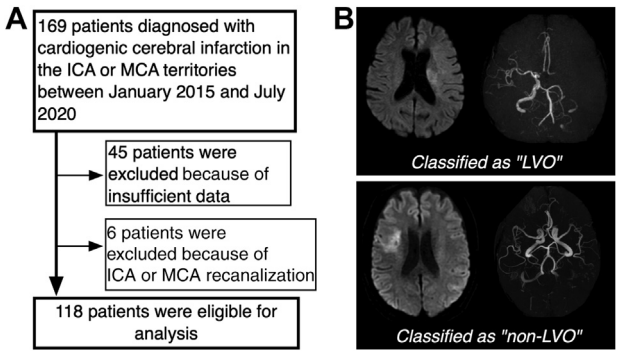

Figure 1. (**A**) The process of patient selection for inclusion in the study. We retrospectively collected the medical records of 169 patients diagnosed with cardiogenic cerebral infarction between January 2015 and July 2020 at our institution with infarction in the internal carotid artery (ICA) or middle cerebral artery (MCA) regions. Of those 169 patients, 45 were excluded from the study because of insufficient data and an additional 6 were excluded because of internal carotid artery or middle cerebral artery recanalization, thus leaving 118 eligible for analysis. (**B**) Images showing representative large-vessel occlusion (LVO) and non–large-vessel occlusion (non-LVO) cases.

The LA volume index (LAVI) is considered to be the most accurate index to estimate the size of the LA. Traditionally, the size of the LA has been estimated via measurement of the LA dimension (LAD) or the LA volume (LAV). However, it is widely known that the LA size depends on the size of the thorax.[3] Thus, LAVI, obtained by dividing the LAV by the body surface area, provides a new tool for a more accurate estimation of LA size. Numerous previous cardiovascular studies have confirmed the value of LAVI,[3,4] and the reported findings in a previous cerebrovascular study suggested the value of LAVI as a predictive index in cases of cardioembolic stroke.[5] However, to the best of our knowledge, there have been no previous reports focused on investigating the association of LAVI and factors indicating the severity of the stroke, such as LVO. Thus, the purpose of this present study is to investigate the relationship between LA size, measured by LAVI, and the occurrence of LVO in patients with CCI.

METHODS

Study Design

In this retrospective single-center cohort study, we reviewed the medical records of 169 patients with CCI seen at the Department of Neurosurgery, Asahikawa Medical University, Hokkaido, Japan between January 2015 and July 2020, who were diagnosed with infarction in the internal carotid artery (ICA) or middle cerebral artery (MCA) regions. The study protocols and use of the presented clinical data were approved by the internal review board of Asahikawa Medical University. Informed consent was obtained from all patients by securing each patient's right to refuse participation in the study via an opt-out selection preference.

In all patients, the specific type of cerebral infarction was determined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype diagnosis criteria.[6] Of the 169 patients reviewed, 45 were excluded from the study because of insufficient data, and an additional 6 were excluded because of recanalization of the ICA or MCA on admission, which rendered further analysis difficult. Thus, 118 patients who had cerebral infarctions within the ICA or MCA regions were deemed eligible for analysis (**Figure 1A** and **Supplementary Table 1**). Data regarding the patients who were excluded are provided in **Supplementary Table 2**. In this study, LVO was defined as positive if ICA, M1, or M2 occlusion was present on magnetic resonance imaging (MRI), whereas non-LVO was defined as previously described (**Figure 1B**).[7,8] In 1 patient, computed tomography angiography was used for classification as LVO or non-LVO, because MRI could not be performed because of an implanted cardiac pacemaker device.

Clinical Variables

To determine the clinical variables in all patients, the National Institutes of Health Stroke Scale (NIHSS) score and Diffusion-Weighted Imaging—Alberta Stroke Program Early Computed Tomography Score on MRI at the time of admission were evaluated,[9,10] as well as several other key clinical characteristics that were recorded (**Table 1**, **Supplementary Tables 1 and 2**). Diabetes mellitus (DM) was defined as being present if the patient required the use of insulin or oral diabetes drugs, or if glycated hemoglobin A_{1c} level was higher than 6.4%. Smokers were defined as patients with a history of habitual tobacco smoking.

Table 1. Characteristics of Patients

Age (years), mean ± SD	75.9 ± 10.1
Gender (women/men), n	57:61
Body mass index (kg/m^2), mean ± SD	22.4 ± 3.4
Smokers, n (%)	35 (30)
Hypertension, n (%)	66 (56)
Heart failure, n (%)	33 (28)
Diabetes mellitus, n (%)	35 (30)
Anticoagulant drug, n (%)	31 (26)
Atrial fibrillation, n (%)	85 (72)
National Institutes of Health Stroke Scale score (IQR)	11.5 (3.0—21.8)
Echocardiogram	
Ejection fraction (IQR) (%)	60.0 (53.0—64.0)
Left atrial dimension (mm) (IQR)	40.0 (37.0—45.0)
Left atrial volume (mL) (IQR)	84.0 (63.3—106.0)
Left atrial volume index (IQR)	55.0 (39.3—69.8)
Number of LVO (%)	70 (59)
Internal carotid artery, n (%)	19 (16)
M1, n (%)	26 (22)
M2, n (%)	25 (21)
DWI-ASPECTS of non-LVO patients (IQR)	9.6 (9.0—10.0)

SD, standard deviation; IQR, interquartile range; LVO, large-vessel occlusion; DWI-ASPECTS, Diffusion-Weighted Imaging—Alberta Stroke Program Early Computed Tomography Score.

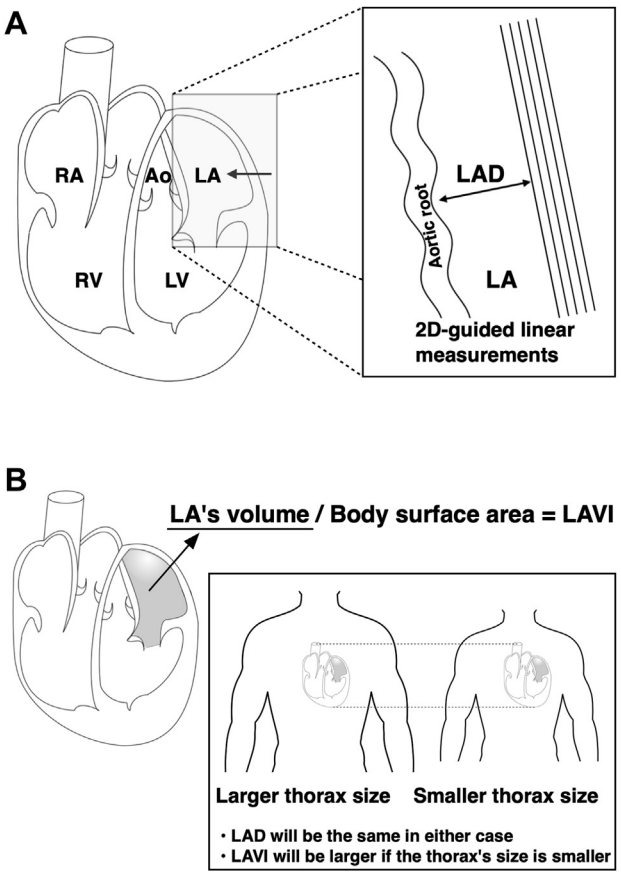

Figure 2. The difference between the left atrial (LA) dimension (LAD) and LA volume index (LAVI) in assessing the LA size. LAD was determined by measuring the distance from the atrial wall to the aortic root (Ao) using M mode ultrasonography (**A**). Echocardiography was used to automatically measure LA volume, which was divided by the body surface area to obtain LAVI (**B**). 2D, two-dimensional; LV, left ventricle; RV, right ventricle.

Echocardiography

All echocardiography measurements were obtained by use of an iE33 Ultrasound System (Philips, Amsterdam, The Netherlands), a LISENDO 880 Ultrasound System (Hitachi Healthcare Americas, Twinsburg, Ohio, USA), an ATRiDA Ultrasound Device (Canon Medical Systems Corp., Otawara, Japan), or a Vivid E9 Ultrasound System (GE Healthcare, Chicago, Illinois, USA). Ejection fraction (EF) was measured by the modified Simpson rule.[11] The LAD was determined by measuring the distance from the atrial wall to the aortic root using M mode ultrasonography in the systolic end (Figure 2A). The LAV and LAVI measurements were determined by the biplane method of disk summation.[11] Because LAVI compensates for the specific chest size of the patient, it generally reflects the LA size more accurately than does the LAD (Figure 2B).

Statistical Analysis

Comparative analysis of the 2 groups was performed using GraphPad Prism 5 (GraphPad Software, San Diego, California, USA) statistical analysis software. Statistical analysis was performed using the Pearson χ^2 test or the Fisher exact test to assess the associations between categorical variables. Normal data distribution for continuous variables was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using the Student *t* test, and nonnormally distributed variables were compared using the Mann-Whitney *U* test. Multivariate logistic regression analysis was performed to identify the significant factor(s) contributing to LVO. A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

There was no difference in age, gender, and affected vessel location between the analyzed and excluded cohort (Supplementary Table 3). Table 1 summarizes the characteristics of the patients in the analyzed cohort. Variables are expressed as mean ± standard deviation or as median (interquartile range [IQR] 25th–75th percentile) and the ratio of patients (%). There were 57 females and 61 males (mean age, 75.9 ± 10.0 years). Forty-two patients received endovascular treatment (Supplementary Table 1: aspiration thrombectomy, *n* = 31; stent retriever

Table 2. Comparison of Large-Vessel Occlusion and Non–Large-Vessel Occlusion

	LVO (N = 70)	Non-LVO (N = 48)	*P* Value
Age (years), mean ± SD	76.1 ± 10.1	75.6 ± 10.2	0.79
Gender (female), n (%)	37 (53)	20 (42)	0.31
Body mass index (kg/m^2), mean ± SD	22.2 ± 3.7	22.6 ± 3.1	0.45
Smokers, n (%)	20 (29)	15 (31)	0.91
Hypertension, n (%)	37 (53)	29 (60)	0.53
Heart failure, n (%)	22 (31)	11 (23)	0.42
Diabetes mellitus, n (%)	18 (26)	17 (35)	0.35
Anticoagulant drug, n (%)	19 (27)	12 (25)	0.96
Atrial fibrillation, n (%)	53 (76)	32 (67)	0.39
National Institutes of Health Stroke Scale score	18.5 (12.0–24.0)	3.0 (1.0–7.0)	<0.01*
Ejection fraction (%) (IQR)	60.0 (51.0–64.0)	61.0 (54.5–63.3)	0.64
Left atrial dimension (mm) (IQR)	40.0 (37.3–44.8)	40.5 (35.0–46.0)	0.93
Left atrial volume (mL) (IQR)	87.5 (68.3–111.5)	71.5 (60.8–102.5)	0.06
Left atrial volume index (IQR)	59.5 (43.0–72.0)	45.5 (34.9–63.0)	0.02*

LVO, large-vessel occlusion; SD, standard deviation; IQR, interquartile range.
*Variables showing significant differences.

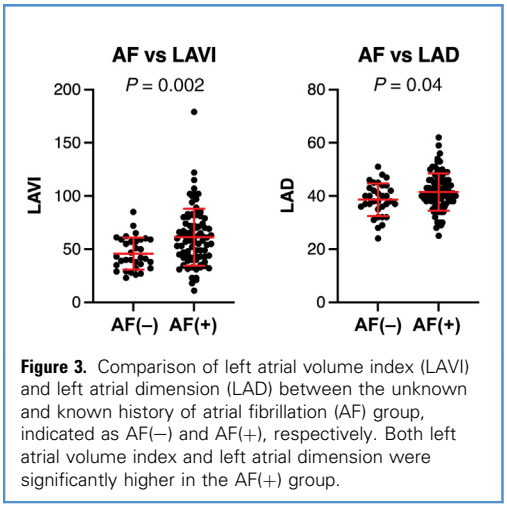

Figure 3. Comparison of left atrial volume index (LAVI) and left atrial dimension (LAD) between the unknown and known history of atrial fibrillation (AF) group, indicated as AF(–) and AF(+), respectively. Both left atrial volume index and left atrial dimension were significantly higher in the AF(+) group.

thrombectomy, n = 8; mechanical thrombectomy, n = 1; combined technic, n = 1; and intra-arterial urokinase infusion, n = 1). The mean body mass index (calculated as weight in kilograms divided by the square of height in meters) was 22.4 ± 3.43. There were 35 smokers (30%), and the number of patients with a history of hypertension, heart failure, and DM was 66 (56%), 33 (28%), and 35 (30%), respectively. Atrial fibrillation (AF) was detected in 85 patients (72%). Of those 85 patients, 46 had chronic AF and 39 had paroxysmal AF. Thirty-one patients (26%) were taking anticoagulants before the event. At the time of admission, the mean NIHSS score was 11.5 (range, 3.0–21.8), and the EF (IQR) (%), LAD (IQR) (mm), LAV (IQR) (mL), and LAVI (IQR) (mL/m^2) were 60.0 (range, 53.0–64.0), 40.0 (range, 37.0–45.0), 84.0 (range, 63.3–106.0), and 55.0 (range, 39.3–69.8), respectively. Seventy patients (59%) were diagnosed as having an LVO infarction (ICA occlusion, 19 patients [16%]; M1 occlusion, 26 patients [22%]; and M2 occlusion, 25 patients [21%]). The mean Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Score of the non-LVO patients (IQR) was 10.0 (range, 9.0–10.0).

LVO-Related Factors

Comparison of the clinical characteristics between the LVO and the non-LVO groups is shown in **Table 2**. No significant difference was found between the LVO group and the non-LVO group regarding patient age (P = 0.79), gender (P = 0.52), body mass index (P = 0.45), history of smoking (P = 0.91), hypertension (P = 0.53), heart failure (P = 0.42), DM (P = 0.35), use of anticoagulant drugs (P = 0.96), and having AF (P = 0.39). Inappropriately reduced DOAC administration or insufficient prolongation of the international normalized ratio of prothrombin time was identified in 12 patients (52%) in the LVO and 5 patients (45%) in the non-LVO groups. On the other hand, NIHSS score was significantly higher in the LVO group (P < 0.01).

Regarding the echocardiographic measurements, no significant difference was found between the LVO and non-LVO groups in EF (P = 0.64), LAD (P = 0.93), and LAV (P = 0.06). However, a statistically significant difference of LAVI was found between the LVO and non-LVO groups (P = 0.02). Moreover, multivariate logistic regression analysis among LAVI and previously reported risk factors (LAD and AF)[12,13] showed that both LAVI and LAD were higher in the group with a known history of AF (P = 0.002 and 0.04, respectively) (**Figure 3**). However, as shown in **Table 3**, LAVI was recognized as the only significant risk factor for LVO (P = 0.01; adjusted odds ratio, 1.03; 95% confidence interval, 1.01–1.06).

DISCUSSION

Although the pathogenesis of thrombosis (thrombogenesis) in AF is multifactorial,[14] dilatation of LAD is a significant risk factor for stroke,[15] so it is important to fully elucidate the relationship between them. LAVI is considered to be the most accurate index to estimate the size of the LA, and it is important to properly estimate the LA size of each subject via dividing the LAV by body surface area.[3] LAVI is used to evaluate left ventricular diastolic function with a maximum normal value of 34 mL/m^2.[16] Although previous studies have suggested that LAVI is associated with cardioembolic stroke,[5] its impact on stroke severity has yet to be elucidated.

The findings in the current study showed that a larger LAVI is a risk factor for developing LVO in CCI (P = 0.02), and our findings showed that LAD and LAV did not differ between the LVO and the non-LVO groups (P = 0.93, P = 0.06). One possible explanation for this discrepancy is that LAD might be less accurate than LAVI for the assessment of LA enlargement. Because LAD depends on the sternum size, it is difficult to determine the LA dilatation from a simple LA diameter. Moreover, LAV is inaccurate, because it does not take individual physical differences into account. On the other hand, LAVI is derived from dividing the LAV by body surface area, in which the measurement compensates for the patient's physical size when assessing LAV.

The thrombus in the LA is a red thrombus (i.e., rich in fibrin components) and is classified as a venous thrombus, which arises from a coagulative reaction as a result of the congestion of blood flow.[17] The size of the thrombus and severity of stroke have already been discussed[18] and we suspect that a higher LAVI indicates blood flow congestion, leading to the formation of a giant blood clot. In this study, both LAVI and LAD were higher in the group of patients with confirmed AF. Moreover, LAVI was the only significant risk factor for developing LVO. Thus, it is possible that patients with no history of AF were already experiencing paroxysmal AF, which was initiating the atrial enlargement.[19] From a practical point of view, LAVI may be a helpful risk indicator for tapering or discontinuing a drug therapy. Although

Table 3. Multivariate Analysis of the Risk Factors for Large-Vessel Occlusion

	Odds Ratio	95% Confidence Interval	*P* Value
Atrial fibrillation	1.25	0.52–2.95	0.61
Left atrial dimension	0.94	0.87–1.01	0.09
Left atrial volume index	1.03	1.01–1.06	0.01*

*Variables showing significant differences.

many patients are benefiting from anticoagulants with the recent launch of DOAC, drug therapy is discontinued in numerous cases because of bleeding complications or a scheduled surgery. In a previous study, the incidence of embolism caused by anticoagulant withdrawal or reduction was reportedly 0.8%, with 0.2% being fatal.[20] Thus, LAVI could be a valuable reference when consulting patients who are entering a period of drug therapy discontinuation.

Limitations

This study has several weaknesses, which limit the validity of the results. First, this study was a single-center analysis, and the number of samples analyzed was small. Thus, a more extensive survey involving multiple centers is necessary to validate our findings. The second limitation was the preliminary examination of the patients. Although we used various tests and referred to the TOAST classification to exclude patients with possible lacunar or atherosclerotic infarction,[6] invasive examinations such as transesophageal ultrasonography could not be performed on some patients because of poor general health condition or old age. Furthermore, the 6 patients who were excluded from analysis because of recanalization could have been of particular interest, because the thrombus in those patients might have been smaller than those in the patients with LVO. Although it is challenging to verify that this was the case, the study design in future prospective studies should consider recanalization cases.

CONCLUSIONS

The findings in this study suggest that a larger LAVI is a predictor of developing LVO in patients with CCI.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Hirotaka Sato: Conceptualization, Methodology, Investigation, Writing — original draft. **Masato Saito:** Data curation. **Nobuyuki Mitsui:** Data curation, Investigation. **Satoru Hiroshima:** Data curation, Investigation. **Jun Sawada:** Investigation (MR images). **Kazumi Akasaka:** Investigation (Echocardiography). **Manabu Kinoshita:** Conceptualization, Investigation, Writing — review & editing, Supervision.

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