



# Analysis of the Serum Components in Acute Period After Subarachnoid Hemorrhage

## *Subaraknoid Kanama Sonrası Akut Dönemde Serum Bileşenleri Analizi*

Tomasz TYKOCKI<sup>1</sup>, Kacper KOSTYRA<sup>2</sup>, Krzysztof BOJANOWSKI<sup>2</sup>, Bogusław KOSTKIEWICZ<sup>2</sup>

<sup>1</sup>Institute of Psychiatry and Neurology, Department of Neurosurgery, Warsaw, Poland

<sup>2</sup>Central Clinical Hospital Ministry of Interior in Warsaw, Department of Neurosurgery, Poland

Corresponding Author: Tomasz TYKOCKI / E-mail: ttomasz@mp.pl

### ABSTRACT

**AIM:** Multi-profile monitoring of various blood serum factors during acute subarachnoid haemorrhage (SAH) is crucial for successful treatment. The aim of the study is to evaluate the serum concentration of different blood factors in the acute period of SAH.

**MATERIAL and METHODS:** 31 patients with confirmed aneurysmal SAH were enrolled in a prospective study. The concentrations of the following serum compounds were assessed on the day of admission and reassessed after 5 days: lipids profile, cardiac functionality enzymes and markers, electrolytes, osmolality, CRP (C-reactive protein), glucose, creatinine, urine.

**RESULTS:** The mean level of high-density lipoprotein (HDL) changed significantly from 43.9±23.9 mg/dL to 27.5±19.8 mg/dL, p=0,013 (mean dif. 16.5±14,1 mg/dL; 37,3%). Concentration of low-density lipoprotein (LDL) decreased by 28.6% (mean dif. 26.78±61.32; p=0.047). Values of triglycerides and total cholesterol did not differ significantly between the initial evaluations and these repeated after 5 days. The overall serum ions (Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) concentrations and osmolality did not differ significantly between the initial measurements and after 5 days from SAH. The only mean value that appeared to be substantially increased at initial measurement was NT-proBNP and reached 1928.8±4952 pg/ml, this value dropped down to 392.87±1147.9 mg/ml after 5 days (mean dif. 1535.96±4808.76 pg/ml; 79,6%; p = 0.247). CRP increased over 2 fold after 5 days up to 29.267±28.614 mg/L (mean dif. 16.06±34.05 pg/L; 121.6%; p=0.028). At 5-day follow up hematocrit dropped to 33.38 ± 3.81% from the initial value of 39.63 ± 2,56% (p=0.02).

**CONCLUSION:** This study showed a significant decrease in the serum level of LDL and HDL, while triglycerides were moderately heightened. Routine monitoring of lipid profile and statin administration at the early stage of SAH is recommended.

**KEYWORDS:** Subarachnoid haemorrhage, Aneurysm, Lipids, Electrolytes, Cardiac enzymes

### ÖZ

**AMAÇ:** Akut subaraknoid kanama (SAK) sırasında çeşitli kan serumu faktörlerinin çoklu profile izlenmesi başarılı bir tedavi için çok önemlidir. Çalışmanın amacı, SAK'nın akut döneminde farklı kan faktörlerinin serum konsantrasyonunu değerlendirmektir.

**YÖNTEM ve GEREÇLER:** Bu prospektif çalışmaya teyit edilmiş anevrizmal SAK durumu olan 31 hasta alındı. Aşağıdaki serum bileşiklerin konsantrasyonları hastaneye yatma gününde ve 5 gün sonra değerlendirildi: lipid profili, kardiyak fonksiyon enzimleri ve belirteçleri, elektrolitler, ozmolalite, CRP (C-reaktif protein), glukoz, kreatinin. Ayrıca idrar tahlili yapıldı.

**BULGULAR:** Yüksek dansiteli lipoprotein (HDL) ortalama seviyesi 43,9±23,9 mg/dL'den 27,5±19,8 mg/dL'ye önemli ölçüde değişti ( p=0,013) (ortalama fark 16,5±14,1 mg/dL; %37,3). Düşük yoğunluklu lipoprotein (LDL) konsantrasyonu %28,6 düştü (ortalama fark 26,78±61,32; p=0,047). Trigliserid ve total kolesterol değerleri açısından ilk değerlendirme ve 5 gün sonra tekrarlananlar arasında anlamlı farklılık yoktu. Genel serum iyon (Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) konsantrasyonları ve ozmolalite açısından ilk değerlendirme ile SAK'tan 5 gün sonra tekrarlananlar arasında anlamlı farklılık yoktu. İlk ölçümde önemli ölçüde artmış gibi görünen tek ortalama değer NT-proBNP idi ve 1928,8±4952 pg/ml'ye ulaştı; bu değer 5 gün sonra 392,87±1147,9 mg/ml'ye düştü (ortalama fark 1535,96±4808,76 pg/ml; %79,6; p = 0,247). CRP 5 gün sonra 2 katına yani 29,267±28,614 mg/L'ye çıktı (ortalama fark 16,06±34,05 pg/L; artış %121,6; p=0.028). Hematokrit 5. gün takibinde ilk değer olan %39,63±2,56'dan %33,38±3,81'e düştü (p=0,02).

**SONUÇ:** Çalışmada trigliserid orta derecede artarken, LDL ve HDL serum seviyesinde önemli bir düşüş görüldü. SAK'nın erken aşamasında lipid profilinin rutin takibi ve statin uygulanması önerilmektedir.

**ANAHTAR SÖZCÜKLER:** Subaraknoid kanama, Anevrizma, Lipidler, Elektrolitler, Kardiyak enzimler

### INTRODUCTION

Fluid and electrolyte disturbances are frequently observed during the acute and subacute period after subarachnoid hemorrhage (SAH). Serum sodium concentration and fluid balance are frequently abnormal in SAH, occurring in up to

50% of patients (8,37), hyper- and hyponatremia are associated with persistent neurological deficits and high mortality (2,10,15). Hypomagnesemia and hypokalemia are observed in one third of cases (40). Serum and cerebrospinal fluid levels of C-reactive protein (CRP) are significantly elevated in patients

with vasospasm and strongly associated with poor clinical outcome (9). Most patients with SAH become relatively hemodiluted, nevertheless recent studies have questioned whether intentional lowering of the hematocrit to this level is actually beneficial (7,30).

Many serum factors might be associated with the prognosis of the early post-SAH medical course of patients. Considerable expectations are related with the statin treatment in the prevention of vasospasm and delayed ischemic deficits. Besides, hyperglycemia was observed in 30% of SAH patients and was found to be a predictor of poor functional outcome and mortality at 3 months (23).

Abnormalities in the serum level of cardiac biomarkers are often encountered after SAH. Troponin I (Tn-I) is elevated in approximately 20–30% of patients with the peak level within 1-2 days from the onset of SAH (21,24). Serum level of the brain natriuretic peptide (BNP) was also found to be increased soon after SAH and returning to baseline in 1 to 2 weeks (34). Increased BNP level is a predictor of worse neurologic outcomes and early in-hospital mortality (36).

In the light of the abovementioned data authors prepared a prospective study to evaluate the serum concentration of different blood factors in the acute period of SAH. 5-day follow up was proposed to investigate the early post SAH dynamics of the serum components.

## METHODS

This is a prospective study from a cohort of patients with confirmed aneurysmal SAH admitted to the Department of Neurosurgery between 2011 and 2013. Patients were enrolled in the study within 48 hours from the onset of SAH. Informed written consent from the patient or family was obligatory before enrolment in the study. The diagnosis of SAH was based on the computed tomography. Patients underwent cerebral angiography or angio-CT to identify the aneurysm morphology and location. Cases with any heart disease such as cardiomyopathy, prior myocardial infarction or atrial fibrillation were not included. All aneurysms were treated with surgical clipping within the first 48 hours from admission and postoperatively managed in the neurointensive care unit. Standard medical management included intravenous infusion of isotonic saline and colloids (Hydroxyethyl starch, HAES) for the purpose of volume expansion. In patients with hypotension and intracranial hypertension continuous infusion of norepinephrine was used. Nimodipine was administered obligatory intravenous or orally. Fluid and sodium balance were calculated daily. The mean arterial blood pressure was maintained at a mean arterial pressure of 100 to 110 mmHg. Atorvastatin was administered at dose 80 mg/day from the day of admission. Follow-up CT scans were typically performed to evaluate unexplained declines in neurological status. The neurological status was graded according to the World Federation of Neurosurgical Societies (WFNS) scale and the radiological severity of SAH was classified in the Fisher score. Clinical data were collected from the patient, family interviews and the medical record.

Blood samples were collected in EDTA tubes, centrifuged, and stored at  $-70^{\circ}\text{C}$ . The concentrations of the following serum compounds were assessed on the day of admission and reassessed after 5 days: lipids profile (low density lipoprotein cholesterol LDL, high density lipoprotein cholesterol-HDL, triglycerides-TG, total cholesterol-TCh), cardiac functionality enzymes and markers (Tn, MB fraction of creatine kinase-CK-MB, creatine kinase-CK, N-terminal pro-brain natriuretic peptide NT – proBNP, aspartate transaminase-AST) electrolytes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ) osmolality, CRP (C-reactive protein), glucose, creatinine, urine.

All the results were statistically analysed using the computer software Statistica 10, StatSoft, Tulsa, OK, US. Statistical significance was assumed for  $p < 0.05$ . A paired t-test was performed to establish the significant differences between repeated measurements of the serum compounds.

## RESULTS

The study included 31 patients with a mean age of  $53.6 \pm 15.2$  years. There were 19 females. The functional impairment at discharge was evaluated with the modified Rankin scale (mRS) and the scores were as follows: mRS 0 in 4 patients; I in 6, II in 4; III in 9; IV in 4; V in 4; and VI in 0 patients. The overall serum ions ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ) concentrations did not differ significantly between the initial measurements and after 5 days from SAH. The mean serum level of  $\text{Na}^+$  increased after 5 days above the upper reference value ( $160.84 \pm 207.8464$  mmol/L), whereas the mean concentration of  $\text{Ca}^{2+}$  declined to  $1.627 \pm 0.9122$  mmol/L. Osmolality levels changed from  $274 \pm 99$  to  $310 \pm 35$  mOsm/kg  $\text{H}_2\text{O}$ . 5-day difference was  $47.6 \pm 35.7$  mOsm/kg  $\text{H}_2\text{O}$  (13%). The detailed results were presented in Table I. The panel of cardiac functionality enzymes and markers included: Tn, CK-MB, CK, AST and NT – proBNP. The only mean value that appeared to be substantially increased at initial measurement was NT–proBNP and reached  $1928.8 \pm 4952$  pg/ml, this value dropped down to  $392.87 \pm 1147.9$  pg/ml after 5 days (mean dif.  $1535.96 \pm 4808.76$  pg/ml; 79.6%;  $p = 0.247$ ). None of other cardiac factors results deviated from the corresponding reference values, both within 24 hours from SAH onset and after 5 days (Table II). These values did not differ substantially between the initial and repeated measurements. In one case with enormous elevated level of NT-proBNP (17897 pg/ml), symptoms of heart failure were observed with the ejection fraction below 50% and regional wall motion abnormalities.

The lipid profile included the serum concentration of LDL, HDL, TCh and TG. The mean level of HDL changed significantly from  $43.9 \pm 23.9$  mg/dL to  $27.5 \pm 19.8$  mg/dL,  $p = 0.013$  (mean dif.  $16.5 \pm 14.1$  mg/dL; 37.3%). Concentration of LDL decreased by 28.6% (mean dif.  $26.78 \pm 61.32$ ;  $p = 0.047$ ) (Figure 1). Values of TG and TCh did not differ significantly between the initial evaluations and these repeated after 5 days. The first measurement of CRP level reached  $13.212 \pm 20.2511$  mg/L and increased over 2 fold after 5 days up to  $29.267 \pm 28.614$  mg/L (mean dif.  $16.06 \pm 34.05$  mg/L; 121.6%;  $p = 0.028$ ). At 5-day follow up HCT dropped to  $33.38 \pm 3.81\%$  from the initial value of  $39.63 \pm 2.56\%$  ( $p = 0.02$ ) (Figure 2).

**Table I:** Mean Values of the Selected Serum Compounds Assessed Within 24 Hours from the Admission and at 5-Day Follow Up

Admission Day			At 5-Day Follow up						
	Mean	SD		Mean	SD	Mean Difference	SD	p	Unit
Osmolality	274.41	99.58	Osmolality 1	310.09	16.50	47.60	35.68	0.103	mOsm/kg H <sub>2</sub> O
Hematocrit	39.63	3.80	Hematocrit 1	33.38	2.50	6.24	1.20	0.02*	%
Na <sup>+</sup>	138.35	4.95	Na <sup>+</sup> 1	160.84	207.85	22.49	20.61	0.589	mmol/L
Ca <sup>2+</sup>	1.97	0.68	Ca <sup>2+</sup> 1	1.63	0.91	0.34	1.26	0.426	mmol/L
K <sup>+</sup>	3.97	0.36	K <sup>+</sup> 1	3.55	1.47	0.42	1.49	0.23	mmol/L
Mg <sup>2+</sup>	1.79	0.64	Mg <sup>2+</sup> 1	1.53	0.87	0.27	1.19	0.508	mmol/L
CRP	13.21	20.25	CRP 1	29.27	28.61	16.06	34.05	0.028*	mg/L
Glucose	104.78	65.00	Glucose 1	87.18	65.45	17.60	88.40	0.146	mg/dL
Creatinine	0.82	0.39	Creatinine 1	0.74	0.51	0.08	0.62	0.41	mg/dL
Urine	25.67	12.37	Urine 1	21.00	15.61	7.67	16.70	0.16	mg/dL
LDL	93.37	51.68	LDL 1	66.59	43.93	26.78	14.10	0.047*	mg/dL
HDL	43.96	23.92	HDL 1	27.46	19.75	16.51	61.32	0.013*	mg/dL
Total cholesterol	136.39	68.11	Total cholesterol 1	101.56	71.13	34.80	99.70	0.157	mg/dL
Triglycerides	78.41	39.40	Triglycerides 1	91.14	63.69	12.72	74.13	0.332	mg/dL

*SD* - standard deviation. *CRP* - C-reactive protein. *LDL* - low density lipoprotein cholesterol. *HDL* - high density lipoprotein cholesterol. \* - difference statistically significant.

**Table II:** Mean Values of the Cardiac Enzymes and Markers Assessed within 24 Hours from the Admission and at 5-Day Follow Up

Admission Day			At 5-Day Follow up						
	Mean	SD		Mean	SD	Mean Difference	SD	p	Unit
NT - proBNP	1748.72	4534.70	NT - proBNP 1	389.39	1103.79	1359.33	4808.76	0.247	pg/mL
CK-MB	17.86	8.27	CK-MB 1	11.59	8.12	6.27	14.32	0.527	ug/L
Troponin	0.08	0.27	Troponin 1	0.10	0.29	0.08	0.24	0.278	ug/L
CK	183.39	282.43	CK 1	133.91	240.04	49.00	414.90	0.554	IU/L
AST	27.67	22.95	AST 1	31.41	57.84	3.74	65.02	0.904	IU/L

*SD* - standard deviation; *NT - proBNP* - N-terminal pro-brain natriuretic peptide; *CK-MB* - MB fraction of creatine kinase; *AST* - aspartate transaminase; *CK* - creatine kinase.

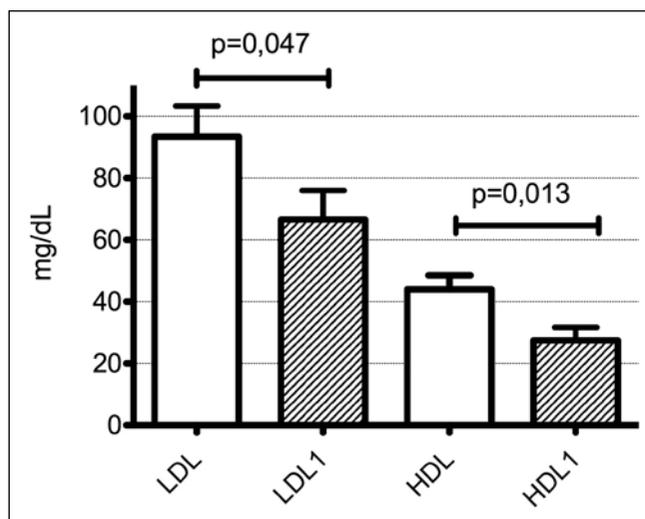
### DISCUSSION

The medical approach to patients with aneurysmal SAH is one of the major challenges in neurosurgical perioperative care. The recommended triple-H therapy, despite the absence of large randomized trials, has been postulated to be the optimal management of SAH patients. However, next to the hemodynamic therapy, multi-profile monitoring and treatment of the imbalance of various blood serum factors during acute SAH is invaluable for the success of the therapy. In this study, selected serum compounds were evaluated in this crucial period of acute SAH to provide an overview and evaluate the dynamics of serum compounds in a patient cohort.

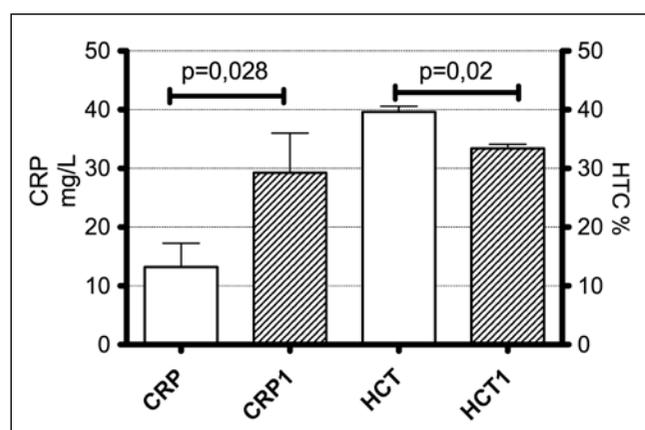
The standard hemodynamic augmentation therapy (triple H; hypervolemia, hypertension, and hemodilution) has

recently shifted the focus to the maintenance of euvolemia and induced hypertension. Euklund et al. compared isovolemic and hypervolemic hemodilution by lowering the hematocrit from 36 to 28% and reported that hemodilution to a hematocrit value of 28% was not beneficial in patients with cerebral vasospasm (7). Our results showed moderate hemodilution of 33% and the reduction of initial hematocrit of 39% was mostly due to the intensive hypervolemic therapy.

The serum concentrations of ions (Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) did not differ significantly between the initial measurements and after 5 days from SAH. However, the magnesium level was postulated to have a neuroprotective impact on prevention of symptomatic vasospasm and for a favourable outcome after SAH. Results from a phase 3 trial (Intravenous Magnesium sulphate for Aneurysmal Subarachnoid Hemorrhage (IMASH)



**Figure 1:** Column bar graph presenting the results of low and high-density lipoprotein at baseline and at 5-day follow up.



**Figure 2:** Column bar graph presenting the results of C-reactive protein and hematocrit at baseline and at 5-day follow up.

did not support any clinical benefit from magnesium infusion over placebo in SAH (42,43).

Data from the Columbia University SAH Outcomes Project proved the correlation between a higher hemoglobin level and improved outcomes after SAH at 14 days or at discharge and 3 months (20). Contrary, perioperative blood transfusion is potentially harmful in patients with SAH and leads to increased risk of cerebral ischemia, developing angiographic cerebral vasospasm and worse modified Rankin score at discharge (20, 29).

The serum concentration of lipids is postulated to be associated with the risk of the aneurysm rupture and post-subarachnoid hemorrhage vasospasm. Nonetheless, different studies present divergent conclusions on the role of lipids. Large population-based studies (11, 4, 44) have advocated the role of hypercholesterolemia as a possible risk factor of SAH. On the contrary, however, a pooled analysis did not

confirm hypercholesterolemia as a predictor of SAH (32). The protective role of statins is based on the upregulation of the endothelial nitric oxide synthase, reduction of low-density lipoprotein (LDL), and modulation of the anti-inflammatory and endothelial activation response after statin administration (25). The recent reports present contrary findings. Whilst a meta-analysis reported no evidence for the clinical benefit (38), some other randomized trials prove approving outcomes (35). The on-going large phase 3 trial SimvasTatin in Aneurysmal Subarachnoid Hemorrhage (STASH) hopefully will convincingly answer this dilemma.

In the study of Tokuda et al. the median serum level of total cholesterol was 161 mg/dl in patients with SAH, and 209 mg/dl in controls (33). Median serum triglycerides were 95 mg/dl in SAH and 122 mg/dl in controls. They also found that a serum total cholesterol of more than 200 mg/dl and serum triglycerides of more than 150 mg/dl were independent protective factors for SAH. Surprisingly, the conclusion from this study was that higher values of both serum cholesterol and triglycerides may be inversely associated with the occurrence of SAH. In another study no association of any serum lipid and the risk of SAH was found, except a negative association of HDL cholesterol in participants younger than 50 years of age (28). The results of serum lipids concentrations from this study have shown decreased values of HLD, LDL, and TCh after 5 days comparing to the baseline. The change was significant for LDL, HDL and was estimated as 29% and 37% respectively. TG levels decreased moderately by 16% at the 5th day. Probably two factors might caused the change in the serum lipid profile; 1) administration of atorvastatin and 2) severe metabolic stress. Although, the full lipid modulating effect can be seen as early as several weeks after starting statins, some studies have shown that a significant reduction in LDL and TCh after 7 days of atorvastatin therapy (18,25). Therefore a significant shift in the lipid profile after 5 days found in this study might be due to the atorvastatin administration. Cumulative review of the randomised, double blind controlled trials reporting to the efficacy of the atorvastatin in hypercholesterolemia showed the mean reduction of LDL by 36% and triglycerides by 17% (6, 41). These results are comparable with our observations. Metabolic shock is another factor alongside the statins, affecting the sudden transition of serum lipids level after SAH. The shifts in serum lipids concentration in the early period after severe trauma probably results from the increased catabolism, higher availability of free fatty acids, oversecretion of catecholamines, cytokines, tumor necrosis factors or interferons (13, 35). It has been proven that the lipid profile may significantly change shortly after burn injury where serum TCh level decreased by 26% and HDL by 52% in the first week, while TG was slightly raised in one week and then decreased by 18.6% compared to normal subjects (27).

CRP level may predict the neurological course after SAH. Interestingly, the surgically treated group demonstrated higher levels of CRP in serum and CSF compared with those who were treated endovascularly. There is some discrepancy about the predictive value of CRP. Fountas et al. reported

that elevated CRP levels in serum and CSF were associated with increased incidence of angiographic vasospasm (9). Additionally, the elevated CSF and serum CRP were associated with worse clinical outcome, as expressed in Glasgow Outcome and mRS scores. On the other hand, Juvola et al. concluded that CRP levels correlate with outcome but do not predict delayed cerebral ischemia or infarction after SAH (12). Generally the serum values of CRP rise in the acute period of SAH and tend to be higher in CSF than in serum. CRP levels increased significantly between the day of hospital admission from 11.4 mg/L to 19.8mg/L during the second week (12). The CRP serum level increased almost 3 fold after 5 days in comparison to the initial level of 4 mg/L, while the baseline level of CRP in CSF was 10 mg/L and doubled within 5 days (9). This is consistent with results from this study where serum CRP level changed from 13 mg/L to 29 mg/L and the difference was statistically significant. CRP is of course a non-specific factor for SAH and its increase may be due to other conditions, in particular inflammation of various origin.

The prevalence of SAH-induced cardiac dysfunction, often named neurogenic stunned myocardium (NSM), has been estimated as at least 20–30% (1). The pathogenesis of the SAH-induced NSM is based on the catecholamine over-secretion. An increased plasma level of troponine was found to be a sensitive and specific indicator of neurogenic stunned myocardium, while creatine kinase-MB is a superior marker of myocardial infarction (14). The elevated sympathetic tone leads to the opening of cardiomyocyte calcium channels through the activation of  $\beta$ 1-adrenergic receptors resulting in myocardial depression (3).

Cardiac injury may be immediately evident or develop within hours after aneurysmal rupture. The timing of recovery in SAH-induced left ventricle dysfunction can be quite variable, with improvement in ejection fraction ranging from days to weeks (3–42 days) (19,39).

Recent results provide indirect evidence that the heart is the primary source of elevated BNP levels after SAH. Nakamura et al. reported a positive correlation between BNP and pulmonary extravascular water content in SAH patients with consciousness disturbance (22).

The overload on the left ventricle or atrium causing increased pulmonary capillary pressure begins immediately after SAH onset and results in cardiopulmonary edema. Elevated BNP level indicates systolic and diastolic dysfunction of the left ventricle, especially regional wall motion abnormalities and reduced ejection fraction (16,45). Patients with increased levels of BNP should not be subjected to much fluid overload based on triple H therapy. In our results the mean value of pro-BNP was 1928 pg/ml, mostly due to the excessively elevated values in two cases above 17.000 and 19.000 pg/ml. However the mean serum levels of pro-BNP decreased excessively after 5 days, but only one patient developed a severe heart incident, although the overall levels of BNP in the patient cohort remained elevated.

The increased levels of BNP are strongly and independently associated with cerebral infarction, and the association is most pronounced in patients without angiographic vasospasm (31). BNP rises gradually over two days and returns to normal within a week after SAH. Its release is associated with myocardial necrosis, but is unrelated to elevation of left ventricular assessed by echocardiography (17).

## CONCLUSION

In the acute phase after SAH onset a meticulous monitoring of different serum components is of great importance, because significant fluctuations and deviations from the reference values might occur. This study showed a significant decrease in the serum level of LDL and HDL, while TG values were moderately heightened. There were no serious disturbances of fluid and electrolyte balance. High levels of BNP did not correlate with the coexistence of severe cardiac complications.

Routine monitoring of lipid profile and statin administration at the early stage of SAH is recommended.

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