Effect of systemic parameters following experimental subarachnoid hemorrhage and cerebral vasospasm in rabbits by injection of blood into the subarachnoidal space

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ABSTRACT

الأهداف: فحص التغيرات الحادة في القياسات الجهازية الحادة عند حدوث نزف تحت العنكبوتية (SAH) وتم خلق حالات من التشنج الوعائي الدماغي بواسطة الحقن داخل الصهريج بالدم الجديد في نموذج الأرانب.

الطريقة: أجريت هذه الدراسة بعيادة جراحة الأعصاب بمستشفى أزمير ومركز التدريب والأبحاث مدينة أزمير –تركيا. خلال الفترة ما بين أبريل 2002 ومارس 2005م. تم تقسيم عدد 32 ذكر أرنب إلى 4 مجموعات: المجموعة الأولى التي تعرضت لنزف بسيط بمقدار 0.5cc، المجموعة الثانية التي تعرضت لنزف متوسط بمقدار 0.7cc، والمجموعة الثالثة والتي تعرضت لنزف 1cc من الدم. والمجموعة الرابعة والتي أجريت لها عملية خادعة بدون دم. تمت مراقبة القياسات السريرية لجميع الحيوانات لساعتين بعد العملية الجراحية وتم إجراء تحليل الدم بعد النزف مباشرة. تم إجراء سلسلة من القياسات الجهازية مثل أخذ قياس درجة الحرارة عن طريق الشرج وفحص ضغط الدم الانقباضي والانبساطي وتحليل غازات الدم قبل وبعد تلقي حقن الدم. تمت مقارنة النتائج بواسطة تحليل التفاوت واختبارات تي، وتم اعتبار قيمة الخطأ أقل من 0.05 أنه ملحوظاً.

النتائج: اختلفت قياسات ضغط الدم الإنقباضي بشكل ملحوظ في المجموعات 1، 2، 3 قبل وبعد فترات النزيف. تم اعتبار قياسات ضغط الدم الانبساطي مختلفاً.

خاتمة: تقترح الدراسة أن وجود جلطة الدم وكمية مختلفة من الدم في موقع تحت العنكبوتية بإمكانه إثارة سلسلة من التغيرات في كلتا الحالتين المحلية والجهازية لنماذج التجربة.

Objectives: To investigate acute changes of systemic parameters following experimental subarachnoid hemorrhage (SAH) and cerebral vasospasm conditions created by intracisternal injection of fresh autologous blood in a rabbit model.

Methods: The study was carried out at the Neurosurgery Clinic, İzmir Training and Research Hospital, İzmir, Turkey between April 2002 and March 2005. Thirty-two male rabbits were divided into the following 4 groups: group one with mild hemorrhage received 0.5 cc of blood, group 2 with moderate hemorrhage received 0.7 cc of blood, group 3 with severe hemorrhage received 1 cc of blood, and the sham-operated group 4 with no blood. The clinical parameters of all animals were monitored 2 hours after the operation, and blood analysis was performed just after hemorrhage. A series of systemic parameters such as rectal temperature, systolic and diastolic blood pressure, and blood gas analysis were measured before and after administration of blood injection. Results were compared by analysis of variance and paired t-tests, and *p*-values less than 0.05 were considered significant.

Results: The systolic blood pressures were significantly different in groups 1, 2, and 3 before and after the bleeding period. The diastolic blood pressures were also considerably different.

Conclusions: This study suggests that the presence of a blood clot and different amounts of blood in the subarachnoid space can evoke a series of changes in both local and systemic states in experimental models.

Neurosciences 2010; Vol. 15 (1): 15-20

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Received 2nd August 2009. Accepted 3rd November 2009.

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Delayed ischemic neurological deficit resulting from posthemorrhagic cerebral vasospasm is a feared complication and cause of morbidity and mortality in patients with subarachnoid hemorrhage

(SAH).[1] Despite extensive experimental and clinical research, the pathogenesis of cerebral vasospasm remains unclear, and no specific therapeutic method has been established. The presence of blood in the basal cisternal space, such as in SAH, usually results in some pathophysiological changes that occur both locally and systemically, either in the early or late phase depending on the amount of blood.[2,3] Clinical consequences of SAH may vary from headache as a result of meningeal irritation to death. Large amounts of blood can cause increased intracranial pressure, diminution of CSF circulation, and epileptic activity. The ECG changes, and increase of blood leucocyte number are examples of systemic events.[4-6] Much research has focused on the late pathophysiological changes after SAH, such as vasospasm, and cerebrospinal hemodynamics. In addition, much attention has been paid to demonstrate some focal and generalized disturbance of several brain functions pertinent to SAH.[2,3] However, systemic hematological events in the acute stage of SAH have not been widely investigated. Only a few studies of acute systemic changes following SAH have been reported in the literature.[1,2,4-15] The present study was designed to monitor a group of changes in systemic parameters following injection of different amounts of blood into the cisternal space in a rabbit model. Understanding this kind of change in the acute stage of SAH could offer some clinical implications for the management of aneurysm patients. Although many facts have been brought to light on subarachnoid bleeding, which features significantly in neurology and neurosurgery, many facts remain in the dark. Despite progress in diagnostic methods making it easy to diagnose SAH, to be informed of post-bleeding complications and metabolic changes, and to take measures against them will certainly influence medical treatments, as vasospasm experienced after SAH is still a considerable problem.

Methods. The study was carried out at the Neurosurgery Clinic, İzmir Training and Research Hospital, İzmir, Turkey between April 2002 and March 2005. The animals were supplied by the Ege University (Animal Center, Ege University, İzmir, Turkey). The Hospital Ethics Committee approved the research protocol. Environmental conditions were standardized for all animals during this study. The experiment followed the Principles of Laboratory Animal Care of NIH.[16] Thirty-two male New Zealand white rabbits weighing from 1.6-1.8 kg were randomly assigned to 4 experimental groups of 8 animals each. The categorization of samples and classification of hemorrhage condition in each group is as follows: group one with mild hemorrhage received 0.5 cc of blood, group 2 with moderate hemorrhage received 0.7 cc of blood, group 3 with severe hemorrhage received 1 cc of blood, and the sham-operated group 4 received no blood. Three rabbits in which we tried to form a model of subarachnoid bleeding with 1.5 cc died during the procedure, and another died 2 hours after the injection; therefore, we did not include this group with a high volume (1.5 cc) of blood in the study. Before the procedure, the arteries at the dorsal end of each rabbit's ears were found. Later, an arterial catheter (PE-90) was inserted into the artery, and the triple tap was fixed onto the catheter in a way that would keep the arterial line ready to use. The mean arterial blood pressure (MABP) was measured by a physiologic pressure transducer (Gould Statham P-23 XL; Gould Inc., Santa Clara, CA) calibrated before each experiment with a blood pressure manometer and was recorded on a multi-channel polygraph (model 5/6H; Gilson Medical Electronics, Inc., Middleton, WI). Each rabbit was monitored for approximately 2 hours before the procedure; their systolic and diastolic arterial blood pressures were measured and noted. The body temperature of the animals was monitored, as well as a measure of the acidity or basicity of blood (PH), partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), hemoglobin (Hb), hematocrit (Htc), sodium (Na), potassium (K), bicarbonate (HCO_3), and oxygen (O_2). Rabbits were anesthetized with urethane (8 mg/kg iv) for all procedures. Venous blood was then drawn without being heparinized, and was injected into the cisterna magna in the predetermined amounts for each group. Injection of blood took 2-3 minutes according to the amount. The atlanto-occipital membrane was exposed. Animals were kept in an up-side-down position to let the injected blood spread through the subarachnoidal space. In the sham group, arachnoid membrane puncture only was performed, and complete puncture was verified by observation of CSF leakage through the puncture site. All animals were monitored before and during the procedure, and over the following 24 hours. Seventy-two hours after the cisternal blood injection, all animals were sacrificed and the brains were collected (**Figures 1 & 2**). For investigational purposes, the collected brains were stored at -15 celsius. Experimental SAH and cerebral vasospasm conditions were created by intracisternal injection of fresh autologous blood. The different sections, of 2 microns thickness, were derived from the basilar artery 24 hours after the fixation. The sections were stained with hematoxylin-eosin (H&E). A histopathologist who was unaware of the treatment the rabbit had received assayed each section.

We analyzed the data with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). The differences between the groups were evaluated using paired t-tests, with a value of $p<0.05$ indicating statistical significance.

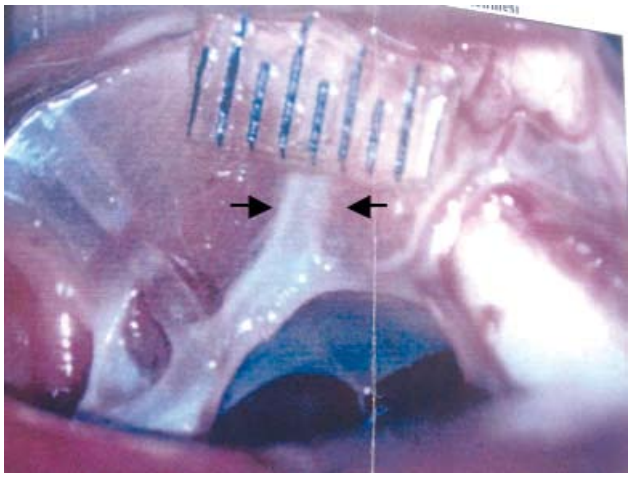

Figure 1 - The internal carotid artery before subarachnoid hemorrhage.

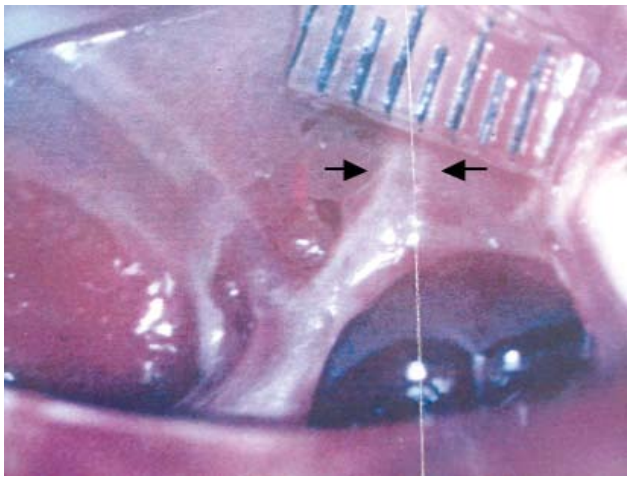

Figure 2 - Vasospasm in the internal carotid artery after subarachnoid hemorrhage.

Results. The differences observed before and after the bleeding periods were examined within each group, and the systolic blood pressures measured before and after the bleeding periods were found statistically significant (p=0.015) in group one (low-level density) (**Table 1**). The difference in pre-bleeding and the post-bleeding temperatures in group one was statistically significantly different (p=0.001), as was the difference in PO_2 values (p=0.022). There were no statistically significant differences found for PH, PCO_2, Hb, Htc, Na, K, HCO_3, and O_2 saturations in group one before and after the bleeding periods (**Table 1**). There was a statistically significant difference (p=0.001) in the systolic and diastolic blood pressures in group 2 (average-level density) before and after the bleeding periods (**Table 2**). There was also a statistically significant difference in PH (p=0.007) with paired t-test, and no significant difference was found between Hb, Htc, K, and HCO_3. There was a statistically significant difference (p=0.026) in the systolic blood pressure measured and diastolic blood pressure measured in group 3 (high-level density) pre and post-bleeding periods (**Table 3**). The difference in pre-bleeding and the post-bleeding temperatures in group 3 was also statistically significantly different (p=0.002), as were the differences in PCO_2 and PO_2, which was different to the other groups. The pre and post-bleeding O_2 saturations in this group were also

Table 1 - Pre and post-bleeding values of the low-level density subarachnoid bleeding model (group one).

Pairs	Systemic parameters	BSH	ASH	n	t	*P*-value
Pair 1	BSH. Syst. (mm Hg) - ASH. Syst. (mm Hg)	65.25	69.38	8	-3.203	0.015
Pair 2	BSH. Diast. (mm Hg) - ASH. Diast. (mm Hg)	50.13	59.63	8	-2.407	0.047
Pair 3	BSH. PH - ASH. PH	7.28	7.253	8	0.48	0.646
Pair 4	BSH. TEMP - ASH. TEMP	36.725	36.975	8	-5.916	0.001
Pair 5	BSH. PCO_2 (mm Hg) - ASH. PCO_2 (mm Hg)	38.36	39.613	8	-0.314	0.763
Pair 6	BSH. PO_2 (mm Hg) - ASH. PO_2 (mm Hg)	98.625	66.188	8	2.93	0.022
Pair 7	BSH. Hb (gr/dl) - ASH. Hb (gr/dl)	9.175	9.200	8	-0.070	0.946
Pair 8	BSH. Htc (%) - ASH. Htc (%)	27.63	27.63	8	0.00	1.000
Pair 9	BSH. NA (mmol/L) - ASH. NA (mmol/L)	144.75	148.63	8	-1.002	0.350
Pair 10	BSH. K (mmol/L) - ASH. K (mmol/L)	3.538	2.888	8	2.63	0.058
Pair 11	BSH. HCO_3 (mmol/L) - ASH. HCO_3 (mmol/L)	30.275	17.063	8	1.278	0.242
Pair 12	BSH. O_2 sat. (%) - ASH. O_2 sat. (%)	93.212	86.063	8	1.726	0.128

BSH - before subarachnoid bleeding, ASH - after subarachnoid bleeding, TEMP - temperature, Syst - systolic, Diast - diastolic, PCO_2 - partial pressure of carbon dioxide, PO_2 - partial pressure of oxygen, HCO_3 - bicarbonate, O_2 sat. - oxygen saturation, PH - measure of the acidity or basicity, Hb - hemoglobin, Htc - hematocrit, NA - sodium, K - potassium, Std - standard

Table 2 - Pre and post-bleeding values of the average-level density subarachnoid bleeding model (group 2).

Pairs	Systemic parameters	BSH	ASH	n	t	*P*-value
Pair 1	BSH. Syst. (mm Hg) - ASH. Syst. (mm Hg)	61.38	75.00	8	-5.435	0.001
Pair 2	BSH. Diast. (mm Hg) - ASH. Diast. (mm Hg)	57.13	68.25	8	-5.627	0.001
Pair 3	BSH. PH - ASH. PH	7.410	7.248	8	3.734	0.007
Pair 4	BSH. TEMP - ASH. TEMP	36.875	36.363	8	-4.529	0.003
Pair 5	BSH. PCO_2 (mm Hg) - ASH. PCO_2 (mm Hg)	32.89	36.550	8	-1.545	0.166
Pair 6	BSH. PO_2 (mm Hg) - ASH. PO_2 (mm Hg)	131.575	95.538	8	3.002	0.020
Pair 7	BSH. Hb (gr/dl) - ASH. Hb (gr/dl)	10.813	10.700	8	0.289	0.781
Pair 8	BSH. Htc (%) - ASH. Htc (%)	31.88	31.09	8	0.662	0.529
Pair 9	BSH. NA (mmol/L) - ASH. NA (mmol/L)	144.25	133.75	8	6.416	0.000
Pair 10	BSH. K (mmol/L) - ASH. K (mmol/L)	3.750	3.125	8	1.276	0.243
Pair 11	BSH. HCO_3 (mmol/L) - ASH. HCO_3 (mmol/L)	20.638	16.725	8	1.744	0.125
Pair 12	BSH. O_2 sat. (%) - ASH. O_2 sat. (%)	97.950	89.187	8	2.110	0.073

BSH - before subarachnoid bleeding, ASH - after subarachnoid bleeding, TEMP - temperature, Syst - systolic, Diast - diastolic, PCO_2 - partial pressure of carbon dioxide, PO_2 - partial pressure of oxygen, HCO_3 - bicarbonate, O_2 sat. - oxygen saturation, PH - measure of the acidity or basicity, Hb - hemoglobin, Htc - hematocrit, NA - sodium, K - potassium, Std - standard

Table 3 - Pre and post-bleeding values of the high-level density subarachnoid bleeding model (group 3).

Pairs	Systemic parameters	BSH	ASH	n	t	*P*-value
Pair 1	BSH. Syst. (mm Hg) - ASH. Syst. (mm Hg)	65.42	85.42	8	-0.440	0.026
Pair 2	BSH. Diast. (mm Hg) - ASH. Diast. (mm Hg)	57.13	75.25	8	-2.826	0.026
Pair 3	BSH. PH - ASH. PH	7.410	7.34	8	1.527	0.171
Pair 4	BSH. TEMP - ASH. TEMP	36.80	36.3	8	-4.782	0.002
Pair 5	BSH. PCO_2 (mm Hg) - ASH. PCO_2 (mm Hg)	32.89	36.56	8	-4.415	0.003
Pair 6	BSH. PO_2 (mm Hg) - ASH. PO_2 (mm Hg)	135.28	97.63	8	-4.812	0.002
Pair 7	BSH. Hb (gr/dl) - ASH. Hb (gr/dl)	10.813	10.700	8	0.954	0.372
Pair 8	BSH. Htc (%) - ASH. Htc (%)	31.88	31.09	8	1.061	0.324
Pair 9	BSH. NA (mmol/L) - ASH. NA (mmol/L)	144.50	133.75	8	5.858	0.001
Pair 10	BSH. K (mmol/L) - ASH. K (mmol/L)	3.750	3.125	8	0.395	0.704
Pair 11	BSH. HCO_3 (mmol/L) - ASH. HCO_3 (mmol/L)	20.638	16.725	8	1.153	0.287
Pair 12	BSH. O_2 sat. (%) - ASH. O_2 sat. (%)	97.955	89.18	8	4.154	0.004

BSH - before subarachnoid bleeding, ASH - after subarachnoid bleeding, TEMP - temperature, Syst - systolic, Diast - diastolic, PCO_2 - partial pressure of carbon dioxide, PO_2 - partial pressure of oxygen, HCO_3 - bicarbonate, O_2 sat. - oxygen saturation, PH - measure of the acidity or basicity, Hb - hemoglobin, Htc - hematocrit, NA - sodium, K - potassium, Std - standard

statistically different (p=0.004) (**Table 3**). When the differences between the Na averages are considered, there is a significant difference between groups one, 2, and 3 (**Tables 1-2**). When compared with group 4 (sham group) (**Table 4**), we observed that the difference between groups 2 and 3 was high. All animals were drowsy the first day after SAH, but showed normal activity, feeding, and drinking behavior on the second day. There were no other signs of neurological deficits. Gross macroscopic inspection revealed no signs of damage to the brain stem. Morphological changes of the vessel wall were assayed using light microscopy. When the sections were examined under light microscopy (Hematoxylin & Eosin x125), endothelial cells regularly lined the lumen, and there were smooth muscle cells and connective tissue cells in the sham group. In SAH groups (2 and 3), there was significant thickening and coiling of the lamina elastica, swelling of the endothelial cells into the lumen and dissection from the nearby elastica. In the media layer, smooth muscle cells were short and thick.

Discussion. Delayed ischemic neurological deficit resulting from posthemorrhagic cerebral vasospasm is a feared complication, and cause of morbidity and mortality in patients with SAH.[1] There are some

Table 4 - Pre and post-bleeding values of the sham group (group 4).

Pairs	Systemic parameters	BSH	ASH	n	t	*P*-value
Pair 1	BSH. Syst. (mm Hg) - ASH. Syst. (mm Hg)	62.50	62.38	8	-0.102	0.922
Pair 2	BSH. Diast. (mm Hg) - ASH. Diast. (mm Hg)	56.13	55.00	8	-1.386	0.208
Pair 3	BSH. PH - ASH. PH	7.32638	7.34750	8	5.401	0.001
Pair 4	BSH. TEMP - ASH. TEMP	36.813	36.563	8	-1.923	0.096
Pair 5	BSH. PCO_2 (mm Hg) - ASH. PCO_2 (mm Hg)	33.10	37.587	8	-0.988	0.356
Pair 6	BSH. PO_2 (mm Hg) - ASH. PO_2 (mm Hg)	90.100	88.863	8	0.065	0.950
Pair 7	BSH. Hb (gr/dl) - ASH. Hb (gr/dl)	8.113	7.938	8	0.32	0.759
Pair 8	BSH. Htc (%) - ASH. Htc (%)	24.13	23.63	8	0.303	0.770
Pair 9	BSH. NA (mmol/L) - ASH. NA (mmol/L)	150.75	147.88	8	2.232	0.061
Pair 10	BSH. K (mmol/L) - ASH. K (mmol/L)	3.113	3.225	8	-0.747	0.479
Pair 11	BSH. HCO_3 (mmol/L) - ASH. HCO_3 (mmol/L)	18.050	21.500	8	-1.447	0.184
Pair 12	BSH. O_2 sat. (%) - ASH. O_2 sat. (%)	96.500	90.363	8	1.361	0.216

BSH - before subarachnoid bleeding, ASH - after subarachnoid bleeding, TEMP - temperature, Syst - systolic, Diast - diastolic, PCO_2 - partial pressure of carbon dioxide, PO_2 - partial pressure of oxygen, HCO_3 - bicarbonate, O_2 sat. - oxygen saturation, PH - measure of the acidity or basicity, Hb - hemoglobin, Htc - hematocrit, NA - sodium, K - potassium, Std - standard

predisposing factors, such as an increased amount of blood in the subarachnoid space, presence of hydrocephalus, leucocytosis of the peripheral blood, hyperthermia, hyponatremia, poor grade of the patient, and middle cerebral artery aneurysm in women. Previous studies demonstrated that vasospasm is multifactorial in etiology. Oxyhemoglobin, angiotensin, serotonin, catecholamine, and histamine were reported to take place in cerebral vasospasm development.[2-6] As soon as subarachnoid bleeding occurs, it causes changes in both the CNS and in the other systems of the body, which could even cause death. There are few studies on the systemic effects of bleeding; they are rather focused on cardiac effects. Autologous fresh blood infection into the cisterna magna in rats, dogs, or rabbits as a model for SAH has been reported in the literature.[2-5,7,8,12] Another animal model has demonstrated the acute change of dynamics of the CSF system after SAH.[2-5,7,8,12-15] However, only a few studies of acute systemic changes following SAH have been reported in the literature to date.[1,2,4-15] In this study, acute changes of systemic parameters were investigated when experimental SAH and cerebral vasospasm conditions were created following injection of different amounts of blood into the cisternal space.

The increase in the amount of noradrenaline is blamed for the stress reaction, which has a negative impact on the cardiovascular system. There is very little norepinephrine and epinephrine in the thromboses. Lambert et al,[3,4,6] stated that they had attained vasospasm following experimentally performed subarachnoid hemorrhage when they used intracisternally norepinephrine concentrations that were much higher than the predicted clinical doses. Bunc et al[5] proved that very high doses had resulted in long-term vasospasm in rabbits and showed that noradrenaline in physiological limits did not cause spasm. These investigations are consistent with the findings described by Germano et al[2] following puncture of subarachnoid arteries and blood injection. In this study, we found a decrease in basilar artery vessel lumen width, and morphological changes developed in the artery wall following SAH and vasospasm.

Germano et al[2] showed an increase in intracranial pressure (ICP) during SAH, which had been formed by him experimentally. During these tests, diastolic blood pressure increases in the beginning and during the following hours, it decreases after reaching a plateau. In a study by Powers et al,[8] it was suggested that cerebral blood flow in subarachnoid bleeding does not depend on the changes in CO_2 tension, but depends on the changes in the average artery blood pressure. Besides, according to the statements of these researchers, it was found that cerebral blood flow decreases with an increase in PCO_2 values.

In a study by Pera et al,[14] it is accepted that the brain controlling its own blood flow is a function of blood mechanism, which shows itself with the changes in extra-cellular pH. In other words, the brain organizes its blood flow in accordance with its metabolic needs. In our experimental study, SAH that was induced in the 4 groups of rabbits at various levels resulted in significant changes in temperature, diastolic blood pressure, and the blood levels of PCO_2 and Na. Large amounts of blood can cause an increase in intracranial pressure, diminution of CSF circulation, and epileptic

activity.[1-6,13,15] As the bleeding increases, the blood Na values decrease; however, the temperature, the diastolic blood pressure, and PCO_2 increase. The values of Hb, Htc, HCO_3, and O_2 saturations in other parameters were compared between the groups, and the difference was found statistically insignificant.

In conclusion, this study suggests that the presence of blood clots and different amounts of blood in the subarachnoid space can evoke a series of changes in both local and systemic states of experimental models. This study also supports the previous studies stating that acute changes of systemic parameters following SAH play a role in vasospasm development.

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