Cerebral Vasospasm and Hemodynamic Alterations Following Aneurysmal Subarachnoid Hemorrhage Revealed with Combined CT Perfusion and CT Angiography

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Abstract: *Purpose:* Vasospasm following aneurysmal subarachnoid hemorrhage (SAH) is considered to be one of the major factors leading to neurological deficits and is associated with poor outcome in SAH. In this study, we utilized combined computed tomography angiography (CTA) and CT perfusion (CTP) techniques to assess radiographic cerebral vasospasm with attempts (1) to determine if cerebral vasospasms can be detected in patients with onset of SAH less than 3 days, and (2) to assess the perfusion deficits or hemodynamic alterations of the affected brain tissues following acute or delayed SAH.

Materials and Methods: Thirty-eight patients with SAH and seven without SAH were recruited in the present study. After SAH was confirmed with a baseline non-enhanced head CT scan, the combined CTA-CTP procedures were performed and the CTP maps were created simultaneously. Quantitative CTP measurements including cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time-to-peak (TTP) were carried out for each of the territories in the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA), respectively.

Results: Among 38 patients with SAH, a total of 33 aneurysms were detected and their anatomic locations were as follows: PCA (17), ACA (10) and MCA (6), respectively. Furthermore, multiple aneurysms were also present in 7 of the 33 patients with SAH. Whole-brain CTP measurements showed perfusion deficits in all of the patients with SAH. Both CBV and CBF values were significantly reduced in the affected areas of brain tissues. The incidence of cerebral vasospasm was significantly higher in the patients with delayed SAH (61.5%) than those with onset of SAH in less than 3 days (12%) (Fisher exact test, $p<0.05$). Additionally, quantitative analysis of CTP measurements of the patient without cerebral vasospasms with those with CVS reveals that, when compared to the control, all the patients with or without cerebral vasospasms showed significant differences in all four parameters measured ($p<0.05$, one-way ANOVA). Furthermore, according to their corresponding territories of the ACA, MCA and PCA, there were significant decreases in the mean CBV and CBF values of the ACA, MCA and PCA of SAH patients compared to the control patients, respectively. Moreover, a significant prolongation in the mean MTT and TTP values in SAH patients was also evident.

Conclusion: Although a much higher incidence of cerebral vasospasms usually occurs in the delayed SAH, cerebral vasospasm could be detected in less than three days following the onset of acute SAH. Furthermore, the combined CTA-CTP procedures, along with the baseline CT scan, could also offer diagnostic benefits for assessing changes in global perfusion following the onset of aneurysmal SAH.

Keywords: Computed tomography, perfusion, subarachnoid hemorrhage, cerebral vasospasm.

INTRODUCTION

Subarachnoid hemorrhage (SAH) following aneurysmal rupture is a devastating disease which accounts for a significant percentage of death and disability [1,2]. There are 25000 to 30000 new cases each year in the USA alone [3]. Furthermore, an estimated 20% to 40% of patients who survived the initial insult may develop delayed cerebral ischemia (DCI) between 3-16 days following aneurysmal SAH [4,5]. Although pathophysiological processes under-lying ischemia or hypoperfusion following the onset of aneurysmal SAH are complex and poorly understood, there is general agreement that, among various factors, development of cerebral vasospasm in the territory of the affected arteries following aneurysmal SAH is one of the most critical steps leading to neurological deficits [5,6]. Therefore, effective ways to prevent the development of neurologic deficits in patients with aneurysmal SAH and promote adequate medical interventions depend essentially on early detection of cerebral vasospasm and dedicated evaluation of capillary-level hemodynamic perfusion in the affected territories following aneurysmal SAH.

Computed tomography angiography (CTA) has been widely implemented in many large hospitals or medical centers to identify cerebral aneurysms and measure changes in cerebral vessel narrowing [7,8]. However, this useful diagnostic tool is limited since it is unable to provide information on more subtle changes in hemodynamics as well as on perfusion status in the affected brain tissue under cerebral hemorrhagic conditions, which are key parameters potentially

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associated with development of neurologic deficits. More recently, with the advent of the Table joggling techniques, especially the availability of multi-detector CT slicing imaging [7,9-11,31], whole brain CT perfusion (CTP) coupled with CTA [11] has begun to be adopted into clinical practices by creating perfusion maps of the brain regionally and globally [12,13]. By curtailing the limitation of inadequate coverage of the brains with conventional CTP techniques, whole-brain CTP offers much more comprehensive assessments of hemodynamic conditions by looking at a set of key parameters that are directly associated with changes in blood perfusion or perfused blood volume in various ischemic conditions [14]. Using similar CTP maps, we have previously reported that there was a significant decrease in perfused blood volume in several cerebral lobes of patients with aneurysmal SAH [15].

Furthermore, clinical manifestations of aneurysmal SAH correlate well with the time course of the development of cerebral vasospasm, which usually occurs in 3-4 days, and reaches its peak between 5-7 days following cerebral hemorrhage [16-18]. Additionally, angiographic vasospasms usually become evident during the same period of time and it was reported that luminal narrowing was rarely pronounced before the third [3] or fourth day following the initial bleeding [19]. Therefore, a large body of data has been exclusively obtained from the fourth days or later after the onset of aneurysmal SAH from the initial bleeding. However, whether or not cerebral vasospasm takes place at a much earlier period of time following an acute onset of aneurysmal SAH is poorly investigated. Recently, Sanelli *et al.* [20] reported that in patients with an acute onset of aneurysmal SAH in less than 3 days from the initial bleeding, CTP maps already demonstrated perfusion deficits due to cerebral vasospasm.

In the present study, we took advantage of the combined CTA and CTP techniques as screening tools for cerebral vasospasm and assessed radiographic cerebral vasospasm with attempts to: (1) determine if cerebral vasospasm can be detected in patients with an acute onset of aneurysmal SAH in less than 3 days from first bleeding, and (2) assess the perfusion deficits and hemodynamic alterations of the affected brain tissue following the onset of SAH in less than 3 days (acute) or after 3 days (delayed).

SUBJECTS AND METHODS

Patient Population

A total of thirty-eight patients with aneurysmal SAH confirmed with non-enhanced head CT (NECT) scans at admission and admitted into our hospital between March and November 2010 were recruited for the present study. Informed consent for the present study was obtained from all patients or their designated decision makers and the study protocols were approved by the ethic committee of China Medical University. Demographic data includes 17 male and 21 female patients, aged from 27 to 72 years old with an average age of 50.5 ± 21 (standard deviation) years. Additionally, 5 female and 2 male patients with dizziness as their only symptom (between 20 to 63 years old with mean age of 48±10.6 years) were recruited as controls. NECT, CT angiograph (CTA) and whole brain CT perfusion (CTP) as one-stage procedures were routinely performed on all 45 patients involved in the study. A standardized management and treatment plan, including correction of hemodynamic instability, blood pressure and electrolytes imbalance, and anti-vasospastic agents such as nimodipine were administrated to all patients. Thirteen patients received CTA-CTP examinations prior to administration of nimodipine while the other 25 patients had CTA-CTP tests performed after administration of nimodipine. No nimodipine was administrated to patients in the control group. Furthermore, 25 patients received CTA-CTP procedures no later than three days following the onset of aneurysmal SAH; while the remaining 13 patients had CTA-CTP done between 3 and 17 days after the onset of aneurysmal SAH. NECT scans revealed normal radiographic findings in all patients with dizziness as their sole symptom.

Study Designs

On admission, all patients received a NECT scan to confirm the presence of SAH.

CTA and CTP Procedures

All CTA and whole-brain perfusion CT imaging studies were performed on a Phillip Brilliance iCT (Phillip Medical System, The Netherlands) by one stop mode. The CTA scan was used to confirm and localize the ruptured aneurysm. In all cases, a 40-50ml bolus of iopromide (300mg/ml of ioidine Ultravist) was injected by a power injector at a rate of 4-6ml per second into an antecubital vein embedded with a 19G trocar.

Perfusion CT was performed with the toggling Table technique (Jog mode) during a total scanning time of 60 seconds. CT scanning was initiated 2 seconds after the start of the injection of the contrast bolus and the scanning interval was 4 seconds for each imaging slice. A total of 15 scans were performed. The imaging

parameters of the perfusion CT were: 80kV, 125mAs, 0.33s rotation time, 128 × 0.625mm detector collimation, and a 512 by 512 reconstruction matrix. Z-section for each imaging was 5mm in dimension using the standard brain (UB) reconstruction parameters without sharpening. Window width: 40Hu, window level: 80Hu. The total DLP of each perfusion CT scanning was 1161mGy*cm (77.4mGy*cm multiplied by 15 times).

Data Analysis

CTP data was analyzed using a Philips Extended Brilliance Workspace Post-processing workstation and volume rendering (VR) images of cerebral arteries were reconstructed using advanced vessel analysis (AVA) software. Whole-brain CTP maps were created using Brain Perfusion Software. CTP measurements were made on the CTP maps. The regions of interest (ROIs) were drawn within corresponding territories of the peripheral flow of the middle cerebralartery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA), respectively. Cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP) of each z-section were measured and averaged, respectively. The incidence of cerebral vasospam were determined based on the method described by Yoon *et al.* [9]. We evaluated the following anatomic segments on CTA images for cerebral vasospams and pefusion abnormality: M1 and M2 segments of MCA, A1 and A2 segments of ACA, and P1 and P2 segments of PCA. After exclusion of artery luminial narrowing or vascular irrregularity caused by calcified patches or increased wall thickness due to atherosclerosis, which were revealed by multiple plane reconstruction (MPR) images, the presence of cerebral vasospams was confirmed if there was change in luminal narrowing greater than 25%[8].

All data presented in the present study were expressed as mean ± SD. SPSS (13.0, SPSS Chicago, IL) was used to determine a statistical significance. Independent student *t*-test and one-way ANOVA were used followed by a post-hoc analysis, when appropriate. Chi-square (χ^2) test and Fisher exact tests were also performed. *P* value <0.05 was considered statistically significant.

RESULTS

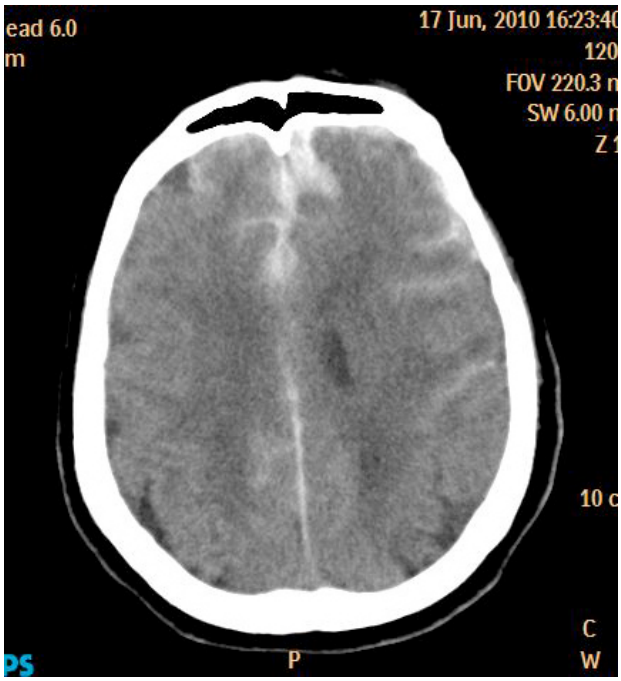
CTA and whole-brain CTP examinations were successfully performed on all 45 patients enrolled in the present study. The M1 and M2 segments of the MCA, the A1 and A2 segments of the ACA as well as the P1 and P2 segments of the PCA were evaluated for vasospasm and perfusion abnormality. In the control group, NECT revealed no abnormalities of the cerebral arteries in all 7 patients who had dizziness as the sole clinical symptom. Additionally, no vasospasm or perfusion abnormality was identified on a whole-brain CTP color map. Of the 38 patients with aneurysmal SAH, a total of 33 identifiable aneurysms were detected and their anatomic locations were as follows: PCA (17), ACA (10) and MCA (6). Additionally, multiple aneurysms were also found in 7 out of the 33 patients with aneurysmal SAH.

Table 1: Incidence of Cerebral Vasospasm During Acute and Delayed Period of SAH

Onset	Patients	Patients with CVS	%
Acute	25	3	12.0
Delayed	13	8	61.5

Based on the timing when the CTA-CTP procedure was performed, the patients were classified into acute or delayed SAH groups: patients in acute SAH group received CTP-CTA procedure in less than 72 hours after the aneurysmal SAH onset while the delayed SAH received the same procedure 72 hours after the first bleeding. The CTP maps were generated from 25 acute and 13 delayed SAH patients. We found that 28.9% (11/38) of the patients with SAH exhibited cerebral vasospasm as defined by vessel narrowing greater than 25%. Among the 11 patients confirmed with cerebral vasospasm, 3 were patients with acute aneurysmal SAH and 2 out of those 3 patients developed DCI later. The incidence of cerebral vasospasm of among patients with acute or delayed SAH was summarized in Table **1**. This data indicated that the incidence of cerebral vasospasm was significantly higher in patients with delayed SAH than those with acute SAH (Fisher exact test, p=0.037). Of those 11 patients showing cerebral vasospasm, vasospasms were observed in 2 ACA and 9 MCA. As shown in Figure **1**, the apparent perfusion deficits were visible in the corresponding territories of arteries with vasospasm in 63.6% (7/11) of the subjects.

We further quantitatively analyzed the CTP measurements of the patients without cerebral vasospasm against those with cerebral vasospasm and the results were shown in Table **2**. First of all, when compared to the control, all SAH patients with or without cerebral vasospasm showed significant differences in all four parameters measured (p<0.05, one-way ANOVA). For instance, the patients with cerebral vasospasm had significantly lower CBV and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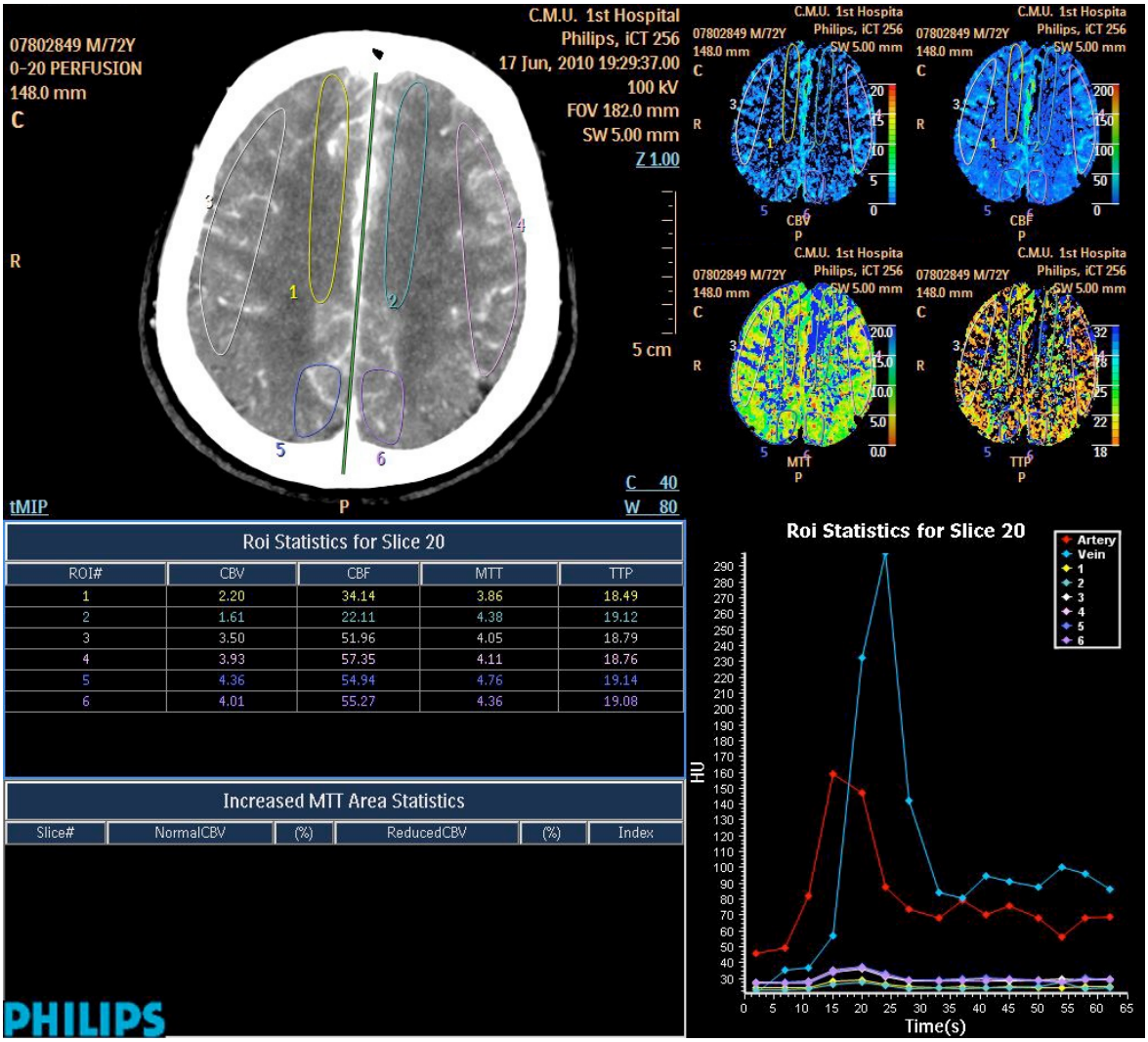
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3 3.50 51.96 4.05 18.79
4 3.93 57.35 4.11 18.76
5 4.36 54.94 4.76 19.14
6 4.01 55.27 4.36 19.08
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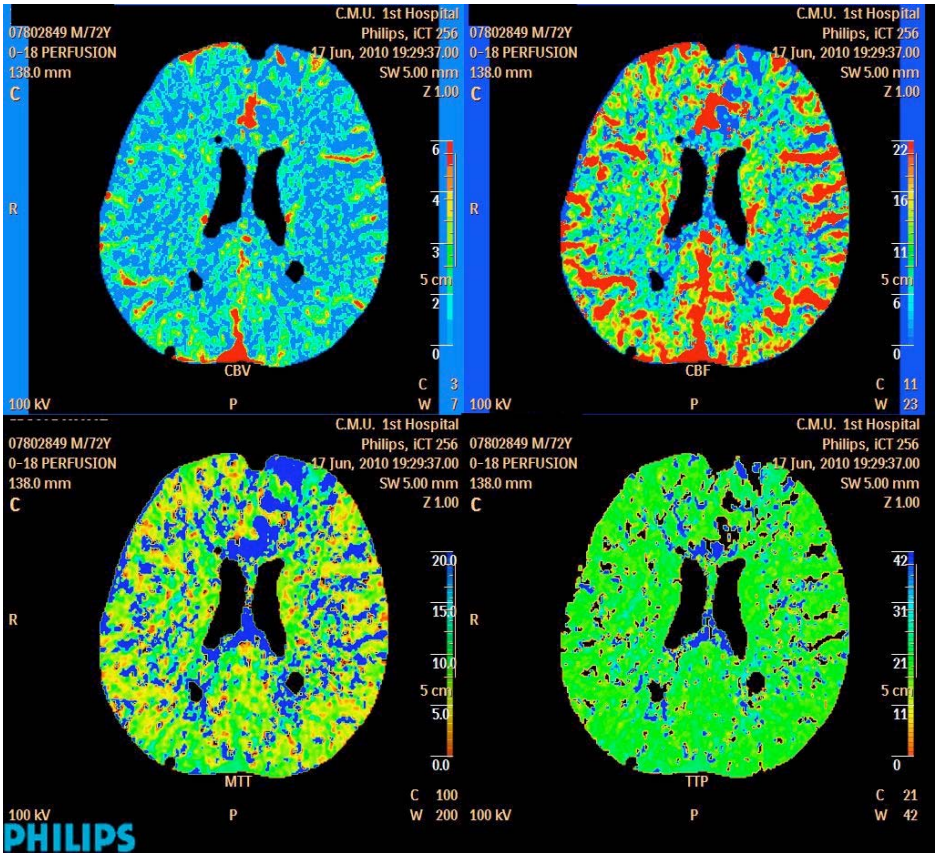

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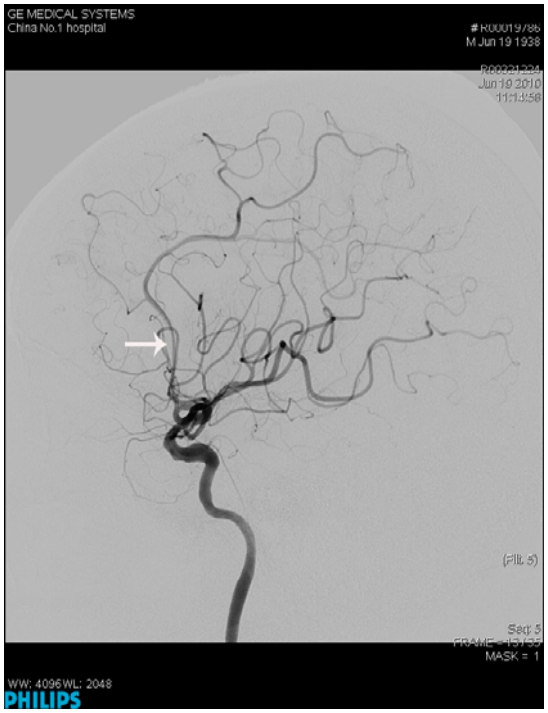


E

Figure 1: A seventy two-year-old man with severe headache for 6 hrs was presented to hospital. NECT imaging demonstrates hyperdensities predominately in both frontal lobes and the left temporal sulcus (**A**), confirming the presence of SAH. Combined CTP-CTA was performed 9 h after the onset of acute SAH. CTA shows an aneurysm at the A2 segment of the right ACA and vasospasm of the left ACA (**B**). CTP maps show a profound hypoperfusion in the territories of ACA (**C** and **D**). Digital subtraction angiogram (DAS) demonstrates the persistence of vasospasm in the left ACA 48 h after symptom onset (**E**).

Table 2: CTP Measurements of Control, Presence and Absence Vasospasms

	Control (n=7)	No vasospasm= (27)	Vasospasm (n=11)
CBV (mL/100g)	5.57±1.25	3.66±0.93*$^{\Delta}$	2.17±0.88*
CBF (mL/100g/ min)	75.11±17.86	43.44±11.74*$^{\Delta}$	26.73±14.00*
MTT (s)	3.47±0.47	5.65±1.37*$^{\Delta}$	6.53±1.58*
TTP (s)	20.03±1.99	21.54±2.89*$^{\Delta}$	23.63±2.02*

*p < 0.05 when compared to control (One-way ANOVA). $^{\Delta}p$ <0.05 when compared to CVS and control (One-way ANOVA).

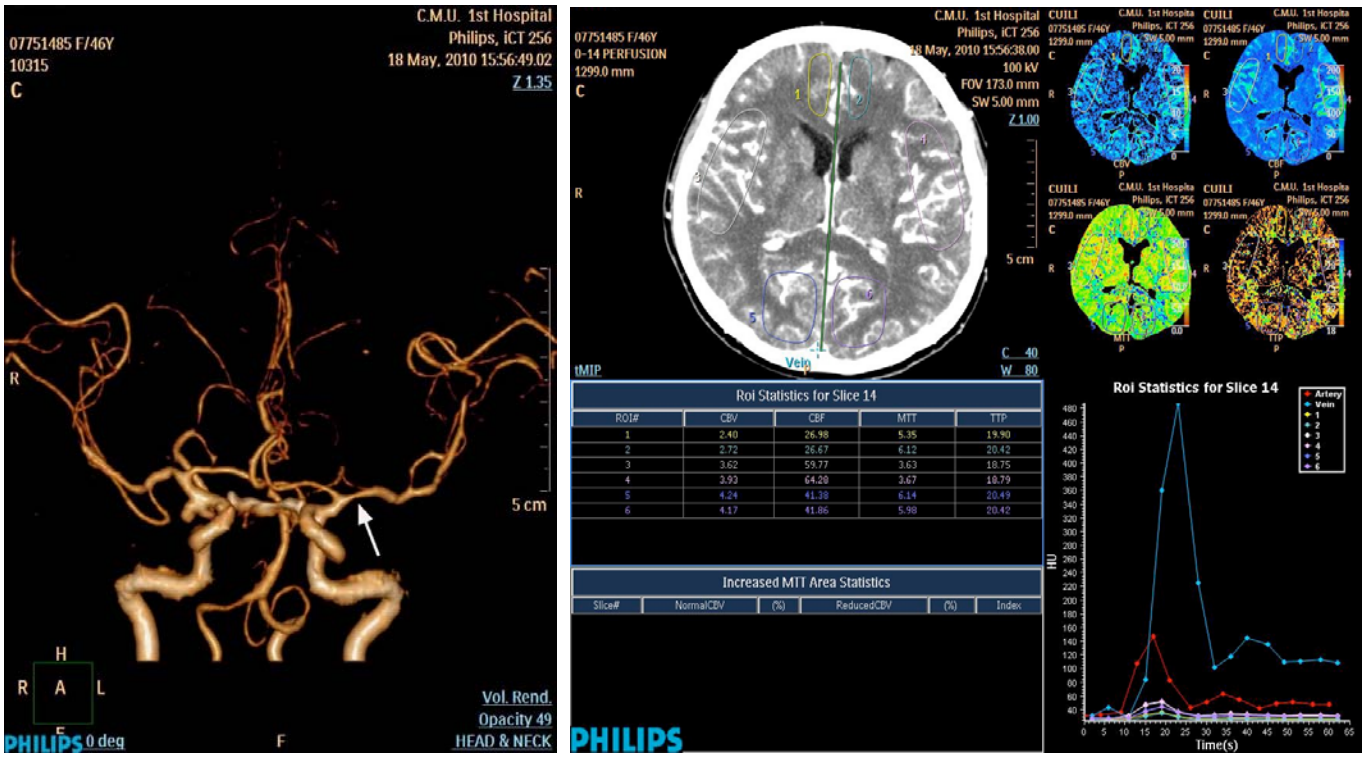
CBF values whereas both MTT and TTP values were significantly prolonged, suggesting a poor microcirculation in the affected region due to perfusion deficits. The difference in MTT values between patients without cerebral vasospasm and the control is 2.18 seconds while it increases to 3.06 seconds in patients with vasospasm. Besides the perfusion deficits frequently encountered in this study, hyper-perfusion was also noted with an increase in blood flow and volume in the territory of cerebral arteries with vasospasm as shown in Figure **2**.

According to the corresponding distributions of the territories of ACA, MCA and PCA, the differences of CTP profiles measured from the patients with acute or delayed SAH were further assessed and the results were shown in Table **3**. One-way ANOVA indicated that there were significant decreases in the mean CBV and CBF values of the ACA, MCA and PCA of SAH patients compared to controls. Moreover, a significant prolongation in the mean MTT and TTP values in SAH patients was also evident. Although there was an overall decrease in both CBV and CBF values and an increase in both MTT and TTP values within the territories of the ACA, MCA and PCA of patients with acute or delayed SAH when compared to controls, no significant changes in all four CTP measurements between patients with acute SAH and delayed SAH were found. This finding indicated that there were no further changes in both blood volume and cerebro-vascular circulation once intracranial hemorrhages took

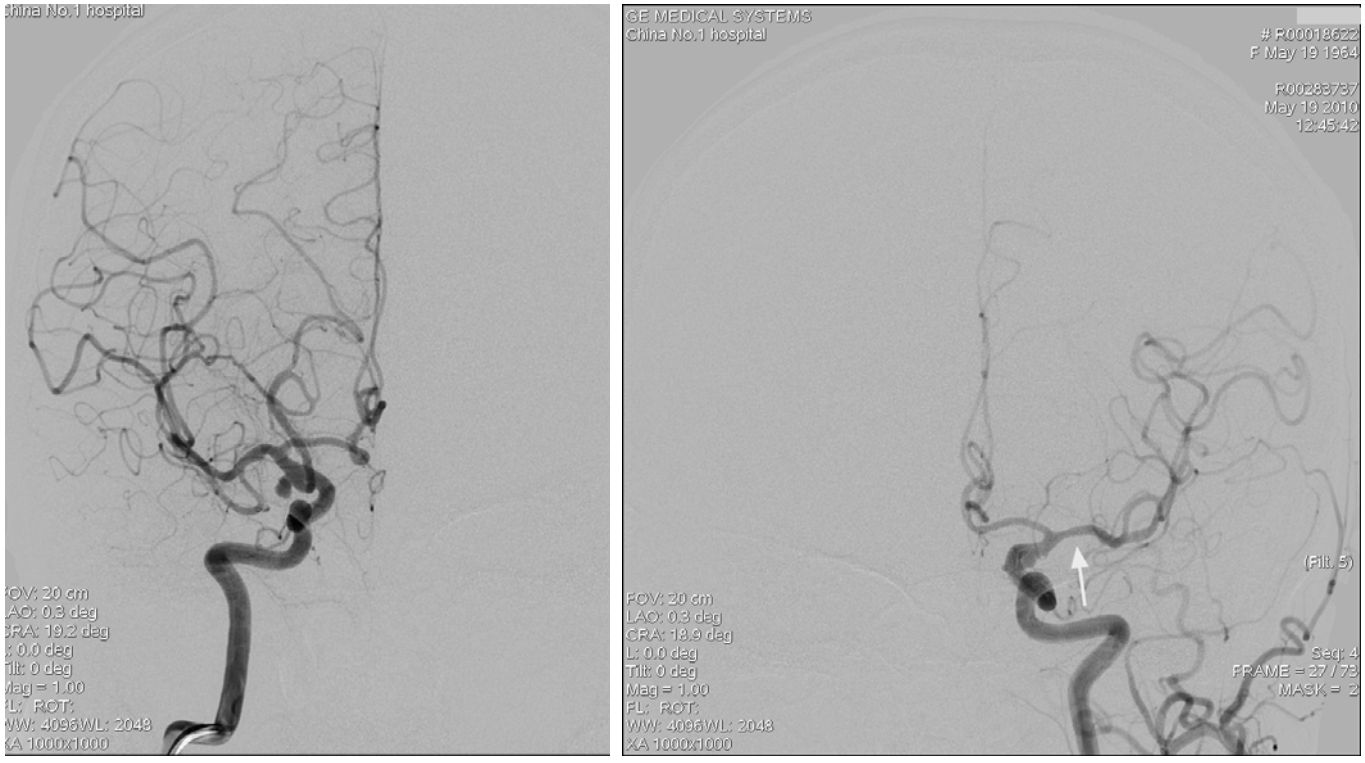
Table 3: CTP Measurements of Control, Acute and Delayed SAH

		Control (n=7)	Acute (n=25)	Delayed (n=13)
CBV	ACA	3.60±0.84	2.06±0.97*$^{\Delta}$	2.47±0.78*$^{\Delta}$
	MCA	5.12±1.26	3.03±1.26*$^{\Delta}$	3.56±0.85*$^{\Delta}$
	PCA	4.83±1.19	2.75±0.96*	3.02±0.73*
CBF	ACA	53.84±11.68	28.03±10.85**	30.90±13.09**
	MCA	73.41±19.14	42.99±12.85**	43.95±11.23**
	PCA	56.46±10.52	36.44±10.21*	34.82±8.68*
MTT	ACA	3.80±0.66	5.25±1.85*	5.56±1.31*
	MCA	3.79±0.80	5.24±1.75*	5.62±1.37*
	PCA	4.25±0.83	5.52±1.60*	5.98±1.39*
TTP	ACA	20.32±2.13	23.97±2.56*	24.34±3.24*
	MCA	20.19±1.95	24.52±2.24*	23.14±3.18*
	PCA	20.94±1.85	23.99±2.33*	23.96±3.4*

Note: *p<0.05 when compared to controls.$^{\Delta}$ when compared to delayed SAH, *when compared to delayed SAH.



A **B**



C **D**

Figure 2: A fourty six-year-old female with severe headache and vomiting for 5 days was presented to hospital. Baseline NECT confirmed SAH. Combined CTP-CTA was performed 5 days after onset of SAH. CTA shows aneurysms at the PCA bilaterally accompanying vasospasms of both MCA territories (**A**). CTP maps show a large region of both MCA territories with reduced MTT and TTP values (**B**). Additionally, there were significant decreases in both CBV and CBF values in this area compared to those in ACA territories. Digital subtraction angiogram (DSA) demonstrates the persistence of vasospasm in the left MCA 6 days after symptom onset (**C** and **D**).

place. However, when compared to ACA and MCA, there were significant changes in both CBV and CBF values within the territories of PCA between the patients with acute and delayed SAH (t-test $p<0.05$), suggesting region-specific perfusion deficits following SAH onset.

DISCUSSION

Ultimately, the goal of clinical management and intervention of aneurysmal SAH is to prevent cerebralvasospasm, which could lead to a delayed cerebral ischemia (DCI) [21]. Thus, it is imperative to understand the subsequent changes in blood perfusion and hemodynamics of brain parenchyma at the microcirculatory level following aneurysmal SAH and identify potential patients at risk for developing cerebral vasospasm and delayed cerebral ischemia. However, the early detection of cerebral vasospasm with conventional modalities of CTA and DSA still remains a challenge for neuroradiologists and neurologists. In the present study, we have employed a combination of non-contrast CT, CTA and CTP as a one-stage procedure to assess the status of a whole brain perfusion in patients with aneurysmal SAH in either less than 3 days (acute SAH) or between 3 to 17 days (delayed SAH) from the initial bleeding. Our results indicate that although the incidence of cerebral vasospasm is significantly lower (12.0%) in acute SAH patients than in delayed SAH ones (63.6%), the abnormalities in whole brain perfusion revealed by the CTP color maps can occur in a much earlier time period following the onset of aneurysmal SAH. This finding is of great clinical importance for the development of an early intervention for this disease.

Subarachnoid hemorrhage following a ruptured intracranial aneurysm is an ominous clinical emergency with high mortality and morbidity [2]. Clinically, the majority of patients who survived initial cerebral hemorrhages could still develop long-term or permanent neurological deficits which greatly impair functional status and quality of life. Cerebral vasospasm after aneurysmal SAH usually occurs and clinical diagnosis of the presence of cerebral vasospasm following aneurysmal SAH, not caused by rebleeding or hydrocephalus, depends mainly on typical clinical manifestations of the occurrence of deteriorating neurologic deficits secondary to aneurysmal SAH retrospectively. However, asymptomatic cerebral vasospasm usually goes unnoticed. For the aforementioned reasons, digital subtraction angiography (DSA) has been used as the gold standard reference [30] for identifying patients with angiographic vasospasm secondary to cerebral hemorrhages including aneurysmal SAH and can provide additional information including locations and numbers of aneurysms, anatomy of cerebral vessels and the degree of collateral circulation as well as cerebral vasospasm. In addition to serving as a means for performing cerebral artery balloon angioplasty and endovascular administration of anti-spastic agents [22], DSA can further distinguish between patients with aneurysmal SAH and patients with SAH due to causes other than a ruptured aneurysm such as brain arteriovenous malformations, Moyamoya disease and angiotumors. Furthermore, it has been demonstrated that cerebral vasospasm revealed by DSA can occur in the distal or proximal end of the affected artery in 70-95% of patients within 7-14 days following an aneurysmal rupture, and 20-40% of them could develop delayed cerebral ischemia [21]. Conversely, CTA possesses a similar sensitivity and specificity with DSA in identifying patients with cerebral vasospasm after cerebral hemorrhage [9] and, more importantly, it is a noninvasive procedure. Otawara *et al.* [23] found that there is a high degree of agreement between the severity of cerebral vasospasm on multi-slice images obtained by CTA and DSA in overall, proximal and distal segments of the affected cerebral arterial territory.

Many studies have been focused on identifying delayed vasospasm which usually develops 3-7 days and is a pivotal determinant of DCI after aneurysmal SAH. Our current results agree with these findings since as high as 63% of incidence of cerebral vasospasm is detected in patients between 3 and 17 days following the onset of aneurysmal SAH. Our results further indicate that some aneurysmal SAH patients show early risk for developing cerebral vasospasm and perfusion deficits. As shown in Figure **1**, the perfusion deficit can occur as early as 9 hours after an acute onset of aneurysmal SAH symptoms. These findings are of great clinical significance simply because the early prevention and treatment of cerebral vasospasm following cerebral hemorrhages may significantly improve the clinical outcome in those cerebral hemorrhagic patients by preventing or ameliorating complications of long-term neurological deficits. Using admission angiography as a baseline, Baldwin *et al.* [24] found that an early vasospasm can be detected in 10% of SAH patients and that a significantly higher incidence of neurological deficits, cerebral infarction and hydrocephalus is associated with early vasospasm detected in the first 48 hours

following aneurysmal SAH. In agreement with this finding and other studies [25], the incidence of vasospasm that we report in this study is comparable to that obtained in the above studies. We found that 12 % of aneurysmal SAH patients show perfusion deficits on the CTP color map at the early stage of acute SAH. It is important to point out that such a lower incidence rate of vasospasm detected in patients with acute aneurysmal SAH may be due to the initiation of compensatory mechanisms. As a result, uncompromised cerebral autoregulation induces vasodilation and thus increases perfusion blood volume as demonstrated by Crubb *et al.* [26]. In addition, we have also noted that the occurrence of cerebral vasospasm appears to be associated with anatomical distributions of cerebral arteries and that vasospasms were observed exclusively in the circulation of ACA and MCA but not in the areas of PCA and vertebrobasilar circulation. These findings suggest that patients with aneurysmal SAH in the anterior cerebral circulation may have a high likelihood of developing cerebral vasospasm and then perfusion abnormality in the territory of vasospastic vessel, and thus the locations of the ruptured SAH could be, therefore, used as a predictor of cerebral vasospasm. It is unknown what causes such a region-specific vasospasm following SAH but the high incidence of cerebral vasospasm mainly in anterior circulation could be due to the difference in nerve innervation between anterior and posterior cerebral circulation. Hirashima *et al.* [27] report a similar result in which a lower incidence of symptomatic vasospasm was observed in the posterior circulation following a ruptured vertebrobasilar aneurysm.

CTA and CTP are relatively noninvasive, fast and easily applied diagnostic techniques. Recently, the ability to detect the microcirculatory disturbance as a surrogate endpoint of cerebral vasospasm by a combined CTP-CTA procedure has been studied and the excellent correlation of CTA-CTP combination with DSA has been described. For example, by quantitative analysis of CTP maps of aneurysmal SAH patients, Aralasmak *et al.* [8] identified that the degree of vasospasm is closely associated with extent of luminal narrowing. When the luminal narrowing is greater than 50%, the likelihood of perfusion deficits in the territory of the vasospastic vessel could be as high as 83%. In another study in which the DSA, CTP-CTA, and transcranial Doppler ultrasonography were compared for their ability to detect vasospasm, Wintermark *et al.* [28] found that combined CTP-CTA study shows a higher positive predictive value than TCD as well as a stronger correlation of CTP-CTA-combination with DSA. It should be pointed out that CTA is a useful tool in detecting aneurysms and can provide extra information with regards to the hemodynamics of cerebral vasculatures when coupled with CTP. In our current study, the CTP measurement profile indicates that there are significant decreases in both CBF and CBV and increases in both prolonged MTT and TTP values measured from the territories of the anterior circulation after SAH. This demonstrates that changes in capillary–level circulation are more robust in the territory of the anterior circulation than in the posterior circulation. This is consistent with the findings that more severed cerebral vasospasm is frequently detected in the same cerebral arterial distribution. Indeed, a mild to moderate vasospasm can be suggested by prolongation of MTT value alone but a severe vasospasm is indicated when the prolonged MTT is coupled with a significant reduction of either CBV or CBF [14] values because CBF and MTT values appear to have the highest diagnostic accuracy for detecting vasospasm. More specifically, an MTT longer than 5.5 seconds and MIT difference of 1.1 seconds have been suggested to be an optimal or cutoff diagnostic threshold value for predicting the occurrence of delayed cerebral ischemia in several studies [20,29]. In patients with vasospasm in our study, the mean MTT value of 6.5 seconds was achieved and this value was significantly longer than that in patients without vasospasm or control. Furthermore, the CTP measurement parameters representing CBF,CBV, MTT, and TTP values in each of the ROIs of the territories of the affected cerebral artery do not show a statistical difference between patients with acute or delayed SAH, suggesting that the overall characteristics of cerebral vasospasm are similar in acute SAH when compared to delayed SAH. This is a very interesting finding that an identifiable cerebral vasospasm with microcirculatory disturbance immediately following the onset of aneurysmal SAH could possess similar impacts on capillary-level circulation as severe as those observed after a delayed period.

Although the perfusion deficits or hypoperfusion were encountered mostly in our patients with aneurysmal SAH, the hyperperfusion or hyperemia following aneurysmal SAH was also detected in a few cases of this study. Similar hyperperfusion or hyperemia after aneurysmal SAH was noted in patients in a study by Aralasmak *et al.* [8]. Altogether, these results suggest that a possible compensating mechanism following cerebrovascular autoregulation or

collateral circulation could be responsible for such a hyperemia or hyperperfusion. Indeed, an increase in CBF and CBV values in the presence of vasospasm may suggest that there is a well-established collateral circulation or breakdown of the blood brain barrier [8]. This is especially true in cases where a recanalization of blood supply has been established in the affected regions [29].

In summary, the results from the present study demonstrate that a combined CTP-CTA procedure is a useful means of detecting and assessing perfusion abnormality of the brain in patients with aneurysmal SAH. Although cerebral vasospasm is frequently encountered in patient with aneurysmal SAH later than 3 days from the initial hemorrhage, an early detection of vasospasm by whole brain CTP measurements offers promising benefits in identifying patients with a high risk to develop DCI due to vessel constriction. Coverage of whole brain with higher temporal resolution using CT scans with 320 row-detectors [10] may further enhance the accuracy of detecting vasospasm in patients with aneurysmal SAH.

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REFERENCES

[1] Broderick JP, Brott TG, Duldner JE, *et al*. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke 1994; 25(7): 1342-1347. http://dx.doi.org/10.1161/01.STR.25.7.1342

[2] Hop JW, Rinkel GJ, Algra A, *et al*. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. Stroke 1997; 28(3): 660-664. http://dx.doi.org/10.1161/01.STR.28.3.660

[3] Oyama K, Criddle L. Vasospasm after aneurysmal subarachnoid hemorrhage. Crit Care Nurse 2004; 24: 58-67.

[4] Weir B, Grace M, Hansen J, et al. Time course of vasospasm in man. J Neurosurg 1978; 48(2): 173-178. http://dx.doi.org/10.3171/jns.1978.48.2.0173

[5] Dietrich HH, Dacey RG Jr. Molecular keys to the problems of cerebral vasospasm. Neurosurgery 2000; 46(3): 517-530. http://dx.doi.org/10.1097/00006123-200003000-00001

[6] Cenic A, Nabavi DG, Craen RA, *et al*. A CT method to measure hemodynamics in brain tumors: validation and application of cerebral blood flow maps. AJNR Am J Neuroradiol 2000; 21(3): 462-470.

[7] Lubicz B, Levivier M, Francois O, *et al*. Sixty-Four-Row Multisection CT Angiography for detection and evaluation of ruptured intracranial aneurysms: Interobserver and intertechnique reproducibility. AJNR Am J Neuroradiol 2007; 28(10): 1949-1955. http://dx.doi.org/10.3174/ajnr.A0699

[8] Aralasmak A, Akyuz M, Ozkaynak C, *et al*. CT angiography and perfusion imaging in patients with subarachnoid hemorrhage: Correlation of vasospasm to perfusion abnormality. Neuroradiology 2009; 51(2): 85-93. http://dx.doi.org/10.1007/s00234-008-0466-7

[9] Yoon DY, Choi CS, Kim KH, *et al*. Multidetector-row CT angiography of cerebral vasospasm after aneurysmal subarachnoid hemorrhage: comparison of volume-rendered images and digital subtraction angiography. AJNR Am J Neuroradiol 2006; 27(2): 370-377.

[10] Shankar JJ, Lum C. Whole Brain CT perfusion on a 320-slice CT scanner. Indian J Radiol Imaging 2011; 21(3): 209-214. http://dx.doi.org/10.4103/0971-3026.85370

[11] Orrison WW Jr, Snyder KV, Hopkins LN, *et al*. Whole-brain dynamic CT angiography and perfusion imaging. Clin Radiol 2011; 66(6): 566-574. http://dx.doi.org/10.1016/j.crad.2010.12.014

[12] Rijsdijk M, van der Schaaf IC, Velthuis BK, *et al*. Global and focal cerebral perfusion after aneurysmal subarachnoid hemorrhage in relation with delayed cerebral ischemia. Neuroradiology 2008; 50(9): 813-820. http://dx.doi.org/10.1007/s00234-008-0416-4

[13] Vajkoczy P, Horn P, Thome C, *et al*. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurismal subarachnoid hemorrhage. J Neurosurg 2003; 98(6): 1227-1234. http://dx.doi.org/10.3171/jns.2003.98.6.1227

[14] Binaghi S, Colleoni ML, Maeder P, *et al*. CT angiography and perfusion CT in cerebral vasospasm after subarachnoid hemorrhage. AJNR Am J Neuroraiol 2007; 28(4): 750-758.

[15] Xiang Li, Chunzhi Li, Songbai Li, *et al*. Clinical Application of CTA coupled with whole brain CT perfused blood flow after onset of aneurismal subarachnoid hemorrhage. J of China Clinic Medical Imaging 2011; 22(6): 385-388.

[16] Liu-Deryke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: an overview of pharmacologic management. Pharmacotherapy 2006; 26(2): 182-203. http://dx.doi.org/10.1592/phco.26.2.182

[17] Bederson JB, Connolly ES Jr, Batjer HH, *et al*. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009; 40(3): 994-1025. http://dx.doi.org/10.1161/STROKEAHA.108.191395

[18] Alaraj A, Charbel FT, Amin-Hanjani S. Peri-operative measures for treatment and prevention of cerebral vasospasm following subarachnoid hemorrhage. Neurol Res 2009; 31(6): 651-659. http://dx.doi.org/10.1179/174313209X382395

[19] Kassell NF, Sasaki T, Colohan AR, *et al*. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Stroke 1985; 16(4): 562-572. http://dx.doi.org/10.1161/01.STR.16.4.562

[20] Sanelli PC, Jou A, Gold R, *et al*. Using CT perfusion during the early baseline period in aneurysmal subarachnoid hemorrhage to assess for development of vasospasm. Neuroradiology 2011; 53(6): 425-434. http://dx.doi.org/10.1007/s00234-010-0752-z

[21] Rabinstein AA, Weigand S, Atkinson JL, *et al*. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke 2005; 36(5): 992-997. http://dx.doi.org/10.1161/01.STR.0000163090.59350.5a

[22] Eskridge JM, McAuliffe W, Song JK, *et al*. Balloon angioplasty for the treatment of vasospasm: results of first 50

cases. Neurosurgery 1998; 42(3): 510-517. http://dx.doi.org/10.1097/00006123-199803000-00016

[23] Otawara Y, Ogasawara K, Ogawa A, *et al*. Evaluation of vasospasm after subarachnoid hemorrhage by use of multislice computed tomographic angiography. Neurosurgery 2002; 51(4): 939-943.

[24] Baldwin ME, Macdonald RL, Huo D, *et al*. Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. Stroke 2004; 35(11): 2506-2511. http://dx.doi.org/10.1161/01.STR.0000144654.79393.cf

[25] Drake CG, Hunt WE, Sano K, *et al*. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988; 68(6): 985-986.

[26] Grubb RL Jr, Raichle ME, Eichling JO, *et al*. Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans. J Neurosurg 1977; 46(4): 446-453. http://dx.doi.org/10.3171/jns.1977.46.4.0446

[27] Hirashima Y, Kurimoto M, Hori E, *et al*. Lower incidence of symptomatic vasospasm after subarachnoid hemorrhage owing to ruptured vertebrobasilar aneurysms. Neurosurgery 2005; 57(6): 1110-1116. http://dx.doi.org/10.1227/01.NEU.0000185632.69374.C9

[28] Wintermark M, Ko NU, Smith WS, *et al*. Vasospasm after subarachnoid hemorrhage: utility of perfusion CT and CT angiography on diagnosis and management. AJNR Am J Neuroradiol 2006; 27(1): 26-34.

[29] Kidwell CS, Saver JL, Mattiello J, *et al*. Diffusion-perfusion MRI characterization of post-recanalization hyperperfusion in humans. Neurology 2001; 57(11): 2015-2021. http://dx.doi.org/10.1212/WNL.57.11.2015

[30] Rajendran JG, Lewis DH, Newell DW, *et al*. Brain SPECT used to evaluate vasospasm after subarachnoid hemorrhage: correlation with angiography and transcranial Doppler. Clin Nucl Med 2001; 26(2): 125-130. http://dx.doi.org/10.1097/00003072-200102000-00007

[31] Dankbaar JW, Rijsdijk M, van der Schaaf IC, *et al*. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology 2009; 51(12): 813-819. http://dx.doi.org/10.1007/s00234-009-0575-y

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