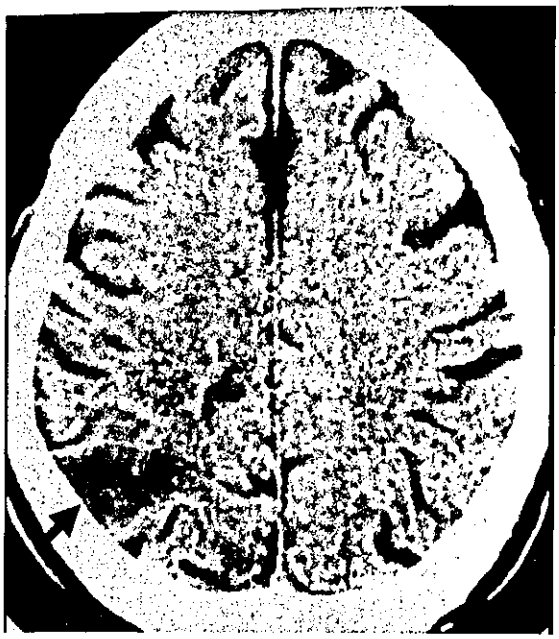

Figure 1. Brain computed tomography (CT) on admission reveals a low-density area in the right parietal cortex (arrow).

intraluminal mass echo was homogeneous, soft and elastic, and oscillated synchronously with the cardiac cycle. Color Doppler flow imaging showed anterograde blood flow in the affected part of the ICA in both systolic and diastolic phases. The peak-systolic and end-diastolic flow velocities of the affected ICA were 202.5 cm/sec and 84.5 cm/sec, respectively. Intra-arterial digital subtraction angiography on the same day demonstrated an intraluminal filling defect in the right ICA extending from the carotid bifurcation to the cervical portion and complete occlusion of the right external carotid artery (Fig. 3). Neither abnormal flow delay nor opacification was detected in the intracranial arteries ipsilateral to the affected side.

We diagnosed the patient as having a cardioembolic stroke. About six hours after the angiography, anticoagulant therapy was started with intravenous heparin infusion to maintain the activated partial thromboplastin time approximately 1.5 times the pretreatment level. Oral administration of warfarin replaced the heparin treatment seven days after the admission, and the intensity was adjusted to an international normalized ratio between 2.0 and 2.5.

On the day following the admission, we performed transtemporal TCD bilaterally for 30 minutes using a DWL Multidop X with the transducer operated at 2.5 MHz. Two microembolic signals (MES) were detected from the right

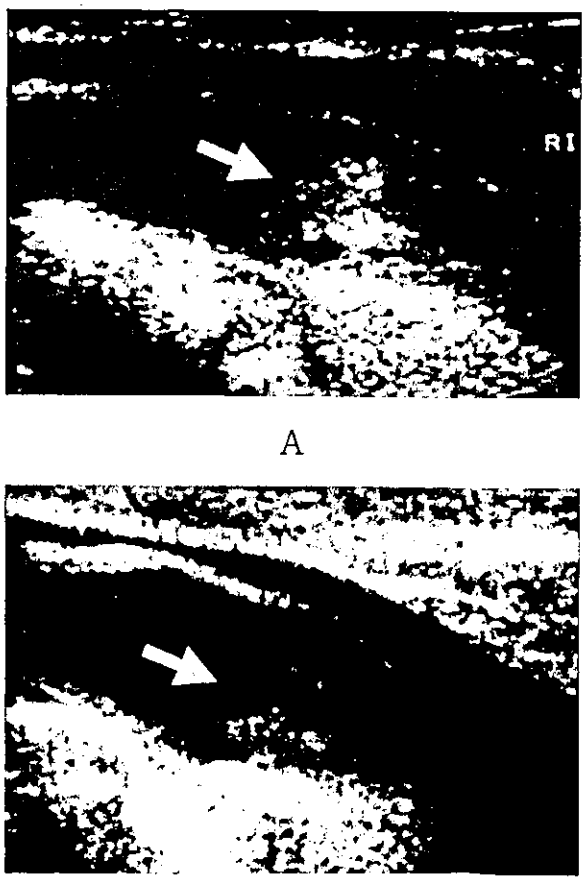

Figure 2. Duplex carotid ultrasonography on admission demonstrates a mobile, homogeneous intraluminal mass echo in the bifurcation of the right CCA through to the proximal ICA (arrow) on longitudinal B-mode scan (A). Following the commencement of immediate anticoagulant therapy, successive ultrasonographic studies on the 8th day (B) and the 11th day (C) of admission show that the intraluminal mass echo gradually decreased in size.

Figure 3. Cerebral angiography performed on the day of admission demonstrates a long, intraluminal filling defect in the right ICA extending from the bifurcation of the CCA to the cervical portion of the ICA (arrows) and complete occlusion of the right external carotid artery.

middle cerebral artery. Transesophageal echocardiography, performed on the same day, detected neither intracardiac thrombi nor right-to-left shunts nor atherosclerotic lesions of the aortic arch.

Follow-up carotid ultrasonographic examinations showed the intraluminal mass echo in the right carotid artery gradually decreased in size (Fig. 2B, 2C) and disappeared completely within two weeks of hospitalization. The peak-systolic and end-diastolic flow velocities of the affected ICA on the 11th day of admission were 39.6 cm/sec and 18.2 cm/sec, respectively. MES were no longer detected from

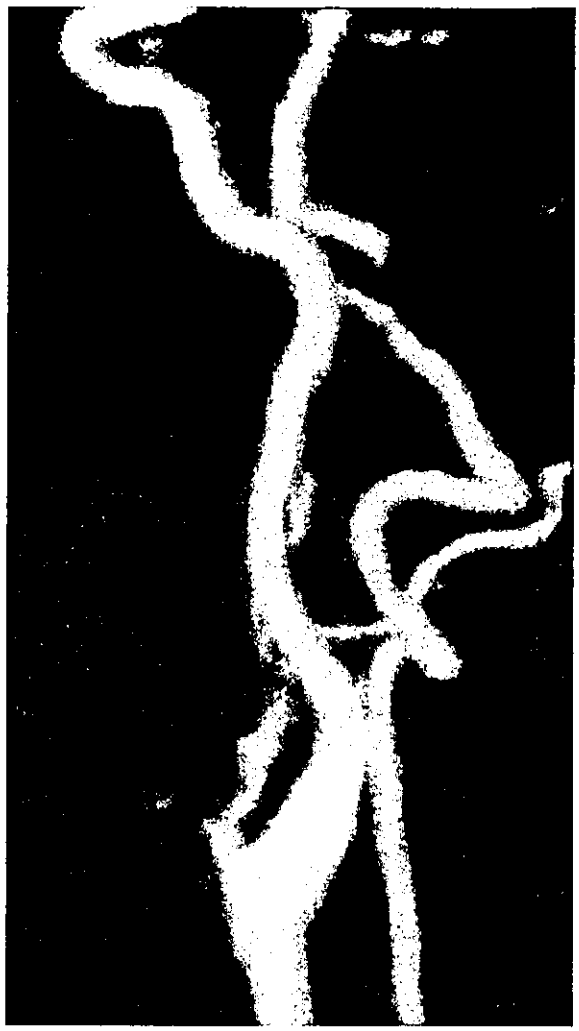

Figure 4. On day 28 of hospitalization, the right ICA appears normal on MR angiography.

bilateral middle cerebral arteries on follow-up TCD studies on the 7th day. Diffusion-weighted MR imaging of brain on the 25th day did not demonstrate fresh infarcts and MR angiography on the 28th day showed normal appearance of the right ICA (Fig. 4). The patient had no additional episodes of brain ischemia and was discharged without neurological deficits on the 30th day of admission.

Discussion

We recently reported that, in some patients with acute cardioembolic ICA occlusion, carotid ultrasonography demonstrated a mobile, echogenic intraluminal mass echo synchronizing with cardiac cycle in the proximal ICA (3, 4). We termed this finding "oscillating thrombus" and emphasized that it is a finding specific to acute embolic ICA occlusion. Although the intraluminal mass echo in the present case was like an "oscillating thrombus", it did not occlude the ICA but became lodged at the carotid bifurcation. This is different

from the previous reports and is unique to the present case. We believe that the intraluminal mass echo was a thromboembolus from the heart lodging at the carotid bifurcation because the patient had obvious emboligenic heart disease such as dilated myopathy and atrial fibrillation but no demonstrable atherosclerotic diseases from the aortic arch through to the ipsilateral CCA. The thrombus may have subsequently propagated in an anterograde fashion into the ICA during the acute stage.

It has been reported that MES are rarely detected in patients with cardioembolic stroke as compared to those with carotid artery disease (5), and that bilateral MES are suggestive of a cardioembolic origin (6). The MES in the present case indicated that the microemboli originated from the thrombus lodged at the carotid bifurcation rather than from the heart, because the MES were detected unilaterally from the right MCA distal to the thrombus and no intracardiac thrombi were evident on transesophageal echocardiography. Detection of MES arising from an intraluminal thrombus supports the concept that intraluminal thrombi have a propensity to produce secondary, distal embolism (1, 2).

Some authors regard the presence of an intraluminal thrombus as an indication for urgent thromboendarterectomy. However, this is a questionable strategy. The perioperative complication rate was high in patients with intraluminal thrombus, accounting for 20 to 30% (7–9). On the other hand, resolution of thrombi was observed without any additional neurologic deficits in the majority of patients receiving only antithrombotic therapy (7, 8). In the present case, the intraluminal thrombus decreased in size and eventually disappeared during anticoagulant therapy. This is probably due to the relative predominance of plasma fibrinolytic activity over anticoagulation-inhibited thrombin activity (10).

Conclusion

In a patient with acute cardioembolic stroke, disappearance of a thromboembolus from the heart lodging at the carotid bifurcation was observed using a series of ultrasonographic studies. Within two weeks after starting immediate anticoagulant therapy, the thrombus completely dissolved without any additional neulorogic symptoms. Neurosonographic studies may be a useful tool for detection and follow-up of an intraluminal thrombus in acute stroke patients undergoing anticoagulant therapy.

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Relationships between Angiographic Findings and National Institutes of Health Stroke Scale Score in Cases of Hyperacute Carotid Ischemic Stroke

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BACKGROUND AND PURPOSE: **Stroke severity in cases of hyperacute carotid ischemic stroke may be related to site of arterial occlusion. We evaluated the relationships between National Institutes of Health Stroke Scale (NIHSS) scores and findings on intra-arterial digital subtraction angiograms (IA-DSA) of patients with ischemic stroke within 6 hr of stroke onset.**

METHODS: **A total of 43 consecutive patients (38 men and five women; mean age, 69.4 ± 8.7 years) with ischemic stroke in the carotid territory underwent IA-DSA within 6 hr of stroke onset. Baseline NIHSS score was assessed immediately before IA-DSA. Patients were divided into four groups according to site of arterial occlusion: 1) the internal carotid artery (ICA group, n = 10); 2) stem of the middle cerebral artery or stem of the anterior cerebral artery (Stem group, n = 14); 3) branches of middle cerebral artery or anterior cerebral artery (Branch group, n = 11); and 4) no arterial occlusion (Normal group, n = 8).**

RESULTS: **Mean (±SD) NIHSS score was 14.7 ± 7.4. The interval from stroke onset to IA-DSA study was 205 ± 76 min. NIHSS score was higher in the ICA group (median, 23; range, 6–32) than in the Branch (median, 17; range, 11–25; $P = .02$) or Normal (median, 15; range, 2–17; $P < .001$) groups but was not higher than in the Stem group (median, 6; range, 1–11; $P = .73$). Sensitivity-specificity curve analysis suggested an NIHSS score ≥10 as indicative of arterial occlusion of the carotid system. A total of 96.9% of patients with NIHSS scores ≥10 displayed arterial occlusion, and 63.6% of patients with NIHSS scores <10 displayed no arterial occlusion.**

CONCLUSION: **NIHSS score is related to site of arterial occlusion in cases of hyperacute carotid ischemic stroke. An NIHSS score of 10 seems to represent the cut-off for discriminating between patients with arterial occlusion and patients without.**

The National Institutes of Health Stroke Scale (NIHSS) is a widely used and well-validated neurologic impairment scale, measuring speech and language, cognition, visual field deficits, motor and sensory impairments, and ataxia (1). NIHSS score assessed during the hyperacute phase of stroke strongly predicts the likelihood of patient recovery after stroke and has been used to include or exclude patients from trials of acute stroke therapy, including thrombolysis (2–7). The NIHSS therefore represents a standard part of clinical assessment for patients with acute stroke in many stroke centers.

Fink et al (8) reported a significant correlation between diffusion-weighted MR imaging lesion volume and NIHSS score. Several studies examined relationships between initial NIHSS score and vascular imaging techniques such as ultrasonography (9, 10), CT angiography (11), and MR angiography (12), reporting that a higher NIHSS score was associated with more severe vascular lesions in patients with acute stroke. However, vascular imaging methods have limitations in clearly displaying occlusion or stenosis of the main stem and branches of the middle cerebral artery (MCA) and anterior cerebral artery (ACA). Relationships between NIHSS score and site of arterial occlusion during the hyperacute phase of stroke, therefore, have yet to be accurately determined.

Intra-arterial digital subtraction angiography (IA-

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DSA) is superior to other methods for detecting the site of arterial occlusion and is considered to represent the gold standard for vascular imaging. During the hyperacute phase of stroke, detailed knowledge of arterial occlusion can be clinically important, particularly regarding thromobolysis (13, 14). The aim of the present study was to evaluate relationships between NIHSS score and IA-DSA findings in patients with ischemic stroke within 6 hr of stroke onset.

Methods

Patients and Techniques

Of the 112 patients admitted to our division within 6 hr of ischemic stroke onset between April 1999 and June 2002, IA-DSA was performed in 43 patients with carotid acute ischemic stroke (38 men and five women; mean age, 69.4 ± 8.7 years). We excluded the patients with posterior circulation strokes because anterior circulation and posterior circulation strokes were thought to be separate entities, with different underlying pathogenesis and natural histories. These 43 patients were enrolled into this study. All patients were assessed by using the NIHSS immediately before IA-DSA. If the patient was aware of symptoms on waking from sleep, time of onset was defined as the last time they were free from symptoms. A modified Rankin Scale (15) score ≥2 before stroke onset was used as an exclusion criterion.

Sex, age, history of stroke or transient ischemic attack, and modified Rankin Scale score were examined, along with vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, smoking, and potential embolic sources of emboli (atrial fibrillation, patent foramen ovale, left ventricular aneurysm, prosthetic heart valves, infective endocarditis, sick sinus syndrome, dilated cardiomyopathy, and complicated lesions in aortic arch).

Vascular risk factors were identified as follows: 1) use of antihypertensive agents for hypertension, with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg at admission for hypertension; 2) use of oral hypoglycemic agents, insulin, or glycosylated hemoglobin >6.4% for diabetes mellitus; 3) use of antihyperlipidemic agents or serum cholesterol level >220 mg/dL for hypercholesterolemia; or 4) history of smoking. To detect potential embolic sources of emboli, all patients underwent 12-lead ECG, 24-hr ECG monitoring, and transthoracic or transesophageal echocardiography.

Informed consent for performance of IA-DSA was obtained from patients and/or their family members. Selective IA-DSA was performed by using a biplane, high resolution angiography system (Angio Rex Super-G and DFP-2000A, Toshiba) with a matrix of 1024 × 1024 pixels. A catheter was inserted into the right brachial artery or femoral artery in accordance with the Seldinger method and then guided to the cerebral arteries for diagnostic four-vessel angiography.

Patients were divided into four groups according to the site of arterial occlusion: 1) occlusion of the internal carotid artery (ICA group); 2) occlusion of the main stem of the MCA or A1 segment of the ACA (Stem group); 3) occlusion of the MCA or ACA branch, including occlusion of M2 or A2 or more distal sites (Branch group); or 4) no arterial occlusion (Normal group). If a patient displayed two or more occluded arteries, the patient was placed in the largest artery group (eg, if occlusions of both the right main trunk of the MCA and the ipsilateral A2 portion were present, the patient was placed in the Stem group).

CT of the brain was performed immediately at admission and 3 days after stroke onset to evaluate ischemic lesions. Within 7 days of stroke onset, MR imaging was performed by using a 1.5-T system (Magnetom Vision, Siemens) equipped with single shot echo-planar imaging to obtain rapid diffusion images. MR imaging studies included axial T1-weighted, axial T2-weighted, and diffusion-weighted sequences (approximately 30 min of imaging time). Imaging parameters were as follows: 4000/103 (TR/TE); matrix, 128 × 128; field of view, 230 mm; section thickness, 4 mm; section gap, 2 mm. Two b values were used (0 and 1000 s/mm^2). Diffusion gradients were applied in successive images in each of the x, y, and z directions, and diffusion-weighted images were formed from the mean of these values. Criteria for diagnosis of acute infarcts on diffusion-weighted images included focal hyperintensity judged not to be due to normal anisotropic diffusion or magnetic susceptibility artifact. These lesions were also categorized as cortical, subcortical, or lacunar infarcts according to location.

Statistical analysis was performed by using StatView 5.0 for Windows (SAS Institute, 1998). The χ^2 test or Kruskal-Wallis *U* test was used to compare baseline characteristics among the four groups. Relationships between baseline NIHSS score and site of arterial occlusion were tested by using the Kruskal-Wallis *U* test, and the differences between NIHSS scores for each group were tested by post hoc analysis under Scheffe's method. To obtain the NIHSS score as the cut-off point for discriminating between patients with arterial occlusion and those without, a sensitivity and specificity curve was drawn. The study protocol followed all principles outlined in the Declaration of Helsinki.

Results

Of the 43 patients enrolled in this study, 20 underwent IA-DSA within 3 hr of stroke onset. Intervals from stroke onset to arrival at hospital and to IA-DSA study were 88 ± 58 min and 205 ± 76 min, respectively.

The Stem group was the largest (n = 14), with the other groups in descending order being the Branch (n = 11), ICA (n = 10), and Normal (n = 8) groups. Demographic data and clinical features of each group are shown in Table 1. Atrial fibrillation was observed most frequently in the Branch group ($P < .014$). No other significant differences in baseline characteristics were observed.

In the ICA group, seven patients displayed ICA occlusion. For one, occlusion of both the ICA and ipsilateral ACA A2 portion was show, and for the remaining two, both ICA occlusion and ipsilateral MCA stem occlusion was shown, despite good collateral flow from the contralateral ACA via the anterior communicating artery. In the Stem group, 11 patients displayed MCA stem occlusion, one had bilateral MCA stem occlusion, one had both MCA stem occlusion and ipsilateral A2 occlusion, and the remaining had both MCA stem occlusion and occlusion of the distal site of ipsilateral ACA. In the Branch group, five patients had MCA M2 branch occlusion, two had M3 branch occlusion, two had both M2 and A2 portion occlusion, one had M2 and A4 portion occlusions, and the other one displayed M4 and A3 portion occlusions.

The median NIHSS score was 16 (range, 1–32). No significant differences were observed between NIHSS scores of patients with left- and right-sided stroke ($P = .874$, Mann-Whitney *U* test). NIHSS score was higher in the ICA group (median, 23; range, 6–32) than in the Branch (median, 15; range, 2–17; $P = .02$)

Clinical characteristics of all patients

Group	ICA	Stem	Branch	Normal	P
Number of patients	10	14	11	8	
Age, median (range) (yr)	71 (48–78)	68 (56–82)	74 (57–86)	64 (55–84)	0.671
Sex, male	10 (100%)	12 (86%)	9 (82%)	7 (88%)	0.598†
Hypertension	8 (80%)	9 (64%)	5 (45%)	8 (100%)	0.065
Diabetes mellitus	2 (20%)	5 (36%)	4 (36%)	1 (13%)	0.405
Hyperlipidemia	5 (50%)	4 (29%)	4 (36%)	6 (75%)	0.181
Smoking	6 (60%)	8 (57%)	2 (18%)	3 (38%)	0.163
Atrial fibrillation	5 (50%)	10 (71%)	9 (82%)	1 (13%)	0.014
Potential emboligenic diseases	2 (20%)	3 (21%)	3 (27%)	4 (50%)	0.467
Patent foramen ovale	0	2	2	2	
Left ventricular aneurysm	0	1	0	0	
Complicated lesion in aorta	2	0	1	2	
History of stroke/transient ischemic attack	1 (10%)	1 (7%)	2 (18%)	1 (13%)	0.858
Interval from stroke onset to angiography mean ± SD (min)	173 ± 75 (150)	211 ± 86 (194)	223 ± 67 (185)	223 ± 76 (199)	0.272†
Affected side (right/left)	6/4	8/6	3/8	3/5	0.353

* Analyzed by using the χ^2 test.

† Analyzed by using the Kruskal-Wallis U test.

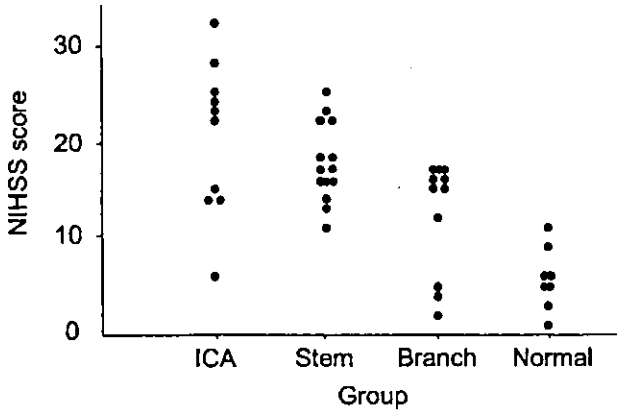

FIG 1. Distribution of the NIHSS score of four groups.

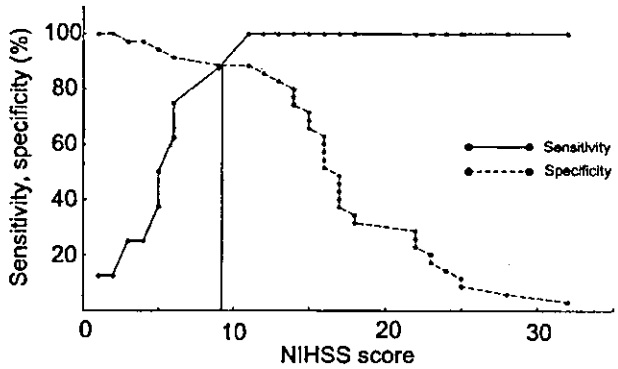

FIG 2. Sensitivity-specificity curve analysis for predicting arterial occlusion. The optimal threshold value of the NIHSS score was 10.

or Normal (median, 6; range, 1–11; $P < .001$) groups but not higher than in the Stem group (median, 17; range, 11–25; $P = .73$). Patients in the Stem group displayed higher NIHSS scores than those in the Normal group ($P < .001$). In sensitivity-specificity curve analysis for predicting arterial occlusion, the optimal threshold value of the NIHSS score was 10 (Figs 1 and 2). Using an NIHSS score of 10 as the cut-off, sensitivity, specificity, positive predictive value, and negative predictive value for any arterial occlusion were 88.6%, 87.5%, 63.6%, and 96.9%, respectively.

MR imaging revealed 33 cortical infarcts, six subcortical infarcts, one lacunar infarct, and no ischemic lesions in three patients. Cortical and subcortical infarcts were present in seven and three of the 10 ICA group patients, respectively, 14 and 0 of the 14 MCA group patients, respectively, 10 and 0 of the 11 Branch group patients, respectively, and two and three of the eight Normal group patients, respectively. Lacunar infarct was observed in only one patient from the Normal group. One patient in the Branch group and three in the Normal group displayed no fresh lesions.

Discussion

Our study showed that an NIHSS score ≥10 represented the optimal value for predicting arterial occlusion in patients within 6 hr of stroke onset; 31 (97.0%) of 32 patients with NIHSS score ≥10 displayed arterial occlusion. Lewandowski et al (4) studied patients with stroke within 3 hr of stroke onset in the Emergency Management of Stroke bridging trial by using angiography. In that study, 17 (77.3%) of 22 patients with NIHSS scores ≥10 displayed occluded arteries in the carotid system. This minor discrepancy may be attributable to the differing interval between stroke onset and vascular imaging and to the methods to evaluate occlusive lesions.

Some studies have reported no significant differences in NIHSS scores between patients with MCA trunk occlusion and ICA/MCA tandem occlusion, a result that is compatible with the present results (9, 16). When the ICA is occluded, the severity of neurologic deficit is contingent on collateral blood flow through the anterior communicating or leptomeningial arteries from the ACA or posterior cerebral artery.

Our study included a small number of small artery diseases presenting as lacunar syndrome. We do not

frequently perform IA-DSA but MRA to evaluate occlusive lesions in patients with lacunar stroke. A previous study reported that 205 (67.0%) of 306 patients with small artery disease had NIHSS scores of 0 to 6 (2). Patients with small artery disease may therefore be likely to achieve NIHSS scores <10.

In the present study, only one (3.0%) of 33 patients with NIHSS scores ≥10 displayed no arterial occlusion. In this case, neurologic symptoms improved immediately after angiography; this was attributed to spontaneous reopening of the occluded artery immediately before IA-DSA. Conversely, four (36.4%) of 11 patients with NIHSS scores <10 displayed arterial occlusions. Naylor et al (17) reported that patients with hyperacute stroke with MCA or ICA occlusions may occasionally display mild stroke severity or mimic lacunar events. Of the four patients, angiography in one case revealed occlusion of the right ICA origin and ipsilateral ACA and good collateral blood flow through the anterior communicating artery from the contralateral ICA system to the ipsilateral MCA. MR imaging of the brain revealed only a small infarct in ACA territory. In the remaining three patients with MCA branch occlusion, good leptomeningeal collateral blood supply from the ACA or posterior cerebral artery was present, and MR imaging revealed small infarcts. The mild neurologic deficits in these cases may therefore be due to good collateral flow.

The present study displayed some limitations. We did not perform IA-DSA for all patients with stroke within 6 hr of onset. In particular, IA-DSA was infrequently performed for patients older than 80 years and patients with lacunar stroke. This represents a source of selection bias in the study.

In conclusion, NIHSS score is associated with site of arterial occlusion in patients with hyperacute carotid ischemic stroke. An NIHSS score ≥10 is predictive of arterial occlusion in hyperacute ischemic stroke within 6 hr of onset.

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Early neurological deterioration represents recurrent attack in acute small non-lacunar stroke

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Abstract

The aim of this study was to identify the frequency and possible pathogenic mechanisms of early neurological deterioration in patients with acute small non-lacunar infarction. We studied 46 patients (35 men, 11 women; age, 70.3 ± 10.4 years) with acute small non-lacunar infarction. Small non-lacunar infarction was diagnosed using diffusion-weighted magnetic resonance imaging (DWI) as being < 15 mm in diameter and located in the cortex and centrum ovale in the middle cerebral artery (MCA) territory. The patients were divided into two groups; Group D ($n=6$) had neurological deterioration within 7 days after symptom onset, while Group N ($n=40$) did not have any neurological deterioration. In Group D, the interval from symptom onset to clinical deterioration was 3.3 ± 1.5 days (range 2–6 days). Blood pressure on admission was higher in Group D than in Group N ($p<0.05$). In Group D, four of these five patients with follow-up DWI had new acute small ischemic lesions in addition to the initial lesions, indicating recurrent attacks of brain infarction. Neurological deterioration occurred within 7 days after symptom onset in 13% of patients. Neurological deterioration was frequently caused by recurrent infarction detected by DWI.

Keywords: Acute stroke; Small non-lacunar infraction; DWI; Neurological deterioration; Recurrent stroke

1. Introduction

Early neurological deterioration is a common event in acute stroke, being 20–40% in frequency [1]. In stroke patients with moderate-to-severe neurological deficits, European Cooperative Acute Stroke Study (ECASS) I reported that the incidence of early and late progressing stroke was 37.5% and 20.3% [2]. The cause of the progressing stroke is often explained by the development of brain edema associated with an brain infarct [2]. In lacunar infarction with mild neurological deficits, the incidence of a progressive course during the acute phase of stroke is also observed in 24–36% of patients [3–5]. The impairment of the microcirculation in penetrating artery may play a major role in this phenomenon. However, there is still no precise knowledge of the cause of progression and we are unable to predict patients at risk. Therefore, it is important to advance the search for the underlying pathogenic mechanisms of neurological deterioration in acute stroke patients.

Recently, we reported that symptomatic small non-lacunar infarcts (small centrum semiovale infarcts and cortical infarcts) were more frequently associated with large vessel disease and cardioembolism than lacunar infarcts [6,7]. We concluded that the mechanism of stroke in this form of infarction was often embolic from artery or heart, and should be differentiated from lacunar infarction, which is a small vessel disease.

Recurrent infarction must be considered as one potential cause of neurological deterioration following stroke. However, it is often difficult to distinguish progressing stroke from a recurrent attack. Neuroimaging may help the diag-

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nosis of a recurrent attack. If neuroimaging can display new lesions separately to the initial lesions, we can diagnose the patient as having a recurrent attack.

Diffusion-weighted imaging (DWI) is a powerful tool for detecting recent small ischemic lesions, particularly in the centrum ovale or cortex [6,8]. We experienced a patient with neurological deterioration in small non-lacunar infarcts, whose follow-up DWI study revealed new small infarcts in addition to the initial infarcts, indicating recurrent attacks. Therefore, we hypothesized that neurological deterioration during the acute phase in patients with small non-lacunar infarcts might be caused by recurrent attacks.

To the best of our knowledge, the frequency and mechanisms of neurological deterioration in patients with small non-lacunar infarcts remain unclear. We studied consecutive patients with small non-lacunar infarcts to solve the above-mentioned problems using DWI.

2. Materials and methods

The aim of this study was firstly to examine the frequency of neurological deterioration within 7 days after symptom onset in patients with small non-lacunar infarcts. Second, we compared clinical characteristics between patients with and without neurological deterioration. Furthermore, in patients with neurological deterioration, we performed a follow-up DWI study to detect new small ischemic lesions in addition to the initial lesions after deterioration.

We enrolled consecutive patients with small non-lacunar infarction admitted to our division of National Cardiovascular Center within 7 days of symptom onset between January 2000 and February 2002 into the present study. DWI was performed within 7 days of symptom onset to detect acute ischemic lesions.

Small non-lacunar infarcts were defined as follows: (1) lesions on DWI were acute; (2) diameter of the lesions was smaller than 15 mm; and (3) lesions were located in the cortex or centrum ovale [9]. An infarct situated in the corona radiata, putamen, globus pallidus, and internal capsule, which are supplied by the deep perforating arteries of the middle cerebral artery (MCA), were excluded from this study [9,10].

We assessed the neurological severity on admission using National Institutes of Health Stroke Scale (NIHSS) score [11] and handicap at discharge using modified Rankin scale (mRS) [12]. Neurological deterioration was diagnosed when NIHSS score increased ≥ 2 points from the baseline NIHSS score during the 7 days after symptom onset. The mode of deterioration was classified into four subgroups; abrupt, stepwise, fluctuating and linear slope-like. Patients were classified into two groups; patients displaying neurological deterioration (Group D), and those without any neurological deterioration (Group N).

MR imaging studies were conducted for all patients within 7 days after symptom onset. When patients had neurological deterioration, a follow-up DWI study was conducted. MR imaging was performed using a Siemens MAGNETOM Vision 1.5-T MR unit with echo-planar capability. DWI was performed simultaneously using a multislice, single-shot, spin echo planar imaging sequence in all patients within 7 days of symptom onset. Diffusion gradients were applied in each of the x-, y-, and z-axes with two b values (0 and 1000 s/mm^2). Fluid-attenuated inversion recovery (FLAIR, TR/TE, 9000/105) images was carried out simultaneously with DWI. The criterion for the diagnosis of acute infarcts on DWI was focal hyperintensity, judged not attributable to normal anisotropic diffusion or magnetic susceptibility artifacts.

Vascular risk factors were identified as follows: (1) use of antihypertensive agents, or systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg on admission for hypertension; (2) use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin (HbA1C) >6.4% for diabetes mellitus; (3) use of antihyperlipidemic agents or serum cholesterol level >220 mg/dl for hypercholesterolemia.

We carried out color-flow duplex carotid ultrasonography, conventional cerebral angiography, and magnetic resonance angiography (MRA) to evaluate arterial diseases in the carotid system. Color-flow duplex carotid ultrasonography (Toshiba SSA 270A, Toshiba Inc., Tokyo, Japan, or Ultramark 9 HDI, ATL, Bothel, WA) was performed in all patients as a routine test. The grade of arterial stenosis was determined according to the criteria used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [13]. Arterial diseases were considered significant when stenosis >70%, occlusion, or ulceration were evident in the ipsilateral carotid system. In addition, the peak systolic blood flow velocity in the internal carotid artery (ICA) greater than 200 cm/s on ultrasonography was considered equivalent to ICA stenosis >70% for the NASCET criteria [14].

To detect an emboligenic cardiac disease, all patients were examined using 12-lead electrocardiography (ECG), 24-h ECG monitoring, and transthoracic echocardiography (TTE). Additionally, we conducted transesophageal echocardiography (TEE) to evaluate patent foramen ovale (PFO) and atherosclerosis of the aortic arch (aortic complicated plaque). Emboligenic cardiac diseases included non-valvular atrial fibrillation (NVAF), mitral stenosis, left ventricular aneurysm, prosthetic cardiac valves, dilated cardiomyopathy, and PFO. An aortic complicated plaque was considered significant as a plaque ≥ 4 mm or mobile plaque in the aortic arch visualized on TEE [15].

Statistical analysis was performed using a commercially available software package (Stat-View, version 5.0; SAS Institute, Cary, NC). Univariate analyses were performed by the Fisher exact test or Chi square test and the Mann–

Table 1
Demographic and clinical feature of patients of Group D

Age/Sex	Day of deterioration	Mode of deterioration	NIHSS score			Site of lesion (distribution, number)		Potential embolic source
			On admission	Before deterioration	After deterioration	Initial DWI	Follow-up DWI (after deterioration)	
						Initial lesion	Additional lesion	
77/M	2	abrupt	7	7	9	Lt MCA (cortex and subcortex), multiple	no change	Lt ICA 50% stenosis with ulceraion, Ao.
57/M	6	abrupt	7	7	13	Rt MCA (subcortex), Lt MCA (cortex), multiple	Rt MCA (subcoetex), single	Ao.
66/M	2	stepwise	5	5	9	Rt MCA (subcortex), Lt MCA (cortex, subcortex), multiple	Lt MCA (subcoetex), single	Bilateral ICA 70% stenosis, Ao.
78/M	3	stepwise	6	4	9	Rt MCA (cortex and subcortex), multiple	Rt MCA (cortex and subcortex), multiple	Rt.ICA 90% stenosis
81/F	3	stepwise	2	2	6	Lt MCA (subcortex), multiple	NA	NVAF, Ao.
74/M	4	fluctuating	6	6	8	Lt MCA (subcortex), multiple	Lt MCA (subcortex), single	>50% MCA stenosis

Ao.: aortic complicated plaque, NVAF: non valvular atrial fibrillation, NA: not available.

Whitney *U*-test between the two groups. Values of $p < 0.05$ were considered statistically significant.

3. Results

A total of 404 patients with acute ischemic stroke or TIA were admitted to our division within 7 days after symptom onset, and 356 (88%) patients were performed DWI within 7 days after symptom onset. Out of them, 46 patients (35 men, 11 women) with a small non-lacunar infarct were enrolled into the present study. Age (mean ± S.D.) of the patients was 70.3 ± 10.4 years (median 72-years-old, range 38–87).

An initial DWI study showed a small ischemic lesion in 14 patients, and multiple lesions in 32 patients. In 14 patients with a single lesion, the lesion was located in the cortex in seven patients, and in the subcortex in the other seven patients. In the 32 patients with multiple lesions, the lesions were located only in the cortex in seven patients, only in the subcortex in seven patients, and in both the cortex and subcortex in the remaining 18 patients.

We performed conventional cerebral angiography in six patients (13%), MRA in 27 patients (59%), and both assessments in 12 patients (26%). Twenty-three patients (50%) had a significant arterial disease. The following arterial lesions were observed; MCA occlusion in one patient, more than 50% stenosis of the horizontal portion of the MCA in three, ICA occlusion in four, more than 70% ICA stenosis in 10, less than 70% ICA stenosis but with ulceration in two, more than 70% ICA stenosis and the anterior cerebral artery occlusion in one, and more than 70% stenosis of the ICA and horizontal portion of the MCA in two.

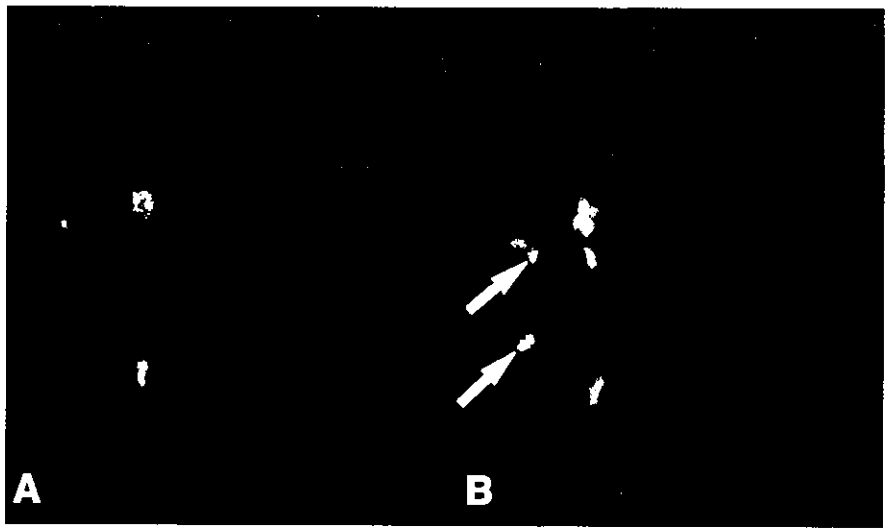

Fig. 1. A 78-year-old man presented with left hemiparesis and unilateral spatial neglect (USN). NIHSS score on admission was 6. Color-flow duplex carotid ultrasonography showed 90% stenosis in the right internal carotid artery. Diffusion-weighted imaging (DWI) on day 2 demonstrated acute small multiple ischemic lesions in the right hemisphere (A). He had stepwise deterioration with left sensory disturbance and hemiparesis from days 3 to 7. The NIHSS score increased from 4 (day 3) to 9 (day 7). Follow-up DWI on day 8 revealed additional acute ischemic lesions (B, arrows).

We conducted the TEE in 30 patients. Emboligenic cardiac diseases were detected in 22 (48%) patients; only NVAF in 10, only PFO in seven, left ventricular aneurysm with thrombus in two, both AF and a prosthetic mitral valve in one, and both NVAF and PFO in two. Aortic complicated plaques were detected in 17 patients. Overall, 41 patients (89%) had a potential embolic source.

Six patients (13%; Group D) had neurological deterioration, and 40 patients (87%; Group N) did not have any deterioration. The interval from symptom onset to neurological deterioration was 3.3 ± 1.5 days (range 2–6 days). No patients had neurological deterioration before the first MRI study. The mode was abrupt in two patients, fluctuating in one and stepwise in three. The demographic and clinical features of the six patients with neurological deterioration are summarized in Table 1. All patients had a potential embolic source. In the Group D, a follow-up MRI study was performed on all the patients except one, who declined an MRI test. Four of the five patients who underwent follow-up imaging had new acute ischemic lesions surrounding the initial lesions (Fig. 1). While the remaining one patient had no new lesions. In the Group N, a follow-up DWI study was performed in only one patient within 7 days of symptom onset. The patient did not have any new lesions except for initial lesions.

Table 2
Patient characteristics

	Group D $n=6$	Group N $n=40$	p
Age, years (mean ± S.D.)	72.2 ± 9.0	70.1 ± 10.7	0.65
Sex (M/F)	5/1	30/10	0.66
TIA within 7 days before symptom onset, *n* (%)	0	6(15)	0.58
Interval from symptom onset to admission, h (mean ± S.D.)	15.4 ± 13.4	17.9 ± 27.3	0.74
Interval from symptom onset to MRI study, h (mean ± S.D.)	32.7 ± 20.6	40.4 ± 42.4	0.76
NIHSS score on admission (median ± S.D.)	6 ± 2	3 ± 4	0.10
mRS at discharge (median ± S.D.)	2 ± 2	1 ± 1	0.73
Body temperature, °C	36.8 ± 0.6	36.3 ± 0.5	0.061
Systolic blood pressure, mm Hg	169.3 ± 22.1	146.4 ± 19.9	0.027
Diastolic blood pressure, mm Hg	90.7 ± 6.4	77.1 ± 10.0	0.0023
Laboratory parameters			
Serum glucose, mg/dl	109.0 ± 20.9	106.0 ± 21.1	0.74
Fibrinogen, mg/dl	384.2 ± 140.2	312.9 ± 70.7	0.22
Hematocrit, %	41.3 ± 6.9	40.3 ± 4.4	0.68
Blood-coagulation factors			
ATIII, %	91.0 ± 14.3	88.1 ± 13.6	0.55
D-Dimer, g/ml	3.0 ± 6.4	1.4 ± 1.7	0.29
TAT, mg/ml	2.9 ± 2.3	5.9 ± 11.0	0.94
Vascular risk factors, *n* (%)			
Hypertension	5(83.3)	33(82.5)	0.96
Diabetes mellitus	2(33.3)	14(35.0)	0.94
Hypercholesterolemia	2(33.3)	16(40.0)	0.76
Cigarette smoking	3(50.0)	17(42.5)	0.73
History of ischemic heart disease, *n* (%)	4(66.7)	13(32.5)	0.11
Peripheral arterial disease, *n* (%)	1(16.6)	2(5.0)	0.20
Emboligenic cardiac diseases, *n* (%)	1(16.6)	21(52.5)	0.10
Arterial diseases, *n* (%)	4(66.7)	19(47.5)	0.38
Aortic complicated plaque, *n*	4/5	13/25	0.25
Medication within 7 days of stroke onset			
Heparin, *n* (%)	5(83.3)	28(70)	0.50
Aspirin, *n* (%)	5(83.3)	25(62.5)	0.32

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale.
ATIII: antithrombin III, TAT: thrombin–antithrombin III complex.

Table 2 shows the clinical characteristics of the two groups. Systolic and diastolic blood pressures on admission were higher in Group D than in Group N. No statistically significant differences in age, sex, TIA within 7 days before symptom onset, the interval from symptom onset to admission, and to initial DWI study, NIHSS score on admission, body temperature on admission, laboratory parameters, blood-coagulation factors, vascular risk factors, history of ischemic heart disease, peripheral arterial disease, arterial and cardiac diseases, aortic complicated plaques and use of medication were observed between the two groups. An mRS score at discharge was not different.

4. Discussion

Our study demonstrated that the frequency of neurological deterioration in patients with small non-lacunar infarcts was 13% during 7 days of symptom onset. In lacunar stroke, frequency of neurological progression was 24–36% [3–5]. Nakamura et al. [4] reported that diabetes mellitus and the severity of motor deficits on admission might predict progression of motor deficits. Lodder et al. [5] showed that progression of symptom was associated with a large infarct volume. Lacunar infarction was caused by occlusion of deep perforators from the horizontal portion of MCA. On the other hand, small non-lacunar infarction was due to occlusion of the MCA branches and the medullary arteries originating from superficial branches of MCA. Furthermore, the frequency of arterial and cardiac disease was different between non-lacunar and lacunar infarction [6,7]. In fact, 89% of our patients had a potential embolic source. We suspect that a small non-lacunar infarct may be caused by embolism from a large artery and heart [6,7]. Therefore, the discrepancy in frequency of neurological deterioration between lacunar and small non-lacunar infarction was explained by the difference in the pathogenic mechanism of stroke.

High serum glucose levels, history of diabetes, stroke severity on admission, and early focal hypodensity and brain swelling on the initial CT scan have been associated with neurological deterioration in acute stroke [2,16–19]. Above-mentioned factors might result in insufficient collateral blood supply, expanding brain edema, or metabolic deterioration during acute phase of stroke. Infarct size in our patients was always too tiny for initial CT findings to represent an important factor. In the present study, no differences in serum glucose levels and history of diabetes were observed between

the two groups. The number of our patients might be too small to find differences between the two groups.

Systolic and diastolic blood pressures on admission were higher in Group D than Group N. Dávalos et al. [17] reported that high systolic blood pressure on admission was independently related with early deterioration after ischemic stroke. Whereas, Jørgensen et al. [18] showed that high systolic blood pressure on admission decreased risk for early progression. In the present study, the exact relationship between high blood pressure and neurological deterioration is unknown. A further study will be needed to solve the issue.

In the present study, NIHSS score and the body temperature was higher in Group D than in Group N, but these difference was not significant. Patients with high NIHSS score at admission were likely to have neurological deterioration in acute phase of ischemic stroke [2,19]. A few investigators reported that patients with higher temperature had a worse stroke outcome [20–22]. However, it has still unknown whether higher temperature is associated with early deterioration at acute phase of ischemic stroke.

In our study, the follow-up DWI study in all the patients but one with neurological deterioration revealed new small infarcts addition to the initial infarcts. Therefore, we concluded that recurrence of small infarcts resulted in neurological deterioration. In patients with small non-lacunar infarcts, prevention of recurrent infarcts is important for avoiding neurological deterioration.

A number of problems were present in this study. Firstly, there was a small sample size of deterioration patients with a follow-up DWI study. Therefore, statistic analysis was weak. Secondly, we could not conduct follow-up DWI studies in many patients without neurological deterioration. Therefore, we could not exclude the possibility that new but asymptomatic lesions appeared if follow-up DWI in those patients is performed.

In conclusion, our study demonstrated that the frequency of neurological deterioration in patients with small non-lacunar infarcts was 13% within 7 days after symptom onset. Neurological deterioration in these patients was frequently accompanied by recurrent infarction visualized with DWI.

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□ ORIGINAL ARTICLE □

Clinical and Radiographic Features of Lobar Cerebral Hemorrhage: Hypertensive Versus Non-hypertensive Cases

Ryo OHTANI, Seiji KAZUI, Hidekazu TOMIMOTO*, Kazuo MINEMATSU and Hiroaki NARITOMI

Abstract

Objectives **The underlying cause of lobar intracerebral hemorrhage (ICH) is often difficult to determine, since these vascular abnormalities are not necessarily visualized in radiographic studies. We sought to determine the clinical features of hypertensive and non-hypertensive lobar ICH, and further predict the presence or absence of vascular abnormalities in terms of clinical features and radiographic abnormalities.**

Patients and Methods **Eighty-one patients with lobar ICH were retrospectively assigned to either hypertensive or non-hypertensive groups based on their blood pressure levels during the chronic phase or a history of antihypertensive medication. The clinical and radiographic features of these two groups were compared.**

Results **Forty-nine patients (60%) were hypertensive, and the other thirty-two (40%) were non-hypertensive. In the non-hypertensive group, amyloid angiopathy (n=6), aneurysms (n=5), arteriovenous malformation (n=4), use of anticoagulants (n=2), liver cirrhosis (n=2) and thrombasthenia (n=1) were found as underlying causes. There were no significant differences between these two groups in the frequencies of stroke risk factors except for hypertension, clinical features and initial neurological findings. On the contrary, subarachnoid extension of the hematoma on CT was significantly more frequent in the non-hypertensive lobar ICH group than in the hypertensive group ($p<0.001$). The patients with subarachnoid extension were more likely to have vascular abnormality than those without subarachnoid extension ($p<0.01$).**

Conclusion **Subarachnoid extension of the hematoma on CT strongly indicates a non-hypertensive cause, and more specifically, it suggests lobar ICH caused by vascular abnormalities.**

(Internal Medicine 42: 576–580, 2003)

Key words: hypertension, lobar hemorrhage, computed tomography, subarachnoid extension, vascular abnormality

Introduction

Hypertension is a relatively infrequent cause of lobar intracerebral hemorrhage (ICH), compared to ICH in the deep regions such as the putamen, thalamus, cerebellum and pons (1). Indeed, lobar ICH is the result of other heterogeneous causes, including arteriovenous malformation, cavernous angioma, aneurysm, brain tumors, especially those of metastatic origin (2, 3), the use of anticoagulant or fibrinolytic agents, cerebral amyloid angiopathy and vasculitis (2). Furthermore, the frequency of lobar ICH complicated by amphetamines (4), pseudoephedrine (5), and cocaine (6) has increased recently. Other relatively rare causes may include moyamoya disease (7), disseminated intravascular coagulation or sepsis (8), cerebral venous thrombosis (9) and leptomeningeal anastomosis after the occlusion of major cerebral artery (10).

Lobar ICH is not necessarily rare, however, there are relatively few studies on lobar ICH in comparison with deep ICH in the thalamus, putamen, pons or cerebellum. In addition, it is often difficult to determine the underlying causes, since vascular abnormalities such as arteriovenous malformation, cavernous angioma or aneurysm are not necessarily visualized in radiological studies. In the present study, we compared the clinical features of hypertensive and non-hypertensive lobar ICH, and further sought to predict the presence or absence of vascular abnormalities in terms of clinical features and CT findings of hematomas.

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Materials and Methods

We retrospectively reviewed the records of 409 patients with ICH who had been admitted to our stroke care unit from January 1, 1985 to December 31, 1996. Among these patients, 81 were diagnosed with lobar ICH based on their CT findings. They consisted of 56 men and 25 women, and their mean age was 63±13 years (mean±SD). Cerebral angiographic studies were performed in 52 patients. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were performed in 76 patients and CT angiography (CTA) was performed in 9 patients. These patients were classified into two groups based on the presence or absence of hypertension in the chronic phase. Hypertension was defined to be present if patients fulfilled at least one of the following criteria: 1) a history of antihypertensive medication, 2) a history of hypertension diagnosed by a referring physician or 3) systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 95 mmHg on two or more discrete occasions, after 1 month has lapsed from the onset of the ICH.

We then investigated the differences in clinical and radiographic features between the hypertensive and non-hypertensive lobar ICH patients. The variables analyzed included 1) age and gender; 2) probable pathogenesis; 3) location of the hematoma; 4) stroke risk factors including diabetes mellitus, hyperlipidemia, habits of smoking and alcoholic beverage, prior symptomatic stroke or transient ischemic attacks, ischemic heart diseases (myocardial infarction or angina) and hepatic diseases; 5) clinical features at onset such as severe headache, convulsions, vomiting, vertigo or dizziness; 6) initial neurological findings such as the level of consciousness (alert, lethargic, stupor, coma), motor and sensory deficits, dysarthria and aphasia; 7) laboratory findings including fasting blood sugar, hematocrit, platelets, total cholesterol, triglyceride, hemoglobin A1c, prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrin/fibrinogen degradation products; 8) initial CT findings such as hematoma volume (cm^3), ventricular enlargement, mass effect (shift of midline structures or any evidence of herniation) and hematoma extension to the ventricles or subarachnoid space; 9) the duration of admission; and 10) the clinical outcome (modified Rankin scale) (11).

The volume of the ICH was determined in the following manner (12, 13). On the CT slice which shared the largest area of ICH, the largest diameter (A) of the hematoma was measured in centimeters. The second diameter (B) was represented by a line perpendicular to the largest diameter. The height of the hematoma was then calculated by multiplying the number of slices and the slice thickness, thus providing the third diameter (C). These three diameters were multiplied and then divided by 2 (A×B×C/2) to obtain the volume of the ICH. We used the χ^2 test and Student's t test for group comparisons. P values of 0.05 or less were considered to be statistically significant.

Results

Of the 81 patients with lobar ICH, 49 patients were hypertensive (60%) and the other 32 (40%) were non-hypertensive. The hypertensive lobar ICH group consisted of 33 men and 16 women with a mean age of 64±12 years. The non-hypertensive lobar ICH group consisted of 23 men and 9 women with a mean age 63±15 years.

In the non-hypertensive lobar ICH group, 6 patients had cerebral amyloid angiopathy. Four patients were diagnosed by pathological diagnosis and 2 patients were diagnosed on the basis of clinical features (14). Five patients had aneurysms and 4 had arteriovenous malformations, all of which were confirmed by angiographic examinations, MRA and CTA. Two were receiving anticoagulating agents, 2 had liver cirrhosis, 1 had thrombasthenia and 12 had no obvious causes (Table 1). In the hypertensive lobar ICH group, none had these specific causes, except for 2 patients who were receiving anticoagulants.

Hematomas were distributed more commonly in the anterior regions than in the posterior regions in both groups (Table 2). There were no significant differences between the two groups in terms of stroke risk factors, clinical features at onset, initial neurologic findings and clinical outcome. Laboratory examination also revealed no significant differences between the two groups (Table 3).

Table 1. Underlying Causes for Non-hypertensive Lobar Intracerebral Hemorrhage

	Number of patients
Cerebral amyloid angiopathy	6
Aneurysm	5
Arteriovenous malformation	4
Anticoagulant use	2
Liver cirrhosis	2
Thrombasthenia	1
Unknown	12
Total	32

Table 2. Location of the Lobar Intracerebral Hemorrhage

	Hypertensive	Non-hypertensive
Frontal	13 (26.5%)	12 (37.5%)
Temporal	13 (26.5%)	4 (12.5%)
Parietal	8 (16.3%)	6 (18.8%)
Occipital	7 (14.3%)	4 (12.5%)
Fronto-parietal	4 (8.2%)	2 (6.3%)
Fronto-temporal	3 (6.1%)	1 (3.1%)
Parieto-temporal	0 (0%)	2 (6.3%)
Parieto-occipital	1 (2.0%)	1 (3.1%)
Total	49	32

Table 3. Clinical Features of the Lobar Intracerebral Hemorrhage

	Hypertensive (n=49)	Non-hypertensive (n=32)	p value
Stroke risk factors			
Diabetes mellitus	11	4	0.26
Hyperlipidemia	3	2	0.98
Smoking	23	20	0.17
Alcoholic beverage	24	17	0.71
History of cerebral infarction	7	5	0.87
Ischemic heart disease	7	10	0.07
Hepatic disease	8	8	0.34
Clinical features at onset			
Severe headache	27	16	0.65
Seizure or convulsion	9	6	0.97
Vomiting	18	10	0.61
Vertigo or dizziness	2	0	0.25
Initial neurological findings			
Glasgow coma scale	12.7±3.1	12.8±3.0	0.89
Manual muscle strength test			
Upper limb	3.5±1.5	3.6±1.5	0.76
Lower limb	3.6±1.5	3.7±1.5	0.56
Clinical outcome			
Modified Rankin scale	2.4±2.1	2.4±2.3	0.91

In the initial CT findings, there were no significant differences in hematoma volume or in the frequency of ventricular enlargement, mass effect and ventricular extension between the two groups. However, subarachnoid extension was significantly more frequent in the non-hypertensive group (11 out of 32, 34.4%) than in the hypertensive group (2 out of 49, 4.1%) (Table 4). Figures 1A and 1B show representative CT findings of lobar ICH with and without subarachnoid extension, respectively. Of 13 patients with subarachnoid extension, 2 were hypertensive patients and 11 were non-hypertensive patients. In the later, 6 had vascular abnormality (2 with cerebral amyloid angiopathy, 2 with aneurysm and 2 with arteriovenous malformation (Table 5). On the other hand, of 68 patients without subarachnoid extension,

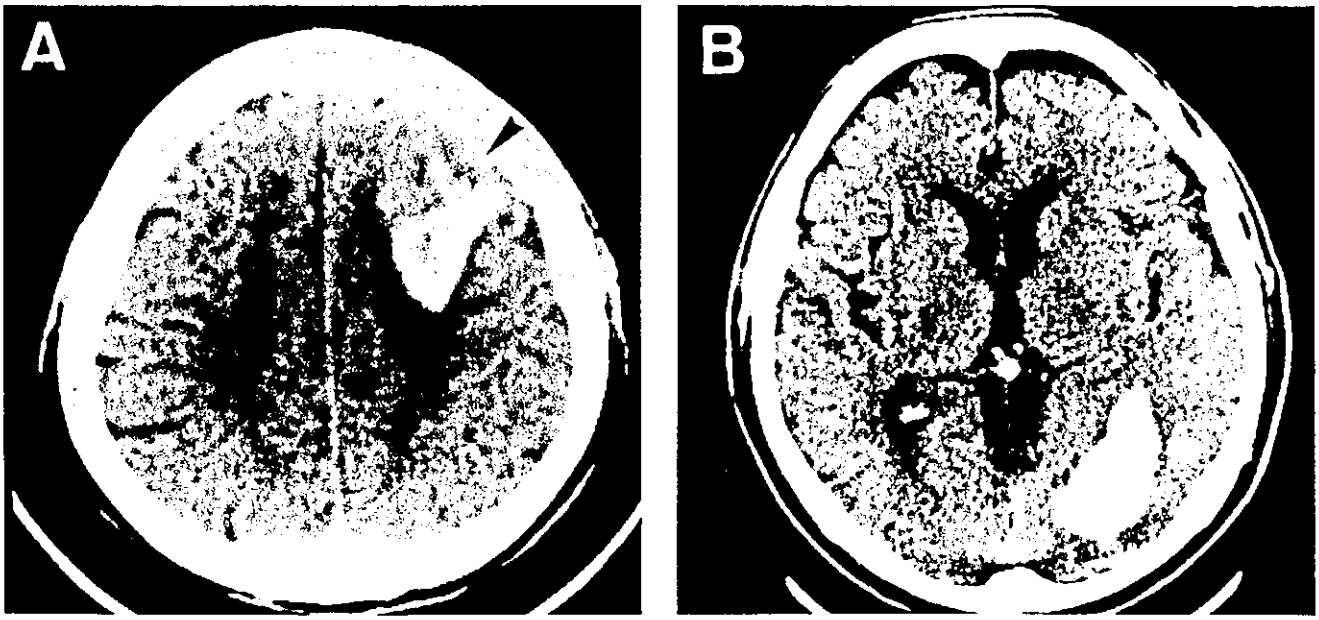

Figure 1. Representative CT findings in patients with and without subarachnoid extension, (A) and (B), respectively. Note extension of the hematoma into the subarachnoid space (arrowhead).

Table 4. CT Findings in the Lobar Intracerebral Hemorrhage

	Hypertensive (n=49)	Non-hypertensive (n=32)
Hematoma volume (cm^3)	34.7	38.1
Ventricular enlargement	5 (10.2%)	4 (12.5%)
Mass effect	42 (85.7%)	25 (78.1%)
Ventricular extension	11 (22.4%)	10 (31.3%)
Subarachnoid extension	2 (4.1%)	11 (34.4%)*

*significant ($p<0.001$) compared with hypertensive lobar ICH.

Table 5. Underlying Causes in Non-hypertensive Lobar Intracerebral Hemorrhage with or without Subarachnoid Extension

	Subarachnoid extension	
	yes	no
Cerebral amyloid angiopathy	2	4
Aneurysm	2	3
Arteriovenous malformation	2	2
Anticoagulant use	0	2
Liver cirrhosis	0	2
Thrombasthenia	1	0
Unknown	4	8
Total	11	21

only 9 patients had vascular abnormality. These results indicate that patients with subarachnoid extension are more likely to have vascular abnormality than those without subarachnoid extension ($p<0.001$).

Discussion

The frequency of hypertension among patients with lobar ICH was reported to range from 20.0% to 47.5% in the 1980's (Table 6) (1, 15–18). The frequency of hypertension in lobar ICH (60.0%) in the present study was higher than previously reported. A similarly high frequency of hypertension was reported in the 1990's by Massaro et al (54.8%) (19) and by Broderick et al (67.0%) (20). These reports pointed out the importance of hypertension as a cause of lobar ICH, and may indicate an increasing trend towards hypertensive lobar ICH, which has become noteworthy in the 1990's (19, 20).

Previous studies have reported the preferential localization of lobar ICH in specific sites in the brain. The most frequent site was the parietal lobe as reported by Weisberg (16), the occipital lobe by Ropper and Davis (15), the temporoparietal lobes by Kase et al (1), and the temporal or temporoparietal lobes by Tanaka et al (17). In the study by Massaro et al, lobar ICH confined to one lobe was observed most frequently in the frontal lobe. Lobar ICH overlying two or more lobes was located predominantly in the parieto-temporal or parieto-occipital lobes (19). In the present study, the frontal lobe was most commonly affected regardless of the presence or absence of hypertension. More than half of the patients with hypertensive lobar ICH had a frontal or temporal lesion, and patients with non-hypertensive lobar ICH showed a preferential localization in the frontal lobe. These results may simply reflect the fact that the frontal lobe has the largest volume of all lobes. Taken together, it is likely that there are no specific lobes which are particularly susceptible to lobar ICH.

Lobar ICH is characterized by clinical features such as seizures, which are more frequent in lobar ICH than in deep ICH (21–23). Between the hypertensive and non-hypertensive lobar ICH groups, the present study failed to detect any difference in clinical features, indicating that the clinical features are not defined by the underlying causes. However, the association of subarachnoid extension with non-hypertensive lobar ICH was intriguing in terms of the radiographic features (Table 4). Since subarachnoid extension was observed in non-hypertensive ICH patients, one half of the patients was expected to have vascular abnormalities (Table 5). Wakai et al examined brain specimens with lobar ICH but without angiographic abnormalities, and found vascular abnormalities such as amyloid angiopathy or vascular malformations in all patients with subarachnoid extension (24). Cerebral amyloid angiopathy occurs almost exclusively in the cerebral cortex (25, 26), and this may also help to explain the association of subarachnoid extension with non-

Table 6. Frequency of Hypertensive Patients in Lobar Intracerebral Hemorrhage

	Reference No.	Number of hypertensive patients	(%)	Mean age (years)
Ropper and Davis (1980)	[15]	8/26	(30.5)	65.0
Kase et al (1982)	[1]	10/22	(45.0)	55.0
Weisberg (1985)	[16]	5/25	(20.0)	–
Tanaka et al (1986)	[17]	13/32	(41.0)	47.0
Lipton et al (1987)	[18]	20/42	(47.5)	–
Massaro et al (1991)	[19]	36/65	(54.8)	68.0
Broderick et al (1993)	[20]	44/66	(67.0)	–
The present study		49/81	(60.0)	63.4

hypertensive ICH. Taken together, it is highly likely that subarachnoid extension is characteristic of lobar ICH caused by vascular abnormalities.

It seems reasonable to assume that hypertensive lobar ICH is caused more often by hypertension *per se* than by vascular or coagulation abnormalities. However, subarachnoid extension in hypertensive lobar ICH patients also warrants an extensive search for the underlying causes, because vascular or coagulation abnormalities may coexist with hypertension. Furthermore, recent advances in molecular biology have demonstrated an association between genetic abnormalities and some types of cerebrovascular disease. ICH is occasionally found in hereditary hemorrhagic telangiectasia, hereditary cerebral cavernous malformation with genetic heterogeneity mapped to 7q22, and hereditary cerebral amyloid angiopathy of either Dutch or Icelandic type (27). These abnormalities should be further investigated in non-hypertensive lobar ICH patients.

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ORIGINAL ARTICLE

Population-based distribution of plasminogen activity and estimated prevalence and relevance to thrombotic diseases of plasminogen deficiency in the Japanese: the Suita Study

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Summary. Reduced plasminogen activity with a normal level of antigen is commonly observed in Japanese individuals. The first reported patient with plasminogen deficiency was accompanied with deep vein thrombosis. The present study examines whether heterozygous or homozygous deficiency of plasminogen is a risk factor for thrombotic disease. This study measures the plasminogen activity of 4517 individuals in the general population, determines the cut-off to define plasminogen deficiency, and identifies plasminogen deficiencies in the control groups and thrombotic disease groups. In another study, we examined the phenotypes of consecutive patients with homozygous plasminogen deficiency detected in our hospital. We found 173 and two of 4517 individuals to have heterozygous and homozygous deficiency with normal plasminogen antigen level, respectively, and 19 to have heterozygous deficiency with reduced antigen levels. The incidence of plasminogen deficiency in an age- and sex-matched control group (13/324, 4.01% for deep vein thrombosis or 13/330, 3.94% for stroke) selected from the 4517 individuals was not significantly different from those in patients with deep vein thrombosis (3/108, 2.78%) or cardioembolic stroke (6/110, 5.55%). Among 19 patients with homozygous plasminogen deficiency showing about 10% plasminogen activity, none had deep vein thrombosis. These findings indicate that neither heterozygous nor homozygous plasminogen deficiency constitutes a significant risk factor for thrombotic disease.

Keywords: deep vein thrombosis, genetic variant, plasminogen deficiency, risk factor.

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Plasminogen deficiency is classified into two groups; one is type I deficiency characterized by the parallel reduction of both activity and antigen and the other is dysplasminogenemia (type II), characterized by reduced activity with a normal antigen level [1].

In 1978, a Japanese patient with recurrent vein thrombosis was found to have a hereditary molecular defect of plasminogen [2]. The patient showed low activity of plasminogen but the antigen level was within normal limits, indicating type II deficiency [2,3]. The molecular defect of this mutant plasminogen, referred to as plasminogen Tochigi, was a G→A transition mutation leading to an Ala→Thr substitution at position 601 near the active site triad [4,5].

A few small studies estimated the frequency of plasminogen deficiency in Japanese and reported the allele frequency of plasminogen Tochigi mutation to be between 1.1 and 2.1% [6–9]. It is now known that over 94% of plasminogen deficiency in the Japanese population is attributable to plasminogen Tochigi [10]. The mutation also was found in the Chinese Han population with an allele frequency of 1.4–1.5% [9,11] and in the Korean population with an allele frequency of 1.6% [9]. A homozygous patient with plasminogen Tochigi has also been reported; the plasminogen showed very low but significant activity [3], and this finding was supported by the molecular model of the plasmin mutant [12]. On the other hand, type I plasminogen deficiency has been detected in isolated families [13–16]. Recently, type I plasminogen deficiency has been reported to be associated with ligneous conjunctivitis, a rare form of chronic conjunctivitis characterized by chronic tearing and redness of the conjunctivas [15,16].

The first report [2] linking plasminogen deficiency to thrombosis was followed by many similar publications [13–16]. However, some recent studies did not support the link [17–19]. Among 1192 consecutive patients with a history of venous and/or arterial thrombosis, plasminogen deficiency was not a risk factor for thrombosis [17]. A large cohort study performed in Scotland also denied the link. That study identified 28 individuals with plasminogen deficiency out of 9611 donors, with a prevalence of 0.29% [18], which was not significantly different from the prevalence (0.54%) calculated from studies of thrombotic cohorts in the literature, indicating that plasminogen deficiency is not a risk factor for thrombosis. However, these studies had some limitations such as comparison of frequencies obtained among populations with geographic distance.

We conducted an epidemiological study of plasminogen deficiency in over 4500 Japanese in the general population. We also measured the plasminogen activity in patient groups with thrombotic complications, most of whom reside in the same area where the epidemiological study was performed.

Materials and methods

Study population for control group

The population for the reference group was based on a random sample selected from the residents of Suita, a city located in the second largest urban area in Japan (Osaka area). The sample comprised 12 200 men and women aged 32–89 years. The basic sampling of the population started in 1989 with a cohort study base [20–22]. The subjects have been visiting the National Cardiovascular Center every 2 years since then for regular health check-ups. In addition to performing a routine blood examination that included total serum cholesterol, HDL cholesterol, triglyceride, and glucose levels and blood pressure and anthropometric measurements, a physician or nurse administered questionnaires covering personal history of cardiovascular diseases, including angina pectoris, myocardial infarction (MI), and/or stroke.

The subjects for the reference group included 4526 blood donors who attended regular health checkups between August 1998 and July 2000. The subjects were only those who agreed to have a blood examination. Eight samples not properly harvested (e.g. hemolyzed blood, incorrect sample volume) were not included. An individual taking anticancer drugs ($n = 1$) was also excluded. Finally, 4517 blood donors (2090 men, 2427 women) were enrolled for measurement of plasminogen activity. Age-matched and sex-matched controls ($n = 324$ and $n = 330$, respectively) for deep vein thrombosis (DVT) and for cardioembolic stroke due to non-valvular atrial fibrillation (NVAF) were selected from among the subjects without cardiovascular diseases.

Patients groups

Between April 1994 and March 1998, 108 consecutive outpatients (54 men, 54 women; mean age ± SD, 57.8 ± 17.2 years, 49.6 ± 18.0 years, respectively) with DVT admitted to the Department of Cardiology of National Cardiovascular Center were enrolled. The diagnoses of DVT were based on radioisotope venography and/or contrast venography. As another patient group, we enrolled 110 patients (77 men, 33 women; mean age ± SD, 66.8 ± 9.6 years, 64.7 ± 11.8 years, respectively) with NVAF at the outpatient clinic of the Cerebrovascular Division of the National Cardiovascular Center in July and August of 1998, who had been diagnosed as cardioembolic stroke according to the criteria previously mentioned more than one month prior to the enrollment [23]. All of them had received warfarin therapy against recurrence of cardioembolic stroke.

Concerning homozygous plasminogen deficiency, we screened for plasminogen activity in patients admitted to our hospital from 1992 to 2000 and identified 19 patients with homozygous plasminogen deficiency. All of the patients were followed for several years to measure their plasminogen activity and again showed very low activities more than twice. Five patients out of 19 were confirmed by the family study (more than one of their family members showed low plasminogen activity [heterozygous deficiency]). We simultaneously measured prothrombin time and activated partial prothrombin time and the plasma levels of antithrombin, protein·C, α_2-plasmin inhibitor, and fibrin degradation products in these patients to exclude the possibility of activation of blood coagulation or fibrinolysis system.

Sample collection and analysis

We obtained blood samples before noon after an overnight fast. Blood samples were collected in siliconized vacuum plastic tubes containing 1/10 volume of 3.13% trisodium citrate. Tubes were centrifuged at $3600 \times g$ for 10 min at room temperature. After separation, if analysis was not to be performed immediately, the plasma samples were frozen at −80 °C for storage until laboratory determinations were performed.

Plasminogen activity was measured by the chromogenic assay method using streptokinase as the activator and the specific substrate S-2251 (Chromogenix AB, Stockholm, Sweden). Plasminogen antigen was measured by the turbidimetric immunoassay method using antiserum to human plasminogen (Behringwerke, Marburg, Germany). Antithrombin activity was measured as a heparin cofactor activity by use of the chromogenic substrate S-2238 (Chromogenix AB). The plasma levels of plasminogen and antithrombin were expressed as percentages of the levels obtained from commercially available standard human plasma (Behringwerke). As measured in our laboratory, the interassay coefficients of variation were 2.0% for the plasminogen activity assay, 3.5% for the plasminogen antigen assay and 2.2% for the antithrombin assay.

Statistical analysis

Spearman correlation analysis was used to assess the association between aging and the level of plasminogen activity and was performed by gender. Plasminogen activity in the 10-year

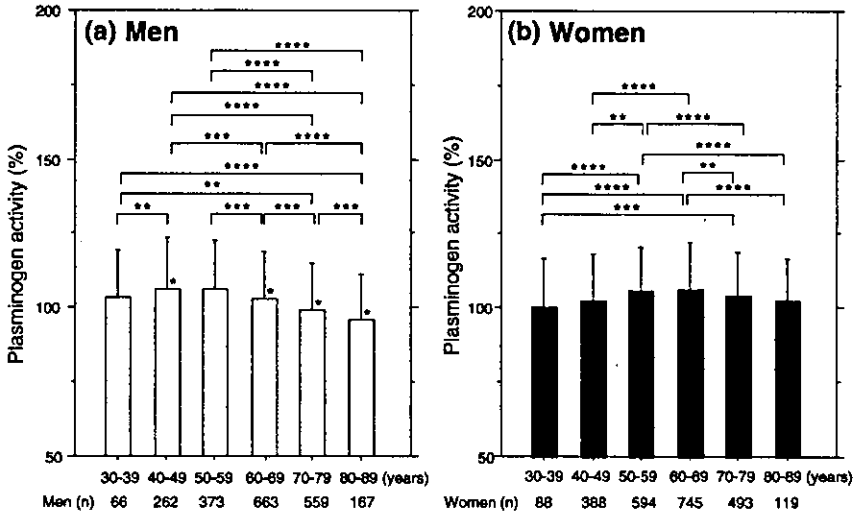

Fig. 1. Age- and sex-related changes in plasminogen activity in the Japanese general population ($n = 4517$). Open and closed bars show the plasminogen activities in men (a) and women (b), respectively. $^{*}P < 0.001$, compared with those in women of the same age group. $^{**}P < 0.05$, $^{***}P < 0.01$, $^{****}P < 0.001$, compared with those in other age groups within the same sex.

age groups in men and women was recorded as mean ± SD. As the data did not show a Gaussian distribution in Fig. 1, we chose the non-parametric Kruskal–Wallis test for comparison among multiple groups. For comparison between two groups, the Mann–Whitney *U*-test was used. Odds ratios with corresponding 95% confidence intervals were used to assess the differences between prevalence rates from different populations. Differences with a value of $P < 0.01$ for the Spearman correlation analysis and $P < 0.05$ for the Kruskal–Wallis test, the Mann–Whitney *U*-test and odds ratios were considered to be significant. Statistical calculations were performed using SPSS version 10.0 (SPSS Inc, Chicago, IL, USA).

Results

Age- and sex-related changes and distribution of plasminogen activity

We measured the activities of plasminogen and antithrombin in 4517 individuals who participated in the Suita Study. The mean ± SD of plasminogen activity in all donors, men and women, was 103.6 ± 15.9 (mean ± 2 SD range; 72–135%), 102.4 ± 16.4 (mean ± 2 SD range; 70–135%), and 104.6 ± 15.3 (mean ± 2 SD range; 74–135%), respectively. Figure 1 shows the age-related distribution (32–89 years) of plasminogen activity in 2090 men (Fig. 1a) and 2427 women (Fig. 1b). As a whole, a linear decrease of plasminogen activity with age was observed in men ($r = -0.24$, $P < 0.0001$), but not in women ($r = 0.02$, $P = 0.36$). When the activity was analyzed in 10-year age groups, a slight increase was observed in the men aged 30–39 years and 40–49 years ($P < 0.05$) and in the women aged 30–39 years and 50–59 years ($P < 0.001$). The levels of plasminogen activity were decreased in both sexes in the elder age groups. As a gender-related change, the level of plasminogen in the age group of 40–49 years in men was significantly higher than that in women. In contrast, the levels in women in the age groups of 60–69, 70–79, and 80–89 years were significantly higher than those in men.

Identification of plasminogen deficiency

Figure 2(a) shows the distribution of the plasminogen activity in 4517 individuals. The plasminogen activity showed one big peak in the number of subjects and a small and broad peak at around 60% plasminogen activity, which consisted of the subjects with plasminogen deficiency. It was hard to distinguish whether an individual who showed marginal activity was plasminogen deficient or not. In identification of protein C deficiency, the ratio of protein C and factor X was recommended for the identification of the deficient by the Scientific

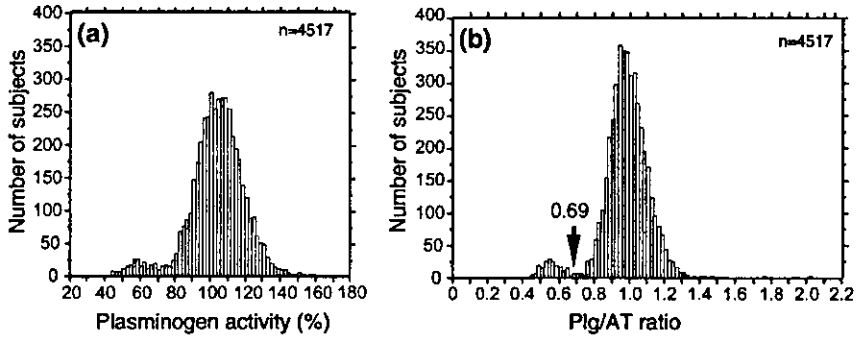

Fig. 2. Distribution of plasminogen activity and plasminogen/antithrombin ratio in the 4517 cohort. Each histogram bar shows the numbers of subjects in every 2% of plasminogen activity (a) or in every 0.02 of the plasminogen/antithrombin activity (Plg/AT) ratio (b). The arrow indicates the cut-off in the plasminogen/antithrombin ratio, 0.69.