Cardiac Diastolic Dysfunction Predicts In-hospital Mortality in Acute Ischemic Stroke with Atrial Fibrillation

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There is no grant support.

Number of tables: 2

Number of figure: 1

Short title: Diastolic dysfunction and mortality of ischemic stroke

Word count: 2030 words (abstract is not included)

Abstract

Background: The aim of this study was to identify whether diastolic dysfunction predicts in-hospital death in ischemic stroke patients with atrial fibrillation.

Method: We retrospectively analyzed data from enrolled patients with ischemic stroke patients with atrial fibrillation who presented within 24 h of onset. All patients underwent transthoracic echocardiography to evaluate diastolic filling pressure estimated as the ratio of early transmitral flow velocity (E) to mitral annular velocity (e') within 24 h of admission. We evaluated initial ischemic lesion volume and National Institute of Health Stroke Scale (NIHSS) score.

Results: Two hundred and sixty-six patients were enrolled. During hospitalization, 30 patients (11%) died. The deceased group had a higher NIHSS score, a higher D-dimer level, a higher creatinine level, a larger initial ischemic lesion volume and a higher E/e' ratio than those in the survival group. In a multivariate analysis, a higher E/e' ratio was an independent predictor of in-hospital death. The cutoff value for the E/e' ratio for prediction in-hospital death was 20 with the sensitivity of 75% and specificity of 86%.

Conclusion: Diastolic dysfunction may be associated with in-hospital death in ischemic

stroke patients with atrial fibrillation.

Key words: Diastolic dysfunction, stroke, atrial fibrillation, mortality, transthoracic echocardiography

Introduction

Cardioembolic stroke due to atrial fibrillation (AF) is a common cause of ischemic stroke and is associated with high mortality or morbidity with subsequent disability [1–3]. Furthermore, AF is one of the strongest predictors of in-hospital mortality among patients with acute ischemic stroke [4]. Several factors may contribute to in-hospital mortality after cardioembolic stroke due to AF, such as larger infarcts, older age, and elevated plasma brain natriuretic peptide (BNP) level [5,6]. Diastolic dysfunction is caused by an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle during diastole [7,8]. Heart failure related to diastolic dysfunction has a considerably high mortality even in patients with preserved left ventricular ejection fraction [9,10]. Recently, Jang et al reported that heart failure with normal ejection fraction was associated with increased risk of ischemic stroke and death in patients with AF [11]. This study investigated whether diastolic dysfunction was independently associated with in-hospital death after acute ischemic stroke with AF.

Methods

Patients

Between September 2008 and August 2013, we studied patients admitted consecutively with acute ischemic stroke patients with atrial fibrillation within 24 h of onset. We excluded patients with transient ischemic attack and those with prior mitral valve surgery. In-hospital death was defined as any cause of mortality during hospitalization. Patients with modified Rankin scale > 2 were defined as having dependence. We divided patients into two groups: the deceased group and the survival group. The study was approved by the institutional review board at the Nagasaki University Hospital (Nagasaki, Japan).

Stroke neurologists made the diagnosis of acute ischemic stroke. Computed tomography (CT) was performed in patients with a contraindication for magnetic resonance imaging (MRI). The other patients underwent MRI. Ischemic lesion volumes on diffusion-weighted magnetic resonance imaging (DWI) were calculated by multiplying the area of abnormal intensity outlined manually by slice thickness. The abnormal lesions on DWI were visually defined by comparison with the contralateral non-affected hemisphere. The window level and window width were chosen to obtain

the best contrast between the lesion and the surrounding normal tissues. The occlusion sites were diagnosed based on CT angiography or MR angiography. Considerable hemorrhagic transformation was defined as a parenchymal hematoma type 2 (PH2; a dense hematoma in >30% of the infarcted area with a substantial space-occupying effect, or any hemorrhagic lesion outside the infarcted area) [12]. Electrocardiography (ECG), continuous ECG monitoring, and 24-h Holter ECG were used to attempt to document AF. We examined carotid duplex ultrasonography, ECG, transcranial Doppler, transthoracic echocardiography, transesophageal echocardiography, CT and/or MRI, and MR angiography and/or CT angiography to identify the mechanism of stroke.

The following patient characteristics were recorded: age, sex, previous ischemic heart disease and ischemic stroke, and vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking). Hypertension was defined as the use of antihypertensive agents, a systolic blood pressure of >140 mm Hg, or a diastolic blood pressure of >90 mm Hg. Diabetes was defined as the use of oral hypoglycemic agents or insulin, or a glycosylated hemoglobin level of >6.5%. Dyslipidemia was defined as the use of antihyperlipidemic agents or a serum cholesterol level of >220

mg/dL. Smoking was defined as having smoked cigarettes within the last 5 years. The National Institutes of Health Stroke Scale (NIHSS) score was used to assess stroke severity. All patients underwent blood tests on admission. The main variables were brain natriuretic peptide (BNP), prothrombin time-international normalized ratio, total cholesterol, C-reactive protein (CRP), glucose, D-dimer, and creatinine.

Patients who presented to our hospital within 4.5 h of symptom onset were treated with IV rt-PA if there were no contraindications. Furthermore, if both a clinical examination with initial NIHSS score $\geq$ 8 and clinical-DWI mismatch (clinical deficit out of proportion to DWI lesion, approximately < 70 ml volume core infarct by visual inspection) with concomitant large-vessel occlusion (intracranial internal carotid artery, middle cerebral artery M1, and Basilar artery) on MR angiography were found, endovascular recanalization therapy was performed using a MERCI device (Concentric medical Inc., Fremont, CA) or the Penumbra Aspiration System (Penumbra Inc., Alemeda, CA), and/or endovascular thrombolysis with urokinase.

Echocardiographic Methods

All patients underwent transthoracic echocardiography, which was examined by an experienced sonographer (AT), who was blinded to a patient's clinical background, within 24 h of hospital arrival. Patients were imaged in the left decubitus position with a commercially available system (iE33, Philips Ultrasound, Bothell, WA, USA; Vivid 7; GE Healthcare, Milwaukee, WI). Diastolic function was assessed by diastolic filling pressure, which was estimated as the ratio of early transmitral flow velocity (E) to mitral annular velocity (e') at the septal mitral annulus (E/e') on transthoracic echocardiography [13]. We also measured left atrial diameter and left ventricular ejection fraction. To determine inter-rater reliability, a second transthoracic echocardiography was performed within 24 h among 90 patients (34%).

Analysis

Clinical and imaging baseline parameters were compared between the deceased and the survival group using the Mann–Whitney U test to analyze numerical variables and the Fisher exact test to analyze categorical variables. The data were presented as median (interquartile range [IQR]) or frequency (%). To identify independent predictors of

in-hospital death, multivariate logistic regression analysis with backward elimination method was performed. We included variables, which were significantly associated with in-hospital death in the univariate analysis (P<0.1), in the multivariate model. Moreover, following variables were forced into the model since they were a priori known as clinical strong predictors related to clinical outcome: age, initial NIHSS score, initial DWI ischemic lesion volume. We conducted a sensitivity-specificity curve analysis to clarify an optimal threshold value of E/e' ratio for predicting in-hospital death. We also calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) if we used the optimal threshold value to predict in-hospital death at admission. Results were considered significant when the *P* value was less than 0.05. All analyses were performed using IBM SPSS software for Windows, version 18 (SPSS Inc., Chicago, IL, USA).

Results

Of 266 enrolled patients, 145 were male (55%), with a median age of 79 years (IQR, 70–85 years), a median NIHSS score of 13 (IQR, 5–20) and a median length of hospital

stay of 19 days (IQR, 15–26). Thirty patients (11%) died during hospitalization. The causes of death were as follows: brain edema, 25; congestive heart failure, 2; respiratory failure, 2; acute myocardial infarction, 1. Their median length of hospital stay was 4 days (IQR 3-9). The intervals of time from onset to first transthoracic echocardiography were similar between the two groups (median, 86 versus 89 min; P=0.797). Twenty-three patients (9%) underwent only CT because of pacemaker implantation.

The results of the univariate analysis are shown in Table 1. The deceased group had a higher initial NIHSS score (median, 20 versus 10; P<0.001), a shorter time from onset to admission (median, 106 minutes versus 145 minutes; P=0.024), a higher D-dimer level (median, 3.3 versus 1.8 μg/mL; P=0.008), a higher creatinine level (median, 1.00 versus 0.86 mg/dL; P=0.022), higher prevalence of internal carotid artery occlusion (62 versus 13 %; P<0.001), lower prevalence of middle cerebral artery M2 occlusion (8 versus 28 %; P=0.031), a larger initial ischemic lesion volume on DWI (median, 107 versus 8 mL; P<0.001), were more likely to have a parenchymal hemorrhage type 2 (64 versus 3 %; P<0.001), and had a higher E/e' ratio (median, 23 versus 14; P=0.001) than those in the survival group. Inter-rater reliability was excellent

for the E/e’ ratio with an intraclass coefficients of 0.819. The E/e’ ratio was weakly correlated with initial ischemic lesion volume (r=0.226, p=0.006).

Age, initial NIHSS score, D-dimer, glucose, creatinine, C-reactive protein, brain natriuretic peptide, albumin, internal carotid artery occlusion, initial ischemic lesion volume on DWI, and E/e’ ratio were chosen as possible predictors associated with in-hospital death. Multivariate logistic regression analysis with backward elimination method demonstrated that the E/e’ ratio (odds ratio, 1.181; 95% confidence interval, 1.025–1.361; P=0.021) was an independent predictor of in-hospital death (Table 2). A sensitivity-specificity curve analysis revealed an optimal threshold value of the E/e’ ratio for predicting in-hospital death. The optimal threshold value was 20 (Figure). The sensitivity, specificity, PPV, and NPV were 75%, 83%, 25%, and 98%, respectively.

Discussion

Diastolic dysfunction was an independent predictor of in-hospital death after acute ischemic stroke with AF. The NPV of an E/e’ ratio $\geq$20 was 98%. Furthermore, the

mortality rate was 25% for patients with an E/e' ratio ≥20, but only 2% for patients with an E/e' ratio < 20.

Possible explanations for the association between a high E/e' ratio and in-hospital death include: First, patients with a high E/e' ratio tend to have a large ischemic lesion. Consequently, that may develop fetal brain edema. Actually, a high E/e' ratio was correlated to initial ischemic lesion volume on DWI in this study. Iwakura et al. reported that diastolic dysfunction was associated with left atrial appendage thrombus in patients with AF [14]. Transesophageal echocardiography sometimes demonstrates large thrombus in left atrium in patients with AF. Therefore, a large thrombus in the left atrium may form a large ischemic lesion because of occlusion of a main artery of the brain. Second, diastolic dysfunction was independently associated with decreased exercise left ventricular systolic performance represented by the systolic index and cardiac index [15]. Oxygen supply may be unsatisfactory at the misery perfusion area, located around the ischemic core, in patients with diastolic dysfunction. Consequently, progression of the ischemic core in patients with diastolic dysfunction could be more apparent than that in patients with normal diastolic function. Third,

deceased patients may have already developed heart failure at presentation. A retrospective cohort study demonstrated a more than doubled risk of in-hospital death after stroke for chronic heart failure patients compared with stroke patients without chronic heart failure [16].

In this study, initial DWI ischemic lesion volume was not an independent predictor of in-hospital death among acute ischemic stroke patients with AF. Large acute DWI lesion volume predicts early neurological deterioration including death in patients with middle cerebral artery or intracranial internal carotid artery occlusion [17]. The reason for this may be that we included patients who suffered both anterior and posterior circulation ischemic stroke. The infarct volume formed in the posterior circulation area is generally smaller than that in the anterior circulation.

Plasma BNP level did not relate to in-hospital death in this study. Shibazaki et al. reported that high plasma BNP level predicted in-hospital death in acute ischemic stroke and TIA patients with AF [6]. According to Keyzer et al, BNP values among elderly subjects were higher than those among younger subjects [18]. In our study, age of patients in both groups was higher than that in their study. Moreover, there was no

significant difference between two groups in the median age.

Although some previous studies have indicated that low serum albumin [19], high plasma CRP [20], and hyperglycemia [21] are correlated to early death after acute ischemic stroke, multivariate logistic regression analysis in our study did not verify a correlation like that in previous reports. It has been previously reported that stroke severity indexed by the NIHSS score is an important predictor of mortality in all types of acute ischemic stroke [22,23]. Our study included cardioembolic stroke patients with AF and did not support those results.

There were some limitations in our study. We performed a retrospective analysis of prospectively collected data with a small sample size. This may result in a type 2 error. Multiple comparisons can lead to a type 1 error. Several cardiologists performed the second transthoracic echocardiography. However, inter-rater reliability was excellent.

Conclusions

Diastolic dysfunction may be associated with in-hospital death in ischemic stroke patients with atrial fibrillation. Clarification of diastolic dysfunction at presentation

might support clinicians in clinical practice. Further study is warranted to improve diagnosis of patients with the worst prognosis in acute ischemic stroke patients with diastolic dysfunction.

Acknowledgements

The authors would like to thank Dr. Minami and other staff of department of cardiology, and Ms. Sanae Kojima, Noriko Sakaguchi, Ayako Asada, Nozomi Kawanami and Aki Shiraishi, who were medical technologists of the ultrasound suite, for performing multiple examinations of transthoracic echocardiography.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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		Deceased group n = 30		Survival group n = 236		p value
Age, y	median (IQR)	80	(75-85)	79	(69-86)	0.319*
Gender	(M/F)	13/17		132/104		0.243†
Past medical history	n (%)					
Ischemic stroke		7	(23)	55	(24)	1.000†
Ischemic heart disease		5	(18)	29	(12)	0.380†
Renal dialysis		1	(4)	3	(1)	0.363†
Vascular risk factors	n (%)					

Hypertension		23	(77)	187	(80)	0.637†
Diabetes mellitus		8	(27)	52	(22)	0.643†
Dyslipidemia		7	(23)	53	(23)	1.000†
Smoking		3	(10)	54	(23)	0.152†
Medication before admission	n (%)					
Antiplatelet agent		13	(45)	68	(29)	0.090†
Anticoagulant agent		9	(32)	71	(30)	0.831†
Dependence before admission		5	(17)	30	(13)	0.566†
Time from onset to admission, min	median (IQR)	106	(60-165)	145	(79-458)	0.024*
Initial NIHSS score	median (IQR)	20	(18-23)	10	(4-18)	< 0.001*

Laboratory findings	median (IQR)					
BNP, pg/mL		246	(135-395)	237	(138-395)	0.837*
D-dimer, μg/mL		3.3	(1.1-7.0)	1.8	(0.9-3.6)	0.008*
PT-INR		1.05	(0.98-1.18)	1.06	(1.00-1.18)	0.656*
Glucose, mg/dL		156	(109-188)	124	(108-154)	0.053*
Total cholesterol, mg/dL		168	(151-199)	171	(153-198)	0.684*
C-reactive protein, mg/dL		0.18	(0.04-0.80)	0.19	(0.07-0.75)	0.150*
Albumin, mg/dL		3.8	(3.4-4.0)	3.8	(3.5-4.0)	0.935*
Creatinine, mg/dL		1.00	(0.82-1.32)	0.86	(0.71-1.07)	0.022*
Location of vessel occlusion	n (%)					

ICA occlusion		16/26	(62)	28/218	(13)	< 0.001†
MCA M1 occlusion		3/26	(12)	36/218	(17)	0.777†
MCA M2 occlusion		2/26	(8)	62/218	(28)	0.031†
PCA occlusion		0/26	(0)	17/218	(8)	0.229†
BA occlusion		2/26	(8)	6/218	(3)	0.205†
VA occlusion		0/26	(0)	4/218	(2)	1.000†
No occlusion		2/26	(8)	63/218	(29)	0.019†
DWI ischemic lesion volume, ml	median (IQR)	107	(59-237)	8	(1-31)	< 0.001*
PH type 2	n (%)	9	(30)	7	(3)	< 0.001†

Transthoracic echocardiography						
Left atrial diameter, mm	median (IQR)	42	(35-47)	42	(37-47)	0.610*
EF<40%	n (%)	4	(17)	18	(7)	0.109†
E/e’	median (IQR)	23	(20-29)	14	(11-18)	0.001*
Acute stroke treatment	n (%)					
IV tPA		7	(23)	47	(20)	0.635†
Endovascular therapy		5	(17)	16	(7)	0.071†

Table 1. Comparisons between Groups (Deceased Versus Survival)

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; BNP, brain natriuretic peptide; PT-INR, prothrombin time-international normalized ratio; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery; DWI, diffusion-weighted imaging; PH, parenchymal hematoma; EF, ejection fraction; and tPA, tissue-type plasminogen activator.

*Mann-Whitney U test.

†Fisher's exact test.

	p value	odds ratio	95% confidence interval		
ICA occlusion,	0.088	4.695	0.792	–	27.820
NIHSS score,	0.094	1.139	0.978	–	1.328
BNP, pg/mL	0.138	0.994	0.987	–	1.002
E/e' ratio,	0.021	1.181	1.025	–	1.361

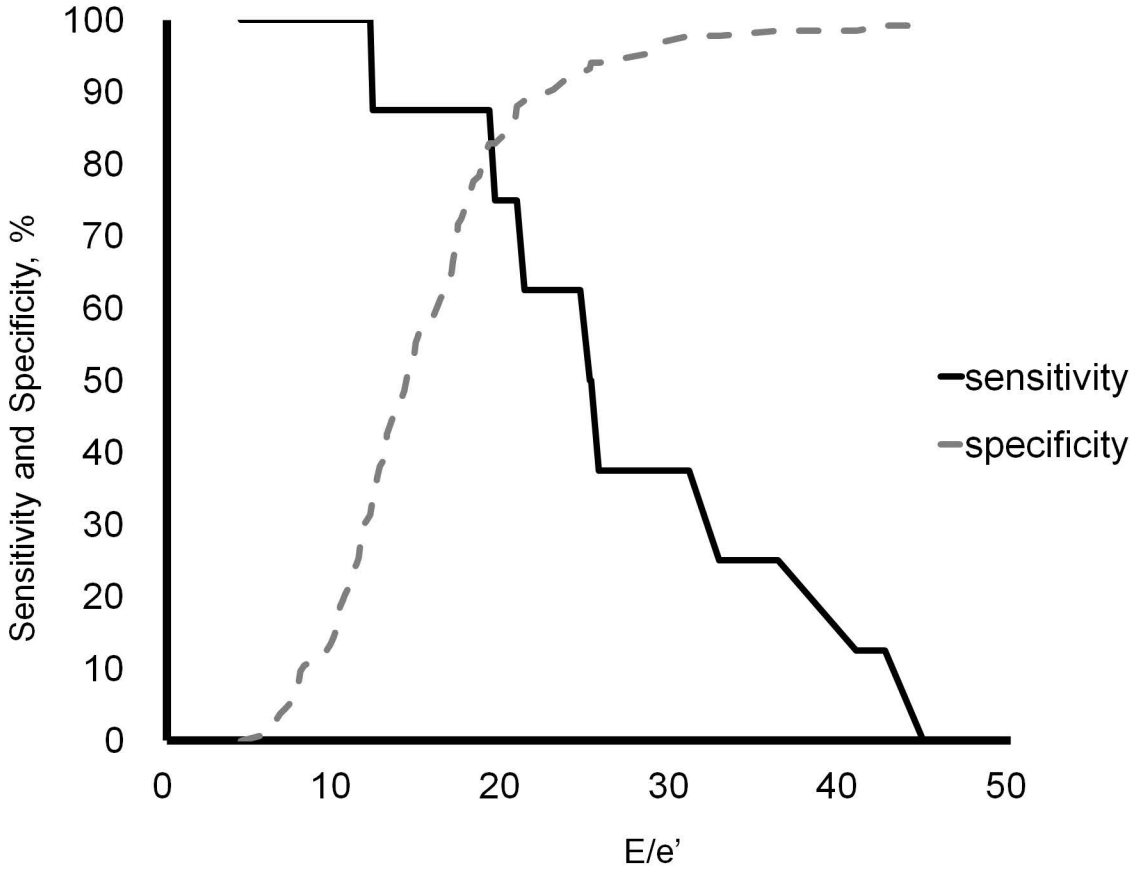
Table 2. Predictors of In-Hospital Death: Multivariate Logistic Regression Analysis

ICA indicates internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; BNP, brain natriuretic peptide.

Figure

An optimal threshold value of E/e’ for predicting in-hospital death was 20. The sensitivity and specificity were 75% and 83%, respectively

Figure


100
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Sensitivity and Specificity, %
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