

Ratio of Peak Early to Late Diastolic Filling Velocity of the Left Ventricular Inflow is Associated With Left Atrial Appendage Thrombus Formation in Elderly Patients With Acute Ischemic Stroke and Sinus Rhythm

Liu LING, MD

Osamu HIRONO, MD

Hidenobu OKUYAMA, MD

Yasuchika TAKEISHI, MD, FJCC

Takamasa KAYAMA, MD*

Isao KUBOTA, MD, FJCC

Abstract

Objectives. To investigate the useful parameters of transthoracic echocardiography (TTE) for the diagnosis of stroke subtypes in patients with acute cerebral infarction.

Methods. One hundred and one acute ischemic stroke patients met all of the following criteria; ≥ 50 years of age, normal sinus rhythm on admission, and transesophageal echocardiography (TEE) within 7 days from the onset. The clinical significance of the TTE parameters on admission was examined for identifying intracardiac thrombus formation as follows: left atrial dimension, left ventricular end-diastolic dimension, percentage fractional shortening, left ventricular mass index, ratio of the transmitral inflow velocities (E/A), and deceleration time of the E wave.

Results. There were 28 patients with $E/A \geq 1.0$ (70 ± 12 years old) and 73 with $E/A < 1.0$ (73 ± 10 years old). No patient showed pulmonary congestion on chest radiography. There were no significant differences in age, TTE parameters, and plasma levels of brain natriuretic peptide between the two groups. Patients with $E/A \geq 1.0$ had higher incidence of left atrial appendage thrombus formation and/or spontaneous echographic contrast than those with $E/A < 1.0$ (25% vs 5%, $p = 0.0058$). There was a significant relationship between E/A and emptying flow velocity of the left atrial appendage ($r = -0.569$, $p < 0.0001$). Multivariate logistic regression analysis showed E/A was an independent predictor for left atrial appendage thrombus (risk ratio 1.531 per 0.1 increase, 95% confidence interval 1.129 - 2.076, $p = 0.0002$).

Conclusions. Increased level of E/A on admission was associated with the occurrence of left atrial appendage thrombus formation in patients with acute ischemic stroke.

J Cardiol 2006 Aug; 48(2): 75-84

Key Words

■ Echocardiography, transthoracic

■ Stroke

■ Doppler ultrasound

■ Thrombosis

山形大学医学部 循環・呼吸・腎臓内科学分野, *脳神経外科学分野: 〒990-9585 山形県山形市飯田西2-2-2
Department of Cardiology, Pulmonology, and Nephrology, *Department of Neurosurgery, Yamagata University School of Medicine,
Yamagata

Address for correspondence: HIRONO O, MD, Department of Cardiology, Pulmonology, and Nephrology, Yamagata University
School of Medicine, Iida-Nishi 2-2-2, Yamagata, Yamagata 990-9585; E-mail: ohirono@med.id.yamagata-u.ac.jp

Manuscript received January 19, 2006; revised March 20 and June 13, 2006; accepted June 14, 2006

INTRODUCTION

The National Institute of Neurological Disorders and Stroke has characterized cardioembolic stroke as an important clinical entity, since it is the most common cause of death in patients with acute ischemic stroke.¹⁻³ Transesophageal echocardiography (TEE) has been established as an essential investigation for detecting thromboembolic sources and determining stroke subtypes.⁴⁻¹² Since TEE is a semi-invasive tool, its importance in acute stroke care is increasing.

Transthoracic echocardiography (TTE) is accepted as a non-invasive assessment for cardiac structural and functional abnormalities worldwide. Furthermore, many recent clinical studies have clearly shown that the analysis of the transmitral inflow velocity profiles obtained by the pulsed Doppler technique is a unique assessment that predicts left atrial and/or ventricular diastolic dysfunction independently of the systolic function.¹³⁻¹⁶ TTE is usually required in patients with emergent ischemic stroke to measure those parameters, but the direct associations of TTE findings with cardioembolic stroke occurrence remain unknown.

Left atrial appendage (LAA) is a major thromboembolic source in cardioembolic stroke.^{7,8} There is a close relationship between LAA thrombus formation and left atrial mechanical remodeling based on TEE findings, such as the presence of spontaneous echo contrast or a progressive reduction in LAA emptying flow velocity.^{6,10,12,17}

In the present study, useful parameters in emergency TTE were identified for determining cardioembolic stroke occurrence by comparison with transmitral inflow velocity patterns and LAA thrombus formation.

SUBJECT AND METHODS

Recruited patients

One hundred and fifty-five patients with acute cerebral infarction were admitted to our hospital from January 2003 to December 2005. Patients were enrolled if they satisfied all of the following criteria: 1) abrupt stroke onset while awake with maximal neurological deficit, 2) admission within 24 hr from symptom recognition, 3) normal sinus rhythm on admission, 4) age older than 50 years, and 5) TEE performed within 7 days from the onset. Assessment included risk factors for cerebral infarction, clinical categories of ischemic stroke

(Oxfordshire Community Stroke Project classification)^{18,19} and disease severity using the National Institute of Health Stroke Scale (NIHSS)²⁰ on admission. All patients underwent cerebral computed tomography and/or magnetic resonance imaging on admission, continuous electrocardiographic monitoring to determine cardiac rhythms, and were treated with a standardized protocol for the management of dehydration, hyperglycemia, hypoxia, and pyrexia. Fifty-four patients were excluded from this study due to: atrial fibrillation on admission ($n = 32$), age younger than 50 years old ($n = 10$), refusal to grant informed consent for TEE ($n = 4$), and hemorrhagic infarction ($n = 8$). The remaining 101 patients were included in the analysis. The local ethics committee approved the study protocol, and informed consent was obtained from all subjects.

Echocardiography

TTE was performed using a Hewlett Packard SONOS 7500 ultrasound instrument equipped with a sector transducer (carrier frequency of 2.5 or 3.75 MHz). A 5 MHz phased-array multiplane probe was used for TEE. The following parameters were measured using standard views and techniques: left ventricular end-diastolic dimension; left ventricular percentage fractional shortening; left ventricular mass index; presence of atrial septal aneurysm and patent foramen ovale; and spontaneous echographic contrast or thrombus formation in the LAA.^{16,21} Maximum transverse length of the left atrial dimension was directly measured by planimetry on the B-mode long-axis view during TTE. The LAA emptying flow velocity at atrial systole was calculated by pulsed-wave Doppler with the sample volume placed 1 cm distal from the mouth of the appendage by scanning the appendage at angles from 0° to 90° during TEE examination.²²

Transmitral inflow velocities were recorded on the apical four-chamber view. With the guidance of a real-time two-dimensional color Doppler flow image, the pulsed Doppler sample volume was placed at the tip of the mitral leaflets and the position was then adjusted to direct the ultrasound beam parallel to the ventricular inflow. The ratio of peak early to late filling velocity (E/A) and the deceleration time of the early diastolic filling (DT) were measured.¹³⁻¹⁵

Mitral annular velocities were recorded on the

Table 1 Clinical characteristics of the patients

	E/A \geq 1.0 (n = 28)	E/A < 1.0 (n = 73)	p value
Age(yr)	70 \pm 12	73 \pm 10	NS
Sex(male/female)	17/11	46/27	NS
NIHSS	10.8 \pm 7.6	9.1 \pm 8.6	NS
Heart rate(beats/min)	64 \pm 14	69 \pm 15	NS
Systolic blood pressure(mmHg)	144 \pm 25	151 \pm 21	NS
Pulse pressure(mmHg)	61 \pm 21	64 \pm 17	NS
Risk factors			
Paroxysmal atrial fibrillation	5(18)	3(4)	0.0068
Hypertension	19(68)	55(75)	NS
Diabetes mellitus	5(18)	15(21)	NS
Hyperlipidemia	7(25)	27(37)	NS
Current smoking	10(36)	31(42)	NS
Past history of ischemic stroke	10(36)	28(38)	NS
Heart diseases			
Ischemic heart disease	0	4(4 in MI)	
Valvular heart disease	1(Post AVR)	1(AS)	NS
Cardiomyopathy	2(DCM, ICM)	1(ICM)	
Others	0	3(3 in HHD)	
Oxfordshire Stroke Classification			
TACI/PACI/POCI/LACI	8/15/3/2	20/32/10/11	NS
Medications(before the onset)			
Anti-hypertensives	15(54)	36(49)	NS
Warfarin	3(11)	6(8)	NS
Anti-platelets	11(34)	21(29)	NS
Statins	2(7)	6(8)	NS

Continuous values are mean \pm SD. () %.

E/A = the ratio of the peak early to late diastolic transmitral filling velocities with pulsed Doppler; NIHSS = stroke severity score prescribed by the National Institute of Health; MI = myocardial infarction; AVR = aortic valve replacement; AS = aortic stenosis; DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; HHD = hypertensive heart disease; TACI = total anterior circulation infarcts; PACI = partial anterior circulation infarcts; POCI = posterior circulation infarcts; LACI = lacunar circulation infarcts.

apical four-chamber view using the Doppler tissue imaging function. The spectral pulsed Doppler signal filters were adjusted to obtain a Nyquist limit of 15 and 20 cm/sec, and the sample volume was placed at the bright lateral margin of the mitral annulus with a fixed sampling gate of 10 mm. Peak early(Ea) and late(Aa) diastolic annular velocities were measured.^{23,24)}

The clinical characteristics, blood markers, and echocardiographic parameters were compared between patients with E/A \geq 1.0(n = 28, age 70 \pm 12 years old) and those with < 1.0(n = 73, 73 \pm 10 years old)

Aortic and carotid echographic studies

After the cardiac examination during TEE, aortic images were obtained. The depth was set to 5 cm, and the transducer was slowly withdrawn from the distal thoracic aorta to the aortic arch in the transverse plane. Maximal intima-medial thickness of the aortic arch without protruding atheromatous plaque was measured at end-diastole if the intima-medial layer was continuously visible. The prevalence of aortic arch ulcerated and/or mobile plaques were examined.^{25,26)}

Imaging of the bilateral carotid arteries was performed with a 7.5 MHz linear transducer connected to a SONOS 7500 system. Longitudinal images of

the bilateral common and proximal internal carotid arteries (and those bifurcations) were obtained. Carotid intima-medial thickness without protruding atheromatous plaques was measured at end-diastole according to Pignoli *et al.*, and was obtained as the mean of the bilateral common carotid arteries.²⁷⁾ Luminal percentage stenosis at the site of maximal narrowing in the infarcted side was calculated according to the European Carotid Surgery Trial method,^{28,29)} and more than 50% stenosis defined as a significant carotid plaque lesion.

All echographic measurements were taken as the mean of five consecutive cardiac cycles. Identification of the LAA thrombus was performed offline, and all findings were evaluated by two independent and experienced echocardiologists (L.L. and O.H.) If the LAA was observed in 20 randomly selected patients by the same observer (L.L.) on two separate occasions, intra-observer difference for identification of thrombus was 5.0% ($n = 1$). If two observers evaluated the LAA in all study subjects, the inter-observer difference was 5.0% ($n = 5$) for thrombus formation.

Blood examinations

Venous blood samples were obtained on admission. General biochemical parameters and serum hemostatic markers (thrombin-antithrombin complex as indices for coagulation and D-dimer for fibrinolysis) were measured by routine laboratory methods. The same blood samples were used for measurements of plasma atrial and brain natriuretic peptides as indices for cardiac function. The samples were transferred to chilled tubes containing 4.5 mg of ethylenediaminetetraacetic acid disodium salt and aprotinin (500 U/ml), and immediately centrifuged at 1,000 G for 15 min at 4 °C. The clarified plasma samples were frozen, stored at -70 °C and thawed just before assay. Concentrations of the atrial and brain natriuretic peptides were measured using a commercially available specific radioimmunoassay kit (Shionogi Co Ltd).^{30,31)}

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation. Statistical analysis was conducted using Stat View 5.0 for Macintosh (Abacus Concepts, Inc). Patient characteristics, blood markers, and echocardiographic parameters were compared between patients with E/A \geq 1.0 and < 1.0

Table 2 Blood examinations

	E/A \geq 1.0 ($n = 28$)	E/A < 1.0 ($n = 73$)	<i>p</i> value
BS (mg/dl)	117 \pm 49	119 \pm 42	NS
Hb A _{1c} (%)	5.8 \pm 1.3	5.7 \pm 1.1	NS
TC (mg/dl)	188 \pm 40	193 \pm 41	NS
TG (mg/dl)	101 \pm 32	112 \pm 48	NS
HDL-C (mg/dl)	55 \pm 14	48 \pm 18	NS
CRP (mg/dl)	2.1 \pm 4.5	1.4 \pm 2.4	NS
D-dimer (μ g/ml)	3.3 \pm 6.4	2.0 \pm 3.3	NS
TAT (μ g/ml)	14.7 \pm 14.6	8.3 \pm 8.1	NS
ANP (pg/ml)	78 \pm 63	47 \pm 46	NS
BNP (pg/ml)	131 \pm 170	107 \pm 147	NS

Values are mean \pm SD.

BS = blood sugar on admission; HbA_{1c} = glycosylated hemoglobin A_{1c}; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; CRP = C-reactive protein; TAT = thrombin-antithrombin complex; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide.

using Student's *t*-test for unpaired continuous variables and the chi-square test for categorical variables.

Transmitral inflow and mitral annular velocities were compared between patients with and without LAA thrombus and/or spontaneous echographic contrast using Student's *t*-test for unpaired continuous variables. Multivariate logistic regression analysis was performed for routine TTE variables with a univariate *p* value < 0.05 to determine independent predictors of LAA thrombus. The univariate regression analysis was used for comparisons of E/A and LAA emptying flow velocity. *p* values of less than 0.05 were considered significant.

RESULTS

The mean age of our recruited patients was relatively high (72 \pm 10 years old, range 50 - 94 years old), and 28 patients (28%) had E/A \geq 1.0 (E/A 1.32 \pm 0.37, age 70 \pm 12 years old) and 73 had E/A < 1.0 (0.62 \pm 0.14, 73 \pm 10 years old). No patients showed pulmonary congestion on chest radiography and clinical symptoms or signs suggestive of congestive heart failure during hospitalization. There were no significant differences in age, prevalence of risk factors, structural heart diseases and stroke subtypes, medications before the onset, blood markers (especially with plasma levels of atrial and brain natriuretic peptides), and the prevalence of aortic-or carotid-plaques between the two

Table 3 Echocardiographic findings

	E/A \geq 1.0 (n = 28)	E/A < 1.0 (n = 73)	p value
Transthoracic echocardiography			
LAD (mm)	38 \pm 6	38 \pm 5	NS
LVDd (mm)	47 \pm 5	46 \pm 6	NS
% FS (%)	34 \pm 9	37 \pm 7	NS
LVMi (g/m ²)	131 \pm 52	141 \pm 43	NS
LV SEC	2 (7)	1 (1)	NS
E (cm/sec)	83 \pm 10	55 \pm 12	< 0.0001
A (cm/sec)	67 \pm 16	92 \pm 19	< 0.0001
E/A	1.32 \pm 0.37	0.62 \pm 0.14	< 0.0001
DT (msec)	184 \pm 50	231 \pm 49	NS
Ea (cm/sec)	10.0 \pm 1.5	7.5 \pm 1.6	< 0.0001
Aa (cm/sec)	7.5 \pm 2.3	12.0 \pm 3.4	< 0.0001
E/Ea	8.4 \pm 1.3	7.7 \pm 2.1	NS
Transesophageal echocardiography			
Atrial septal aneurysm	4 (14)	15 (21)	NS
Patent foramen ovale	2 (7)	9 (12)	NS
Aortic arch plaque	5 (18)	14 (19)	NS
Aortic arch IMT (mm)	3.3 \pm 2.1	3.7 \pm 1.9	NS
LAA area (cm ²)	4.9 \pm 1.4	3.9 \pm 1.3	0.0395
LAA eV (cm/sec)	45 \pm 14	59 \pm 21	0.0027
LAA thrombus	4 (14)	2 (3)	0.0312
LAA SEC	3 (11)	2 (3)	0.0402
LAA thrombus or SEC	7 (25)	4 (5)	0.0058
Carotid echography			
Common carotid IMT (mm)	0.8 \pm 0.2	0.8 \pm 0.2	NS
Carotid plaque*	7 (25)	17 (23)	NS

Continuous values are mean \pm SD. () %.

*Carotid plaque: Plaque with more than 50% luminal stenotic lesion at the site of maximal narrowing in the infarcted side according to the European Carotid Surgery Trial method.

LAD = left atrial dimension; LVDd = left ventricular end-diastolic dimension; %FS = left ventricular percent fractional shortening; LVMi = left ventricular mass index; SEC = spontaneous echographic contrast; E = peak early diastolic transmitral filling velocity; A = peak late diastolic transmitral filling velocity; DT = deceleration time of the E wave; Ea = peak early diastolic velocity at the lateral corner of the mitral annulus by Doppler tissue imaging; Aa = peak late diastolic velocity at the lateral corner of the mitral annulus by Doppler tissue imaging; Aortic arch plaque = ulcerated and/or mobile plaque in the arch; IMT = intima-media thickness; LAA = left atrial appendage; eV = emptying flow velocity. Other abbreviation as in Table 1.

groups (Tables 1, 2 and 3).

TTE showed patients with E/A \geq 1.0 had higher E and Ea, and lower A and Aa wave velocities than those with E/A < 1.0. There was no significant difference in E/Ea between the two groups (Table 3). Patients with E/A \geq 1.0 had larger LAA area, slower emptying flow velocity at atrial systole, and higher incidence of LAA thrombus formation and/or spontaneous echographic contrast than those with E/A < 1.0 (Table 3). LAA emptying flow

velocity had a significant relationship with E/A ($r = -0.569$, $p < 0.001$; Fig. 1). Patients with LAA thrombus and/or spontaneous echographic contrast had higher E, Ea and E/A, and lower A and Aa wave velocities, but no difference in DT and E/Ea, compared to those with no thrombus (Table 4).

Multivariate logistic regression analysis of routine TTE parameters showed E/A was an independent predictor for LAA thrombus (risk ratio 1.531

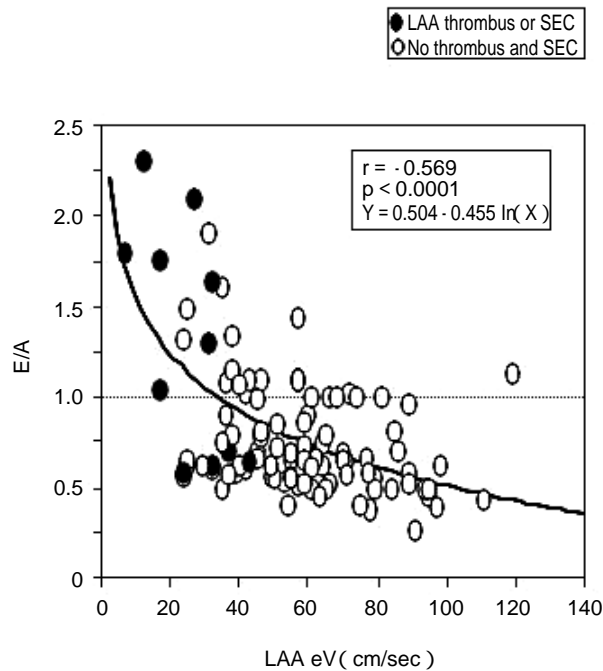


Fig. 1 Scatter plots showing the relationship between E/A and left atrial appendage emptying flow velocity in all patients with acute ischemic stroke

Left atrial appendage emptying flow velocity had a significant relationship with E/A.

Abbreviations as in Tables 1, 3.

Table 4 Transmitral inflow and mitral annulus velocity in patients with and without left atrial appendage thrombus or spontaneous echographic contrast

	LAA thrombus or SEC (n = 11)	No thrombus and SEC (n = 90)	p value
E (cm/sec)	78 ± 15	61 ± 16	0.0016
A (cm/sec)	70 ± 28	86 ± 20	0.0132
E/A	1.33 ± 0.64	0.75 ± 0.29	< 0.0001
DT (msec)	217 ± 79	218 ± 51	NS
Ea (cm/sec)	9.5 ± 2.2	8.0 ± 1.9	0.0147
Aa (cm/sec)	5.6 ± 2.0	11.4 ± 3.4	< 0.0001
E/Ea	8.3 ± 1.4	7.8 ± 2.0	NS

Values are mean ± SD.

Abbreviations as in Tables 1, 3.

per 0.1 increase, 95% confidence interval 1.129 - 2.076, $p = 0.0002$; **Table 5**).

During hospitalization (mean 26 ± 6 days), paroxysmal atrial fibrillation was identified in 5 patients with $E/A \geq 1.0$ and 3 with $E/A < 1.0$ by

Table 5 Multivariate logistic regression analysis for left atrial appendage thrombus

	Risk ratio	95% CI for risk ratio	p value
LAD (per 1 mm increase)	1.009	0.771 - 1.322	NS
LVDd (per 1 mm increase)	0.950	0.690 - 1.308	NS
%FS (per 1% increase)	0.832	0.650 - 1.065	NS
LVMi (per 1 g/m ² increase)	0.980	0.940 - 1.022	NS
E/A (per 0.1 increase)	1.531	1.129 - 2.076	0.0002
DT (per 1 msec increase)	1.031	0.997 - 1.067	NS

CI = confidence interval. Other abbreviations as in Tables 1, 3.

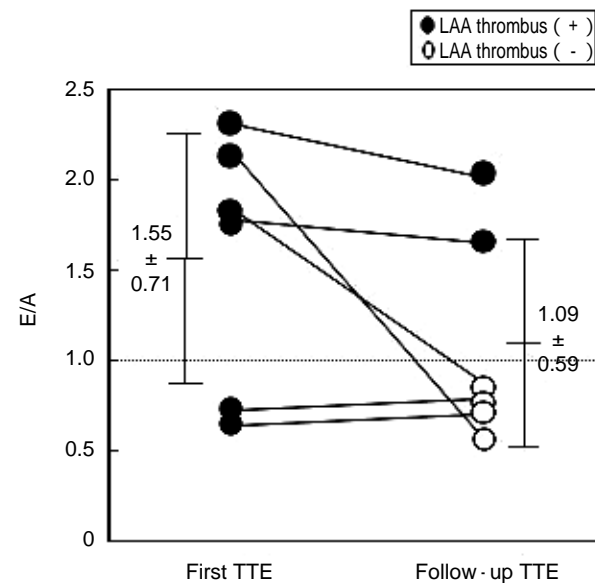


Fig. 2 Changes in E/A levels in six patients with left atrial appendage thrombus between the first and follow-up TTE (at 2 weeks after the first study)

E/A levels on admission decreased in both patients with $E/A \geq 1.0$ whose left atrial appendage thrombus disappeared, and did not change in the other two.

TTE = transthoracic echocardiography. Other abbreviations as in Tables 1, 3.

24 hr Holter or monitor electrocardiography (18% vs 4%, $p = 0.0068$).

Six patients with LAA thrombus underwent follow-up TTE and TEE at 2 weeks after the first study. All patients received appropriate warfarin treatment [international normalized ratio of prothrombin time (PT-INR) 1.65 - 2.45], and LAA thrombus disappeared in two patients with $E/A \geq 1.0$ and two patients with $E/A < 1.0$. E/A levels on admission decreased in both patients with $E/A \geq 1.0$ in whom LAA thrombus disappeared, and did

not change the other two (**Fig. 2**)

DISCUSSION

TEE is a widely accepted tool for identifying intracardiac embolic sources and for identifying cardioembolic stroke in the stroke care unit. Reduction in the LAA emptying flow velocity or the development of spontaneous echocardiographic contrast reflects atrial mechanical remodeling and thrombus formation.³²⁾ However, TEE is a semi-invasive examination that is not easy to repeat frequently to follow changes in intracardiac thrombus formation and thus help prevent recurrent attacks, although its importance in the acute stroke care unit is increasing. The present study investigated TTE parameters of patients with acute ischemic stroke and compared them with LAA thrombus formation and/or spontaneous echographic contrast confirmed by TEE to clarify useful routine TTE parameters in an emergency for identifying LAA thrombus formation and cardioembolic stroke occurrence.

Analysis of the transmitral diastolic filling velocity obtained by routine pulsed Doppler technique may provide a simple and accurate method for predicting left atrial and ventricular diastolic dysfunction.¹³⁻¹⁶⁾ E/A decreases and DT prolongs with advancing age in healthy persons (E/A = 1.0 is commonly shown around at 60 years of age)¹⁵⁾ On the other hand, review of many clinical reports examined the clinical significance for assessing transmitral diastolic filling waves by routine echocardiographic examination.¹⁴⁾ Gradual increase in the E velocity (E/A > 1.0) and shortened DT (< 200 msec) commonly found in patients with structural heart disease progression, were characterized by increase in left atrial pressure and the driving pressure across the mitral valve, and poor ventricular compliance. Furthermore, early diastolic mitral annular velocity (Ea) expressed by Doppler tissue imaging may be a preload-independent index of left ventricular relaxation.^{23,24)} An E/Ea ratio > 10 reflects high left ventricular filling pressure > 15 mmHg.²³⁾ In our present study, patients with E/A \geq 1.0 had markedly lower A and Aa wave velocities and higher prevalence of LAA thrombus formation than patients with E/A < 1.0, and there were no significant differences in age and E/Ea ratio (< 10) between the two groups. Furthermore, E/A levels had a significant relationship with LAA emptying flow velocity. These findings suggest that increased levels of E/A in acute ischemic stroke

patients with normal sinus rhythm might be associated with LAA dysfunction and thrombus formation.

Left ventricular systolic dysfunction is an independent risk factor for systemic thromboembolism in patients with chronic atrial fibrillation.³²⁾ Therefore, a joint committee of American College of Cardiology, American Heart Association, and European Society of Cardiology have proposed guidelines for management of patients with atrial fibrillation, and have recommended oral administration of warfarin (PT-INR 2.0 - 3.0), as an evidence level A, for patients with left ventricular ejection fraction \leq 0.35 to prevent thromboembolism, without concerns with advancing age, hypertension, diabetes mellitus, coronary artery disease, and other cardiac structural abnormalities.³³⁾ On the other hand, our multivariate logistic regression analysis for routine TTE parameters showed E/A was an independent predictor for LAA thrombus. Our results suggest that increased levels of E/A during the acute period might be more important to predict LAA thrombus formation and cardioembolic stroke occurrence than the parameters of left ventricular systolic function, such as left ventricular end-diastolic dimension and/or fractional shortening in ischemic stroke patients with sinus rhythm. Further large-scale clinical study is needed to define the relationship between transmitral inflow velocity pattern abnormalities and the occurrence of ischemic stroke in patients with normal left ventricular systolic function.

Our study had the following limitations. First, the number of subjects with LAA thrombus and/or spontaneous echographic contrast was relatively small. Second, we could not assess E/A in patients aged < 50 years old or with atrial fibrillation because of the good left ventricular diastolic compliance (increase in E wave) or the absence of active atrial contractile wave (A wave), so whether these are useful routine TTE parameters for predicting LAA thrombus formation in younger or chronic atrial fibrillation patients remained unknown. Finally, patients with E/A \geq 1.0 had higher incidence of paroxysmal atrial fibrillation. This result suggested that paroxysmal atrial fibrillation-mediated LAA mechanical remodeling or atrial stunning,³⁴⁾ characterized by sustained atrial contractile dysfunction, might reflect reduced or absent active atrial contractile waves (A and Aa) and thus increased E/A levels. We should pay more attention

to the value of E/A after the termination of paroxysmal atrial fibrillation in the acute stroke care unit.

CONCLUSIONS

Increased level of the ratio of the transmitral

inflow velocities via TTE on admission was associated with the occurrence of left atrial appendage thrombus formation in acute ischemic stroke patients with normal sinus rhythm and normal left ventricular systolic function.

要 約

高齢者の洞調律の急性期脳梗塞における左心耳内血栓と 左室流入血流速度のE/A比の関連性

劉 凌 廣 野 撰 奥山 英伸
竹石 恭知 嘉山 孝正 久保田 功

目的: 虚血性脳卒中の塞栓源検索と病型診断における経食道心エコー図法の有用性は確立されている。今回我々はより簡易で有用な心内血栓の予測指標を確立するために、脳梗塞急性期に依頼される経胸壁心エコー図法のルーチン検査項目を、経食道心エコー図所見との対比を介して詳細に解析した。

方法: 50歳以上の急性非出血性脳梗塞症例で、来院時は洞調律であり、発症から1週間以内(6±1日)に経食道心エコー図法が施行された101例を対象とした。来院時に施行された経胸壁心エコー図法のルーチン検査項目を用いた心内血栓形成の予測を目的として、多変量ロジスティック回帰分析が行われた。

結果: 全症例の平均年齢が72±10歳と高齢であるにもかかわらず、パルスドップラー法により描出された経僧帽弁流入血流速度の比(E/A)が1.0以上を示す偽正常化パターンが28例に認められた(E/A ≥ 1.0群, 28例, 年齢70±12歳; E/A < 1.0群, 73例, 年齢73±10歳)。入院時に肺うっ血を合併した症例は1例もなかった。2群間におけるE/A以外のルーチン検査項目や血漿脳性ナトリウム利尿ペプチド値に差は認められなかった。E/A ≥ 1.0群において、左心耳内に血栓形成またはもやもやエコーを認める頻度はE/A < 1.0群に比べ有意に高かった(25% vs 5%, $p = 0.0058$)。E/Aは左心耳駆出血流速度との間に有意な相関関係を認めた($r = -0.569$, $p < 0.0001$)。多変量ロジスティック回帰分析において、E/Aの上昇は左心耳内血栓形成を予測する独立した危険因子であった(risk ratio 1.531 per 0.1 increase, 95%信頼区間1.129 - 2.076, $p = 0.0002$)。

結論: 経胸壁心エコー図法のルーチン検査項目において、脳梗塞急性期に測定されるE/Aは、左心耳内血栓形成を予測しうる可能性を示唆した。

J Cardiol 2006 Aug; 48(2): 75 - 84

References

- 1) Special report from the National Institute of Neurological Disorders and Stroke: Classification of cerebrovascular disease III. *Stroke* 1990; **21**: 637 - 676
- 2) Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, Hogelin G, Marler J, McGovern P, Morosco G, Mosca L, Pearson T, Stamler J, Stryer D, Thom T: Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: Findings of the national conference on cardiovascular disease prevention. *Circulation* 2000; **102**: 3137 - 3147
- 3) Sacco RL, Wolf PA, Kannel WB, McNamara PM: Survival and recurrence following stroke: The Framingham study. *Stroke* 1982; **13**: 290 - 295
- 4) Pollick C, Taylor D: Assessment of left atrial appendage function by transesophageal echocardiography: Implications for the development of thrombus. *Circulation* 1991; **84**: 223 - 231
- 5) Cujec B, Polasek P, Voll C, Shuaib A: Transesophageal echocardiography in the detection of potential cardiac source of embolism in stroke patients. *Stroke* 1991; **22**: 727 - 733
- 6) Shinokawa N, Hirai T, Takashima S, Kameyama T, Obata Y, Nakagawa K, Asanoi H, Inoue H: Relation of transesophageal echocardiographic findings to subtypes of cerebral infarction in patients with atrial fibrillation. *Clin Cardiol* 2000; **23**: 517 - 522

- 7) Suetsugu M, Matsuzaki M, Toma Y, Anno T, Okada K, Konishi M, Ono S, Tanaka N, Hiro J: Detection of mural thrombi and analysis of blood flow velocities in the left atrial appendage using transesophageal two-dimensional echocardiography and pulsed Doppler flowmetry. *J Cardiol* 1988; **18**: 385 - 394
- 8) Garcia-Fernandez MA, Torrecilla EG, San Roman D, Azevedo J, Bueno H, Moreno MM, Delcan JL: Left atrial appendage Doppler flow patterns: Implications on thrombus formation. *Am Heart J* 1992; **124**: 955 - 961
- 9) The Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation: Echocardiographic features of patients at risk. *Ann Intern Med* 1992; **116**: 6 - 12
- 10) Verhorst PM, Kamp O, Visser CA, Verheugt FW: Left atrial appendage flow velocity assessment using transesophageal echocardiography in nonrheumatic atrial fibrillation and systemic embolism. *Am J Cardiol* 1993; **71**: 192 - 196
- 11) Mugge A, Kuhn H, Nikutta P, Grote J, Lopez JA, Daniel WG: Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: Identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol* 1994; **23**: 599 - 607
- 12) Kamp O, Verhorst PM, Welling RC, Visser CA: Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation. *Eur Heart J* 1999; **20**: 979 - 985
- 13) Giannuzzi P, Imparato A, Temporelli PL, de Vito F, Silva PL, Scapellato F, Giordano A: Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994; **23**: 1630 - 1637
- 14) Nishimura RA, Tajik AJ: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997; **30**: 8 - 18
- 15) Voutilainen S, Kupari M, Hippelainen M, Karppinen K, Ventila M, Heikkila J: Factors influencing Doppler indexes of left ventricular filling in healthy persons. *Am J Cardiol* 1991; **68**: 653 - 659
- 16) Blum A, Reisner S, Farbstein Y: Transesophageal echocardiography (TEE) vs. transthoracic echocardiography (TTE) in assessing cardio-vascular sources of emboli in patients with acute ischemic stroke. *Med Sci Monit* 2004; **10**: 521 - 523
- 17) Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM: Mechanical remodeling of the left atrium after loss of atrioventricular synchrony: A long-term study in humans. *Circulation* 1999; **100**: 1714 - 1721
- 18) Tei H, Uchiyama S, Ohara K, Kobayashi M, Uchiyama Y, Fukuzawa M: Deteriorating ischemic stroke in 4 clinical categories classified by the Oxfordshire Community Stroke Project. *Stroke* 2000; **31**: 2049 - 2054
- 19) Bamford J, Sandercock P, Dennis M, Burn J, Warlow C: Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; **337**: 1521 - 1526
- 20) Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V: Measurements of acute cerebral infarction: A clinical examination scale. *Stroke* 1989; **20**: 864 - 870
- 21) Fatkin D, Kuchar DL, Thorburn CW, Feneley MP: Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: Evidence for "atrial stunning" as a mechanism of thromboembolic complications. *J Am Coll Cardiol* 1994; **23**: 307 - 316
- 22) Fatkin D, Feneley MP: Patterns of Doppler-measured blood flow velocity in the normal and fibrillating human left atrial appendage. *Am Heart J* 1996; **132**: 995 - 1003
- 23) Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997; **30**: 1527 - 1533
- 24) Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW: Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997; **30**: 474 - 480
- 25) Amarencu P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, Chauvel C, Touboul PJ, Bousser MG: Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994; **331**: 1474 - 1479
- 26) Amarencu P, Duyckaerts C, Tzourio C, Henin D, Bousser MG, Hauw JJ: The prevalence of ulcerated plaques in the aortic arch in patients with stroke. *N Engl J Med* 1992; **326**: 221 - 225
- 27) Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. *Circulation* 1986; **74**: 1399 - 1406
- 28) European Carotid Surgery Trialists Collaborative Group: Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; **351**: 1379 - 1387
- 29) U-King-Im JM, Trivedi RA, Cross JJ, Higgins NJ, Hollingworth W, Graves M, Joubert I, Kirkpatrick PJ, Antoun NM, Gillard JH: Measuring carotid stenosis on contrast-enhanced magnetic resonance angiography: Diagnostic performance and reproducibility of 3 different methods. *Stroke* 2004; **35**: 2083 - 2088
- 30) Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M: Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; **135**: 825 - 832
- 31) Niizeki T, Takeishi Y, Arimoto T, Takahashi T, Okuyama H, Takabatake N, Nozaki N, Hirono O, Tsunoda Y, Shishido T, Takahashi H, Koyama Y, Fukao A, Kubota I: Combination of heart-type fatty acid binding protein and brain natriuretic peptide can reliably risk stratify patients hospitalized for chronic heart failure. *Circ J* 2005; **69**: 922 - 927
- 32) Gonzalez-Torrecilla E, Garcia-Fernandez MA, Perez-David E, Bermejo J, Moreno M, Delcan JL: Predictors of left atrial spontaneous echo contrast and thrombi in patients with mitral stenosis and atrial fibrillation. *Am J Cardiol* 2000; **86**: 529 - 534

- 33) Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, Halperin JL, Kay GN, Klein WW, Levy S, McNamara RL, Prystowsky EN, Wann LS, Wyse DG, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC Jr, Klein WW, Alonso-Garcia A, Blomstrom-Lundqvist C, de Backer G, Flather M, Hradec J, Oto A, Parkhomenko A, Silber S, Torbicki A ; American College of Cardiology/American Heart Association Task Force on Practice Guidelines ; European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) ; Developed in Collaboration With the North American Society of Pacing and Electrophysiology : ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation : Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. *Circulation* 2001 ; **104** : 2118 - 2150
- 34) Louie EK, Liu D, Reynertson SI, Loeb HS, McKiernan TL, Scanlon PJ, Hariman RJ : “ Stunning ” of the left atrium after spontaneous conversion of atrial fibrillation to sinus rhythm : Demonstration by transesophageal Doppler techniques in a canine model. *J Am Coll Cardiol* 1998 ; **32** : 2081 - 2086