ORIGINAL

Reversibility of ischemic findings on 3-tesla magnetic resonance T2*-weighted image after recanalization

Nobuaki Yamamoto[1], Yuka Terasawa[1], Junichiro Satomi[2], Ryoma Morigaki[2], Koji Fujita[1], Masafumi Harada[3], Yuishin Izumi[1], Shinji Nagahiro[2], and Ryuji Kaji[1]

[1]*Department of Neurology, Institute of Health Biosciences, the University of Tokushima Graduate School, Tokushima, Japan,* [2]*Department of Neurosurgery, Institute of Health Biosciences, the University of Tokushima Graduate School, Tokushima, Japan,* [3]*Department of Radiology, Institute of Health Biosciences, the University of Tokushima Graduate School, Tokushima, Japan*

Abstract : Ischemic vessel signs (IVS) can be detected on 3-tesla T2*-weighted magnetic resonance images as a vessel enlargement at the territory of acute ischemia caused by major vessel occlusion or stenosis. Here, we studied changes in IVS before and after recanalization by the administration of intravenous recombinant tissue plasminogen activator (IV rtPA), carotid artery stenting or percutaneous transluminal angioplasty in patients with major vessel occlusion or stenosis. We performed magnetic resonance imaging for all patients treated by IV rtPA at the time of admission, shortly after and 24-72 hours after treatment with IV rtPA. We reviewed the IVS to assess its natural course of IVS by assessing patients who did not recanalize. IVS tended to disappear after recanalization. Conversely, in patients without recanalization, IVS did not disappear shortly after IV rtPA ; rather, it disappeared 24-72 hours after IV rtPA, especially in the presence of complete infarction. Recanalization by IV rtPA or endovascular treatment contributed to improved clinical deficits or the prevention from further progression. IVS can be a parameter of misery perfusion and an important factor to detect the patients who have an indication of treatment for recanalization. J. Med. Invest. 61 : 190-196, February, 2014

Keywords **:** *ischemic vessel sign, recanalization, 3T MRI, CAS, PTA, rtPA*

INTRODUCTION

T2*-weighted magnetic resonance imaging (T2*WMRI) is widely known as a useful tool for detecting microbleeds and thrombi in patients after stroke (1-5). A new finding indicating ischemia on 3-tesla (3T) T2*WMRI, called the 'ischemic vessel sign' (IVS), is hypointense signals of medullary and cortical veins in the ischemic territory due to major vessel occlusion or severe stenosis (6). Although, IVS was previously reported to possibly indicate the ischemic penumbra (6), no further reports have been published. In fact, the natural course and change of this sign in IVS after recanalization remain unclear. The aim of this study was to evaluate the change in IVS in patients who did or did not recanalize by treatments. Our hypothesis is that IVS may disappear or decrease after reperfusion if it resulted from hypoperfusion. To test this, we studied those patients who underwent urgent treatment consisting of reperfusion of major vessel occlusion or stenosis of carotid circulation.

Received for publication November 15, 2013 ; accepted January 23, 2014.

Address correspondence and reprint requests to Nobuaki Yamamoto, Department of Clinical Neurosciences, Institute of Health Biosciences, the University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7208.

We had been treating patients with acute ischemic stroke by only intravenous recombinant tissue plasminogen activator (IV rtPA) for approximately 3 years before 2009. All the patients who were treated by IV rtPA underwent magnetic resonance imaging (MRI) at the time of admission, shortly after and about 24-72 hours after IV rtPA treatment. We often identified recanalization failure after IV rtPA treatment, allowing us to evaluate the natural course of IVS over time in patients who did not recanalize.

METHODS

Patient selection, image analysis

We retrospectively investigated cases of acute ischemic stroke caused by major vessel occlusion or stenosis of the carotid circulations between January 2007 and December 2012. We obtained patients' agreement about use of their laboratory, radiological, clinical data as research data and official conference presentation. Present study was on the basis of patents' consent.

We included 26 patients who underwent MRI scans at the time of admission or symptomatic worsening, shortly after and 24-72 hours after treatment during this period in this study. We divided our 26 patients into groups, that did (group 1, n=17), or did not recanalize (group 2, n=9). A summary of the intended patients is presented in the Table 1.

In group 1, we included patients who underwent successful treatments such as carotid artery stenting, percutaneous transluminal angioplasty (PTA) or IV rtPA, for recanalization of stenotic or occlusive lesions of carotid circulation. Patients who underwent CAS or PTA were not treated by IV rtPA but only endovascular treatment. Because patients who underwent endovascular treatment had progression several days after onset, we could not use rtPA. A successful treatment was defined as thrombolysis in cerebral infarction (TICI) grade 3 on conventional angiography (7) or modified Mori grade 3 on magnetic resonance angiography (MRA) (8). We performed MRI evaluation over time as fellows : at

Table 1. Baseline characteristics

	group 1 n=17	group 2 n=9	*p*
age, mean±SD	75.5±9.2	75.4±13.2	1.000
gender, male, %	70	33	0.079
etiology, CES, %	35	67	0.048
Occlusion site, n			
ICA	7	1	0.009
M1	7	6	0.079
M2	3	2	0.538
duration between onset to treatmentment, mininites	1750.1±218.6	139.2±21.4	0.052
Duration between onset to first MRI, minitues	91.1±26.3	72.9±30.5	0.161
ASPECTS, median			
Pre-treatment	7.7±1.1	7.3±0.9	0.560
Post-treatment	6.6±2.0	3.6±0.7	0.004
24-72 hrs after treatment	6.5±2.0	3.3±0.9	0.005
IVS score			
Pre-treatment	4.2±2.1	4.4±1.3	1.000
Post-treatment	1.4±1.6	3.6±1.4	0.005
24-72 hrs after rtPA	0.2±0.4	0.4±0.3	0.506
NIHSS			
initial	11.8±6.7	18.0±6.4	0.048
at the time of discharge	6.9±5.5	16.4±4.4	<0.001
mRS at the time of discharge	2.5±1.6	4.0±1.4	0.041

EVT, endovascular treatment ; ICA, internal carotid artery ; M1, lesion of horizontal segment of middle cerebral artery ; M2, lesion of the sylvian segment of middle cerebral artery ; CES, cardioembolic stroke ; ASPECTS, Alberta stroke program early CT score on diffusion-weighted image ; IVS, ischemic vessel sign ; NIHSS ; National Institute of Health stroke scale ; mRS, modified Rankin Scale
The duration between onset and first Magnetic resonance image (MRI) of group 1 was difficult to compare with that of group 2 because we performed percutaneous transluminal angioplasty (PTA) or carotid artery stenting (CAS) for the patients with progression several days after onset. We defined the duration of patients who underwent PTA or CAS as the duration between clinical progression we detected and first MRI

the time of admission or symptomatic worsening (Pre-treatment), shortly after (Post-treatment) and about 24-72 hours after the treatment. We studied all of the MRI scans that were examined for intended patients during hospitalization. In group 2, patients with stenosis or occlusion of the major vessels of the carotid circulation who did not recanalize after IV rtPA confirmed by MRA shortly after IV rtPA were included. No recanalization was defined as modified Mori grade 0 and 1 on MRA.

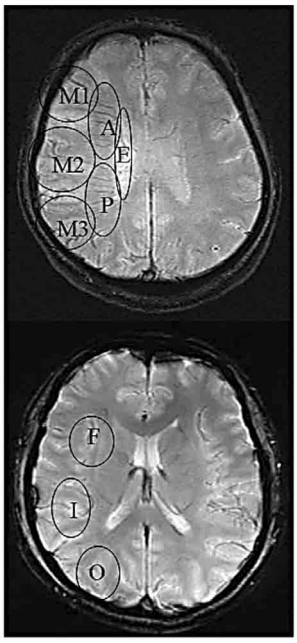
We established a simple scoring system (IVS score) to easily evaluate the presence of IVS. We separated the middle cerebral artery (MCA) territory into 9 areas (cortical 4, medullary 5) according to venous territory (9). When IVS was positive in each area, we assigned one point for each, and summed the points to get an IVS score (maximum, 9). We gave each patients an IVS score (Fig. 1) of Pre-treatment, Post-treatment and 24-72 hours after treatment. A Single neurosurgeon (R.M.) and neurologist (Y.T.) who were blinded to the patients' information evaluated 3T T2*WMRI. We used mean IVS score and ASPECTS that were evaluated by a single neurosurgeon and neurologist. We also evaluated the Alberta Stroke Program Early CT scores (ASPECTS) (10) on diffusion-weighted images (DWI) all of the MRI scans that were examined for the intended patients and the clinical presentation according to the National Institute of Health (NIH) stroke scale of Pre-treatment and at the time of discharge.

MRI evaluation

MRI scans were acquired on a 3T Signa EXITE HD 3.0-T scanner (GE Healthcare, Milwaukee, WI, USA). The scan parameters for standard DWI echo-planar imaging included the following : TR, 6,000 ms ; TE, 70 ms ; b values, 0 and 1,000 s/mm^2 ; field of view, 24 cm ; acquisition matrix ; and EPI factor, 37. For T2-WI, they were as follows : TR of 3,500 ms and TE of 100 ms. For T2*WI gradient-echo, the parameters were TR of 400 ms and TE of 30 ms in the axial plane. The slice thickness was 7 mm.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Analyses of these variables among groups were performed using the Mann-Whitney *U* test, categorical variables were compared among groups on univariate analyses using the Fisher's exact test, analyses of variables among 3 groups ; i.e. Pre-treatment, Post-treatment and 24-72 hours after treatments, were performed using Friedman test or Bonferroni correction. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS program, version 20.0 for Windows 7 (SPSS, IBM Corporation).



	lesion	Score
Cortical	M1	0 or 1
	M2	0 or 1
	M3	0 or 1
	I (insula)	0 or 1
Subcortical	A (anterior)	0 or 1
	P (posterior)	0 or 1
	E(ependymal)	0 or 1
	F (frontal)	0 or 1
	O (occipital)	0 or 1
	Total	0～9

Fig. 1. Ischemic vessel sign (IVS) on 3-T T2*-weighted magnetic resonance imaging
IVS was defined as hypointensity and vessel enlargement compared with the contralateral hemisphere. IVS score was defined as the total number of lesions with hypointensity in the territory of the middle cerebral artery

RESULTS

In group 1, we included 17 patients (age 75.5±9.2 ; 12 males, and 5 females) with major vessel occlusion or stenosis who underwent recanalization by endovascular treatment or IV rtPA. In group 2, we included 9 patients (age 75.4±13.2 ; 3 males and 6 females) who did not recanalize by IV rtPA.

In group 1, the causative arteries included 7 ICA, and 9 MCA (7 M1 : horizontal segment, 2 M2 : sylvian segment). We performed CAS for all of the ICA lesions and PTA for 2 MCA lesions and administered rtPA for 5 M1 and 3 M2. After recanalization, the IVS tended to decrease. The mean IVS score before the procedure was 4.2, whereas that after the procedure was 1.4 (p=0.030, Fig. 2). The mean IVS 24-72 hours after the procedure was 0.2 (Pre-treatment vs. 24-72 hours after treatment, p=0.015, Fig. 2). In contrast, the ASPECTS score did not differ before and after treatment (Pre-treatment vs. Post-treatment, 7.7 vs. 6.6, p=0.102, Fig. 3). Clinical presentations expressed according to the NIH stroke scale, improved during hospitalization (Pre-treatment vs. at the time of discharge, 11.8 vs. 6.9, p=0.003). In group 2, causative arteries included 2 M2 and 6 M1 and 1 ICA. The median IVS score of Pre-treatment, Post-treatment and about 24-72 hours after treatment were 4.4, 3.6 and 0.4. The ASPECTS scores in group 2 tended to be worse (Pre-treatment vs. Post-treatment, 7.3 vs. 3.6, p=0.021, Fig. 3), than those in group 1. This finding meant that ischemic lesions became complete infarcts that were perfused by occlusive arteries 24-72 hours after IV rtPA administration in group 2. NIH stroke scale did not differ between before IV rtPA and at the time of discharge (Pre-treatment vs. at the time of discharge ; 18.0 vs. 16.4, p=0.404, Table 1). In addition, NIH stroke scale at the time of discharge significantly differed between group 1 and 2 (group 1 vs. group 2, 6.9 vs. 16.4, p<0.001, Fig. 4). Representative cases in group 1 are shown in Fig. 5, and one from group 2 was in Fig. 6.

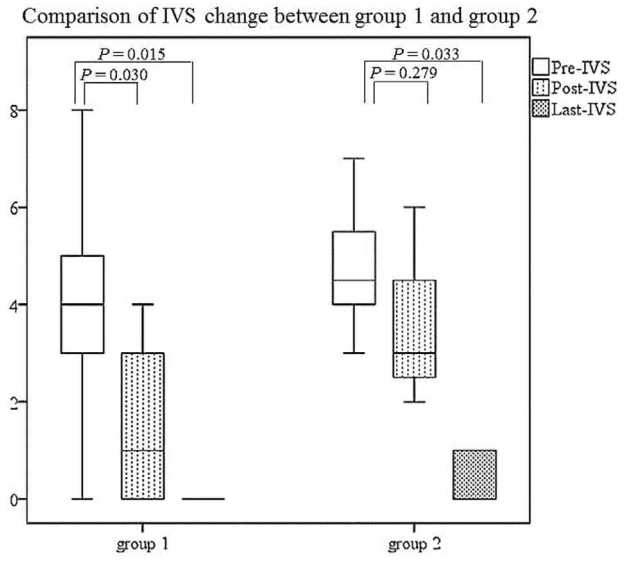


Fig. 2. Comparison of ischemic vessel sign (IVS) between the recanalization and no revascularization groups
Pre-IVS, IVS before treatment ; Post-IVS, IVS shortly after treatment ; Last-IVS, IVS 24-72 hours after treatment

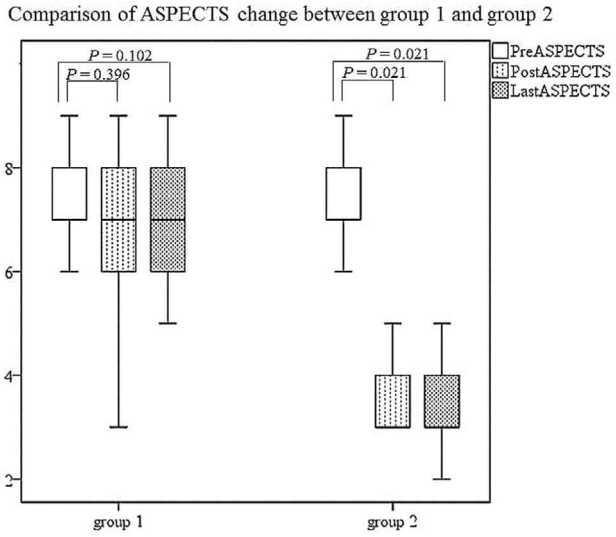


Fig. 3. Comparison of Alberta Stroke Program Early CT scores (ASPECTS) between the recanalization and no revascularization groups
PreASPECTS, ASPECTS on diffusion-weighted image (DWI) before treatment ; PostASPECTS, ASPECTS on DWI shortly after treatment ; LastASPECTS, ASPECTS 24-72 hours after treatment

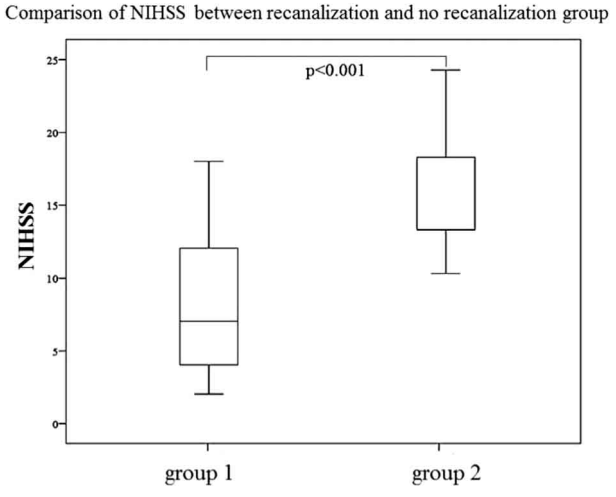


Fig. 4. Comparison of National Institute of Health stroke scale between the recanalization and no revascularization groups

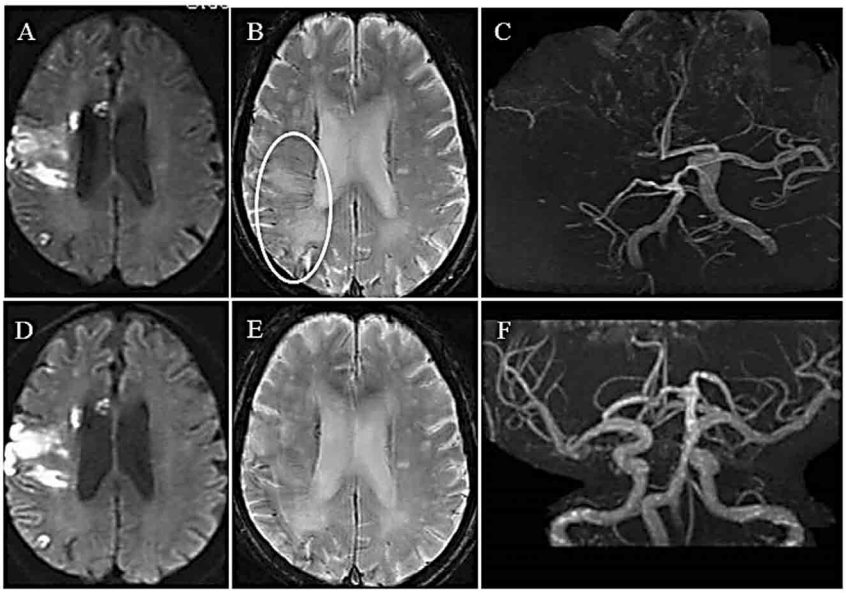


Fig. 5. Representative case from group 1
A 76-year-old man, had left hemiparesis and dysarthria as well as progressive symptoms under medical treatment due to right internal carotid artery stenosis. We performed carotid artery stenting (CAS) for the lesion. Hypointense signals in the territory of ischemia disappeared after CAS. IVS score was 3, and ASPECTS was 9 before treatment. After treatment, IVS score was 0, and ASPECTS was 9. The white circle shows IVS in B. A, B and C : diffusion-weighted imaging (DWI), T2*weighted imaging (T2*WI), and magnetic resonance angiography at the time of the worsening, C, D and E : DWI, T2*WI and MRA after CAS

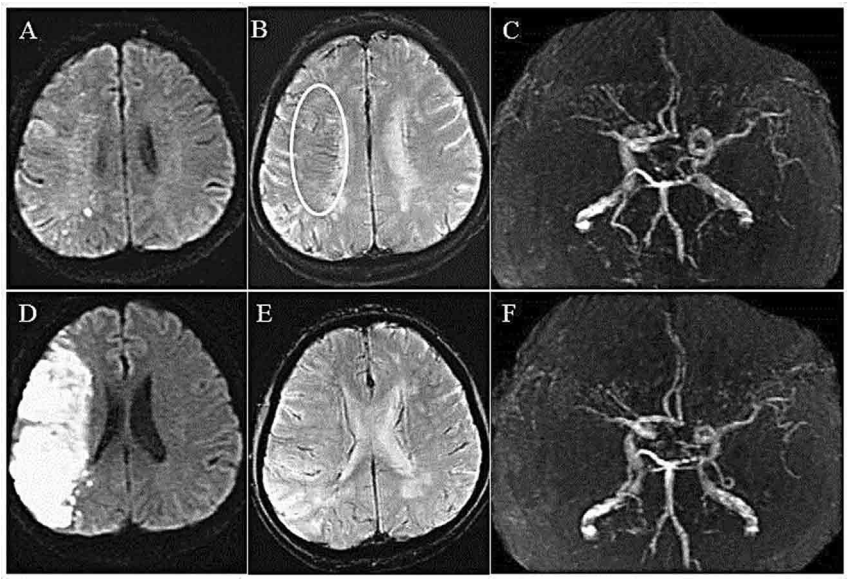


Fig. 6. Representative case of group 3
A 64-year-old man had left hemiparesis, dysarthria and hemispatial neglect. The administration od recombinant tissue plasminogen activator (rtPA) resulted in failed recanalization. The white circle shows IVS in B. The IVS disappeared in the territory of complete infarction on diffusion-weighted imaging (DWI, D). IVS score was 4, and ASPECTS was 10 before treatment. After treatment, IVS score was 0, and ASPECTS was 2. A, B and C : diffusion-weighted imaging (DWI), T2*weighted imaging (T2*WI), and magnetic resonance angiography at the time of the worsening, C, D and E : DWI, T2*WI and MRA shortly after rtPA administration

No patients in group 1 and 2 had severe complications such as hyperperfusion syndrome, procedural complications (distal embolization that presented symptoms or dissection, hematoma that needed treatment at puncture site (11-14) or symptomatic intracranial hemorrhage (15-18)).

DISCUSSIONS

This study showed that patients with major vessel occlusion or stenosis who have high-grade reperfusion flow after treatment were manifested decrement of IVS, whereas those patients who did not

recanalize showed no decrement of IVS. The decrement of IVS after treatment may be associated with improved hemodynamic compromised status. However, a natural course of IVS was not reported previously. In this study, a natural course of IVS may be shown as change of IVS in group 2. IVS also decreased in patients with low ASPECTS score caused by complete infarction. Our findings may suggest that the presence of IVS is associated with hypoperfusion and matched perfusion after ischemia may contribute to the disappearance of IVS. IVS would be useful for evaluating the extensive ischemia due to major vessel occlusion and may be correlated with the blood-oxygen-level-dependent (BOLD) effect due to increased deoxyhemoglobin (19-21). In the area where we can observe IVS, the deoxyhemoglobin level in veins is high and hypointense signals are detected on T2*WMRI (21). IVS may be a predictor of misery perfusion and imminent infarction (22).

IVS could also be reversible by recanalization ; Liu *et al.* (22) observed decreased numbers of hyperintense vessels (HV) on fluid attenuated inversion recovery (FLAIR) images after endovascular recanalization of symptomatic ICA occlusion. A postoperative decrease in HV can be considered as a marker for hemodynamic improvement. Hohenhaus *et al.* (23) reported on FLAIR vascular hyperintensities (FVH) in acute ICA and MCA infarcts, which indicates larger ischemic areas in the brain and can be a marker for mismatch and stroke severity. FVH and IVS might regress in the same way, after recanalization. FVH is an arterial sign and means arterial flow insufficiency (24). In contrast, IVS may be a venous sign, and IVS changes may represent change of cerebral oxygen metabolism associated with hypoperfusion, reperfusion after hypoperfusion or complete infarction after hypoperfusion (25, 26).

There are limitations in this study. We did not evaluate the perfusion images of the certain patients. Morita *et al.* (6) reported area with IVS appeared in hypoperfused area on flow-sensitive alternating inversion recovery images. An actual perfusion in the area with IVS was not examined to determine whether hypoperfusion improved after recanalization.

In conclusion, IVS may be a useful sign for detecting extensive ischemia and indicate reversibility. IVS can be a parameter of misery perfusion and an important factor to detect the patients who have an indication of treatment for recanalization. Reperfusion is useful for preventing further progression and to improve clinical symptoms of patients with acute ischemic stroke, who have IVS and high ASPECTS scores.

REFERENCES

1. Roob G, Lechner A, Schmidt R, Flooh E, Hartung HP, Fazekas F : Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke 31 : 2665-2669, 2000
2. Hermier M, Nighoghossian N, Derex L, Berthezene Y, Blanc-Lasserre K, Trouillas P, Froment JC : MRI of acute post-ischemic cerebral hemorrhage in stroke patients : Diagnosis with T2*-weighted gradient-echo sequences. Neuroradiology 43 : 809-815, 2001
3. Lesnik Oberstein SA, van den Boom R, van Buchem MA, van Houwelingen HC, Bakker E, Vollebregt E, Ferrari MD, Breuning MH, Haan J : Cerebral microbleeds in cadasil. Neurology 57 : 1066-1070, 2001
4. Kato H, Izumiyama M, Izumiyama K, Takahashi A, Itoyama Y : Silent cerebral microbleeds on T2*-weighted MRI : Correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke 33 : 1536-1540, 2002
5. Rovira A, Orellana P, Alvarez-Sabin J, Arenillas JF, Aymerich X, Grive E, Molina C, Rovira-Gols A : Hyperacute ischemic stroke : Middle cerebral artery susceptibility sign at echo-planar gradient-echo mr imaging. Radiology 232 : 466-473, 2004
6. Morita N, Harada M, Uno M, Matsubara S, Matsuda T, Nagahiro S, Nishitani H : Ischemic findings of T2*-weighted 3-tesla MRI in acute stroke patients. Cerebrovasc Dis 26 : 367-375, 2008
7. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D : Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke 34 : 109-137, 2003
8. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T : Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion : Japan alteplase clinical trial ii (J-ACT ii). Stroke 41 : 461-465, 2010
9. Meder JF, Chiras J, Roland J, Guinet P, Bracard

S, Bargy F : Venous territories of the brain. J Neuroradiology 21(2) : 118-133, 1994
10. Barber PA, Demchuk AM, Zhang J, Buchan AM, for the ASPECTS Study Group : The validity and reliability of a novel quantitative CT score in predicting outcome in hyperacute stroke prior to thrombolytic therapy. Lancet 355 : 1670-1674, 2000
11. Meyers PM, Higashida RT, Phatouros CC, Malek AM, Lempert TE, Dowd CF, Halbach VV : Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. Neurosurgery 47(2) : 335-343, 2000
12. McCabe DJ, Brown MM, Clifton A : Fatal cerebral reperfusion hemorrhage after carotid stenting. Stroke 30(11) : 2483-2486, 1999
13. Manninen HI, Räsänen HT, Vanninen RL, Vainio P, Hippeläinen M, Kosma VM : Stent placement versus percutaneous transluminal angioplasty of human carotid arteries in cadavers in situ : distal embolization and findings at intravascular US, MR imaging and histopathologic analysis. Radiology 212(2) : 483-492, 1999
14. Qureshi AI, Luft AR, Sharma M, Guterman LR, Hopkins LN : Prevention and treatment of thromboembolic and ischemic complications associated with endovascular procedures : Part II--Clinical aspects and recommendations. Neurosurgery 46(6) : 1360-1375, 2000
15. Wang X, Tsuji K, Lee SR, Ning M, Furie KL, Buchan AM, Lo EH : Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. Stroke 35 : 2726-2730, 2004
16. Ribo M, Montaner J, Molina CA, Arenillas JF, Santamarina E, Quintana M, Alvarez-Sabín J : Admission fibrinolytic profile is associated with symptomatic hemorrhagic transformation in stroke patients treated with tissue plasminogen activator. Stroke 35(9) : 2123-2127, 2004
17. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH : Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke : The European Cooperative Acute Stroke Study (ECASS). JAMA 274 : 1017-1025, 1995
18. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P : Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 352 : 1245-1251, 1998
19. Toronov V, Walker S, Gupta R, Choi JH, Gratton E, Hueber D, Webb A : The roles of changes in deoxyhemoglobin concentration and regional cerebral blood volume in the fMRI bold signal. Neuroimage 19 : 1521-1531, 2003
20. Geisler BS, Brandhoff F, Fiehler J, Saager C, Speck O, Rother J, Zeumer H, Kucinski T : Blood-oxygen-level-dependent MRI allows metabolic description of tissue at risk in acute stroke patients. Stroke 37 : 1778-1784, 2006
21. Greve JM : The BOLD effect. Methods Mol Biol 771 : 153-169, 2011
22. Schwarzbauer C, Heinke W : Investigating the dependence of BOLD contrast on oxidative metabolism. Magn Reson Med 41 : 537-543, 1999
23. Liu W, Yin Q, Yao L, Zhu S, Xu G, Zhang R, Ke K, Liu X : Decreased hyperintense vessels on FLAIR images after endovascular recanalization of symptomatic internal carotid artery occlusion. Eur J Radiol 81 : 1595-1600, 2012
24. Hohenhaus M, Schmidt WU, Brunecker P, Xu C, Hotter B, Rozanski M, Fiebach JB, Jungehulsing GJ : Flair vascular hyperintensities in acute ICA and MCA infarction : A marker for mismatch and stroke severity? Cerebrovasc Dis 34 : 63-69, 2012
25. Ziyeh S, Rick J, Reinhard M, Hetzel A, Mader I, Speck O : Blood oxygen level-dependent MRI of cerebral CO2 reactivity in severe carotid stenosis and occlusion. Stroke 36 : 751-756, 2005
26. Christen T, Bolar DS, Zaharchuk G : Imaging brain oxygenation with MRI using blood oxygenation approaches : Methods, validation, and clinical applications. Am J Neuroradiol 34 : 1113-1123, 2013