The rCBV Ratio Is a Predictive Factor for Developing Malignant Middle Cerebral Artery Infarction within 6 Hours of Symptom Onset

Hyo-Jin Bae, Eun-Hwan Jeong, Dae-Hyun Kim, and Jae-Kwan Cha
Busan-Ulsan Regional Cardio-Cerebral Vascular Center, Department of Neurology, Dong-A University Hospital, Busan, Korea

Background: Malignant middle cerebral artery (MCA) infarction is one of the leading cause of death for patients with acute MCA infarction. We investigated the predicting factors for developing malignant MCA infarction (MMI) using multi-parametric magnetic resonance imaging (MRI).

Methods: We included 159 MCA infarction patients who visited Dong-A University Stroke Center from January 2007 to December 2010 and were diagnosed MCA occlusion within 6 hours after symptom onset. All patients underwent brain MRI including diffusion and perfusion-weighted image. The definition of the malignant MCA infarction is as follows: 1) deterioration of neurological symptoms and consciousness with clinical signs of uncal herniation, and 2) at least two-thirds of the MCA territory with compression of ventricles or midline shifting. The neurological deterioration was observed for 7 days. The severity of neurological symptom and clinical outcome were assessed by using National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS).

Results: Among 159 patients, 49 patients (30.8%) developed MMI. In a multivariate analysis, a larger diffusion volume on diffusion-weighted image, a lower regional cerebral blood volume (rCBV) ratio on perfusion-weighted image, and a higher NIHSS score on admission were identified as the predictive factors of MMI. The cut-off values of diffusion volume, NIHSS on admission and rCBV ratio were 69 mL, 15 points and 0.78.

Conclusion: A large diffusion volume, a high NIHSS score and particularly a low rCBV ratio can predict a malignant course in MCA infarction within 6 hours of symptom onset in MCA occlusion. (Korean J Stroke 2012;14:128-135)

KEY WORDS: Malignant MCA infarction, rCBV ratio, MCA occlusion

Introduction

The middle cerebral artery (MCA) is the most frequent site of arterial occlusion among acute ischemic stroke. MCA occlusion is related to poor clinical outcome, such as a malignant MCA infarction (MMI). A number of patients with permanent proximal MCA occlusions have minor strokes or no symptoms. However, some patients with MCA occlusions, especially caused by an embolic source, have severe malignant strokes.

Early reperfusion by recanalization of MCA occlusion can salvage the hypo-perfused tissue and improve neurological outcomes. Recanalization is correlated with good clinical outcomes in most, but not all, reported cases. Recently, randomized controlled trials of decompressive craniectomy have demonstrated the clear benefit of early hemicraniectomy. These studies suggest that hemicraniectomy should be made before clinical deterioration occurs. The results of many studies have raised interest in the use of markers to identify patients who are at risk for developing MMI. However, in situations of 6 hours of symptom onset, determining which patients should undergo recanalization is not an easy decision for stroke clinicians.

Multiparametric magnetic resonance imaging (MRI) methods, including diffusion-weighted images (DWI) and perfusion-weighted images (PWI), are superior to ordinary CT, because they provide more varied and useful information about acute...
ischemic stroke that facilitates the detection of MMI.\(^{10}\)

We evaluated acute MCA infarction patients with MCA occlusions using brain MRI, including DWI and PWI.

Several recent studies have reported predictive factors for malignant MCA infarction.\(^{9,11-13}\) However, these studies have usually used only parameters such as CT\(^{11}\) or diffusion volume,\(^{12,13}\) moreover, they have not shown a relationship with recanalization. No previous studies have reported a threshold value of the rCBV ratio for predicting MMI. Therefore, we compared the demographics, clinical and imaging parameters between malignant and non-malignant groups to identify the predictive factors for developing MMI.

### Subjects and Methods

We included 258 patients who were diagnosed with an MCA infarction with MCA occlusion within 6 hours of symptom onset between January, 2007 and December, 2010 at the Dong-A University Hospital Stroke center.

The inclusion criteria were as follows: 1) acute hemispheric ischemic stroke involving the MCA territory, 2) brain MRI performed within 6 hours of symptom onset including DWI and time-of-flight (TOF)-MRA and PWI calculated by time-to-peak (TTP) maps, 3) occlusion of the MCA diagnosed by TOF-MRA and 4) a follow-up brain MRI including DWI and MRA to evaluate the state of vessel recanalization.\(^6\) The follow-up brain MRI was performed 24 hours after the previous scan. Exclusion criteria were as follows: 1) previous contralateral hemispheric infarction, 2) inability to perform a brain MRI and 3) severe underlying disease that influences mental deterioration, such as dementia or severe premorbid disability.

Seventeen patients were excluded due to previous contralat-
eral stroke, 36 patients were excluded because of incomplete MRI studies, especially PWI. Eighteen patients were excluded because they had a severe previous underlying disease. Twenty-eight patients were excluded because follow-up brain imaging was not performed (Figure 1).

The brain MRIs were retrospectively reviewed by a specialized neuroradiologist. All patients were admitted to the stroke care unit and were treated according to the international stroke guidelines.

The severity of the neurological deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS) on admission and Day 1 and 5. Clinical outcome was assessed using the modified Rankin Scale (mRS) at discharge and at 90 days. Stroke etiology was classified according to the TOAST classification. The local institutional review board approved this study. A MMI was defined as: 1) deterioration of neurological symptoms (more than 4 points of NIHSS during observation period) and consciousness with clinical signs of uncal herniation and 2) at least two-thirds of the MCA territory showing compression of the ventricles or midline shifting on follow-up FLAIR MRI (Figure 2, 3). The neurological deterioration was observed for 7 days.

MRI protocol

All patients underwent brain MRI (1.5T, General Electric Medical Systems, Milwaukee, Wisc., USA). MRI images included T1-weighted image, axial fluid-attenuated inversion recovery (FLAIR), TOF-MRA, DWI, PWI and a gradient-echo sequence to exclude intracerebral hemorrhage.

The ischemic lesion volume of DWI was determined by manually tracing the edge of the hyperintense signal in each frame of the DWI scan. The region of interest (ROI) was multiplied by the section thickness plus the intersection gap and then summed to obtain the lesion volume.

PWI was performed using a contrast bolus injection combined with rapid Echo-planar imaging (EPI) based image acquisition. A large-bore, 18-gauge intravenous cannula was inserted into the artery, and a 0.02 mmol/kg bolus of gadolinium diethylene-triamine penta-acetic acid was administered over 4-5 seconds with an MRI-compatible power injector. After processing for reconstruction, the PWI data were transferred to a workstation (ADW 4.2; GE Healthcare, Milwaukee, Wisc., USA). The time-intensity curve for the dynamic image was converted into a time-concentration curve using the Functool program (version 4.2;
GE Healthcare, Milwaukee).

We analyzed the PWI results to obtain maps of the TTP and rCBV. A TTP map was generated by calculating the difference of the arrival time of the contrast material and the timing of the maximum contrast agent concentration following its injection. After eliminating the contrast agent recirculation by gamma-variate curve fitting, the rCBV was computed by numerical integration of the curve. TTP lesion volumes were determined by manually tracing the area of the prolonged TTP, which was considered to reflect a hemodynamically disturbed area. The TTP delay was calculated as the TTP in the occlusive hemisphere subtracted from the TTP in the contralateral hemisphere. A TTP delay of more than 4s was defined as the threshold for identifying the ischemic penumbra in the TTP maps.

The same ROI used in the TTP map was applied to the rCBV map. We evaluated the rCBV ratio by comparing the blood volume within the ischemic lesion with the blood volume of a contralateral region (the ipsilateral value divided by the contralateral value). The diffusion-perfusion mismatch (DPM) was defined as the volume of the PWI-based TTP map with a 4-s delay in which the lower threshold exceeded the DWI by at least 20%.

Recanalization was defined as an improvement of more than 2 points according to the thrombolysis in myocardial infarction (TIMI) grade. Symptomatic intracerebral hemorrhage (sICH) was defined as the evidence of hemorrhage on follow-up MRI scan (axial FLAIR, TOF-MRA, DWI) according to the ECASS III.

Statistical Analysis

We compared baseline demographics and clinical characteristics, baseline MRI findings, treatment information and outcomes using the student’s t-test or Fisher’s exact test. P-value less than 0.05 was considered statistically significant between MMI and non-MMI group. Multivariate analysis was performed with logistic regression using a backward elimination method, and the probability for removal was set at 0.10. The odds ratio (OR) for the comparison of the two groups was calculated at a 95% confidence interval (CI).

Receiver operating characteristic (ROC) curves analysis was performed to determine the optimal thresholds for DWI volume, NIHSS upon admission and rCBV ratio for the prediction of MMI based on sensitivity and specificity. The cut-off thresholds were chosen to maximize sensitivity and specificity equally using an event-specific classification table.

All statistical analyses were performed using SAS 9.1 (SAS Inc., Cary, NC, USA). We used the STATA/SE package (version 11.1, Stata Corp., College Station, TX, USA) to compare the statistical significance of the ROC curves.

Results

Among the 159 total patients, 49 (30.8%) patients developed MMI, and 110 (69.2%) patients did not (non-MMI). Table 1 summarizes the baseline demographic and clinical features of the two groups. The mean age of the MMI group was greater than that of the non-MMI group (67.73 years vs. 62.85 years). The incidence of MCA infarction with additional lesions in the ACA or PCA territory was similar in both groups (2.0% vs. 1.8%). NIHSS on admission and days 1 and 5 were higher in the MMI group than in the non-MMI group (P<0.001). Hypertension (HTN) was more frequent in the MMI group than in the non-MMI group (57.1% vs. 40.0%, respectively, P=0.045). TOAST classification did not differ between two groups. The serum markers, i.e., glucose, total cholesterol and triglyceride value, did not differ in the two groups.

Table 2 summarizes the baseline MRI findings of the two groups. The mean time from symptom onset to imaging was similar for the two groups (166.12 min vs. 171.03 min). Ipsilateral internal carotid artery (ICA) occlusion was more frequent in the MMI patients (71.4% vs. 40.9% in the non-MMI patients, P<0.001). The mean ischemic lesion volume of the DWI was larger (75.36 mL vs. 19.83 mL, respectively, P<0.001) and the rCBV ratio was significantly lower (0.62 vs. 0.88, respectively, P<0.001) in the MMI patients than in the non-MMI patients. However, the presence of TTP based DPM on MRI was more frequent in the non-MMI group (65.2% vs. 84.1%, P=0.009).

The treatment of thrombolysis was not statistically different between the two groups (59.2% vs. 66.4%, Table 3). Additionally, the symptomatic ICH after thrombolysis was not statistically different in the non-MMI group when compared with the MMI group (12.7% vs. 22.4 %, respectively, Table 1). The recanalization rates, including spontaneous recanalization and thrombolysis, were not statistically different in the two group (32.6% vs. 46.4%). MMI group had worse outcome (5 or 6 of mRS) on 90 days compared to non-MMI group (66.6% vs. 17.6%).

In a multivariate analysis, three parameters were identified as
rCBV Ratio as a Predictive Factor for Malignant Middle Cerebral Artery

**TABLE 1.** Baseline clinical and laboratory findings

|                      | MMI [n=49]                     | Non-MMI [n=110]                   | P-value  |
|----------------------|-------------------------------|-----------------------------------|----------|
| Age, yr (SD)         | 67.73±10.06                   | 62.85±11.98                       | 0.014    |
| Female, n (%)        | 24 (40.7%)                    | 35 (31.8%)                        | 0.039    |
| Left MCA infarction, n (%) | 23 (46.9%)                      | 52 (47.3%)                       | n.s.    |
| MCA+ ACA or PCA infarction, n (%) | 1 (2.0%)                        | 2 (1.8%)                         | n.s.    |
| Median NIHSS on admission | 16 (8-27)                       | 12 (1-20)                         | <0.001  |
| Median NIHSS on day 1 | 18 (8-27)                      | 10 (1-20)                         | <0.001  |
| Median NIHSS on day 5 | 18 (8-44)                      | 8 (1-21)                          | <0.001  |
| Hypertension         | 28 (57.1%)                    | 44 (40.0%)                        | 0.045    |
| DM                   | 9 (18.4%)                     | 19 (17.3%)                        | 0.867    |
| Myocardial infarct   | 3 (6.1%)                      | 3 (2.7%)                          | 0.373    |
| Atrial fibrillation  | 22 (44.9%)                    | 41 (37.3%)                        | 0.364    |
| Smoking              | 10 (20.4%)                    | 34 (30.9%)                        | 0.172    |
| TOAST classification |                              |                                   | 0.565    |
| Large artery atherosclerosis | 23 (46.9%)                   | 61 (55.5%)                       |         |
| Cardioembolism       | 22 (44.9%)                    | 43 (39.1%)                        |         |
| Small vessel disease | 0                             | 0                                 |         |
| Other determined     | 0                             | 0                                 |         |
| Undetermined         | 4 (8.2%)                      | 6 (5.4%)                          |         |
| Serum glucose (mg, %)| 87.83±109.98                  | 85.70±106.63                      | 0.911    |
| Thrombolysis         | 29 (59.2%)                    | 73 (66.4%)                        | n.s.    |
| Only IV tPA, n (%)   | 11 (22.4%)                    | 26 (23.6%)                        | 0.870    |
| Only IA thrombolysis, n (%) | 8 (16.3%)                      | 17 (15.5%)                       | 0.889    |
| IV tPA + IA thrombolysis | 10 (20.4%)                    | 29 (23.6%)                       | 0.420    |
| Recanalization, n (%)| 16 (32.6%)                    | 51 (46.4%)                        | 0.166    |
| Spontaneous          | 6 (12.2%)                     | 9 (8.2%)                          |         |
| Thrombolysis         | 10 (20.4%)                    | 42 (38.2%)                        |         |
| Hemicraniectomy      | 6 (12.2%)                     | 0 (0%)                            | <0.001  |

MMI: malignant MCA infarction, MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, NIHSS: national Institutes of Health Stroke Scale, DM: diabetes mellitus, LDL: low-density lipoprotein.

**TABLE 2.** Baseline MRI findings

|                      | MMI [n=49]                     | Non-MMI [n=110]                   | P-value  |
|----------------------|-------------------------------|-----------------------------------|----------|
| Mean time to image (min) | 166.12±71.12                  | 171.03±81.25                     | n.s.    |
| Vessel occlusion, n (%) | 14 (28.6%)                    | 65 (59.1%)                       | <0.001  |
| Isolated MCA occlusion | 14 (28.6%)                    | 65 (59.1%)                       | n.s.    |
| MCA + ICA occlusion   | 35 (71.4%)                    | 45 (40.9%)                       | n.s.    |
| Mean diffusion volume (mL)| 75.36±52.75                   | 19.83±28.05                      | <0.001  |
| rCBV ratio            | 0.62±0.26                     | 0.88±0.23                        | <0.001  |
| DPM, n (%)            | 30 (65.2%)                    | 90 (84.1%)                       | 0.009    |

MMI: malignant MCA infarction, MCA: middle cerebral artery, ICA: internal cerebral artery, rCBV: regional cerebral blood volume, DPM: diffusion-perfusion mismatch.

Predictive factors for MMI: NIHSS on admission (OR: 1.23, CI: [0.70-0.86], P<0.001), diffusion volume of ischemic lesion on DWI (OR: 1.02, CI: [0.78-0.92], P<0.001), and rCBV ratio on perfusion image (OR: 0.97, CI: [0.70-0.86], P=0.012, Table 4).

Figure 4 shows the ROC curves when MMI prediction was performed using these three parameters. A DWI lesion volume of 69 mL (k=0.570, P<0.001) was identified as the optimal threshold, with a sensitivity of 59% and a specificity of 94%. The cutoff threshold for the NIHSS score on admission was 15 points (k=0.381, P<0.001), with a sensitivity of 69% and a specific of
Hyo-Jin Bae, et al.

TABLE 3. Treatment information and outcomes

|                              | MMI (n=49) | Non-MMI (n=110) | P-value |
|------------------------------|------------|-----------------|---------|
| Thrombolysis                 | 29 (59.2%) | 73 (66.4%)      | n.s.    |
| Only IV tPA, n (%)           | 11 (22.4%) | 26 (23.6%)      | 0.870   |
| Only IA thrombolysis, n (%)  | 8 (16.3%)  | 17 (15.5%)      | 0.889   |
| IV tPA + IA thrombolysis     | 10 (20.4%) | 29 (23.6%)      | 0.420   |
| Hemicraniectomy              | 6 (12.2%)  | 0 (0%)          | <0.001  |
| sICH, n (%)                  | 11 (22.4%) | 14 (12.7%)      | n.s.    |
| Recanalization, n (%)        | 16 (32.6%) | 51 (46.4%)      | n.s.    |
| Spontaneous                  | 6 (12.2%)  | 9 (8.2%)        |         |
| Thrombolysis                 | 10 (20.4%) | 42 (38.2%)      |         |
| mRS-90, n (%)                | 5 (10.2%)  | 53 (48.2%)      | <0.001  |
| mRS 0-2                      |            |                 |         |
| mRS 3-6                      | 44 (89.8)  | 57 (51.8)       |         |

MNI, malignant MCA infarction; sICH, symptomatic intracerebral hemorrhage; mRS, modified Rankin Score.

TABLE 4. Prediction of malignant MCA infarction: Multivariate logistic regression analysis

|                              | OR estimate | 95% CI         | P-value |
|------------------------------|-------------|----------------|---------|
| ICA + MCA occlusion          | 1.38        | 0.42-4.54      | 0.298   |
| NIHSS on admission           | 1.23        | 1.08-1.40      | <0.001  |
| Diffusion volume (per mL)    | 1.02        | 1.01-1.04      | <0.001  |
| rCBV ratio (per percentage)  | 0.97        | 0.95-0.99      | 0.012   |

ICA, internal cerebral artery; MCA, middle cerebral artery; rCBV, regional cerebral blood volume.

FIGURE 4. Receiver operating characteristic (ROC) curves for the prediction of malignant MCA infarction (MMI) from diffusion-weighted volume, NIHSS on admission, and rCBV ratio. Model prediction was performed using diffusion volume, NIHSS on admission and rCBV ratio as parameters.

73%, and the threshold for the rCBV ratio was 0.78 (k=0.415, P<0.001), with a sensitivity of 76% and a specificity of 71%. The model prediction including all of the parameters was superior for predicting the MMI than that with any of the individual parameters. Comparing the separate parameters, the DWI ischemic lesion volume is better than the other parameters for predicting MMI. However, these differences are not statistically significant.

Discussion

In this study, we determined that an ischemic lesion in a DWI with a large diffusion volume (greater than 69 mL), and rCBV ratio of less than 0.78 in a PWI and NIHSS score over 15 points on admission are predictive factors for MMI. MCA with ipsilateral ICA occlusion was frequent in MMI patients in a univariate analysis; however, this association was not statistically significant in a multivariate analysis.

Based on our results, an ischemic lesion on DWI with diffusion volume >69 mL was the optimal threshold for the prediction of MMI development, with a 59% sensitivity and a 94% specificity. A previous study reported DWI lesion volumes of >66 mL and >79 mL as optimal thresholds for the identification of MMI when optimizing sensitivity and specificity, respectively. In a retrospective study by Yoo et al. among patients undergoing intra-arterial therapy, a baseline DWI lesion volume >70 mL was identified as the threshold for defining the futile group. For clinical purposes, predictive values of DWI ischemic lesion...
volume are helpful in guiding treatment decision, particularly when considering recanalization therapy or the initiation of lifesaving treatments such as craniectomy or hypothermia.

We determined that the rCBV ratio was significantly lower in the MMI group than in the non-MMI group. The threshold rCBV ratio for developing MMI was 0.78, with a sensitivity of 76% and a specificity of 71%. Various different parameters for PWI have been used in clinical settings; among them, time-based parameters such as mean transit time (MTT) or TTP are considered the most reliable methods in ischemic stroke. However, these parameters share a critical weak point in that they are easily contaminated by a severe arterial occlusive state, leading to the overestimation of the benign oligemia into the ischemic penumbra in acute ischemic stroke. Moreover, these parameters do not indicate the status of the collateral flow after ischemic stroke. Previous studies have shown that the rCBV map in perfusion MRI reveals the extent of collateral circulation and is a good predictor of tissue fate and clinical outcomes. However, the calculation of rCBV is not as straightforward as the calculations of the TTP or MTT maps in PWI. It is much easier to estimate the rCBV ratio than to evaluate the rCBV directly, because the rCBV ratio is automatically calculated within the ROI outlined by the TTP method upon perfusion imaging. Therefore, determining the rCBV ratio in PWI provides an easier technique for estimating the extent of collateral flow in an emergency situation.

Several studies have found that the presence of DPM on the MRI predicts subsequent ischemic lesion expansion. However, in our previous studies, its expansion was not related with the presence of DPM, but with extent of rCBV ratio on perfusion MRI. In this study, DPM was infrequent in the malignant group compared with the non-malignant group. One of the most important problems with identifying DPM via MRI is that TTP maps derived from PWI overestimate its presence during the vessel occlusion. Therefore, there have been several attempts to improve the ability to detect the real portion of the ischemic penumbra using the collateral flow. These facts demonstrate that the evaluation of collateral flow using rCBV may be an essential step in weighing the benefits of recanalization therapy.

In our study, the percentage of patients with thrombolysis did not differ in the two groups. Additionally, in a univariate analysis, the recanalization rates were similar in both groups. In a multivariate analysis, thrombolysis and the presence of symptomatic ICH were not predictive factors for MMI. The presence of recanalization was not a marker of a good clinical outcome in the MMI group in our study. The benefits of recanalization in acute stroke patients are established; however, early reperfusion can cause additional injury to the ischemic arterial wall and microvasculature, leading to cerebral edema. Patients with large volumes of severely ischemic tissue are associated with poor outcomes following reperfusion. Thus, the exclusion of patients with predictive factors for MMI is important to achieve the beneficial effects of recanalization in acute ischemic stroke. In some cases of main artery occlusion, collateral flow may potentially be more important than recanalization.

There are some limitations to our study. First, MCA occlusion and ICA occlusion have different etiologies. Bang et al. reported different clinical features and neuroradiological characteristics in ICA and MCA occlusive diseases. Therefore, we must evaluate the relationship between only pure MCA occlusive disease and MMI groups in the future. Second, visualization by TOF-MRA has a tendency to overestimate the state of vessel occlusion. Therefore, we need more exact information based on 4-vessel angiography. Third, although we excluded patients who had a history of contralateral stroke, there was some selection bias in the inclusions of patients with mild or moderate stenosis of the contralateral vessels, and there may be an effect due to perfusion defects in these stenotic vessels. Finally, this study involved a single center and a small sample size, so the validity of our conclusions should not be confirmed. A multicenter study with a larger sample will be required to prove our results.

**Conflicts of Interest**

The authors have no financial conflicts of interest.

**REFERENCES**

1. del Zoppo GJ, Pooe K, Pessin MS, Wolpert SM, Furlan AJ, Furlan A, et al. Recombination tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78-86.
2. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial. *JAMA* 1999;282:2003-2011.
3. Tanaka M, Shimosegawa E, Kajimoto K, Kajimoto K, Kimura Y, Kato H, Oku N, et al. Chronic middle cerebral artery occlusion: a hemodynamic and metabolic study with positron-emission tomography. *AJNR* 2008;29:1841-1846.
4. Olsen TS, Lassen NA. A dynamic concept of middle cerebral artery occlusion and cerebral infarction in the acute state based interpreting severe hyperemia as a sign of embolic migration. *Stroke* 1984;15:458-468.
5. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. DEFUSE investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol 2006;60:508-517.

6. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38:967-973.

7. Vahedi K, Hofmeijer J, Juttler E, Vicaut E, George B, Algra A, et al. DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials. Lancet Neurol 2007;6:215-222.

8. Thomalla G, Hartmann F, Juttler E, Singer OC, Lehnhardt FG, Köhrmann M, et al. Clinical Trial Net of the German Competence Network Stroke. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. Ann Neurol 2010;68:435-445.

9. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369:293-298.

10. Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology 1999;210:519-527.

11. Bivard A, McElduff P, Spratt N, Levi C, Parsons M. Defining the extent of irreversible brain ischemia using perfusion computed tomography. Cerebrovasc Dis 2011;31:238-245.

12. Oppenheim C, Samson Y, Manaï R, Lalam T, Vandamme X, Crozier S, et al. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. Stroke 2000;31:2175-2181.

13. Thomalla GJ, Kucinski T, Schoder V, Feilner J, Knah R, Zeumer H, et al. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. Stroke 2003;34:1892-1899.

14. Adams HP Jr, Bendzien BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

15. Lee SY, Cha JK, Kang MJ. Regional cerebral blood volume ratio on perfusion MRI on the growth of infarct size in acute ischemic stroke. Eur Neurol 2009;62:281-286.

16. Park HI, Cha JK, Kang MJ, Kim DH, Yoo NT, Choi JH, et al. Reduced rCBV ratio in perfusion-weighted MR images predicts poor outcome after thrombolysis in acute ischemic stroke. Eur Neurol 2011;65:257-263.

17. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. DIAS Study Group. 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.

18. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.

19. Yoo AJ, Verduzco LA, Schaefer PW, Hirsch JA, Rabinov JD, Gonzalez RG. MRI-based selection for intra-arterial stroke therapy: value of pre-treatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke 2009;40:2046-2054.

20. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. Ann Neurol 2000;47:462-469.

21. Yamada K, Wöllstein S, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, et al. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy. Stroke 2002;33:87-94.

22. Neumann-Haefelin T, Wittsack HJ, Fink GR, Wenserski F, Li TQ, Seitz RJ, et al. Diffusion- and perfusion-weighted MRI: influence of severe carotid stenosis on the DWI/PWI mismatch in acute stroke. Stroke 2003;34:1311-1317.

23. Liu Y, Karonen JO, Vanninen RL, Nuutila J, Koskela A, Soimakallio S, et al. Acute ischemic stroke: predictive value of 2D phase-contrast MR angiography—serial study with combined diffusion and perfusion MR imaging. Radiology 2004;231:517-527.

24. Bang YO, Saver JL, Back BH, Alger JR, Starkman S, Ovbiagele B, et al. UCLA Collateral Investigators. Impact of collateral flow on tissue fate in acute ischemic stroke. J Neurol Neurosurg Psychiatry 2008;79:625-629.

25. Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M, et al. Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI. Stroke 1999;30:2043-2052.

26. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. Ann Neurol 2006;60:508-517.

27. Puetz V, Dzialowski I, Hill MD, Steffenhagen N, Coutts SB, O’Reilly C, et al. Malignant profile detected by CT angiographic information predicts poor prognosis despite thrombolysis within three hours from symptom onset. Cerebrovasc Dis 2010;29:584-591.

28. Oh SH, Lee PH, Joo SY, Bang OY, Joo JS, Huh K. Comparison of clinical and neuroradiological characteristics between internal carotid artery and middle cerebral artery occlusive diseases. J Korean Neurol Assoc 2003;21:461-467.

29. Choi JW, Kim IK, Choi BS, Lim HK, Kim SJ, Kim JS, et al. Angiographic pattern of symptomatic severe M1 stenosis: comparison with presenting symptoms, infarct patterns, perfusion status, and outcome after recanalization. Cerebrovasc Dis 2010;29:297-303.