J Neurol (2015) 262:623–628
DOI 10.1007/s00415-014-7601-7

ORIGINAL COMMUNICATION

CT perfusion on admission and cognitive functioning 3 months after aneurysmal subarachnoid haemorrhage

Irene M. C. Huenges Wajer · Charlotte H. P. Cremers · Martine J. E. van Zandvoort · Mervyn D. I. Vergouwen · Irene C. van der Schaaf · Birgitta K. Velthuis · Jan Willem Dankbaar · Pieter C. Vos · Johanna M. A. Visser-Meily · Gabriel J. E. Rinkel

Received: 27 August 2014 / Revised: 26 November 2014 / Accepted: 29 November 2014 / Published online: 19 December 2014

Abstract Many survivors of aneurysmal subarachnoid haemorrhage (aSAH) have persistent cognitive deficits. Underlying causes of these deficits have not been elucidated. We aimed to investigate if cerebral perfusion in the acute phase after aSAH measured with CT perfusion (CTP) is associated with cognitive outcome 3 months after aSAH. We included 71 patients admitted to the University Medical Center Utrecht who had CTP performed within 24 h after ictus and neuropsychological examination after 3 months. Perfusion values were measured in predefined regions of interest for cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). The relationship with global cognitive functioning, as measured with a mean z score of all cognitive tests, was examined by linear regression analyses. Adjustments were made for age, education, method of aneurysm treatment, and presence of non-acute medical complications. TTP was associated with cognitive functioning in the univariable analysis ($B = -0.042$, 95 % CI -0.076 to -0.008), but not after adjustment for age ($B = -0.030$, 95 % CI -0.065 to 0.004). For CBF, CBV and MTT no relationship with cognitive functioning was observed. Cerebral perfusion measured with CTP within 24 h after onset of aSAH is not associated with cognitive outcome after 3 months. The lack of an association might be explained by the delay between onset of aSAH and CTP. However, CTP assessment within the first minutes after aSAH is impossible in large series of patients.

Keywords Subarachnoid haemorrhage · Outcome · CT perfusion · Cognitive functioning

I. M. C. Huenges Wajer and C. H. P. Cremers contributed equally to this paper.

I. M. C. Huenges Wajer (✉) · C. H. P. Cremers · M. J. E. van Zandvoort · M. D. I. Vergouwen · G. J. E. Rinkel
Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
e-mail: i.m.c.huengeswajer@umcutrecht.nl

C. H. P. Cremers · I. C. van der Schaaf · B. K. Velthuis · J. W. Dankbaar
Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

M. J. E. van Zandvoort
Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands

P. C. Vos
Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands

J. M. A. Visser-Meily
Center of Excellence in Rehabilitation Medicine, Rehabilitation Center de Hoogstraat and Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is associated with substantial case fatality and morbidity. Although survivors of aSAH often regain independence in basic activities of daily living (ADL), many have persistent cognitive deficits across multiple cognitive domains [1]. These cognitive deficits often lead to restrictions in daily activities and are related to a decreased long-term health-related quality of life [2].

Several studies aimed to elucidate which factors after aSAH explain these cognitive deficits [1]. It has been suggested that measures of the extent of the haemorrhage

or the impact of the haemorrhage such as the amount of extravasated blood [3, 4], the initial condition of the patient [5], global cerebral oedema [6], and acute hydrocephalus [5] are related to cognitive deficits. However, these factors only explain a part of the variance of the cognitive deficits after aSAH. A better marker of the initial impact of the haemorrhage may be cerebral perfusion. We, therefore, studied the relationship between CT perfusion on admission and cognitive outcome 3 months after aSAH.

Methods

Design

This study was approved by the Medical Ethics Review Committee of the University Medical Center of Utrecht. Patients were retrieved from a prospectively collected series of aSAH patients admitted to the University Medical Center Utrecht between September 2006 and August 2008. In our institution all patients with aSAH routinely undergo non-contrast CT (NCCT), CTP and CT-angiography (CTA) on admission, unless there are contraindications for CT with contrast, such as pregnancy or impaired renal function. Patients discharged from the hospital to home or to a rehabilitation institution on a temporary basis, are invited to the SAH outpatient clinic 3 months after SAH. Here, patients are interviewed by a nurse practitioner specialised in SAH, visit a rehabilitation physician for a physical examination, and undergo a neuropsychological examination by a neuropsychologist. Inclusion criteria for this study were: (1) 18 years of age or older; (2) CTP scan made $<$24 h after ictus; and (3) neuropsychological examination at the SAH outpatient clinic. Exclusion criteria were: (1) aSAH in medical history; (2) movement artefacts on CTP imaging or other CTP failures.

CTP imaging

The imaging studies were performed on a 16- or 64-multidetector CT scanner (Philips Mx8000 IDT 16, Philips Brilliance 16P, Philips Brilliance 64; Best, the Netherlands). For the CTP scan 40 mL of non-ionic contrast agent (lopromide, Ultravist, 300 mg iodine/mL, Schering, Berlin, Germany) was injected into the cubital vein (18 gauge needle) at a rate of 5 mL/s followed by 40 mL saline flush at a rate of 5 mL/s using a dual power injector (Stellant Dual CT injector, Medrad Europe BV, Beek, the Netherlands). The following parameters were used: 16 slice, 90 kVp, 150 mAs, 8 $\times$ 3 mm collimation; 64 slice, 80 kVp, 150 mAs, 64 $\times$ 0.625 mm collimation. For both scanners, 1 image was acquired per 2 s from initiation of contrast injection during 60 s, with a 512 $\times$ 512 matrix, a field of view ranging from 160 to 220 mm, UB filter and standard resolution.

CTP post-processing

CTP scans were reconstructed to 5 mm slices for the 64- and 6 mm slices for the 16-multidetector CT scanner. Perfusion data were analysed using free software package called Perfusion Mismatch Analyser (PMA, version 4.0.4.4, ASIST Japan). The arterial input function (AIF) was automatically selected by PMA, and manually corrected if the automatic selection failed. A time-insensitive CTP algorithm, block-circulant singular value decomposition (bSVD) [7], was used to calculate cerebral perfusion maps for four different perfusion parameters: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP).

Perfusion values were measured in standard regions of interest (ROIs). ROIs were drawn in the cortical and subcortical flow territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) and in the basal ganglia using in-house developed software (®MevisLab, software for medical image processing and visualisation; http://www.mevislab.de) (Fig. 1).

Absolute mean perfusion values were determined for each ROI for each patient. For CBF and CBV, the ROI with the minimal value and; for MTT and TTP, the ROI with the maximal perfusion value was selected per patient.

Neuropsychological examination

The neuropsychological examination consisted of 11 subtests covering four main cognitive domains: memory, executive functioning, attention, and visuospatial functioning. Memory was assessed by the Digit Span backward of the Wechsler Adult Intelligence Scale III (WAIS-III), the immediate recall, delayed recall and recognition scores of the Rey Auditory Verbal Learning Task-Dutch version (RAVLT-D), the delayed Rey–Osterrieth Complex Figure Test (Rey-CFT) and Category Fluency (using animals). Executive functioning was measured using the Brixton Spatial Anticipation Test and the Letter Fluency (using 'N' and 'A'). The Digit Span forward of the WAIS-III and the Stroop Colour Word Test were administered to measure attention. To evaluate visuospatial functioning and construction, we used the copy score of the Rey-CFT.

Raw test scores from the individual tests were transformed into z scores based on the means and standard deviations of a control group containing 62 subjects with a mean age of 57.8 (58 % women). Test scores are classified as mild deficit if between 1.5 and 2 standard deviations below the control mean and severe deficit if more than 2

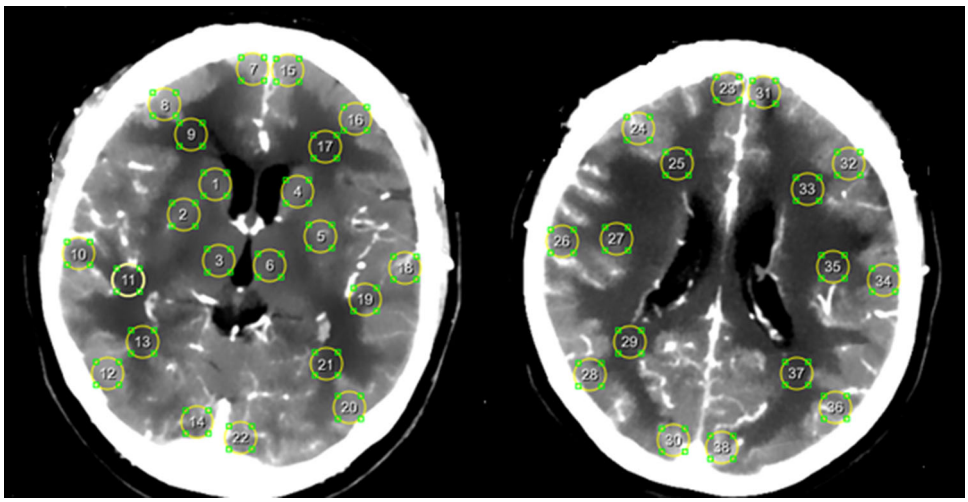

Fig. 1 Standard ROIs in the cortical and subcortical flow territories of the anterior cerebral artery, middle cerebral artery and posterior cerebral artery and in the basal ganglia, *left* standard ROIs on the level of the thalamus and basal ganglia, *right* standard ROIs on the level just cranial to the basal ganglia

standard deviations from the control mean. For an indication of global cognitive functioning, z scores of all tests were summarised by a mean score.

Other possible determinants of cognition

For each patient, we collected the following variables: age, sex, educational level [using a Dutch classification system ranging from 1 (did not complete primary school) to 7 (university degree)] [8], method of aneurysm treatment (clipping or endovascular), and occurrence of non-acute neurological complications between CTP and discharge from hospital. Non-acute complications were dichotomized in $\geq$1 complication(s) and no complications. Rebleeding was defined as a sudden clinical deterioration with signs of increased haemorrhage on CT scan compared with previous CT imaging, or a sudden clinical deterioration suspect for rebleeding with fresh blood in the ventricular drain in which no CT scan was obtained. Delayed cerebral ischemia was defined as a clinical deterioration (new focal deficit, decreased Glasgow Coma Scale of at least two points on the total score or one of its individual components, or both) lasting 1 h or longer with no evidence for rebleeding or hydrocephalus on CT and no other medical explanation, such as cardiovascular or pulmonary complications, infections or metabolic disturbances [9]. Subacute hydrocephalus was determined as a bicaudate index above the 95th percentile for age [10] and $\geq$20 % increase with respect to the admission CTP. Procedure-related ischemia was defined as ischemia in the neurosurgical trajectory or in the trajectory of an external ventricular drain. Asymptomatic infarction was defined as ischemia seen on follow-up imaging that was not present on imaging on admission and was not accompanied by clinical symptoms. Bacterial meningitis was defined as fever in combination with a positive cerebrospinal fluid culture.

Power analysis

To find an effect size of 0.15 (small effect according to Cohen's classification) with a number of 71 patients and an alpha of 0.05 in a regression analysis of both 3 and 4 predictors (as we did in our analyses) we had a power of 0.8, which can be seen as a good.

Analyses

The relationship between CTP parameters (CBF, CBV, MTT and TTP) and cognitive functioning was analysed using univariable linear regression analyses. Additionally, adjustments were (simultaneously) made for the three factors that had most influence on the regression coefficient, as well as for the four factors that affected the regression coefficient between CTP parameters and cognitive functioning most. Analyses were checked for collinearity. We considered a p value <0.05 as statistically significant.

Results

We included 71 patients. At the time of their visit to the outpatient clinic, 62 patients (87 %) were living at home and 9 (13 %) resided temporarily in a rehabilitation institution. Seventy patients (99 %) were reasonably or completely functionally independent (Barthel Index 17–20). Characteristics of the included patients are listed in Table 1. The results of CTP imaging are shown in Table 2.

Neuropsychological examination

The Rey-CFT (copy and delayed recall) was not administered in five patients because of visual problems ($n = 3$)

Table 1 Characteristics of the 71 included aSAH patients

Demographic characteristics	
Women, *n* (%)	60 (85)
Mean age in years (SD)	53 (11)
Education level (Verhage), *n* (%)	
Low (1–5)	58 (82)
High (6–7)	13 (18)
aSAH characteristics	
Admission WFNS score, *n* (%)	
I	40 (56)
II	16 (23)
III	5 (7)
IV	5 (7)
V	5 (7)
Aneurysm location, *n* (%)	
Internal carotid artery	3 (4)
Anterior communicating and cerebral arteries	31 (44)
Middle cerebral artery	13 (18)
Posterior communicating artery	15 (21)
Vertebrobasilar circulation[a]	9 (13)
Treatment received, *n* (%)	
Clipping	22 (31)
Coiling	49 (69)
Acute complications, *n* (%)	
Acute hydrocephalus	7 (10)
Intraparenchymal haemorrhage	14 (20)
Non-acute complications, *n* (%)	
Rebleeding	1 (1)
Delayed cerebral ischemia	12 (17)
Subacute hydrocephalus	5 (7)
Procedure related or asymptomatic ischemia	13 (18)
Bacterial meningitis	1 (1)
Mean follow-up time after aSAH in weeks (SD)	11.4 (4.5)

aSAH aneurysmal subarachnoid haemorrhage, *n* number, % percentage, *SD* standard deviation, *WFNS* World Federation of Neurosurgeons

[a] Including the vertebral artery, basilar artery, cerebellar arteries and posterior cerebral artery

Table 2 CT perfusion values

	Lowest perfusion value (SD)[a]	Mean perfusion value (SD)
CBF (mL/100 g/min)	14.5 (5.5)	34.5 (9.1)
CBV (mL/100 g)	1.1 (0.3)	2.0 (0.6)
MTT (s)	10.5 (1.3)	8.2 (0.9)
TTP (s)	18.6 (3.9)	16.2 (3.2)

To have a frame of reference also the mean perfusion values (of all ROIs) are presented (column 3)

SD standard deviation, *CBF* cerebral blood flow, *CBV* cerebral blood volume, *MTT* mean transit time, *TTP* time to peak

[a] Lowest perfusion value represents means of the ROIs with the lowest perfusion value: for CBF and CBV this is a minimal value and for MTT and TTP a maximal value

Table 3 Performance on neuropsychological tests

Neuropsychological tests	*n*	Mild deficit *n* (%)	Severe deficit *n* (%)	Total deficits *n* (%)
Memory				
Digit span backward	71	1 (1)	0 (0)	1 (1)
RAVLT-immediate recall	71	6 (8)	3 (4)	9 (13)
RAVLT-delayed recall	71	12 (17)	7 (10)	19 (27)
RAVLT recognition	70	5 (7)	9 (13)	14 (20)
Rey-CFT-delayed recall	62	12 (19)	2 (3)	14 (23)
Category fluency	71	6 (8)	1 (1)	7 (10)
Executive functioning				
Brixton spatial anticipation test	67	2 (3)	3 (4)	5 (7)
Letter fluency	71	15 (21)	1 (1)	16 (23)
Attention				
Digit span forward	71	5 (7)	0 (0)	5 (7)
Stroop colour word test	59	0 (0)	1 (2)	1 (2)
Visuospatial functioning				
Rey-CFT copy	65	6 (9)	8 (12)	14 (22)

n number, % percentage, *RAVLT* Rey auditory verbal learning task, *Rey-CFT* Rey–Osterrieth complex figure test

and hemiparesis ($n = 2$). In addition, some patients did not complete all neuropsychological tests within the available time resulting in missing delayed Rey-CFT scores ($n = 2$), Brixton Spatial Anticipation Test scores ($n = 4$), and Stroop Colour Word Test scores ($n = 12$). The mean z score of global cognitive functioning was -0.43 (range -1.75 to 0.73). Results of the separate cognitive tests are shown in Table 3.

Twenty patients (28 %) had severe cognitive deficits and 37 patients (52 %) had mild cognitive deficits on one or more neuropsychological tests. The proportions of patients with cognitive deficits across the different domains were, with the exception of the domain attention, comparable (15–20 %).

Analyses

In the univariable regression analyses TTP ($B = -0.042$. 95 % CI -0.076 to -0.008) but no other CTP parameter

Table 4 Relationship between perfusion and cognitive functioning

	Min CBF		Min CBV		Max MTT		Max TTP	
	B	95 % CI	*B*	95 % CI	*B*	95 % CI	*B*	95 % CI
Unadjusted	0.001	−0.008 to 0.010	−0.043	−0.506 to 0.419	−0.043	−0.149 to 0.064	−0.042	−0.076 to −0.008
Sex	0.001	−0.008 to 0.010	−0.056	−0.526 to 0.414	−0.040	−0.149 to 0.068	−0.042	−0.077 to −0.007
Age	0.001	−0.007 to 0.009	−0.028	−0.461 to 0.405	−0.016	−0.118 to 0.085	−0.027	−0.062 to 0.008
Level of education	0.002	−0.007 to 0.011	0.000	−0.462 to 0.461	−0.038	−0.144 to 0.067	−0.045	−0.079 to −0.011
Treatment	0.002	−0.007 to 0.011	−0.015	−0.485 to 0.456	−0.046	−0.153 to 0.061	−0.043	−0.077 to −0.008
Non-acute complications	0.001	−0.008 to 0.010	−0.018	−0.482 to 0.446	−0.032	−0.141 to 0.077	−0.041	−0.076 to −0.007
3 Factors[a]	0.003	−0.006 to 0.012	0.036	−0.436 to 0.508	−0.043	−0.144 to 0.075	−0.045	−0.079 to −0.011
4 Factors[b]	0.003	−0.005 to 0.011	0.050	−0.391 to 0.492	−0.008	−0.112 to 0.096	−0.030	−0.065 to 0.004

Min minimal, *CBF* cerebral blood flow, *CBV* cerebral blood volume, *Max* maximal, *MTT* mean transit time, *TTP* time to peak, *B* unstandardized regression coefficient, *95 % CI* 95 % confidence interval

[a] Adjustment for level of education, treatment and non-acute complications

[b] Adjustment for level of education, treatment, non-acute complications and age

was associated with cognitive functioning after aSAH. Adjustment for the level of education, treatment and non-acute complications did not influence the relationship between TTP and cognition. However, when age was added to the model, the relationship between TTP and cognition was no longer significant (Table 4).

Discussion

We found no relationship between cerebral perfusion assessed within 24 h after aSAH and cognitive outcome after 3 months. Although there was an association between TTP and cognitive outcome in a univariable analysis, multivariable analysis showed that this association was age dependent.

To our knowledge, no other studies have investigated the relationship between perfusion measured with CTP and cognitive outcome in patients with aSAH. In a study on perfusion heterogeneity measured with single-photon emission computed tomography (SPECT) made before aneurysm treatment and clinical outcome 1 year after aSAH, a relationship between perfusion heterogeneity, which determines the variation in perfusion, and executive functioning was found [11]. However, in contrast to our study, no corrections were made for confounders such as age.

In recent years, there is increasing interest in early brain injury after aSAH. Many factors contribute to brain injury in the acute phase, such as increased intracranial pressure, microvascular alterations in the basal lamina, platelet aggregation, acute vasospasm and reperfusion injury [12–16]. We hypothesised that perfusion deficits related to early brain injury affect cognition. Since no relationship between reduced cerebral perfusion within the initial 24 h after aSAH and cognitive outcome in longer term was found in this study, the cause of the cognitive deficits after an aSAH is still not understood. The previously reported associations between the initial conditions of the patient on admission with the development of cognitive deficits [1, 3–5] explain only a part of the cognitive deficits. As suggested in a previous review [1], non-acute complications occurring during the clinical course may also play a role in cognitive deficits after aSAH. Therefore, in our analyses we adjusted for non-acute complications such as rebleeding, delayed cerebral ischemia, non-acute hydrocephalus, procedure related or asymptomatic ischemia, and meningitis. We were, however, not able to include all these complications as different dependent variables because of a lack of power and dispersion. Using a grouped-dependent variable for the non-acute complications could underestimate a potential association.

Besides the use of non-acute complications as one grouped variable, other potential limitations of our study need further explanation. First, we included patients with a CTP up to 24 h after ictus. Since the peak in intracranial pressure and corresponding dip in cerebral blood flow might be most clear in the first minutes after aSAH [17], we cannot exclude that impaired cerebral perfusion within the first hour after ictus is associated with cognitive deficits after SAH. However, since most aSAH patients cannot be scanned within 1 h after ictus, it is impossible to collect data on ultra-early CTP in a large series of patients. Second, since we included patients who were able to visit the SAH outpatient clinic, we only investigated patients with a relatively good recovery. Although the deficits in the overall cognitive score in aSAH patients are relatively subtle, an overall decrease in

the scores is seen compared to the control group. Moreover, on separate neuropsychological tests almost one-third of the patients showed severe cognitive deficits and more than half of the patients had mild cognitive deficits in one or more tests. Thus, we assume that the lack of association between cognition and perfusion is not caused by selecting a group of patients with no or only minor cognitive deficits. Our sample is the group of patients who make a physically good recovery, but are hampered in daily life because of cognitive deficits. Finally, in this study, patients were scanned at the time of clinical deterioration. At that time often no infarctions were visible yet on CT. No CT imaging was done before hospital discharge or at a standard time, for example, 6 weeks after SAH. Therefore, in our regression analyses we adjusted for clinical deterioration due to DCI instead of (volume of) cerebral infarction due to DCI. Since areas with perfusion deficits were widespread and not confined to specific regions, no adjustments were made for location of the affected brain tissue. In addition, only the ROI with the maximum or minimum value depending on the perfusion map was used in our analysis. We did not take into account the number of ROIs with abnormal perfusion.

Conclusion

Perfusion in the initial 24 h after aSAH does not explain the neuropsychological deficits 3 months after SAH. This lack of association might be explained by the delay between onset of aSAH and CTP, whereas the sharpest reduction in cerebral perfusion occurs during and directly following the haemorrhage. CTP assessment within the first minutes after aSAH, however, is impossible in large series of patients.

Conflicts of interest The authors declare no conflicts of interest.

Ethical standards This study was approved by the Medical Ethics Review Committee of the University Medical Center of Utrecht.

References

1. Al-Khindi T, Macdonald RL, Schweizer TA (2010) Cognitive and functional outcome after aneurysmal subarachnoid haemorrhage. Stroke 41:e519–e536
2. Passier PE, Visser-Meily JM, van Zandvoort MJ et al (2012) Predictors of long-term health-related quality of life in patients with aneurysmal subarachnoid haemorrhage. NeuroRehabilitation 30:137–145
3. Hutter BO, Kreitschmann-Andermahr I, Mayfrank L et al (1999) Functional outcome after aneurysmal subarachnoid haemorrhage. Acta Neurochir Suppl 72:157–174
4. Orbo M, Waterloo K, Egge A et al (2008) Predictors for cognitive impairment one year after surgery for aneurysmal subarachnoid haemorrhage. J Neurol 255:1770–1776
5. Haug T, Sorteberg A, Sorteberg W et al (2007) Cognitive outcome after aneurysmal subarachnoid haemorrhage: time course of recovery and relationship to clinical, radiological, and management parameters. Neurosurgery 60:649–656
6. Kreiter KT, Copeland D, Bernardini GL et al (2002) Predictors of cognitive dysfunction after subarachnoid haemorrhage. Stroke 33:200–208
7. Wu O, Ostergaard L, Weisskoff RM et al (2003) Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. Magn Reson Med 50:164–174
8. Verhage F (1964) Intelligentie en leeftijd: onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar (Intelligence and Age: a study among Dutch people from age 12 to 77). Van Gorcum, Assen
9. Vergouwen MD, Vermeulen M, Van Gijn J et al (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid haemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke 41:2391–2395
10. Van Gijn J, Hijdra A, Wijdicks EF et al (1985) Acute hydrocephalus after aneurysmal subarachnoid haemorrhage. J Neurosurg 63:355–362
11. Mustonen T, Koivisto T, Vanninen R et al (2008) Heterogeneity of cerebral perfusion 1 week after haemorrhage is an independent predictor of clinical outcome in patients with aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 79:1128–1133
12. Sehba FA, Hou J, Pluta RM et al (2012) The importance of early brain injury after subarachnoid hemorrhage. Prog Neurobiol 97:14–37
13. Sehba FA, Mostafa G, Knopman J et al (2004) Acute alterations in microvascular basal lamina after subarachnoid hemorrhage. J Neurosurg 101:633–640
14. Sehba FA, Mostafa G, Friedrich V Jr et al (2005) Acute microvascular platelet aggregation after subarachnoid hemorrhage. J Neurosurg 102:1094–1100
15. Bederson JB, Levy AL, Ding WH et al (1998) Acute vasoconstriction after subarachnoid hemorrhage. Neurosurgery 42:352–362
16. Claassen J, Carhuapoma JR, Kreiter KT et al (2002) Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke 33:1225–1232
17. Grote E, Hassler W (1988) The critical first minutes after subarachnoid haemorrhage. Neurosurgery 22:654–661