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Journal of the Chinese Medical Association 77 (2014) 437–442

www.jcma-online.com

Original Article

New grading of moyamoya disease using color-coded parametric quantitative digital subtraction angiography

Sheng-Che Hung [a,b,c], Muh-Lii Liang [b,d], Chun-Fu Lin [b,d], Chung-Jung Lin [a,b], Wan-Yuo Guo [a,b,*], Feng-Chi Chang [a,b], Tai-Tong Wong [b,e], Cheng-Yen Chang [a,b]

[a] *Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[c] *Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan, ROC*
[d] *Department of Neurosurgery, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[e] *Department of Surgery, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC*

Received October 15, 2013; accepted January 14, 2014

Abstract

Background: Moyamoya disease (MMD) is an uncommon cerebrovascular disorder characterized by idiopathic progressive stenosis or the occlusion of the intracranial arteries. Digital subtraction angiography (DSA) is the reference diagnostic imaging modality for MMD. Use of the conventional Suzuki grading remains the gold standard for evaluating the severity of MMD. In this study, we propose a quantitative method using color-coded parametric quantitative DSA (QDSA) to improve prediction of the severity of MMD.
Methods: Eighteen DSA examinations from 18 patients with MMD and 14 control participants were included. All patients with MMD underwent DSA and dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI). QDSA was used to determine the delay time of maximal opacification (Td) between the internal carotid artery and the M2 segment of the middle cerebral artery. The time-to-peak (TTP) was measured in the medial frontal, lateral frontal, parietal, and occipital lobes from the DSC-PWI. The relative TTP (rTTP) values were then obtained by subtracting the TTP of the cerebellum.
Results: The Td was significantly longer in the patients with MMD presenting with infarction than in the control group. The Td significantly correlated with the angiographic Suzuki grading system and showed closer correlation with prolonged rTTP in the medial frontal, lateral frontal, and parietal regions compared with Suzuki grading.
Conclusion: The Td significantly correlated with conventional angiographic grading and with the status of hemodynamic impairment in patients with MMD. QDSA and Td measurements can provide a simple and quantitative angiographic grading system for patients with MMD.

Keywords: angiography; digital subtraction; magnetic resonance imaging; moyamoya disease

1. Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disorder characterized by idiopathic progressive stenosis or by intracranial artery occlusion.[1] Stenosis begins in the supraclinoid portions of the internal carotid artery and can progress to the proximal cerebral arteries. The conventional classification scheme for digital subtraction angiography (DSA), Suzuki grading, remains the reference standard for evaluating the

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Wan-Yuo Guo, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: wyguo@vghtpe.gov.tw (W.-Y. Guo).

http://dx.doi.org/10.1016/j.jcma.2014.05.007

severity of MMD. However, Suzuki grading does not represent the hemodynamic status of the whole brain parenchyma.[2–4] In addition, it provides qualitative information and is insensitive to longitudinal follow-up.[5] Previous studies have shown that color-coded parametric quantitative DSA (QDSA) increases the conspicuity of subtle blood flow changes[6] and enables the quantitative monitoring of hemodynamics in the angiographic suite.[7,8] For example, a study by Lin et al[7] demonstrated the feasibility of QDSA for the measurement of cerebral circulation time as a surrogate hemodynamic marker in patients with carotid stenosis.[7]

In this study, we hypothesized that QDSA could provide a more sensitive indicator of disease severity than conventional DSA. We measured the delay time of maximal opacification (Td) between the internal carotid artery (ICA) and the middle cerebral artery (MCA) in patients with MMD, and correlated these Tds with the hemodynamic parameters obtained from dynamic susceptibility-weighted perfusion-weighted magnetic resonance imaging (DSC-PWI).

2. Methods

2.1. Patient selection

This study was approved by the Taipei Veterans General Hospital Institutional Review Board. From March 2011 to January 2013, 18 patients with MMD were referred for DSA examination (mean age 22.8 years; range, 2–53 years; 7 men and 11 women). The patients were prospectively enrolled into our study and underwent DSA and DSC-PWI at intervals of <3 months. Informed consent was obtained prior to conducting DSA. Data on the control group were obtained from a group of 14 patients with no evidence of hemodynamic abnormality (mean age, 46.6 years; range, 21–63 years).[7]

2.2. Imaging protocol and data analysis

2.2.1. Cerebral angiography

All angiographic examinations were performed using a biplane angiography suite (AXIOM-Artis; Siemens, Erlangen, Germany). A 4 F angiocatheter was placed at the level of the C4 vertebral body for DSA. The imaging parameters were six frames per second for the DSA throughout the entire acquisition series for 12 seconds or until maximal opacification of the superior sagittal sinus.[7,9] Twelve milliliters of a 60% diluted contrast medium (340 mgI/mL) were injected into the patients at a rate of 6–8 mL/s using a power injector (Liebel-Flarsheim Angiomat Illumena; Cincinnati, OH, USA).

Two neuroradiologists, with 7 years and 5 years of experience, respectively, classified the stenoocclusive changes in the ICA into six angiographic stages as defined by Suzuki et al[1,10]: Stage I, narrowing of the carotid bifurcation only; Stage II, dilation of the main cerebral arteries with the appearance of moyamoya vessels; Stage III, partial disappearance of the anterior and middle cerebral arteries with increased moyamoya vessels around the circle of Willis; Stage IV, advanced stenoocclusive changes in the ICA, with the anterior cerebral artery (ACA) and MCA traced very dimly or in a completely different shape; Stage V, absence of the ACA and MCA with further reduction of the moyamoya vessels; and Stage VI, blood supply from the external carotid artery only and almost complete disappearance of the moyamoya vessels. The final Suzuki grades were determined by consensus.

Subsequently, the DSA images were color-coded using postprocessing software, syngo iFlow (Siemens Healthcare, Siemens, Erlangen, Germany), based on the X-ray attenuation along the angiographic frames.[6,7] The time point at maximal X-ray attenuation was defined as the time of maximal opacification (Tmax). Four regions of interest (ROIs), the distal cervical, petrous, and supraclinoid portions of the ICA, as well as the M2 of the MCA, were measured on the anteroposterior DSA views. The Td of the MCA was defined as the difference in the Tmax between the M2 and the ICA (the average Tmax of the distal cervical, petrous, and supraclinoid portions of the ICA; Fig. 1). The same two neuroradiologists measured the Tds independently, blinded to the perfusion and magnetic resonance imaging (MRI) findings of the patients.

2.2.2. MRI and DSC-PWI

Brain MRI was obtained on a 1.5 T (Signa HD, GE Healthcare, Milwaukee, WI, USA) or a 3 T scanner

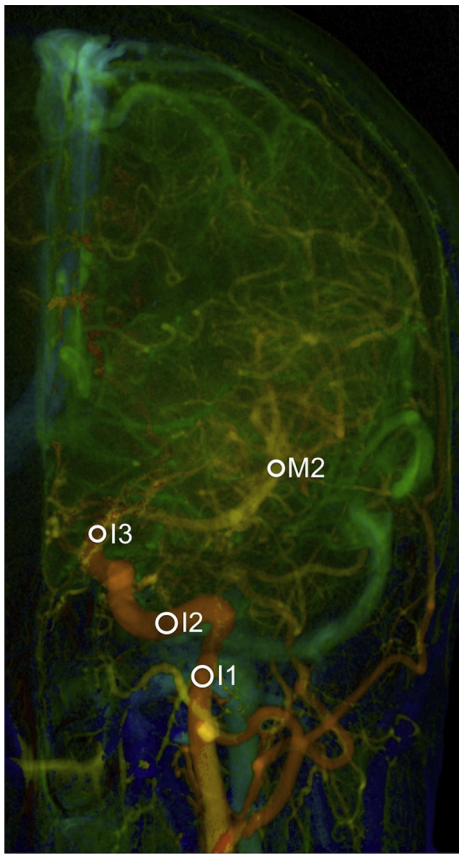

Fig. 1. Left common carotid color-coded angiogram of a 26-year-old woman with MMD. Four regions of interest: I1, cervical portion of the ICA; I2, petrous portion of the ICA; I3, supraclinoid portion of the ICA; M2, the midpoint of the MCA M2 segment. ICA = internal carotid artery; MCA = middle cerebral artery; MMD = moyamoya disease.

(Discovery MR750, GE Medical System, Milwaukee, WI, USA). Thereafter, DSC-PWI was acquired using a multislice gradient-echo EPI pulse sequence [repetition time/echo time (TR/TE), 1000/40 ms; flip angle, 60° on a 1.5 T scanner; or TR/TE, 1000/27 ms; flip angle, 35° on a 3 T scanner]. The matrix was 128 × 128 and the section thickness was 7 mm. An intravenous single dose (0.5 mmol/mL, 0.2 mL/kg body weight) of gadoterate meglumine (Gd-DOTA, Dotarem, Guerbet, Roissy CdG, France), followed by 20 mL of normal saline, was injected at a rate of 2–4 mL/s.

The DSC-PWI results were postprocessed using software implemented on MATLAB (MathWorks, Inc, Natick, MA, USA) as described previously.[11] Briefly, the algorithm was based on a mixture of multivariate gaussians and the expectation-maximization algorithm initialized according to the results of hierarchical clustering.[12] The brain regions were dissected automatically to extract various perfusion compartments from DSC-PWI so that each compartment consisted of pixels of similar signal-time curves. The perfusion parametric maps in the slice that passed through the body of the lateral ventricle were then evaluated. In each hemisphere, four ROIs were drawn semiautomatically on the time-to-peak (TTP) map: medial frontal region, lateral frontal region, parietal region, and occipital region (Fig. 2). The relative TTP (rTTP) was normalized by subtracting the TTP values of the cerebellum.

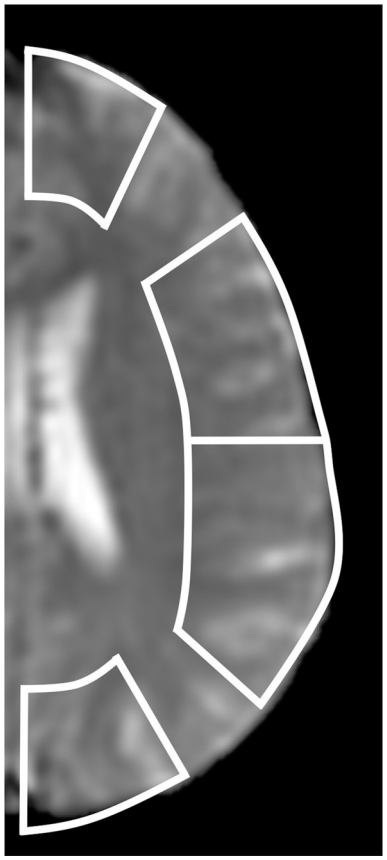

Fig. 2. Dynamic susceptibility contrast perfusion-weighted imaging is analyzed in the slice through lateral ventricles. Four regions of interest (medial frontal, lateral frontal, parietal, and occipital regions) are drawn semi-automatically in each hemisphere.

2.3. Statistical analysis

All statistical analyses were performed using SPSS 20.0 (IBM Corporation, Somers, NY, USA). The intraclass correlation coefficient (ICC) with a 95% confidence interval (CI) and absolute agreement was calculated to assess the interobserver reliability of the Suzuki grading scores, the Tmax of each ROI, and the Td measurements. The ICC values were compared using the following scale: almost perfect agreement (1.00–0.8), substantial agreement (0.8–0.6), moderate agreement (0.6–0.4), fair agreement (0.4–0.2), and slight agreement (<0.2). If the 95% CI of the ICC was zero, it indicated nonsignificant correlation between the two observers' ratings. The Kruskal–Wallis test was used to compare the Tds among the control group, patients without infarction, and patients with infarction, and also to compare the Tds among different types of infarction. Spearman rho correlations were applied to compare the Tds among different Suzuki stages and the correlations among the Tds, Suzuki stages, and rTTPs. Correlations were considered significant if $p < 0.05$.

3. Results

Of the 18 examined patients, two had received a unilateral extracranial-intracranial bypass, with the operated hemisphere excluded. Therefore, this study included 34 carotid angiograms. According to the Suzuki grading system (mean; 3.32),[1,10] two hemispheres were Stage I, 10 hemispheres were Stage II, eight hemispheres were Stage III, five hemispheres were Stage IV, seven hemispheres were Stage V, and two hemispheres were Stage VI. The interval between DSA and MRI ranged from 0 days to 21 days (mean; 3.8 days). We divided the hemispheres into four groups: Group 1, asymptomatic and no evidence of infarction ($n = 6$); Group 2, symptomatic, including transient ischemic attack or mild ischemic symptoms, but no evidence of acute or old infarction ($n = 8$); Group 3, presence of acute or old infarction ($n = 18$); and Group 4, presence of intraparenchymal hemorrhage ($n = 2$). According to the patterns of infarction, 10 hemispheres had lacunar infarcts, including one embolic infarct, four watershed infarcts, and five territorial infarcts.

The Tmax at all ROIs and Td measurements showed substantial to perfect agreement between the two neuroradiologists' ratings (ICC range, 0.741–0.912). The neuroradiologists' Suzuki grading results showed moderate agreement (ICC = 0.539; 95% CI, 0.223–0.755; Table 1). The Td of the control group was 0.47 ± 0.26 seconds. The Td of the MMD patients was measurable in 32 hemispheres. In two hemispheres of Stage VI, the MCA was not opacified in the DSA (mean, 0.97 ± 0.81 seconds; range, 0–3.5 seconds). The Tds showed significant differences among the Suzuki stages ($p < 0.05$, Kruskal–Wallis test). The Td was significantly longer in the patients with MMD than in the control group ($p = 0.002$, Mann–Whitney U test). The Tds of the patients

Table 1
Interobserver reliability of two physicians.

ROI (Tmax)	ICC (95%, CI)
I1	0.741 (0.512, 0.871)
I2	0.858 (0.715, 0.932)
I3	0.858 (0.717, 0.932)
M2	0.877 (0.747, 0.943)
Delay time (Td)	0.912 (0.814, 0.959)
Suzuki grading	0.539 (0.223, 0.755)

CI = confidence interval; ICC = intraclass correlation coefficient; ROI = region of interest.

presenting with infarction and those with less severe symptoms displayed nonsignificant differences. The Tds in patients with different patterns of infarction also displayed nonsignificant differences.

The Suzuki grading scores, Tds, and rTTPs of the different regions are shown in Table 2. We identified a strong correlation between the Td and the Suzuki stages ($r = 0.798$; $p < 0.001$, Spearman rho correlation test; Fig. 3). The Td showed significantly higher correlation with prolonged rTTP in the medial and lateral frontal regions than the Suzuki grading system (Fig. 4A and B). The Td correlated significantly with the rTTP in the parietal region (Fig. 4C).

4. Discussion

The principal findings of this study were that the Td was significantly prolonged in the patients with MMD compared with the control group, and that the Td correlated with Suzuki staging, and showed a higher correlation with the cerebral perfusion abnormalities than conventional Suzuki staging. This finding was not unexpected because Suzuki staging is primarily based on the extent of basal stenoocclusive changes. Hemodynamic changes are not considered in the Suzuki staging system.[1]

Recent advances in flat detector angiography and post-processing software have enabled the quantitative evaluation of time-density curves and the transit times of contrast media in angiographic suites.[6,7] When a comparable radiation dose is applied to conventional DSA,[13] flat detector DSA provides higher temporal resolution imaging and richer hemodynamics of vascular diseases. We used the frame rates of six frames per second in the current study for moyamoya disease. The frame rate is still suboptimal for high-flow cerebrovascular diseases, such as dural arteriovenous fistula or arteriovenous malformation.[9] The color-coding algorithm can enhance the subtle hemodynamic changes on DSA images without extra radiation doses and extra contrast medium. In this study, we measured the Td of the MCA to determine the severity of MMD for two reasons. First, the Td of the MCA represents the time interval for a contrast bolus to travel from the internal carotid artery and collateral arteries to the distal MCA, and can be used to estimate the bolus delay and the degree of stenoocclusive change. Second, several previous studies have observed that the cerebral circulation time (CCT) is inversely correlated with the cerebral blood flow (CBF)[14,15] and the cerebrovascular reserve[16] in patients with stenoocclusive arterial diseases. However, defining the CCT in MMD is complicated using conventional DSA because of reduced blood irrigation and flattening of the contrast-filling slopes of the distal small arterial branches.[17] Because the stenoocclusive changes in MMD predominantly involve the circle of Willis, and the distal capillary bed and venous system are fully dilated to compensate for reduced blood flow, we hypothesized that the Td might play a key role in defining the CCT and indicating the severity of MMD.

Table 2
Comparison between the delay time (Td), Suzuki grading, and hemodynamic abnormalities.

	Suzuki staging ($n = 34$)	Td ($n = 32$)
Relative time to peak (rTTP)		
Medial frontal region	0.392*	0.528**
Lateral frontal region	0.394*	0.495**
Parietal region	NS	0.512**
Occipital region	NS	NS
Suzuki staging		0.798***

Data are Spearman rho correlation coefficients.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
NS = not significant; Td = delay time.

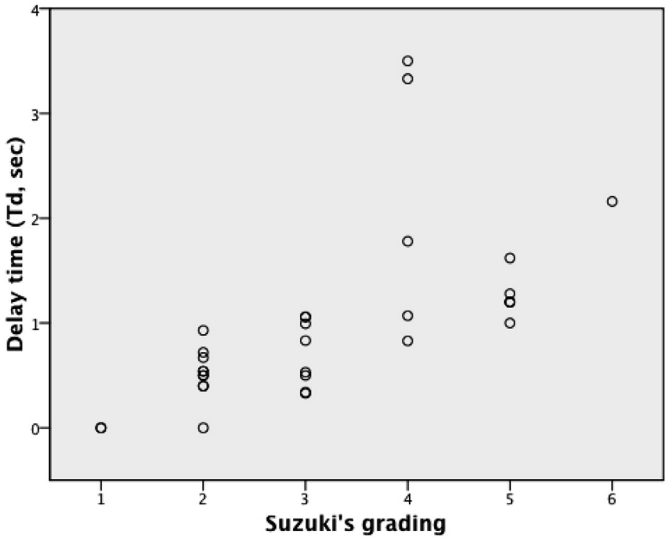

Fig. 3. A significant correlation is noted between delay time (Td) and Suzuki grading.

Because MMD is a disease associated with bilateral involvement, and posterior cerebral artery involvement would occur at relatively advanced stages of the disease, we used the cerebellum as the internal reference for evaluation of the perfusion impairment of both cerebral hemispheres. Our study results showed that the Td of the MCA showed higher correlation with the rTTP than with Suzuki staging. We used the TTP of the time-signal curve as a parameter of perfusion. The TTP map provides higher contrast-to-noise ratios than other parametric mapping [e.g., CBF, cerebral blood volume (CBV), and mean transit time (MTT)]. In addition, the TTP map is independent of deconvolution algorithms or the selection of the arterial input function.

Because of the combination of macro- and microvascular information, the TTP is one of the most sensitive parameters

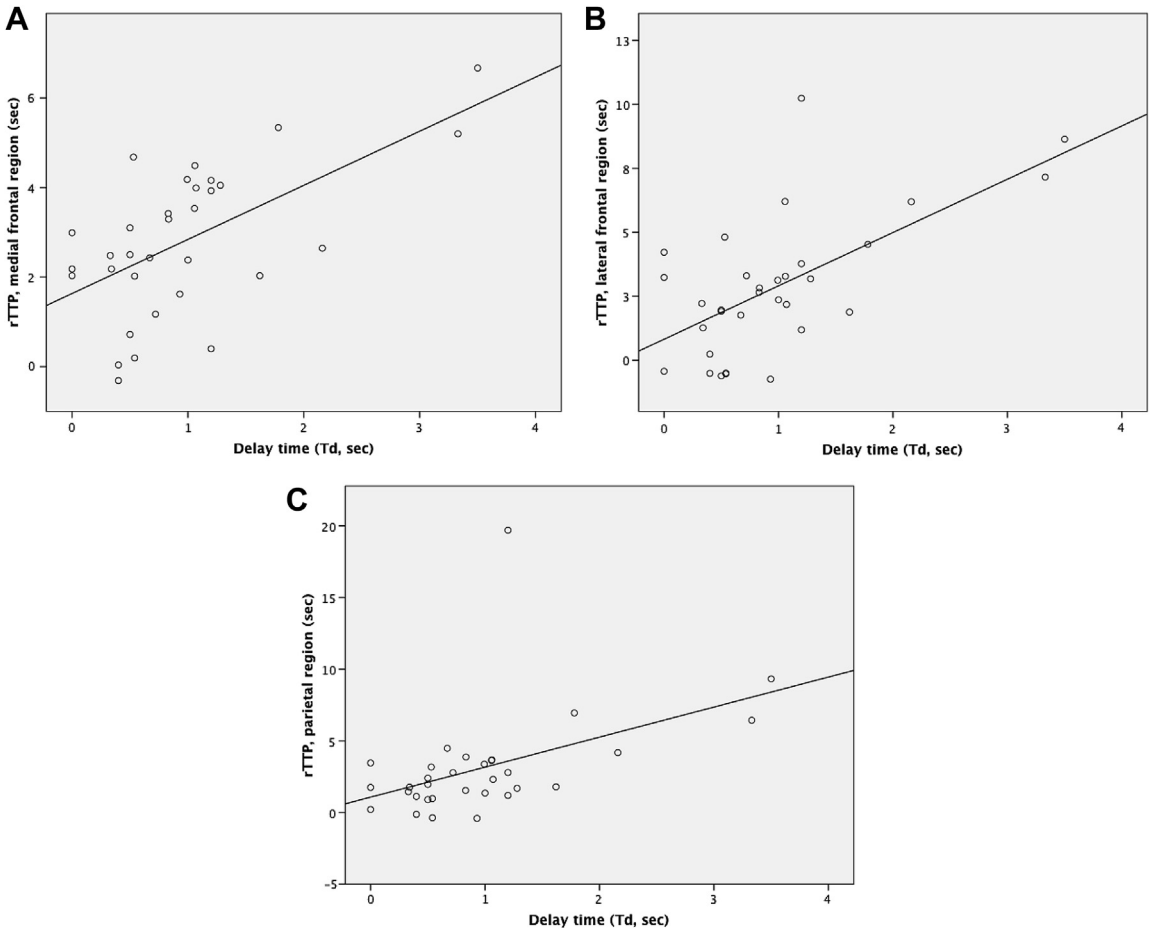

Fig. 4. Correlation between delay time (Td) and relative time-to-peak (rTTP) in (A) medial frontal region, (B) lateral frontal region, and (C) parietal regions.

of perfusion, used by previous studies to discriminate the infarct core and penumbra[18] and to determine the diffusion–perfusion mismatch in several clinical trials.[19–22] The changes of TTP perfusion maps after revascularization surgery were also correlated with clinical outcome in patients with moyamoya disease.[23] A study by Calamante et al[22] effectively demonstrated the dependency of the TTP on bolus delay and, to a small degree, on the MTT. Therefore, the perfusion deficits in MMD might result from the delayed contrast bolus (as indicated by the Td of the MCA). A prolonged Td of an artery can indicate that its territorial tissues are at risk of hypoperfusion, although the collateral blood supply and cerebrovascular reactivity might have compensated and masked the hemodynamic impairment. In regions with a long bolus delay, even in a well-compensated status, tissues remain at higher risk if the cerebral perfusion pressure declines further.

Several possible explanations could exist for the Td showing nonsignificant differences between the patients with infarction and those without infarction. First, patients with MMD display various and characteristic infarct patterns.[24] These patterns of infarction vary with age of onset and might be associated with age-related selective vulnerability of the cortical gray matter. Second, thrombus formation frequently occurs in MMD, as identified in a previous histopathological study.[25] Investigators have also proposed that in addition to hypoperfusion of the progressive cerebral arteries, thromboembolism underlies the development of large infarctions in patients with MMD.[24]

It was reported that the mean dose-area product (DAP) of a diagnostic cerebral angiography was 85.7 Gy·cm^2 (mean, 68–149 Gy·cm^2).[13] It was also recommended that a complete DSA workup of moyamoya disease should include five vessels (bilateral common carotid, external carotid, and 1 vertebral artery).[26] In the current study, the DAP per vessel (including both posteroanterior (PA) and left lateral projections) from the DSA automatic dose reports was approximately 30 Gy·cm^2. As a result, the total DAP of current comprehensive moyamoya DSA workup was approximately 150 Gy·cm^2. This value is still similar to that reported in the literature.

This study suffers from several limitations. First, we showed that Td can improve the prediction of hemodynamic status in MMD using QDSA. However, we were unable to establish if the Td can be used for the evaluation of patients who have undergone bypass surgery or patients with other cerebral stenoocclusive vasculopathy. Second, the Td was defined according to the angiographic time-density curves. The parameters of contrast medium administration in DSA (e.g., the injection rate, injection volume, catheter tip, and the patient's cardiac function) might alter the contrast bolus, resulting in different shapes and waveforms of the time-density curves and

Tmax.[27] Standardizing the DSA procedures throughout the entire study could have minimized these intramethod variabilities. Finally, the Suzuki grading system and Td measurements both focus predominantly on the stenoocclusive changes in anterior circulation. Therefore, the extent and degree of collaterals, particularly those from the posterior circulation, are not effectively assessed, despite being critical in the tissue salvaging of chronic cerebral ischemia.

In conclusion, the Td of the MCA provides closer correlation with the hemodynamic severity of MMD than the conventional Suzuki grading. Prolonged Td of the MCA corresponds with the degree of hemodynamic impairment in the frontal and parietal regions in patients with MMD. The Td of the MCA could provide a simple and quantitative angiographic measurement for predicting cerebral perfusion status in patients with MMD.

Acknowledgments

This research is sponsored by Taipei Veterans General Hospital (V101B-026) and cosponsored by Taipei Veterans General Hospital and Siemens Healthcare (grant number: T1100200).

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