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Assessment of Cerebral Circulation in the Acute Phase of Subarachnoid Hemorrhage Using Perfusion Computed Tomography

Kojiro Tateyama[1], Shiro Kobayashi[2], Yasuo Murai[1] and Akira Teramoto[1]

[1]Department of Neurosurgery, Nippon Medical School
[2]Department of Neurosurgery, Neurological Institute, Nippon Medical School Chiba Hokusoh Hospital

Abstract

Background and Purpose: Primary brain damage, caused by acute ischemic changes during initial hemorrhage, is an important cause of death and disability following subarachnoid hemorrhage (SAH). However, the mechanism underlying the reduction in cerebral circulation in patients in the acute stage of SAH remains unclear. The goal of this study was to clarify this mechanism with the aid of perfusion computed tomography (CT).

Methods: We prospectively evaluated 21 patients who had been undergone perfusion CT within 3 hours of SAH onset. Mean transit time (MTT) was estimated. Forty circular regions of interest 5 mm in diameter were delineated in the cortical region of the bilateral hemispheres on perfusion CT images. Neurological condition was graded with the Hunt and Hess scale, and initial CT findings were graded with the Fisher scale. We defined a good outcome as a modified Rankin scale (mRs) score of ≤2at 3 months after SAH onset.

Results: Global MTT was an independent predictor of outcome. The global MTT of patients with poor outcomes was longer than that of patients with good outcome. Furthermore, global MTT correlated significantly with Hunt & Hess grades, and disturbances in higher cerebral function.

Conclusion: Hemodynamic disturbances frequently occur after SAH. These abnormalities probably reflect the primary brain damage caused by initial hemorrhage. Perfusion CT is valuable for detecting hemodynamic changes in the acute stages of SAH.
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Key words: cerebral blood flow, ischemia, mean transit time, subarachnoid hemorrhage, perfusion computed tomography

Introduction

Reduced cerebral blood flow (CBF) has been documented in patients in the acute stage of subarachnoid hemorrhage (SAH)[1,2]. In addition several studies using animal models have shown evidence of the relationship between initial ischemia and primary brain damage[3–10]. However, the relationship between cerebral circulation assessment and outcome in patients with SAH remains unclear. Primary brain damage is related to outcome in

Correspondence to Kojiro Tateyama, MD, Department of Neurosurgery, Neurological Institute, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Inzai, Chiba 270–1694, Japan
E-mail: s3065@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

patients with SAH. SAH results in death in approximately 40% of patients whereas in survivors, it results in a high incidence of important neurological and cognitive disturbances in survivors[11,12]. Most deaths occur within hours of ictus[13], and it is well established that the events during the first few minutes following SAH are of great importance for patient outcome[11,14–16]. However, cerebral vasospasm has been identified as the primary cause of secondary ischemia, and great efforts have been made to understand the pathogenic mechanisms of vasospasm, and to find ways to prevent and treat it. Studies with animal models have demonstrated that CBF is reduced in the acute phase of SAH[3–10]. It would be of great value to acquire more knowledge on the early hemodynamic effects of SAH and primary brain damage. Few studies have demonstrated a global reduction in CBF in patients with SAH[1,15,17–19]. Only 2 studies have performed positron emission tomography (PET) in the acute phase of SAH[1,20] However, PET scanning in these studies was performed 4 to 53 hours after the onset of SAH. Therefore the results of this delayed evaluation may have reflected changes in cerebral circulation over time due to recovery from initial ischemia. Perfusion computed tomography (CT) is more suitable and more readily available for urgent assessment compared with PET and single-photon emission computed tomography (SPECT). The primary aim of the present study was to use perfusion CT to investigate cerebral circulation in the acute phase of SAH.

Patients and Methods

Patients

We retrospectively evaluated 21 patients with SAH who were admitted to Hakujikai Memorial Hospital from June 2006 through June 2007 or from April 2009 through March 2010. (Patients admitted from July 2007 through March 2009 were included in another study and were not included in the present study.). The clinical characteristics of the 21 patients are summarized in **Table 1**. The diagnosis of SAH was established on the basis of CT findings on admission, and perfusion CT evaluations were performed within 3hours of SAH onset. Patients were excluded from the analysis if they had been admitted to the hospital 3 hours or more after SAH onset, had nonaneurysmal causes of SAH (trauma, arterio-venous malformation, or perimesencephalic hemorrhage), or had intracerebral hemorrhage. No patient showed clinical deterioration leading to delayed cerebral ischemia. Neurological conditions were graded on a scale of 1 to 5 with the Hunt and Hess scale, and initial CT findings were graded on a scale of 1 to 4 with the Fisher scale. Diagnostic digital subtraction angiography performed on day1 revealed. 26 saccular aneurysms were in 21 patients. Cerebral angiography revealed no findings indicative of cerebral ischemia such as stenosis, occlusion, and vasospasm of cerebral arteries. All patients were sedated with midazolam during perfusion CT. Nineteen patients underwent aneurysm clipping within 24 hours of SAH onset, two patients underwent ventricular drainage, and three patients (Patients3, 7, and 9) underwent transluminal balloon angioplasty to treat cerebral vasospasm.

Informed consent was obtained from the family of each patient.

This study was approved by the medical ethics committee of Hakujikai Memorial Hospital.

Perfusion CT Technique and Measurements

Imaging studies were performed with a 16-slice spiral CT scanner (Brilliance 16; Philips Healthcare, Amsterdam, The Netherlands). The CT source data were derived from sequential scans covering a slab 6 mm thick, 2.4 cm above the sella turcica and angulated parallel to the meato-orbital line to include the upper parts of the lateral ventricles and the basal ganglia. Forty milliliters of the nonionic contrast agent iopromide (Proscope, Tanabe Seiyaku Co, Ltd, Tokyo; 300 mg iodine/mL) was injected at a rate of 5 mL/second and was followed by a 40 mL saline flush at a rate of 5 mL/second. The following parameters were used: 90 kVp, 200 mAs, 16 × 1.5 mm collimation, 512 × 512 matrix, 1 image/second over 60 seconds (total 60 images maximum), 6 mm thickness × 4 slices, UB filter, and standard resolution. Data were transferred to a Philips

Table 1 Characteristics of the 21 patients with SAH who underwent perfusion computed tomography

Case number	Age (years), Sex	Hunt and Hess grade	Fisher grade	Aneurysm location	Hydrocephalus	Treatment	symptomatic vasospasm	Modified Rankin Scale score at 3 months	Disturbance of higher cortical function	Global MTT	Global CBV	Global CBF
1	73, F	3	3	L ICA	−	Clipping	−	2	+	6.026	3.867	38.05
2	66, F	5	3	A-com	−	Clipping	−	3	+	9.375	5.019	33.15
3	65, F	2	3	R VA	−	Clipping	−	0	−	6.171	3.860	37.87
4	57, M	3	3	R MCA	−	Clipping	−	1	+	6.586	3.201	29.57
5	65, F	4	3	BA, R+L MCA	+	Ventricular drainage	−	6		6.627	5.191	47.66
6	68, F	5	3	A-com	−	Ventricular drainage	−	6		6.698	3.536	31.77
7	57, F	4	3	A-com	+	Clipping	+	2	+	5.842	4.183	43.04
8	45, F	3	3	R ICA	−	Clipping	−	0	−	5.175	4.11	47.73
9	76, F	4	3	R+L MCA	+	Clipping	+	4	+	7.157	4.981	41.78
10	47, M	2	3	R ICA	−	Clipping	−	0	−	4.722	3.828	48.62
11	52, M	3	3	R ICA	−	Clipping	−	1	+	6.859	4.647	40.79
12	64, F	3	3	A-com	+	Clipping	−	0	−	5.244	4.378	50.57
13	66, F	4	3	A-com	−	Clipping	−	1	+	7.654	8.85	69.56
14	76, M	5	3	L ACA	−	Clipping	−	6		7.980	6.478	48.58
15	52, M	4	3	A-com	−	Clipping	−	1	+	5.405	6.059	67.63
16	61, F	5	3	A-com, R ICA	−	Clipping	−	6		7.759	4.784	36.96
17	57, F	2	3	A-com	−	Clipping	−	0	−	5.681	4.549	48.03
18	58, F	3	3	L ACA	−	Clipping	−	0	−	6.738	4.620	41.33
19	56, F	2	3	A-com	−	Clipping	−	0	−	5.986	6.060	61.17
20	55, F	2	3	R ICA	−	Clipping	−	0	−	5.538	6.285	68.36
21	50, F	2	3	R ACA	−	Clipping	+	1	+	5.791	4.396	45.49

ICA=internal carotid artery, A-com=anterior communicating artery, VA=vertebral artery, BA=basilar artery, MCA=middle cerebral artery, ACA=anterior cerebral artery, MTT=mean transit time, CBV=cerebral blood volume, CBF=cerebral blood flow

H&H=Hunt and Hess scale; SVS=symptomatic vasospasm; mRs=modified Rankin scale at 3 months; V.D.=ventricle drainage

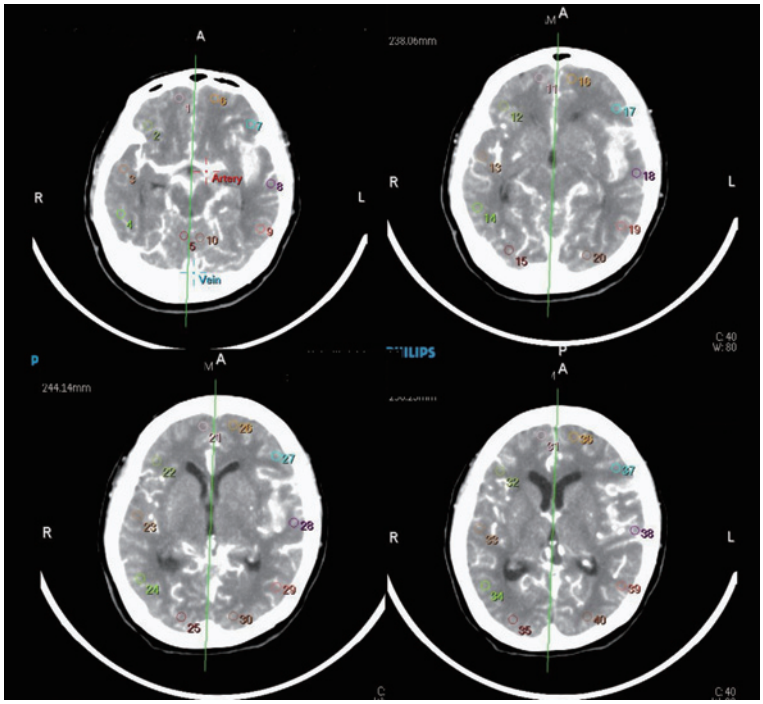

Fig. 1 Regional CT images of case 20. The standardized region of interest (ROIs) strategy is demonstrated. Circular ROIs were delineated in the peripheral (cortical) flow territories of the anterior cerebral artery, middle cerebral artery, and cerebellum, resulting in 40 ROIs per patient.

workstation for post-processing. We estimated cerebral blood volume (CBV), CBF, and mean transit time (MTT). Regions of interest (ROIs) were delineated in the peripheral (cortical) flow territories of the anterior cerebral artery (ACA), the middle cerebral artery (MCA), and the cerebellum thus resulting in 40 ROIs (5 mm in diameter) located in the cortical region of the bilateral hemispheres on the perfusion CT images of each patient (**Fig. 1**). The mean value of the 40 ROIs was defined as the global MTT. Post-processing and measurements could be performed within 5minutes of each other.

Outcome Measurement

Three months after SAH onset, neurological outcomes were evaluated with the modified Rankin scale (mRs). We defined a good outcome as mRs scores of ≤2. CT was performed to document signs of permanent ischemic damage. Neuropsychological tests were performed on the basis of the revised Hasegawa dementia scale (HDS-R). A neuropsychological deficit was defined as <20 points on this scale.

Analysis

Analyses were performed with JMP 7.02 software (SAS Institute, Inc, Cary, NC, USA) Differences between groups were evaluated with unpaired t-tests, Wilcoxon Mann-Whitney tests. Two-sided probability values less than 0.05 were considered to indicate statistical significance.

We chose global MTT as the indicator of brain perfusion for two reasons. First, sedative drugs affect brain perfusion. In healthy volunteers sedative drugs had been reported to decrease CBV and CBF and to increase CBF responsiveness to CO_2. However, midazolam does not affect the CBF/CBV ratio[21]. Because MTT is equal to the CBV/CBF (central volume principle), global MTT is independent of any sedative effect.

Results

Twenty-one patients were included in this study (**Table 1**). All patients were noted to have a Fisher grade of 3 and 9 (42.9%) patients presented with a

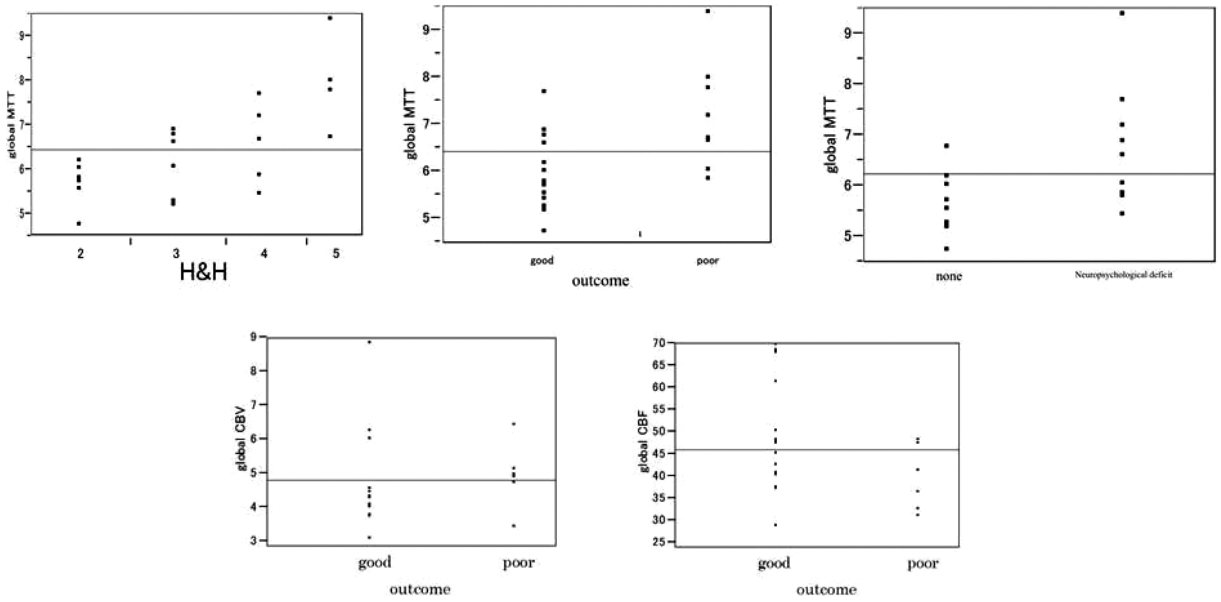

Fig. 2 The MTT is longer in patients with higher Hunt and Hess grades than in patients with lower Hunt and Hess grades.
Outcomes and higher cerebral functions are more favorable in patients with a shorter MTT than in patients with a longer MTT.
Global CBV and CBFwere not correlated with outcome.

Table 2 Logistic regression analysis in outcome

Variable	P value
Age	0.0035
Sex	0.9998
Hunt and Hess score	0.0023
Global MTT	0.0070

poor neurological condition (Hunt and Hess grade≥ 4). The global MTT was significantly correlated with outcome (p=0.0244), Hunt and Hess grade (Wilcoxon test p=0.0363), and disturbances in higher cerebral function (p=0.0329) **(Fig. 2)**. However, neither global CBV nor CBF were correlated with outcome. Logistic regression analysis determined the clinical variable. The following clinical variables were included age, sex, Hunt and Hess grade, and global MTT. Age, and Hunt and Hess grade, global MTT were identified as significant predictor of outcome **(Table 2)**.

Illustrative Cases

Case 4

The patient was a 57-year-old man with a ruptured aneurysm of the right MCA. On admission the Hunt and Hess grade was 3, and the Fisher grade was 3. **Figure 3** shows CT and perfusion CT images. In the affected hemisphere the CBF was reduced and MTT was elongated, as compared to the opposite hemisphere. The patient underwent clipping on the first day. Diagnostic digital subtraction angiography showed no acute vasospasm or stenosis in the intracranial arteries. Three months after the onset of SAH, the mRs was 1.

Case 5

The patient was a 65-year-old woman with a ruptured basilar artery aneurysm. On admission the Hunt and Hess Grade was 4, and the Fisher group was 3. **Figure 4** shows CT and perfusion CT images. The MTT was diffusely elongation, especially in the temporo-occipital regions. The patient underwent ventricular drainage, but showed no clinical improvement.

Diagnostic digital subtraction angiography showed no acute vasospasm or stenosis in the intracranial arteries.

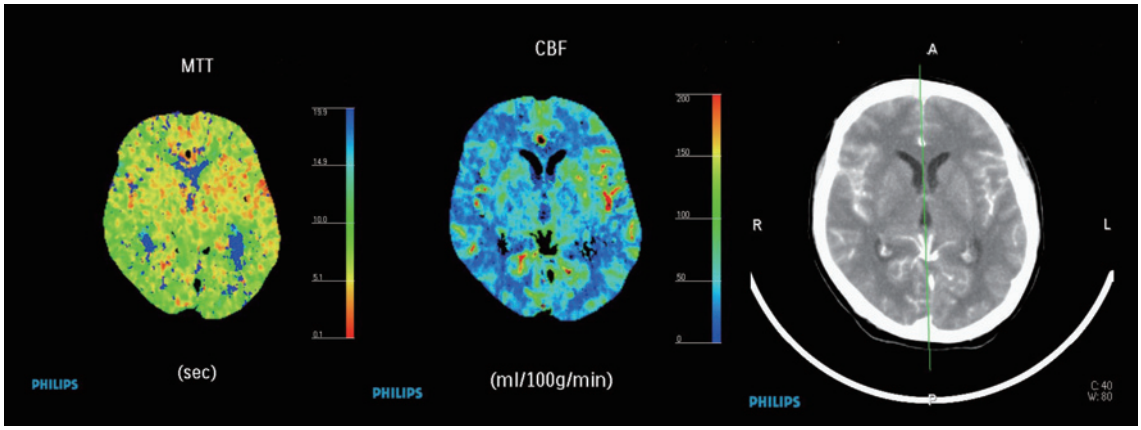

Fig. 3 Case4. Perfusion CT performed 1 hour after rupture of the right MCA aneurysm. [left, mean transit time (MTT); middle, cerebral blood flow (CBF); right, plain CT image]. The CBF is significantly reduced and MTT is extended compared with the opposite hemisphere.

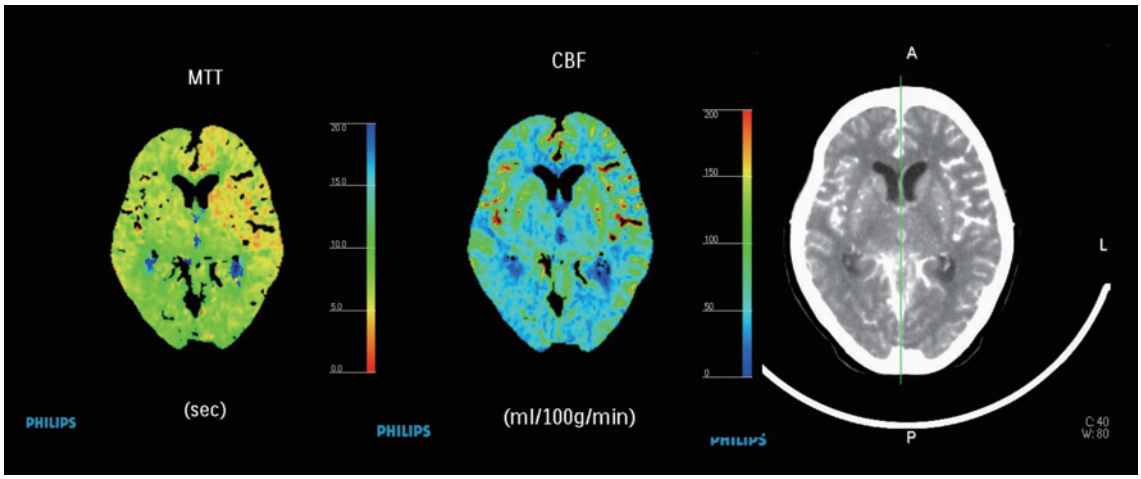

Fig. 4 Case5. Perfusion computed tomography performed 2 hours after rupture of a basilar artery top aneurysm. [left, mean transit time (MTT); middle, cerebral blood flow (CBF); right, plain CT image]. The CBF is reduced and MTT is significantly extended bilaterally in the temporal and thalamic regions. Because basilar artery top aneurysm was in the center of the brain, hemodynamic disturbances affect both hemispheres.

Discussion

To our knowledge, this is the first study to measure cerebral circulation in the early acute stage (<3 hours after SAH). This study found hemodynamic changes after SAH, and found that global MTT was significantly correlated with outcome. Two PET studies have demonstrated globally reduced CBF and cerebral metabolic rate of oxygen in patients with SAH[1,20]. Yet, the findings in these studies could be attributed to the interval from the onset of rupture to time of PET (4 to 53 hours after SAH), and the changes in cerebral circulation over time due to recovery from the initial ischemia.

Most of the information regarding the pathogenic mechanisms of acute cerebral injury after SAH has been obtained from experimental animal models. A sudden rise in intracranial pressure (ICP) and a fall in CBF are the primary signs at the onset of SAH[22]. After the initial reduction of CBF, this tends to normalize by 48 hours after SAH[4]. Autoregulation is impaired within the first few minutes after SAH[3,5,23]. The pressure-buffering system then begins to function and is followed by a decrease in ICP and a concomitant increase in cerebral perfusion pressure (CPP), which is invariably succeeded by a rapid

elevation of CBF and reactive hyperemia[10,22,24]. The decrease in CBF is often closely followed by a hyperemic phase during which CBF increases above normal values, but the CBF returns towards baseline and 60 minutes later assumes a value that serves to predict the 24-hour outcome[5]. In an experimental rabbit model MTT elevation 1 hour after SAH is a significant predictor of early mortality (within 48 hours)[25]. High MTT could reflect increased ICP, leading to decreased CPP, and prolonged cerebral circulation (increased MTT)[26]. Acute increases in ICP lead to reductions in CPP for up to 1 hour following SAH[27]. Several studies have demonstrated 2 distinct patterns of ICP change after SAH:a rise followed by a quick return to baseline and a rise that is maintained for more than 1 hour[23,24,28]. The duration of ICP elevation, which causes ischemia owing to low perfusion pressure, may affect the degree of brain damage reflected by disturbance of consciousness. This increase in ICP and decrease in CPP would be expected to result in a global increase in MTT. In addition to acute increases in ICP, acute vasospasm has been observed as a transient reduction in arterial diameter, followed by a return to normal arterial diameter within 1hour after experimental SAH[25]. The acute vasospasm leads to increase MTT in the territory supplied by the arteries with acute vasospasm.

In ischemic stroke, there is often an ischemic core and an adjacent dynamic penumbra. In patients with SAH, the pathogenesis of ischemia is different. Previous studies have found the changes in brain perfusion in the acute phase of SAH to be global[1,20,22]. However, in the present study we found the changes in brain perfusion to be local. In the regions around the rupture point brain perfusion improved later than in other regions (patients 4 and 5). The duration of improvement in brain perfusion probably affects the degree of ischemia in patients with SAH. In this study, we could perform perfusion CT before recovery from the initial ischemia.

Sedative drugs affect brain perfusion. In healthy volunteers sedative drugs were reported to decrease CBV and CBF and to increase CBF responsiveness to CO_2. However, midazolam does not affect the CBF/CBV ratio[21]. Because MTT is equal to CBV/CBF (central volume principle), global MTT is independent of any sedative effect. Therefore, in the present study global MTT accurately reflected the change in brain circulation, and showed a significant correlation with outcome. Perfusion CT provides quantitative information on CBV, CBF, and MTT, and interpretation of these 3 variables gives information on the functionality of autoregulation. This information is valuable, because changes in brain perfusion cause primary brain damage in patients with SAH. Nevertheless, the interpretation of quantitative perfusion values as measured with perfusion CT has several limitations. Although the accuracy of perfusion CT has been validated many times in animal and human models[29-32], the quantification of perfusion CT is controversial[29]. Another limitation of brain perfusion measurements with perfusion CT is the limited brain volume included in the analysis (1 slab 2.4 cm thick), which may lead to an underestimation of the relation between the change in brain perfusion and the primary brain damage.

Although MTT as measured with perfusion CT is a good predictor of outcome, and perfusion CT can easily be performed directly after CT with quick post-processing and straightforward interpretation, it has a few disadvantages. Despite the fact that perfusion CT can replace the time lapse, exposure to an additional dose and contrast medium compared with the conventional time lapse, cannot be overlooked. In addition, a 5-minute delay before CT angiograhy is required to maintain venous enhancement.

Conclusions

Hemonamic disturbances occur frequently after SAH. These abnormalities probably reflect the primary brain damage caused by the initial hemorrhage. Although the small number of patients and their diversity do not allow definite conclusions about causal relationships to be drawn, we can still speculate that global MTT reflects the degree of primary brain damage.

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