Ltd., Osaka, Japan). Briefly, this assay uses 2 monoclonal antibodies against human BNP, 1 recognizing a carboxyl-terminal sequence and the other the ring structure of BNP, and measures BNP by sandwiching it between the 2 antibodies. BNP can be accurately quantified within 11 minutes. The normal value of BNP is ≤18.4 pg/ml in our hospital. The minimal detectable quantity of BNP is 3.9 pg/ml. The intra-assay coefficient of variation ranges from 1.6% to 3.6%, and the interassay coefficient of variation ranges from 1.3% to 4.5%. Investigators were not blinded to BNP results.

First, we investigated the detection rate of new AF, the method of identifying AF, and the interval to detection of AF during hospitalization. Second, we divided the patients into 2 groups according to the presence of AF: the new AF group, whose patients had newly documented AF during hospitalization, and the non-AF group. We compared the clinical characteristics, including BNP level, between the 2 groups using chi-square tests and Mann-Whitney U tests, and linear regression analysis was used to examine factors associated with plasma BNP level. The optimal cut-off points for each continuous variable to distinguish the new AF group from the non-AF group were determined from receiver-operating characteristic curves. Then, the factors with p values <0.10 on univariate analysis and the optimal level of plasma BNP were entered into a multivariate analysis to determine adjusted odds ratios. Finally, we evaluated the frequency of new AF detection for the following BNP levels: <50, 50 to <100, 100 to <200, 200 to <400, and ≥400 pg/ml. Data were statistically analyzed using StatView version 5 (SAS Institute Inc., Cary, North Carolina) and SPSS version 11 (SPSS Japan, Inc., Tokyo, Japan). Differences were considered statistically significant at p <0.05.

Results

During the study period, 844 patients were admitted to our hospital <24 hours after the onset of acute ischemic stroke. We excluded 260 patients with AF on admission ECG or with histories of AF or dialysis-dependent chronic renal failure. Finally, 584 patients were included in the present study (mean age 71.1 years, 209 women). The mean NIHSS score on admission was 7.1 ± 7.4.

All patients underwent continuous electrocardiographic monitoring, and 24-hour Holter ECG was performed in 536 patients (91.8%) (large artery atherosclerosis 91%, small vessel occlusion 100%, cardioembolism 81%, and other or undetermined findings 91%). AF was documented in 40 patients (6.8%) during hospitalization (new AF group). Delayed AF was detected in 28 patients by ECG and in 12 by 24-hour Holter ECG. The median interval from admission to the appearance of AF was 3 days (range 0 to 25; Figure 1). The non-AF group consisted of 544 patients (93.2%).

The baseline characteristics of the patients in the present study are listed in Table 1. The median age in the new AF group (78 years, interquartile range [IQR] 71 to 84) compared to the non-AF group (72 years, IQR 62 to 80) (p = 0.0007) and the median NIHSS score on admission (14 [IQR 5 to 20] vs 4 [IQR 2 to 9], p <0.0001) were significantly higher in the new AF group than in the non-AF group. There were no differences in the other variables.

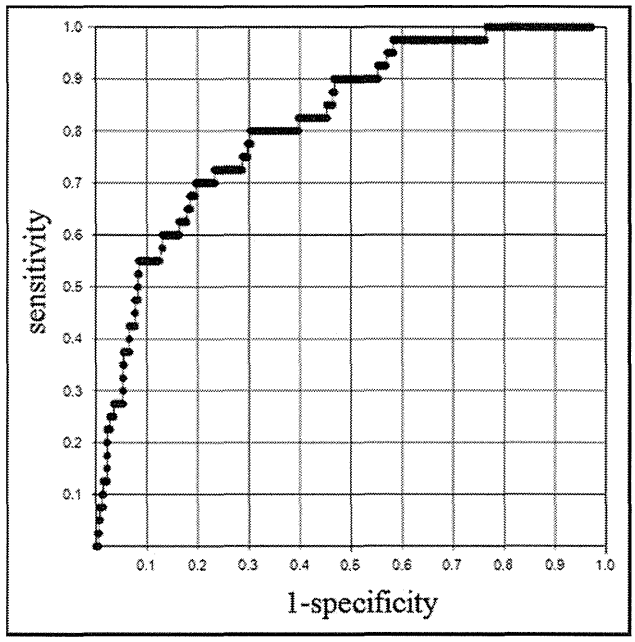

Figure 2. Receiver-operating characteristic curve analysis. The optimal cut-off value, sensitivity, and specificity required to distinguish new AF from non-AF were 65.0 pg/ml, 80.0% and 70.0%, respectively. The area under the curve using BNP to predict new AF was 0.82 (95% confidence interval 0.753 to 0.881).

Table 2
Multivariate logistic regression analysis models for probability of new atrial fibrillation

Variable	Odds Ratio	95% Confidence Interval	p Value
Age >75 years	1.4	0.693–2.987	0.3290
Female gender	1.2	0.595–2.493	0.5895
NIHSS score on admission >7	3.4	1.685–7.006	0.0007
BNP >65.0 pg/ml	6.8	2.975–15.359	<0.0001

The mean interval from stroke onset to blood sample collection was 8.2 ± 6.9 hours. The median plasma BNP level of the new AF group was significantly higher than that of the non-AF group (186.6 pg/ml [IQR 68.7 to 386.3] vs 35.2 pg/ml [IQR 15.9 to 80.1], p <0.0001). Plasma BNP level was significantly associated with female gender (p <0.0001) and previous coronary artery disease (p = 0.0013). Furthermore, plasma BNP level was correlated with age (r = 0.194, p <0.0001) and NIHSS score (r = 0.260, p <0.0001).

Age, female gender, NIHSS score on admission, and plasma BNP level were chosen as possible admission factors associated with delayed AF. The ability of BNP to identify the new AF group was assessed using receiver-operating characteristic curve analysis. A BNP level of 65.0 pg/ml had sensitivity of 80% and specificity of 70% (Figure 2). The area under the curve when BNP was used to differentiate the new AF group from the non-AF group was 0.82 (95% confidence interval 0.753 to 0.881). The cut-off levels

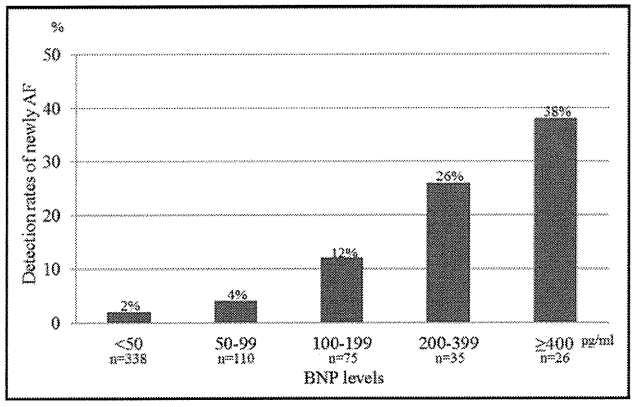

Figure 3. Detection rates of new AF according to the plasma BNP levels. The detection rates of new AF were increased with elevation of BNP levels.

of other variables that identified new AF with high sensitivity and high specificity were age >75 years (60% and 63%, respectively) and NIHSS score >7 (68% and 60%, respectively). On multivariate logistic regression analysis using these variables, NIHSS score >7 (odds ratio 3.4, 95% confidence interval 1.685 to 7.006, p = 0.0007) and plasma BNP >65.0 pg/ml (OR 6.8, 95% confidence interval 2.975 to 15.359, p <0.0001) were found to be independently associated with new AF (Table 2). The detection rates of new AF according to BNP levels were as follows: 2% of patients with BNP <50 pg/ml, 4% of those with 50 to <100 pg/ml, 12% of those with 100 to <200 pg/ml, 26% of those with 200 to <400 pg/ml, and 38% of those with ≥400 pg/ml (Figure 3).

Discussion

A plasma BNP level >65.0 pg/ml in acute ischemic stroke was an independent predictor of new AF. Furthermore, elevated BNP levels increased the frequency of detection of new AF.

A previous smaller study identified a BNP threshold level of >66.0 pg/ml with sensitivity of 92.3% and specificity of 97.5% as a predictor of cardioembolic stroke with paroxysmal AF,[7] and our larger population study supports this threshold. Therefore, in patients with acute ischemic stroke without AF on admission ECG or without histories of AF with plasma BNP levels >65.0 pg/ml, new AF should be considered and a diagnostic workup performed.

There are a few possible explanations for why elevated BNP levels increased the frequency of detection of new AF after ischemic stroke. It has been reported that plasma BNP is elevated in patients with congestive heart failure, and therefore, BNP is regarded as a hallmark of disease severity. Congestive heart failure is usually absent at BNP levels <100 pg/ml and usually present in patients with BNP levels >400 pg/ml.[17] The Framingham Heart Study demonstrated that congestive heart failure was significantly associated with the development of AF.[18] Tsang et al[19] demonstrated that the presence and severity of diastolic dysfunction are independently predictive of first documented nonvalvular AF in the elderly. Therefore, the presence and severity of congestive heart failure may induce the onset of AF because of an increase in atrial pressure, atrial stretch, and neurohormonal activation, including the release of atrial natriuretic factor.

In the present study, the total detection rate of new AF was 6.8%, which is compatible with previous studies.[20] However, we found that the detection rate of new AF increased accordingly as the BNP level increased, as follows: 2% of patients with BNP <50 pg/ml, 4% of those with 50 to <100 pg/ml, 12% of those with 100 to <200 pg/ml, 26% of those with 200 to <400 pg/ml, and 38% of those with ≥400 pg/ml. Douen et al[21] reported that serial electrocardiographic assessments within the first 72 hours of an acute stroke significantly improve the detection of AF (17.5%). Furthermore, Rizos et al[22] demonstrated that continuous bedside ECG monitoring for >48 hours diagnosed new AF (21.3%). We propose routine BNP measurement as screening for AF in acute ischemic stroke patients without either AF on admission ECG or histories of AF, and in patients with high plasma BNP levels, a more intensive diagnostic examination, such as serial ECG or continuous bedside ECG, should be performed.

Stroke severity is known to be associated with AF,[23] and our data by multivariate logistic regression analysis support this previous finding. In contrast, factors that commonly predict the risk to develop AF, such as older age, hypertension, and diabetes mellitus, were not independently associated with AF in our study.

The present study had some limitations. First, continuous ECG and 24-hour Holter ECG might have failed to diagnose AF in a small number of patients. Second, we did not evaluate cardiac function on admission. Further detailed investigation into cardiac function, such as left atrial diameter, mitral valve disorder, the ejection fraction, and E/E′ ratio, should be performed.

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ORIGINAL ARTICLE

Stroke patients with cerebral microbleeds on MRI scans have arteriolosclerosis as well as systemic atherosclerosis

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Cerebral microbleeds (CMBs) are recognized as a manifestation of arteriolosclerosis in cerebral small vessels. However, little is known regarding whether stroke patients with CMBs often have systemic atherosclerosis. The aim of the present study was to elucidate this issue using the cardio–ankle vascular index (CAVI), a new index of systemic atherosclerosis, in acute ischemic stroke patients. We prospectively studied 105 patients (71 males, median age = 70.0 years) with acute ischemic stroke. All of the patients were examined using T2*-weighted gradient echo magnetic resonance imaging (MRI) to look for and assess the CMBs and using fluid-attenuated inversion recovery to evaluate white matter hyperintensity (WMH). We assigned the patients into CMB and non-CMB groups and compared the clinical characteristics of these groups. The factors associated with CMBs were investigated using multivariate logistic regression analysis. T2*-weighted gradient echo MRI revealed CMBs in 47 patients (44.8%) and no CMBs in 58 patients (55.2%). The CAVI was significantly higher in the CMBs group (10.5 *vs.* 8.6, $P<0.001$). In the multivariate logistic regression analysis, CAVI per one point increase (odds ratio (OR), 1.50; 95% confidence interval (CI), 1.12–2.00; $P=0.006$), advanced WMH (OR, 4.78; 95% CI, 1.55–14.74; $P=0.006$) and impaired kidney function (OR, 3.31; 95% CI, 1.16–9.81; $P=0.031$) were independent factors associated with the presence of CMBs. A high CAVI was independently associated with CMBs in patients with acute ischemic stroke. Our results indicated that ischemic stroke patients with CMBs may have cerebral arteriolosclerosis as well as systemic atherosclerosis.
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Keywords: arteriolosclerosis; cardio–ankle vascular index; cerebral microbleeds; ischemic stroke; systemic atherosclerosis

INTRODUCTION

Cerebral microbleeds (CMBs), represented on T2*-weighted gradient echo magnetic resonance imaging (MRI) scans as spotty low-intensity areas, are found in 33.5–40.0% of patients with ischemic stroke,[1,2] and the presence of CMBs is recognized as a risk factor for subsequent intracerebral hemorrhage in such patients.[3] Histopathological analyses of the small cerebral vessels associated with CMBs have generally identified vascular pathological changes indicative of hypertensive arteriolosclerosis.[4,5]

Atherosclerosis of the systemic medium or large arteries is caused mainly by aging[6] and hypertensive wall damage.[7] Pulse wave velocity (PWV) is typically determined in the clinical setting to assess the grade of systemic atherosclerosis. Recently, the novel cardio–ankle vascular index (CAVI) was developed as an indicator of atherosclerosis.[8] A previous study showed that a CAVI $\geqslant 9.0$ was associated with the presence of carotid plaques, increased intima media thickness and coronary artery disease.[9] Furthermore, Suzuki *et al.*[10] reported that CAVI was statistically greater in ischemic stroke patients with leukoaraiosis and small-vessel occlusion. However, no evidence has yet indicated that CAVI is associated with CMBs in patients with ischemic stroke. The present study examined the association between CMBs and CAVI and determined whether ischemic stroke patients with CMBs exhibited not only cerebral arteriolosclerosis but also systemic atherosclerosis.

METHODS

Patients

We prospectively enrolled consecutive patients with acute cerebral infarction or transient ischemic attack within 7 days after onset between October 2009 and September 2010. All of the patients underwent diffusion-weighted imaging, fluid-attenuated inversion recovery (FLAIR) and T2*-weighted gradient echo MRI imaging. Cerebral infarction was diagnosed as an acute neurological event lasting $\geqslant 24$ h, which was explained by representative lesions on the MRI scan, including diffusion-weighted imaging. A transient episode of neurological dysfunction caused by focal brain ischemia lasting $\leqslant 24$ h was defined as transient ischemic attack. We examined blood biochemistry, blood count, electrocardiogram, MRI and chest X-rays upon admission, and CAVI was determined within 14 days thereafter. Patients with heart valve replacements,

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pacemakers or clipped cranial arteries were excluded from this study, as MRI is contraindicated for such patients.

The following clinical data were collected from all of the patients: (1) age and gender; (2) National Institutes of Health Stroke Scale (NIHSS) score upon admission; (3) vascular risk factors, including hypertension, diabetes mellitus and hyperlipidemia; (4) atrial fibrillation; (5) impaired kidney function; (6) previous illness, such as stroke, ischemic heart disease or peripheral artery disease; (7) current smoking status and history of alcohol consumption; (8) pre-admission use of antithrombotic agents, such as antiplatelet agents and warfarin; (9) CAVI; and (10) ischemic stroke subtype, using Trial of Org 10172 in the Acute Stroke Treatment (TOAST) criteria.[11]

Risk factors

We assessed vascular risk factors based on the following definitions: (1) hypertension was defined as a history of using antihypertensive agents, a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg 14 days after the stroke; (2) diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, a fasting blood glucose of $>126\,mg\,dl^{-1}$, or a glycosylated hemoglobin level $>6.4\%$; (3) hyperlipidemia was defined as the use of antihyperlipidemic agents or a serum cholesterol level $>220\,mg\,dl^{-1}$; (4) impaired kidney function was defined as a serum estimated glomerular filtration rate of $<60\,ml^{-1}$ min per $1.73\,m^2$; (5) previous stroke was defined as a history of cerebral infarction or intracranial hemorrhage; (6) previous ischemic heart disease was defined as a history of angina pectoris or myocardial infarction; and (7) peripheral artery disease was defined as an ankle–brachial index of <0.9 on at least one side.

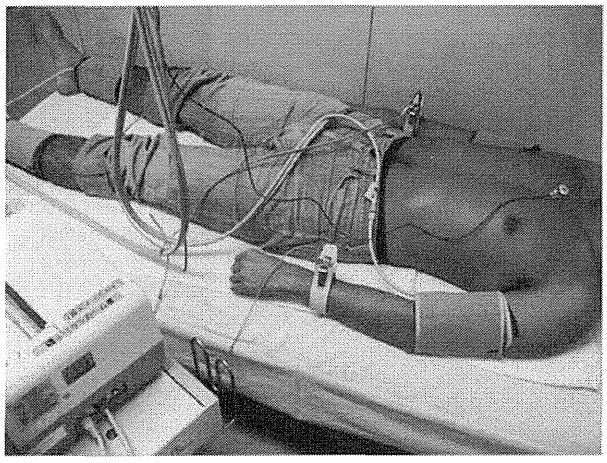

Figure 1 Measurement of the CAVI. The CAVI was automatically calculated from the pulse volume, blood pressure and vascular length from heart to ankle. CAVI, cardio–ankle vascular index.

Measurement of the CAVI

Technologists who were blinded to the clinical data measured the CAVI using an automated Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan). Cuffs were applied to the four extremities, and electrocardiogram electrodes were attached to the upper arm. A microphone was placed on the sternal angle to obtain phonocardiograms. The patients rested in the supine position for 5 min (Figure 1). The PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the time between the sound of the aortic valve closing and the notch of the brachial pulse wave and the time between the increase in the brachial and ankle pulse waves.

The CAVI was calculated from blood pressure and the PWV using the following equation:

$$CAVI = 2\rho \times 1/(Ps - Pd) \times \ln(Ps/Pd) \times PWV^2$$

(Ps, systolic blood pressure; Pd, diastolic blood pressure; ρ, blood density).

The higher CAVI obtained from either the left or right side was included in the analysis.

Neuroimaging of CMBs and white matter hyperintensity

We examined all of the patients by MRI within 7 days of admission using a Symphony Vision 1.5-T system (Siemens, Munich, Germany). The imaging protocol consisted of T2*-weighted gradient echo sequences (TR/TE, 484 ms/40 ms; field of view, 26 cm; acquisition matrix, 163×260; section thickness, 5.0 mm with a 0.5-mm intersection gap); a FLAIR sequence (TR/TE, 8550 ms/111 ms; field of view, 23 cm; acquisition matrix, 208×230; section thickness, 5.0 mm with a 0.5-mm intersection gap); and a diffusion-weighted imaging sequence (TR/TE, 2600 ms/79 ms; *b* values, 1000 and $50\,s\,mm^{-2}$; field of view, 23 cm; acquisition matrix, 230×230; section thickness, 5.0 mm with a 0.5-mm intersection gap). We defined CMBs as hypointense lesions 2–5 mm in diameter in the brain parenchyma identified in T2*-weighted gradient echo images (Figure 2a).

Patients with probable cerebral amyloid angiopathy according to the Boston criteria (multiple CMBs restricted to the cortical/corticosubcortical regions)

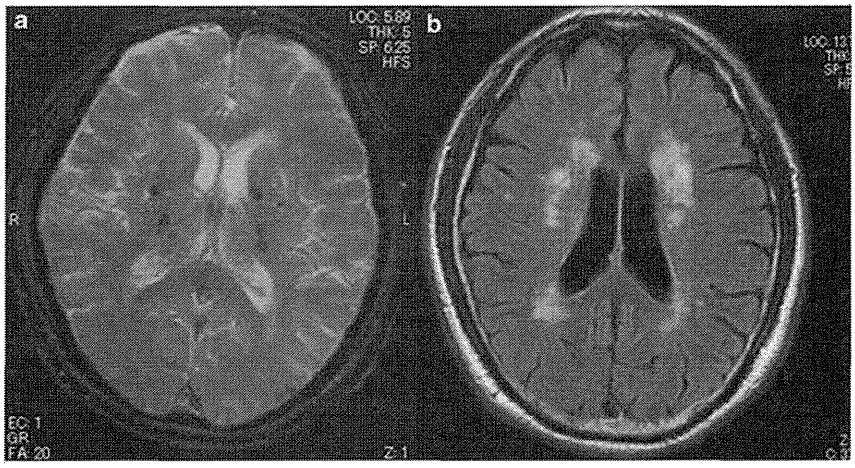

Figure 2 MRI scan of the brain of a 73-year-old male patient with lacunar infarction and a CAVI of 11.5. (**a**) A T2*-weighted gradient echo image shows multiple CMBs in the bilateral basal ganglia. (**b**) A FLAIR image shows advanced WMH. CAVI, cardio–ankle vascular index; CMBs, cerebral microbleeds; FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensity.

Table 1 Baseline clinical background of groups with and without CMBs

	All (n = *105*)	*CMBs* (n = *47*)	*Non-CMBs* (n = *58*)	P-*value*
Age, years; median (IQR)	70.0 (68.0–76.5)	72.0 (65.0–80.0)	66.5 (53.8–76.0)	0.017
Male, *n* (%)	71 (67.6)	36 (76.6)	35 (60.3)	0.095
NIHSS score; median (IQR)	3 (2–8)	3 (2–5)	2 (1–6)	0.461
Classification of stroke, n (%)				
Transient ischemic attack	9 (8.6)	3 (6.4)	6 (10.3)	
Large artery atherosclerosis	23 (21.9)	15 (31.9)	8 (13.8)	
Cardioembolism	26 (24.8)	9 (19.1)	17 (29.3)	
Small-vessel occlusion	18 (17.1)	11 (23.4)	7 (12.1)	
Other or undetermined cause	29 (27.6)	9 (19.1)	20 (34.5)	
Risk factors, n (%)				
Hypertension	79 (75.2)	42 (89.4)	37 (63.8)	0.003
Diabetes mellitus	39 (37.1)	17 (36.2)	22 (37.9)	1.000
Hyperlipidemia	52 (49.5)	21 (44.7)	31 (53.4)	0.434
Atrial fibrillation	21 (20.0)	5 (10.6)	16 (27.6)	0.048
Impaired kidney function	41 (39.0)	24 (51.1)	17 (29.3)	0.028
Previous stroke	24 (22.9)	17 (36.2)	7 (12.1)	0.005
Previous ischemic heart disease	11 (10.5)	7 (14.9)	4 (6.9)	0.213
Peripheral artery disease	23 (21.9)	13 (27.7)	10 (17.2)	0.239
Smoking	54 (51.4)	25 (53.2)	29 (50.0)	0.845
Alcohol	54 (51.4)	24 (51.1)	30 (51.7)	1.000
Antithrombotic agents	45 (42.9)	24 (51.1)	21 (36.2)	0.165
Advanced WMH, *n* (%)	47 (44.8)	32 (68.1)	15 (25.9)	<0.001
CAVI; median (IQR)	9.3 (8.1–10.7)	10.5 (9.2–11.7)	8.6 (7.6–10.2)	<0.001

Abbreviations: CAVI, cardio–ankle vascular index; CMBs, cerebral microbleeds; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; WMH, white matter hyperintensity.
Advanced WMH was defined as WMH of grades 2 or 3 using scoring system of Fazekas *et al.*

were excluded from this study.[12] Hypointense lesions within the subarachnoid space were regarded as pial blood vessels. Symmetric hypointense lesions in areas of the globus pallidus were regarded as calcification, and intracerebral lesions with a hemorrhagic component were excluded.

The severity of white matter hyperintensity (WMH) in the FLAIR images was scored as described by Fazekas *et al.*[13] into grades of 0, absent; 1, punctuate; 2, early confluent; and 3, confluent. Grade 2 or 3 WMH was regarded as advanced WMH (Figure 2b). One neurologist (TS) who was blinded to the clinical information evaluated the MRI images. The medical ethics committee of the Jikei University School of Medicine approved the study.

Statistical analysis

All of the patients were assigned to groups based on the presence or absence of CMBs, and their clinical characteristics were compared. Univariate analysis was performed using Fisher's exact test and the Mann–Whitney *U* test. Receiver operating characteristic curves analysis was performed to determine the cut-off values of CAVI to differentiate the two groups. Variables with *P*-values of <0.1 were included in the multivariate logistic regression analyses to determine factors that are independently associated with the presence of CMBs.

Then, linear regression analysis was used to test the association between the number of CMBs and the CAVI. Moreover, we also compared the clinical characteristics between the patients with single and multiple ($\geqslant 2$) CMBs. The data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS ver. 17.0) software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 113 patients were admitted to the Jikei University Hospital with acute ischemic stroke during the study period. We excluded two patients who were diagnosed with cerebral amyloid angiopathy, three with pacemakers and three who did not undergo CAVI determination because of a leg fracture ($n=1$) or death soon after admission ($n=2$). We therefore enrolled 105 patients (median age, 70.0 years; male, $n=71$; median NIHSS score, 3).

T2*-weighted gradient echo MRI revealed CMBs in 47 patients (44.8%) and no CMBs in 58 patients (55.2%). The characteristics of the two groups are shown in Table 1. The CMB group was significantly older than the non-CMB group (72.0 *vs.* 66.5 years; $P=0.017$). Hypertension, impaired kidney function and advanced WMH were more frequent (89.4% *vs.* 63.8%, $P=0.003$; 51.1% *vs.* 29.3%, $P=0.028$ and 68.1% *vs.* 25.9%, $P<0.001$), whereas atrial fibrillation was less frequent, in the CMB group than in the non-CMB group (10.6% *vs.* 27.6%, $P=0.048$). The use of antithrombotic agents before admission did not significantly differ between the two groups. The CAVI was significantly higher in the CMB group (10.5 *vs.* 8.6, $P<0.001$).

The factors with representative values of $P<0.1$ in the univariate analysis were age per 10 year increase, male sex, hypertension, previous stroke, atrial fibrillation, impaired kidney function, advanced WMH and CAVI per one point increase; these factors were included in the multivariate logistic regression analysis (Table 2, Model 1). CAVI per one point increase (odds ratio (OR), 1.50; 95% confidence interval (CI), 1.12–2.00; $P=0.006$), advanced WMH (OR, 4.78; 95% CI, 1.55–14.74; $P=0.006$) and impaired kidney function (OR, 3.31; 95% CI, 1.16–9.81; $P=0.031$) were independent factors associated with the presence of CMBs. Using receiver operating characteristic curves, the cut-off level for the CAVI in the presence of CMBs was 9.2

Table 2 Multivariate logistic analysis model to evaluate independent factors for the presence of CMBs

	Model 1			*Model 2*		
	OR	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*
Male	1.15	0.39–3.40	0.806	1.12	0.38–3.32	0.842
Age (per 10 years)	0.98	0.93–1.03	0.806	0.98	0.93–1.03	0.842
Hypertension	1.11	0.29–4.18	0.880	1.28	0.34–4.74	0.715
Impaired kidney function	3.31	1.16–9.81	0.031	2.81	0.97–8.20	0.058
Previous stroke	1.96	0.53–7.24	0.310	1.79	0.50–6.36	0.376
Atrial fibrillation	0.16	0.04–0.70	0.015	0.18	0.05–0.73	0.017
CAVI (per one point increase)	1.50	1.12–2.00	0.006	—	—	—
CAVI ⩾9.2	—	—	—	5.46	1.59–18.75	0.007
Advanced WMH	4.78	1.55–14.74	0.006	3.92	1.30–11.84	0.016

Abbreviations: CAVI, cardio-ankle vascular index; CI, confidence interval; CMBs, cerebral microbleeds; OR, odds ratio; WMH, white matter hyperintensity.
Advanced WMH is defined as grade 2 or 3 WMH using the scoring system of Fazekas *et al.*
Impaired kidney function is defined as serum estimated glomerular filtration rate $<60\,ml^{-1}\,min$ per $1.73\,m^2$.
Model 1: male, age (per 10 years), hypertension, impaired kidney function, previous stroke, atrial fibrillation, CAVI (per one point increase) and advanced WMH.
Model 2: male, age (per 10 years), hypertension, impaired kidney function, previous stroke, atrial fibrillation, CAVI ⩾9.2 and advanced WMH.

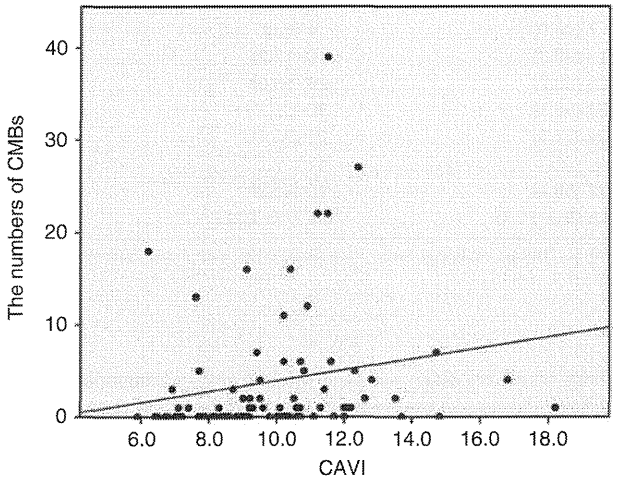

Figure 3 Linear regression analysis of the number of CMBs and the CAVI. There was a weak but statistically significant relationship between the number of CMBs and the CAVI ($R^2=0.040$, $P=0.041$). CAVI, cardio-ankle vascular index; CMBs, cerebral microbleeds.

(sensitivity, 78.7%; specificity, 65.5%). We also tested two categories (CAVI⩾9.2 or <9.2) with the same adjustment applied (Table 2, Model 2). A CAVI⩾9.2 was independently associated with CMBs (OR, 5.46; 95% CI, 1.59–18.75; $P=0.007$).

There was a weak but statistically significant relationship between the number of CMBs and the CAVI ($R^2=0.040$, $P=0.041$; Figure 3). Thirty-one patients (29.5%) had multiple CMBs on T2*-weighted gradient echo MRI scans. No significant differences in age, sex or any risk factors were observed between the two groups. There was no difference in the CAVI between the patients with single and multiple CMBs (10.4 *vs.* 10.5, $P=0.613$).

DISCUSSION

The present study found that the CAVI is independently associated with the presence of CMBs. It also found that advanced WMH and impaired kidney function are associated with the presence of CMBs. However, there was no factor, including the CAVI, that significantly distinguished patients with single CMBs from those with multiple CMBs.

We found a correlation between the CAVI (the new index of atherosclerosis) and CMBs in patients with acute ischemic stroke. Our results were partially in line with the previous findings of a close association between the PWV and CMBs.[14–16] However, the PWV is affected by changes in blood pressure during measurement and might not accurately reflect atherosclerosis in hypertensive patients.[8] In contrast, the CAVI is less influenced by blood pressure during measurement than is the PWV.[8] However, the mechanisms linking the CAVI and CMBs are complex and therefore not well understood. One possibility is that the CAVI reflects atherosclerosis in systemic large arteries, including the carotid, coronary and peripheral arteries.[8] Moreover, atherosclerosis in large extracranial[17] or intracranial arteries[18] also leads to arteriolosclerosis in small cerebral vessels and to the development of CMBs. Thus, systemic atherosclerosis may have a key role in the occurrence of cerebral arteriolosclerosis and CMBs. Indeed, the presence of CMBs is a risk factor not only for subsequent intracerebral hemorrhage in patients with ischemic stroke[3] but also for antithrombotic-related intracerebral hemorrhage.[19,20] Therefore, patients with a history of ischemic stroke and an elevated CAVI should be evaluated for CMBs and appropriately treated with antihypertensive and antithrombotic drugs to avoid intracerebral hemorrhage.

The present study demonstrated a significant relationship between advanced WMH and CMBs, which supports the results of other studies indicating a higher frequency of CMBs in patients with ischemic stroke accompanied by severe leukoaraiosis.[21,22] Pathologically, WMH and CMBs are attributed to cerebral small-vessel disease, such as the loss of smooth muscle cells, lumen restriction, vessel wall thickening, vessel wall damage and microaneurysms.[4,5] Interestingly, Suzuki *et al.*[10] showed that WMH was also correlated with the CAVI in ischemic stroke patients. Moreover, previous studies have established a strong association between the CAVI and small-vessel disease of other organs.[23,24] Kubozono *et al.*[23] reported a relationship between the CAVI and a low estimated glomerular filtration rate. Kim *et al.*[24] identified a correlation between the CAVI and microvascular complications in type 2 diabetes mellitus patients without a history of macrovascular disease. The CAVI may thus be a marker of small-vessel disease of various organs, including the brain.

Impaired kidney function was associated with CMBs in this study, which was in agreement with the finding that a low GFR is associated with CMBs.[25] We postulated that endothelial dysfunction might have a key role in impaired kidney function and in the development of CMBs. The kidneys and the brain are early targets for damage by elevated blood pressure.[26] Blood pressure is the major determinant of arteriosclerosis and endothelial dysfunction in patients with chronic kidney disease,[27] and endothelial dysfunction within capillaries appears to contribute to the development of CMBs.[28] Recent studies have shown that endothelial dysfunction is an important mechanism of cerebrovascular damage in patients with lacunar infarction[29] that is correlated with an increased risk of acute ischemic stroke.[30] However, the exact mechanism remains unclear.

The present study has several limitations. First, measurements of the CAVI might not be accurate in patients with severe aortic stenosis, peripheral arterial disease or atrial fibrillation.[22] Second, antihypertensive agents influence arteriosclerosis, and it cannot be excluded that the CAVI was affected in patients taking such drugs.[31] Finally, we could not find any significant factors, including the CAVI, that distinguish between the patients with single CMBs and those with multiple CMBs. The number of patients in our study was relatively small. Further studies are needed to evaluate the association of the CAVI with systemic atherosclerosis and CMBs.

In conclusion, we found that CMBs are independently associated with a high CAVI. We also found that stroke patients with CMBs more frequently exhibit arteriolosclerosis and systemic atherosclerosis than those without CMBs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients — A preliminary study

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ABSTRACT

Background and purpose: The aim of the present study was to investigate whether administration of edaravone during t-PA infusion can enhance early recanalization in acute stroke patients.
Methods: This trial was undertaken as a multicenter, single blind, randomized, open-labeled study. Acute stroke patients with M1 or M2 occlusion within 3 h of onset were studied prospectively. The subjects were randomly allocated to edaravone (Edaravone group: when t-PA was intravenously infused, intravenous edaravone (30 mg) was started at the same time) and no edaravone (Non-Edaravone group). Early recanalization within 1 h after t-PA infusion and neurological recovery 24 h after t-PA infusion were compared between the two groups.
Results: 40 patients (23 men, 17 women; mean age, 76.4 ± 8.2 years, median 79 years) were enrolled; 23 patients were assigned to the Edaravone group and 17 to the Non-Edaravone group. Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072). Eight patients who underwent endovascular therapy immediately after t-PA infusion were excluded, and neurological recovery was analyzed. Remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (80.1% vs. 45.5%, P = 0.0396).
Conclusion: Early recanalization and good neurological recovery were more frequently observed in the Edaravone group than in the Non-Edaravone group. These results demonstrate that administration of edaravone during t-PA infusion should enhance early recanalization in acute stroke patients.

1. Introduction

As a treatment intervention for acute stroke patients, it has been proven that intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes [1]; t-PA-related early arterial recanalization has been recognized as a marker of a good outcome after t-PA infusion [2–7].

Edaravone, a free radical scavenger and neuroprotectant, was approved by the Japanese Ministry of Health, Labour and Welfare in 2001 for the treatment of ischemic stroke within 24 h of onset to improve the neurological symptoms, disorders of activities of daily living, and functional outcomes. [8] The Japanese Guidelines for the management of stroke 2009 suggest edaravone for acute stroke as a grade B recommendation. Therefore, edaravone is now widely used for acute stroke in Japan.

In healthy individuals, the vascular endothelium activates an acute thromboprotective response if intravascular clotting occurs. A pivotal part of this response is a massive release of the key fibrinolytic enzyme t-PA. [9] Once embolus occludes a major artery, endothelial cells are impaired, and sufficient t-PA may not be released from damaged endothelial cells. Therefore, endothelial cell damage should be avoided when intravascular clotting occurs.

Free radicals are generated soon after vessel occlusion and damage the neurovascular unit, including endothelial cells. [10] Edaravone exerts an antioxidant action that suppresses free radicals and inhibits vascular endothelial cell injury. [10,11] Therefore, we hypothesized that administration of edaravone during t-PA infusion in acute stroke patients could inhibit the endothelial cell injury at the occluded artery, and release of t-PA from endothelial cells could be maintained, which could enhance early recanalization. Thus, a multicenter study to investigate whether administration of edaravone during t-PA infusion can enhance the early recanalization in t-PA patients was conducted.

2. Subjects and methods

2.1. Study designs

This trial was undertaken as a multicenter, single blind, randomized, open-labeled study, which was approved by the ethics committee of

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Kawasaki Medical School. The subjects were randomly allocated to edaravone (Edaravone group) and no edaravone (Non-Edaravone group) by the envelope method. That is, papers representing assignments of Edaravone group or Non-Edaravone group were in envelope, and the physician randomly pulled one paper from the envelope and made treatment decision according to assignments on the paper. The frequency of early recanalization and neurological recovery was compared between the two groups (Fig. 1).

2.2. Subjects

This trial was conducted in two departments (Kawasaki Medical School and Red Cross Okayama Hospital) from November, 2009 to March, 2011. The subjects were selected according to the following selection criteria. The inclusion criteria were: 1) patients who met the criteria of the Japan Alteplase Clinical Trial [12]; and 2) patients with M1 or M2 occlusion on MRA before t-PA infusion. The major exclusion criteria were: 1) patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded due to contraindications for MRI; and 2) patients with renal impairment whose serum creatinine exceeded 1.5 g/dl.

2.3. Treatment regimen

2.3.1. Edaravone group

When t-PA was intravenously infused, edaravone (30 mg) was started by intravenous drip infusion over 30 min at the same time. From the next day, edaravone was given in the morning and evening for 7 days.

2.3.2. Non-Edaravone group

Edaravone was not used during t-PA infusion. Edaravone was given after follow-up MRI study, which was performed within 1 h of the end of t-PA infusion. From the next day, edaravone was given in the morning and evening for 7 days.

2.4. Evaluation

The following clinical data were collected from all patients: 1) patient age and sex; 2) arterial blood pressure before t-PA infusion; 3) NIHSS score before and 24 h after t-PA infusion; 4) DWI-ASPECTS [13] on DWI before t-PA infusion; 5) presence or absence of early recanalization of occluded arteries within 60 min after t-PA administration; 6) vascular risk factors including hypertension (HT), Diabetes mellitus (DM), hyperlipidemia (HL), and smoking; 7) stroke subtype; 8) laboratory parameters before t-PA infusion; 9) M1 susceptibility vessel sign(SVS) on T2* before t-PA infusion [14], and 10) hemorrhagic transformation on T2* at 24 h after t-PA infusion.

Before t-PA infusion, MRI studies including DWI, T2*, and MRA to assess DWI-ASPECTS and to identify the occluded arteries were performed. The M1 SVS was defined as a hypointense signal of the proximal MCA on T2* within a vascular cistern in corresponding symptomatic occlusive vessels. [14] Follow-up MRA was performed within 60 min after the end of t-PA administration to identify the presence or absence of early recanalization in the occluded arteries. Recanalization was graded as complete, partial, or no recanalization

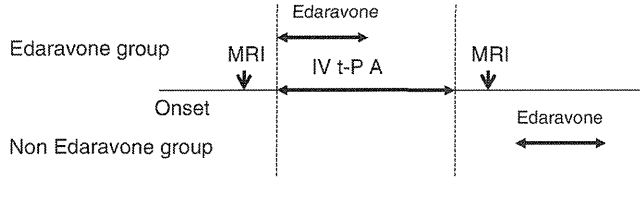

Fig. 1. Schematic of study protocol with IV t-PA treatment phases.

based on our previous report [14], as follows: 1) complete recanalization, reappearance of the entire occluded artery and the distal branches of vessels; 2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery; and 3) no recanalization, persistent occlusion. The presence and absence of recanalization were defined as complete or partial recanalization, and persistent occlusion 60 min after t-PA infusion, respectively. Next, to determine whether hemorrhagic transformation was present, follow-up T2* was performed 24 h after t-PA therapy. Hemorrhagic transformation was defined as the new appearance of low intensity lesions on the follow-up T2* compared to the initial T2*. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of ≥ 4 when the cerebral hemorrhage was likely to be the cause of clinical deterioration. The experienced researchers (KK and KK) who evaluated the MRI findings were blinded to patient clinical background data.

MRI was performed using a commercially available echo planar instrument operating on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). The imaging protocol consisted of T2*-weighted gradient echo (repetition time [TR]/echo time [TE] = 600/17 ms, flip angle 30°), a diffusion-weighted echo planar (TR/TE = 8000/70 ms) imaging series, and intracranial and extracranial MR angiography.

A neurologist determined the NIHSS scores before and 24 h after t-PA infusion. Remarkable recovery was defined as a ≥ 8-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. Good recovery was defined as a ≥ 4-point reduction in the total NIHSS score. Worsening was defined as a ≥ 4-point increase in the total NIHSS score [15].

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography (ECG), 24-h ECG monitoring, and transthoracic echocardiography. The following potential emboligenic cardiac diseases were considered: atrial fibrillation (AF); acute and previous myocardial infarction; mitral valve disease; and dilated cardiomyopathy. All patients underwent color-flow duplex carotid ultrasonography on the day of admission. Significant arterial stenosis was identified if stenosis >50% or ulcerated plaque was found in the affected artery corresponding to the neurological deficits.

All patients had baseline blood samples drawn in the emergency room before MRI. The leukocyte count, erythrocyte count, and platelet count, as well as $HbA1_C$, CRP, creatinine, glucose, and D-dimer levels, were determined.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [16] to determine stroke subtype. Large-vessel disease (LVD) was defined as >50% arterial stenosis or occlusion corresponding to neurological deficits in the absence of a source of cardiac embolism. Cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Undetermined stroke was used when no etiological source of emboli could be identified.

Statistical analysis was performed using StatView version 5 statistical software. The frequencies of early recanalization and remarkable and good recovery 24 h after t-PA infusion were compared between the two groups. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann–Whitney *U* test and Kruskal–Wallis *U* test for continuous variables. Values of $p<0.05$ were considered significant.

3. Results

A total of 90 consecutive stroke patients were treated with t-PA. Three patients were excluded because they had a pacemaker. Eighteen patients had no occlusion and twelve had vertebral-basilar stroke. Of the remaining 57 patients, initial MRA demonstrated M1 occlusion in 22 patients and M2 occlusion in 22 patients. Of these, four were excluded because of renal impairment (2), malignancy

(1), and registration error (1). Thus, 40 patients (23 men, 17 women; mean age, 76.4 ± 8.2 years, median 79 years) were enrolled in the present study.

Twenty-three patients were assigned to the Edaravone group, and seventeen were assigned to the Non-Edaravone group. Table 1 shows the clinical characteristics of the two groups. The proportion of females was higher in the Edaravone group than in the Non-Edaravone group (60.9% vs. 17.6%, P = 0.0097). However, other clinical characteristics did not differ between the two groups.

Follow-up MRA within 60 min after t-PA infusion revealed early recanalization in 15 (37.5%) patients (complete in 6 patients, partial in 9) and no recanalization in 25 (62.5%). Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072)(Table 2 and Fig. 2). The occurrence of hemorrhagic transformation 24 h after t-PA infusion did not differ between the two groups (60.9% vs. 64.7%, P = 0.9999) Symptomatic intracranial hemorrhage was observed in 2 Non-Edaravone group patients (Table 2).

Before t-PA infusion, the NIHSS scores did not differ between the two groups (12.7 ± 6.4 for the Edaravone group vs. 12.8 ± 6.4 for the Non-Edaravone group, P = 0.9455). Remarkable recovery, good recovery and worsening were 65.2% for the Edaravone group vs. 29.4% for the Non-Edaravone group, 13.0% vs. 5.9%, and 4.4% vs. 17.6%, respectively. Therefore, remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (78.3% vs. 35.3%, P = 0.0061). However, worsening was not different between the two groups (4.4% vs. 17.6%, P = 0.1657). Immediately after t-PA infusion, endovascular therapy was performed in 8 patients (2 in Edaravone group, and 6 in Non-Edaravone group). When those patients were excluded from the analysis of neurological recovery 24 h after t-PA infusion, remarkable recovery, good recovery and worsening were 66.7% for the Edaravone group vs. 36.4% for the Non-Edaravone group, 14.3% vs. 9.1%, and 4.8% vs. 18.2%, respectively. Thus, remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (80.1% vs. 45.5%, P = 0.0396). However, worsening was not different between the two groups (4.8% vs. 18.2%, P = 0.2661) (Table 2 and Fig. 3).

Table 1
Clinical characteristics of the two groups.

Clinical symptoms (%)	Edaravone group	Non-Edaravone group	P
	No = 23	No = 17	
Female	14(60.9%)	3(17.6%)	0.0097
Age (years)	76.9 ± 7.3	75.8 ± 9.5	0.8055
Hypertension	13(56.5%)	12(70.6%)	0.3637
Diabetes mellitus	5(21.7%)	6(35.3%)	0.3426
Hyperlipidemia	4(17.4%)	2(11.8%)	0.6223
Smoking	2(8.7%)	1(5.9%)	0.9999
Atrial fibrillation (AF)	17(73.9%)	13(76.5%)	0.9999
Stroke type			0.6833
Cardioembolic stroke	17(73.9%)	13(76.5%)	
Large artery disease	1(4.4%)	0(0%)	
Others	5(21.7%)	4(23.5%)	
Baseline NIHSS score	12.7 ± 6.4	12.8 ± 6.4	0.9455
Systolic blood pressure (mm Hg)	137.5 ± 20.0	149.2 ± 19.7	0.0591
Diastolic blood pressure (mm Hg)	77.6 ± 14.3	82.2 ± 12.5	0.3523
Time from symptom onset to t-PA infusion, min	140.4 ± 27.5	131.2 ± 45.2	0.7017
Laboratory data			
HbA1C (%)	5.7 ± 0.7	6.2 ± 2.3	0.7426
Glucose (mg/dl)	139.1 ± 33.7	166.5 ± 111.6	0.9346
CRP (mg/dl)	0.9 ± 1.3	1.1 ± 2.3	0.6815
Leucocytes (/μl)	7309.6 ± 2074.1	7409.4 ± 2790.2	0.6916
Erythrocytes (X10000/μl)	441.4 ± 55.4	411.6 ± 67.6	0.1470
Platelets (X10000/μl)	19.5 ± 6.0	17.9 ± 4.6	0.4601
Creatinine (mg/dl)	0.7 ± 0.3	0.8 ± 0.2	0.1255
PT-INR	1.1 ± 0.2	1.8 ± 3.1	0.8374
Site of occlusion			0.9999
M1	11(47.8%)	9(52.9%)	
M2	12(52.2%)	8(47.2%)	
Baseline DWI-ASPECTS	7.2 ± 1.9	7.1 ± 1.8	0.8161
M1 SVS on T2*	1(4.3%)	3(17.6%)	0.2941

Table 2
Early recanalization rate, hemorrhagic transformation, and neurological recovery of the two groups.

Clinical symptoms (%)	Edaravone group	Non-Edaravone group	P
	No = 23	No = 17	
Early recanalization	13(56.5%)	2(11.8%)	0.0072
Complete	5(21.7%)	1(5.9%)	
Partial	8(34.8%)	1(5.9%)	
Hemorrhagic transformation	14(60.9%)	11(64.7%)	0.9999
Symptomatic	0(0.0%)	2(11.8%)	0.1744
Baseline NIHSS score	12.7 ± 6.4	12.8 ± 6.4	0.9455
NIHSS score 24 h after t-PA infusion	6.9 ± 6.8	10.9 ± 8.7	0.0924
Remarkable recovery	15(65.2%)	5(29.4%)	0.0252
Good recovery	3(13.0%)	1(5.9%)	0.6235
Worsening	1(4.4%)	3(17.6%)	0.2941
Dramatic and good recovery	18(78.3%)	6(35.3%)	0.0061
Excluding 8 patients with endovascular therapy after t-PA infusion			
	No = 21	No = 11	
Baseline NIHSS score	12.9 ± 6.5	12.4 ± 7.5	0.7062
NIHSS score 24 h after t-PA infusion	7.3 ± 6.9	9.5 ± 9.2	0.5386
Remarkable recovery	14/21(66.7%)	4/11(36.4%)	0.1422
Good recovery	3/21(14.3%)	1/11(9.1%)	0.9999
Worsening	1/21(4.8%)	2/11(18.2%)	0.2661
Dramatic and good recovery	17/21(80.1%)	5/11(45.5%)	0.0396

4. Discussion

Early recanalization was more frequently observed in the Edaravone group than the Non-Edaravone group. Thus, administration of edaravone during t-PA infusion in acute stroke patients should enhance early recanalization of the occluded artery.

Vascular endothelium releases massive amounts of t-PA as an acute thromboprotective response when intravascular clotting occurs. [9] Therefore, it is important to avoid vascular endothelial cell injury when embolus occludes the artery. Pharmacological studies using cultured bovine aorta have demonstrated that edaravone inhibits vascular endothelial cell injury. [11] Simultaneous administration of edaravone and t-PA should inhibit endothelial cell injury, and release of t-PA from endothelial cells may be maintained. Therefore, t-PA released from vascular endothelial cells in addition to intravenously administered t-PA should enhance early recanalization.

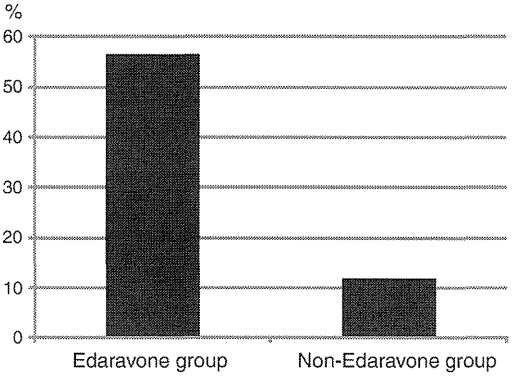

Fig. 2. The early recanalization rate for the Edaravone and Non-Edaravone groups. Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072).

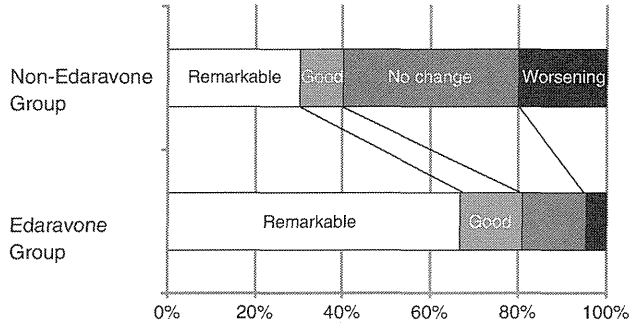

Fig. 3. The frequency of neurological recovery 24 h after t-PA infusion for the Edaravone and Non-Edaravone groups. Remarkable and good recovery was more frequently observed in the Edaravone group than in the Non Edaravone group (80.1% vs. 45.5%, P = 0.0396).

Recently, the EDO trial demonstrated that edaravone was effective for the treatment of acute noncardioembolic ischemic stroke within 24 h of onset. [17] Edaravone inhibited brain edema, prevented infarct expansion, improved the neurological symptoms, and attenuated delayed neuronal cell death in ischemic animal models. [18–22] Uno et al. [23]. reported that edaravone reduced oxidative damage in patients with acute stroke. Furthermore, several investigators reported that edaravone inhibited rt-PA-induced cerebral hemorrhage in the ischemic brains of rats. [10,24] The reason for this was that edaravone inhibited the dissociation of the basement membrane and prevented endothelial cell damage and BBB disruption in acute ischemic stroke. Therefore, edaravone should also be effective for acute stroke patients treated with t-PA.

The internationally recommended dosage of t-PA is 0.9 mg/kg, but in Japan, the 0.6 mg/kg dose has been selected according to the J-ACT study results. [12] Therefore, there may be a problem of dosage efficacy. However, J-MARS showed that the frequency of favorable outcome at 3 months in patients between 18 and 80 years with a baseline NIHSS score <25 was 39%, which suggested that 0.6 mg/kg intravenous alteplase should be safe and effective. [25] In J-MARS, edaravone was used in 74.6% of 7492 patients (unpublished), but it was not known when edaravone was administered before and after t-PA infusion. Furthermore, J-ACT II showed that the frequency of early recanalization of the occluded MCA within 6 h after t-PA infusion was about 50% and induced a favorable clinical outcome, compatible to that previously reported with the 0.9 mg/kg dose [26]. In the Edaravone group in the present study, the frequency of early recanalization of the occluded MCA was about 50%, which was similar to the J ACT II results. In J-ACT II, 91.4% of patients were treated with edaravone (unpublished), but it was not known when edaravone was administered before and after t-PA infusion. In J-ACT II and J-MARS, it is possible that edaravone enhanced early recanalization, resulting in favorable outcomes.

The present study had several limitations. Firstly, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis. [27] Secondly, MRI cannot be performed in patients with implantation of metallic materials such as pacemakers and metal clips; three patients were excluded from our study. Thirdly, the results of patients treated without edaravone for 7 days were not examined. Therefore, the effects on patient outcome and hemorrhagic transformation between patients with and without use of edaravone for 7 days were not established. Fourthly, the distribution of the number of patients between the two groups was not even due to use of the envelope method. Finally, although the sample size was small, the difference in the frequency of early recanalization between the two groups was very significant. We believe that edaravone should enhance early recanalization.

In conclusion, early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group. Thus, administration of edaravone during t-PA infusion in acute stroke patients should enhance early recanalization of the occluded artery. Edaravone should be given for acute stroke patients as soon as possible.

Conflicts of interest

The authors have no conflict of interests to disclose.

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Admission hyperglycemia causes infarct volume expansion in patients with ICA or MCA occlusion: association of collateral grade on conventional angiography

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Background and purpose: Hyperglycemia (HG) is associated with infarct volume expansion in acute ischaemic stroke patients. However, collateral circulation can sustain the ischaemic penumbra and limit the growth of infarct volume. The aim of this study was to determine whether the association between HG and infarct volume expansion is dependent on collateral circulation.

Methods: We performed a retrospective analysis of 93 acute ischaemic stroke patients with internal carotid artery or middle cerebral artery occlusion within 24 h of onset were retrospectively studied. HG was diagnosed in patients with an admitting blood glucose value ≥140 mg/dl. Angiographic collateral grade 0–1 was designated as poor collateral circulation and grade 2–4 as good collateral circulation. Infarct volume was measured at admission and at again within 7 days using diffusion-weighted magnetic resonance images.

Results: Among 34 patients with poor collateral grade, the change in infarct volume was significantly greater in the HG group than in the non-HG group (106.0 ml vs. 22.7 ml, $P = 0.002$). Among the 59 patients with good collateral circulation, the change in infarct volume was greater in the HG group than in the non-HG group (53.3 ml vs. 10.9 ml, $P = 0.047$). Multiple regression analysis indicated that admission HG ($P = 0.004$), baseline National Institutes of Health Stroke Scale score ($P = 0.018$), and poor collateral circulation ($P = 0.040$) were independently associated with infarct volume expansion.

Conclusions: Infarct volume expansion was greater in individuals with HG on admission regardless of collateral circulation status.

Introduction

Hyperglycemia (HG) is common in acute ischaemic stroke patients, and often occurs without a preexisting diagnosis of diabetes [1]. Previous studies have shown that HG is associated with infarct volume expansion and poor outcomes in acute ischaemic stroke patients [2,3]. HG is thought to influence neuronal damage via the facilitation of lactic acid production in ischaemic tissue [2]. In animal studies, HG increases with oxidative stress and matrix metalloproteinase-9 activity and causes cerebral edema formation after ischaemia [4].

On the other hand, collateral circulation plays an important role in maintaining tissue viability during large vessel occlusion [5] and can limit infarct volume expansion and improve functional status in ischaemic stroke patients [5]. However, few previous studies have reported on collateral circulation grade in acute ischaemic stroke patients.

The aim of this study was to determine whether collateral circulation alters the relation between HG and the expansion of infarct volume and functional outcome in acute ischaemic stroke patients with internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion.

Subjects and methods

Patients

Between April 2004 and July 2011, 426 acute ischaemic stroke patients with ICA or MCA occlusion were

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admitted within 24 h of stroke onset according to our stroke registry. We retrospectively examined the records of patients who underwent conventional angiography. We excluded patients treated with intravenous tissue plasminogen activator (t-PA) or endovascular therapy, because early recanalization after thrombolysis should rescue the ischaemic penumbra and does not affect infarct volume expansion [6]. The protocol of this study was approved by the medical ethics committee of Kawasaki Medical School.

Clinical characteristics

Routine blood biochemistry, blood count, and electrocardiograph examinations were performed on admission. From these data, we obtained leukocyte, erythrocyte and platelet count, and hematocrit, plasma glucose and glycated hemoglobin levels. We classed patients as having HG if blood glucose levels were $\geq$140 mg/dl [7]. We also determined the presence of vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation. The ischaemic stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria [8]. The severity of neurological deficits was graded on admission according to the National Institutes of Health Stroke Scale (NIHSS) [9].

Neuroimaging

Magnetic resonance imaging (MRI) was performed on admission (baseline) and within 7 days after admission (follow-up) using a 1.5-T Vision MRI (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). Diffusion-weighted imaging (DWI) MRI was used to determine infarct volume and T2* gradient echo MRI was used to determine the occurrence of hemorrhagic transformation at each time point. Two neurologists (T.S. and J.U.), who were blind to the clinical information, performed these evaluations. Infarct volume was quantified using image analysis software (NIH Image). The regions of hyperintense lesions were manually outlined on each slice, and multiplied by the slice thickness and inter-slice gap to obtain a volume measure. The window level and window width were chosen to obtain the best between the lesion and the normal surrounding tissue. The change in infarct volume (ΔInfarct) was considered the difference between baseline and follow-up MRI volumes (Fig. 1).

Hemorrhagic transformation was defined as the appearance of low intensity lesions that were at least partially in the ischaemic lesion on the follow-up image.

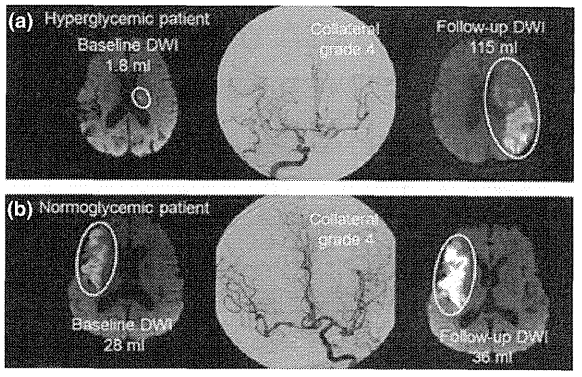

Figure 1 Representative diffusion weighted MRI at baseline (left) and follow-up (right) from a patient with HG (top panel; admission glucose level of157 mg/dl) and a patient without HG (bottom panel; admission glucose level 120 mg/dl). Both patients were classified as having good collateral circulation.

Magnetic resonance angiography (MRA) was performed on admission (baseline) and within 7 days after admission (follow-up) and used to identify spontaneous recanalization of the occluded arteries. Spontaneous recanalization was defined as complete (i.e., reappearance of the entire occluded artery and distal branches) or partial (i.e., resolution of part of the distal vessel supplied by an occluded artery) [10] on the follow-up MRA.

Conventional angiography

Conventional angiography included injection of both common carotid arteries and the dominant vertebral artery through the late venous phase. Two neurologists (T.S. and J.U.), who were blind to the clinical information, evaluated the collateral grade of occluded arteries according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System [11]. The grades assigned were 0) no collaterals visible to the ischaemic site, 1) slow collaterals to the periphery of the ischaemic site with persistence of some of the defect, 2) rapid collaterals to the periphery of the ischaemic site with persistence of some of the defect and to only a portion of the ischaemic territory, 3) collaterals with slow but complete angiographic blood flow of the ischaemic bed by the late venous phase, or 4) complete and rapid collateral blood flow to the vascular bed in the entire ischaemic territory by retrograde perfusion. Grades 0 and 1 were classified as poor collateral circulation, and grades 2–4 were classified as good collateral circulation [12]. The Kappa coefficient for inter-observer agreement was 0.817 for collateral grade.

Patient outcomes

Patient outcome was quantified using the modified Rankin Scale (mRS) score [13] at discharge. Poor outcome was defined as mRS score of 5 at discharge, or death during hospitalization.

Analysis

Patients were classified in the HG and non-HG groups according to admission glucose level. Patient characteristics were compared across these two groups using a Mann–Whitney U test for continuous variables and a chi-squared test for categorical variables. The primary outcome variables were ΔInfarct and the patient outcome. The secondary outcome measures were the presence or absence of spontaneous recanalization and hemorrhagic transformation.

Patients were further divided according to collateral circulation (poor; good). The primary outcome variables (ΔInfarct and patient outcome) were compared among four subgroups according to admission glucose level (HG; non-HG) and collateral circulation (poor; good).

Multiple regression analysis was performed to identify variables that predicted ΔInfarct. Regression models included HG status (HG; non-HG), collateral circulation grade (poor; good), and other potentially predictive variables (NIHSS score, baseline infarct volume, spontaneous recanalization, hemorrhagic transformation and past history of hypertension).

Statistical analyses were carried out using Statistical Package for the Social Science (SPSS version 17.0) software for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation in the text and tables. Values of $P < 0.05$ were considered statistically significant.

Results

Of the 426 acute ischaemic stroke patients examined, 176 underwent conventional angiography. Of these 176 patients, we excluded 45 patients treated with endovascular therapy, 23 patients treated with intravenous t-PA and seven patients treated with combined endovascular and intravenous t-PA therapy. We also excluded four patients with pacemakers, three patients who did not undergo follow-up MRI because of severe stroke and one patient who did not undergo complete conventional angiography. The remaining 93 patients (65 men, age 67.7 ± 13.3 years) formed the sample for this study. There were 52 patients with ICA occlusion, 23 patients with M1 occlusion, and 18 patients with M2 occlusion (Table 1).

Table 1 Clinical characteristics and outcomes in the HG and non-HG groups

	HG group (n = 50)	non-HG group (n = 43)	P
Age (years)	68.5 ± 13.9	66.2 ± 13.3	0.500
Male, n (%)	35 (70.0)	30 (69.8)	1.000
Risk factors, n (%)			
Hypertension	45 (90.0)	25 (58.1)	0.001
Hyperlipidemia	10 (20.0)	16 (37.2)	0.104
Diabetes mellitus	23 (46.0)	6 (14.0)	0.001
Atrial fibrillation	19 (38.0)	9 (20.9)	0.112
Laboratory data			
Leukocytes (per μl)	7766.0 ± 2264.7	7252.1 ± 1796.5	0.363
Erythrocytes (× 10 000/μl)	434.3 ± 64.6	434.4 ± 50.0	0.994
Hematocrit (%)	39.5 ± 6.4	40.3 ± 5.0	0.450
Platelets (× 10 000/μl)	20.7 ± 5.2	21.7 ± 7.5	0.929
Glucose (mg/dl)	188.2 ± 67.8	114.3 ± 15.2	<0.001
HbA1c (%)	6.3 ± 1.3	5.6 ± 0.5	<0.001
Stroke type, n (%)			
Cardioembolic stroke	20 (40.0)	17 (39.5)	1.000
Large vessel disease	17 (34.0)	16 (37.2)	0.829
Others or undetermined stroke	13 (26.0)	10 (23.3)	0.813
Time from symptom onset to initial MRI (h)	5.4 ± 4.8	5.4 ± 5.0	0.761
Interval between initial and follow-up MRI (days)	4.5 ± 2.6	4.1 ± 2.4	0.437
Time from symptom onset to conventional angiography (h)	27.5 ± 43.5	29.6 ± 50.4	0.945
Occluded artery, n (%)			
ICA	27 (54.0)	25 (58.1)	0.834
M1	14 (28.0)	9 (20.9)	0.478
M2	9 (18.0)	9 (20.9)	0.795
Infarct volume (ml)			
Baseline	32.8 ± 65.3	36.3 ± 63.0	0.627
Follow-up	103.0 ± 116.6	52.1 ± 77.3	0.056
Δ(follow-up – baseline)	70.1 ± 86.4	15.8 ± 40.0	0.001
Spontaneous recanalization, n (%)	6 (12.0)	16 (37.2)	0.004
Hemorrhagic transformation, n (%)	12 (24.0)	9 (20.9)	0.806
Baseline NIHSS score	10.7 ± 7.9	8.2 ± 6.8	0.133
Poor outcome, n (%)	22 (44.0)	8 (18.6)	0.014

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale. MRI, magnetic resonance imaging; ICA, internal carotid artery; M1,M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery.

HG

Fifty patients (53.8%) were classified in the HG group and 43 patients (46.2%) in the non-HG group. The clinical characteristics and outcome variables for both

groups are shown in Table 1. Hypertension and diabetes mellitus were more prevalent in the HG group than in non-HG group (90.0% vs. 58.1%, $P = 0.001$ for hypertension and 46.0% vs. 14.0%, $P = 0.001$ for diabetes mellitus). Glycated hemoglobin level was higher in the HG group than in the non-HG group (6.3 ± 1.3% vs. 5.6 ± 0.5%, $P < 0.001$). The baseline infarct volume was similar in the two groups (32.8 ± 65.3 ml vs. 36.3 ± 63.0 ml, $P = 0.627$), as was the interval between baseline and follow-up MRI (4.5 ± 2.6 days vs. 4.1 ± 2.4 days; $P = 0.437$). ΔInfarct was larger in the HG group than in non-HG group (70.1 ± 86.4 ml vs. 15.8 ± 40.0 ml, $P = 0.001$) and poor outcome at discharge was more common (44.0% vs. 18.6%, $P = 0.014$). Spontaneous recanalization was less frequent in the HG group than in the non-HG group (12.0% vs. 37.2%, $P = 0.004$); however, hemorrhagic transformation was similar (24.0% vs. 20.9%, $P = 0.806$).

Collateral grade

Thirty-four patients (36.6%) were classified as having poor collateral circulation and 59 patients (63.4%) as having good collateral circulation. The clinical characteristics and outcome variables for both groups are shown in Table 2. Hypertension and hyperlipidemia were more prevalent in patients with good collateral circulation than in patients with poor collateral circulation (83.1% vs. 61.8%, $P = 0.027$ for hypertension and 37.3% vs. 11.8%, $P = 0.009$ for hyperlipidemia). Atrial fibrillation was more prevalent in patients with poor collateral circulation than in patients with good collateral circulation (44.1% vs. 22.0%, $P = 0.035$). There was a higher prevalence of cardioembolic strokes (61.8% vs. 27.1%, $P = 0.002$) and a lower rate of large vessel disease (14.7% vs. 47.5%, $P = 0.002$) in patients with poor collateral circulation, and a lower rate of ICA occlusion (32.4% vs. 69.5%, $P = 0.001$). The severity of neurological deficits was also greater in patients with poor collateral circulation (NIHSS score; 11.4 ± 6.2 vs. 8.4 ± 7.9, $P = 0.026$).

Infarct volume was larger in patients with poor collateral circulation (63.9 ± 86.2 ml vs. 17.5 ± 38.1 ml, $P < 0.001$ at baseline, and 125.8 ± 127.4 ml vs. 52.8 ± 75.0 ml, $P = 0.001$ at follow-up), and ΔInfarct was similar across groups (61.9 ± 89.5 ml vs. 35.3 ± 61.8 ml, $P = 0.089$). Spontaneous recanalization and hemorrhagic transformation were more frequent in the poor collateral group than the good collateral group (41.2% vs. 13.6%, $P = 0.005$ for spontaneous recanalization and 35.3% vs. 15.3%, $P = 0.039$ for hemorrhagic transformation). The frequency of poor outcome was similar in the two groups (41.2% vs. 27.1%, $P = 0.175$).

Table 2 Clinical characteristics and outcomes of patients with poor collateral circulation and patients with good collateral circulation

	Poor collateral ($n = 34$)	Good collateral ($n = 59$)	P
Age (years)	69.0 ± 12.8	66.5 ± 14.1	0.219
Male, *n* (%)	21 (61.8)	44 (74.6)	0.242
Risk factors, *n* (%)			
Hypertension	21 (61.8)	49 (83.1)	0.027
Hyperlipidemia	4 (11.8)	22 (37.3)	0.009
Diabetes mellitus	7 (20.6)	22 (37.3)	0.109
Atrial fibrillation	15 (44.1)	13 (22.0)	0.035
Laboratory data			
Leukocytes (per μl)	7355.3 ± 1668.0	7628.1 ± 2272.6	0.895
Erythrocytes (× 10 000/μl)	422.3 ± 59.8	441.3 ± 56.3	0.080
Hematocrit (%)	39.6 ± 5.8	40.1 ± 5.8	0.836
Platelets (× 10 000/μl)	21.0 ± 5.8	21.3 ± 6.7	0.943
Glucose (mg/dl)	147.4 ± 43.4	157.9 ± 71.5	0.753
HbA1c (%)	5.8 ± 0.7	6.0 ± 1.3	0.506
Stroke type, *n* (%)			
Cardioembolic stroke	21 (61.8)	16 (27.1)	0.002
Large vessel disease	5 (14.7)	28 (47.5)	0.002
Others or undetermined stroke	8 (23.5)	15 (25.4)	1.000
Time from symptom onset to initial MRI (h)	5.3 ± 5.6	5.5 ± 5.4	0.274
Interval between initial and follow-up MRI (days)	4.1 ± 2.6	4.5 ± 2.5	0.493
Time from symptom onset to conventional angiography (h)	23.8 ± 43.4	31.2 ± 48.4	0.283
Occluded artery, *n* (%)			
ICA	11 (32.4)	41 (69.5)	0.001
M1	9 (26.5)	14 (23.7)	0.806
M2	14 (41.2)	4 (6.8)	<0.001
Infarct volume (ml)			
Baseline	63.9 ± 86.2	17.5 ± 38.1	<0.001
Follow-up	125.8 ± 127.4	52.8 ± 75.0	0.001
Δ(follow-up - baseline)	61.9 ± 89.5	35.3 ± 61.8	0.089
Spontaneous recanalization, *n* (%)	14 (41.2)	8 (13.6)	0.005
Hemorrhagic transformation, *n* (%)	12 (35.3)	9 (15.3)	0.039
Baseline NIHSS score	11.4 ± 6.2	8.4 ± 7.9	0.026
Poor outcome, *n* (%)	14 (41.2)	16 (27.1)	0.175

NIHSS, National Institutes of Health Stroke Scale. MRI, magnetic resonance imaging; ICA, internal carotid artery; M1,M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery.

Hyperglycemia and collateral grade

Table 3 shows infarct volume and patient outcome between poor and good collateral circulation in the HG group and non-HG group. Of the 50 patients in the HG

Table 3 Infarct volume and patient outcome between poor and good collateral circulation in the HG group and non-HG group

	HG group (n = 50)			Non-HG group (n = 43)		
	Poor collateral (n = 16)	Good collateral (n = 34)	P	Poor collateral (n = 18)	Good collateral (n = 25)	P
Infarct volume (ml)						
Baseline	66.2 ± 93.7	17.1 ± 39.2	0.002	61.8 ± 81.5	17.9 ± 37.2	0.010
Follow-up	172.2 ± 138.6	70.4 ± 89.7	0.005	84.5 ± 103.6	28.8 ± 37.2	0.085
Δ(follow-up – baseline)	106.0 ± 101.4	53.3 ± 74.1	0.018	22.7 ± 54.9	10.9 ± 24.4	0.730
Spontaneous recanalization, n (%)	4 (25.0)	2 (5.9)	0.074	10 (55.6)	6 (24.0)	0.055
Hemorrhagic transformation, n (%)	5 (31.3)	7 (20.6)	0.486	7 (38.9)	2 (8.0)	0.023
Baseline NIHSS score	13.3 ± 6.5	9.5 ± 8.2	0.116	9.7 ± 5.7	7.0 ± 7.4	0.084
Poor outcome, n (%)	9 (56.3)	13 (38.2)	0.360	5 (27.8)	3 (12.0)	0.247

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

group, 16 had poor collateral circulation and 34 had good collateral circulation. Infarct volume was larger in hyperglycemic patients with poor collateral circulation than in HG patients with good collateral circulation (66.2 ± 93.7 ml vs. 17.1 ± 39.2 ml, P = 0.002 at baseline and 172.2 ± 138.6 ml vs. 70.4 ± 89.7 ml, P = 0.005 at follow-up), as was ΔInfarct (106.0 ± 101.4 ml vs. 53.3 ± 74.1 ml, P = 0.018).

Of the 43 patients in the non-HG group, 18 had poor collateral circulation and 25 had good collateral circulation. Infarct volume at baseline was larger in non-hyperglycemic patients with poor collateral circulation than in non-hyperglycemic patients with good collateral circulation (61.8 ± 81.5 ml vs. 17.9 ± 37.2 ml, P = 0.010); however, infarct volume at follow-up was similar in the two groups (84.5 ± 103.6 ml vs. 28.8 ± 37.2 ml, P = 0.085). However, ΔInfarct was not statistically different (22.7 ± 54.9 ml vs. 10.9 ± 24.4 ml, P = 0.730).

Table 4 shows infarct volume and patient outcome between the HG group and non-HG group in poor and good collateral circulation. Of the 34 patients with poor collateral circulation, 16 were in the HG group and 18 were in the non-HG group. Of the 59 patients with good collateral circulation, 34 were in the HG group and 25 were in the non-HG group. Infarct volume at baseline was similar in the HG and non-HG groups, regardless of collateral circulation status (66.2 ± 93.7 ml vs. 61.8 ± 81.5 ml, P = 0.746 for patients with poor collateral circulation and 17.1 ± 39.2 ml vs. 17.9 ± 37.2 ml, P = 0.569 for patients with good collateral circulation). Among patients with poor collateral circulation, ΔInfarct was larger in the HG group than in the non-HG group (106.0 ± 101.4 ml vs. 22.7 ± 54.9 ml, P = 0.002), but the prevalence of poor outcome at discharge was similar (56.3% vs. 27.8%, P = 0.163). Among patients with good collateral circulation, ΔInfarct was also larger in the HG group than in the non-HG group (53.3 ± 74.1 ml vs. 10.9 ± 24.4 ml, P = 0.047) and poor outcome at discharge was more common (38.2% vs. 12.0%, P = 0.038).

Table 5 shows results of the multiple regression analysis of infarct volume change. Admission HG (P = 0.004), poor collateral circulation (P = 0.040), and baseline NIHSS score (P = 0.018) were independently associated with infarct volume expansion.

Table 4 Infarct volume and patient outcome between the HG group and non-HG group in poor and good collateral circulation

	Poor collateral (n = 34)			Good collateral (n = 59)		
	HG group (n = 16)	Non-HG group (n = 18)	P	HG group (n = 34)	Non-HG group (n = 25)	P
Infarct volume (ml)						
Baseline	66.2 ± 93.7	61.8 ± 81.5	0.746	17.1 ± 39.2	17.9 ± 37.2	0.569
Follow-up	172.2 ± 138.6	84.5 ± 103.6	0.036	70.4 ± 89.7	28.8 ± 37.2	0.206
Δ(follow-up – baseline)	106.0 ± 101.4	22.7 ± 54.9	0.002	53.3 ± 74.1	10.9 ± 24.4	0.047
Spontaneous recanalization, n (%)	4 (25.0)	10 (55.6)	0.092	2 (5.9)	6 (24.0)	0.061
Hemorrhagic transformation, n (%)	5 (31.3)	7 (38.9)	0.729	7 (20.6)	2 (8.0)	0.278
Baseline NIHSS score	13.3 ± 6.5	9.7 ± 5.7	0.135	9.5 ± 8.2	7.0 ± 7.4	0.190
Poor outcome, n (%)	9 (56.3)	5 (27.8)	0.163	13 (38.2)	3 (12.0)	0.038

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

Table 5 Multiple regression analysis of factors related to infarct volume expansion

	R^2	P
Admission HG	0.269	0.004
Baseline NIHSS score		0.018
Poor collateral		0.040
Spontaneous recanalization		0.073
Baseline infarct volume		0.339
Hemorrhagic transformation		0.482
Hypertension		0.571

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

Discussion

In this study, we retrospectively examined the medical records of acute ischaemic stroke patients and found that admission HG was associated with infarct expansion and poor outcome. These findings are consistent with previous reports [2,3]. The novel finding of this study is that admission HG is associated with infarct expansion regardless of collateral circulation status. This was confirmed by multiple regression analysis, where admission HG was independently associated with infarct expansion, regardless of collateral circulation grade and other factors. However, poor collateral circulation might not adversely affect infarct volume expansion in the non-HG group. Spontaneous recanalization occurred less frequently in patients with HG and good collateral circulation.

Our results show that admission HG is an important determinant of infarct expansion, even in patients with good collateral circulation. Only one previous report has examined the relationship between HG and infarct expansion at the same time as evaluating collateral circulation, and these authors found that serum glucose levels did not influence infarct size when collateral circulation was accounted for [14]. However, infarct expansion was evaluated using computer tomography, and angiographic findings were classified according to the presence or absence of collateral circulation rather than by detailed collateral grade. To the best of our knowledge, this study is the first to demonstrate the association between HG and infarct expansion according to collateral grade assessed using conventional angiography.

Collateral circulation plays a key role in maintaining tissue viability and rescues the ischaemic penumbra [5]. When collateral circulation was present, infarct volume was more strongly affected in patients with diabetics than patients with no diabetics [14]. The relation between HG and infarct expansion has been demonstrated in the available collateral circulation. Prado *et al.* [15] reported that cortical infarct regions are vulnerable to the deleterious effects of HG in the presence of collateral circulation, whereas striatum infarct regions are not. Variations in collateral circulation anatomy may be associated with infarct volume expansion in HG patients with good collateral circulation. There is limited accuracy in the evaluation of collateral circulation for end-arterial vascular territories by conventional angiography [5]. On the other hand, cortical circulation supplied by leptomeningeal collaterals is insufficient to sustain adequate cerebral perfusion pressure [16]. Therefore, HG may reduce pial collateral circulation and lead to cortical infarct volume expansion in patients with good collateral circulation.

Poor collateral circulation is insufficient to sustain cerebral perfusion in the penumbra and increased infarct volume [5]. In animal models, cerebral circulation in the penumbra is more reduced in the acute hyperglycemic state [17]. Therefore, HG may accelerate the reduction in cerebral circulation in the penumbra and lead to marked infarct expansion with poor collateral circulation. We found that poor collateral circulation affected infarct volume expansion in the HG group, but not in the non-HG group. These findings may support the hypothesis that HG causes fatal tissue damage in cases of poor collateral circulation. Previous reports showed that hemorrhagic transformation [12] and infarct growth [18] were more frequently observed in patients with poor collateral circulation, if recanalization has been achieved following endovascular therapy. Thus, management of HG may be a therapeutic option to limit infarct volume expansion in patients with poor collateral circulation.

Spontaneous recanalization occurred less frequently in patients with HG. This may be due to accelerated procoagulant activity in patients with HG [19]. A recent study demonstrated that acute HG decreased plasma fibrinolytic activity in rats and that this was associated with increased plasminogen activator inhibitor type 1 activity and decreased plasma t-PA activity [20]. The acute hyperglycemic state may hamper the fibrinolytic process, delaying reperfusion of the ischaemic penumbra in tPA-treated patients [21]. Delayed recanalization should rescue the ischaemic penumbra, but HG might not adversely affect patient outcome to the same extent as in patients without delayed recanalization [3]. The interval between baseline and follow-up MRIs in this study precluded assessment of early recanalization. Therefore, we did not observe any difference in spontaneous recanalization between patient outcomes in the two groups. Prospective studies that include detailed coagulant markers and a strict protocol of follow-up MRIs are needed to confirm our hypothesis.

We found that spontaneous recanalization was less frequent in patients with good collateral circulation. This differs from one previous report that angiographic collateral grade determined the recanalization rate after endovascular revascularization therapy [18]. In the present study, cardioembolic stroke was less frequent and large vessel occlusion was more frequent in patients with good collateral circulation. Moreover, ICA occlusion was more frequent in these patients. Kimura *et al.* [22] reported that the recanalization rate of ICA occlusions was lower than that of MCA occlusions after intravenous t-PA therapy. Differences in stroke etiology and the occluded artery may affect the rate of spontaneous recanalization and its relation to collateral circulation.

This present study is limited by the retrospective design. Patients were classified into HG and non-HG groups according to blood glucose levels measured at a single time point, whereas classification is more accurate with serial blood glucose measures. We did not perform perfusion weighted imaging. Although diffusion-perfusion mismatch volume is not dependent on collateral grade [23], evaluation of penumbral volume alongside angiographic collateral grade may provide new insights about the harmful effects of HG. Finally, the number of patients studied was small, and a larger sample is needed to more rigorously test our hypothesis.

In conclusion, admission HG was associated with infarct volume expansion and poor outcome in patients with ICA or MCA occlusion. Moreover, admission HG influenced infarct volume expansion regardless of collateral circulation.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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