Three-dimensional analysis of the left atrial appendage for detecting paroxysmal atrial fibrillation in acute ischemic stroke

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Background Atrial fibrillation impairs left atrial appendage function and the thrombus formation in the left atrial appendage is a major cause of cardioembolic stroke.

Aims To evaluate the association between the volume of the left atrial appendage measured by real-time three-dimensional transesophageal echocardiography and presence of paroxysmal atrial fibrillation in patients with cerebral infarction or transient ischemic attack.

Methods Real-time three-dimensional transesophageal echocardiography was performed to measure left atrial appendage end-diastolic and end-systolic volumes to calculate left atrial appendage ejection fraction. Patients with normal sinus rhythm at the time of real-time three-dimensional transesophageal echocardiography were divided into groups with and without paroxysmal atrial fibrillation. Volumetric data were corrected with the body surface area.

Results Of 146 patients registered, 102 (29 women, 72·2 ± 10·7 years) were normal sinus rhythm at the examination. In 23 patients with paroxysmal atrial fibrillation, left atrial appendage end-diastolic volume (4·78 ± 3·00 ml/m^2 vs. 3·14 ± 2·04 ml/m^2, $P = 0·003$) and end-systolic volume (3·10 ± 2·47 ml/m^2 vs. 1·39 ± 1·56 ml/m^2, $P < 0·001$) were larger and left atrial appendage ejection fraction (37·3 ± 19·1% vs. 57·1 ± 17·5%, $P < 0·001$) was lower than in the other 79 patients without paroxysmal atrial fibrillation. The optimal cutoff for left atrial appendage peak flow velocity to predict paroxysmal atrial fibrillation was 39·0 cm/s (sensitivity, 54·6%; specificity, 89·7%; c-statistic, 0·762). The cutoffs for left atrial appendage end-diastolic volume, end-systolic volume, and ejection fraction were 4·52 ml/m^2 (sensitivity, 47·8%; specificity, 82·3%; c-statistic, 0·694), 1·26 ml/m^2 (sensitivity, 91·3%; specificity, 60·3%; c-statistic, 0·806), and 47·9% (sensitivity, 78·3%; specificity, 74·7%; c-statistic, 0·774), respectively. In multivariate analysis, all these parameters were independently associated with paroxysmal atrial fibrillation after adjusting for sex, age, diabetes mellitus, and previous stroke.

Conclusions Left atrial appendage volumetric analysis by real-time three-dimensional transesophageal echocardiography is a promising method for detecting paroxysmal atrial fibrillation in acute cerebral infarction or transient ischemic attack.

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Key words: atrial fibrillation, ejection fraction, ischemic stroke, left atrial appendage, real-time three-dimensional transesophageal echocardiography, volume measurement

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is a major risk factor of ischemic stroke (1). Paroxysmal AF (PAF) has a similar risk of embolism compared with chronic AF (2). Therefore, the identification of hidden AF in acute cerebral infarction or transient ischemic attack (TIA) patients with normal sinus rhythm (NSR) on admission is important for preventing further brain ischemia. In previous reports, left atrial volume index/late diastolic peak tissue Doppler velocity on transthoracic echocardiography (3), or plasma brain natriuretic peptide levels on admission (4) were useful for ruling out or predicting PAF in patients with NSR on admission.

The left atrial appendage (LAA) is an important site of thrombus formation in patients with AF. Two-dimensional (2D) transesophageal echocardiography (TEE) has been widely used for characterizing LAA structure and function. Enlargement of the 2D area of LAA and decreased LAA flow velocity were reported to be associated with AF, spontaneous echo contrast, and thrombus formation (5–7). Moreover, in patients with PAF, LAA flow velocity was significantly decreased even if their electrocardiogram (ECG) showed NSR at the time of TEE (8).

Three-dimensional TEE (3D-TEE) has advantages for volumetric analysis because it allows rotation of heart structures and slicing the images in any plane to enable accurate visualization of the cardiac chambers. Recently, real-time (RT) 3D-TEE was developed to allow real-time acquisition and display of cardiac structures with high quality images (9) that correlate well with cardiac CT (10).

In previous reports on RT 3D-TEE, the volume of LAA was larger (11) and ejection fraction (EF) of LAA was lower in patient with AF (12). However, there is little information on volumetric analysis of the LAA and the utility of volume and function parameters derived from TEE in stroke patients. This study aimed to elucidate the association between volume of the LAA measured by RT 3D-TEE and the presence of PAF in patients with acute cerebral infarction or TIA.

Methods

Study subjects

We retrospectively analyzed data from prospectively collected consecutive acute stroke patients who were admitted to our facility and underwent RT 3D-TEE. Participants referred for RT 3D-TEE were diagnosed with acute cerebral infarction or TIA on admission.

They admitted principally within 14 days of symptom onset. Cerebral infarction was diagnosed by clinical course, neurological examinations, and CT or MRI. TIA was diagnosed based on the Classification of Cerebrovascular Diseases III from the National Institute of Neurological Disorders and Stroke (13). Clinical indication for TEE was made mainly for the detection of embolic sources by an independent attending physician. Two-dimensional and RT 3D-TEE were performed to assess any embolic sources such as intracardiac thrombus, right-to-left shunt, and complicated atherosclerotic changes of the aortic arch. Patients with an evident embolic source such as chronic AF, significant valvular heart disease, a prosthetic heart valve or mitral valve repair, or those with technically inadequate echocardiographic studies were excluded. Informed consent for RT 3D-TEE was obtained from all patients. The following information was obtained from the medical records of each patient: age, sex, vascular risk factors (systemic hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking), extracranial and intracranial large artery atherosclerosis defined as greater than 50% stenosis or occlusion, previous stroke, congestive heart failure, and the left atrial diameter (LAD) measured by transthoracic echocardiography. According to the Oxfordshire Community Stroke Project (OCSP) criteria, patients were classified from their clinical symptoms by two experienced neurologists into four categories, as having total anterior circulation stroke, partial anterior circulation stroke, posterior circulation stroke, or lacunar stroke. The neurologists were blinded to the neuroimaging and vascular imaging results.

The presence of PAF was defined as a history of PAF diagnosed previously or newly diagnosed by continuous ECG monitoring for at least several days after admission or 24-hour Holter ECG monitoring during hospitalization. Patients were allocated to a group with PAF (PAF group) or a group without PAF (non-PAF group). The diagnosis of PAF was based on a history of PAF or recurrent episodes of AF lasting for more than 30 s documented by continuous ECG monitoring or 24-hour Holter ECG monitoring. This study is a retrospective analysis of our prospective stroke registry and was approved by the institutional review committee at the National Cerebral and Cardiovascular Center.

Two- and three-dimensional transesophageal echocardiography

RT 3D-TEE was performed using a commercially available iE 33 Ultrasound machine and fully sampled X7-2t TEE transducer (Philips Medical Systems, Andover, MA, USA). Routine 2D TEE and RT 3D-TEE examinations were performed using the same transducer.

LAA flow velocity was measured by pulsed-wave Doppler echocardiographic interrogation at the orifice of the LAA. The presence of a patent foramen ovale based on the detection using saline contrast technique and atherosclerotic changes of the aorta were assessed with 2D TEE. Atherosclerotic changes of the aorta were defined as ≥4 mm thick, or with mobile components of plaques of the aorta. The scan volume was the wide-angled acquisition mode that included the LAA and surrounding structures acquired at the maximal frame rate. This 3D Full volume mode had high time resolution and provided ECG-gated acquisition of a large 3D volume created from subvolumes stitched together and synchronized to a single cardiac cycle. To avoid stitch artifacts, special care was taken to stabilize the probe during data acquisition. The acquisition was repeated whenever obvious artifacts were found. Images were reviewed online to ensure adequate 3D visualization of the LAA.

Three-dimensional data analysis

Images were digitally stored for subsequent offline analysis using QLAB 7·0 software (Philips Medical Systems). LAA volumes are measured using the multiplanar reconstruction mode of the General Imaging 3D Quantification plug-in to visualize LAA in the three different dimensions. Offline 3D analysis was performed by personnel who were blinded to the clinical information. The image was rotated in order to provide a long-axis view of the LAA (Fig. 1a) and to allow simultaneous visualization of the LAA orifice in the short-axis view (Fig. 1b). The LAA orifice was determined by two lines: one was drawn between the vestibule of the mitral valve annulus near the left coronary artery and the lateral ledge of the left superior pulmonary vein, and the other was drawn between a point near the aortic valve annulus and the left superior pulmonary vein limbus (11,14,15). Using the Stacked Contours mode in the software, a line was drawn from the LAA orifice to the apex, and then 15 short-axis multiplanar slices of the LAA from the orifice to the apex were automatically generated. By manual tracing the LAA contour in each slice (Fig. 1c), a virtual 3D image was automatically created from the stacking of multiple slices, and the volume of the LAA was calculated (Fig. 1d).

LAA end-diastolic volume was measured just before the *P* wave in the ECG and the end-systolic volume was measured at the QRS

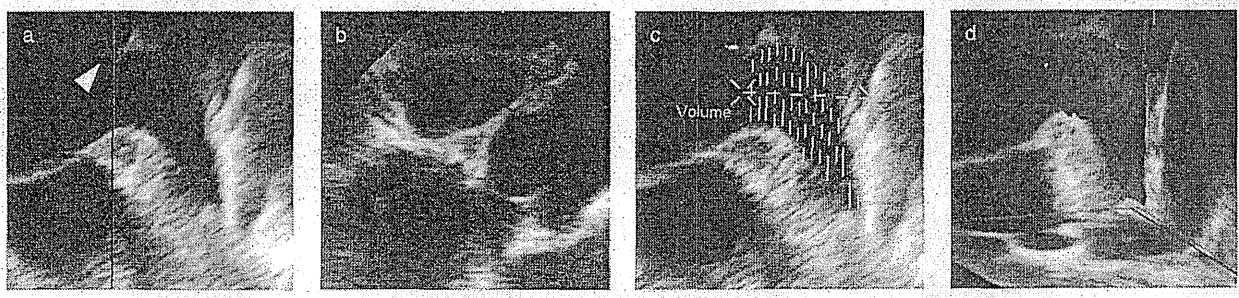

Fig. 1 Offline measurement of the left atrial appendage (LAA). (a) LAA long-axis view at the level of the mitral valve annulus, and lateral ridge of the left superior pulmonary vein (white arrowhead). (b) LAA orifice in the short-axis view. (c) The long-axis view of the LAA that results from the stacking of multiple short-axis segments. (d) By manually tracing the endocardial border of the individual short-axis segments, a virtual three-dimensional image of the LAA is obtained that can be used to calculate the LAA volume.

complex (5). Volumetric data were corrected by area of the body surface based on the Du Bois formula (end-diastolic volume index, end-systolic volume index). LAA-EF was calculated using the following equation: LAA-EF = [(end-diastolic volume – end-systolic volume) * 100]/end-diastolic volume (%).

Statistical analysis

Statistical analysis was performed using JMP 8·0 statistical software (SAS Institute Inc, Cary, NC, USA). Continuous data are expressed as mean ± standard deviation. Categorical data are presented as absolute numbers (percentages). Differences in continuous variables between two groups were assessed using a Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Differences in categorical variables between two groups were assessed using a chi-square test or Fisher's exact test, as appropriate. Observer variability was assessed by the coefficient of variation, and the concordance correlation coefficient for TEE-derived measurements repeating the analysis at least one-month later by the same observer who performed the first analysis and by a second independent blinded observer. Correlations between two variables were evaluated by linear regression analysis. To evaluate the ability of LAA flow velocity, end-diastolic volume index, end-systolic volume index, and LAA-EF to predict PAF, receiver operating characteristic (ROC) curves were constructed. The c-statistic (area under the ROC curve) was used as a scalar measure to assess the performance of each parameter. The c-statistics for different parameters were compared by a nonparametric method (16). To determine whether each TEE parameter was associated with PAF, multivariate logistic regression analysis was performed. The multivariate logistic regression model was adjusted for, age, sex, and variables with a probability value <0·1 in univariate analysis to assess the independent impact of each cutoffs of TEE parameter on PAF. Probability values <0·05 were considered significant.

Results

Between July 2010 and November 2012, a total of 150 patients were referred for RT 3D-TEE. Four patients were excluded because we were unable to insert a probe in two patients, and it was difficult to view the LAA in the other two patients. The remaining 146 patients underwent RT 3D-TEE without complications. Among them, 102 patients (73 men, mean age 72·2 ± 10·7 years) were in NSR at the time of TEE and were included in this study. The other 44 patients including 43 with chronic AF and 1 with a prosthetic mitral valve and AF at the TEE examination were excluded. Twenty-three patients were allocated to the PAF group, and 79 to the non-PAF group. The baseline characteristics of each group are listed in Table 1. Diabetes mellitus was less frequent in patients with than without PAF (4% vs. 25%, $P = 0·038$). OCSP categories were not different in the groups.

The intraobserver and interobserver correlation coefficients for LAA volume measurement were 0·900 and 0·861, respectively; and the interclass correlation coefficients were 0·891 and 0·847, respectively. The imaging characteristics derived from echocardiography are shown in Table 2. Patients with PAF tended to have larger LAD (39·3 ± 5·9 mm vs. 36·3 ± 7·7 mm, $P = 0·086$), lower LAA flow velocity (46·1 ± 27·3 cm/s vs. 66·3 ± 24·2 cm/s, $P < 0·001$), larger end-diastolic volume index (4·78 ± 3·00 ml/m^2 vs. 3·14 ± 2·04 ml/m^2, $P = 0·003$) and end-systolic volume index (3·10 ± 2·47 ml/m^2 vs. 1·39 ± 1·56 ml/m^2, $P < 0·001$), and lower LAA-EF (37·3 ± 19·1% vs. 57·1 ± 17·5%, $P < 0·001$) than those without PAF.

The correlations between each TEE parameter are shown in Fig 2. The end-diastolic volume index was strongly correlated with the end-systolic volume index, and was moderately correlated with the LAA flow velocity and LAA-EF.

ROC curve analysis showed that the optimal cutoff value of the LAA flow velocity to predict PAF was 39·0 cm/s, with a c-statistic

Table 1 Baseline clinical characteristics

Characteristics	Total (n = 102)	PAF (n = 23)	non-PAF (n = 79)	P value
Sex, men, n (%)	73 (72)	15 (65)	58 (73)	0·443
Age (years)	72·2 ± 10·7	73·7 ± 9·0	71·8 ± 11·2	0·654
Body surface area (m^2)	1·59 ± 0·17	1·59 ± 0·21	1·59 ± 0·16	0·935
Hypertension, n (%)	72 (71)	14 (61)	58 (73)	0·245
Diabetes mellitus, n (%)	21 (21)	1 (4)	20 (25)	0·038
Dyslipidemia, n (%)	58 (57)	12 (52)	46 (58)	0·606
Smoking, n (%)	20 (20)	3 (13)	17 (22)	0·368
Congestive heart failure, n (%)	6 (6)	1 (4)	5 (6)	0·772
Previous stoke, n (%)	26 (25)	2 (9)	24 (30)	0·054
Extracranial large artery atherosclerosis, n (%)	13 (13)	2 (9)	11 (14)	0·727
Intracranial large artery atherosclerosis, n (%)	29 (28)	8 (35)	21 (27)	0·443
Clinical subtypes				
Total anterior circulation stroke, n (%)	10 (10)	1 (4)	9 (11)	0·232
Partial anterior circulation stroke, n (%)	26 (25)	10 (43)	16 (20)	
Posterior circulation stroke, n (%)	27 (26)	5 (22)	22 (28)	
Lacunar stroke, n (%)	38 (37)	7 (30)	31 (39)	
Unclassified, n (%)	1 (1)	0 (0)	1 (1)	

Continuous values are reported as the mean ± SD. PAF, paroxysmal atrial fibrillation.

Table 2 Echocardiographic parameters

Characteristics	Total (n = 102)	PAF (n = 23)	non-PAF (n = 79)	P value
Left atrial diameter (mm)	37·0 ± 7·5	39·3 ± 5·9	36·3 ± 7·7	0·086
*Patent foramen ovale, n (%)	36 (41)	3 (23)	33 (44)	0·225
Atherosclerotic changes at the aorta, n (%)	37 (36)	6 (26)	31 (39)	0·327
LAA flow velocity (cm/s)	61·8 ± 26·1	46·1 ± 27·3	66·3 ± 24·2	<0·001
End diastolic volume (ml)	5·52 ± 3·68	7·98 ± 5·16	4·90 ± 2·93	0·006
End-diastolic volume index (ml/m²)	3·51 ± 2·38	4·78 ± 3·00	3·14 ± 2·04	0·003
End-systolic volume (ml)	2·78 ± 2·98	5·00 ± 4·14	2·13 ± 2·18	<0·001
End-systolic volume index (ml/m²)	1·78 ± 1·93	3·10 ± 2·47	1·39 ± 1·56	<0·001
LAA-EF (%)	52·6 ± 19·6	37·3 ± 19·1	57·1 ± 17·5	<0·001

*Data on patent foramen ovale was available in 13 patients of the PAF group and 75 of the non-PAF group.
Continuous values are reported as the mean ± SD. PAF, paroxysmal atrial fibrillation; LAA, left atrial appendage; EF, ejection fraction.

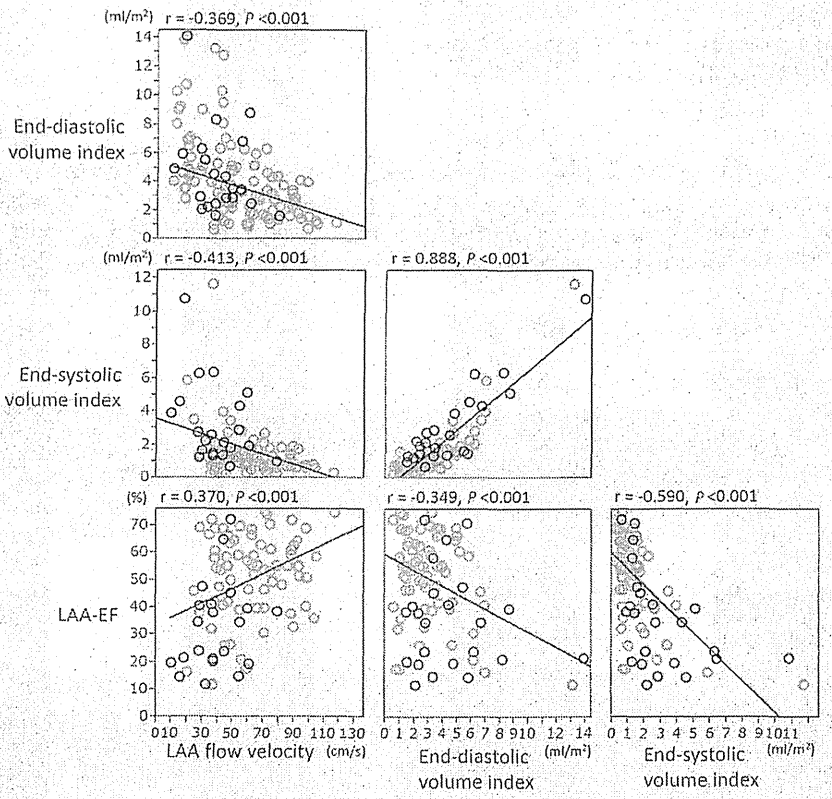

Fig. 2 Relations between transesophageal echocardiographic parameters. Regression lines among all subjects are shown. Black open circles = patients with paroxysmal atrial fibrillation (AF); Gray open circles = patients without AF.

of 0·762. The cutoff values of the end-diastolic volume index and the end-systolic volume index were 4·52 ml/m² and 1·26 ml/m², with c-statistics of 0·694 and 0·806, respectively. The cutoff of LAA-EF was 47·9%, with a c-statistic of 0·774 (Table 3, Fig. 3). There was a significant difference in the c-statistics among the four TEE-derived parameters (P = 0·007), and the end-systolic volume index was superior to the end-diastolic volume index for predicting PAF (P = 0·007).

In multivariate analysis, the LAA flow velocity ≤39·0 cm/s (odds ratio 12·91, 95% CI 3·70–53·90), the end-diastolic volume index ≥4·52 ml/m² (odds ratio 4·03, 95% CI 1·36–12·44), the end-systolic volume index ≥1·26 ml/m² (odds ratio 13·37, 95% CI 3·40–89·75), and LAA-EF ≤47·9% (odds ratio 10·02, 95% CI 3·33–35·34) were independently associated with PAF after adjusting for age, sex, and a history of diabetes mellitus, and previous stroke (Table 4).

Discussion

In this study, we determined the association between LAA volumetric parameters assessed by RT 3D-TEE and PAF in patients with acute cerebral infarction or TIA. This is the first report to show the association between LAA volumetric parameters and the presence of PAF in patients with acute stroke, although some 2D

Table 3 Receiver-operating-characteristic curve analysis of 3D-TEE parameters for predicting PAF

Variable	c-Statistic (95% CI)	Optimal cutoff	Sensitivity	Specificity	PPV	NPV
LAA flow velocity (cm/s)	0·762 (0·622–0·862)	≤39·0	54·6	89·7	60·0	87·5
End-diastolic volume index (ml/m²)	0·694 (0·565–0·798)	≥4·52	47·8	82·3	44·0	84·4
End-systolic volume index (ml/m²)	0·806 (0·696–0·883)	≥1·26	91·3	60·3	40·4	96·0
LAA-EF (%)	0·774 (0·635–0·871)	≤47·9	78·3	74·7	47·3	92·2

3D-TEE, three dimensional transesophageal echocardiography; CI, confidence interval; EF, ejection fraction; LAA, left atrial appendage; NPV, negative predictive value; PAF, paroxysmal atrial fibrillation; PPV, positive predictive value.

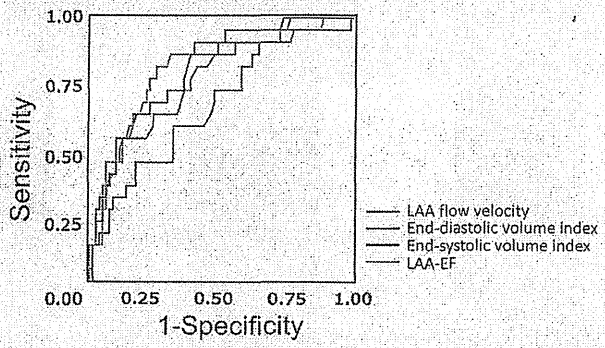

Fig. 3 Receiver operating characteristic curves comparing transesophageal echocardiographic parameters for the prediction of paroxysmal atrial fibrillation. Curves are shown for the left atrial appendage (LAA) flow velocity, end-diastolic volume index, end-systolic volume index, and LAA ejection fraction (EF).

Table 4 Multivariate logistic regression analysis of 3D-TEE parameters for predicting PAF

Variable	Odds ratio (95% CI)	*P* value
LAA flow velocity ≤39·0 cm/s	12·91 (3·70–53·90)	<0·001
End-diastolic volume index ≥4·52 ml/m²	4·03 (1·36–12·44)	0·010
End-systolic volume index ≥1·26 ml/m²	13·37 (3·40–89·75)	<0·001
LAA-EF ≤47·9%	10·02 (3·33–35·34)	<0·001

The regression model was adjusted for age, sex, diabetes mellitus, and previous stroke. 3D-TEE, three-dimensional transesophageal echocardiography; CI, confidence interval; EF, ejection fraction; LAA, left atrial appendage; PAF, paroxysmal atrial fibrillation.

parameters on LAA are known predictors for PAF. The first major finding was that LAA volumetric parameters as well as low LAA flow velocity were independently associated with the presence of PAF. The second finding was that not only a large LAA volume but also reduced EF was significantly associated with PAF. Third, the LAA end-systolic volume seems to be superior to the end-diastolic volume for detecting PAF in acute stroke patients. Finally, the intraobserver and interobserver variabilities for LAA volume assessment were excellent.

A large LAA volume, low EF and low flow velocity were independently associated with the presence of PAF in patients with acute cerebral infarction or TIA in the present study. Taguchi *et al.* (8) reported a significant difference in the LAA flow velocity between acute stroke patients with and without PAF (34·7 ± 9·3 cm/s vs. 64·0 ± 12·1 cm/s). In 2D- and 3D-TEE in patients without stroke, a large 2D LAA area (5) and large 3D LAA volume (11) were found to be significantly association with the presence of AF. Nucifora *et al.* (17) reported a progressive increase in LAA orifice size on RT 3D-TEE with an increasing frequency of AF in patients that were candidates for LAA closure endotherapy. Recently, Shimizu *et al.* (18) reported the correlation between LAA-EF derived from 2D-TEE area measurement and PAF in acute stroke patients. In their report, LAA-EF could predict PAF more accurate than the LAA flow velocity. There are several reports regarding LAA volumetric comparison between patients with AF and those with NSR in the absence of stroke (11,19). Chen *et al.* (12) reported lower LAA-EF in 62 patients with AF (24 ± 14%) than that in 34 with NSR (38 ± 17%, $P < 0·01$). Their LAA-EF value in patients with NSR was relatively low compared with ours (57·1 ± 17·5%). This difference is most likely due to the time resolution of 3D image acquisition. Compared with the 3D Zoom mode, the 3D Full volume mode provides higher time resolution and allows more accurate measurements of the end-diastolic and end-systolic volumes, and LAA-EF based on the ECG.

After spontaneous conversion of AF, diminishment of LAA function was reported as LAA 'stunning' (20). The persistence of AF produces changes in atrial function and structure, electrical remodeling, structural remodeling and contractile remodeling as there is reduced contraction and dilatation of the left atrium (21). The end-systolic volume appeared to be most sensitive parameter to detect contractile remodeling, since it reflects systolic dysfunction of a dilated LAA in patients with PAF, even if they return to NSR. Although LAA-EF and the LAA flow velocity are widely used to evaluate contractile function, they might not be appropriate for detecting volume enlargement of LAA. In contrast, the end-diastolic volume directly reflects volume enlargement, but is not useful to evaluate contraction of LAA. The end-systolic volume appears to indicate both volume enlargement and reduced contraction of LAA. However, a direct comparison of these parameters in multivariate analysis is difficult because of the strong correlations.

Our method is feasible for the measurement of LAA volume because of low interobserver and intraobserver variability. In order to analyze LAA volumes precisely based on the ECG, we investigated only patients with NSR at the time of TEE. We used the 3D Full volume mode, and this mode can be used only in patients with a regular cardiac rhythm. This mode provides 3D images with adequate width and depth and has high time resolution. On the other hand, the 3D Zoom mode is commonly used

for patients in AF. The time resolution of the routine 3D Zoom mode is reduced by increasing the area of interest. Because ECG gating is not applicable with the 3D Zoom mode, ECG-based analysis with reduced time resolution may be unreliable. LAA flow velocity can be measured easily by 2D-TEE; however, LAA flow velocity was reported to vary about 1·5 times from the measurement site of the LAA orifice or apex (22). In contrast, our LAA volumetric evaluation with high time resolution seems to be consistent and reproducible. Classification of LAA morphology may also enable us to assess the risk of ischemic stroke, but it is still controversial (23,24).

This study had several limitations and our results could not be readily compared with previous reports. First, there was a risk of statistical error because of the small number of patients. Second, this study was not performed for all the consecutive stroke patients, because TEE is an invasive procedure and is not well-tolerated in patients with a poor general condition. Therefore there may be a selection bias. Third, continuous ECG monitoring and 24-hour Holter ECG monitoring during hospitalization might have failed to detect PAF. This leaves the possibility that PAF may be present in some of patients in the non-PAF group. Longer ECG monitoring, such as 7-day Holter ECG monitoring and outpatient telemetry monitoring (25,26), might have improved PAF detection and that may enable for further assessment of the correlations between TEE parameters and duration or frequency of PAF. Fourth, echocardiographic parameters in patients with PAF would not be different from those without PAF if we underwent TEE without recent PAF-attack because of the lack of a recovery effect from LAA stunning. A large prospective cohort study is needed to confirm the association between the LAA volumetric parameters and PAF in patients with acute cerebral infarction or TIA.

Conclusions

LAA function appeared to be impaired in patients with PAF, even though RT 3D-TEE was performed during NSR. Three-dimensional analysis of the LAA is a promising method for detecting PAF in patients with acute cerebral infarction or TIA.

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Factors Associated with Proximal Carotid Axis Occlusion in Patients with Acute Stroke and Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) are more likely to exhibit proximal carotid axis occlusion than those without AF. However, clinical characteristics associated with proximal arterial occlusion (PAO) in acute stroke patients with AF are not fully known. This study was aimed to elucidate the factors correlated with PAO. *Methods:* Consecutive patients with acute ischemic stroke developed in the middle cerebral artery (MCA) territory and AF who underwent magnetic resonance angiography (MRA) within 24 h from onset were retrospectively enrolled. Prior users of warfarin were excluded. Patients were divided into 3 groups based on the site of arterial occlusion: occlusion at the internal carotid artery (ICA), at the horizontal segment of the MCA (M1), and at the MCA branch or no identifiable occlusion. Clinical characteristics were compared between the 3 groups, and the factors associated with proximal vessel occlusion were evaluated with ordinal logistic regression analysis. All variables identified on univariable analyses with *P* values less than .1 were entered into the model. *Results:* A total of 244 patients (124 women, median 80 years old [interquartile range 72-87], median National Institutes of Health Stroke Scale [NIHSS] score 16 [7-22]) were studied. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Occlusion site was the ICA in 34 patients, M1 in 78, and MCA branch or no occlusion in the remaining 132. As the occlusion site was more proximal, patients were older and more female, the initial NIHSS score was higher, levels of D-dimer and brain natriuretic peptide (BNP) were higher, and histories of heart failure and systemic embolism were more common. On multivariable ordinal logistic regression analysis, female sex (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.03-3.26), advanced age (OR 1.37, 95% CI 1.02-1.84 for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75), and higher BNP level (OR 1.03, 95% CI 1.01-1.07 for every 100 pg/mL) were independent factors associated with the risk of occlusion at more proximal arteries. The risk was 2.68-fold higher (95% CI 1.28-5.61) in patients having 2 of the following factors: female sex, age more than 80 years, systemic embolism, and BNP greater than 250 pg/mL; and 4.50-fold (2.11-9.59) higher in those having 3 or 4 of the 4 factors compared with those without any of these factors. *Conclusions:* Female sex, advanced age, history of systemic embolism, and higher BNP level were independently associated with more proximal carotid axis occlusion. Patients with AF having

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Disclosures None.

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these factors may be prone to have relatively large thrombi in the heart. **Key Words:** Acute ischemic stroke—magnetic resonance angiography—atrial fibrillation—arterial occlusion.

Introduction

The site of arterial occlusion plays a key role in neurologic severity and outcome in patients with acute ischemic stroke. Patients with proximal arterial occlusion (PAO) show more severe symptoms,[1,2] poorer outcomes,[3] and more limited response to intravenous tissue plasminogen activator therapy than those with distal artery occlusion.[4,5] The factors associated with PAO are not fully known, and related factors are considered to differ according to the etiologies. Embolic PAO seems to be correlated with embolus size. Patients with atrial fibrillation (AF) often develop severe ischemic stroke and poor outcomes,[6,7] even after thrombolytic therapy,[8] mainly because they are more likely to have PAO on admission than patients without AF.[8] However, clinical factors associated with PAO in patients with AF are not well known.

The aim of this study was to clarify the clinical characteristics related to PAO in acute stroke patients with AF.

Methods

A prospective database of consecutive patients with acute stroke treated in the Stroke Care Unit in the National Cerebral and Cardiovascular Center was created (National Cerebral and Cardiovascular Center Stroke Registry).[9] From April 2006 to May 2012, consecutive acute stroke patients (<24 h from onset) with AF who fulfilled the following criteria were retrospectively enrolled from the registry: (1) underwent magnetic resonance imaging (MRI) examinations including diffusion-weighted imaging (DWI) and time-of-flight magnetic resonance angiography (MRA) on admission and (2) developed ischemic stroke in the middle cerebral artery (MCA) territory confirmed on initial DWI with compatible acute neurologic deficits. Patients with contraindications to MRI (eg, cardiac pacemakers or mechanical heart valve replacements) were excluded. Stroke patients having concomitant etiology other than AF (eg, >50% stenosis on the responsible artery) and patients on anticoagulant therapy were also excluded because anticoagulant therapy could reduce intracardiac thrombi and then affect the site of arterial occlusion in subjects with AF.[10] The institutional ethics committee approved this study.

Clinical Background Characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and medical history, were obtained on admission. Cardiovascular risk factors were defined as: (1) hypertension, history of using antihypertensive agents, systolic blood pressure of 140 mm Hg or more, or diastolic blood pressure of 90 mm Hg or more before or 2 or more weeks after stroke onset; (2) diabetes mellitus, use of hypoglycemic agents, random glucose level of 200 mg/dL or more, or glycosylated hemoglobin of 6.5% or more on admission; (3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level of 220 mg/dL or more; and (4) current smoking habit. Routine blood biochemistry examinations were performed on admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcome was estimated by the modified Rankin scale[11] score at hospital discharge or 30 days from onset. AF was diagnosed on 12-lead electrocardiogram or a history of AF was confirmed.

Neuroimaging

MRI studies including DWI and time-of-flight MRA were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Siemens MAGNETOM Vision or MAGNETOM Sonata scanner, Erlangen, Germany). DWI was obtained using the following parameters: repetition time/echo time, 4000/100 ms; *b* values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 96 × 128; and slice thickness, 4.0 mm, with a 1.0-mm intersection gap. The occluded vessel was determined on initial MRA. All patients were divided into 3 groups based on the occluded site: at the internal carotid artery (ICA) group, at the MCA horizontal segment (M1 group), and at the MCA branch occlusion or no identifiable occlusion (Branch group).

Statistical Analysis

First, clinical background characteristics were compared among the 3 groups. Univariable analyses were performed using the chi-square test, Fisher exact test, or the Kruskal–Wallis test, as appropriate. The data are presented as median values (interquartile range) or frequencies (%). Next, multivariable ordinal logistic regression analysis was performed to identify independent factors associated with more proximal arterial occlusion. This model allows the outcome variable to have more than 2 categories and estimates a proportional odds ratio (OR) for each predictor of shifting to a more proximal arterial occlusion category (eg, the ICA group versus the M1 and Distal groups or the ICA and M1 groups versus the Distal group). Sex, age, and all clinical characteristics identified on univariable analyses with *P* values less

than .1 were entered into the model. Receiver operating characteristic (ROC) curve analyses were conducted to obtain the practical cutoff value of continuous variables. All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL). Results were considered significant at P less than .05.

Results

Overall, 503 patients with both acute ischemic stroke and AF were admitted to our stroke center during the study period. Of these, 61 patients were excluded because of absent or incomplete MRI, 29 were excluded because the site of the index stroke was outside the MCA territory, 14 were excluded because of concomitant etiology, and 155 were excluded for taking prestroke anticoagulant therapy. Finally, 244 patients (124 women, median age 80 [interquartile range 72-87] years, median NIHSS score 16 [7-22]) were enrolled in the present study.

Table 1 shows the clinical background characteristics of the included patients. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Of the 244 patients, 34 (14%) had ICA occlusion (ICA group), 78 (32%) had M1 occlusion (M1 group), and 132 (54%) had MCA branch occlusion or no arterial occlusion (Branch group) on initial MRA. As the occlusion site was more proximal, patients were older ($P < .001$), the initial NIHSS score was higher ($P < .001$), levels of D-dimer ($P = .002$) and brain natriuretic peptide (BNP, $P = .029$) were higher, and female sex ($P = .004$) and histories of heart failure ($P = .047$) and systemic embolism ($P = .001$) were more common.

The results of multivariable ordinal logistic regression analysis are shown in Table 2. Female sex (OR 1.83, 95% confidence interval [CI] 1.03-3.26, $P = .039$), advanced age (OR 1.37, 95% CI 1.02-1.84, $P = .037$ for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75, $P = .025$), and higher BNP level (OR 1.03, 95% CI 1.01-1.07, $P = .048$ for every 100 pg/mL) were independent factors associated with increased risk of more proximal arterial occlusion. The practical cutoff values for age and BNP to predict ICA or M1 occlusion were 80 years (sensitivity, 57%; specificity, 64%; area under the ROC curve, .645) and 250 pg/mL (sensitivity, 57%; specificity, 61%; area under the ROC curve, .578), respectively. Having more of the following 4 factors, female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL was also independently related to more proximal arterial occlusion ($P = .001$, chi-square test, Fig 1). The risk of more proximal arterial occlusion was 2.68-fold higher (95% CI 1.28-5.61) in patients having

Table 1. *Clinical background characteristics*

Variables	Total, n = 244	ICA group, n = 34	M1 group, n = 78	Distal group, n = 132	P
Female sex, n (%)	124 (51)	24 (71)	45 (58)	55 (42)	.004
Age, y, median (IQR)	80 (72-87)	85 (74-88)	82 (74-89)	79 (69-84)	<.001
Onset to MRI, h, median (IQR)	2.7 (1.5-8.9)	2.3 (1.7-6.6)	2.4 (1.4-4.8)	3.8 (1.6-11.4)	.193
Vascular risk factors, n (%)					
Hypertension	171 (70)	24 (71)	52 (68)	95 (72)	.794
Diabetes mellitus	34 (14)	4 (12)	8 (10)	22 (17)	.400
Hyperlipidemia	62 (25)	8 (24)	18 (23)	36 (27)	.768
Current smoking	43 (18)	5 (15)	10 (13)	28 (21)	.286
History, n (%)					
Ischemic stroke	53 (22)	8 (24)	16 (21)	29 (22)	.934
Hemorrhagic stroke	10 (4)	1 (3)	2 (3)	7 (5)	.586
Ischemic heart disease	21 (9)	4 (12)	7 (9)	10 (8)	.732
Heart failure	44 (18)	10 (29)	17 (22)	17 (13)	.047
Peripheral artery disease	10 (4)	2 (6)	2 (3)	6 (5)	.662
Systemic embolism	4 (2)	3 (9)	1 (1)	0 (0)	.001
Prior antiplatelet therapy, n (%)	99 (41)	12 (35)	29 (37)	58 (44)	.500
Initial NIHSS score, median (IQR)	16 (7-22)	22 (18-26)	18 (16-23)	10 (4-17)	<.001
Biochemistry sign at admission, median (IQR)					
Leukocyte count, /μL	6700 (5400-8900)	6700 (4800-9300)	7100 (5600-8600)	6400 (5500-8900)	.580
Blood glucose, mg/dL	124 (107-152)	126 (109-152)	129 (109-152)	119 (106-153)	.467
Total cholesterol, mg/dL	182 (161-206)	172 (164-202)	176 (155-204)	186 (167-211)	.191
D-dimer, μg/mL	2.1 (1.4-3.3)	2.6 (2.0-3.1)	2.1 (1.4-3.5)	1.8 (1.2-3.3)	.002
Brain natriuretic peptide, pg/mL	236 (127-437)	340 (197-666)	266 (130-409)	215 (104-409)	.029

Abbreviations: Distal group: patients with more distal occlusion or no identifiable occlusion; ICA group: patients with internal carotid artery occlusion; IQR, interquartile region; M1 group: patients with middle cerebral artery horizontal segment occlusion; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

Table 2. *Result of multivariate ordinal logistic regression analysis for factors associated with larger vessel occlusion*

Variables	OR	95% CI	*P*
Female sex	1.83	1.03-3.26	.039
Age (for every 10 y)	1.37	1.02-1.84	.037
History of heart failure	1.11	.54-2.28	.773
History of systemic embolism	14.9	1.41-158	.025
D-dimer (for every 1.0 μg/mL)	1.01	.91-1.11	.887
BNP (for every 100 pg/mL)	1.03	1.01-1.07	.048

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio.

2 of the above 4 factors, and 4.50-fold (95% CI 2.11-9.59) higher in those with 3 or 4 of the 4 factors compared with those without any of these factors on ordinal logistic regression analysis (Fig 2).

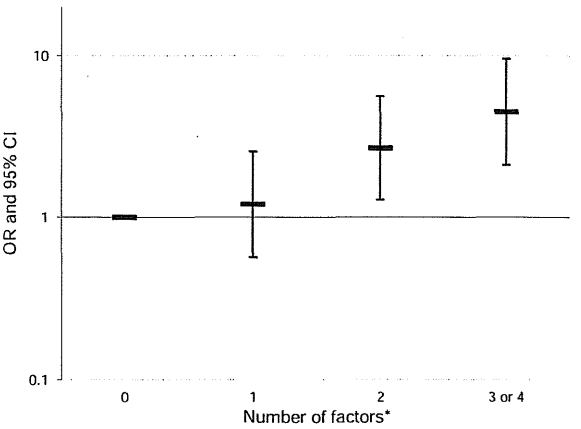

Figure 2. *OR and 95% CI of the risk of more proximal arterial occlusion according to the number of factors independently associated with larger arterial occlusion on ordinal logistic regression analysis. Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

Discussion

The first major finding of the present study was that 46% of the patients with both acute ischemic stroke and AF without prior anticoagulant therapy had ICA or M1 occlusion on initial MRA. This percentage was between that of patients within 3 h from onset (75%)[8] and that of patients within 7 days from onset (33%)[12] because the percentage decreases with spontaneous recanalization as onset-to-imaging time increases.[13]

The second major finding was that female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with the risk of more proximal arterial occlusion. In addition, coexistence of 2 or more of these 4 factors clearly increased the risk. This finding is partly in line with the previous reports that showed that advanced age,[14-16] history of systemic embolism,[17] and elevated BNP level[18] were correlated with the presence of intracardiac thrombi in AF patients. However, there is no study investigating the relationships between intracardiac clot size and patients' characteristics. It is possible that a prothrombotic state and large intracardiac thrombi are induced by these factors and cause PAO.

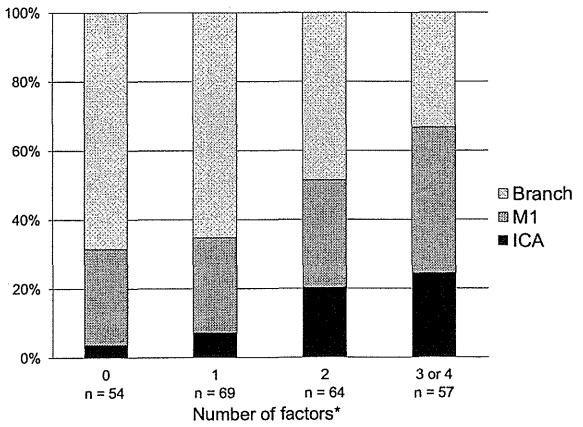

Figure 1. *The site of arterial occlusion based on the number of factors independently associated with larger arterial occlusion. Abbreviations: BNP, brain natriuretic peptide; Branch, middle cerebral artery branch or no identifiable occlusion; ICA, internal carotid artery; M1, middle cerebral artery horizontal segment. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

The female hormone, estrogen, increases fibrinolytic potential[19] and accelerates the recovery of injured endothelial cells.[20] Estrogen production is reduced after menopause, and elderly women with AF have a higher clot formation marker level[21] and worse outcomes after stroke[12] than men. Most women in the present study were considered to be postmenopausal because the median age of the included women was 84 years.

Advanced age may represent a longer period with a pathologic condition, such as hypertension, heart failure, and AF. Prolonged exposure to these pathologic conditions leads to cardiac remodeling, including left atrial enlargement and reduced atrial contractility.[22-24] This remodeling causes blood stasis in the left atrium and left atrial appendage and could contribute to form large thrombi. Furthermore, advanced age itself may be associated with a prothrombotic state.[25]

BNP is proven to be well correlated with heart failure,[26] though a high BNP level remained an independent predictor for PAO in the present patients using the regression model containing both heart failure and BNP as variables. The association of BNP with PAO independently from heart failure was because a high BNP level also stands for high left ventricular filling pressure,[27] which leads to left atrial enlargement[28] and left atrial appendage dysfunction[29]; all these cause formation of large thrombi. A history of systemic embolism may also indicate that the patients were prothrombotic.

This study had some limitations. First, the retrospective design might have contributed to some selection bias. Second, PAO might be overestimated because distal arterial occlusion and slow flow velocity in the proximal arteries are sometimes difficult to distinguish from PAO on MRA. On the other hand, the inclusion criteria of less than 24 h of onset might lead underestimation of the presence of PAO because of spontaneous recanalization, despite the MRI examinations were performed 2.7 h (median) from onset in the present study. Third, only the internal validity of the present results was assessed. The present findings should be confirmed with a prospective cohort.

In conclusion, nearly half of acute stroke patients with AF who did not receive anticoagulant therapy had ICA or MCA horizontal segment occlusion. Female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with PAO. Patients having these factors may be prone to having larger thrombi in the heart than those without these factors.

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1. 脳

10. 欧州血管外科学会ガイドライン 頸動脈狭窄に対する外科的治療：適応と技法

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出典
Liapis CD, et al：
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Eur J Vasc Endovasc Surg 37（4 Suppl）：1-19, 2009

要　約

はじめに

本ガイドラインは，頸動脈狭窄に対する外科的治療に焦点を絞り，最新の知見に基づき要点をまとめたものである．頸動脈病変の専門医家が頸動脈狭窄症例に対する日常臨床の中で必要な多くの情報を得られるだけでなく，他領域を専門とする医師・プライマリケア医にとっては患者紹介の手引きとなったり，さまざまな治療選択肢の期待される結果を知り得るものとなっている．

推奨度はエビデンスの質により，下記のように分類されている．

グレードA：質の高い無作為化対照比較試験に基づく推奨

グレードB：良くデザインされているが無作為化ではない臨床試験に基づく推奨

グレードC：専門家の報告・意見・経験に基づく推奨

A. 適応について

頸動脈狭窄に対する外科的治療の適応について，下記の5つの観点を考慮すべきである：神経学的症候学，頸動脈狭窄度，併存症，血管と局所の解剖学的特徴，プラーク組織性状診断．

A1　神経学的症候学と頸動脈狭窄度

多くのRCTにおいて，過去6ヵ月以内に頸動脈支配領域の一過性脳虚血発作あるいは機能障害を残さない脳梗塞を起こした症例が症候性とみなされている．狭窄率に関しては，NASCET（North American Symptomatic Carotid Endarterectomy Trial）[1] criteriaが広く用いられている（図1）．

A1.1　頸動脈内膜剥離術（Carotid Endarterectomy：CEA）に関して

NASCET狭窄率70%を超える症候性頸動脈狭窄に対しては手術的治療の絶対適応である．NASCET狭窄率50～70%の症候性頸動脈狭窄に対しては，手術的治療を考慮する［グレードA］．周術期の脳卒中/死亡合併症が6%未満でなければならない［グレードA］．50%未満の症候性頸動脈狭窄に対してはCEAは非適応である［グレードA］．CEAは最終虚血発作より2週間以内に施行されるべきである［グレードA］．狭窄率が70-99%の無症候性頸動脈狭窄に関しては，75歳未満の男性で，周術期の脳卒中/死亡合併症が3%未満であればCEAが勧められる［グレードA］．女性の無症候性頸動脈狭窄に対するCEAは，男性に比べて有用性が低い［グレードA］．若く健康な女性の場合にのみCEA

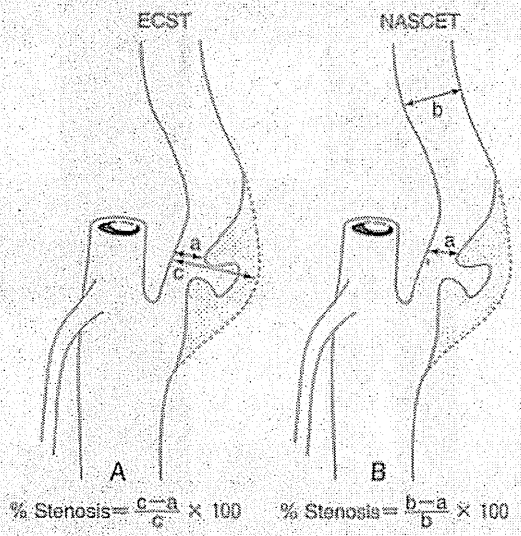

図1　NASCET，ECSTの狭窄率測定法
NASCET criteriaの狭窄率70%はECST criteriaの狭窄率83%に相当する

を考慮すべきである［グレードA］．

A1.2　症候性頸動脈狭窄に対する頸動脈ステント留置術(Carotid Artery Stenting：CAS)に関して

現在得られているレベルⅠエビデンスから，症候性患者に対しては外科手術(CEA)が最良の治療選択肢である［グレードA］．CASの中期的な脳卒中予防効果は，CEAと同程度である［グレードA］．CASは，CEAハイリスクの症候性頸動脈狭窄症例であれば，周術期脳卒中/死亡合併症率が低い(＜6%)治療経験が豊富なハイボリュームセンターにおいて，あるいはRCTにおいて提供されるべきである［グレードC］．症候性頸動脈狭窄に対するCASの役割を確立するためには，周術期と長期的な予後に関するエビデンスがさらに必要である．

A1.3　無症候性頸動脈狭窄に対するCASに関して

無症候性頸動脈狭窄に対するCASは，周術期脳卒中/死亡合併症率が低い(＜3%)治療経験が豊富なハイボリュームセンターにおいて，あるいは良くデザインされた臨床試験においてのみ勧められる治療である［グレードC］．無症候性頸動脈狭窄に対するCASの有用性については依然として論証が必要である．

A1.4　症候と狭窄率に関して．CASの適応はCEAと同じか？

CEAの適応である(症候性で50%を超える，あるいは無症候性で70%を超える)頸動脈狭窄症例を同様にCASの適応とすべきかどうかについては検証されていない．症候性・無症候性いずれについても，CASの適応となる狭窄度の明確な閾値に関する無作為化されたエビデンスはない．

A2　併存症と高リスク患者

NASCET/ACAS (Asymptomatic Carotid Atherosclerosis Study)[2]の除外基準が高リスクと見なされる．SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy)[3]試験の高リスク群は下記のうち1つの臨床的特徴を持つものである：NYHAクラスⅢ/Ⅳのうっ血性心不全，6週間以内の開心術，最近の心筋梗塞既往，不安定狭心症，重症肺疾患．

高リスク患者に対するCEAは，心イベント，脳卒中，死亡合併症が許容される基準以下であれば施行しても良い［グレードB］．特に高リスクな無症候性頸動脈狭窄症例に関しては，最良の内科的治療が侵襲的治療に取って代わり最も良い治療選択肢となる［グレードC］．80歳以上の高齢者においてCASは遠位塞栓の高リスクと関連する［グレードB］．80歳以上の高齢者におけるCEAは，遠位塞栓のリスクを増加させることはなく，神経学的イベント・心イベントについては認容できる発生率である［グレードC］．CASは高リスクの無症候性頸動脈狭窄症例で周術期合併症の発生率が3%を超えるならば勧められない［グレードC］．

A3　血管と局所の解剖学的特徴

対側の喉頭神経麻痺のある症例，根治的頸部郭清術の既往，頸部放射線照射歴，CEA後再狭窄，高位病変や頭側方向への狭窄進展病変においてはCEAの合併症が認容できる発症率よりも高いため，CASの適応である［グレードC］．大動脈や

大動脈分枝血管に著明なプラークや高度石灰化を有する症例や，非常に蛇行の強い血管に対するCASは，周術期脳卒中・死亡合併症率が低い，治療経験が豊富なハイボリュームセンター以外では勧められない［グレードC］．

A4 プラーク組織性状診断とCAS中の遠位塞栓リスク

すべての症例で術前にプラーク組織診断を行うべきである［グレードB］．画像評価（gray-scale median：GSM，など）あるいはバイオマーカーのような他の診断技術を用いて周術期塞栓リスクのあるプラークかどうか同定しておかなければならない［グレードC］．血管内治療時に使用する脳保護デバイスは，術後の遅発性塞栓症を予防できない．塞栓リスクの低いプラークを選別することが遅発性合併症の減少に必要不可欠である．テーパード型ステントとストレート型ステント，オープンセルステントとクローズドセルステント，いずれの種類のステントが神経学的合併症の減少において優れているかを示した無作為試験はない．

B. 手技について

B1 CEAの手技

B1.1 シャントについて

CEAの際にルーチンでシャントを使用した方が良いという明確なエビデンスはない［グレードA］．CEAの際にルーチンで，あるいは症例を選択してシャントを使用することを指示する，あるいは否定するのに十分な無作為比較試験からのエビデンスは存在しない．

B1.2，B1.3 パッチによる血管形成と1次閉創

頸動脈パッチによる血管形成は，脳卒中・死亡，ならびに再狭窄・閉塞のリスクを減少させる［グレードA］．パッチの素材の違いによる影響は少なく，明確な結論を得るためにはより多くのデータが必要である．

B1.4 内膜剥離手技の違い

従来のCEAは，動脈縦切開によって実施される．外転CEAでは動脈横切開と頸動脈の再移植が用いられ，周術期の脳卒中および再狭窄の発現率が低下すると報告されているが，遠位動脈内膜弁に伴う合併症のリスクが上昇する．CEA手技の選択は個々の外科医の経験と熟達度によって決定されるべきである［グレードA］．

B1.5 局所麻酔 vs 全身麻酔

局所麻酔，全身麻酔いずれも安全である．麻酔医および外科医は，患者と相談し，麻酔の方法を決定すべきである．特に対側頸動脈閉塞のある患者については，局所麻酔は利点がある［グレードA］．

B1.6 質の管理

手術終了時にエコーあるいは血管造影による評価が望ましい［グレードB］．

B1.7 周術期の薬物療法

術前から術後まで，75-325 mg/日のアスピリンとスタチンの組み合わせが投与されるべきである［グレードA］．クロピドグレルの有用性についてはより多くの無作為試験のデータが必要である．

B2 CASの手技

B2.1 はじめに

この項では，CASの基本的手技と合併症について述べている．また，周術期の合併症に影響する因子を明らかにすることを目的としている．手技にはさまざまなバリエーションがあり，手技を規定するものではない．

B2.2 基本手技

CASの施行は学際的多職種チームによって決定されるべきである．危険因子の管理がなされ，通常，二重抗血小板療法を行うべきである．アクセスに関しては総大腿動脈アプローチが典型的であるが，頸動脈直接穿刺や上腕動脈アプローチがなされることもある．5,000-7,500国際単位のヘパリンを投与し，ACTを正常の2倍になるよう管理する．ロングシースかガイディングカテーテルを頸動脈分岐下に留置する．多くのケースでは，脳保護器具がこの段階で使用される：近位側閉塞（血管内閉塞や血流逆転），遠位側バルーン閉塞，あるいはフィルター．頸動脈洞圧受容体刺激による徐脈・低血圧を予防するため，アトロピン0.6-1.2 mgあるいはグリコピロレート0.6 mgを投与する．高度狭窄例ではステント留置を容易にするために前拡張を行う．病変を完全に覆うように自己拡張型ステントを留置する．バルーン拡張型ステントはプラーク圧壊による血管閉塞の危険があるため現在は使用されない．自己拡張型ステントはいずれの型にも優劣は示されていない．続いて，後拡張を施行する．遠位塞栓を予防するためには，控えめの拡張が推奨され

る．最後に，脳保護デバイスを回収する．安静時間の短縮のため，しばしば血管閉鎖デバイスが使用される．

B2.3　合併症

手技中に標的血管の血流を妨げるものとして，血管攣縮，血管解離，急性ステント血栓症がある．血管拡張・ステント留置により圧受容体を刺激し徐脈や低血圧を来す．術後，微小塞栓の有無はMRIで確認すべきである．また，出血性脳卒中も画像にて除外すべきである．穿刺部位の合併症は3%程度である．その他，腎機能悪化など血管内治療で一般的なものがある．

B2.4　CASの治療効果改善のために

アスピリンとクロピドグレルの二重抗血小板療法下に行われるべきである［グレードA］．二重抗血小板療法はCAS術前より開始し，術後3ヵ月間継続されるべきである［グレードC］．技術の習熟のため，有効な訓練プログラムを開発すべきである［グレードB］．脳保護デバイスは有用であると思われる［グレードC］．脳保護デバイスの有用性については，グレードAのエビデンスは存在しない．どのタイプの脳保護デバイスが最も適切であるかは依然不明である．理想的なステントは依然開発中である．

B3，B4　頭動脈病変と末梢動脈疾患(Peripheral artery disease：PAD)，冠動脈病変との併存に対する治療方針

頭動脈狭窄が6ヵ月以上無症候であれば，PADの外科的治療を遅らせる必要はない［グレードC］．重度の冠動脈病変と頭動脈病変が併存する症例に対しての外科的アプローチは，無作為化試験の結果が明らかになるまでは個々の症例のリスクに基づいて個別に決定されるべきである［グレードC］．

論　評

適応に関して

NASCET[1]，ECST (European Carotid Surgery Trial)[4]，ACAS (Asymptomatic Carotid Atherosclerosis Study)[5]，ACST (Asymptomatic Carotid Surgery Trial)[6]といった1990年代後半～2000年代前半に発表された無作為化比較試験(Randomized Controlled Trial：RCT)の結果により，症候性ならびに無症候性頭動脈高度狭窄に対するCEAの有用性は確立された．これらを基に，1998年の米国心臓協会(American Heart Association：AHA)のガイドラインでは，70%を超える症候性狭窄で再適応，50-69%の症候性狭窄に対しては適応とされ，無症候性に関しては60%を超える狭窄で5年以上の生命予後が期待される症例が最適応とされた．ただし，症候性で6%未満，無症候性で3%未満の周術期脳卒中/死亡合併症という厳しい施設基準が設けられた．ACASのサブ解析では女性ではCEAの有効性が示されず，ACSTでは74歳以下，頭動脈エコー検査で狭窄率70%以上の症例においてCEAの有効性が認められている．それを踏まえ，本ガイドラインでは無症候性頭動脈狭窄に関しては74歳以下の男性で狭窄率が70-99%であり，周術期合併症リスクが3%未満の場合にのみCEAが推奨されている．

前述のRCTではCEA高リスクとして多くの除外項目が設定されており，それらの群に対してより非侵襲的な治療であるCASの有用性が期待された．2004年にSAPPHIRE試験[7]が発表され，CEA高リスク群に対するCASの非劣性が証明された．さらにCEAの通常リスク群に対してもCASの有用性が期待されたが，欧州で行われた3つのRCT，SPACE (Stent-Supported Percutaneous Angioplasty for the Carotid Artery Versus Endarterectomy)[6]，EVA-3S (Endarterectomy Versus Angioplasty in Patinets with Symptomatic Severe Carotid Stenosis)[7]，ICSS (International Carotid Stenting Study)[8]ではいずれもCASに不利な結果であった．よって本ガイドラインでは，CASの適応はCEA高リスク群に限定されている．ただしこれら3つのRCTは遠位塞栓保護デバイスの使用率が低い，術者の経験症例数の基準が低いといった問題点があった．その後の2010年にCREST (Carotid Revascularization Endarterectomy vs. Stenting Trial)[9]が公表され，CEA高リスク群に限らずCASのCEAに対する非劣勢が証明された．これを受け，2011年に改訂されたAHAのガイドラインでは，CASの適応はCEA高リスク群のみでなくCAS自体の治療リスクから判断して良いとされている．本ガイドラインは2009年に公開されたため，この点が反映されていないことに注意したい．

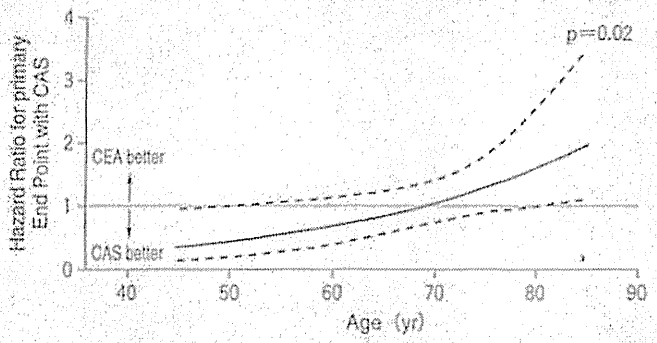

図2　CEAに対するCASのPrimary End Point
すべての脳卒中，死亡，心筋梗塞に関するハザード比(年齢と症候の有無で調整)．点線は95%信頼区間．

CRESTで得られた知見でもう1つ重要な点は，年齢と治療成績の関係である．70歳未満ではCASが，70歳以上ではCEAのほうが治療成績が優れていることが示された(図2)．

近年，内科的治療の進歩により無症候性頭動脈狭窄の脳卒中発症リスクは減少傾向がみられている．ACASでは内科的治療群の同側脳卒中発症リスクは年間2.3%であったが，最近の無症候性頭動脈狭窄に対する内科的治療の前向き研究では年間0.6-1.3%となっており，これはACASにおけるCEA群の同側脳卒中発症率(年間1.5%)を下回っている[9]．したがって，無症候性頭動脈狭窄に対する外科的治療の適応については再考が必要な時期にさしかかっていると考えられる．無症候性頭動脈狭窄に対する外科的治療に関しては，CEAとCASの比較であるACST-2，ACT-1 (Asymptomatic Carotid Trial)や，最良の内科的治療とCEA，CASの3群間で比較したSPACE-2等のRCTが進行中であり，結果が待たれるところである．

画像評価に関して

近年のトピックの1つとして，プラーク組織性状診断の進歩が挙げられる．原文においてさまざまな画像検査，バイオマーカーについて述べられているが，紙面の都合で割愛した．本邦では，プラーク組織性状診断のための術前検査として頸動脈エコー検査ならびにMRI検査が広く普及している．頸動脈エコー検査は簡便かつ非侵襲的で，プラーク輝度，潰瘍形成などの形態，ならびに動態の評価が可能である．低輝度プラークや可動性を示すプラークは，脆弱でCAS時の遠位塞栓リスクが高いと報告されている．MRIはエコーやCTと比較しコントラストが明瞭で，また石灰化が評価の妨げにならない点で有用である．MRI Black-Blood法でT1強調画像が高信号を示す病変は不安定プラーク(lipid necrotic coreあるいはintraplaque hemorrhage)であるとされ，time-of-flight (TOF) MRAの原画像で高信号を示す病変はプラーク内出血が多く，CASの周術期塞栓性合併症が多いことが報告されている[11][12]．これらを含めた多様な画像評価により，治療法の選択や手技の工夫を行うことが重要であると考える．

抗血小板療法に関して

CASの周術期において，二重抗血小板療法(Dual Antiplatelet Therapy：DAPT)は出血性合併症を増やすことなく虚血性合併症を減少させることが示されている．欧米ではアスピリン＋クロピドグレルが推奨されているが，本邦ではアスピリン，クロピドグレルに加えシロスタゾールもDAPTの選択肢の1つとして実臨床において使用されている．シロスタゾールについては，CAS後のステント内再狭窄予防効果が報告されている[13][14]．DAPTの至適期間については，いまだ質の高いエビデンスは得られていない．本ガイドラインではCAS後3ヵ月間のDAPTが推奨されている一方で，AHAのガイドラインでは，1ヵ月以上のDAPTが推奨されている(いずれも推奨レベルはグレードC)．

合併症に関して

過還流症候群(Cerebral Hyperperfusion Syndrome：CHS)は，CEA/CASの重要な術後合併症の1つであり，頻度は少ないが頭蓋内出血を来せば致命的となり得る．しかし，本ガイドラインではCHSについては触れられていない．

最後に

頸動脈狭窄の治療目的は，第一に健康寿命の延伸と生活の質の改善，ついで同側の虚血性脳卒中の発症予

防であり，狭窄部位の安易な拡張や血管整形ではない[151]．このことを念頭に置き，ガイドラインを参考に適切な治療を選択されたい．

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ORIGINAL ARTICLE

Hybrid stage I palliation for hypoplastic left heart syndrome has no advantage on ventricular energetics: a theoretical analysis

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Abstract A hybrid procedure combining bilateral pulmonary artery banding with ductal stenting has recently been used as stage I palliation for hypoplastic left heart syndrome. However, the advantage of the hybrid procedure over the Norwood procedure on ventricular energetics remains unclear. To clarify this, we performed a computational analysis with a combination of time-varying elastance chamber model and modified three-element Windkessel vascular model. Although mean pulmonary artery (PA) pressure, pulmonary flow, and oxygen saturation were almost equivalent with the Norwood procedure, the hybrid procedure delivered higher systolic and lower diastolic systemic arterial pressures compared to the Norwood procedure with right ventricle (RV) to PA shunt. As a result, the hybrid procedure yielded increased systolic pressure–volume area and impaired mechanical efficiency. Therefore, the hybrid procedure has probably no advantage on ventricular energetics compared to the Norwood procedure with a RV-PA shunt.

Keywords Hypoplastic left heart syndrome · Hybrid procedure · Norwood procedure · Ventricular energetics · Computational model

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Introduction

Advances in surgical techniques for hypoplastic left heart syndrome (HLHS) in the past several decades have improved outcomes after stage I palliation. In 1993, Gibbs et al. [1] first reported stenting of the arterial duct combined with banding of the pulmonary arteries and atrial septectomy or septostomy as a new palliation approach for HLHS. Since this approach can be performed without the use of cardiopulmonary bypass (CPB), the hybrid procedure has recently been conducted as stage I palliation for HLHS to salvage high-risk neonates [2]. Several studies demonstrated its comparable outcomes to those of the Norwood procedure [3, 4]. At the same time, despite the lower invasiveness, a recent study reports that this procedure does not improve outcome with respect to survival beyond stage II palliation [5] compared to the Norwood procedure. Furthermore, Sasaki et al. [6] reported that this procedure was associated with high interstage morbidity.

On the other hand, since Sano et al. [7] reported their experience with the right ventricle (RV)-to-pulmonary artery (PA) shunt as a modification of the Norwood procedure in 2003, this modified procedure has been performed widely with lower interstage mortality [8]. The reason why this modification improves interstage mortality may be due to the improvement of ventricular energetics. Lee et al. [9] have reported that RV stroke work (SW) may be useful to quantify RV inefficiency. Bove et al. [10] have reported that the RV-PA shunt demonstrates lower SW and higher mechanical efficiency. We have also reported that the RV-PA shunt reduces systolic pressure–volume area (PVA) and increases mechanical efficiency in spite of the presence of diastolic regurgitation [11].

The reason why the hybrid procedure does not improve outcome despite its less invasiveness may be that the