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Current Neurovascular Research, 2016, *13*, 271-276

ORIGINAL ARTICLE

Magnetic Resonance Perfusion Imaging Provides a Significant Tool for the Identification of Cardioembolic Stroke

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ARTICLE HISTORY

Received: May 06, 2016
Revised: July 15, 2016
Accepted: July 18, 2016

DOI:
10.2174/1567202613666160901143040

Abstract: Despite advances in imaging techniques and detailed examinations to determine the etiology of a stroke, the cause still remains undetermined in about one fourth of all ischemic strokes. The aim of this prospective study was to determine whether perfusion magnetic resonance imaging (MRI) can differentiate cardioembolic stroke from large artery atherosclerosis (LAA). We recruited 17 cardioembolic stroke and 22 LAA stroke patients, who were classified according to the Trial of Org 10172 in Acute Stroke Treatment and underwent perfusion MRI within 24 hours after the onset of stroke. The patients with cardioembolic stroke had more severe initial stroke severity and larger volumes of initial and final infarct compared to those with LAA stroke. Receiver operating characteristic curve analysis showed that the ratio of time to maximum of the residual curve (T_{max}) volume for a 2-, 3-, 4- or 5-s lag over T_{max} volume for a 8s lag all had excellent area under the curve values (> 0.9) to predict cardioembolic stroke. After adjusting for initial National Institute of Health Stroke Scale scores, a threshold of 3.73 for (T_{max} > 4s volume)/(T_{max} > 8s volume) had the highest odds ratio to predict cardioembolic stroke (p=0.012; odds ratio: 58.5; 95% confident interval: 2.5-1391.1), with 87.5% sensitivity and 94.4% specificity. In conclusion, perfusion MRI could be a reliable tool to identify cardioembolic stroke with its lower collateral. This is important as it could be used to reveal the exact mechanism and provide supportive evidence to classify a stroke.

Keywords: Cardioembolism, stroke, MRI, perfusion, LAA.

1. BACKGROUND AND PURPOSE

Accurate classification of ischemic stroke is crucial, as it allows for the effective management of a stroke in the acute phase and the prevention of further stroke [1]. Cardioembolic stroke has been reported to account for about one fifth of all ischemic strokes [2], and it is associated with a higher stroke severity and higher recurrence rate [3, 4]. Oral anticoagulants are the most effective method to prevent recurrence of cardioembolism in most patients [5]. Therefore, the early diagnosis of cardioembolic stroke is critical not only to identify the cause of the cardioembolism, but also to allow for the early initiation of anticoagulant treatment.

The ischemic stroke is usually classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST), including large-artery atherosclerosis (LAA), cardioembolism, small vessel disease, undetermined etiology and other determined etiology [6]. The clinical diagnosis of cardioembolic stroke is based on the presence of a potential major cardiac source of embolism and the absence of significant arterial stenosis (≥50% stenosis). However, when cardiac and arterial diseases coexist, it is difficult to determine the exact mechanism underlying the stroke, and as such they are classified as being undetermined etiology. Moreover, the cardioembolic stroke may be classified as undetermined stroke if the cardiac source of embolism is not identified such as paroxysmal atrial fibrillation. Despite advances in imaging techniques and detailed examinations to determine the etiology of a stroke, the cause of about one fourth of all ischemic strokes is undetermined. Persuasive evidence has shown that most undetermined strokes are thromboembolic, including potential embolism from minor risk or covert cardiac sources [7]. Therefore, the accurate diagnosis of a cardioembolic stroke or the identification of a cardioembolic source in an undetermined stroke is important but rarely achieved.

Magnetic resonance imaging (MRI) is widely used in clinical practice for patients with acute ischemic stroke. MR angiography provides a reliable tool to evaluate the intracranial and extracranial vessels for the diagnosis of LAA stroke. Multiple simultaneous infarcts located in one or more major arterial territories of the anterior and/or posterior circulation

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1567-2026/16 $58.00+.00

without significant arterial stenosis may support the diagnosis of cardioembolism [8]. However, the cardioembolism and LAA may share similar stroke patterns in MRI, such as a territory infarction (corticosubcortical) or a solitary infarction (cortical or subcortical) [8, 9]. In real world practice, the borders between LAA and cardioembolism are not clear-cut. For example, there may be a solitary infarction with relevant artery stenosis (<50%), a territory infarction without artery stenosis and cardiac source of embolism, or an infarction with both artery stenosis (≥50%) and major cardiac source of embolism.

Perfusion-weighted imaging (PWI), including dynamic susceptibility contrast or arterial spin labeling technique, is a sensitive tool used to detect abnormalities in perfusion [10], which is a dynamic process after the onset of stroke and involves varying degrees of ischemia [11, 12]. According to the degree of cerebral blood flow impairment, brain regions with perfusion abnormalities can be further classified into infarct core, penumbra and oligemia. The mismatch between the infarct core on diffusion-weighted imaging (DWI) and the hypoperfused region on PWI may indicate potentially salvageable cerebral ischemic tissue [13]. DWI lesions or a maximum of the residual curve (T_{max}) of >8 or >10 s has been widely used to predict the infarct core [14], and the mismatch of DWI core infarct and a T_{max} of > 5 or > 6 s has been reported to provide a more realistic estimate of the penumbra [15, 16]. Kim et al. observed that ischemic stroke resulting from intracranial LAA had a larger salvageable area compared to other stroke subtypes, probably due to good collateral circulation [17]. In contrast, they found that cardioembolism was related to a larger core infarct and less salvageable area. These results suggest the application of PWI in identifying cardioembolic stroke due to the different mismatch profiles.

To the best of our knowledge, mismatch profiles in PWI have not been used in the classification of stroke subtype. We hypothesized that cardioembolic stroke is related to fewer non-core hypoperfused areas, including oligemia and penumbra, due to poor collateral circulation. The aim of this study was to determine whether PWI can differentiate cardioembolic stroke from LAA stroke.

2. METHODS

2.1. Patients

This prospective study was part of an integrated stroke project conducted at Chang Gung Memorial Hospital from December 2010 to August 2015. Patients were eligible to participate if they were 18 years or older, had a clinical diagnosis of ischemic stroke without thrombolytic therapy, and could undergo a complete MRI protocol (described later) within 24 hours after the onset of stroke, which was defined as the last time the patient was known to be without any neurological deficits. The exclusion criteria were patients: (1) with contraindications for MRI studies or gadolinium injections such as those with an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2, claustrophobia, or the presence of pacemakers or metal objects; (2) in whom DWI demonstrated no acute ischemic stroke; (3) with an acute ischemic stroke in the territories of posterior circulation; (4) with a perfusion defect < 15 cm^3 in T_{max} maps for a 2-s delay; (5) with a premorbid modified Rankin Scale (mRS) score of 2 or higher. We excluded small perfusion defects because small perfusion defect is difficult to assess and causes higher bias [18].

Neurological deficits were evaluated using the National Institute of Health Stroke Scale (NIHSS) on admission by a stroke neurologist or study nurse who was blinded to the patient's PWI-DWI profiles. Data on age, sex, cigarette smoking status, and a medical history of hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, prior coronary artery disease and prior cerebrovascular disease were recorded. Systolic and diastolic blood pressure values, blood biochemistry and cell counts were determined on admission. Complete surveys for stroke etiologies including electrocardiogram, carotid and transcranial Doppler and/or echocardiography were performed. The stroke subtypes were classified according to the TOAST classification, including LAA, cardioembolism, small vessel disease, undetermined etiology and other determined etiology. LAA stroke was defined as any cortical infarct or subcortical infarct >1.5 cm that was associated with significant stenosis (>50%) or occlusion of a major brain artery or branch cortical artery in magnetic resonance angiography. Same infarct patterns associated with medium- or high-risk sources of cardioembolism were classified as cardioembolic stroke. Patients with two or more potential causes of stroke such as those with both atrial fibrillation and extracranial internal carotid artery stenosis (>50%) were classified as having an undetermined etiology. Only patients with cardioembolic and LAA stroke were selected in this study for further analysis.

Clinical outcomes at 3 months were evaluated by using the mRS by a study nurse who was blinded to the patient's brain imaging. A good outcome was defined as a mRS score of 2 or less, and a favorable outcome was defined as a mRS score of 0 or 1. Mortality at 3 months was also recorded.

This study was 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.

2.2. MRI Protocol

All data were collected using a 3 Tesla Siemens Verio MRI system (Siemens Medical System, Erlangen, Germany) using a 16-channel head coil. The first MRI protocol included axial DWI, axial T1- and T2 images, MR angiography, and dynamic susceptibility contrast perfusion imaging. The follow-up protocol included DWI, axial T1- and T2 images, MR angiography and fluid-attenuated inversion recovery (FLAIR) imaging.

The perfusion imaging with dynamic susceptibility contrast was acquired using a gradient echo echo-planar imaging (EPI) sequence (TR = 1500 ms, TE = 36 ms, field-of-view (FOV) = 220 mm, matrix = 92 × 92, 17 × 6-mm slices, and scan time = 1 minute 36 seconds) with an intravenous bolus injection of gadolinium contrast agent (0.2 mmol/kg) at the fifth dynamic. DWI was performed using an EPI sequence with b = 0 and b = 1000 s/mm^2, in three dimensions in space resulting in four images per section. The imaging parameters used for this were TR/TE = 5600/93 ms, an acquisition matrix of 130 × 130, 4.0-mm slice thickness, and a 230-mm

FOV. DWI were processed to generate pixel-by-pixel trace apparent diffusion coefficient (ADC) imaging. MR angiography used three-dimensional time of flight (TR/TE = 21/3.6 ms and 0.6-mm thickness) covering the extracranial carotid artery and the circle of Willis with two separate scans.

2.3. Post-processing and Image Analysis

Perfusion Mismatch Analyzer software (Ver. 3.4.0.6, ASIST, Japan) was used to calculate the PWI for each patient [19]. The quantitative T_{max} maps for a 2-8-second delay were generated using standard singular value decomposition. Automatic arterial input function (AIF) was used with the manual addition or deletion of AIF if the quality of the automatic AIF was not satisfactory. The volumes of PWI lesions in the T_{max} maps, acute infarct volumes in ADC imaging and final infarcts in FLAIR imaging were measured using Image J software (Version 1.43). All of the imaging data were evaluated by an experienced stroke neurologist (Y. C. H.) and a neuroradiologist (Y. H. T.), both of whom were blinded to the clinical information.

2.4. The Index to Predict Cardioembolic Stroke

We used PWI to define the degree of hypoperfusion, including core infarct, penumbra and oligemia. The ratio of PWI lesion volume to core infarct volume (PWI/core) was used to represent the degree of non-core hypoperfusion. The PWI lesion volumes were measured using the T_{max} maps with a 2-7-s delay respectively, whereas the core infarct volumes were calculated by $T_{max} > 8$ s.

2.5. Statistical Analysis

All statistical analyses were performed using Stata version 12.1 statistical software (StataCorp LP, College Station, Texas, USA). Continuous variables were expressed as means ± SD or median and interquartile range. 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 using Fisher's exact or Person's Chi-Square test, as appropriate. In this study, we used threshold-independent receiver-operating characteristic (ROC) curve analysis to estimate the optimal T_{max} lag in predicting cardioembolic stroke. The highest values of sensitivity and specificity were used to calculate the optimal diagnostic cut-off point for a (T_{max} volume) / (T_{max} > 8s volume) ratio predicting cardioembolic stroke. For each ratio of (T_{max} volume) / (T_{max} > 8s volume) in predicting cardioembolic stroke, a multivariate logistic regression model was constructed to adjust for baseline variables when a p-value <0.1 was found in the univariate analysis. All p values were two-tailed and a p value < 0.05 was considered to be statistically significant.

3. RESULTS

A total of 236 patients with suspected stroke within 24 hours of the onset of symptoms were selected during the study period. Thirty of these patients were unable to complete the MRI scan. Of the remaining 206 patients, 148 had an acute ischemic stroke in the anterior circulation territory, including 28 cardioembolic and 42 LAA strokes. However, 31 of these patients were excluded because of small or no perfusion defects, defined as a perfusion defect < 15 cm^3 in T_{max} maps for a 2-s delay. Finally, 17 patients with cardioembolic stroke and 22 patients with LAA stroke were included. The demographic data of these patients are shown in Table **1**.

The patients with cardioembolic stroke had a more severe initial stroke severity and larger volumes of initial and final infarct than those with LAA stroke. Because atrial fibrillation was used to determine the diagnosis of cardioembolic stroke, it was higher in the patients with cardioembolic stroke. There were no significant differences in age, sex or other stroke risk factors between the two groups. The mRS at 3 months was higher in the patients with cardioembolic stroke. Examples of represented patients are shown in Figure **1**.

ROC curve analysis showed that the ratio of (T_{max} volume)/(T_{max} > 8s volume) for a 2-, 3-, 4- and 5-s lag all had excellent area under the curve (AUC) values (> 0.9) to predict cardioembolic stroke, and there were no significant differences among them. The optimal thresholds in each T_{max} lag are shown Table **2**. In the univariate logistic regression for all baseline variables, including age, sex, onset-MRI duration, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, old stroke, smoking, systolic and diastolic blood pressure, initial NIHSS score and (T_{max} volume) / (T_{max} > 8s volume) ratio, only the initial NIHSS score, atrial fibrillation and (T_{max} volume) / (T_{max} > 8s volume) ratio had significant difference (p-value < 0.05) in predicting cardioembolism. Because atrial fibrillation was used to determine the diagnosis of cardioembolic stroke, it was therefore not selected for adjustment in the multivariate logistic regression. After adjusting for initial NIHSS score, a threshold of 3.73 for (T_{max} > 4 s volume)/ (T_{max} > 8 s volume) had the highest odds ratio to predict cardioembolic stroke (p=0.012; odds ratio: 58.5; 95% confidence interval: 2.5-1391.1), with 87.5% sensitivity and 94.4% specificity (Table **2**).

4. DISCUSSION

In patients with acute stroke with completely or partially occluded vessels, perfusion MRI could detect varying degrees of perfusion defects. Our results demonstrate that the ratio of the perfusion defect volume to core infarct volume was lower in the patients with cardioembolic stroke than in those with LAA stroke. This difference could be used to distinguish cardioembolic stroke from LAA stroke.

In the current study, a ratio of (T_{max} volume) / (T_{max} > 8s volume) for 2-, 3-, 4- or 5-s lag had better AUC values than those for a 6- or 7-s delay. Because a T_{max} of > 6 s has been reported to provide a more realistic estimate of the penumbra [15, 16], the hypoperfused areas selected by a T_{max} of > 6 s or > 7 s may exclude oligemic tissue. Since oligemia is highly related to collateral flow [20], the lower ratio of (T_{max} volume) / (T_{max} > 8s volume) for 2-, 3-, 4- or 5-s lag in predicting cardioembolic stroke may hint at less collateral flow. The finding supports our hypothesis that cardioembolic stroke is related to fewer non-core hypoperfused areas due to poor collateral circulation.

Table 1. Demographic data of patients with cardioembolic and large artery atherosclerosis (LAA) strokes.

	Cardioembolism	LAA	*p*
Number	17	22	
Age (years)	75.5±9.8	69.6±13.2	0.126
Sex (F/M)	5/12	8/14	0.648
Onset–MRI duration (hour)	10.8±6.8	14.3±8.2	0.164
Atrial fibrillation (%)	14(82.4%)	0(0%)	<0.001*
Diabetes mellitus (%)	4(23.5%)	7(31.8%)	0.725
Hypertension (%)	10(58.8%)	17(77.3%)	0.216
Hyperlipidemia (%)	5(29.4%)	5(22.7%)	0.635
Coronary artery disease (%)	2(11.8%)	0(0%)	0.184
Old stroke or TIA (%)	6(35.3%)	6(27.3%)	0.590
Smoking (%)	3(17.6%)	7(31.8%)	0.464
Systolic blood pressure (mmHg)	164.9±30.6	159.9±32.9	0.647
Diastolic blood pressure (mmHg)	95.6±23.5	92.6±16.9	0.658
NIHSS baseline, median	20(14.5–25.5)	6(3–11)	<0.001*
Initial infarct volume (ml)	109.7±106.5	12.8±18.7	<0.001*
Final infarct volume (ml)	164.8±136.4	24.4±28.3	0.001*
T_{max} > 2-s volume (ml)	190.1±148.6	114.8±85.0	0.053
mRS at 3M, median	5(3–6)	2.5(0–4)	0.019*
Favorable outcome at 3M	2(11.8%)	8(36.4%)	0.133
Good outcome at 3M	3(17.6%)	10(45.5%)	0.083
Mortality	4(23.5%)	1(4.5%)	0.149

*p<0.05;
Abbreviations: TIA: transient ischemic attack; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; T_{max}: time to maximum of the residual curve

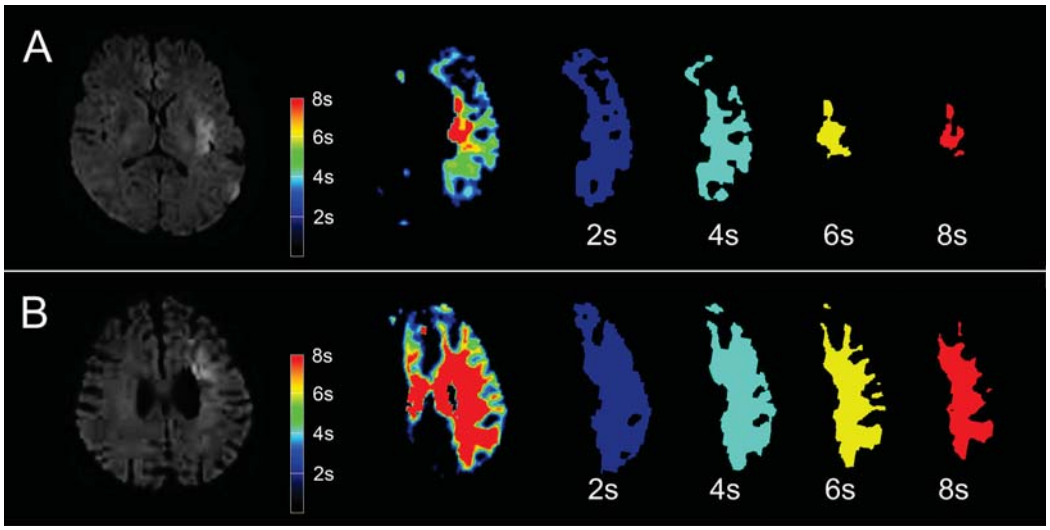

Fig. (1). DWI and T_{max} maps with 2-, 4-, 6-, and 8-s delay of representative patients. (A) A 45-year-old woman underwent MRI 9.6 hours after stroke onset. DWI showed an acute infarct in the left MCA territory and was classified as a LAA stroke. The ratio of (T_{max} > 4 s volume) / (T_{max} > 8 s volume) was 15.0, indicating a LAA stroke. (B) An 82-year-old man underwent MRI 4.6 hours after stroke onset. DWI showed an acute infarct in the left MCA territory and was classified as a cardioembolic stroke. The ratio of (T_{max} > 4 s volume) / (T_{max} > 8 s volume) was 2.8, indicating a cardioembolic stroke.

Table 2. Receiver-operating characteristic curve analysis and multivariate logistic regression in predicting cardioembolism.

Ratio	Area Under Curve (AUC)	Standard Error	Optimal Cut-Off Point	Sensitivity	Specificity	Odds Ratio	95% Confidence Interval	*p*
(T_{max} >2s volume) / (T_{max}>8s volume)	0.941	0.037	≦5.52	0.938	0.833	27.16	2.2-342.0	0.011*
(T_{max} >3s volume) / (T_{max}>8s volume)	0.946	0.036	≦4.68	0.938	0.833	31.5	2.5-395.2	0.008*
(T_{max} >4s volume) / (T_{max}>8s volume)	0.944	0.037	≦3.73	0.875	0.944	58.5	2.5-1391.1	0.012*
(T_{max} >5s volume) / (T_{max}>8s volume)	0.924	0.045	≦2.79	0.875	0.889	19.2	1.4-267.0	0.028*
(T_{max} >6s volume) / (T_{max}>8s volume)	0.839	0.070	≦2.06	0.875	0.778	4.1	0.4-38.3	0.222
(T_{max} >7s volume) / (T_{max}>8s volume)	0.790	0.080	≦1.35	0.813	0.778	4.2	0.6-31.8	0.164

*p<0.05; multivariate logistic regression was used to adjust initial National Institute of Health Stroke Scale.

The exact duration of penumbra is uncertain and varies in different individuals because of different hemodynamic status. In proximal artery occlusion, the development of collateral flow plays a critical role in maintaining perfusion in the penumbral region [20-22]. In LAA stroke, the collateral flow may have been established previously, and preconditioning and adaptive cellular responses to chronic ischemia may also lead to a higher threshold to ischemic injury after stroke. These are the reasons why there are more non-core hypoperfused areas in LAA stroke than in cardioembolic stroke. Our results showed that a higher ratio of (T_{max} > 4 s volume) / (T_{max} > 8 s volume) predicted LAA stroke. This result may suggest that penumbra and oligemia exist more and last longer in LAA stroke. A recent study using DWI and perfusion MRI to evaluate the temporal evolution of ischemic lesions in nonhuman primates found that a mismatch was visible at 6 hours and gradually diminished until 48 hours after the onset of stroke [23]. This result supports our findings in that perfusion defects may last beyond 24 hours, and that they can still be used to predict cardioembolic stroke.

Increasing evidence suggests that most cryptogenic strokes are thromboembolic, originating from any of several well established potential embolic sources including cardiac sources, veins via paradoxical embolism, and atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries [7]. MRI may provide supportive evidence for the diagnosis of embolic stroke. For example, multiple acute infarcts in one or more major arterial territories of the anterior and/or posterior circulation without stenosis of relevant vessels is supportive of cardioembolic stroke according to the Causative Classification of Stroke system [24] and Chinese Ischemic Stroke Sub-classification [25]. However, a territory infarction or a solitary infarction (cortical or subcortical) is commonly observed in both LAA and cardioembolic stroke [8;9]. For a cardioembolic stroke, the embolic risk may not be identified so that it would be misclassified as an undetermined stroke. Moreover, a cardioembolic stroke may coincide with stenotic vessels (> 50%), and thereby misclassified as LAA stoke if the embolic risk is not identified. Our results using perfusion MRI may provide a practical way to distinguish between cardioembolic and LAA strokes in such ambiguous situations. In addition to a large territorial infarct, it may also be applied to a small solitary infarct because there are still some hypoperfused areas surrounding it. Recent studies has shown that T2*-weighted gradient echo imaging and susceptibility-weighted imaging has both been used to identify a thrombus in the form of hypointense signals within occluded arteries, which is termed a "susceptibility vessel sign" (SVS). The SVS was reported to be associated with cardioembolic stroke [26, 27]. Taken together, perfusion MRI and the SVS may provide supportive evidences for cardioembolic stroke when classifying a stroke. These findings may be adopted in further stroke classification systems, however further studies are needed to validate our results.

There are several limitations to this study. First, our findings were only derived from the anterior circulation with certain perfusion defects. Moreover, hemodynamic change after stroke is a dynamic process and perfusion defects may disappear due to adequate collateral or recanalization after thrombolytic therapy. Small perfusion defects may also have been missed by our criteria. Second, our findings could not distinguish the embolic source from the heart, proximal artery or other determined stroke. However, our findings may provide additional evidence for an embolic stroke, supporting the need for more complete surveys for its source. Third, the number of cases was small, and the study duration for each patient was diverse. Further studies are necessary to validate our results, especially when applied to clinical practice.

In conclusion, perfusion MRI could be a reliable tool to identify cardioembolic stroke by its lower collateral. This result is important as it could be used to reveal the exact mechanism and provide supportive evidence for stroke classification.

STUDY FUNDING

Supported by Chang Gung Memorial Hospital research grants (CORPG690453, CORPG6D0131 and CORPG6D 0132) and by a Ministry of Science and Technology research grant (MOST 104-2314-B-182A-033).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We thank Yi-Chen Kuo and Wang Hsueh-Lin for assisting us with this study.

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