Table 3 Univariate and multivariate logistic regression analysis of the probability of a favorable outcome (modified Rankin Scale 0–2) at 3 months

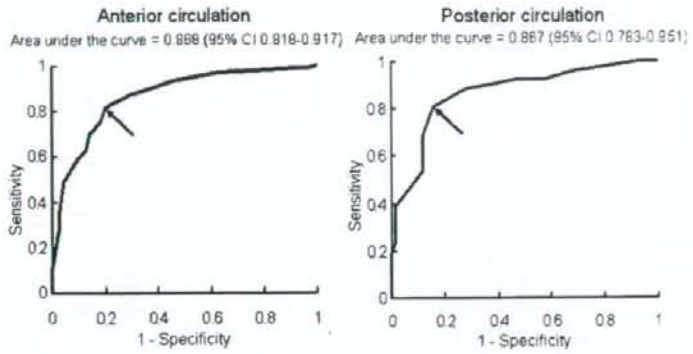
	Univariate analysis			Multivariate analysis		
Variables	Favorable	Unfavorable	p Value	OR	95% CI	p Value
Anterior circulation (n = 209)						
Age	71 ± 10	73 ± 10	0.976	0.998	0.959–1.038	0.910
Gender, male	82 (71%)	53 (57%)	0.549	1.276	0.584–2.788	0.542
Previous stroke	37 (32%)	22 (24%)	0.190			
Hypertension	86 (74%)	66 (71%)	0.609			
Diabetes mellitus	33 (28%)	32 (34%)	0.355			
Hyperlipidemia	43 (37%)	40 (43%)	0.383			
Ischemic heart disease	19 (16%)	20 (22%)	0.346	0.744	0.301–1.839	0.522
Valvular heart disease	7 (6%)	8 (9%)	0.477			
Atrial fibrillation	35 (30%)	42 (45%)	0.026	1.282	0.497–3.308	0.607
Peripheral artery disease	9 (8%)	6 (7%)	0.716			
Stroke subtype						
Small-vessel	30 (26%)	5 (5%)	<0.001	2.034	0.541–7.648	0.293
Cardioembolism	34 (29%)	58 (62%)	<0.001	0.862	0.257–2.898	0.811
Large-artery	17 (15%)	16 (17%)	0.616			
Other/undetermined	35 (30%)	14 (15%)	0.012	2.547	0.788–8.229	0.118
Baseline NIHSS score, median (interquartile range)	4 (3–7)	15 (10–19)	<0.001	1.279	1.188–1.376	<0.001
Posterior circulation (n=101)						
Age	67 ± 12	72 ± 11	0.124	1.023	0.963–1.087	0.456
Gender, male	53 (71%)	14 (54%)	0.121	2.745	0.686–10.980	0.153
Previous stroke	22 (32%)	9 (36%)	0.708			
Hypertension	53 (71%)	18 (69%)	0.890			
Diabetes mellitus	26 (35%)	13 (50%)	0.169			
Hyperlipidemia	28 (37%)	8 (31%)	0.548			
Ischemic heart disease	9 (12%)	7 (27%)	0.080	0.103	0.020–0.544	0.007
Valvular heart disease	6 (8%)	3 (12%)	0.587			
Atrial fibrillation	23 (31%)	10 (39%)	0.466	0.739	0.130–4.189	0.733
Peripheral artery disease	4 (5%)	1 (4%)	0.764			
Stroke subtype						
Small-vessel	13 (17%)	2 (8%)	0.247	0.546	0.059–5.052	0.594
Cardioembolism	22 (29%)	12 (46%)	0.121	0.364	0.057–2.318	0.285
Large-artery	17 (23%)	8 (31%)	0.411			
Other/undetermined	23 (31%)	4 (15%)	0.138	1.518	0.201–11.489	0.686
Baseline NIHSS score, median (interquartile range)	3 (1–5)	8 (6–14)	<0.001	1.547	1.232–1.941	<0.001

NIHSS = NIH Stroke Scale.

minority of patients who were deemed to have symptoms that were too mild to warrant IV rt-PA were unable to be discharged home.[25]

Since MRI and MRA including diffusion-weighted imaging were performed in this study for all consecutive patients with stroke unless contraindicated, the classification of stroke into AC and PC groups was highly reliable. This study had a few limitations. Since our series is from a single, highly specialized medical center that deals with cardiovascular diseases and emergent cases, the percentage of cardioembolism was high compared to a typical Japanese epidemiologic study.[26] Furthermore, the small study population might have introduced statistical error. Because this is a development model and has not been validated, our findings should only be considered hypothesis creating,

Figure 2 Receiver operating characteristic (ROC) curves to show optimal cutoff point of the baseline NIH Stroke Scale (NIHSS) scores of the patients with anterior circulation (AC) and posterior circulation (PC) stroke to predict a favorable outcome (modified Rankin Scale of 0–2)



Arrows indicate optimal cutoff points.

and applicability and generalizability of our models have not yet been evaluated.

ACKNOWLEDGMENT

The authors thank Akiko Kada, MPH, for advice on the statistical analyses.

Received June 19, 2007. Accepted in final form December 7, 2007.

REFERENCES

1. Brott T, Adams Jr. HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
2. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH Stroke Scale. Arch Neurol 1989;46:660–662.
3. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group.Stroke1994;25:2220–2226.
4. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006;5:603–612.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581–1587.
6. Adams Jr. HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126–131.
7. Frankel MR, Morgenstern LB, Kwiatkowski T, et al. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. Neurology 2000;55: 952–959.
8. Weimar C, Konig IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke 2004; 35:158–162.
9. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke 2003;34:134–137.
10. Schlegel DJ, Tanne D, Demchuk AM, Levine SR, Kasner SE. Prediction of hospital disposition after thrombolysis for acute ischemic stroke using the National Institutes of Health Stroke Scale. Arch Neurol 2004;61: 1061–1064.
11. Fink JN, Selim MH, Kumar S, et al. Is the association of National Institutes of Health Stroke Scale scores and acute magnetic resonance imaging stroke volume equal for patients with right- and left-hemisphere ischemic stroke? Stroke 2002;33:954–958.
12. Nakajima M, Kimura K, Ogata T, Takada T, Uchino M, Minematsu K. Relationships between angiographic findings and National Institutes of Health stroke scale score in cases of hyperacute carotid ischemic stroke. AJNR Am J Neuroradiol 2004;25:238–241.
13. Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36:2121–2125.
14. Libman RB, Kwiatkowski TG, Hansen MD, Clarke WR, Woolson RF, Adams HP. Differences between anterior and posterior circulation stroke in TOAST. Cerebrovasc Dis 2001;11:311–316.
15. Li H, Wong KS, Kay R. Relationship between the Oxfordshire Community Stroke Project classification and vascular abnormalities in patients with predominantly intracranial atherosclerosis. J Neurol Sci 2003;207:65–69.
16. Pinto AN, Melo TP, Lourenco ME, et al. Can a clinical classification of stroke predict complications and treatments during hospitalization? Cerebrovasc Dis 1998;8: 204–209.
17. Jones Jr. HR, Millikan CH, Sandok BA. Temporal profile (clinical course) of acute vertebrobasilar system cerebral infarction. Stroke 1980;11:173–177.
18. Adams Jr. HP, Bendixen BH Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Stroke 1993; 24:35–41.
19. Woo D, Broderick JP, Kothari RU, et al. Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? NINDS t-PA Stroke Study Group. Stroke 1999;30:2355–2359.
20. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19: 604–607.
21. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS Study: a randomized controlled trial: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999;282:2019–2026.
22. Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36: 66–73.
23. Yamaguchi T, Mori E, Minematsu K, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of

onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37:1810–1815.

24. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. Neurology 2001; 56:1015–1020.
25. Smith EE, Abdullah AR, Petkovska I, Rosenthal E, Koroshetz WJ, Schwamm LH. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. Stroke 2005;36:2497–2499.
26. Kimura K, Kazui S, Minematsu K, Yamaguchi T. Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan: a hospital-based prospective registration study. Cerebrovasc Dis 2004; 18:47–56.

Heart and Vessel Pathology Underlying Brain Infarction in 142 Stroke Patients

Jun Ogata, MD,[1] Chikao Yutani, MD,[1] Ryoichi Otsubo, MD,[2] Hiromichi Yamanishi, MD,[3] Hiroaki Naritomi, MD,[2] Takenori Yamaguchi, MD,[2] and Kazuo Minematsu, MD[2]

Objective: This study was designed to determine the histopathological characteristics of cardiac and vascular lesions responsible for various subtypes of ischemic stroke.

Methods: Postmortem pathological examination was performed on 142 patients who died within 30 days of the onset of ischemic stroke in the National Cardiovascular Center, Osaka, Japan.

Results: The numbers of cases with autopsy-proven diagnoses of atherothrombotic, cardioembolic, and lacunar strokes, ischemic stroke of other determined causes, and ischemic stroke of undetermined cause were 17, 107, 2, 12, and 4, respectively. Thrombi that developed at the culprit plaques of the cerebral arteries were responsible for atherothrombotic stroke. In 70% of the cases with cardioembolic stroke, the presence of thrombi as potential embolic sources were confirmed in the heart or, in some cases, in the venous circulation of patients with patent foramen ovale and tetralogy of Fallot.

Interpretation: In most atherothrombotic strokes, fibrin- and platelet-rich thrombi of various thicknesses develop at the culprit plaques of the cerebral arteries, which are finally occluded with fibrin- and red-cell–rich thrombi (red thrombi). In most cardioembolic strokes, red thrombi generated in the heart or peripheral veins are dislodged to embolize the cerebral arteries.

Ann Neurol 2008;63:770–781

To effectively prevent and treat brain ischemia, clinicians must understand the mechanism underlying the development of various subtypes of ischemic stroke based on pathological materials. Information about arterial pathology leading to atherothrombotic stroke, especially regarding thrombi and emboli occluding the vessels, is limited.[1–8] Therefore, inferences have been derived mainly from studies of the coronary circulation, which has been the subject of extensive pathological analysis.[9–14] Information about the pathology of cardioembolic stroke, especially regarding intracardiac thrombi and emboli occluding the cerebral arteries, is also limited,[2–6,15,16] whereas the pathology of the thrombi in the diseased heart and veins has been studied extensively.[15–18] Advances in echocardiographic techniques increased the sensitivity for detecting intracardiac thrombi, although the complex structure of the heart and the minute size of clinically important thrombi make identification of small thrombi problematic.[19] The types of the emboli occluding the cerebral artery, such as clots rich in fibrin and red cells or those rich in fibrin and platelets, cannot be reliably determined using the present imaging techniques.[20,21] Therefore, the pathological findings on autopsies of cases of ischemic stroke provide important information for the prevention and treatment of stroke.

We previously analyzed the vascular lesions responsible for certain varieties of ischemic stroke,[7,8,22–24] but the results obtained from these studies described only selected aspects of cerebrovascular disease. A study on the developmental mechanisms of all the subtypes of ischemic stroke using a common methodology for analysis on a large number of cases is needed. Pathological materials must be analyzed before the responsible lesions are organized, which obscures decisive findings, to elucidate the cardiac and vascular lesions responsible for ischemic stroke. In view of the rate of tissue organization evident by histopathological techniques, a period of less than 30 days after the onset of stroke was considered appropriate. Therefore, we performed postmortem pathological examinations of the patients who died within 30 days of suffering an ischemic stroke.

Subjects and Methods

Cases and Definitions

Among the 1,107 adult whole-body autopsy cases at the National Cardiovascular Center, Osaka, Japan, between 1979 and 2004, patients with ischemic stroke who died within 30 days after onset were analyzed. Patients with cerebral infarction associated with interventions were excluded. Ten cases with septic embolism associated with infective endocarditis

From the [1]Department of Pathology, National Cardiovascular Center; [2]Department of Medicine, Cerebrovascular Division, National Cardiovascular Center; and [3]Hirakataryoikuen, Osaka, Japan.

Received Sep 1, 2007, and in revised form Mar 12, 2008. Accepted for publication Mar 14, 2008.

Published online May 21, 2008, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21401

Address correspondence to Dr Ogata, Hirakataryoikuen, 2-1-1 Tsudahigashi-machi, Hirakata, Osaka 573-0122, Japan.
E-mail: jogata@hirakataryoiku-med.or.jp

resulting in intracranial hemorrhages as the major clinical presentation were also excluded because the features differ from those found in nonseptic cardioembolic stroke.[22] After excluding these cases, 142 autopsy cases were included in this study. Previous reports describe atherothrombotic occlusion of the intracranial cerebral artery in seven cases[8,25] and of the internal carotid artery (ICA) in three,[7] cerebral atheroembolism in three,[23] and cerebral artery thrombosis in essential thrombocythemia in one.[24]

We analyzed the clinical data and postmortem pathological findings. History of hypertension, diabetes mellitus, dyslipidemia, and cardiac disease, and previous ischemic stroke and transient ischemic attack were used in the data analysis. Old myocardial infarction was defined as a history of acute myocardial infarction (AMI) more than 6 weeks before the stroke occurred, whereas AMI was defined as occurring less than 6 weeks before the stroke. Nonvalvular atrial fibrillation (AF) included cases of idiopathic, hypertensive, and ischemic origin, as well as cases associated with hypertrophic cardiomyopathy and chronic sinoatrial disorder.[26,27] AF in patients with dilated cardiomyopathy and specific cardiac pathology, such as primary systemic amyloidosis and polyarteritis nodosa, were not included in nonvalvular AF.

After analyzing the clinical data, together with relevant postmortem pathological findings, we established autopsy-proven diagnoses of the subtypes of ischemic stroke, which correspond to the clinical categories of the National Institute of Neurological Disorders and Stroke Classification of Cerebrovascular Diseases III.[28] Atherothrombotic stroke was that occurring with compromised arterial lumen or artery-to-artery embolism associated with atherosclerosis of extracranial and intracranial cerebral arteries. The diagnosis of cardioembolic stroke was based on cardiac conditions that may produce emboli in the heart or through the heart and no evidence of other causes of stroke. Lacunar stroke was associated with a small, deep infarct (<1.5cm) on brain imaging resulting from the involvement of a single deep, penetrating artery.[29,30] Those cases in which we failed to define the cause of stroke were categorized as ischemic stroke of undetermined cause.[28,31]

The brains and organs obtained at autopsy were fixed in 10% formalin. The hearts were histologically examined when macroscopic examination showed or suggested the presence of thrombus. Histological examination was always made of the left atrial appendage. When needed, the cervical vertebral column and skull base encompassing the vertebral arteries (VAs) and distal ICAs were removed to obtain the whole length of the arteries after fixation. Serial sections of the site of thrombotic or embolic occlusion or mural thrombi were made when needed. For lacunar stroke cases, the responsible arterial system was examined with serial sections. Tissue blocks were cut into 6μm-thick sections and stained with hematoxylin and eosin, Masson's trichrome method, Mallory's phosphotungstic acid hematoxylin method (which stains fibrin blue and collagen brownish red), and other conventional techniques.

To describe the culprit vascular lesions associated with atherosclerosis, we used the terms *plaque rupture* and *erosion*, as described for the coronary arteries in cases with AMI.[9–14] Plaque rupture is fibrous cap disruption or plaque fissure formation, whereby the overlying thrombus is in continuity with the underlying lipid core. Plaque erosion is identified when serial sectioning of the thrombosed arterial segment fails to demonstrate fibrous cap rupture at the plaque and confirms the absence of the endothelium.

Fresh thrombi were described as platelet-rich thrombi, fibrin- and platelet-rich thrombi, or fibrin- and red-cell–rich thrombi (red thrombi).[9–14] Platelet-rich thrombi consist of agglutinated platelets with a small amount of fibrin. Fibrin- and platelet-rich thrombi consist of dense agglutinated fibrin and platelets. Red thrombi consist of fibrin strands enmeshing red blood cells. A red thrombus occasionally shows irregular, ill-defined laminations, consisting of alternating pale layers of fibrin and darker layers containing more red cells; this is reminiscent of the lines of Zahn,[32,33] which exclusively characterize antemortem development of the red thrombus. The diameter of the largest intracardiac thrombus in each lesion was measured to express the size. The term *reopening* was used to describe breakup or migration of the embolus occluding the artery. A moist coagulum, not adherent to the wall of vessels or endocardium, was considered a product of postmortem sedimentation of the formed elements of the blood.[33]

Intracardiac thrombi were regarded as traces of potential embolic sources, regardless of whether the thrombi were attached to the endocardium with early organizing tissue (plump fibroblasts and small vascular channels) in the sections examined. Some of the red thrombi themselves showed an early stage of tissue organization and were totally or partially covered by endothelium. Mural thrombi at the late stage of organization with prominent collagen fibers and lesser cellular components covered by the endothelium were not considered as potential embolic sources.

Statistical Analyses

Results are expressed as mean ± 1 standard deviation. Differences in categorical variables between groups were assessed by χ^2 tests, or by Fisher's exact test when the expected cell count was less than 5. A value of $p < 0.05$ was considered statistically significant.

Results

Among the 142 patients examined, 85 were men and 57 were women (age ± standard deviation, 69 ± 13 years). The numbers of cases with diagnoses of atherothrombotic, cardioembolic, and lacunar stroke, ischemic stroke of other determined causes, and ischemic stroke of undetermined cause were 17, 107, 2, 12, and 4, respectively (Table 1). The mean duration from the onset of stroke to death among the various subtypes of ischemic stroke ranged from 8.6 ± 7.4 to 11.5 ± 5.2 days.

In eight patients with cardioembolic stroke, there were nine recurrent ischemic strokes within the last 30 days of life: eight recurrent cardioembolic stokes in seven and one atherothrombotic stroke in one patient. Nonvalvular AF occurred in three patients with atherothrombotic stroke and three patients with ischemic stroke of other determined causes (see Table 1). One case of atherothrombotic stroke had a mural red

Table 1. Characteristics of 142 Cases with Various Subtypes of Ischemic Stroke

Characteristics	Atherothrombotic Stroke (n = 17)	Cardioembolic Stroke (n = 107)	Lacunar Stroke (n = 2)	Ischemic Stroke of Other Determined Cause (n = 12)	Ischemic Stroke of Undetermined Cause (n = 4)
Mean age ± SD (range), yr	69.5 ± 6.5 (55–81)	69.0 ± 14.7 (28–96)	70 (66–74)	69.7 ± 5.5 (62–80)	57.2 ± 13.9 (46–77)
Mean duration after stroke ± SD, days	8.8 ± 6.9	9.8 ± 7.7	12	8.6 ± 7.4	11.5 ± 5.2
Men, n	10 (59%)	62 (58%)	2 (100%)	9 (75%)	2 (50%)
Hypertension	15 (88%)[a]	58 (54%)	2 (100%)	10 (83%)	0 (0%)
Diabetes mellitus	6 (35%)	23 (21%)	1 (50%)	3 (25%)	0 (0%)
Dyslipidemia	5 (29%)	15 (14%)	1 (50%)	3 (25%)	0 (0%)
Previous ischemic stroke or TIA	9 (53%)	34 (32%)	1 (50%)	3 (25%)	1 (25%)
Heart diseases other than nonvalvular AF	1 (6%)	81 (76%)	0 (0%)	1 (8%)	0 (0%)
Nonvalvular AF	3 (18%)	26 (24%)	0 (0%)	3 (25%)	0 (0%)
Thrombi, intracardiac or transcardiac, as potential embolic sources	1 (6%)	75 (70%)	0 (0%)	0 (0%)	0 (0%)
Systemic arterial thromboembolism	0 (0%)	40 (37%)	0 (0%)	0 (0%)	1 (25%)
Malignant neoplasm	2 (12%)	15 (14%)	0 (0%)	1 (8%)	1 (25%)

[a] $p = 0.0080$ compared with cases with cardioembolic stroke.
SD = standard deviation; TIA = transient ischemic attack; AF = atrial fibrillation.
One cardioembolic stroke followed by one atherothrombotic stroke is shown as one case of cardioembolic stroke. Systemic arterial thromboembolism denotes those outside the brain, heart, and lungs.

thrombus (3mm in diameter) in the left atrial appendage.

Atherothrombotic Stroke

In the 17 patients with atherothrombotic stroke, the frequency of hypertension was 88% and diabetes mellitus 35% (see Table 1). Other than these 17 patients, 1 patient with cardioembolic stroke developed one atherothrombotic stroke. Twelve of the 17 patients died of their brain infarcts. The other five patients died of diseases unrelated to the stroke.

ATHEROTHROMBOTIC OCCLUSION OF THE ARTERIES.

Table 2 shows sites of arterial occlusion and the mechanisms in the 18 cases of atherothrombotic stroke. One case was separately described because of the heterogeneous mechanism of development. There was a high-grade luminal stenosis at all of the 17 extracranial and intracranial cerebral arteries with culprit plaques (area of stenosis: 86 ± 10%; range, 61–99%; luminal diameter: 1.2 ± 0.7mm; range, 0.2–2.9mm). The ruptured plaques had a lipid core covered by intraluminal fibrin- and platelet-rich thrombi occupying various proportions of the lumen. In case of luminal occlusion at the plaque, the rest of the lumen was occluded with red thrombi (Figs 1A, B and 2). In three ruptured plaques of the intracranial arteries, there was no direct contact between the intraluminal thrombi and the lipid core (see Fig 2), whereas in all the other ruptured plaques, there was such contact. Among the occlusive red thrombi, only one occluding the intracranial portion (VA4) of the VA at a ruptured plaque had laminations (see Fig 2). All the emboli derived from the ruptured plaques of the extracranial arteries were red clots without laminations.

Table 2. **Mechanisms of Development of 18 Atherothrombotic Strokes**

Mechanism					n
ICA origin plaque rupture	→	ICA origin thrombotic occlusion	→	thromboembolism to MCA1 (2); no collaterals (1)	3
ICA origin plaque rupture	→	no in situ occlusion	→	thromboembolism to distal ICA (reopening)	1
ICA origin plaque rupture	→	no in situ occlusion	→	atheroembolism (borderzone infarct)	1
ICA origin mural thrombus under old proximal CCA occlusion	→	no in situ occlusion	→	thromboembolism to MCA1	1
VA1 plaque rupture	→	VA1 thrombotic occlusion	→	thromboembolism to BA top	1
MCA1 plaque rupture	→	MCA1 thrombotic occlusion			2
MCA2 plaque rupture	→	MCA2 thrombotic occlusion			1
MCA1 mural thrombus	→	no in situ occlusion	→	thromboembolism to MCA2	1
ACA2 intraplaque hemorrhage	→	ACA2 thrombotic occlusion			1
VA4 plaque rupture	→	VA4 thrombotic occlusion (VA/BA branch occlusion)			3
VA4 plaque rupture	→	VA4 thrombotic occlusion (VA/BA branch occlusion)	→	atheroembolism (borderzone infarcts)	1
VA4 plaque erosion	→	VA4 thrombotic occlusion (VA/BA branch occlusion)			1
VA4 mural thrombus	→	no in situ occlusion	→	thromboembolism to PICA	1

Numbers in parentheses denotes number of cases.
ICA = internal carotid artery; MCA = middle cerebral artery; CCA = common carotid artery; VA = vertebral artery; BA = basilar artery; ACA = anterior cerebral artery; VA/BA = vertebral and basilar arteries; PICA = posterior inferior cerebellar artery.

EXTRACRANIAL ARTERY LESIONS. Plaque rupture at the ICA origin developing in situ occlusive thrombi (see Figs 1A, B) caused embolic occlusion of the proximal portion (MCA1) of the middle cerebral artery (MCA) in two cases, and produced an infarct in the absence of collaterals in one. Plaque rupture at the ICA origin developing no in situ occlusive thrombi caused embolic occlusion of the distal ICA and subsequent reopening in one, and atheroembolism to produce a borderzone infarct in the other case, which was under anticoagulation for posterior circulation cardiogenic embolism. Plaque rupture at the proximal portion (VA1) of the VA developing in situ occlusive thrombi caused embolic occlusion of the top of the basilar artery.

A heterogeneous extracranial artery lesion was seen in one case with an infarct of the left MCA1 territory. Angiography showed occlusion of the common carotid artery and MCA1 with retrograde flow from the posterior communicating artery. Pathological examination demonstrated an old occlusion of the proximal common carotid artery, mural red thrombi with laminations at the uncomplicated intima of the bulbous dilatation of the ICA origin, and embolic occlusion of the MCA1. Slowly moving blood supplied from collaterals to the ICA was presumably responsible for developing the ICA mural thrombi, which subsequently embolized to the MCA1.

INTRACRANIAL CEREBRAL ARTERY LESIONS. Thrombotic occlusion of the intracranial cerebral arteries occurred on plaque rupture (see Fig 2) in six cases, and on plaque erosion (Fig 3) and intraplaque hemorrhage in one case each. Pathological examination of a case with repeated transient ischemic attacks before developing infratentorial infarcts showed thrombotic occlusion at the VA4 plaque rupture and atheroembolism, producing borderzone infarcts of the occipital lobes. Thrombotic occlusion of the distal portion (ACA2) of the anterior cerebral artery associated with intraplaque hemorrhage occurred in one case with segmental arterial mediolysis.[25] A platelet-rich mural thrombus generated on an uncomplicated plaque of the MCA1 embolized to the distal branch (MCA2) in one case, and red thrombi generated on an organizing mural thrombus at a VA4 plaque embolized to the posterior inferior cerebellar artery in another case.

Cardioembolic Stroke

In the 107 patients with cardioembolic stroke, the frequency of hypertension was 54% and diabetes mellitus

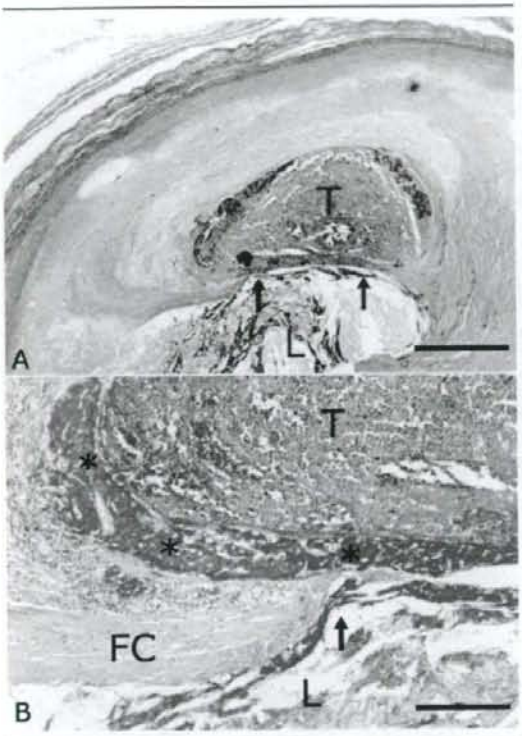


Fig 1. (A) Photomicrograph of a histological transverse section of an occlusive thrombus overlying ruptured plaque (arrows) *of the stenotic internal carotid artery origin. The lipid core* (L) *contains irregularly shaped masses of thrombus. The intraluminal thrombus consists of fibrin strands encircling conglomerates of paler staining red-cell–rich thrombus* (T). *Phosphotungstic acid hematoxylin (PTAH) staining. (B) Enlargement of the left lower portion of the thrombotic occlusion shown in (A). Intraluminal thrombus consists of a dense mass of fibrin- and platelet-rich thrombus* (asterisks) *encircling red thrombus* (T). Arrow *denotes plaque rupture. FC, fibrous cap. Masson's trichrome. Scale bar = 1mm (A); 0.2mm (B). Patient died 7 days after the stroke.*

21% (see Table 1). Hypertension was the only risk factor significantly less frequent ($p = 0.0080$) in patients with cardioembolic stroke compared with those with atherothrombotic stroke. Of 73 patients with AF, the AF was sustained in 64 and paroxysmal in the others. Intravenous or regional intraarterial tissue plasminogen activator injections were given to three patients for clinical trials without clinical improvement during the period before its use was approved in Japan.[34]

Eighty-six of the 107 patients died of their brain infarcts. Of the other 21 patients, 19 died of systemic complications directly associated with cardiac disease such as embolism to other organs; the other 2 died of AMI unrelated to the stroke.

Fig 2. Photomicrograph of thrombotic occlusion of the intracranial portion (VA4) of the vertebral artery at the site of plaque fissure (arrows) *on which an intraluminal thrombus* (asterisk) *is attached. The occlusive thrombus* (T) *shows laminations with alternating layers. Masson's trichrome. Patient died 4 days after the stroke. Scale bar = 0.5mm.*

PREVENTIVE ANTICOAGULATION AT THE ONSET OF STROKE. Eleven patients had been receiving oral anticoagulant therapy in the last several months of life. The anticoagulation was at a therapeutic international normalized ratio in four and was inadequate (international normalized ratio, 1.2–1.4)[35,36] in the other four patients. The therapy was discontinued for surgery or because of poor compliance in the other three for 2 to 22 days before the onset of stroke. The rest of the patients did not receive anticoagulation during this period.

HEART DISEASES AND THROMBI AS POTENTIAL EMBOLIC SOURCES. Table 3 lists the heart diseases and the location of thrombi as potential embolic sources in the

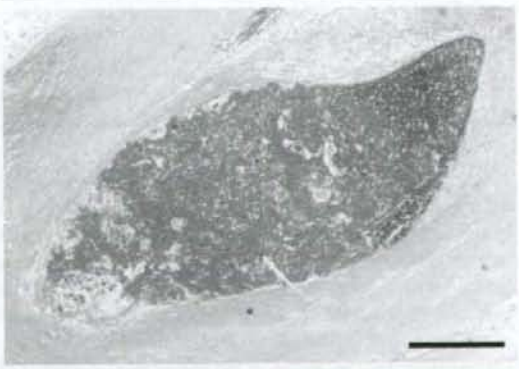


Fig 3. Photomicrograph of plaque erosion with occlusive thrombus of the intracranial portion (VA4) of the vertebral artery. Hematoxylin and eosin staining. Patient died 4 days after the stroke. Scale bar = 0.5mm.

Table 3. **Heart Diseases with and without Atrial Fibrillation and Left Atrial Appendage Thrombus and Location of Thrombi as Potential Embolic Sources in 107 Cases with Cardioembolic Stroke**

Heart Disease	n	Location of Potential Emboli			
		Atrial Fibrillation		No Atrial Fibrillation	
		LAA Thrombi (n = 37)	No LAA Thrombus (n = 36)	LAA Thrombi (n = 13)	No LAA Thrombus (n = 21)
Valvular disease	31	LAA thr only (12), LA ball thr (3), MV thr (2), LA mural thr (1)	LA mural thr (2), MV thr (3), MV veg (1), none (4)	LAA thr only (1), MV veg (1)	LV thr (1)
AF, nonvalvular	26	LAA thr only (10), LA mural thr (1)	LA ball thr (1), MV thr (1), none (13)		
Myocardial infarction, old	13	LAA thr only (2)	LV thr (2), none (4)	LV thr (1)	LV thr (1), none (3)
Dilated cardiomyopathy	10	LAA thr only (4)	None (1)	LAA thr only (1), LV thr (2)	None (2)
Nonbacterial thrombotic endocarditis	8		A/MV thr (1)	AV thr (2)	A/MV thr (3), AV thr (2)
Prosthetic valve complication	5	LA mural thr (1)			AVR annular veg (2), AVR veg (1), AVR annular thr (1)
SSS/complete A-V block with pacemaker implantation	5			LAA thr only (2)	None (3)
Myocardial infarction, acute	3	LA ball/LV thr (1)		LAA thr only (1)	LV thr (1)
Left atrial myxoma	1			LA myxoma thr (1)	
Patent foramen ovale	1		Iliofemoral vein thr (1)		
Tetralogy of Fallot	1				Iliofemoral vein thr (1)
Primary systemic amyloidosis	1		None (1)		
Polyarteritis nodosa	1		None (1)		
Pericardial mesothelioma	1			LAA thr only (1)	

Numbers in parentheses denotes number of cases. The location and type of thrombi with number of cases in each cell indicate the presence of the particular thrombus in the presence or absence of atrial fibrillation (AF) and left atrial appendage thrombus as shown in the separated columns.
LAA = left atrial appendage; thr = thrombus; LA = left atrial main cavity; MV = mitral valve; veg = vegetation; LV = left ventricular; A/MV = aortic and mitral valves; AV = aortic valve; AVR = replaced aortic valve; SSS = sick sinus syndrome; A-V block = atrioventricular block.

107 cases with cardioembolic stroke. Thrombi were potential embolic sources in the heart or through the heart in 75 cases (70%): intracardiac thrombi in 73 cases and iliofemoral vein thrombi associated with lower limb venous occlusion in 2. The intracardiac thrombi were found in one location in 28 cases but in more than one location in the remaining 45 cases. Other than the intracardiac and iliofemoral vein red thrombi, thrombi of different types were found on the valves: platelet-rich thrombi associated with nonbacterial thrombotic endocarditis (NBTE), vegetations associated with infective endocarditis and prosthetic valve complication, and fibrin- and platelet-rich thrombi associated with prosthetic valve complication.

Valvular Disease. Among 31 cases with valvular disease, 28 had AF. There were 25 cases with rheumatic heart disease, 4 with nonrheumatic valvular disease, and 1 each with mitral valve prolapse and mitral valve endocarditis without specific underlying cardiac disease. Of the 25 cases with rheumatic heart disease, the mitral valve was involved in 24 (with associated aortic valve involvement in 3 cases) and the aortic valve in 1. Of the four cases with nonrheumatic valvular disease,

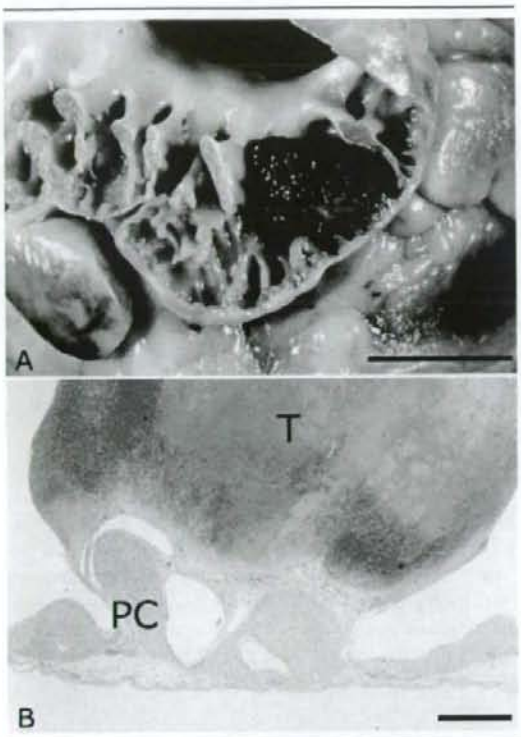


Fig 4. (A) A mural thrombus of the left atrial appendage. (B) Photomicrograph of the thrombus in (A). The base of the fibrin- and red-cell–rich thrombus (T) *is organized to attach to trabeculated pectinate muscles* (PC). *Hematoxylin and eosin staining. Patient with rheumatic heart disease (mitral stenosis) and atrial fibrillation died 6 days after internal carotid artery embolic occlusion. Scale bar = 10mm (A); 1mm (B).*

the mitral valve was involved in three and the aortic valve in one. Among the 31 cases with valvular disease, 26 had intracardiac thrombi. In 20 cases, the left atrial appendage contained thrombi (4.6 ± 3.8mm in diameter; range, 0.6–14mm; Figs 4A, B). The left atrial main cavity contained ball thrombi (33mm average diameter; range, 15–45mm) and mural thrombi (21mm average diameter; range, 3–50mm; Fig 5A) in three cases each, and small thrombi attached to the deformed mitral valve leaflets in five. There were vegetations consisting of collection of coccal organisms, polymorphonuclear leukocytes, and superimposed thrombi circumscribing the mitral valve associated with infective endocarditis in one case with rheumatic heart disease and in another without specific underlying cardiac disease. One case with mitral valve prolapse had a mural thrombus (3.3mm in diameter) in the left ventricle.

Nonvalvular Atrial Fibrillation. The 26 patients with nonvalvular AF were aged 77 ± 9 (range, 56–96) years. The frequency of hypertension was 81%; diabetes mellitus 23%; prior stroke or transient ischemic attack 19%; and coronary heart disease (angina pectoris and AMI after stroke), hypertrophic cardiomyopathy, and congestive heart failure 12% each. Twenty-three patients had high stroke risk features, and the other three moderate ones, as reported previously.[26,27] Among the 26 patients, pathological examination of the heart demonstrated left ventricular hypertrophy consistent with sustained hypertension in 11 cases, coronary heart disease in 3, and hypertrophic cardiomyopathy in 3; the other 9 (age, 80 ± 10 years; range, 67–96 years) had no specific pathological changes. There were left atrial appendage thrombi (3.6 ± 2.6mm in diameter; range, 1–8mm) in 11 cases, 1 of which was associated with a mural thrombus (5mm in diameter) in the left atrial main cavity. The thrombi in the left atrial appendage appeared single or multiple, mural or nonmural, among the trabeculated pectinate muscles. In cases without the left atrial appendage thrombus, there was a left atrial ball thrombus (15mm in diameter) and a small thrombus attached to the mitral valve in one case each. No intracardiac thrombus was found in the other 13 cases.

Nonbacterial Thrombotic Endocarditis. Of eight cases with NBTE, platelet-rich thrombi (2.3 ± 1.3mm in diameter; range, 0.9–6mm) were attached to both the aortic and mitral valves in four and to the aortic valve in four (Figs 6A, B). The valves affected with the thrombi had no specific pathological changes, except for one showing valve deformities characteristic of rheumatic heart disease. The main components of the thrombi were platelets and a small amount of fibrin, with an absence of inflammatory cellular reaction (see Fig 6B). They were partially covered by endothelium and were quite friable and liable to be separated from the valves. Early organization at the base of the thrombi was confirmed in two cases. All patients had carcinoma, and six showed disseminated intravascular coagulation. Red thrombi were found in the left atrial appendage in two cases (6 and 20mm in diameter). One case had two recurrent embolic strokes caused by platelet-rich clots.

Prosthetic Cardiac Valve Complication. Replaced valves were mechanical prosthetic and bioprosthetic aortic valves in two cases each and a bioprosthetic mitral valve in one. The underlying cardiac disease was rheumatic heart disease in three cases, and atherosclerosis and Takayasu's arteritis involving the aortic valve in one case each. Of two cases with mechanical aortic valves, one had a fibrin- and platelet-rich thrombus growing from the annulus to the valve (10mm in diameter), and the other had vegetations growing from the site of valve attachment to the aorta. In two cases

Fig 5. (A) Photomicrograph of a mural thrombus of the left atrium (LA) *showing laminations with alternating layers. Phosphotungstic acid hematoxylin (PTAH) staining. (B) Photomicrograph of the proximal portion (MCA1) of the middle cerebral artery occluded with a thromboembolus showing laminations. PTAH staining. (C) Enlargement of the top left portion of the thrombus in (B). The thrombus shows laminations. Hematoxylin and eosin staining. Incarceration of a left atrial ball thrombus (30mm in diameter) to the mitral valve associated with simultaneous thromboembolism to the MCA1 caused sudden death in a patient with rheumatic heart disease (mitral stenosis) and atrial fibrillation. Scale bar = 0.5mm (A); 1mm (B); 0.1mm (C).*

with a bioprosthetic aortic valve, prosthetic valve endocarditis with vegetations (2.3mm in diameter) was seen in one and vegetations growing from the site of valve attachment to the aorta in the other. The case with bioprosthetic mitral valve had mural thrombi in the left atrial main cavity (40mm in diameter) and its appendage (3mm in diameter).

Patent Foramen Ovale. One patient with lower limb venous occlusion developed embolic occlusion of the distal ICA. Pathological examination showed patent foramen ovale (8mm in diameter) and iliofemoral vein thrombi. Among the 142 cases, patent foramen ovale was found in 7 other cases, although the ischemic stroke was not related to the patent foramen ovale. The mean diameter of patent foramen ovale was 4.7 ± 3.2mm (range, 1–8mm).

Others. Left ventricular mural thrombi (5.3 ± 4.1mm in diameter; range, 0.6–12mm) were found in four cases with old myocardial infarction (ventricular aneurysm in one) and in two each with AMI and dilated cardiomyopathy. A ball thrombus (30mm in diameter) was found in the left atrial main cavity in one case with AMI. In two AF cases, the heart was involved with polyarteritis nodosa in one and primary systemic amyloidosis in the other. One case showed a pedunculated myxoma covered by a red thrombus (15mm in diameter) at the atrial septum.

Brain Embolism

Embolic occlusion of the arteries resulted in territorial infarcts of the brain. Arterial territories involved in the 115 cardioembolic strokes were the carotid territory in 92 strokes, the vertebrobasilar territory in 18, and both the carotid and vertebrobasilar territories in 5. All the strokes involving the carotid territory caused a single infarct, except for one with infarcts involving the bilateral MCA2 territory. Of the 97 strokes involving the carotid territory, the whole carotid territory was involved in 57 cases.

Table 4 shows the type of thrombus as embolic

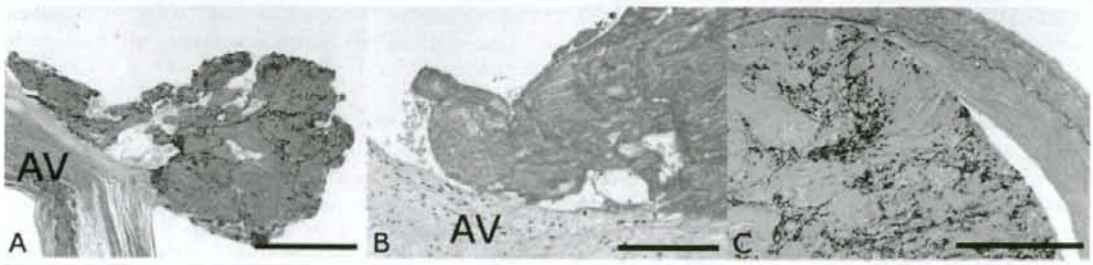


Fig 6. (A) Photomicrograph of a thrombotic lesion of nonbacterial thrombotic endocarditis (NBTE) attached on the right aortic coronary cusp (AV). *Phosphotungstic acid hematoxylin (PTAH) staining. (B) Enlargement of the thrombus attached on the cusp* (AV) *shown in (A). Hematoxylin and eosin staining. (C) Photomicrograph of the proximal portion (MCA1) of the left middle cerebral artery occluded with a clot. Fibrin occupies a small portion of the clot. PTAH staining. Patient with pulmonary carcinoma died 8 days after left MCA1 thromboembolic occlusion. Scale bar = 1mm (A); 0.2mm (B); 0.5mm (C).*

Table 4. **Type of Thrombus as Embolic Source and Embolus Occluding the Cerebral Artery in 115 Cardioembolic Strokes**

Thrombus as Embolic Source	n	Embolus Occluding Cerebral Artery	n
Intracardiac red thrombus (laminations: 36%)	61	Red clot (laminations: 55%)	53
		Reopening	8
Heart disease without intracardiac thrombus	35	Red clot (laminations: 32%)	25
		Reopening	10
Platelet-rich thrombus (NBTE)	10	Platelet-rich clot	10
Vegetation associated with infectious endocarditis	6	Red clot, infectious (laminations: 0%)	3
		Reopening	3
Iliofemoral vein red thrombus through heart (laminations: 50%)	2	Red clot (laminations: 0%)	1
		Reopening	1
Fibrin- and platelet-rich thrombus on prosthetic aortic valve	1	Fibrin- and platelet-rich clot	1

The percentages in parentheses denote percentage of cases with clots showing laminations. Red thrombus/clot = fibrin and red-cell–rich thrombus/clot.
NBTE = nonbacterial thromboendocarditis.

source and embolus occluding the cerebral artery in the 115 cardioembolic strokes. Emboli occluding the cerebral arteries were the same type as their parent lesions. Among 53 strokes in which red thrombi and clots were found both in the embolic source and the occluded cerebral artery, 22 (42%) showed the laminations both in the intracardiac thrombus and the embolus (see Figs 5A–C). No reopening occurred in the intracranial cerebral arteries occluded with platelet-rich clots (see Fig 6C) in all eight cases with NBTE, or in the MCA1 occluded with fibrin- and platelet-rich clots derived from the complicated prosthetic aortic valve. Of six cases with vegetations associated with infective endocarditis of native and artificial valves, intracranial cerebral arteries were occluded with red clots containing polymorphonuclear leukocytes in three.

EMBOLISM TO THE OTHER ORGANS. Fresh thromboembolism to the other organs was found in 40 (37%) of the 107 patients with cardioembolic stroke

Lacunar Stroke

In this series, there were two cases with lacunar stroke. The intracerebral branches of a lenticulostriate artery supplying one infarct showed significant stenosis, suggesting hypovolemia as the stroke mechanism. A branch of the anterior choroidal artery supplying the other infarct showed no occlusive change, suggesting embolism as the stroke mechanism. The former case died of rupture of atherosclerotic aneurysm of the thoracic aorta, and the latter died of dissecting aortic aneurysm.

Ischemic Stroke of Other Determined Causes

ATHEROEMBOLISM. In three cases, the atheroemboli occluding the large arteries (ICA and MCA) consisted of fibrin- and platelet-rich clots admixed with various numbers of cholesterol crystals (Table 5; Fig 7). The materials from the lipid core with overlying thrombi of the proximal aorta were considered the embolic source. The emboli occluding the small vessels causing border-zone infarcts on the brain surface in two cases mainly consisted of cholesterol crystals. In the latter two cases, atherosclerotic changes of both the aorta and carotid arteries were so advanced that they appeared to be equally responsible for the atheroembolism.

OTHER DETERMINED CAUSES. In two cases with embolic occlusion at the top of the basilar artery with red clots, the embolic source was thought to be the proximal aorta with severe atherosclerosis (see Table 5). Red thrombi generated at the luminal surface of an old prosthetic aortic graft for DeBakey type I aortic dissection embolized to the MCA1 in one case. The enlarged arteries in two cases with basilar artery dolichoectasia contained mural fibrin- and platelet-rich thrombi and red thrombi, which caused occlusion of its branches. Paradoxic embolism from iliofemoral vein red thrombi to the distal ICA through a single pulmonary arteriovenous fistula occurred in one case. In one case with essential thrombocythemia, the stenotic MCA2 and distal portion of the anterior cerebral artery (ACA2) without plaque complications were occluded with

Table 5. **Mechanisms of Development of 12 Ischemic Strokes of Other Determined Causes**

Mechanisms	n
Aortic plaque → atheroembolism to ICA origin (1); distal ICA (1); MCA2 (1)	3
Aortic or carotid artery plaque → atheroembolism → borderzone infarct	2
Aortic plaque → thromboembolism to BA top	2
Prosthetic aortic arch mural thrombi → thromboembolism to MCA1 → reopening	1
BA dolichoectasia → BA mural thrombi → BA branch occlusion	2
Iliofemoral vein thrombi → pulmonary arteriovenous fistula → paradoxic thromboembolism to distal ICA	1
Essential thrombocythemia: MCA2/ACA2 thrombotic occlusion	1

Numbers in parentheses denotes number of cases.
ICA = internal carotid artery; MCA = middle cerebral artery; BA = basilar artery; ACA = anterior cerebral artery.

platelet-rich thrombi.[24] No case showed extracranial or intracranial artery dissection, fibromuscular dysplasia, or moyamoya disease.

Ischemic Stroke of Undetermined Cause

Four cases had ischemic stroke caused by anterior circulation thromboembolism of undetermined cause (see Table 1). The first three cases showed ICA occlusion with red clots with laminations, whereas the fourth case showed reopening of the distal ICA occlusion. These patients had no history of hypertension and diabetes mellitus, whereas two suffered from alcoholism. Pathological examination showed absence of advanced atherosclerosis, culprit plaque, and cardiac conditions that may produce emboli. One case with metastatic rectal cancer and disseminated intravascular coagulation showed renal and splenic artery occlusion with red clots. Cardiogenic thromboembolism associated with clinically unrecognized paroxysmal AF remains a possibility in these cases.

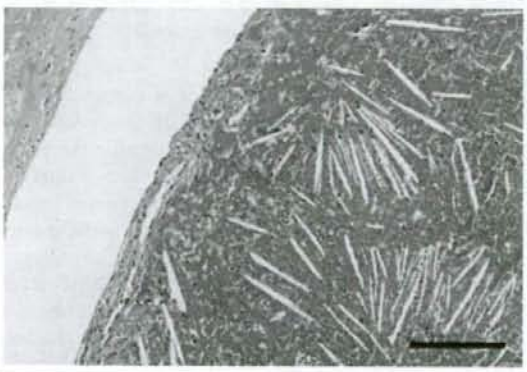


Fig 7. Photomicrograph of an atheroembolus occluding the internal carotid artery origin. The embolus derived from the aorta consists of a fibrin- and platelet-rich clot containing many cholesterol crystals. Hematoxylin and eosin staining. Patient died 19 days after the stroke. Scale bar = 0.2mm.

Discussion

Thrombotic occlusion of the extracranial and intracranial cerebral arteries at the site of plaque rupture or erosion and artery-to-artery embolism were the characteristic features of atherothrombotic stroke. Thrombotic occlusion at ruptured plaque consists of overlying intraluminal fibrin- and platelet-rich thrombi of various thicknesses and red thrombi finally occluding the lumen. These findings are similar to those described in the coronary arteries.[9–14] The thromboemboli occluding the intracranial cerebral arteries derived from the ruptured cervical artery plaque were red clots. We assume that red thrombi on the process occluding the site of plaque rupture were washed away distally.

This series contained a high proportion of patients with cardioembolic stroke among a variety of subtypes of ischemic stroke. This skew reflects the fact that patients were studied at the National Cardiovascular Center.[37,38] In addition, we examined patients who died within 30 days of an ischemic stroke, and a higher proportion of patients die shortly after the acute brain damage of cardioembolic stroke compared with the other subtypes of ischemic stroke.[37]

The diagnosis of cardioembolic stroke in this study was based on cardiac conditions that may produce emboli in the heart or through the heart. This denotes that the diagnosis of cardioembolic stroke may include cases in which postmortem pathological examinations fail to prove thrombi in the heart or through the heart as embolic sources. Pathological examinations actually showed no thrombus in the heart in 30% of cases with a diagnosis of cardioembolic stroke. Absence of the thrombus as a potential embolic source at autopsy suggests either that the thrombus in question was flushed into the bloodstream at the time of the stroke or afterward without leaving a trace, or the thrombi were originally nonmural. The high efficacy of anticoagulation to prevent embolic stroke in patients with valvular disease[39] and in high-risk nonvalvular AF patients[26,27]

further supports the cardiogenic thromboembolic mechanism.

Reopening was a characteristic feature of the cerebral artery occluded with red clots in cardioembolic stroke in this series. In patients with proximal MCA occlusion treated with intravenous tissue plasminogen activator, Molina and colleagues[40] demonstrated that early recanalization was more frequent, faster, and more complete in patients with cardioembolic stroke compared with those with other stroke subtypes such as large-vessel disease stroke, according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment.[41] They suggested that cardioembolic stroke likely represents a stroke subtype with more uniform fibrin-rich clots occluding the cerebral arteries in contrast with the well-organized fibrin- and platelet-rich thrombi in large-vessel disease stroke. Our observations in the autopsy cases agree with these results. From the histopathological viewpoints, the red clots are apt to be dissolved by the endogenous fibrinolytic activity within the loose texture of the fibrin enmeshing the red blood cells. The susceptibility of red clots to fibrinolysis, whether natural or administered therapeutically, would be different than the densely packed fibrin- and platelet-rich thrombi developing at the ruptured plaques in cases with atherothrombotic stroke and the platelet-rich clots in cases with NBTE. Although, to various extents, red thrombi appear to be responsible for the occlusion at the culprit plaques in atherothrombotic stroke, a high-grade luminal stenosis at the arterial occlusion argues against reopening, whereas reopening is likely to occur in cases of red clot embolism regardless of the arterial stenosis.

In a substantial proportion of the cases with cardioembolic stroke, laminations with alternating layers were found both in the thrombus as an embolic source and embolus occluding the cerebral artery. The fact that thrombi and emboli show a similar appearance (laminations) in the same case may serve as a histopathological landmark of a relation between the thrombus and embolus.

Atheroemboli mainly consisting of cholesterol crystals occluded the distal small vessels to produce border-zone infarcts, whereas emboli consisting of fibrin- and platelet-rich clots containing cholesterol crystals occluded larger arteries. Emboli mainly consisting of cholesterol crystals enmeshed in a loose network of fibrin could be readily broken into smaller fragments that move distally to occlude smaller vessels,[42,43] whereas densely packed fibrin- and platelet-rich clots would most likely remain intact, and thus occlude the proximal arteries.

In conclusion, postmortem pathological examinations of fresh ischemic brain infarctions showed that most atherothrombotic occlusions of cerebral arteries begin with fibrin- and platelet-rich thrombi developing at ruptured plaques and lead to eventual occlusion with red thrombi, whereas most cardioembolic occlusions are caused by red thrombi derived from intracardiac thrombi or venous thrombi through the heart.

This study was supported by the Ministry of Health, Labor and Welfare, Japan (Research Grants for Cardiovascular Disease 15C-1, 18C-5, K.M.).

We express our particular appreciation to Drs L. R. Caplan and L. Pantoni for their advice and encouragement during this study.

References

1. Paterson JC. Capillary rupture with intimal hemorrhage in the causation of cerebral vascular lesions. Arch Pathol 1940;29: 345–354.
2. Adams RD, Vander Eecken HM. Vascular diseases of the brain. Annu Rev Med 1953;4:213–252.
3. Fisher M. Concerning strokes. Can Med Assoc J 1953;69: 257–268.
4. Jörgensen L, Torvik A. Ischemic cerebrovascular diseases in an autopsy series. Part 1. Prevalence, location and predisposing factors in verified thrombo-embolic occlusions, and their significance in the pathogenesis of cerebral infarction. J Neurol Sci 1966;3:490–509.
5. Constantinides P. Pathogenesis of cerebral artery thrombosis in man. Arch Neurol 1967;83:422–428.
6. Jörgensen L, Torvik A. Ischemic cerebrovascular diseases in an autopsy series. Part 2. Prevalence, location, and clinical course of cerebral infarcts. J Neurol Sci 1969;9:285–320.
7. Ogata J, Masuda J, Yutani C, Yamaguchi T. Rupture of the atheromatous plaque as a cause of thrombotic occlusion of stenotic internal carotid artery. Stroke 1990;21:1740–1745.
8. Ogata J, Masuda J, Yutani C, Yamaguchi T. Mechanisms of cerebral artery thrombosis: histopathological analysis on eight necropsy cases. J Neurol Neurosurg Psychiatry 1994;57:17–21.
9. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 1990;82(suppl I): I1138–I1146.
10. Fuster V, Badimon L, Badimon J, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–250.
11. van der Wal AC, Becker AE, van der Loos AM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of dominant plaque morphology. Circulation 1994;89: 36–44.
12. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93: 1354–1363.
13. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. Circulation 1996;94:2013–2020.
14. Davies MJ. Coronary disease: the pathophysiology of acute coronary syndromes. Heart 2000;83:361–366.
15. Vinters HV. Interactions between the heart and brain. In: Silver MD, ed. Cardiovascular pathology. 2nd ed. London: Churchill Livingstone, 1991:1029–1071.
16. Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: a review. Am Heart J 1987;113: 773–784.
17. Rose AG. Diseases of veins. In: Silver MD, ed. Cardiovascular pathology. 2nd ed. London: Churchill Livingstone, 1991: 195–223.

18. Schoen FJ. The heart. In: Cotran RS, Kumar V, Collins T, eds. Robbins pathologic basis of disease. 6th ed. Philadelphia: Saunders, 1999:543–599.
19. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. Stroke 2001;32:803–808.
20. Schellinger PD, Chalea JA, Kang D-W, et al. Diagnostic and prognostic value of early MR imaging vessel signs in hyperacute stroke patients imaged <3 hours and treated with recombinant tissue plasminogen activator. Am J Neuroradiol 2005;26: 618–624.
21. Molina CA. Imaging the clot: does clot appearance predict the efficacy of thrombolysis? Stroke 2005;36:2333–2334.
22. Masuda J, Yutani C, Waki R, et al. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. Stroke 1992;23:843–850.
23. Masuda J, Yutani C, Ogata J, et al. Atheromatous embolism in the brain: a clinicopathological analysis of 15 autopsy cases. Neurology 1994;44:1231–1237.
24. Ogata J, Yonemura K, Kimura K, et al. Cerebral infarction associated with essential thrombocythemia: an autopsy case study. Cerebrovasc Dis 2005;19:201–205.
25. Slavin RE, Saeki K, Bhagavan B, Maas AE. Segmental arterial mediolysis: a precursor to fibromuscular dysplasia? Mod Pathol 1995;8:287–294.
26. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–1457.
27. Hart RG, Sherman DG, Easton JD, Cairns JA. Prevention of stroke in patients with nonvalvular atrial fibrillation. Neurology 1998;51:674–681.
28. National Institute of Neurological Disorders and Stroke. Special report: classification of cerebrovascular diseases III. Stroke 1990;21:637–676.
29. Fisher CM. Lacunes: small, deep cerebral infarcts. Neurology 1964;15:774–784.
30. Fisher CM. The arterial lesions underlying lacunes. Acta Neuropathol 1969;12:1–15.
31. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS stroke data bank. Ann Neurol 1989;25:382–390.
32. Mitchel RN, Cotran RS. Hemodynamic disorders, thrombosis, and shock. In: Cotran RS, Kumar V, Collins T, eds. Robbins pathologic basis of disease. 6th ed. London: Saunders, 1999: 113–138.
33. Rose AG. Diseases of peripheral arteries. In: Silver MD, ed. Cardiovascular pathology. 2nd ed. London: Churchill Livingstone, 1991:341–383.
34. Ad Hoc Committee of Japan Stroke Society for Writing Guidelines. Guidelines for intravenous application of rt-PA in acute ischemic stroke. Jpn J Stroke 2005;27:327–354.
35. Yamaguchi T, for Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter prospective, randomized trial. Stroke 2000;31: 817–821.
36. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. Intern Med 2001;40:1183–1188.
37. Yokota C, Minematsu K, Hasegawa Y, Yamaguchi T. Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-bases study over a 20-year period. Cerebrovasc Dis 2004;18:111–116.
38. Kimura K, Kazui S, Minematsu K, Yamaguchi T, for the Japan Multicenter Stroke Investigators Collaboration (J-MUSUC). Hospital based prospective registration of acute ischemic stroke and transient ischemic attack in Japan. J Stroke Cerebrovasc Dis 2004;13:1–11.
39. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease: native and prosthetic. The Seventh ACCP Conference on Antithrombitic and Thrombolytic Therapy. Chest 2004;126:457S–482S.
40. Molina CA, Montaner J, Arenillas JF, et al. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke 2004; 35:486–490.
41. Albanese MA, Clarcke WR, Adams HP Jr, Woolson RF. Ensuring reliability of outcome measures in multicenter clinical trials of treatment for acute ischemic stroke: the program developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Stroke 1994;25:1746–1751.
42. Pollanen MS, Deck JHN. Direct embolization is an alternate cause of cerebral watershed infarction. Arch Pathol Lab Med 1989;113:1139–1141.
43. Pollanen MS, Deck JHN. The mechanism of embolic watershed infarction: experimental studies. Can J Neurol Sci 1990; 17:395–398.

Original Paper

European Neurology

Eur Neurol 2008;59:38–43
DOI: 10.1159/000109259

Received: October 4, 2006
Accepted: April 11, 2007
Published online: October 4, 2007

Relationship between Detectability of Ischemic Lesions by Diffusion-Weighted Imaging and Embolic Sources in Transient Ischemic Attacks

Hisakazu Uno[a] Akihiko Taguchi[a] Hiroshi Oe[a] Keiko Nagano[a]
Naoaki Yamada[b] Hiroshi Moriwaki[a] Hiroaki Naritomi[a]

Departments of [a]Cerebrovascular Medicine and [b]Radiology, National Cardiovascular Center, Suita, Japan

Key Words
Diffusion-weighted imaging · Embolic sources · Transient ischemic attacks

Abstract
Background/Aims: The aim of this study is to clarify the relationship between lesion detectability by diffusion-weighted magnetic resonance imaging (DWI) and the etiology of transient ischemic attacks (TIAs). ***Methods:*** A retrospective study was performed on 72 patients with carotid TIAs who underwent DWI studies within 2 weeks after the last episode. ***Results:*** Lesions were detected in 24 of 72 patients (33%). The detectability of lesions was 12% (3/25) in the large-artery atherosclerosis (LA) group, 57% (8/14) in the cardioembolism (CE) group, 8% (1/13) in the small-artery occlusion (SA) group, and 60% (12/20) in the other etiology or undetermined etiology (UD) group. Detectabilities in the CE group and the UD group were higher than those in the LA and SA groups. Of 24 patients with DWI-positive lesions, 17 (71%) had embolic sources in the heart; 9 were classified in the UD group because they had embolic sources both in the heart and large artery. ***Conclusion:*** Ischemic DWI lesions in TIAs are most likely caused by a cardioembolic mechanism. In TIA patients showing lesions on DWI, heart disease should be surveyed as the possible embolic source.

Introduction

According to the Ad Hoc Committee on classification of cerebrovascular disease of 1975, transient ischemic attacks (TIAs) are defined as ischemic cerebrovascular disease in which focal cerebral dysfunction resolves within 24 h [1]. It has been known for years that CT or T_1- and T_2-weighted magnetic resonance imaging (MRI) may occasionally depict small ischemic lesions in TIA patients [2–7]. More recently, diffusion-weighted imaging (DWI) has made it possible to demonstrate ischemic lesions in TIA patients with relatively high frequency [8]. Several studies have shown that the detectability of DWI lesions in TIA patients increases in correlation with the duration of TIA symptoms. However, clarification as to whether the detectability of DWI lesions is related to the etiology of TIA is still lacking. In the majority of previous studies reporting DWI detectability of TIA lesions, both types of TIAs – in the carotid artery territory and the vertebral artery territory – were included indiscriminately. This makes accurate evaluation of TIA duration difficult, since onset and end of symptoms are often obscure in a vertebral artery territory TIA. Therefore, we included only patients with carotid TIA in the present study, examining the relationship between the etiology of TIA and the detectability of DWI lesions.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0014–3022/08/0592–0038$24.50/0

Accessible online at:
www.karger.com/ene

Hiroaki Naritomi
Department of Cerebrovascular Medicine
National Cardiovascular Center
5-7-1 Fujishiro-dai, Suita 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6835 5137, E-Mail hnaritom@hsp.ncvc.go.jp

Subjects and Methods

A retrospective analysis was performed on 72 patients with carotid TIA who were admitted to our department during the interval from May 1998 to July 2005, and who underwent DWI studies within 14 days of symptom onset after the last TIA. Fifty-two patients were male. The mean (± SD) age of patients was 69 ± 10 years. Patients with isolated amaurosis fugax were excluded. MRI was performed using a Siemens Magnetom Vision 1.5-tesla MR unit. DWI scanning was performed with a single-shot, multislice spin echo and echo planar imaging sequence. DWI parameters comprised: TE = 123 ms; FOV = 23 × 23 cm; matrix = 128 × 200, and slice thickness = 4 mm. Diffusion gradients were applied in the through-plane direction with a b value of 1,100 s/mm^2. Since 1999, imaging parameters have been changed to TE = 100 ms and matrix = 98 × 128. Diffusion gradients were applied in each x, y, and z direction with b values of 1,000 s/mm^2, and trace imaging was calculated. Conventional MRI studies included T_1-weighted (TR/TE: 630/14) and T_2-weighted (TR/TE: 5,400/99) images, and fluid attenuation inversion recovery (TR/TE/TE: 9,000/105/2,400) images were obtained when required.

We assessed whether each patient had ischemic lesions and/or arterial disease compatible with symptoms by reviewing DWI films and the results of conventional cerebral angiography, MR angiography, and carotid ultrasonography. We assessed the presence or absence of cardiac embolic sources based on 12-lead ECG findings, transthoracic and/or transesophageal echocardiography and, when required, 24-hour ECG monitoring. Referring to the TOAST classification [9], all patients were classified into four groups: large-artery atherosclerosis (LA) group, cardioembolism (CE) group, small-artery occlusion (SA) group, and other etiology or undetermined etiology (UD) group. The LA group included patients with more than 50% stenosis of intracranial or extracranial large arteries or with a complicated lesion of more than 3.5 mm in the aortic arch based on findings of conventional cerebral angiography, MR angiography, carotid ultrasonography and transesophageal echocardiography. Patients in this group should not have had significant heart disease. The CE group included patients with significant heart disease that can become an embolic source, such as mechanical prosthetic valves, mitral stenosis with atrial fibrillation, atrial fibrillation, left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction within 4 weeks prior to the study, left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis or patent foramen ovale with peripheral thrombus but without LA. The SA group included patients who had neither significant heart disease nor LA, nor other evidence of disease. The TIA symptoms in this group should have corresponded to any of the traditional clinical lacunar syndromes and should not have been associated with cortical symptoms. The UD group included patients who could not have been classified into other groups because of the following reasons: (1) they had other causes of cerebral ischemia, such as dissection of cervical/cranial arteries, vasculitis or hypercoagulopathy, (2) they had cortical symptoms in spite of an absence of association with significant heart disease, large-artery lesions or evidence of other diseases, and (3) they had both significant heart disease and more than 50% stenosis in a large artery or aortic complicated lesions greater than 3.5 mm. This classification was made by mutual agreement by three neurologists. We also examined the duration of TIA symptoms and the time from onset of TIA to DWI in each patient. Furthermore, we reviewed the correlation between these factors and the detectability of lesions. We also studied whether patients had risk factors for atherosclerosis such as hypertension, diabetes mellitus, hyperlipidemia and smoking, and whether they had a history of cerebral infarction.

Statistical Analysis

Statistical analysis was performed using a commercially available software package (Statview, version 5, SAS Institute Inc., Cary, N.C., USA). Data were expressed as means ± SD. The level of $p < 0.05$ was determined to indicate statistical significance. We statistically compared the four groups as classified above using one-way factorial ANOVA or the Kruskal-Wallis test.

The table of baseline patient characteristics was analyzed using the Yates corrected χ^2 or Fisher test, as appropriate.

Results

Twenty-four of 72 patients (33%) had small ischemic lesions on DWI. There was no significant difference in baseline characteristics between patients with positive DWI lesions and those with negative DWI lesions (table 1). As shown in table 2, the duration of symptoms was significantly longer in patients with positive DWI lesions (4.0 ± 5.1 h) than in those with negative DWI lesions (1.4 ± 2.5 h) ($p < 0.01$). The time from TIA onset to DWI study was also significantly longer in patients with positive lesions (4.5 ± 4.1 days) than in those with negative lesions (2.0 ± 3.2 days) ($p < 0.01$). The detectability of lesions increased in correlation with the duration of TIA symptoms, as shown in figure 1. The detectability of lesions was also influenced by time from TIA onset to DWI, as follows: detectability was 14% (4/29) in the group undergoing DWI at 0–12 h after TIA, 33% (5/15) in the group undergoing DWI at 12–24 h after TIA, 43% (3/7) in the group undergoing DWI at 1–3 days after TIA, 60% (6/10) in the group undergoing DWI at 3–7 days after TIA, 57% (4/7) in the group undergoing DWI at 7–10 days after TIA, and 50% (2/4) in the group undergoing DWI at 10–14 days after TIA. Thus, the detectability of lesions was somewhat lower in patients undergoing DWI within 24 h after TIA than in those undergoing DWI more than 24 h after TIA.

Cerebral angiography was carried out on 25 patients, MR angiography on 58 patients, carotid ultrasonography on 71 patients, transthoracic echocardiography on 58 patients and transesophageal echocardiography on 60 patients. The type of etiology was classified as LA group, 25 patients; CE group, 14 patients; SA group, 13 patients, and UD group, 20 patients. The breakdown of the 20 patients

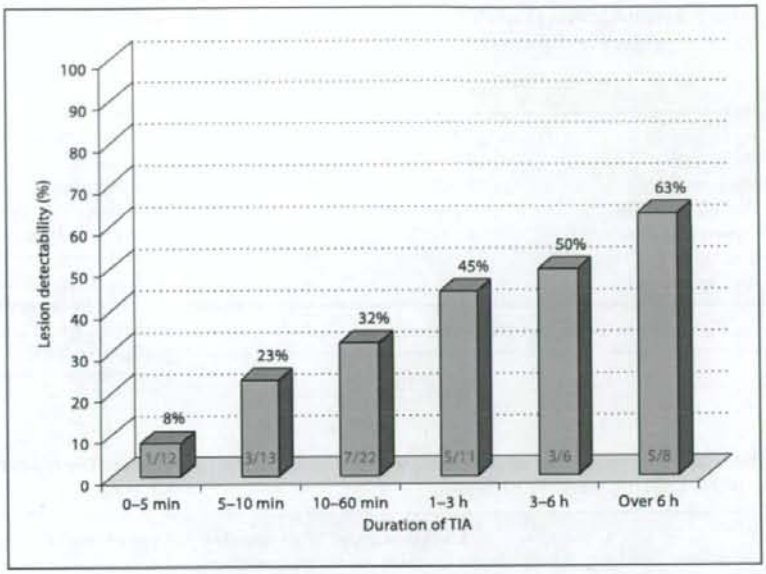


Fig. 1. The duration of TIA symptoms and DWI lesion detectability. The DWI lesion detectability increases in correlation with the duration of TIA symptoms.

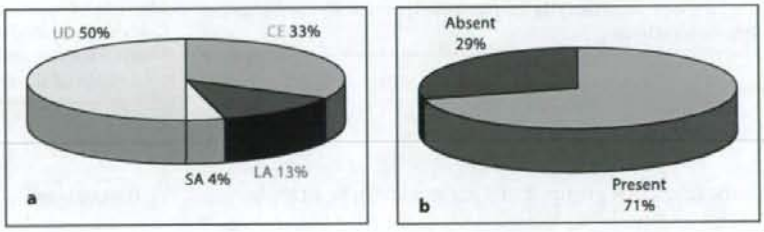


Fig. 2. Details of 24 TIA patients with DWI-positive lesions. **a** 83% of DWI-positive patients belong to the CE or UD groups. **b** 71% of DWI-positive patients have heart disease, either independently or in association with other etiologies.

in the UD group was as follows: (1) 1 patient with both antiphospholipid antibody syndrome and a significant lesion in a large artery, and 1 other patient with cervicocranial dissection and significant atherosclerotic lesions in a large artery, (2) 2 patients with cortical symptoms in association with no abnormality in the heart, large artery and other tests, and (3) 16 patients with both significant heart disease and significant stenotic lesions in large cerebral arteries and/or aorta. As shown in table 3, the detectabilities of lesions in the CE group (57%) and the UD group (60%) were significantly higher as compared with those in the LA group (12%) and the SA group (8%).

The duration of symptoms in the CE group was somewhat longer than in the other three groups, although the difference was not significant (table 3). Time from TIA onset to DWI was somewhat longer in the CE and UD groups as compared with the other two groups. However, results of one-way factorial ANOVA indicated that there was no significant difference in time from TIA to DWI studies between the groups (table 3). DWI studies were performed within 24 h after TIA in 39 patients and more than 24 h after TIA in 33 patients. Percentages of patients undergoing DWI studies within 24 h after TIA were 64% (16/25) in the LA group, 50% (7/14) in the CE group, 62% (8/13) in the SA group, and 40% (8/20) in the UD group. There were no significant differences in the frequency of early DWI studies between the four groups (Kruskal-Wallis test). The CE and UD groups had higher lesion detectability irrespective of time from TIA to DWI studies.

A total of 14 patients had multiple lesions on DWI. The frequency of multiple lesions in each group was as fol-

Table 1. Baseline patient characteristics

	DWI positive (n = 24)	DWI negative (n = 48)
Age, years	68 ± 10	69 ± 10
Male gender	18 (75)	34 (71)
Hypertension	15 (63)	34 (71)
Diabetes mellitus	4 (17)	10 (21)
Hypercholesterolemia	9 (38)	21 (44)
Smoking	13 (54)	31 (65)
History of stroke	1 (4)	8 (17)

Figures in parentheses indicate percentages.

Table 2. Duration of symptoms and time to MRI studies in DWI-positive and DWI-negative patients

	DWI positive	DWI negative
Duration of symptoms, h	4.0 ± 5.1*	1.4 ± 2.5
Time from TIA to MRI, days	4.5 ± 4.1*	2.0 ± 3.2

* $p < 0.01$: significantly longer as compared with the diffusion-negative patients.

Table 3. Comparison of four TIA groups

	LA (n = 25)	CE (n = 14)	SA (n = 13)	UD (n = 20)
Positive DWI lesions	3 (12)	8 (57)[1]	1 (8)	12 (60)[1]
Duration of symptoms, h	1.5 ± 3.0	3.8 ± 5.2	1.7 ± 2.8	2.5 ± 3.9
Time from TIA to DWI, days	1.8 ± 2.6	3.6 ± 4.1	2.6 ± 4.5	3.6 ± 4.1

Figures in parentheses indicate percentages.
[1] The frequency of DWI-positive lesions is significantly higher in the CE and the UD groups as compared with the LA and SA groups ($p < 0.05$).

Table 4. The type of heart diseases and lesion detectability in the CE group

Type of heart diseases	DWI positive	DWI negative
Atrial fibrillation	5	2
Mechanical prosthetic valve	1	1
Akinetic left ventricular segment	2	0
Sick sinus syndrome	0	1
Patent foramen ovale with peripheral thrombus	0	2

lows: in the LA group, 2 of 3 patients with positive lesions (67%) had multiple lesions; the number of lesions was 3 and 5, respectively. In the CE group, 3 of 8 patients (38%) had multiple lesions; the number of lesions was 3 in 2 cases and 4 in the other. In the SA group, 1 positive patient had only a single lesion (0%). In the UD group, 9 of 12 patients (75%) had multiple lesions; the number of lesions was 2 in 5 cases, 3 in 3 cases and 6 in the remainder. Thus, no remarkable relationship was observed between the number of lesions and the etiology.

Of all 24 patients with ischemic lesions on DWI, 8 patients (33%) belonged to the CE group, 12 patients (50%) to the UD group, 3 patients (13%) to the LA group, and 1 patient (4%) to the SA group (fig. 2). Of the 12 patients with positive DWI lesions who belonged to the UD group, 9 had significant heart disease in association with significant large-artery lesions. Thus, of all 24 patients with ischemic lesions on DWI, 17 patients (71%) had significant heart disease either independently or concomitantly with large-artery lesions (fig. 2). In the CE group, 5 of 7 patients with atrial fibrillation had positive DWI lesions (table 4).

Discussion

In recent years, quite a few studies have reported the presence of ischemic lesions on DWI following TIA. In these previous studies, the detectability of TIA lesions on DWI ranged from 20 to 70% [8, 10–16]. Detectability in the present study was 33%, showing a somewhat lower value as compared with previous studies. This may be partly related to the difference in the timing of DWI examinations between the present study and the previous studies. In the present study, approximately 54% of patients underwent DWI within 24 h after TIA onset; the detectability in these patients was low, at 21%. On the other hand, in most previous studies the majority of TIA patients underwent DWI examinations more than 24 h after TIA onset. When we calculated only the detectability of lesions in our patients undergoing DWI more than 24 h after TIA onset, the detectability increased to 48%, showing similar values to those reported in previous studies. The above-mentioned reasoning can also be inferred from the study of Rovira et al. [10]. In their study,

only 9% of patients underwent DWI within 48 h after TIA, and the detectability of lesions in the entire group showed a high value, reaching 67%. In a transient ischemia experiment using rats, the value of the average apparent diffusion coefficient decreased significantly during the ischemic period and then normalized at 60–90 min after ischemia, followed again subsequently by a significant reduction more than 12 h after ischemia [17]. As confirmed in the above experiment, the detectability of lesions on DWI may decrease for a while after a short period of transient cerebral ischemia, and may increase thereafter, although the mechanisms remain unclear. Kidwell et al. [8] first pointed out that the detectability of lesions on DWI in patients with TIA increases in correlation with the duration of symptoms. Since then, similar results have been reported by several authors. In the study by Rovira et al. [10], the detectability of lesions in TIA patients with symptoms lasting less than 6 h was 59%, whereas the value was 100% in patients with symptoms lasting more than 6 h. Crisostomo et al. [11] reported that the detectability of lesions in patients with symptoms lasting more than 1 h was significantly higher as compared with patients with symptoms lasting less than 1 h. Inatomi et al. [12] also reported that the detectability of lesions was significantly higher in TIA patients with symptoms lasting more than 30 min than in those with symptoms lasting less than 30 min. In our study, the detectability of lesions also tended to increase according to the increase in TIA duration.

Previously, few workers performed detailed investigations on the relationship between the detectability of DWI lesions and the etiology of TIA. Rovira et al. [10] reported that the detectability of DWI lesions was higher in TIA patients with large-artery lesions than in those with cardiac lesions. However, the report lacks credibility, since the number of patients in their study was small; only 4 patients had cardiac lesions, whereas 19 patients had large-artery lesions. Nakamura et al. [16] reported higher detectability of DWI lesions in TIA patients with atrial fibrillation as compared with those without atrial fibrillation. However, they focused only on atrial fibrillation and did not clarify DWI detectability in TIA patients without atrial fibrillation who had other types of heart diseases. In the present study, the presence or absence of large-artery lesions and/or cardiac disease was surveyed in a retrospective manner reviewing the results of conventional cerebral angiography, MR angiography, carotid ultrasonography, 12-lead ECG, transthoracic or transesophageal echocardiography, and 24-hour ECG monitoring. The patients were then classified into four groups according to the etiology of TIA, such as LA, CE, SA and UD groups. The results indicated that the detectability of lesions in the CE group and the UD group was higher than that in the other groups. Time from TIA to DWI studies was almost the same in the four groups. Lesion detectability was higher in the CE and UD groups than in the other groups, even when the comparison among the subgroups undergoing DWI studies had been made within 24 h after TIA onset. Therefore, the higher detectability in the CE and UD groups is unrelated to time from TIA to DWI studies. The mean duration of TIA symptoms in the CE group was more than 3 h, which was the longest of all the groups. In general, cardioembolic stroke produces severer symptoms than artery-to-artery embolic stroke. This may be attributable to the fact that emboli originating in the heart tend to occlude larger blood vessels for longer durations as compared with artery-to-artery emboli. This is probably also true in cases of TIA. Microemboli originating in the heart likely occlude larger blood vessels for longer durations as compared with artery-to-artery microemboli. Accordingly, ischemic duration may be longer in TIA patients with heart disease than in those with other types of etiology, and ischemic lesions may be larger in TIA patients with heart disease than in those with other types of etiology. Probably for such reasons, ischemic lesions in cardioembolic TIA may be more readily found on DWI than those in other types of TIA. In the present study, 16 of 20 patients in the UD group had heart disease, and 9 had ischemic lesions on DWI. In these 9 patients, TIA was most likely caused by a cardioembolic mechanism rather than another type of etiology. Johnston et al. [18] conducted a follow-up study in 1,707 patients with TIA for 90 days. In their study, 10.5% of patients developed cardioembolic stroke during the follow-up period, and approximately half of them had stroke within 48 h after TIA. Thus, cardioembolic stroke may occur soon after TIA at a considerably high frequency. A DWI study is considered useful to evaluate etiological mechanisms of TIA. If ischemic lesions are detected on DWI, the presence of heart disease should be suspected, and appropriate medication should be considered to prevent cardioembolic stroke.

Acknowledgement

This work was supported by a Research Grant for Cardiovascular Diseases (18C-2) funded by the Japanese Ministry of Health and Labor.