動脈狭窄症の治療選択に関するおもな項目を以下にあげた。

1 米国心臓協会（American Heart Association：AHA）・米国脳卒中協会（American Stroke Association：ASA）・米国心臓学会議（American College of Cardiology Foundation：ACCF）ほか14学会合同ガイドライン（2011年）[1]

①血管内手術リスクが平均以下の症候性患者は、同側内頸動脈径が非侵襲的画像検査で70％以上またはカテーテル血管撮影で50％以上（Class I、Evidence Level：B）減少し、周術期脳卒中率・致死率が6％未満の場合、CEAの代替としてCASが示唆される。

②血行再建術が示唆される高齢者、とくに動脈の病理解剖が血管内手術に好ましくない場合に、CASよりCEAを選択するのは理にかなっている。（Class Ⅱa、Evidence Level：B）

③血行再建術が示唆される患者で頸部の解剖が血管手術に好ましくない場合に、CEAよりCASを選択するのは理にかなっている。（Class Ⅱa、Evidence Level：B）

④脳血管撮影で60％、DUSで70％以上の無症候性頸動脈狭窄に対する予防的CASは考慮してもよいが、内科的治療のみと比較してより効果的かどうかは確立されていない。（Class Ⅱb、Evidence Level：B）

⑤合併疾患のためにCEAまたはCAS後合併症率が高いハイリスクの症候性または無症候性頸動脈狭窄患者は、内科的治療のみと比較して頸部血行再建がより効果的かどうかは確立されていない。（Class Ⅱb、Evidence Level：B）

⑥特殊な状況を除いて、動脈硬化による内腔狭窄が50％未満のとき、CEA、CASどちらの頸動脈血行再建も推奨されない。（Class Ⅲ、Evidence Level：A）

＊米国神経学会（American Academy of Neurology：AAN）は2005年に独自にCEAの治療指針[13]を出しているが、本ガイドラインを承認すると表明している。（http://www.aan.com/go/practice/guidelines）

2 本邦の脳卒中治療ガイドライン（2009年）[11]

①内頸動脈狭窄症において、CEAの危険因子（うっ血性心不全、冠動脈疾患、開胸手術が必要な心臓疾患、重篤な呼吸器疾患、対側頸動脈閉塞、対側喉頭神経麻痺、頸部直達手術または頸部放射線治療の既往、CEA再狭窄例、80歳以上）をもつ症例に対して、CASを行うことが奨められる。（Grade B）

②内頸動脈狭窄症において、CEAの危険因子を持たない症例においては、CASを行うことを考慮してもよいが、十分な科学的根拠はない。（Grade C1）

＊本邦の現行ガイドラインはSAPPHIRE研究にもとづいて作成されたもの（CREST研究前）であり、80歳以上の高齢者についてCASが推奨されている。

おわりに

上述したように、頸動脈狭窄症の治療について、現状ではCASはCEAと同等の効果があるとする大規模試験とそうでないとする研究結果があり、いまだ一定した結論は得られていない。治療ガイドラインも、AHA等では高齢者に対する治療についてCREST研究の結果を踏まえてCEA推奨とされるなど、依然流動的である。

ここで紹介した試験結果も執筆時には最新の情報を心がけたが、とくにCASに関する器具・手技の進歩は日々目覚ましいものがある[14]。長

年にわたりほぼ確立され安定した手技と結果をもたらすCEA[15]との関係とともに、とりわけ無症候性頸動脈狭窄症における新規薬剤・内科的治療の発展と外科治療適応との関係は今後も変容していくであろう。新しいデバイスやテクニック、薬剤を用いた進行中の比較試験の結果も逐次明らかとなっていく。本項を踏まえたうえで、臨床家としてさらなる不断の知識更新が必要なことはいうまでもない。

（片野広之、間瀬光人、山田和雄）

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Letter to the Editor

Predictors of an increase in the number of cerebral microbleeds after a first-ever stroke ☆

Keywords:
Blood pressure
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MRI
Stroke
Risk factor
Hypertension

To the Editor:

Gradient-echo T2*-weighted magnetic resonance imaging (MRI) can detect the paramagnetic effect of blood breakdown products and visualize clinically silent cerebral microbleeds (CMBs) with high sensitivity [1]. Chronic hypertension is considered to be an important causative factor of CMBs. [2] We hypothesized that high blood pressure (BP) after a stroke may lead to an increase in the number of CMBs, and result in subsequent stroke recurrence. The aim of this study was to determine predictors of an increase in CMBs after a first-ever stroke and address the association between changes in frequency of CMBs and BP parameters including ambulatory BP, which is a better predictor of cardiovascular disease than casual BP [3].

This was a prospective study and was approved by the Institutional Research and Ethics Committee. A total of 157 consecutive patients with first-ever stroke, including transient ischemic attack (TIA), who were admitted to our institute within 7 days of onset from 2003 through 2004, were considered for entry into this study. After 33 patients were excluded from the study (contraindication for MRI, neurosurgical operation, and so on), we enrolled 124 patients. Baseline characteristics, including age, sex, smoking habit, alcohol consumption, presence of hypertension, dyslipidemia, diabetes mellitus, heart disease, and past history of stroke, were investigated as our previous report [4].

MRI was performed on 1.5-T scanners (Magnetom vision; Siemens, Erlangen, Germany). We obtained gradient-echo T2*-weighted MRI in the axial plan. The parameters of T2*-weighted MRI and definition of CMBs were noted in our previous report [5]. Two investigators (C.Y. and N.Y.) reviewed the number of CMBs.

Casual BP was measured on admission in a supine position before any drugs were given. Ambulatory BP was determined in patients with ischemic stroke, but not in patients with brain hemorrhage, because antihypertensive agents were often started soon after the admission. Ambulatory BP was measured every 30 min in the daytime and every 60 min in the nighttime by the use of a portable monitoring device (TM2425 or TM2431, A&D Co Ltd). The averages of systolic, diastolic, and mean BP were evaluated. At 2 years after the onset, follow-up MRI and BP measurement were performed in the same manner as the baseline assessments.

We divided the patients into 3 groups: patients with increase in CMBs, decrease in CMBs, and no change in CMBs. The mean follow-up period was 741 ± 67.2 days (± standard deviation). Seven patients died during the follow-up period and an additional 41 patients (dropped-out, severe disability, and so on) were excluded. The remaining 76 patients underwent the follow-up examinations. The number of CMBs increased in 16 patients (21%), decreased in 8 patients (11%), and did not change in 52 patients (68%). Patient characteristics were comparable among these three groups. Three patients had stroke recurrence; one with TIA and 1 with brain infarction in the group of no change in CMBs, and 1 with brain hemorrhage in the group of decrease in CMBs. Among patients with an increase in CMBs, the frequency of alcohol consumption was higher than those with a decrease and those without a change (86% vs. 58% vs. 13%, $p = 0.013$). Patients with either an increase or a decrease in CMBs had a significantly higher frequency of hemorrhagic stroke at baseline (44% and 38%, respectively) than those without a change in CMBs (14%, [$p = 0.022$]). Patients with an increase in CMBs as well as a decrease had a significantly higher frequency of presence of CMBs at baseline (81% and 100%, respectively) than patients with no change (8%, [$p < 0.001$]). Patients with increase in CMBs as well as decrease were less frequently treated with antithrombotic agents during the follow-up period than patients with no change ($p = 0.013$). At the baseline assessment, casual diastolic BP in patients with an increase in CMBs as well as a decrease was significantly higher than those with no change ($p = 0.013$). Ambulatory BP parameters at both the baseline and follow-up studies were not significantly different among the three groups. In a logistic regression analysis, alcohol consumption (odds ratio; OR 15.7, 95% confidence interval; 95% CI 2.2–235.0) and presence of CMBs at baseline (OR 28.8, 95% CI 1.5–320.0) were independent predictors of an increase in CMBs (Table 1).

There was no significant association between changes in CMBs during the follow-up period and BP levels in the chronic stage, or with stroke recurrence rate in the present study. Staals et al. [6] reported that higher 24-hour ambulatory BP was an important risk factor for CMBs in lacunar stroke patients. We previously reported that high ambulatory BP and casual BP were associated with CMBs in acute stroke patients [5]. In the present study, however, the relationship between casual BP at the baseline and increase in CMBs in the univariate analysis was not upheld in the multivariate analysis.

Table 1
Logistic regression analysis for predictors of an increase in CMBs.

Independent factors	Odds ratio	95% CI	*p* value
Hemorrhagic stroke at baseline	2.1	0.1–99.9	0.671
Alcohol consumption	15.7	2.2–235.0	0.002
Antithrombotic agents	0.7	0.03–26.0	0.812
Casual DBP >90 mmHg at baseline	0.8	0.10–5.9	0.822
Presence of the CMBs at baseline	28.8	1.5–320.0	<0.001

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Instead of BP parameters, the presence of CMBs at baseline or alcohol consumption is independent predictor of increase in CMBs although large 95% CIs were determined. It was previously reported that the initial existence of CMBs was associated with increase in CMBs [7]. The initial existence of CMBs might be contributed from vascular fragility. The association between alcohol consumption and risk of brain hemorrhage or an increase in CMBs might share common pathophysiology [8]. Although there was only a small sample with decrease in CMBs, dynamic temporal change of CMBs was shown in the present study, being consistent with the other recent study [9]. We think that mechanisms of changes in CMBs would be heterogeneous [10], such as the progression of cerebral amyloid angiopathy, inflammation, hypertensive angiopathy or other vasculopathy. The present study had several limitations: the small sample size, many patients lost to follow-up, over or underestimation on MRI, and so on. The present study is, however, the first to use serial brain MRI to address the association between changes in frequency of CMBs and BP parameters. A prospective study with a larger population and a longer follow-up period is needed to clarify the clinical implications of CMBs.

Conflict of interest statement

The authors report no conflicts of interest.

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9 August 2012

High Plasma D-Dimer is a Marker of Deep Vein Thrombosis in Acute Stroke

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This study investigated whether plasma D-dimer level is useful for detection of deep vein thrombosis (DVT) in patients with acute stroke. A total of 133 patients hospitalized within 3 days after stroke onset underwent duplex venous ultrasonographic examination of the lower limbs and repeated measurements of plasma D-dimer level. DVT was detected in 36 of 100 patients with ischemic stroke and in 25 of 33 patients with intracerebral hemorrhage (ICH) (76%; $P < .001$). Plasma D-dimer level on admission (7.5 ± 10.7 μg/mL vs 3.7 ± 10.1 μg/mL; $P = .040$) and its maximum level before the ultrasonographic examination (29.1 ± 48.7 μg/mL vs 5.5 ± 11.0 μg/mL; $P < .001$) were higher in the patients with DVT compared with those without DVT. On multivariate logistic regression analysis, the maximum D-dimer level was independently related to the identification of DVT (odds ratio [OR] 1.05; 95% confidence interval [CI], 1.00-1.09 per 1-μg/mL increase; $P = .045$), but the admission D-dimer level was not when it was included instead of the maximum D-dimer level. In addition, female sex (OR, 4.99), ICH (OR, 5.20), high Wells clinical score (OR, 2.40 per 1-point increase), and low protein level (OR, 0.21 per 1-g/dL increase) were independently related to the identification of DVT. The optimum cutoff value of the maximum D-dimer level for positive DVT was 5.5 μg/mL (sensitivity, 89%; specificity, 82%). Our findings suggest that high plasma D-dimer level during the course of acute stroke can help detect DVT on duplex venous ultrasonography. **Key Words:** Venous thromboembolism—ultrasonography—ischemic stroke—cerebral infarction—intracerebral hemorrhage.
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Deep vein thrombosis (DVT) is relatively common and can cause sudden, fatal embolic events in the pulmonary arteries and other regions. Although prompt detection and treatment of DVT are necessary, DVT is usually subclinical and often underdiagnosed. Measurement of plasma D-dimer level has been used as a screening strategy for subclinical DVT.[1-9] A systematic review reported that a normal range of a highly sensitive D-dimer level accurately ruled out DVT in patients classified as having a low or moderate clinical probability of DVT.[10]

Stroke is a high-risk factor for DVT because of advanced age, hemiplegia, and coagulation disorders, and DVT can cause paradoxical embolic stroke via a right-to-left shunt. Thus, it is important to understand the incidence and characteristics of DVT in acute stroke patients. Plasma D-dimer level has proven to be useful for DVT screening in chronic stroke patients undergoing rehabilitation.[11,12] No such relationship has yet been identified in acute stroke patients, however. A recent

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study from our institute found no difference in admission D-dimer levels in patients with intracerebral hemorrhage (ICH) with DVT and those without DVT.[13]

The goal of the present study was to determine whether plasma D-dimer level could be useful for detecting DVT in acute stroke patients and to define the optimal cutoff D-dimer level for detecting DVT in such patients.

Methods

Between February 2004 and February 2006, patients who were hospitalized in our stroke care unit within 3 days after stroke onset were recorded in our stroke patient database. Duplex venous ultrasonographic studies of the lower limbs were performed in consecutive patients who met any one of the following criteria: (1) a patent foramen ovale on transesophageal echocardiography, with paradoxical embolism as a possible cause of stroke; (2) a possible pulmonary thromboembolism based on symptomatology or pulmonary scintigraphy; (3) edema, swelling, or tenderness in a lower limb, suggesting the presence of DVT; (4) severe motor palsy in a lower limb; and (5) above-normal levels of D-dimer or thrombin-antithrombin III complex (TAT), which are routinely measured in all stroke inpatients. Patients with active cancer or who underwent neurosurgery for cerebrovascular disease during hospitalization were excluded.

Duplex venous ultrasonography of the lower limbs was performed with a high-resolution 7.5-MHz linear-array transducer (Prosound α10; ALOKA, Tokyo, Japan) by experienced vascular neurologists who were blinded to the results of the clinical and laboratory assessments. Deep veins were imaged in B-mode and color Doppler mode and evaluated for compressibility from the common femoral vein through the popliteal vein and consecutively to the distal point of the peroneal vein, the posterior tibial vein, and the soleal vein. DVT was disgnosed when a thrombus was visualized on B-mode ultrasound or when noncompressibility or a color Doppler flow signal defect was noted in the deep veins.

Patient risk factors included sex, age, smoking habit (previous and current), alcohol drinking habit (≥ 2 drinks per day), hypertension (a history of antihypertensive medication use, or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on admission), diabetes mellitus (fasting blood glucose ≥126 mg/dL, positive 75-g oral glucose tolerance test, or a history of antidiabetic medication and insulin use), hypercholesterolemia (serum total cholesterol ≥ 220 mg/dL or a history of antihypercholesterolemic medication use), atrial fibrillation, and use of antithrombotic agents for ≥ 6 months before or after stroke onset. On admission and at discharge, neurologic deficits were evaluated using the National Institutes of Health Stroke Scale (NIHSS). Stroke type (ischemic or hemorrhagic), bedridden period, and time to start of rehabilitation were assessed as well. At discharge, ability to perform activities of daily living was assessed using the modified Rankin Scale (mRS). The clinical pretest probability of DVT was assessed using the clinical score model described by Wells and coworkers,[1,14] an 8-point scoring method based on the patient's underlying condition and leg symptoms. In addition, stroke type (ischemic or hemorrhagic), bedridden period, and time from admission to the start of the rehabilitation program were assessed.

Blood tests were performed on admission. Plasma D-dimer level was measured quantitatively using a latex agglutination assay technique (NANOPIA D-dimer; Daiichi Pure Chemicals, Tokyo, Japan). TAT level was measured quantitatively using a latex photometric immunoassay technique (LPIA-F/TAT test II; Mitsubishi Chemical Medience, Tokyo, Japan). D-dimer and TAT values were measured at least twice before the venous ultrasonography study, and the maximum levels of these parameters were determined. A D-dimer level >1.0 μg/mL and a TAT level >3.0 ng/mL were considered abnormal.

Continuous values are expressed as mean ± SD or as median and interquartile range (IQR). Clinical characteristics and laboratory findings were compared in the patients with DVT and those without DVT using the χ^2 test, unpaired Student t test, and Mann-Whitney U test, as appropriate. A P value <.05 was considered significant. To identify the independent predictors for detecting DVT on ultrasonography, a multivariate logistic regression analysis was performed using sex, age, and clinical characteristics that showed significant correlation on univariate analyses, with adjustments for sex and age. Because the initial and maximum levels of D-dimer and TAT were correlated, these variables were analyzed separately in different models. An optimal D-dimer cutoff level for predicting DVT was determined using receiver operating characteristic (ROC) curves. The sensitivity, specificity, and positive and negative predictive values using the determined cutoff level were calculated. Statistical analysis was performed using the JMP 7 software package (SAS Institute, Cary, NC).

Results

Out of 948 consecutive acute stroke patients, 100 patients with ischemic stroke (IS) and 33 patients with ICH (66 men and 67 women; mean age, 71.6 ± 10.4 years) were included in this study. Venous ultrasonographic examination was performed at a median of day 7 after stroke (IQR, day 4-15).

DVT was detected in 36 of the 100 IS patients and in 25 of the 33 ICH patients (76%; $P < .001$). The locations of DVT in these 61 patients are documented in Table 1. DVT was most commonly identified in the soleal veins, followed by the posterior tibial veins. DVT was more common in veins in paralytic legs than in veins in nonparalytic legs.

Table 1. *Locations of DVT in 61 patients with DVT*

Location	Paralytic legs (n = 66)	Nonparalytic legs (n = 56)
Proximal veins	13 (20%)	3 (5%)
Peroneal veins	21 (32%)	4 (7%)
Posterior tibial veins	24 (36%)	7 (13%)
Soleal veins	43 (65%)	16 (29%)

Proximal veins include common femoral, superficial femoral, and popliteal veins. For 8 patients with paraplegia, both legs are regarded as paralytic. For 3 patients without motor paralysis, both legs are considered nonparalytic.

Compared with patients without DVT, patients with DVT were more likely to have hypertension (85% vs 71%; $P = .048$) and less likely to have diabetes (13% vs 28%; $P = .039$) (Table 2). Patients with DVT also had a higher admission NIHSS score ($P < .001$) and its subscore for "motor leg" ($P < .001$), Wells clinical score ($P < .001$), discharge NIHSS score ($P < .001$), and discharge mRS score ($P < .001$) and a longer completely bedridden period ($P < .001$), and were less likely to receive antithrombotic therapy after onset of stroke (62% vs 88%; $P < .001$). Patients with DVT had higher admission plasma D-dimer ($P = .040$) and TAT ($P = .042$) levels, as well as maximum levels ($P < .001$ for both), and a lower admission total protein level ($P = .040$) (Table 3). D-dimer reached its maximum level at a median of day 4 after stroke (IQR, day 2–7), and TAT achieved its maximum level at a median of day 5 after stroke (IQR, day 2–9).

Table 2. *Baseline clinical characteristics and stroke features*

Characteristic	Patients with DVT (n = 61)	Patients without DVT (n = 72)
Baseline characteristics		
Age, years	73.2 ± 9.7	70.2 ± 10.8
Female	36 (59%)	31 (43%)
Smoking	18 (30%)	21 (29%)
Drinking	26 (43%)	35 (49%)
Hypertension	52 (85%)*	51 (71%)
Diabetes mellitus	8 (13%)*	20 (28%)
Hypercholesterolemia	24 (39%)	28 (39%)
Atrial fibrillation	15 (25%)	10 (14%)
Antithrombotic therapy before stroke onset	17 (28%)	19 (26%)
Stroke features		
ICH	25 (41%)†	8 (11%)
NIHSS score on admission	16 (8-18)†	4 (2-10)
NIHSS subscore for "motor leg" on admission	3 (2-4)†	1 (0-2)
Wells clinical score	2 (1-2)†	0 (0-1)
Antithrombotic therapy after stroke onset	38 (62%)†	63 (88%)
Bedridden period before leaving bed, days	4 (3-9)†	3 (1-5)
Time interval to starting rehabilitation, days	5 (4-7)	5 (4-7)
NIHSS score at discharge	9 (4-16)†	1 (0-4)
mRS score at discharge	4 (3-5)†	1 (1-3)

Values are reported as number (percentage), mean ± SD, or median (IQR).
*$P < .05$.
†$P < .01$.

When the maximum D-dimer level was included in the multivariate logistic regression analysis, it was found to be independently related to the identification of DVT (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.00–1.09 per 1-μg/mL increase; $P = .045$) (Table 4). In addition, female sex (OR, 4.99; 95% CI, 1.18–21.0; $P = .029$), ICH (OR, 5.20; 95% CI, 1.27–21.3; $P = .022$), high Wells clinical score (OR, 2.40; 95% CI, 1.13–5.09 per 1-point increase; $P = .022$), and total protein level (OR, 0.21; 95% CI, 0.07–0.64 per 1-g/dL increase; $P = .006$) were independently related to the identification of DVT (Table 4). When admission plasma D-dimer level (OR, 1.02; 95% CI, 0.97–1.07 per 1-μg/mL increase; $P = .565$), admission TAT level (OR, 0.99; 95% CI, 0.92–1.06 per 1-ng/mL increase; $P = .728$), or maximum TAT level (OR, 1.03; 95% CI, 0.98-1.08 per 1-ng/mL increase; $P = .327$) was

Table 3. *Laboratory test results*

Variable	Patients with DVT (n = 61)	Patients without DVT (n = 72)
On admission		
Total protein, g/dL	6.8 ± 0.5 *	7.0 ± 0.6
Albumin, g/dL	4.0 ± 0.4	4.1 ± 0.4
Hematocrit, %	40.2 ± 5.3	41.4 ± 4.7
Platelets, $\times 10^4/\mu L$	19.0 ± 8.2	19.9 ± 11.5
Asparate aminotransferase, IU/L	32.9 ± 26.1	30.1 ± 13.8
Alanine aminotransferase, IU/L	22.4 ± 14.0	23.8 ± 15.6
Prothrombin time, INR	1.04 ± 0.24	1.03 ± 0.22
Activated partial thromboplastin time, seconds	29.4 ± 7.9	28.9 ± 4.7
D-dimer, μg/mL	7.5 ± 10.7*	3.7 ± 10.1
TAT, ng/mL	7.6 ± 8.4*	4.4 ± 7.8
Before ultrasonography scanning		
Maximum D-dimer, μg/mL	29.1 ± 48.7†	5.5 ± 11.0
Maximum TAT, ng/mL	16.7 ± 20.7†	6.2 ± 8.9

Values are reported as mean ± SD.
*$P < .05$.
†$P < .01$.

Table 4. *Multivariate regression analysis for identification of DVT*

Variable	OR (95% CI)	*P* value
Age, per 1-year increase	0.99 (0.92-1.07)	.845
Female	4.99 (1.18-21.0)	.029
Hypertension	1.72 (0.39-7.55)	.473
Diabetes mellitus	0.34 (0.08-1.41)	.138
ICH	5.20 (1.27-21.3)	.022
NIHSS score on admission, per 1-score increase	1.09 (0.96-1.23)	.196
Wells clinical score, per 1-score increase	2.40 (1.13-5.09)	.022
Total protein level, per 1-g/dL increase	0.21 (0.07-0.64)	.006
Bedridden period before leaving bed, per 1-day increase	0.94 (0.77-1.15)	.538
Maximum D-dimer level, per 1-μg/mL increase	1.05 (1.00-1.09)	.045

included in the analysis instead of maximum D-dimer level, none was found to be related to the identification of DVT.

The ROC curve revealed the optimal maximum D-dimer cutoff value in acute stroke patients with DVT. The area under the curve (AUC) was 0.919 (95% CI, 0.874-0.964). The optimal threshold value of plasma D-dimer for positive DVT was 5.5 μg/mL (sensitivity, 89%; specificity, 82%; positive predictive value, 80%; negative predictive value, 88%) (Fig 1).

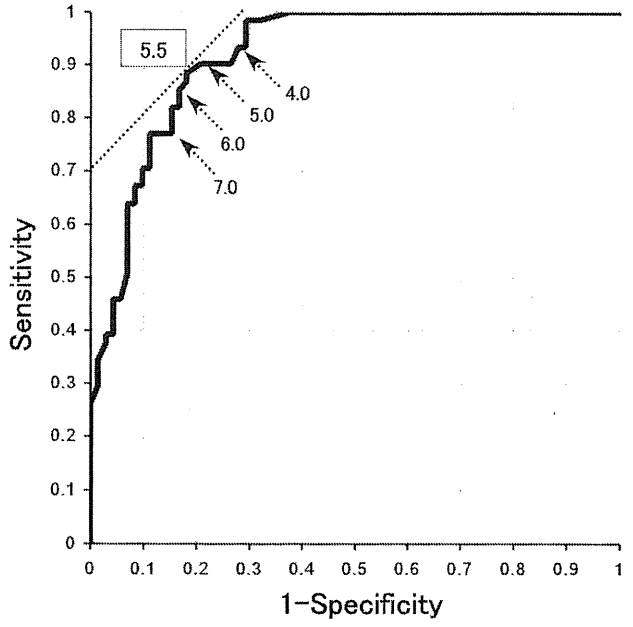

Figure 1. *ROC curve showing the optimal cutoff point of the maximum D-dimer level of acute stroke patients with DVT. The optimal threshold value for the D-dimer level is 5.5 μg/mL (sensitivity, 89%; specificity, 82%). The AUC is 0.919 (95% CI, 0.874-0.964).*

Discussion

In the present study, plasma D-dimer level was found to be effective for diagnosing DVT in acute stroke patients independent of underlying characteristics and stroke features, and an optimal maximum D-dimer cutoff value during the acute stage for detecting DVT was identified. In addition, female sex, ICH, high Wells clinical score, and low serum protein levels were independently related to the presence of DVT.

Several previous studies have demonstrated the utility of D-dimer level for DVT detection. In a prospective study involving 1096 patients, D-dimer measurement resulted in a significant reduction in the use of ultrasonography for detecting DVT, from a mean of 1.34 tests per patient without D-dimer testing to 0.78 test per patient with D-dimer testing.[1] Another study reported a large difference in the frequency of DVT detected by serial ultrasonography between patients with a normal D-dimer level (1 of 176 patients; 0.6%) and those with an abnormal D-dimer level (306 of 597 patients; 51.3%).[6] In contrast to those previous studies, which measured D-dimer levels using only qualitative methods, such as with a simplified kit, the present study compared D-dimer values of individual cases quantitatively, and our findings demonstrate the effectiveness of plasma D-dimer measurement.

In the present study, the baseline admission D-dimer level was higher in patients with DVT than in those without DVT in the unadjusted analysis, but the difference was not significant after multivariate adjustment. Admission D-dimer levels differed significantly between patients with and without DVT in some,[15] but not all, studies of patients with acute ICH.[13] A study of 102 IS patients reported that D-dimer level measured on day 9 after stroke had good discriminatory power for DVT detection.[16] Thus, elevated D-dimer level during the first several days after stroke, as well as elevated baseline level, seem to be important for DVT screening.

Previous studies found that plasma D-dimer level had a relatively high sensitivity (87%-95%) but low specificity (41%-65%) for detecting DVT.[17] In a study of 105 chronic stroke patients in the rehabilitation setting, the optimal D-dimer cutoff level for predicting DVT was 1.591 μg/mL measured by enzyme-linked immunosorbent assay technology (normal was <0.5 μg/mL in that study).[11] A reason for the much higher cutoff point in the present study might be that several situations other than DVT formation increased the D-dimer level during acute stroke, including several prothrombotic conditions associated with acute stroke. In addition, most patients were included in the present study because of elevated admission D-dimer or TAT level. The optimal D-dimer cutoff level for positive DVT would have been lower than the present level (5.5 μg/mL) had consecutive stroke inpatients been included.

Few studies have investigated the use of plasma TAT level for detection of DVT. A study involving 135 patients with suspected DVT reported significantly higher TAT levels in patients with definite DVT compared with those without DVT.[9] There have been no reports on TAT measurement for DVT detection in stroke patients. In the present study, we did not identify plasma TAT level as an independent factor related to DVT after multivariate adjustment, although it had a significant relationship on univariate analysis.

Other than hemostatic markers, a high Wells clinical score appears to be effective for identifying DVT during acute stroke. Although numerous Western studies have reported a male dominance of venous thromboembolism,[18-21] a study of Asian IS patients and a study of Japanese ICH patients showed a female predominance.[13,22] Racial differences might be a key factor in the relationship between DVT formation and sex. Several studies have identified ICH, but not IS, as an independent risk factor for DVT.[23,24] One reason for this might be that acute ICH patients have less opportunity to receive antithrombotic therapy compared with IS patients.

The present study has several limitations. First, because we did not enroll all stroke inpatients, a selection bias might exist. Second, duplex venous ultrasonography and follow-up D-dimer measurement were not done on the same days in all patients. Third, the details of antithrombotic therapy during acute stroke were not documented.

In conclusion, although various stroke-associated conditions affect D-dimer levels, measurement of this hemostatic marker was found to be useful for DVT screening in acute stroke patients. Patients with a high D-dimer level ($\geq$ 5.5 μg/mL) should undergo venous ultrasonographic examination.

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Preserved acetazolamide reactivity in lacunar patients with severe white-matter lesions: ^{15}O-labeled gas and H_2O positron emission tomography studies

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Limited evidence exists on the relationships between severity of white-matter lesions (WMLs) and cerebral hemodynamics in patients without major cerebral artery disease. To examine changes of cerebral blood flow (CBF), oxygen metabolism, and vascular reserve capacity associated with severity of WML in patients with lacunar stroke, we used a positron emission tomography (PET). Eighteen lacunar patients were divided into two groups according to the severity of WMLs, assessed by Fazekas classification; grades 0 to 1 as mild WML group and grades 2 to 3 as severe WML group. Rapid dual autoradiography was performed with ^{15}O-labeled gas-PET followed by ^{15}O-labeled water-PET with acetazolamide (ACZ) challenge. Compared with the mild WML group, the severe WML group showed lower CBF (20.6 ± 4.4 versus 29.9 ± 8.2 mL/100 g per minute, $P = 0.008$), higher oxygen extraction fraction (OEF) (55.2 ± 7.4 versus 46.7 ± 5.3%, $P = 0.013$), and lower cerebral metabolic rate of oxygen ($CMRO_2$) (1.95 ± 0.41 versus 2.44 ± 0.42 mL/100 g per minute, $P = 0.025$) in the centrum semiovale. There were no significant differences in the ACZ reactivity between the two groups (48.6 ± 22.6% versus 42.5 ± 17.2%, $P = 0.524$). Lacunar patients with severe WMLs exhibited reduced CBF and $CMRO_2$, and increased OEF in the centrum semiovale. The ACZ reactivity was preserved in both patients with severe and mild WMLs in each site of the brain.
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Keywords: acetazolamide challenge; centrum semiovale; cerebrovascular reactivity; ischemic stroke; leukoaraiosis

Introduction

White-matter lesions (WMLs), observed as white-mater hyperintensity in T2-weighted magnetic resonance imaging or fluid-attenuated inversion recovery (FLAIR) image, are commonly observed among elderly people (Hachinski *et al*, 1987). However, they are also associated with hypertension, diabetes, and other vascular risk factors (Murray *et al*, 2005; Pantoni and Garcia, 1997). Development of WMLs is known to be a cause of cognitive impairment, dementia, and disability (Prins *et al*, 2005). Recent studies showed that WMLs are not only a stroke risk factor (Streifler *et al*, 2002) but also a predictor of unfavorable stroke outcome (Koton *et al*, 2009). Despite accumulating evidence of the clinical significance of WMLs, the pathogenesis of WMLs has not been fully clarified.

Healthy elderly subjects with severe WMLs were reported to have reduced cerebral blood flow (CBF) and preservation of oxygen metabolism

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(Meguro *et al*, 1990). Patients with dementia of the Binswanger type have marked decrease of both CBF and oxygen metabolism in the white matter; however, patients without dementia have a lesser decrease in CBF with preservation of almost-normal oxygen metabolism (Yao *et al*, 1992). These findings indicated that chronic hypoperfusion due to the progression of small artery disease is associated with the development of WMLs. In addition, hemodynamic disturbance induced by internal carotid artery occlusive disease was suggested to contribute to the development of extensive WMLs (Yamauchi *et al*, 1999).

Limited evidence exists on the relationships between severity of WMLs and hemodynamic disturbance in patients without major cerebral artery occlusive disease. Some studies showed that vascular reactivity was not related to severity of WMLs (Birns *et al*, 2009; Turc *et al*, 1994). Other studies reported that vascular reactivity in patients with severe WMLs is impaired (Bakker *et al*, 1999; Chabriat *et al*, 2000; Fu *et al*, 2006; Isaka *et al*, 1994; Kozera *et al*, 2010; Mochizuki *et al*, 1997). These inconsistencies may be due to differences in modalities for evaluation of vascular reserve capacity; i.e., transcranial Doppler ultrasound (Bakker *et al*, 1999; Birns *et al*, 2009; Fu *et al*, 2006; Kozera *et al*, 2010), perfusion MRI (Chabriat *et al*, 2000), xenon inhalation computed tomography (Isaka *et al*, 1994; Mochizuki *et al*, 1997), and single photon emission computed tomography (Turc *et al*, 1994). There are also differences in the vasodilatory stimulus used; i.e., CO_2 inhalation (Bakker *et al*, 1999), breath holding, hyperventilation tests (Birns *et al*, 2009; Kozera *et al*, 2010), and acetazolamide (ACZ) challenge test (Chabriat *et al*, 2000; Fu *et al*, 2006; Isaka *et al*, 1994; Mochizuki *et al*, 1997; Turc *et al*, 1994). Although single photon emission computed tomography study with ACZ challenge can detect stage II hemodynamic failure (Powers, 1991) by positron emission tomography (PET) in patients with major cerebral artery occlusive disease (Hirano *et al*, 1994), the relationship between ACZ reactivity and oxygen metabolism in patients with WMLs without major artery disease has not been elucidated. We hypothesized that either impairment of vascular reserve capacity or chronic hypoperfusion in the white matter contributes to the development of WMLs without major artery disease.

The aim of this study was to examine the changes of CBF, oxygen metabolism, and vascular reserve capacity associated with the severity of WMLs in patients with lacunar stroke.

Materials and methods

Patients

This study was a single-center hospital-based prospective study. The study protocol was governed by the guidelines of national government based on the Helsinki Declaration revised in 1983, and it was approved by the Institutional Research and Ethics Committee of our hospital. All patients gave written informed consent to participate in the study. Patients with lacunar stroke, at least 3 weeks after the onset, were enrolled between April 2009 and April 2010. All patients underwent PET studies with ^{15}O-labeled gas ($C^{15}O_2$, $^{15}O_2$, $C^{15}O$) inhalation and ^{15}O-water with ACZ challenge autoradiography as described previously (Kudomi *et al*, 2005, 2007), as well as MRI studies. Lacunar stroke was defined as a typical clinical syndrome associated with a small infarct, <15 mm in diameter on MRI, restricted to the territory of a perforating artery without adjacent major artery occlusive lesions. Patients with stenosis ($>50\%$ in diameter) or occlusion of the internal carotid artery or the trunk of the middle cerebral artery on magnetic resonance angiography or ultrasonography were excluded from the study. The median time interval between the onset of stroke and PET studies was 1,017 days (interquatile range 519 to 1,856).

Baseline clinical characteristics including age, sex, hypertension, diabetes mellitus, dyslipidemia, and current smoking were recorded. Information of risk factors and medical history was collected from a self-reported medical history or inferred from prescribed medication by the primary physicians. Criteria for hypertension, diabetes mellitus, and dyslipidemia were as previously defined (Yokota *et al*, 2009). Cognitive function was evaluated in all patients by the mini-mental state examination (Folstein *et al*, 1975) and clinical dementia rating (Hughes *et al*, 1982). Dementia was defined as clinical dementia rating ≥ 1, and patients with dementia met the criteria proposed by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA Alzheimer's Criteria) (Roman *et al*, 1993).

Magnetic Resonance Imaging

Magnetic resonance imaging was performed on a 1.5-T scanner (Magnetom Vision or Magnetom Sonata; Siemens Medical Systems, Erlangen, Germany). The imaging protocol consisted of a T1-weighted spin-echo, a T2-weighted spin-echo, and FLAIR image. Severity of WMLs was assessed using the FLAIR (repetition time 900 ms, echo time 119 ms, field-of-view 230×201 mm^2, matrix 256×210, 4 mm slice thickness, and 2 mm gap between slices).

Two investigators (CY and TN), who were unaware of all clinical data, graded the degree of severity of WMLs by visual inspection using the Fazekas classification of WMLs as follows: none (grade 0), punctate (grade 1), early confluent (grade 2), and confluent lesions (grade 3) (Fazekas *et al*, 1987). The patients with grades 0 to 1 were defined as the mild WMLs group and those with grades 2 to 3 were defined as the severe WMLs group. Additionally, WMLs volume was measured manually based on FLAIR imaging (20 slices) using Dr View/LINUX software (AJS, Ver R2.5, Tokyo, Japan).

Positron Emission Tomography Imaging

We used an ECAT47 PET scanner (Siemens Medical Systems), which provided an intrinsic spatial resolution of 4.5 mm full-width at half-maximum at the center of the field-of-view. Data were acquired in 2D mode, and corrected for scatter compensation. A catheter was placed in the brachial artery for continuous monitoring of the arterial blood radioactivity concentration and arterial input function using a scintillator block detector system (BeCON; Molecular Imaging Labo, Suita, Japan) (Kudomi *et al*, 2003).

Quantitative images of CBF and oxygen extraction fraction (OEF) were obtained from a series of PET scans with ^{15}O-labeled gas ($C^{15}O_2$, $^{15}O_2$, and $C^{15}O$) inhalation after a rapid dual autoradiography protocol as reported in a series of publications by Kudomi *et al* (2005, 2007). Briefly, after a 10-minute transmission scan for the attenuation correction and an ^{15}O-labeled carbon monoxide ($C^{15}O$) scan for the blood volume assessment, a single dynamic scan was performed for 8 minutes, during which 4,000 MBq of oxygen ($^{15}O_2$) and 5,000 MBq of ^{15}O-labeled carbon dioxide ($C^{15}O_2$) gases were inhaled each >1 minute, sequentially at an interval of 5 minutes. Time to complete the whole dual autoradiography protocol was ~40 minutes. Cerebral metabolic rate of oxygen ($CMRO_2$) was calculated by multiplying the arterial oxygen content to the product images of OEF times CBF.

Additionally, two sets of PET scans were performed, each followed with ^{15}O-labeled water injection to assess regional CBF images using ^{15}O-water autoradiography (Kanno *et al*, 1987). The first scan was initiated without any pharmacological or physiological stress (at rest) and the second scan was performed at 10 minutes after an intravenous injection of ACZ titrated to 17 mg/kg. Physiological and laboratory data such as blood pressure, heart rate, and blood gas analysis (Siemens RAPIDLab 1265; Siemens Medical Systems) were obtained during the PET study.

Data Analysis

The small circular regions of interest (ROIs) (10 mm in diameter) were placed in the frontal cortex, parietal cortex, occipital cortex, basal ganglia, and centrum semiovale based on automatic registration of MRI to PET by using PVElab (the PVEOut Consortium) (Quarantelli *et al*, 2004; Svarer *et al*, 2005). The program is followed by automatic segmentation (running with Statistical Parametric Mapping 5 (SPM5) Software (Institute of Neurology, University College of London, London, UK) and correction of PET counts for fractional volume as determined from the segmentation. The ROIs were manually placed on the FLAIR images and transferred to the CBF images for analysis (Figure 1). We defined the ACZ reactivity as the percentage increase in CBF after ACZ administration relative to baseline CBF. In each subject, the mean measures were obtained by averaging the values for both hemispheres.

Statistical Analysis

Statistical analysis was performed using JMP 7.0 software (SAS Institute, Cary, NC, USA). The statistical significance of intergroup differences was assessed by χ^2 tests, unpaired *t*-tests, and the Mann–Whitney *U*-test, as appropriate. Logarithmic transformation was performed on WMLs volumes, which was a skewed variable. The relationship between each parameter of PET and log-WML was examined by Pearson's correlation. A value of $P<0.05$ was considered statistically significant.

Results

Patients were divided into two groups of severe WMLs ($n=9$) and mild WMLs ($n=9$) on the basis of MRI findings. There were no significant differences in age, sex, and vascular risk factors between the two groups (Table 1). Three patients with dementia defined as clinical dementia rating ≥ 1 were enrolled in the severe WMLs group; however, the rating of mini-mental state examination was not significantly different between the two groups. There were no significant differences in baseline CBF values between the gas-PET and H_2O-PET results. Compared with patients in the mild WMLs group, the patients

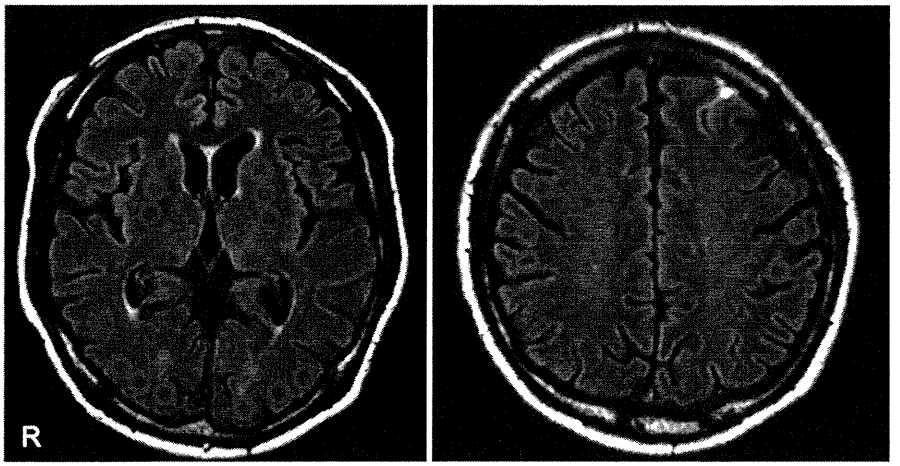

Figure 1 Regions of interest (ROIs) on fluid-attenuated inversion recovery (FLAIR). The small circular ROIs (10 mm in diameter) were placed on the frontal cortex, parietal cortex, occipital cortex, basal ganglia, and the centrum semiovale based on FLAIR image.

Table 1 Baseline characteristics

	Severe WMLs group (n = 9)	*Mild WMLs group (n = 9)*	P
Age (years)	76 (73–78)	74 (70–77)	0.329
Male	6 (67)	8 (89)	0.577
Current smoker	7 (78)	7 (78)	0.999
Hypertension	9 (100)	8 (88)	0.999
Diabetes mellitus	3 (33)	3 (33)	0.999
Dyslipidemia	6 (67)	6 (67)	0.999
WMLs (cm^3)	33.3 (21.5–90.9)	3.1 (1.3–4.4)	0.003
History of stroke	3 (33)	2 (22)	0.999
Time interval between stroke onset and PET study (days)	953 (445–1,958)	1,017 (519–1,623)	0.847
MMSE	24.0 (20.5–28.5)	28.0 (24.5–29.5)	0.140
CDR	0.5 (0–1)	0 (0–0.5)	0.185
Dementia	3 (33)	0 (0)	0.206

WMLs, white-matter lesions; PET, positron emission tomography; MMSE, mini-mental state examination; CDR, clinical dementia rating.
Data are number of patients (%), median (interquartile range) for discontinuous variables.

in the severe WMLs group had lower CBF (20.6 ± 4.4 versus 29.9 ± 8.2 mL/100 g per minute, $P = 0.008$), higher OEF (55.2 ± 7.4 versus 46.7 ± 5.3%, $P = 0.013$), and lower $CMRO_2$ (1.95 ± 0.41 versus 2.44 ± 0.42 mL/100 g per minute, $P = 0.025$) in the centrum semiovale, by gas-PET study (Table 2). There were no significant differences in any other parameters of the gas-PET in other ROIs between the two groups. Cerebral blood flow and $CMRO_2$ had a negative correlation with the severity of WMLs, and OEF had a positive correlation with the severity of WMLs (Figure 2). There were no significant differences in ACZ reactivity between the severe and mild WMLs groups in each site of the brain by H_2O-PET examination (Table 3). The results of physiological data and blood gas analysis during ACZ challenge were comparable between the two groups (data not shown). The ACZ reactivity was not correlated with the OEF or with the severity of WMLs ($P = 0.422$ and $P = 0.316$, respectively) (Figure 3).

Discussion

This study showed reduced CBF, reduced $CMRO_2$, and increased OEF in patients with severe WMLs compared with those with mild WMLs in the centrum semiovale. All patients in this study had lacunar stroke without major cerebral artery disease. The study also showed that ACZ reactivity was not impaired in either the cortex or the white matter of the patients of both groups.

Hatazawa *et al* (1997) found asymptomatic WMLs subjects exhibited reduction of CBF in the white matter and basal ganglia without decrease in $CMRO_2$. They also observed an increase in OEF in these areas, suggesting a chronic hypoperfusion in these territories. The present study provided additional information of reduction of both CBF and $CMRO_2$ with an increase in OEF in the WML in the patient groups with severe WMLs. Centrum semiovale is

Table 2 Comparison of each parameter of the gas-PET study between patients with severe or mild WMLs in the brain

	Severe WMLs group (n = 9)	*Mild WMLs group (n = 9)*	P
Frontal cortex			
CBF (mL/100 g per minute)	35.7 ± 9.0	37.8 ± 8.5	0.630
CBV (mL/100 g)	3.0 ± 0.9	3.0 ± 0.6	0.969
OEF (%)	54.1 ± 14.7	48.3 ± 5.2	0.275
$CMRO_2$ (mL/100 g per minute)	3.24 ± 0.49	3.26 ± 0.73	0.946
Parietal cortex			
CBF	40.2 ± 6.9	44.1 ± 11.6	0.403
CBV	2.8 ± 0.7	3.1 ± 0.5	0.284
OEF	50.6 ± 6.9	46.3 ± 4.9	0.146
$CMRO_2$	3.53 ± 0.35	3.62 ± 0.80	0.743
Occipital cortex			
CBF	40.4 ± 8.6	47.4 ± 16.1	0.266
CBV	3.5 ± 0.9	3.7 ± 1.5	0.745
OEF	55.8 ± 8.8	50.4 ± 4.5	0.116
$CMRO_2$	3.88 ± 0.63	4.22 ± 1.16	0.442
Basal ganglia			
CBF	45.1 ± 9.4	49.5 ± 13.1	0.426
CBV	2.3 ± 0.7	2.5 ± 0.5	0.521
OEF	52.8 ± 7.9	50.5 ± 6.3	0.505
$CMRO_2$	4.14 ± 0.66	4.43 ± 0.90	0.441
Centrum semiovale			
CBF	20.6 ± 4.4	29.9 ± 8.2	0.008
CBV	1.2 ± 0.4	1.4 ± 0.3	0.217
OEF	55.2 ± 7.4	46.7 ± 5.3	0.013
$CMRO_2$	1.95 ± 0.41	2.44 ± 0.42	0.025

CBF, cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; PET, positron emission tomography; WMLs, white-matter lesions.
P value by Mann–Whitney *U*-test.

located at the border of an area supplied by deep perforating arteries and the terminal branches of the middle cerebral artery. A decrease in CBF with reduction of $CMRO_2$ in the centrum semiovale in the present study should indicate a consequence of a reduced tissue metabolism in this terminal zone.

In the present study, patients with severe WMLs without major artery disease had increased OEF showed by gas-PET; however, their ACZ reactivity by H_2O-PET was preserved. The vascular reserve capacity evaluated by ACZ reactivity was preserved in both patients with severe and mild WMLs. Reduction of both CBF and $CMRO_2$ in the white matter was previously shown in patients with the Binswanger type dementia (Yao *et al*, 1990), being consistent with our results. Postmortem neuropathologic studies have shown decreased neuronal connectivity in the white matter in progressive subcortical vascular encephalopathy of Binswanger type (Yamanouchi *et al*, 1989, 1990). Functional reduction in cortical neuronal activity due to disruption of connections between the cortex and subcortex, as indicated previously (Pozzilli *et al*, 1987; Sette *et al*, 1989), is likely to be associated with a reduction of $CMRO_2$ in the centrum semiovale

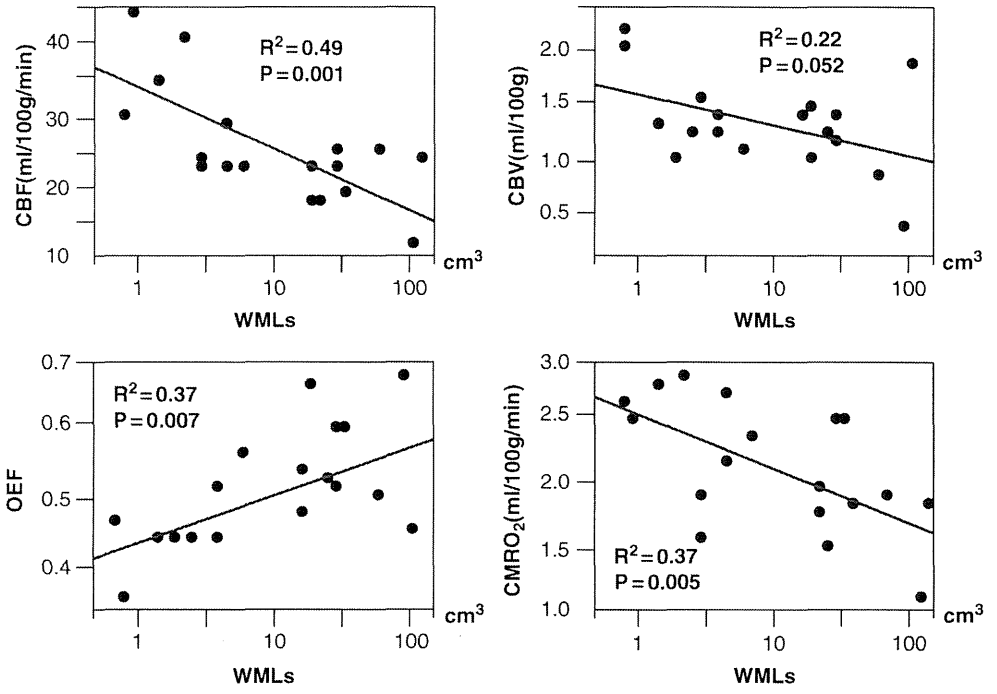

Figure 2 Correlation between WML volume and each gas-PET parameter in the centrum semiovale. CBF and $CMRO_2$ had a negative correlation with the severity of WMLs, while OEF was positively correlated with the severity of WMLs. CBF, cerebral blood flow; CBV, cerebral blood volume; OEF, oxygen extraction fraction; $CMRO_2$, cerebral metabolic rate of oxygen; WMLs, white-matter lesions; PET, positron emission tomography.

Table 3 Comparison of CBF between patients with severe or mild WMLs in the brain by H_2O-PET

	Severe WMLs group (n = 9)	*Mild WMLs group (n = 9)*	P
Frontal cortex			
CBF baseline	36.1 ± 7.2	40.2 ± 7.3	0.244
CBF ACZ	58.5 ± 10.2	59.9 ± 10.3	0.770
ACZ reactivity (%)	64.6 ± 28.5	49.7 ± 14.9	0.183
Parietal cortex			
CBF baseline	39.7 ± 4.8	45.7 ± 10.5	0.136
CBF ACZ	62.0 ± 7.1	66.9 ± 14.6	0.387
ACZ reactivity (%)	57.2 ± 17.1	47.1 ± 13.5	0.181
Occipital cortex			
CBF baseline	38.1 ± 7.1	45.7 ± 11.5	0.109
CBF ACZ	61.7 ± 13.3	70.1 ± 17.0	0.259
ACZ reactivity (%)	62.2 ± 21.5	54.2 ± 16.6	0.392
Basal ganglia			
CBF baseline	47.1 ± 9.8	54.6 ± 11.3	0.148
CBF ACZ	73.7 ± 10.5	85.7 ± 24.6	0.200
ACZ reactivity (%)	60.9 ± 31.0	55.7 ± 22.9	0.694
Centrum semiovale			
CBF baseline	19.0 ± 4.1	29.8 ± 9.2	0.005
CBF ACZ	28.5 ± 5.9	41.8 ± 10.9	0.005
ACZ reactivity (%)	48.6 ± 22.6	42.5 ± 17.2	0.524

ACZ, acetazolamide; CBF, cerebral blood flow; PET, positron emission tomography; WMLs, white-matter lesions.
P value by Mann–Whitney *U*-test.

in the patients with severe WMLs. Furthermore, the cerebral vessels would not dilate during fluctuations in systemic arterial pressure in daily life in these conditions of disruption of connections. Chronic hypoperfusion with a reduction of $CMRO_2$ in accordance with a disconnection between the cortex and subcortex may be the cause of development of WMLs without major artery disease.

To our knowledge, this is the first report of alterations in CBF, $CMRO_2$, and OEF, with preservation of ACZ reactivity in patients with mild or severe WMLs, with careful consideration of possible methodological errors. Indeed, quantitation of physiological parameters using PET is still a challenging issue, particularly in the white-matter area. As shown in earlier studies (Herscovitch and Raichle, 1983; Huang *et al*, 1987), the absolute values of both CBF and $CMRO_2$ could be biased because the spatial resolution of PET devices is limited compared with the physical size of the brain tissue component, or the partial volume effects. Oxygen extraction fraction is relatively stable and is less affected by partial volume effects. Our observation of increased OEF could not be explained by partial volume effects alone. Scatter is smaller in 2D mode in PET as compared with 3D acquisition. In this study, scatter correction was applied to minimize the contribution of radioactivity from the surrounding tissue components due to scatter. The ROIs were placed carefully with a guide of anatomical MRI to

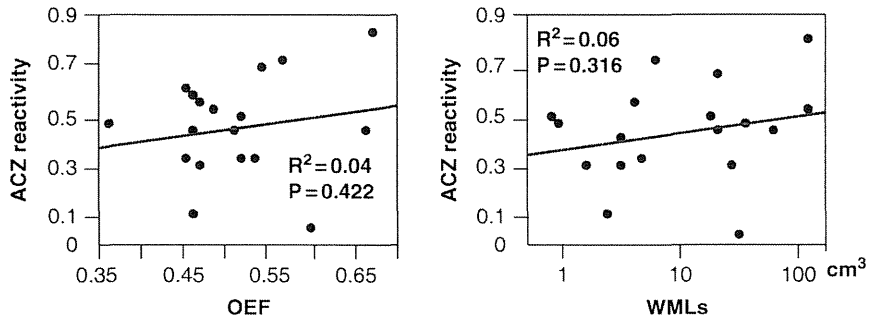

Figure 3 The correlation between ACZ reactivity and OEF or WML volume in the centrum semiovale. Neither OEF nor WML volume was correlated with ACZ reactivity. ACZ, acetazolamide; OEF, oxygen extraction fraction; WMLs, white-matter lesions.

minimize the errors arising from radioactivity counts of surrounding tissues. These factors remain concerns to be dealt with in future investigations.

There are several issues that need to be addressed, as follows. First, we intended to avoid possible bias in the patient selection, but a relatively small number of subjects could cause selection bias despite our efforts. Second, three patients with dementia were enrolled in the severe WMLs group. Because oxygen metabolism in demented patients was reported to be different from that in non-demented patients (Yao *et al*, 1992), a reduced $CMRO_2$ with reduced CBF in the severe WMLs group could be attributed to secondary effects arising from decreased cognitive function. Third, we examined the vascular reserve capacity by ACZ challenge. Recently, ACZ-induced vasodilation was reported not to inhibit the visually evoked flow response (Yonai *et al*, 2010), which indicates that the vasodilatory mechanism during neurovascular coupling may be different from the mechanism of ACZ-induced vasodilation. Acetazolamide at a dose of 17 mg/kg would not cause maximal cerebral vasodilatation. However, there were no significant differences in ACZ reactivity between the two groups, and ACZ reactivity was preserved in all patients in the present study. Fourth, PET imaging in the present study was a single scatter subtraction technique based on the Klein–Nishina formulation which was implemented in the reconstruction software (Watson, 2000). This technique was shown to provide reasonable accuracy in several phantom experiments. It should also be noted that the data were acquired in 2D mode, which has much smaller amount of scatter as compared with recently available 3D mode. Further, the filtered-back projection technique was applied for the image reconstruction. In this procedure, the scatter contribution is likely reduced in the reconstructed images. However, limited spatial resolution of PET devices is a significant source of errors that causes possible contamination of radioactivity counts of cortical grey matter tissue. Exact magnitude of errors in the calculated parameters in the WML cannot be well defined. In addition, PET scanning in the present study has not been applied to age-matched normal subjects. Further systematic study is needed.

In conclusion, we showed that there is reduced CBF and $CMRO_2$, and increased OEF in the centrum semiovale of patients with severe WMLs compared with patients with mild WMLs. The ACZ reactivity was preserved in both patients with severe and mild WMLs. Further studies will be needed to clarify the pathogenesis of WMLs.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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Low DWI-ASPECTS is associated with atrial fibrillation in acute stroke with the middle cerebral artery trunk occlusion

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ABSTRACT

Background and purpose: For optimal acute stroke management and secondary prevention, discrimination of stroke etiology is crucial. We hypothesized that a low Alberta Stroke Program Early CT Score (ASPECTS) on diffusion-weighted imaging (DWI) immediately after stroke onset was associated with the presence of atrial fibrillation (AF).

Methods: Consecutive patients admitted within 24 h from stroke onset with an occlusion at the horizontal segment of the middle cerebral artery (M1) on initial MRA were retrospectively enrolled. AF was diagnosed based on continuous electrocardiogram monitoring during acute hospitalization or its confirmed history.

Results: Of the 206 patients (95 women, median age 77 [IQR 69–85] years, NIHSS score 18 [13–23]) enrolled, AF was identified in 138 patients (AF group): chronic AF in 89, known paroxysmal AF (pAF) in 13, and masked pAF on admission in 36. The ASPECTS score on the initial DWI, performed a median of 2.5 h after onset, was lower in the AF group than in the others (4 [2–6] vs. 7 [4–8], $p<0.001$). With the optimal cut-off value of ≤6 (sensitivity, 78%; specificity, 57%; area under the ROC curve, 0.682), DWI-ASPECTS was independently associated with the presence of any AF (OR 5.05, 95%CI 2.36 to 10.8), as well as the presence of any pAF (OR 8.64, 95%CI 3.00 to 24.9) and that of masked pAF on admission (OR 10.0, 95%CI 3.06 to 32.9).

Conclusion: Extensive early ischemic change assessed by DWI-ASPECTS predicts the presence of AF, even initially masked pAF, in acute stroke patients with M1 occlusion.

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1. Introduction

The etiological mechanisms of cardioembolic stroke differ from those of other ischemic strokes, and accordingly, there are unique strategies for acute management and secondary prevention, including urgent anticoagulant therapy and rapid exploration for cardiac thrombi. Thus, prompt diagnosis of cardioembolic stroke is crucial, especially in the hyperacute phase. However, detection of atrial fibrillation (AF), the leading cause of cardioembolic stroke, is often difficult due to the existence of paroxysmal AF (pAF) [1].

Diffusion-weighted magnetic resonance imaging (DWI, MRI) depicts ischemic lesions clearly [2]. Combined with magnetic resonance angiography (MRA), DWI contributes to rapid and accurate diagnosis of ischemic stroke subtype [3]. Although the presence of atherosclerotic changes of the responsible artery on MRA is a good indicator to distinguish atherothrombotic infarction from cardioembolism [3], this information is not available when MRA reveals complete arterial occlusion. Large infarct volume is another promising factor to distinguish cardioembolic infarcts with high-risk embolic sources from infarcts with internal carotid artery (ICA) atherosclerosis [4], and it is applicable to patients with arterial occlusion. The Alberta Stroke Program Early CT Score (ASPECTS) on DWI is a semi-quantitative topographic score that can simply estimate the extent of infarct area immediately after stroke [5,6], and it has been proven to correlate inversely with DWI lesion volume [7,8]. The aim of this study was to examine the hypothesis that acute stroke patients with occlusion at the horizontal segment (M1) of the middle cerebral artery (MCA) who had AF had lower DWI-ASPECTS scores than those without AF.

2. Methods

2.1. Subjects

Consecutive acute ischemic stroke patients who underwent MRI/MRA on admission to our stroke center within 24 h from stroke onset from April 2006 through August 2011 and were diagnosed as having

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M1 occlusion with compatible acute neurological deficits were retrospectively enrolled. Patients with contraindications to MRI were excluded.

This study was approved by the institutional ethics committee.

2.2. Clinical backgrounds and characteristics

Clinical backgrounds, including sex, age, and cardiovascular risk factors, were reviewed. Cardiovascular risk factors were defined as: 1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg before or ≥2 weeks after stroke onset; 2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥200 mg/dl, or glycosylated hemoglobin ≥6.5% on admission; 3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level ≥220 mg/dl; and 4) current smoking and alcohol intake. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

2.3. Identification of atrial fibrillation

For detecting AF, a 12-lead electrocardiogram (ECG) on admission and continuous ECG monitoring for the initial several days of hospitalization (at least 24 h) were conducted in all patients. These examinations were repeated during acute hospitalization when patients were suspected to have AF based on complaints of palpitations. Patients with AF (the AF group) were classified into three subgroups: those with chronic AF (cAF), those with known paroxysmal AF (pAF) as a confirmed history or identification on the initial ECG, and those with masked pAF on admission that was later identified. Patients who did not have a history of AF or in whom AF was not detected on ECG were defined as the non-AF group.

2.4. Neuroimaging

MRI studies including DWI and MRA were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Siemens MAGNETOM Vision or MAGNETOM Sonata scanner, Erlangen, Germany). DWI was obtained using the following parameters: TR/TE, 4000/100 ms; b values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 96×128; and slice thickness, 4.0 mm, with a 1.0-mm intersection gap.

DWI-ASPECTS was scored by a neurologist (Y.S.) who was blinded to all clinical information, based on the method described by Barber et al. [5]. The MCA territory was allotted 10 points, and a single point was subtracted for an area of hyperintensity on initial DWI. A score of 0 indicated complete ischemic involvement throughout the MCA territory. The inter-rater reliability of DWI-ASPECTS was evaluated using scores by another neurologist (T.O.) with weighted κ statistics. The intra-rater reliability was examined with scores recorded after a 2-month interval from the initial evaluation by the same neurologist (Y.S.). The site of arterial occlusion was determined on the initial MRA. M1 occlusion was judged irrespective of the presence of ipsilateral ICA occlusion. Patients with the horizontal distance from the ICA bifurcation to the distal end of the flow signal at M1 in an anteroposterior view <5 mm were defined as having M1 proximal occlusion, while those in whom this residual vessel length was ≥5 mm were defined as having M1 distal occlusion [9].

2.5. Statistical analysis

Clinical backgrounds and characteristics were compared between the AF and non-AF groups. Univariate analyses were performed using the chi-square test, Fisher's exact test, or the Mann–Whitney U test as appropriate. The data are presented as median values (interquartile range [IQR]) or frequencies (%). To obtain the optimal cut-off value of DWI-ASPECTS for discriminating the AF group from the non-AF group, receiver-operating characteristic (ROC) curve analysis was conducted. Multivariate logistic regression analyses were performed to identify independent factors associated with the presence of AF. DWI-ASPECTS and all variables of clinical manifestations identified on univariate analyses with p values <0.1 were entered into the model. Multivariate analyses were also performed to identify factors related to the presence of pAF after removing patients with cAF from the cohort, while factors related to the presence of masked pAF were identified after removing patients with cAF and those with known pAF.

All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Results were considered significant at $p<0.05$.

3. Results

Overall, 1461 patients with acute ischemic stroke were admitted to our stroke center during the study period (Fig. 1). Of these, 123 patients were excluded due to: MRI contraindicated in 105; missing the MRA sequence on the initial MR examination in 12; and difficult evaluation of the imaging due to motion artifact in 6. Of the remaining 1338 patients, arterial occlusion at M1 was observed in 206 patients. Finally, these 206 patients (95 women, median age 77 [IQR 69–85] years, NIHSS score 18 [13–23]) were enrolled in the present study.

AF was observed in 138 patients (AF group), while it was not observed in the remaining 68 patients (non-AF group). In the AF group, 89 (65%) patients had cAF, 13 (9%) had known pAF, and the remaining 36 (26%) had masked pAF. The clinical characteristics of the included patients are presented in Table 1. Patients in the AF group were older ($p<0.001$) and had a higher NIHSS score ($p=0.004$) than those in the non-AF group. Male sex ($p=0.037$), hyperlipidemia ($p=0.005$), and current smoking ($p=0.001$) were less common, and the plasma D-dimer ($p=0.029$) level was higher in the AF group than in the non-AF group.

The initial MRI was performed a median 2.5 h (IQR 1.5–8.2 h) after stroke onset. Overall, 121 patients (59%) had M1 proximal occlusion. The DWI-ASPECTS was significantly lower in the AF group than in the non-AF group (median 4 [IQR 2–6] vs. 7 [4–8], $p<0.001$, Table 1). The inter-rater reliability of DWI-ASPECTS was $\kappa=0.69$, and intra-rater reliability was $\kappa=0.72$. The proportion of patients with AF decreased along with the increase in DWI-ASPCETS ($r=-0.843$, $p=0.001$ with Spearman's rank correlation test, Fig. 2). Using the ROC curve, the optimal cut-off value of DWI-ASPECTS distinguishing the AF group from the non-AF group was ≤6 (sensitivity, 78%; specificity, 57%; area under the ROC curve, 0.682).

The results of multivariate regression analysis for association with AF are presented in Table 2. DWI-ASPECTS ≤6 (OR 5.05, 95%CI 2.36 to 10.8, $p<0.001$) and advanced age (OR 1.47, 95%CI 1.03 to 2.09, $p=0.034$ for every 10 years) were positively associated, and hyperlipidemia (OR 0.48, 95%CI 0.24 to 0.99, $p=0.047$) and current smoking (OR 0.31, 95%CI 0.13 to 0.73, $p=0.007$) were inversely associated with having AF. DWI-ASPECTS ≤6 was associated with having AF when the analysis was done only for patients with M1 proximal occlusion (OR 6.92, 95%CI 2.11 to 22.7, $p=0.001$) and only for those with M1 distal occlusion (OR 6.95, 95%CI 1.96 to 24.6, $p=0.003$). DWI-ASPECTS was also associated with having AF as a continuous variable (OR 0.76, 95%CI 0.65 to 0.88 for every 1 point).

The results of multivariate analyses for association with pAF are presented in Table 3. DWI-ASPECTS ≤6 was positively associated with the presence of any pAF (both known and masked pAF, OR 8.64, 95%CI 3.00 to 24.9) and with the presence of masked pAF (OR 10.0, 95%CI 3.06 to 32.9).

4. Discussion

In the present study, a significant association between the initial DWI-ASPECTS and the presence of AF was demonstrated in acute ischemic stroke patients with M1 occlusion. DWI-ASPECTS of 6 or less could predict AF irrespective of the M1 occlusion site. Moreover,

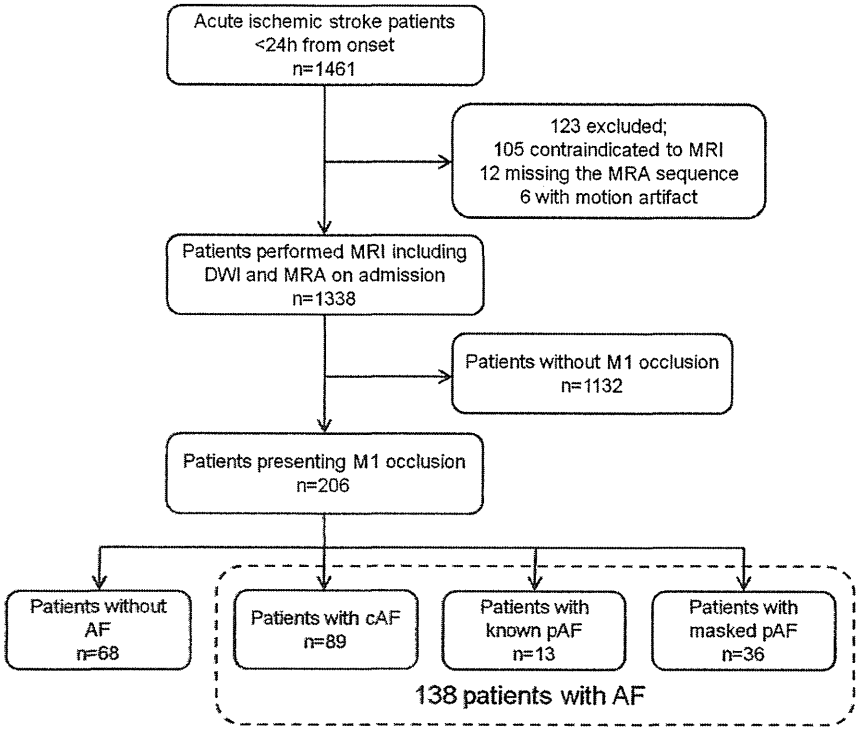

Fig. 1. Patient flow chart.

DWI-ASPECTS could distinguish patients with unidentified AF at presentation that was later documented from those with sinus rhythm.

The finding that DWI-ASPECTS discriminates patients with AF from those without AF was partly consistent with previous reports that showed a larger infarct volume on DWI in patients with cardioembolism than in those with internal carotid artery disease [4]. For acute stroke patients with M1 occlusion, AF seems to cause sudden main trunk occlusion and poor collateral circulation, and it may result in extensive ischemia [10]. However, visual assessment of the infarct volume depends on the reader's experience and skill and is time-consuming, and the intra-rater and inter-rater reliabilities are not sufficiently high [11]. On the other hand, DWI-ASPECTS can be scored promptly with good inter-rater reliability [5], and it is a simple and handy indicator in the emergent clinical setting. The cut-off of DWI-ASPECTS >6 was proven to be associated with complete or functional independency 3 months after IV t-PA [6,12]. The one-third of cerebral hemisphere rule on CT [13] appears to generally coincide with this cut-off of ASPECTS. In addition, AF was recently reported to predict poor outcome after IV t-PA [14,15]. The positive association of AF with DWI-ASPECTS ≤6 in our cohorts can be a good explanation for poor outcome of AF patients after thrombolysis.

The occluded sites of the M1 affect various clinical characteristics, including neurological severity, initial ASPECTS, and response to thrombolytic therapy [9]. It is interesting that DWI-ASPECTS ≤6 predicted

Table 1
Baseline characteristics.

Variables	Total	AF group	Non-AF group	p
	n = 206	n = 138	n = 68	
Male sex, n (%)	111 (54)	67 (49)	44 (65)	0.037
Age, y, median (IQR)	77 (69–85)	80 (71–88)	74 (68–79)	<0.001
Vascular risk factors, n (%)				
Hypertension	144 (70)	95 (69)	49 (72)	0.747
Diabetes mellitus	28 (14)	14 (10)	14 (21)	0.051
Hyperlipidemia	69 (34)	37 (27)	32 (47)	0.005
Current smoking	41 (20)	18 (13)	23 (34)	0.001
Alcohol intake	77 (37%)	48 (35%)	29 (43%)	0.461
Blood pressure on admission, median (IQR)				
Systolic, mm Hg	156 (136–169)	153 (134–165)	160 (140–176)	0.115
Diastolic, mm Hg	83 (70–91)	82 (70–91)	84 (72–91)	0.777
Time from onset to initial MRI, h, median (IQR)	2.5 (1.5–8.2)	2.5 (1.5–7.9)	2.6 (1.5–8.7)	0.873
NIHSS score, median (IQR)	18 (13–23)	20 (15–23)	16 (12–20)	0.002
M1 proximal occlusion, n (%)	121 (59)	82 (59)	39 (57)	0.880
DWI-ASPECTS, median (IQR)	5 (3–7)	4 (2–6)	7 (4–8)	<0.001
Biochemistry results on admission, median (IQR)				
Leukocyte count, /μl	7300 (5700–9000)	7200 (5600–8900)	7900 (6200–9300)	0.120
hs-CRP, mg/dl	0.13 (0.06–0.53)	0.14 (0.06–0.59)	0.13 (0.06–0.45)	0.571
D-dimer, μg/ml	1.9 (1.2–3.5)	2.2 (1.3–4.0)	1.6 (1.0–2.6)	0.017

AF indicates atrial fibrillation; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health stroke scale; M1, middle cerebral artery horizontal segment; hs-CRP, high-sensitivity C-reactive protein; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

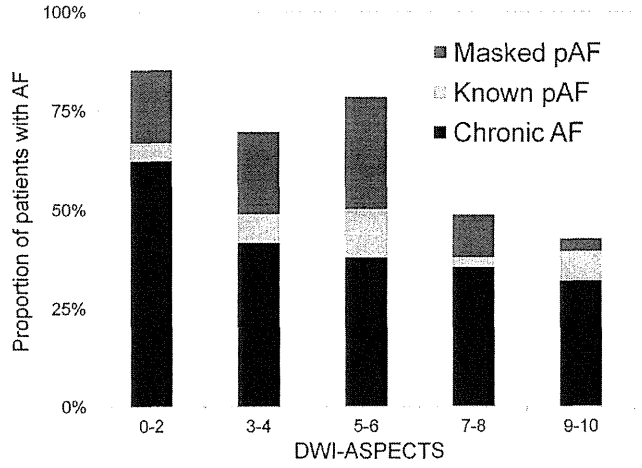

Fig. 2. The frequency of atrial fibrillation and the DWI-ASPECTS. The frequency of atrial fibrillation decreases along with the increase in DWI-ASPECTS ($r = -0.843$, $p = 0.001$ with Spearman's rank correlation test).

the presence of AF irrespective of the occluded sites. Atherosclerotic change in the MCA occurs predominantly in the stem [16], and embolic occlusion due to AF seems to be relatively common in the distal trunk where the caliber becomes smaller. Similar percentages of M1 proximal occlusion in the present AF and non-AF groups suggest that our cohort included many patients having large cardiogenic emboli.

Paroxysmal AF has similar risks of ischemic stroke to cAF [17,18] and is more prevalent than cAF in acute stroke patients [19]. Although guidelines recommend 24-h holter monitoring for patients with ischemic stroke of unknown cause [20], 24-h monitoring was reported to misdiagnose pAF in more than half of patients with confirmed pAF using 7-day Holter monitoring [1]. The left atrial volume index divided by diastolic velocity on echocardiogram and frequent atrial premature beats on ECG were other predictors of pAF in acute stroke [21,22], but their predictive values are not known. The present finding that DWI-ASPECTS predicted masked pAF even after removal of patients with cAF and previously known pAF helps in the quick selection of possible cardioembolic cases from cryptogenic stroke patients.

This study had some limitations. First, the retrospective design might have contributed to some selection bias. Second, ASPECTS is validated for ischemic strokes in the MCA territory, and the present finding cannot be applied to patients developing ischemic stroke in the posterior circulation. In addition, patients with MCA branch occlusion were not evaluated. Third, although every attempt was made to detect AF, some patients with pAF might have been overlooked. Fourth, most of the included patients were admitted and performed MRI in ultra-early phase in the present study. The median onset-to-MRI time was 2.5 h in this study, and our results should be carefully interpreted in generalization.

Table 2
Multivariate logistic regression analysis for predicting the presence of atrial fibrillation.

Variables	OR	95% CI	P
Male sex	0.65	0.30–1.41	0.276
Age (for every 10 years)	1.47	1.03–2.09	0.034
Diabetes mellitus	0.43	0.16–1.14	0.090
Hyperlipidemia	0.48	0.24–0.99	0.047
Current smoking	0.31	0.13–0.73	0.007
Initial NIHSS (for every 1 point)	1.01	0.96–1.07	0.635
DWI-ASPECTS ≤6	5.05	2.36–10.8	<0.001
D-dimer (for every 1.0 μg/ml)	1.04	0.91–1.19	0.587
DWI-ASPECTS (for every 1 point)	0.76	0.65–0.88	<0.001

NIHSS indicates the National Institutes of Health stroke scale; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

Table 3
Multivariate logistic regression analyses for predicting the presence of paroxysmal atrial fibrillation (pAF).

Variables	OR	95% CI	p
Any pAF (both known and masked)			
Male sex	0.42	0.16–1.12	0.084
Age (for every 10 years)	1.66	1.00–2.75	0.050
Diabetes Mellitus	0.11	0.02–0.64	0.014
Initial NIHSS (for every 1 point)	1.04	0.96–1.13	0.306
DWI-ASPECTS ≤6	8.64	3.00–24.9	<0.001
D-dimer (for every 1.0 μg/ml)	0.98	0.84–1.15	0.820
Masked pAF			
Male sex	0.49	0.17–1.43	0.191
Age (for every 10 years)	1.80	1.05–3.06	0.031
Diabetes mellitus	0.16	0.03–0.90	0.038
Initial NIHSS (for every 1 point)	1.02	0.94–1.12	0.582
DWI-ASPECTS ≤6	10.0	3.06–32.9	<0.001

NIHSS indicates National Institutes of Health stroke scale; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

In conclusion, extensive early ischemic change assessed by DWI-ASPECTS can discriminate the presence of AF from sinus rhythm in patients with acute ischemic stroke due to M1 occlusion, irrespective of the type of AF and the occluded site. DWI-ASPECTS ≤6 is a good indicator for thorough investigation of AF, including, for example, using implantable cardiac monitors.

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None.

Conflict of interest statement

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None.

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