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Perfusion-diffusion Mismatch Predicts Early Neurological Deterioration in Anterior Circulation Infarction without Thrombolysis

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Abstract: Perfusion-diffusion mismatch in magnetic resonance imaging (MRI) represents the non-core hypoperfused area in acute ischemic stroke. The mismatch has been used to predict clinical response after thrombolysis in acute ischemic stroke, but its role for predicting early neurological deterioration (END) in acute ischemic stroke without thrombolysis has not been clarified yet. In this study, we prospectively recruited 54 patients with acute non-lacunar ischemic stroke in anterior circulation without thrombolysis. All patients received the first perfusion MRI within 24 hours from stroke onset. Target mismatch profile was defined as a perfusion-diffusion mismatch ratio ≥ 1.2. END was defined as an increase of ≥ 4 points in the National Institute of Health Stroke Scale (NIHSS) score within 72 hours. There were 13 (24.1%) patients developing END, which was associated with larger infarct growth ($p = 0.002$), worse modified Rankin Scale ($p = 0.001$) and higher mortality rate at 3 months ($p = 0.025$). Target mismatch profiles measured by $T_{max} \geq 4$, 5 and 6 seconds were independent predictors for END after correcting initial NIHSS score. Among the 3 T_{max} thresholds, target mismatch measured by $T_{max} \geq 6$ seconds had the highest odd's ratio in predicting END ($p < 0.01$, odd's ratio = 17), with an 80% sensitivity and a 79.5% specificity. In conclusion, perfusion-diffusion mismatch could identify the patients at high risk of early clinical worsening in acute ischemic stroke without thrombolysis.

Keywords: Early neurological deterioration, acute ischemic stroke, perfusion-diffusion mismatch.

INTRODUCTION

Up to one-third of all ischemic stroke patients may suffer from early neurological deterioration (END), which often leads to greater mortality and functional disability [1]. Several reversible or irreversible mechanisms are proposed to cause END, such as recurrent stroke, seizure, brain edema, hemorrhagic transformation and infectious or metabolic complications [2]. A substantial proportion of END is referred to as "progressive stroke" when infarct area expands in the same vascular territory [2]. Although specific managements can be applied for some causes of END, there is no effective treatment for "progressive stroke" because infarct growth is often irreversible [2, 3]. Therefore, developing a guide to predict which patients are at risk for END and applying preventive strategies are important issues in clinical practice.

Perfusion abnormalities are likely to play a crucial role in the mechanisms of "progressive stroke" [4]. Ischemic stroke is a dynamic process involving varying degrees of early ischemic injury due to the local cerebral blood flow impairment [5]. Ischemic region with very low cerebral blood flow (<2~10 mL/100 g/min) rapidly become irreversibly damaged and is referred to as the infarct core [5]. In the surrounding region with less severely impaired cerebral blood flow, the brain tissue that is functionally impaired but can be salvaged if the blood flow is restored is defined as the penumbra, and the brain tissue that is ischemic but still functional is defined as the oligemia [4-6]. The combination of penumbra and oligemia is referred to as "non-core hypoperfused area" [6]. Theoretically, salvage of the penumbra may contribute to clinical improvement [5, 7], and progression of the oligemic tissue to a non-functional state and ultimately to infarction may contribute to clinical deterioration [4, 5]. Based on this theory, the ischemic stroke patients who have larger non-core hypoperfused area are more likely to benefit from reper-

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fusion, while they are also prone to deterioration if reperfusion does not happen.

In magnetic resonance imaging (MRI), diffusion weighted imaging (DWI) can detect the infarct core and perfusion-weighted imaging (PWI) can detect the hypo-perfused area in the hyper-acute stage of ischemic stroke [8]. The mismatch between PWI and DWI represents the non-core hypoperfused area containing both the penumbra and the oligemia [8]. The DEFUSE and DEFUSE-2 studies had found the ischemic stroke patients with PWI-DWI mismatch had more favorable clinical response after reperfusion by intravenous thrombolysis or endovascular treatment [9, 10]. By the theory mentioned above, the mismatch may also have the capacity to predict the ischemic stroke patients who are at higher risk for END in the absence of reperfusion. Some studies had found that PWI-DWI mismatch was associated with infarct growth [11, 12], but few studies had explored the linkage between mismatch and END. Sener et al. had found that larger mismatch volume was associated with unexplained END occurring after thrombolysis therapy [13], but the association between the mismatch and the END in natural course has not been examined yet.

In this prospective, observational study, we aim to investigate whether perfusion-diffusion mismatch can predict END occurred within 72 hours after acute ischemic stroke without thrombolysis.

METHOD

Study Population and Clinical Assessment

This prospective study was conducted from December 2010 to November 2013. Patients were recruited if they were 18 years or older, had a clinical diagnosis of ischemic stroke, and could receive MRI examination within 24 hours after the stroke onset. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. Exclusion criteria of the study were as follows: (1) patients with contraindications to MRI study or gadolinium injection; (2) DWI demonstrated no acute ischemic stroke; (3) acute lacunar ischemic stroke, which was defined as a single DWI lesion less than 20mm in diameter in the territories of penetrating arteries; (4) acute ischemic stroke in the brainstem or cerebellum; (5) patients who received intravenous or intra-arterial thrombolysis for the index stroke; (6) premorbid modified Rankin Scale (mRS) score of 1 or higher.

Neurological deficits were evaluated with the National Institute of Health Stroke Scale (NIHSS) on admission and after 24, 48 and 72 hours by the same neurologist or study nurse (YC Kuo), who was blinded to the patients' MRI data. Age, sex, cigarette smoking, and medical history of hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, prior coronary artery disease and prior cerebrovascular disease were recorded. Blood sugar and systolic and diastolic blood pressure values were determined when arriving hospital. Good supportive care and attention to temperature, oxygenation, hydration, blood pressure and sugar control, positioning, and bowel and bladder care were done for all patients according to the guidelines [14].

Clinical outcome as mRS and mortality at 3 months was evaluated by a study nurse (YC Kuo), who was blinded to the patients' MRI data. Good outcome was defined as a mRS score of 2 or less, and favorable outcome was defined as a mRS score of 0 or 1.

The study was performed under a protocol approved by the Institutional Review Board of Chang Gung Memorial Hospital, and all examinations were performed after obtaining written informed consent from the patients or appropriate family members.

Definition of END

END was defined as an increase in the NIHSS score of 4 points or more during the first 72 hours after stroke onset [1]. Any patient who developed END had an urgent CT and/or MRI scan and a detailed laboratory survey. END was excluded if it was associated with hemorrhagic transformation, new ischemic strokes in different vascular territories, seizure or medical complications, such as pneumonia or anemia.

MRI Protocol and Postprocessing

All data were collected using a 3 Tesla Siemens Verio MRI system (Siemens Medical System, Erlangen, Germany) using a 16 channel head coil. The protocol for first MRI scan included axial T1- and T2-weighted images, axial DWI, MR angiography, and dynamic susceptibility contrast perfusion imaging; the protocol for follow-up MRI scan included axial T1- and T2-weighted images, axial DWI, MR angiography and fluid-attenuated inversion recovery (FLAIR) imaging. The imaging above were acquired as described previously [15].

Perfusion Mismatch Analyzer (Ver.3.4.0.6, ASIST, Japan; http://asist.umin.jp/index-e.htm) was used to generate a T_{max} (time to maximum of the residue function) map and calculate the PWI volume for each patient using standard singular value decomposition. Automatic arterial input function was used automatically but was added or deleted if its quality was not satisfactory. The volume of perfusion defect measured by $T_{max} \geq 4$, 5 and 6 seconds was estimated. The volume of infarct core was measured by apparent diffusion coefficient imaging in the first MRI, and the final infarct size was measured by FLAIR imaging in the follow-up MRI. All the imaging data were evaluated by an experienced stroke neurologist (Y.C.H.) and a neuroradiologist (Y.H.T.), both blinded to the clinical information.

Definition of PWI-DWI Mismatch and Infarct Growth

PWI-DWI mismatch profiles were determined according to the following definitions from DEFUSE trial (10). The "Target Mismatch profile" was defined as a perfusion-diffusion mismatch ratio (PWI lesion volume / DWI lesion volume) $\geq$ 1.2 with the DWI lesion less than 100ml. The "Malignant profile" was defined as a DWI lesion larger than 100ml. The "No Mismatch" profile was defined as a perfusion-diffusion mismatch ratio $\leq$ 1.2 with a DWI lesion less than 100 ml. The infarct growth was defined as final infarct size minus baseline infarct core volume. MRI data of the representative patients of each mismatch profile are shown in Fig. (**1**).

Statistical Analysis

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) statistical software (ver-

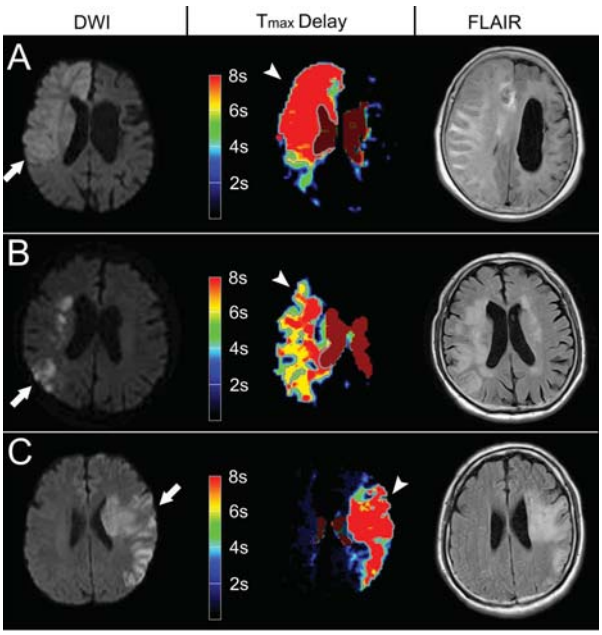

Fig. (1). Perfusion-diffusion mismatch profiles of the representative patients.

(**A**) The DWI at 3.2 hours after stroke onset showed an acute large infarct in the right internal carotid artery territory (148.0ml, arrow), indicating a malignant profile. The follow-up FLAIR imaging showed progressed infarct and brain swelling. (**B**) The DWI at 8.6 hours after stroke onset showed an infarct in the right middle cerebral artery (MCA) territory (18.7ml, arrow) with larger perfusion defect ($T_{max} \geq 6$ seconds: 97.9 ml; arrowhead), indicating a target mismatch profile. The follow-up FLAIR imaging showed infarct growth (58.2 ml). (**C**) The DWI at 5.4 hours after stroke onset showed an infarct in the left MCA territory (73.2ml, arrow) with similar perfusion defect in the T_{max} map ($T_{max} \geq 6$ seconds: 67.1ml; arrowhead), indicating a no mismatch profile. There was no infarction growth in the follow-up FLAIR imaging (70.3 ml).

sion 18, Chicago, IL, USA). The differences between the two groups were analyzed with the Mann-Whitney U test or Student t-test after testing for normality. Categorical data were analyzed by Fisher's exact test or Pearson's Chi Square test, as appropriate. Univariate logistic regression was used to evaluate the association between mismatch profiles and END. A multivariate logistic regression model was constructed adjusting for baseline variables when a *p*-value <0.1 was found in the univariate analysis. A receiver operating characteristic (ROC) curves were used to calculate the sensitivity and specificity for prediction of END by the different T_{max} thresholds, while the Youden index, defined as the maximum of sensitivity + specificity -1, was used to assess the most optimal T_{max} /DWI ratio. All *p* values were two-tailed and a *p* value < 0.05 was considered statistically significant.

RESULTS

During the study period, a total of one hundred and sixty-three patients with suspected stroke within 24 hours from symptom onset were enrolled. Twenty-five of them could not finish the MRI scan and 9 patients finished MRI scan beyond 24 hours after stroke onset. In the remaining 129 patients, 75 patients were excluded: 17 because of no acute ischemic stroke or transient ischemic attack, 16 because of acute infarction in the brainstem or cerebellum, and 42 because of lacunar infarctions. Finally, 54 patients fulfilled all criteria to enter this study.

Table 1. Baseline characteristics, imaging findings and outcomes between the patients with and without END.

	END	No END	*p*
Number	**13**	**41**	
Age (year)	72.1±11.9	71.2±14.6	0.835
Sex (F/M)	4/9	22/19	0.207
Atrial fibrillation	2 (15.4%)	12 (29.3%)	0.475
Diabetes mellitus	4 (30.8%)	10 (24.4%)	0.725
Hypertension	8 (61.5%)	27 (65.9%)	0.776
Hyperlipidemia	2 (15.4%)	12 (29.3%)	0.475
Coronary artery disease	1 (7.7%)	2 (4.9%)	1.000
Old stroke	3 (23.1%)	13 (31.7%)	0.732
Smoking	4 (30.8%)	8 (19.5%)	0.453
Systolic blood pressure (mmHg)	181.5±40.6	172.5±41.0	0.506
Diastolic blood pressure (mmHg)	93.9±24.4	98.0±19.5	0.551
Sugar (mg/dL)	127.6±43.4	147.7±77.0	0.472
Onset-MRI duration (hour)	11.0±5.0	12.0±6.6	0.642
Core infarct volume (ml)	75.7±133.4	16.9±32.4	0.103
Partial or complete vessel occlusion†	11 (84.6%)	27 (65.9%)	0.301
T_{max} ≥4s volume (ml)	125.8±124.7	36.4±66.8	0.020*
T_{max} ≥5s volume (ml)	114.4±124.2	26.7±53.4	0.007*
T_{max} ≥6s volume (ml)	99.3±123.4	21.6±48.3	0.004*
Final infarct volume (ml)	120.7±144.6	26.5±58.5	0.001*
Infarct growth (ml)	39.8±41.3	11.8±32.7	0.002*
NIHSS baseline	11 (6-19.5)	6 (3-15)	0.050
NIHSS on 3rd day	15 (11-27)	4 (2-14)	<0.001*
mRS at 3-months	5 (3.5-6)	2 (1-4)	<0.001*
Favorable outcome at 3-months	0 (0%)	17 (41.5%)	0.005*
Good outcome at 3-months	1 (7.7%)	22 (53.7%)	0.004*
Mortality at 3-months	4 (30.8%)	2 (4.9%)	0.025*

All data was expressed as mean ± standard deviation, number (percentage) or median (interquartile range). †Complete occlusion or >50% stenosis of middle cerebral artery or internal carotid artery on magnetic resonance angiography attributing to acute infarct on its territory. *$p < 0.05$

Abbreviations: END: early neurological deterioration; MRI: magnetic resonance imaging; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale.

The baseline characteristics, imaging findings and outcomes between the patients with and without END are shown in Table **1**. The mean time from stroke onset to baseline MRI was 11.7 ± 6.2 hours and END occurred in 13

Table 2. Target mismatch profile in different T_{max} thresholds to predict END by univariate and multivariate analysis.

Predict END			
Target Mismatch Profile	***p***	**Odds Ratio**	**95% Confidence Interval**
T_{max} ≥4s	0.02*	7.1	1.3-38.4
T_{max} ≥5s	0.01*	9.0	1.7~48.9
T_{max} ≥6s	< 0.01*	15.5	2.7~87.7
T_{max} ≥4s (adjusted)†	0.03*	7.1	1.3~39.3
T_{max} ≥5s (adjusted)†	0.01*	8.8	1.6~48.2
T_{max} ≥6s (adjusted)†	< 0.01*	17.0	2.8~105.0

†Adjusted for initial NIHSS score.
*$p < 0.05$.
Abbreviations: END: early neurological deterioration; NIHSS: National Institute of Health Stroke Scale.

(24.1%) patients. Patients with END had larger PWI volumes for $T_{max} \geq 4$, 5 and 6 seconds compared with those without END. The presence of END was significantly associated with larger final infarct volume ($p = 0.001$), larger infarct growth ($p = 0.002$), higher NIHSS score at day 3 ($p < 0.001$), worse mRS at 3 months ($p < 0.001$), less possibility of favorable and good outcome at 3 months ($p = 0.005$ and $p = 0.004$, respectively) and higher mortality rate ($p = 0.025$).

The associations of target mismatch profile with END are shown in Table **2**. The target mismatch profile by T_{max} map ≥ 4, 5 or 6 seconds was significantly associated with END by univariate analysis and by multivariate analysis after adjustment for initial NIHSS score (Table **2**). Among the T_{max} thresholds, the target mismatch profile measured by $T_{max} \geq 6$ seconds had the highest odds ratio in predicting END (Table **2**). An ROC curve found that the T_{max} threshold of 4-6 seconds all had acceptable AUC values for END prediction (Table **3**). For the T_{max} threshold of 6 seconds, the optimal ratio of T_{max} lesion volume/infarct core volume was 1.2 in predicting END, with an 80% sensitivity and a 79.5% specificity, whereas the optimal ratio for $T_{max} \geq 5$ seconds was 2.2 in predicting END (Table **3**).

Among 46 patients with follow-up MRI, the infarct growth volume was significantly larger in patients with target mismatch profile than those with no mismatch profile by $T_{max} \geq 5$ seconds (78.4 ml vs. 20.3 ml, $p = 0.034$) and $T_{max} \geq 6$ seconds (60.8 ml vs. 15.0 ml, $p = 0.017$). Patients with target mismatch profile by $T_{max} \geq 6$ seconds were less likely to have favorable outcome (6.2% vs. 48.5%, $p = 0.009$) at 3 months compared to those with no mismatch profile (Table **4**). Furthermore, three patients (60%) with malignant profile developed END, and none of them had good or favorable outcomes at 3 months (Table **4**).

DISCUSSION

This is the first study demonstrating that perfusion-diffusion mismatch can reliably predict END in non-lacunar anterior circulation infarct without thrombolysis. The perfusion-diffusion mismatch ratio ≥ 1.2 determined by a T_{max} threshold of 6 seconds was optimal for the prediction of END and was associated with worse long-term functional outcome.

The definitions of END, no matter regarding the degree or the timeframes, have been inconsistent in different studies and are still a matter of debate [1]. Nonetheless, NIHSS was the most commonly used scoring system for evaluating and defining deterioration [1]. Siegler et al had found that END defined by an increase in NIHSS ≥ 2 points and NIHSS ≥ 4

Table 3. Receiver operating characteristic curve to assess the sensitivity and specificity of target mismatch profile in different T_{max} thresholds to predict END.

Predict END					
	AUC	**Standard Error**	**Optimal Mismatch Ratio (PWI Volume /DWI Volume)**	**Sensitivity**	**Specificity**
T_{max} ≥4s	0.728	0.106	≥ 3.1	0.800	0.821
T_{max} ≥5s	0.772	0.101	≥ 2.2	0.800	0.846
T_{max} ≥6s	0.769	0.100	≥ 1.2	0.800	0.795

Abbreviations: AUC: area under curve; END: early neurological deterioration; PWI: perfusion weighted imaging; DWI: diffusion weighted imaging.

Table 4. Clinical outcomes in patients with different mismatch profiles.

	Patient	**END (%)**	**Favorable Outcome at 3 Months**	**Good Outcome at 3 Month**
Target mismatch profile (T_{max} ≥6s)	16	8 (50.0%)*	1 (6.2%)*	4 (25.0%)*
Malignant profile	5	3 (60%)	0	0
No mismatch profile	33	2 (6.1%)	16 (48.5%)	19 (57.6%)

Abbreviations: END: early neurological deterioration.
* P < 0.05 when comparing to No mismatch group.

points were both related to poorer functional outcome at discharge [1]. We selected an increase in NIHSS ≥ 4 points to define END because our study focused on "non-lacunar" infarct, in which the baseline NIHSS was higher (mean NIHSS was 7 in our study) and small changes in NIHSS might have limited clinical significance. Moreover, we defined a timeframe of END as the neurological worsening occurring within 72 hours after stroke onset because one study had found that most neurological worsening occurring beyond 72 hours was caused by systemic complications [16].

END after ischemic stroke has heterogeneous mechanisms, including infection, medication, edema, seizure, recurrent stroke, progressive stroke or hemorrhagic transformation [2]. Siegler *et al.* had found the most common etiology of END was "progressive stroke", which was defined as the infarct growth in the same vascular territory of the original stroke [2]. Progressive stroke is often irreversible and is associated with poor functional outcome [2]. Therefore, effective preventive strategies for high-risk patients are important in acute stroke management. Our study showed that perfusion-diffusion mismatch, an estimate of non-core hypoperfused area, was an independent predictor for END. Therefore, managements to preserve the perfusion status in the hypoperfused area may prevent the occurrence of END. There had been some studies showed that giving low molecular weight heparin or dual antiplatelet therapy within 48 hours from the stroke onset might reduce the possibilities of END [17-19]. A pilot randomized trial conducted by Hillis et al. found that induced blood pressure elevation given within 7 days from the stroke onset could improve the functional outcome and reduce the volume of hypoperfused tissue in the patients with perfusion-diffusion mismatch [20]. Larger randomized trials are needed to prove the effectiveness of these preventive strategies, and our study provides a reliable tool to select the candidates for the study entry.

DEFUSE and DEFUSE-2 studies proved the usefulness of perfusion-diffusion mismatch to provide an estimate of the ischemic penumbra [9, 10]. Because penumbra is not expected to predict clinical deterioration (it is already functionally impaired by its definition) [4], the result of our study may suggest the presence of oligemic tissue in the area of mismatch. Actually, the oligemia often intermix with the penumbra. Given that the ischemic tolerance of the neurons may be different, some neurons may be functionally impaired but others may not even under the same degree of hemodynamic compromise [21]. Furthermore, the hemodynamics changing following an ischemic stroke is a dynamic process and a threshold of single MRI parameter to differentiate the penumbra and the oligemia may oversimplify the perfusion changes. Therefore, the mismatch is better regarded as a critically hypoperfused area containing different proportions of the penumbra and the oligemia [5]. That explains why perfusion-diffusion mismatch could predict clinical response in ischemic stroke patients receiving thrombolysis (salvage of the penumbra) [9, 10] but also could predict END in those not receiving thrombolysis (progression of the oligemia) in our study.

Recently, an increasing number of studies have promoted the use T_{max} to define the PWI lesion [22], and a T_{max} threshold between 4 to 6 seconds were suggested to provide a reliable estimate for the penumbra [23, 24]. In our study, the target mismatch defined by $T_{max} \geq 4$ to 6 seconds all independently predict END, but $T_{max} \geq 6$ seconds had the highest odd's ratio for the prediction. Moreover, the mismatch ratio chosen by previous perfusion studies ranged from 1.2 to 2.6 [9, 10, 25]. The present study found the optimal mismatch ratio for END prediction by $T_{max} \geq 6$ seconds was ≥ 1.2 but that for $T_{max} \geq 5$ seconds was ≥ 2.2. Because there is still no consensus on the best PWI parameter, threshold or mismatch ratio, we suggest the optimal definition for meaningful mismatch should depend on the purpose to perform the perfusion images.

Our study has certain limitations. First, the findings of our study may not be extended to patients with lacunar infarctions or infarctions in brainstem or cerebellum. Mismatch is difficult to be determined in these patients due to small size of PWI and DWI lesions [26]. Second, the time from stroke onset to MRI scan was up to 24 hours in our study. The golden time to save the ischemic neurons and prevent the END may gradually pass away. But a recent study using PWI-DWI mismatch to evaluate the temporal evolution of ischemic lesions in nonhuman primates found the mismatch was visible at 6 hours and gradually diminished until 48 hours after the stroke onset [27]. Therefore, substantial salvageable tissues may still exist in the time window selected by our study. Last, to predict END with a single MRI scan may oversimplify the underlying pathophysiology since the hemodynamic change after stroke is a dynamic process.

In conclusion, our study demonstrates the usefulness of perfusion MRI in predicting END in acute non-lacunar anterior circulation infarct without thrombolysis. Our study highlights the role of perfusion abnormalities in the pathogenesis of END and provides a reference to select study candidates for novel approaches to prevent END in high-risk patients.

ETHICAL STATEMENT

Work was the reported experiments in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC, Martin-Schild S. What change in the National Institutes of Health Stroke Scale should define neurologic deterioration in acute ischemic stroke? J Stroke Cerebrovasc Dis : The Official Journal of National Stroke Association 2013; 22(5): 675-82.

[2] Siegler JE, Boehme AK, Albright KC, *et al.* A proposal for the classification of etiologies of neurologic deterioration after acute ischemic stroke. J Stroke Cerebrovasc Dis : The Official Journal of National Stroke Association 2013; 22(8): e549-56.

[3] Thanvi B, Treadwell S, Robinson T. Early neurological deterioration in acute ischaemic stroke: predictors, mechanisms and management. Postgraduate Med J. 2008; 84(994): 412-7.

[4] Alawneh JA, Moustafa RR, Baron JC. Hemodynamic factors and perfusion abnormalities in early neurological deterioration. Stroke; J Cereb Circ 2009; 40(6): e443-50.

[5] Motta M, Ramadan A, Hillis AE, Gottesman RF, Leigh R. Diffusion-perfusion mismatch: an opportunity for improvement in cortical function. Front Neurol 2014; 5: 280.

[6] Alawneh JA, Jones PS, Mikkelsen IK, *et al.* Infarction of 'non-core-non-penumbral' tissue after stroke: multivariate modelling of clinical impact. Brain : J Neurol 2011; 134(Pt 6): 1765-76.

[7] Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol 2009; 8(3): 261-9.

[8] Farr TD, Wegener S. Use of magnetic resonance imaging to predict outcome after stroke: a review of experimental and clinical evidence. J Cereb Blood Flow Metab : Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2010; 30(4): 703-17.

[9] Lansberg MG, Straka M, Kemp S, *et al.* MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol 2012; 11(10): 860-7.

[10] Albers GW, Thijs VN, Wechsler L, *et al.* Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Annals Neurol 2006; 60(5): 508-17.

[11] Gawlitza M, Gragert J, Quaschling U, Hoffmann KT. FLAIR-hyperintense vessel sign, diffusion-perfusion mismatch and infarct growth in acute ischemic stroke without vascular recanalisation therapy. J Neuroradiol 2014; 41(4): 227-33.

[12] Wheeler HM, Mlynash M, Inoue M, *et al.* Early diffusion-weighted imaging and perfusion-weighted imaging lesion volumes forecast final infarct size in DEFUSE 2. Stroke; J Cereb Circ 2013; 44(3): 681-5.

[13] Seners P, Turc G, Tisserand M, *et al.* Unexplained early neurological deterioration after intravenous thrombolysis: incidence, predictors, and associated factors. Stroke; J Cereb Circ 2014; 45(7): 2004-9.

[14] Jauch EC, Saver JL, Adams HP, Jr., *et al.* Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; J Cereb Circ 2013; 44(3): 870-947.

[15] Huang YC, Liu HL, Lee JD, *et al.* Comparison of arterial spin labeling and dynamic susceptibility contrast perfusion MRI in patients with acute stroke. PloS One 2013; 8(7): e69085.

[16] Karepov VG, Gur AY, Bova I, Aronovich BD, Bornstein NM. Stroke-in-evolution: infarct-inherent mechanisms versus systemic causes. Cerebrovasc Dis 2006; 21(1-2):42-6.

[17] Yi X, Lin J, Wang C, Zhang B, Chi W. Low-molecular-weight heparin is more effective than aspirin in preventing early neurologic deterioration and improving six-month outcome. J Stroke Cerebrovasc Dis : The Official Journal of National Stroke Association. 2014; 23(6): 1537-44.

[18] Wang Q, Chen C, Chen XY, *et al.* Low-molecular-weight heparin and early neurologic deterioration in acute stroke caused by large artery occlusive disease. Arch Neurol 2012; 69(11): 1454-60.

[19] Nakamura T, Tsuruta S, Uchiyama S. Cilostazol combined with aspirin prevents early neurological deterioration in patients with acute ischemic stroke: a pilot study. J Neurol Sci 2012; 313(1-2): 22-6.

[20] Hillis AE, Ulatowski JA, Barker PB, *et al.* A Pilot Randomized Trial of Induced Blood Pressure Elevation: Effects on Function and Focal Perfusion in Acute and Subacute Stroke. Cerebrovasc Dis. 2003; 16(3): 236-46.

[21] Zemke D, Smith JL, Reeves MJ, Majid A. Ischemia and ischemic tolerance in the brain: an overview. Neurotoxicology. 2004; 25(6): 895-904.

[22] Calamante F, Christensen S, Desmond PM, Ostergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. Stroke; J Cereb Circ 2010; 41(6): 1169-74.

[23] Olivot JM, Mlynash M, Zaharchuk G, *et al.* Perfusion MRI (Tmax and MTT) correlation with xenon CT cerebral blood flow in stroke patients. Neurology 2009; 72(13): 1140-5.

[24] Zaro-Weber O, Moeller-Hartmann W, Heiss WD, Sobesky J. Maps of time to maximum and time to peak for mismatch definition in clinical stroke studies validated with positron emission tomography. Stroke; J Cereb Circ 2010; 41(12): 2817-21.

[25] Kakuda W, Lansberg MG, Thijs VN, *et al.* Optimal definition for PWI/DWI mismatch in acute ischemic stroke patients. J Cereb Blood Flow Metab : Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2008; 28(5): 887-91.

[26] Poppe AY, Coutts SB, Kosior J, Hill MD, O'Reilly CM, Demchuk AM. Normal magnetic resonance perfusion-weighted imaging in lacunar infarcts predicts a low risk of early deterioration. Cerebrovascular diseases. 2009; 28(2): 151-6.

[27] Zhang X, Tong F, Li CX, *et al.* Temporal evolution of ischemic lesions in nonhuman primates: a diffusion and perfusion MRI study. PloS One 2015; 10(2): e0117290.