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Asymptomatic Mild Hyperperfusion for the Prediction of Clinical Outcome in Postoperative Patients After Subarachnoid Hemorrhage

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Delayed cerebral ischemia (DCI) is one of the main causes of poor outcomes after subarachnoid hemorrhage (SAH). The early identification of DCI by noninvasive imaging modalities would provide valuable information of therapeutic intervention for improving the patient outcomes. We aimed to describe the clinical features of cerebral blood flow (CBF) data obtained from the single-photon emission computed tomography (SPECT) during the risk period for DCI after SAH.


Material/Methods: Clinical data from 94 SAH patients who underwent surgical clipping of anterior circulation aneurysms were reviewed retrospectively. ^{99m}Tc-HMPAO SPECT images were visually and semiquantitatively analyzed on days 7 and 14 after SAH.

Results: In all cases, the areas of hypoperfusion were found in the middle cerebral artery territories. By contrast, the areas of mild hyperperfusion were always detected on the surgical side, the prevalence which increased from days 7 (n=28; 30%) to 14 (n=48; 51%) without neurological defects. Univariate analysis revealed that the hyperperfusion on day 14 had a significant relationship with functional outcome at 3 months (P=0.04). Multivariate analysis including age, clinical SAH grade, DCI, and hyperperfusion on day 14 showed that DCI (P=0.004; odds ratio [OR], 0.10; 95% confidence interval [CI], 0.02-0.48) and hyperperfusion on day 14 (P=0.002; OR, 2.44; 95% CI, 1.40-4.29) were independently associated with functional outcome at 3 months.

Conclusions: Delayed mild hyperperfusion around the surgical site can predict good prognosis after SAH, although it may hinder the CBF diagnosis of focal ischemia attributable to DCI.

MeSH Keywords: **Brain Ischemia • Patient Outcome Assessment • Subarachnoid Hemorrhage • Tomography, Emission-Computed, Single-Photon • Vasospasm, Intracranial**

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Background

Delayed cerebral ischemia (DCI) is the most serious complication of aneurysmal subarachnoid hemorrhage (SAH), in which 20–40% of patients are deteriorated after 6 to 10 days of ictus, constituting a prime cause of morbidity and mortality [1]. DCI has been related to the multifactorial process linked to reduction in cerebral blood flow (CBF) resulting from the development of cerebral vasospasm, cerebrovascular autoregulatory dysfunction, and cortical spreading depression [2]. Therefore, the early identification of tissue hypoperfusion by noninvasive imaging techniques would be of diagnostic value for DCI and could provide an objective basis for evaluating the therapeutic intervention [3].

Regional CBF measurement with single-photon emission computed tomography (SPECT) has been established as a measure of tissue perfusion and detects relative changes of cerebral perfusion associated with DCI [4]. Clinically, SPECT is helpful in the time window in which CT scan and magnetic resonance imaging (MRI) do not reveal abnormalities. On the other hand, it has also been suggested that the diagnostic accuracy of SPECT measurements for detection of post-SAH DCI varies significantly with time during the vasospasm risk period [5]. In fact, we sometimes encounter both hypo- and hyperperfusion during days 7 to 14 after surgery, and thus the need for repeated measurements has been recommended [6]. In terms of the loss of vascular reserve following SAH, relative hyperperfusion attributable to vasoparalysis has been demonstrated in patients after surgical clipping [7–9], which may have a risk of misleading to contradictory forms of postoperative management.

Given these observations, a more understanding of clinical features regarding the CBF-SPECT are expected for the best assessment of clinical picture after SAH. Thus, the aim of this study was to determine the characteristics of CBF changes obtained from serial SPECT measurements within the DCI risk period in postoperative patients after SAH and its impact on clinical outcome.

Material and Methods

Patients

After Institutional Review Board approval by the Office of Research Administration at the Research Institute for Brain and Blood Vessels-AKITA, we conducted a retrospective review of all consecutive patients with SAH registered in a prospective cohort trial (Information Network Clinical Trials Registry no. UMIN000007509) between January 2008 and December 2012. Clinical, hemodynamic and radiological data on patients

included: 1) age: 18 years or older; 2) pre-morbid modified Rankin scale (mRS) score 0 or 1; 3) acute surgery performed during the first 24 hours after SAH onset (designated study day 0); and 4) ruptured anterior circulation aneurysms treated with surgical clipping.

General management

After surgery, all patients were transferred to the stroke care and were treated according to the SAH treatment protocol of our institution [10–17]. The patients received a baseline crystalloid intravenous (IV) infusion of 1,500–3,000 mL/d and supplemental fluid/drug administration up to day 14, in accordance with predefined fluid therapy. They were rested in bed without sedation and with intravenous fluids and oral food intake if possible. Systolic blood pressures were controlled below 180 mmHg by administering calcium antagonists. Nimodipine was not used in this study because of ethical concerns (i.e., unapproved drug in Japan). Fasudil hydrochloride (30mg/kg, IV) was administered three times a day from day 1 to 14 [18]. For anticonvulsant prophylaxis, phenytoin (250–375 mg/day) was administered IV or orally from the day of surgery until day 14 [19] unless the patient experienced any side effects.

DCI was suspected clinically as a new focal neurological deficit or global neurological deterioration (a decrease of ≥ 2 points on the Glasgow Coma Scale) lasting > 2 hours, after exclusion of any probable cause such as hydrocephalus, seizures, metabolic derangements, and infection [20]. On days 7 and 14, diffusion-weighted magnetic resonance (MR) imaging was performed in addition to conventional sequences and MR angiography sequences routine screening with MR angiography and stable technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc -HMPAO) SPECT was performed for evaluation of DCI. If clinical DCI was suspected, the schedule for imaging studies was shifted earlier for further diagnosis and the patients received either mild hypervolemia using colloid solutions or hyperdynamic therapy with dobutamine or milrinone where appropriate. DCI was defined radiologically as the development of a new lesion consistent with infarction on diffusion-weighted MR imaging (days 7 and 14) or follow-up computed tomography CT scan (day 21).

SPECT imaging

CBF imaging was carried out with a ring type SPECT scanner (HeadTome SET-080, Shimadzu Co, Kyoto, Japan) using 740 MBq (20 mCi) of ^{99m}Tc -HMPAO as described [21]. The scanner simultaneously produces 31 tomographic axial images that cover the whole brain. A low-energy, high-resolution collimator was used for data acquisition. Image matrix size was 128 \times 128. A third-order Butterworth filter with a cutoff frequency of 0.05 cycles/cm and a ramp filter were used for image reconstruction. In-plane and axial spatial resolutions of

the scanner were 14 and 22 mm full width at half maximum, respectively. The CBF imaging started 10 minutes after the injection of ^{99m}Tc-HMPAO, and data acquisition continued for 24 minutes. The image slices were parallel to the orbitomeatal line with a 5-mm interslice distance. Reconstructed images were corrected for tissue absorption using an attenuation coefficient of 0.065 cm⁻¹, and for the nonlinear uptake of ^{99m}Tc-HMPAO in high-flow areas with the method developed by Lassen et al. [22]. Three of the 19 axial sections were selected for study: one included the cerebellar hemisphere. We selected 12.5×12.5-mm square regions of interest (ROI) on the three sections. Multiple regions of interest were placed symmetrically in the frontal, temporal, parietal, and occipital cortices of each hemisphere, and the cerebellar hemispheres.

Diagnostic criteria

SPECT images of brain perfusion were visually evaluated to determine whether HMPAO was distributed symmetrically in both cortical or cerebellar hemispheres or decreased and increased uptake of the tracer was present [23]. To assist in determination of areas of hypo- or hyperperfusion, the CBF was assessed semiquantitatively by calculating the ratio of regional activity (R) to cerebellar activity (CE) (R/CE ratio=A/C), where A represents a mean count of the regions of interest in the affected hemisphere, B that on the opposite side, and C that in the cerebellar hemisphere on the affected side. According to the relative CBF value based on our database and previous results [24–26], each ROI was classified as normal when the R/CE ratio between 1.2 and 0.8. Two trained board-certified radiologists who were blinded to the brain location of the lesion and the type of clinically relevant stroke symptoms evaluated the images and reached agreement on all findings.

Outcome Measures

The primary outcome measures were: mRS score (good: 0–3 or poor: 4–6) at 3 months after SAH. An experienced stroke neurologist who was blinded to the treatment allocation and MR findings assessed the clinical outcomes of all patients.

Statistical analysis

Data are expressed as the mean (standard deviation) or median (interquartile range), unless otherwise indicated. Continuous data that were normally distributed according to the D’Agostino-Pearson normality test were compared using the *t* test or analysis of variance with the *post hoc* Bonferroni-Dunn correction, as appropriate. Univariate analyses of the relationships of categorical variables with outcomes of interest were compared using the χ^2 test, or Fisher’s exact test when a cell size was <5. Univariate analyses of the relationships of normally distributed variables with outcomes of interest were

Table 1. Baseline clinical characteristics of SAH patients.

Variable		
Age (years)	65	(59–72)
Gender (female/male)	72/22	
WFNS grade		
I – III (good grade)	68	(72%)
IV, V (poor grade)	26	(28%)
Modified Fisher CT grade		
2	8	(9%)
3	61	(65%)
4	25	(26%)
Aneurysm location		
ACoA/ACA	29	(31%)
MCA	34	(36%)
ICA	31	(33%)
mRS at 3 months		
0–3	55	(59%)
4–6	39	(41%)

Data are presented as median (interquartile range) or number (%). SAH – subarachnoid hemorrhage; WFNS – World Federation of Neurosurgical Surgeons; CT – computed tomography; ACoA – anterior communicating artery; ACA – anterior cerebral artery; MCA – middle cerebral artery; ICA – internal carotid artery; mRS – modified Rankin Scale.

assessed using the Student’s *t* test, and of non-normally distributed variables were assessed using the Mann-Whitney *U* test. The variables showing significant associations with good functional outcome (mRS scores of 0-3) at 3 months on univariate analyses and known risk factors (age of ≥68 years, World Federation of Neurosurgical Surgeons [WFNS] clinical SAH grade, and occurrence of DCI) [27] were entered into a multivariate logistic regression analysis. *P*<0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software (Chicago, IL, USA).

Results

There were 115 consecutive aneurysmal SAH patients treated during the study period, with 94 qualifying for inclusion in this study. Characteristics for the study population are shown in Table 1. In this study surgical clipping was carried out using pterional approach through a fronto-temporal approach for internal carotid and middle cerebral artery aneurysms (n=35) or interhemispheric approach through a bifrontal craniotomy for anterior communicating and anterior cerebral artery aneurysms (n=29).

Summary of the serial CBF changes during the DCI risk period are shown in Figure 1. The first SPECT measurement (mean, day

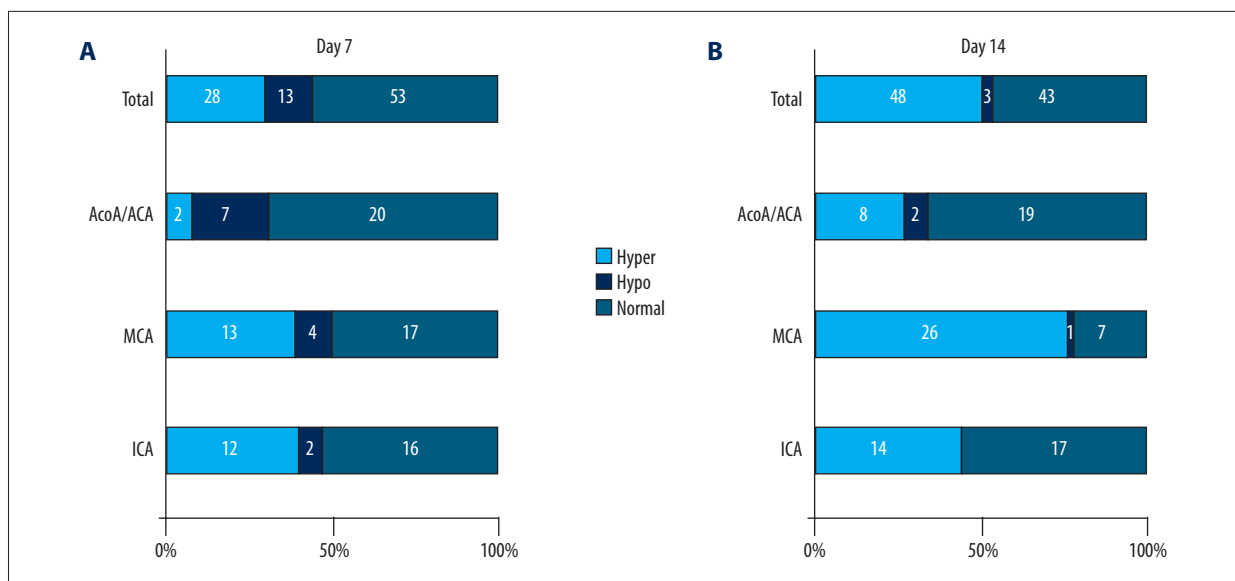


Figure 1. Classification of relative CBF changes by ^{99m}Tc HMPAO SPECT images based on the visual and semiquantitative evaluation. Number of patients presented hypoperfusion was greater on day 7 than on day 14, while those who had hyperperfusion increased from day 7 to day 14. Hyperperfusion on day 14 was more frequently observed in patients with ruptured MCA aneurysms.

7; range, days 5–7) revealed relative hypoperfusion (R/CE ratio, 0.68 ± 0.08 ; $n=13$) and hyperperfusion (R/CE ratio, 1.31 ± 0.07 ; $n=28$) in 31 patients (33%) (Figure 1A). The second measurement performed on day 14 demonstrated relative CBF changes in 51 patients (54%) mostly classified into mild hyperperfusion (R/CE ratio, 1.34 ± 0.07 ; $n=48$) (Figure 1B). None of the patients experienced seizures throughout the study period.

In all cases, the areas of hypoperfusion were observed in the middle cerebral artery territories with ($n=4$, 31%) and without ($n=9$, 69%) MRA-evidenced distal vasospasm (Figure 2A). In this study, moderate to severe narrowing of the proximal arteries ($\geq 50\%$) was not detected on MRA. By contrast, the areas of hyperperfusion were always detected on the surgical side where the aneurysms ruptured (Figure 2B), which increased in number from days 7 ($n=28$; 30%) to 14 ($n=48$; 51%) but did not correlate with the patients' neurological deterioration. Serial SPECT measurements demonstrated the conversion from hypoperfusion on day 7 to hyperperfusion ($n=5$, 10%) on day 14, which was smaller in number than that from normo- to hyperperfusion ($n=15$, 31%) ($P=0.005$).

Univariate analysis revealed that mild hyperperfusion on day 14 had a significant relationship with functional outcome at 3 months ($P=0.04$) (Table 2). Although DCI was observed in 13 patients (14%), SPECT evidence of regional hypoperfusion ($n=5/13$) was not significantly associated with the occurrence ($P=0.07$). Multivariate analysis including age, clinical grade, DCI, and hyperperfusion on day 14 showed that DCI ($P=0.004$; odd's ratio [OR], 0.10; 95% confidence interval [CI],

0.02–0.48) and hyperperfusion on day 14 ($P=0.002$; OR, 2.44; 95% CI, 1.40–4.29) were independently associated with functional outcome at 3 months (Table 3).

Discussion

The main finding of this study was that both hypo- and hyperperfusion can occur during the DCI risk period in postoperative SAH patients, in which mild hyperperfusion on day 14 was associated with good functional outcome at 3 months. To the authors' knowledge, this is the largest study ($n=94$) to describe a nonlinear time-course of cerebral perfusion after SAH who had brain SPECT imaging after aneurysm clipping.

Several previous studies suggest that post-SAH SPECT measurements are difficult to interpret and thus its clinical value is controversial. Rosen et al. [28] found areas of hypoperfusion near the operative site in 85% of postoperative SAH patients being suggestive of perifocal edema attributable to surgical invasiveness, whereas symptomatic vasospasm occurred in 55%. On the other hand, Powsner et al. [29] evaluated SPECT measurements for prediction of vasospasm with a sensitivity and specificity of 89% and 71%, respectively and concluded poor recovery from perfusion defects was the best predictor of poor outcome. In another report, SPECT performed between day 3 and day 10 was not found to be as useful as transcranial Doppler (TCD) for evaluating clinical vasospasm [30]. Tranquart et al. [5] concluded that SPECT performed on day 8 after surgery allowed prediction of the clinical outcome. Unfortunately,

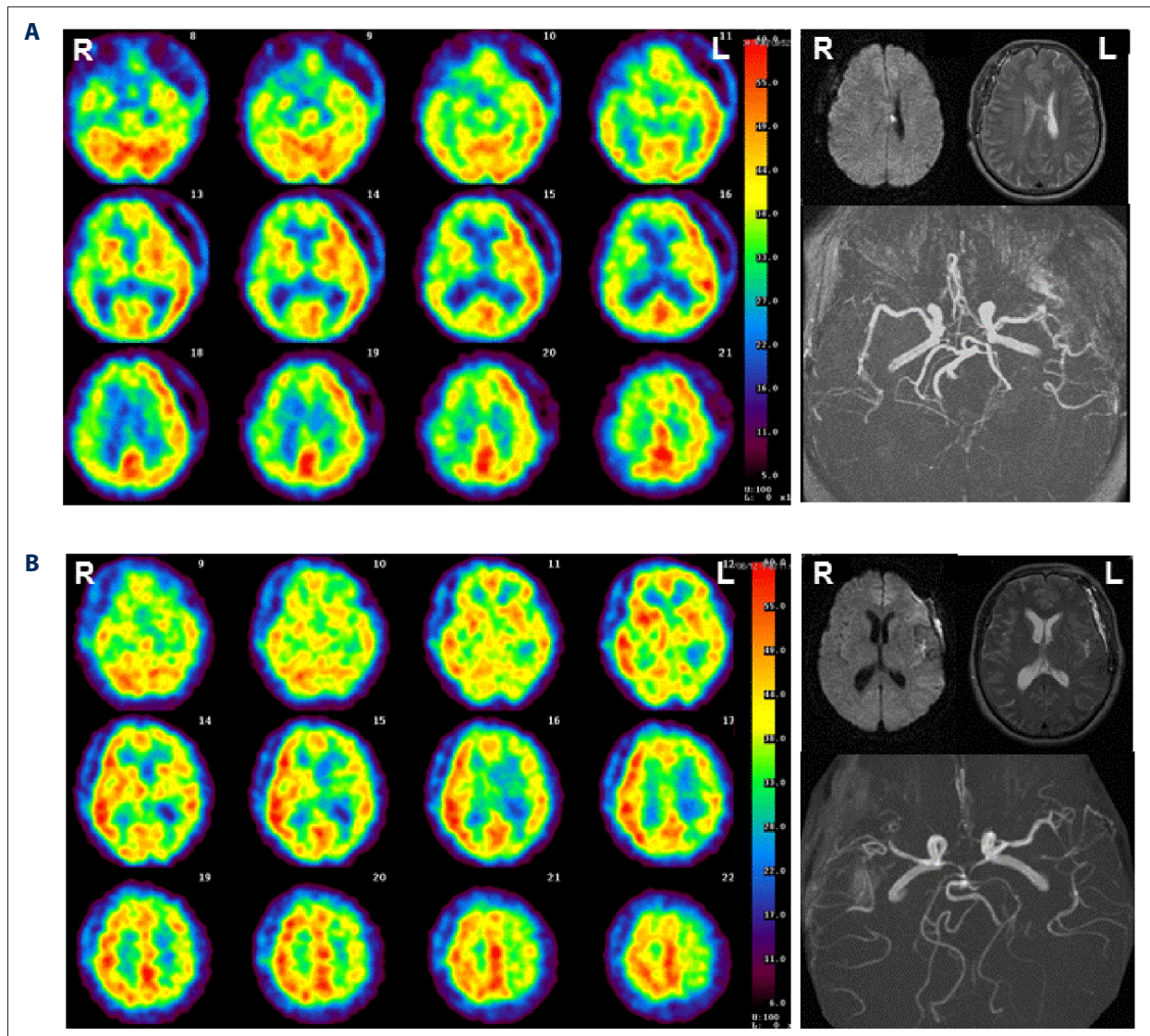


Figure 2. Examples of CBF-SPECT images in patients after SAH caused by ruptured middle cerebral artery (MCA) aneurysms. (A) Hypoperfusion (R/CE ratio, 0.65) in the right MCA territory on day 7 after SAH. DCI was suggested by neurological deterioration (left hemiparesis and dysarthria) and partially attenuated signals in the cortical segment on MR angiography (MRA) (right lower panel) without evidence of acute infarction on MR diffusion-and T2-weighted images (right upper panels). (B) Hyperperfusion (R/CE ratio, 1.25) in the right MCA territory on the surgical/ruptured side on day 14 after SAH. No clinical symptoms or MRI/MRA (right upper and lower panels, respectively)-evidenced abnormalities were observed in this patient R – right; L – left.

present traditional SPECT evaluation of relative hypoperfusion on both days 7 (or earlier exam when clinical DCI suspected) and 14 failed to predict DCI or functional outcome. Because diagnostic accuracy of SPECT measurements for detection of DCI varies significantly with time, it would seem practical that the information of cerebral perfusion gained from SPECT methods can be complementary to information of flow velocities provided by the TCD, and the date of serial examinations should not be fixed but adjust flexible timing whenever DCI was clinically suspected.

Conversely, it is interesting that the number of mild hyperperfusion visualized by the SPECT images increased from day 7 to day 14 with similar R/CE ratio (1.31 ± 0.07 vs. 1.34 ± 0.06 ; $P=0.06$), in which the presence of the relative hyperperfusion predicts favorable outcome of postoperative SAH patients. It is unclear whether such CBF changes can be explained simply by post-ischemic luxury perfusion [31] during the recovery phase from vasospasm. Early brain damage associated with aneurysm rupture (primary brain injury) and/or surgical invasiveness (mechanical injury including brain retraction

Table 2. Regional CBF-SPECT findings and 3-month functional outcome after SAH.

Variables	mRS 0-3 (n=55)		mRS 4-6 (n=39)		P
Day 7					
Hypoperfusion	5	(9%)	8	(21%)	0.10
Hyperperfusion	20	(36%)	8	(21%)	0.10
Day 14					
Hypoperfusion	12	(22%)	2	(5%)	0.37
Hyperperfusion	33	(60%)	15	(38%)	0.04

Values are given as absolute numbers (%). CBF – cerebral blood flow; SPECT – single-photon emission computed tomography; SAH – subarachnoid hemorrhage; mRS – modified Rankin Scale.

Table 3. Variables associated with good functional outcome (mRS 0–3 at 3 months) after SAH on multivariate analysis.

Predictors	Odds ratio (95% confidence interval)	P
Age 68 years or older	1.15 (0.43–3.14)	0.77
WFNS grade I-III at presentation	1.89 (0.60–5.90)	0.27
DCI on MRI on day 14	0.10 (0.02–0.48)	0.004
Hyperperfusion on day 14	2.44 (1.40–4.29)	0.002

mRS – modified Rankin Scale; SAH – subarachnoid hemorrhage; WFNS – World Federation of Neurosurgical Surgeons; DCI – delayed cerebral ischemia.

and SAH clot evacuation) to cause vasodilation in the absence of CBF impairment (so-called ‘vasoparalysis’) [7,8] could be a plausible explanation for delayed hyperemia on the approach side [32]. According to a traditional neuroncentric view of SAH using experimental models [33, 34], our patients who showed a change from hypo- to hyperperfusion (10%) may in part, support the recovery of inverted neurovascular coupling from vasoconstriction to vasodilation to neuronal activation to elicit increased CBF, supplying oxygen and nutrients to the active neurons, termed as functional hyperemia [35]. On the other hand, the prevalence of hyperperfusion observed by serial SPECT measurements (Figure 1) was not iatrogenic because we consistently employed mild hypervolemia rather than inotropic hyperdynamic therapy for treating clinical DCI to avoid acute rise in cerebral perfusion pressure [36], in case of hyperperfusion detected by initial SPECT images.

The limitations of this study include the retrospective nature and its design. First, this was a single-center double-blind study and the treatment modality included only surgical clipping (i.e., less-invasive endovascular coiling has been excluded). Therefore, our findings require validation by multicenter randomized controlled studies in larger cohorts. Second, this study provides only a relative and qualitative estimation of the CBF because SPECT is not absolutely quantitative if arterial blood sampling and analysis are not performed. Hypoperfusion with concomitant mild hyperperfusion on the other hemisphere may be undetected because absolute CBF values are not obtained. Therefore, we used a semiquantitative index of CBF alterations

(R/CE ratio) in regional perfusion. Current SPECT devices with multi-detector configurations have a spatial resolution of approximately 8 mm which may limit traditional SPECT evaluation of SAH particularly in determining subtle changes in areas of hypoperfusion. Such a small ischemic lesion attributable to microvascular dysfunction (e.g., distal vasospasm, microthrombosis, and cortical spreading ischemia) may not be detectable even using the TCD-based cerebral blood flow velocities or MRA-evidenced peripheral irregular signals [10]. The use of quantitative software (e.g., three-dimensional surface projection [3D-SSP] [37] or Hermes brain registration and analysis software [BRASS] [38]) may be useful for evaluation of small and/or mild hypoperfusion as an adjunct to the present visual/semiquantitative interpretation to direct further interpretation and therapeutic intervention.

Conclusions

Brain SPECT imaging in the late phase of the DCI risk period has a potentially valuable role to play in the evaluation of patients’ prognosis. At present, CBF-SPECT is a complementary technique to provide better assessment of ongoing clinical picture of the brain function during the risk period for DCI and the diagnostic value will increase in harmony with other imaging modalities.

Conflicts of interest statement

The authors declare that they have no competing interest.

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