Subaraknoid kanama sonrası erken beyin hasarı

Early brain injury after subarachnoidal hemorrhage

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Özet
Subaraknoid kanama, dünya nüfusu göz önüne alındığında en önemli morbidite ve mortalite nedenlerinden biridir. Geç komplikasyonların (tekrar kanama,hidrosefali,geç iskemik nörolojik defisit,elektrolit imbalansı) yönetimi,sonuçların daha iyi olmasını sağlayabilir. Fakat,serebral hemodinamiğin bozulması ,vasküler-nöronal apopitoz gelişmesi, genetik faktörler gibi patofizyolojik süreçler, önlenemeyen erken heyin hasarına yol açmaktadır. Bu makalede, subaraknoid kanama sonrası serebral kan akımının önemi ve erken beyin hasarına yol açan patofizyolojik mekanizmalar özetlenmiştir.

Anahtar kelimeler: *Subaraknoid kanama, serebral vazospazm, apopitoz, beyin yaralanmaları*
Türkçe kısa makale başlığı: *Subaraknoid kanama*

Abstract
Subarachnoidal hemorrhage is one of the most important causes of mortality and morbidity among the world's population. Management of late complications (including rebleeding, hydrocephaly, late ischemic neurological deficit, or electrolyte imbalance) can improve outcomes. However, pathophysiological processes, such as deterioration of cerebral hemodynamics, development of vascular-neuronal apoptosis, and genetic factors that occur with the hemorrhage, lead to early brain injury that cannot be prevented. In this review, the significance of the cerebral blood flow after subarachnoidal hemorrhage and pathophysiological mechanisms that lead to early brain injury are summarized.
Key words*: Subarachnoid hemorrhage, cerebral vasospasm, apoptosis, brain injuries*
İngilizce kısa makale başlığı: *Subarachnoid hemorrhage*

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Introduction

Brain tissue cannot store energy, and its source of energy must be provided by continuous blood flow. After subarachnoidal hemorrhage caused by aneurysm (aSAH), pathophysiological processes including cerebral vasospasm, narrowing of the major cerebral arteries, and deterioriation of autoregulation in the arterioles triggered by hemoglobin and its products, cause morbidity and mortality (1-4). Vasospasm occurs after a SAH 67% of the time (5) and it is biphasic. Classically, the acute phase occurs within 3-4 hours, progresses rapidly, and can improve spontaneously; the chronic phase begins within 3-5 days and reaches its maximum on day 6-8, improving in about 14 days (6). Rebleeding, one of the most important complications of intracranial aneurysm bleeding, can be prevented by early detection and surgical management (7,8). Despite all prophylactic and therapeutic trials, vasospasm remains a problem that can be a cause of late neurological deficit (9).

The incidence of a SAH is 1 in 10,000 annually (10). Of these, 11% die before being admitted to the hospital, and 40% die within the first 4 weeks (11). In 50% of the survivors, lifetime memory and cognitive dysfunctions develop (12). This high rate of mortality and morbidity cannot be attributed only to vasospasm. The sudden fall in cerebral blood flow (CBF), increase in intracranial pressure (ICP), damage to the blood-brain barrier, cerebral edema, deterioration in microcirculation autoregulation, and apoptosis, any of which occur in the first 72 hours, result in early brain injury (2,13-19). In this literature review, the significance of CBF after SAH and the pathophysiological mechanisms that lead to early brain injury are discussed.

Cerebral blood flow and acute pathophysiological changes

In experimental models of SAH, a rise in ICP is observed along with a sudden fall in CBF and cerebral perfusion pressure (CPP) in many trials (15,20-22). Following SAH, CBF autoregulation is damaged and its level has been shown to be a significant factor affecting mortality, apart from the ICP and Cerebral Blood Pressure (CBP) (2,4,15,20,23). In the experimental trial of Jackowski et al, there was no significant change in CBF, but there was a 20% fall in CBP; in SAH, groups, together with deterioration in perfusion pressure and cerebral autoregulation, there was a decline in CBF by up to 50% (15). In the experimental trial of Punnel
et al, the rise in ICP and the fall in CPP that occurred following SAH were less important in terms of outcome than the fall in CBF in all three models (20). It is suggested that ischemia is caused by the sudden fall in CBF and acute vasospasm rather than the amount of bleeding, but the pathophysiology is not fully explained (20,21,24,16,25). In clinical practice, transient loss of consciousness is accepted as a possible protective mechanism. It occurs when aSAH results in a decline in CBF together with a rise in ICP.

Following SAH, the injury that occurs with the pathophysiological mechanisms is called early brain injury (17,19,24,26). The sudden fall in CPP and rise in ICP subsides within minutes (15,20,21,23,27,28). The roles of CBF falling below baseline (2,4) and acute microvascular endotelial dysfunction when endotelial vascular width control is lost (30) in early brain injury are thought to be more significant than changes in CPP and ICP (15,20,21,28). Moreover, following SAH, vascular endothelial growth factor, oxidative stress, activation of the inflammatory cytokines (tyrosine kinase and its substrate, mitogen activation protein kinase), disruption of the blood-brain barrier, and development of cerebral edema all play a role in the pathophysiology of early brain injury (17,31-34). Contributing to the development of such injury are: expansion of cortical depolarization from widespread neuronal ion hemostasis impairment during the early phases of SAH (16,42); impairment of the neuronal, endothelial, and vascular smooth cell intracellular hemostasis of calcium ion, which plays an important role in the etiology of vasospasm (7,65); and impairment of hemostasis of ions such as magnesium (42) and sodium (81).

The significance of nitric oxide (NO) and endothelin-1 is well known in the etiology of

acute vasospasm, ischemia, and CBF changes that occur after experimental SAH (27,29,40-46). Oxyhemoglobin from the erytrocites in the subarachnoidal space plays an important role in the development of vasospasm by reducing the biological activity of NO (1,29). As in the acute stage of SAH, the equilibrium between NO and nitric oxide synthase (NOS), which ensures vasodilation, is disrupted (29,47) while the level of endothelin-1, a strong vasoconstrictor, rises in CSF (42,46). In a trial in which NO is increased, acute vasospasm was reported to develop from NO insufficiency (43). The same research team also reported that NOS inhibitor had no effect on CBF in the first half hour, but after one hour, it caused a fall in CBF, suggesting that NO caused a biphasic change from the loss in its vasodilation effect (29). A biphasic change exhibited by NO is thought to be the cause of the sudden fall and slow rise in CBF after SAH.

In experimental and clinical trials involving microdialysis, a rise in the lactate/pyruvate ratio and glutamate concentration showed ischemia existed soon after SAH (19,25). Furthermore, a marker of neuronal damage, neuron specific enolase, reportedly rises in the first 24 hours of aSAH, and is found to be associated with the amount of bleeding in the subarachnoidal region and the bad neurological state during admission (48,49). In the experimental trial, astrocyte and oligodendrocyte cell deaths were shown in addition to the neurons in the first 24 hours, and these cell deaths were shown to be related to the sudden fall of CBF and its duration (18,50).

EARLY VASCULAR CHANGES

The inflammatory response created by the erytrocyte degradation products surrounding the vascular structures in the subarachnoidal space, endothelial damage, disruption of the paranchymal vascular autoregulation, and decrease in internal vessel diameter also contribute to the development of ischemia (32). Vasospasm is not a vessel narrowing from simple muscle contraction, but is known to be a proliferative vasculopathy and is accompanied by disruption of the blood-brain barrier (15,51,33,52,53). In animal models, great and small vessels become spastic minutes after SAH (15,52,53) and morphological and functional changes begin (51). Friedrich et al showed deterioration in the endothelial cell lines, separation from the basal lamina in minutes, and onset of apoptosis in the endothelial nucleus 3 hours after SAH (54,55). It is reported that for 24 hours, the degradation of lamina propria proteins continues (34,56) and, as evidenced by damage to the blood-brain barrier, an increase in the vessel permeability and cerebral edema lead to early brain injury (33, 57,58).

Potential growth factors such as platelet derived growth factor-AB (PDGF-AB), transformin growth factor-ß1, and vascular endothelial growth factor are released from the coagulum in the subarachnoidal space (57,59). In particular, PDGF, which is produced in high amounts in the trombus region, generates vascular and perivascular cell proliferation (57). Around 48 hours after SAH, infiltration of periadventitial inflammation cells reaches its maximum and, as cellular immunity turns into humoral immunity, it contributes to the development of vasospasm and early brain injury (60).

Vasospasm, occuring in the acute stage of SAH, develops especially in the lamina elastica from the first hour, and then the changes taking place in the endothelium and media continues independently from those in the CBF (23). Though trials show that apoptosis (54), genetics (61), perivascular cellular and humoral factors (60), and enzyme activity changes (17) are causes of vascular wall pathologies, it is not obvious why the lamina elastica and endothelium are affected first.

Early brain injury begins from the first moment of SAH, and the fact that this affects prognosis might not be preventable, but many experimental trials have found factors that inhibit vasospasm and ischemia. For example, vasospasm was improved or prevented by inhibiting the potential vasoconstrictor endotelin (42), NO donor (43), the mitogen activation protein kinase pathway (17), PDGF (57), or the agents that act upon the pathophysiological mechanisms such as statins, fasudil, erytropoetin, or sildenafil citrate (57). Though the factors relating to vasospasm are simultaneously activated, it is not clear why or how, with the deactivation or

activation of only one of them (while the pathophysiological proccesses continue), vasospasm is improved or cured. Despite the trials that attempt to find the mechanisms contributing to the development of vasospasm following aSAH and preventive agents, knowledge of the pathophysiology remains inadequate. For example, in clinical and preclinical trials, there was improvement in angiographical vasospasm treated with clazosentan, an endothelin receptor antagonist, but no improvement was seen in neurological outcome (8). When treated with the calcium channel antagonist nimodipin, improvement in functional outcome was achieved, but no effect on angiographical vasospasm was seen (87). Using magnesium, another calcium antagonist, vasospasm was improved in animal experiments, but had no effect on mortality (57). In patients with SAH, the relationship between the density of bleeding observed on CT and the risk of vasospasm formation is associated with the Fisher classification (64), but in our clinical practice, there is no relationship between the Fisher grade and the clinical stage of vasospasm. In a clinical trial concerning this condition, no significant relationship between the Fisher grade and vasospasm development was found (65). Therefore the role of genetics and apoptosis is gaining attention in VS.

APOPTOSIS

Apoptosis-related cell death begins in the first 10 minutes of SAH (54) and is shown to be related to the early activation of the intrinsic pathway by caspase, activated by an increase in intracellular calcium ions (14,66). The extrinsic pathway of apoptosis takes place with the death receptors located on the cell surface (67). The process begins with activation of the tumor necrosis factor receptor family p53 (66, 68), a nuclear transcription factor induced by tumor necrosis factor alpha (69), and is related to ischemia through neuron, astrocyte, and oligodendrycyte death, blood-brain barrier damage, necrosis, and smooth cell hypertrophy in vascular walls and the spastic artery following SAH (18,57, 70, 71). Though it is reported that blood-brain barrier damage related to apoptosis develops in later stages (14), in various animal models, it is shown to occur in 1 and 6 hours (13,31). In the early stages of the biphasic change, vasogenic edema alone (18) or together with cytotoxic edema in more recent studies (72,73) takes place and, as the result of damage to the blood brain barrier, a rise in ICP and fall in CBP lead to ischemia (32, 74).

Vasospasm and genetics

Clinical trials show that genetic predisposition is an important risk factor in developing vasospasm following SAH. Catecholamines are shown to cause vasopasm, and the incidence of acute vasospasm is high in patients with COMT-A alleles versus those with COMT-G alleles (75,76).

Marshden et al showed that the eNOS gene, located on the 7q35-36 chromosome, is coded polymorphically (77), and in another trial, a single nucleotide polymorphism on the gene is found to be related to the development of vasospasm (78,79). In patients with the same gene polymorphism, there is not only a high risk of cerebral vasospasm, but an association with cardiovascular diseases such as coronary heart disease, atherosclerosis, hypertension, and aortic aneurysm (80,81).

Haptoglobulin, located on 16q22, is coded as alpha and beta subunits (82). This gene can be coded as alpha1 or alpha 2, and the alpha 2 subunit is shown to be associated with insufficient neutralization of free radicals related to hemoglobin, leading to increased in vitro inflammatory response (83). In clinical trials, Borsody et al examined the relationship between the haptoglobulin type and vasospasm in the patients with Fisher grade 3 SAH (84). In transcranial follow up, patients with the haptoglobulin alpha 2 subunit were found to have an 87% risk of vasospasm. In cerebral angiography performed 3-14 days later, 17% were found with the alpha 1 subunit and 56% with the alpha 2 or other subunits.

Apolipoprotein E, a very low density lipoprotein located on the E 19q13k chromosome, has predominantly the epsilon 3 subunit. Patients having the uncommon epsilon 4 subunit experience vasoconstriction from endothelin-1, alzheimer's disease, and a predisposition to oxidative stress together

with functional and cognitive morbidity following aSAH (85,86).

In clinical trial performed by Reuffort et al the ryanodine receptor gene polymorphism, which plays a role in the intracellular calcium hemostasis, was shown to possibly have a role in symptomatic vasospasm (87).

Angiographical vasospasm observed after aSAH does not always lead to vasospasm and ischemia, and the amount of blood in the subarachnoidal space is not always proportional to the development of vasospasm. The reason could be attributed to the genetic discrepancies.

Acute pathophysiological events occurring when CBF declines, along with oxyhemoglobin and endothelial damage following SAH, initiate vascular and neuronal damage before admission to the hospital. While it is well known that vasospasm and late neurological deficits affect morbidity and mortality, severity of the early brain injury and its effect on later stages are gaining significance. Although the pathophysiological processes in early brain injury are similar, genetic discrepancies and apoptosis are the morbidity and mortality factors that are gaining importance. In laboratory trials using subjects without genetic polymorphism, the effect of genetics on cellular damage and VS is being ignored. Therefore, more trials are needed to examine early brain injury and VS.

References

1.Asano T: Oxyhemoglobin as the principal cause of cerebral vasospasm: a holistic view of its actions. Crit Rev Neurosurg 1999; 9:303-318.

2.Rasmussen G, Hauerberg J, Waldemar G, et al. Cerebral blood flow autoregulation in experimental subarachnoid haemorrhage in rat. Acta Neurochir 1992; 119:128-33.

3.Schievink WI, Riedinger M, Jhutty TK, et al. Racial disparities in subarachnoid hemorrhage mortality: Los Angeles County, California, 1985-1998. Neuroepidemiology 2004; 23: 299-305.

4.Schmieder K. Möller F, Engelhardt M, et al. Dynamic cerebral autoregulation in patients with ruptured and unruptured aneurysms after induction of general anesthesia. Zentralbl Neurochir 2006; 67: 81-7.

5.Dorsch NW, King MT: A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: Incidence and effects. J Clin Neurosci 1994; 1:19-26.

6.Weir B, Grace M, Hansen J, et al. Time course of vasospasm in man. J Neurosurg 1978; 48:173-78.

7.Kassell NF, Torner JC, Jane JA, et al.The Internationa l Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. J Neurosurg 1990; 73:37-47.

8.Roos YB, Beenen LF, Groen RJ, et al. Timing of surgery in patients with aneurysmal subarachnoid haemorrhage: rebleeding is still the major cause of poor outcome in neurosurgical units that aim at early surgery. J Neurol Neurosurg Psychiatry 1997; 63:490-93.

9.Siasios I, Kapsalaki EZ, Fountas KN: Cerebral vasospasm pharmacological treatment: an update. Neurol Res Int 2013; 2013: 571328.

10.Linn FH, Rinkel GJ, Algra A, et al. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. Stroke 1996; 27:619-25.

11.Hijdra A, Braakman R, van Gijn J , et al. Aneurysmal subarachnoid hemorrhage. Complications and outcome in a hospital population. Stroke 1987; 18:1061-67.

12.Kreiter KT, Copeland D, Bernardini GL, et al. Predictors of cognitive dysfunction after subarachnoid hemorrhage. Stroke 2002; 33:200-08.

13.Doczi, T: The pathogenetic and prognostic significance of blood-brain barrier damage at the acute stage of aneurysmal subarachnoid haemorrhage. Clinical and experimental studies. Acta Neurochir 1985; 77:110-32.

14.Gules I, Satoh M, Nanda A, et al. Apoptosis, blood-brain barrier, and subarachnoid hemorrhage. Acta Neurochir Suppl 2003; 86:483-87.

15.Jackowski A, Crockard A, Burnstock G, et al. The time course of intracranial pathophysiological changes following experimental subarachnoid haemorrhage in the rat. J Cereb Blood Flow Metab 1990; 10:835-49.

16.Jakobsen M: Role of initial brain ischemia in subarachnoid hemorrhage following

aneurysm rupture. A pathophysiological survey. Acta Neurol Scand Suppl 1992; 141:1-33.
17.Kusaka G, Ishikawa M, Nanda A, et al. Signaling pathways for early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2004; 24: 916-25.
18.Prunell GF, Svendgaard NA, Alkass K, et al.Delayed cell death related to acute cerebral blood flow changes following subarachnoid hemorrhage in the rat brain. J Neurosurg 2005; 102:1046-54.
19.Sehba FA, Bederson JB: Mechanisms of acute brain injury after subarachnoid hemorrhage. Neurol Res 2006; 28:381-98.
20.Bederson JB, Levy AL, Ding WH, et al. Acute vasoconstriction after subarachnoid hemorrhage. Neurosurgery 1998; 42:352-60.
21.Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new noncraniotomy model of subarachnoid hemorrhage in the rat. Stroke 1995; 26:1086-91.
22.Solomon RA, Antunes JL, Chen RYet al. Decrease in cerebral blood flow in rats after experimental subarachnoid hemorrhage: a new animal model. Stroke 1985; 16:58-64.
23.Alkan T, Tureyen K, Ulutas M, et al. Acute and delayed vasoconstriction after subarachnoid hemorrhage: local cerebral blood flow, histopathology, and morphology in the rat basilar artery. Arch Physiol Biochem 2001; 109:145-53.
24.Cahill J, Calvert JW, Zhang JH: Mechanisms of early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2006; 26:1341-53.
25.Sarrafzadeh AS, Haux D, Lüdemann L, et al. Cerebral ischemia in aneurysmal subarachnoid hemorrhage: a correlative microdialysis-PET study. Stroke 2004; 35:638-43.
26.Cahill J, Calvert JW, Solaroglu I, et al. Vasospasm and p53-induced apoptosis in an experimental model of subarachnoid hemorrhage. Stroke 2006; 37:1868-74.
27.Andresen J, Shafi NI, Bryan RM: Endothelial influences on cerebrovascular tone. J Appl Physiol 2006; 100:318-27.
28.Dorsch N, Branston NM, Symon L, et al. Intracranial pressure changes following primate subarachnoid haemorrhage. Neurol Res 1989; 11: 201-04.
29.Schwartz AY, Sehba FA, Bederson JB: Decreased nitric oxide availability contributes to acute cerebral ischemia after subarachnoid hemorrhage. Neurosurgery 2000; 47:208-14.
30.Park KW, Metais C, Dai HB, et al.Microvascular endothelial dysfunction and its mechanism in a rat model of subarachnoid hemorrhage. Anesth Analg 2001; 92:990-96.
31.Dóczi T, Joó F, Adám G, et al. Blood-brain barrier damage during the acute stage of subarachnoid hemorrhage, as exemplified by a new animal model. Neurosurgery 1986; 18:733-39.
32.Doczi TP: Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 2001; 32:817.
33.Ohta T, Satoh G, Kuroiwa T: The permeability change of major cerebral arteries in experimental vasospasm. Neurosurgery 1992; 30:331-35.
34.Scholler K, Trinkl A, Klopotowski M, et al. Characterization of microvascular basal lamina damage and blood-brain barrier dysfunction following subarachnoid hemorrhage in rats. Brain Res 2007; 1142:237-46.
35.Dreier JP, Woitzik J, Fabricius M, et al. Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain 2006; 129:3224-37.
36.van den Bergh WM, Algra A, van der Sprenkel JW, et al. Hypomagnesemia after aneurysmal subarachnoid hemorrhage. Neurosurgery 2003; 52: 276-81.
37.Ishiguro M, Murakami K, Link T, et al. Acute and chronic effects of oxyhemoglobin on voltage-dependent ion channels in cerebral arteries. Acta Neurochir Suppl 2008; 104:99-102.
38.Meguro T, Klett CP, Chen B, et al.Role of calcium channels in oxyhemoglobin-induced apoptosis in endothelial cells. J Neurosurg 2000; 93:640-46.
39.Berendes E, Walter M, Cullen P, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet 1997; 349: 245-49.
40.Dietrich HH, Dacey RG Jr: Molecular keys to the problems of cerebral vasospasm. Neurosurgery 2000; 46:517-30.

41.Faraci FM, Heistad DD: Regulation of the cerebral circulation: role of endothelium and potassium channels. Physiol Rev 1998; 78:53-97.
42.Josko J, Hendryk S, Jedrzejowska-Szypuła H, et al. Influence endothelin ETA receptor antagonist--BQ-123--on changes of endothelin-1 level in plasma of rats with acute vasospasm following subarachnoid hemorrhage. J Physiol Pharmacol 1998; 49:367-75.
43.Sehba FA, Ding WH, Chereshnev I, et al. Effects of S-nitrosoglutathione on acute vasoconstriction and glutamate release after subarachnoid hemorrhage. Stroke 1999; 30:1955-61.
44.Sehba FA, Friedrich V Jr, Makonnen G, et al. Acute cerebral vascular injury after subarachnoid hemorrhage and its prevention by administration of a nitric oxide donor. J Neurosurg 2007; 106:321-29.
45.Weir B: The pathophysiology of cerebral vasospasm. Br J Neurosurg 1995; 9:375-90.
46.Wang X, Zhu C, Zhang G, et al. Changes of endothelin during cerebral vasospasm after experimental subarachnoid hemorrhage. Chin Med J 1995; 108:586-90.
47.Sehba FA, Schwartz AY, Chereshnev I, et al. Acute decrease in cerebral nitric oxide levels after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2000; 20:604-11.
48.Kuroiwa T,Tanabe H, Arai M, et al. [Measurement of serum neuron-specific enolase levels after subarachnoid hemorrhage and intracerebral hemorrhage]. No Shinkei Geka 1994; 22:531-35.
49.Mabe H, Suzuki S, Mase M, et al. Serum neuron-specific enolase levels after subarachnoid hemorrhage. Surg Neurol 1991; 36:170-74.
50.Lee JY, He Y, Sagher O, et al. Activated autophagy pathway in experimental subarachnoid hemorrhage. Brain Res 2009; 1287:126-35.
51.Hughes JT, Schianchi PM: Cerebral artery spasm. A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage. J Neurosurg 1978; 48:515-25.
52.Takemae T, Branson PJ, Alksne JF: Intimal proliferation of cerebral arteries after subarachnoid blood injection in pigs. J Neurosurg 1984; 61:494-500.
53.Tanabe Y, Sakata K, Yamada H, et al. Cerebral vasospasm and ultrastructural changes in cerebral arterial wall. An experimental study. J Neurosurg 1978; 49:229-38.
54.Friedrich V, Flores R, Sehba FA. Cell death starts early after subarachnoid hemorrhage. Neurosci Lett 2012; 512:6-11.
55.Friedrich V, Flores R, Muller A, et al. Escape of intraluminal platelets into brain parenchyma after subarachnoid hemorrhage. Neuroscience 2010; 165: 968-75.
56.Sehba FA, Mostafa G, Knopman J, et al. Acute alterations in microvascular basal lamina after subarachnoid hemorrhage. J Neurosurg 2004; 101: 633-40.
57.Borel CO, McKee A, Parra A, et al. Possible role for vascular cell proliferation in cerebral vasospasm after subarachnoid hemorrhage. Stroke 2003; 34: 427-33.
58.Hamann GF, Okada Y, Fitridge R, et al. Microvascular basal lamina antigens disappear during cerebral ischemia and reperfusion. Stroke 1995; 26:2120-26.
59.Thai QA, Oshiro EM, Tamargo RJ: Inhibition of experimental vasospasm in rats with the periadventitial administration of ibuprofen using controlled-release polymers. Stroke 1999; 30:140-47.
60.Kubota T, Handa Y, Tsuchida A, et al. The kinetics of lymphocyte subsets and macrophages in subarachnoid space after subarachnoid hemorrhage in rats. Stroke 1993; 24:1993-2000.
61.Aihara Y, Kasuya H, Onda H, et al. Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. Stroke 2001; 32:212-17.
62.Macdonald RL, Higashida RT, Keller E, et al. Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. Stroke 2012; 43:1463-69.
63.Barker FG 2nd, Ogilvy CS: Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. J Neurosurg 1996; 84 405-14.
64.Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized

tomographic scanning. Neurosurgery 1998; 6:1-9.
65.Khurana VG, Sohni YR, Mangrum WI, et al. Endothelial nitric oxide synthase gene polymorphisms predict susceptibility to aneurysmal subarachnoid hemorrhage and cerebral vasospasm. J Cereb Blood Flow Metab 2004; 24:291-97.
66.Zhou C, Yamaguchi M, Kusaka G, et al. Caspase inhibitors prevent endothelial apoptosis and cerebral vasospasm in dog model of experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab 2004; 24:419-31.
67.Broughton BR, Reutens DC, Sobey CG: Apoptotic mechanisms after cerebral ischemia. Stroke 2009; 40: 331-39.
68.Zhou C, Yamaguchi M, Colohan AR, et al. Role of p53 and apoptosis in cerebral vasospasm after experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab 2005; 25:572-82.
69.Yeung MC, Lau AS: Tumor suppressor p53 as a component of the tumor necrosis factor-induced, protein kinase PKR-mediated apoptotic pathway in human promonocytic U937 cells. J Biol Chem 1998; 273:25198-202.
70.Park S, Yamaguchi M, Zhou C, et al. Neurovascular protection reduces early brain injury after subarachnoid hemorrhage. Stroke 2004; 35: 2412-17.
71.Zubkov AY, Tibbs RE, Aoki K, et al. Morphological changes of cerebral penetrating arteries in a canine double hemorrhage model. Surg Neurol 2000; 54: 219.
72.Orakcioglu B, Fiebach JB, Steiner T, et al. Evolution of early perihemorrhagic changes--ischemia vs. edema: an MRI study in rats. Exp Neurol 2005; 193:369-76.
73.Sibon I, Menegon P, Rouanet F, et al. MRI of acute brainstem ischaemia: cytotoxic versus vasogenicoedema? Eur J Neurol 2004; 11:497-98.
74.Laszlo FA, Varga C, Doczi T: Cerebral oedema after subarachnoid haemorrhage. Pathogenetic significance of vasopressin. Acta Neurochir 1995; 133: 122-33.
75.Dilraj A, Botha JH, Rambiritch V, et al. Levels of catecholamine in plasma and cerebrospinal fluid in aneurysmal subarachnoid hemorrhage. Neurosurgery 1992; 31:42-50.
76.He Z, Sun X, Guo Z, et al. The correlation between COMT gene polymorphism and early cerebral vasospasm after subarachnoid hemorrhage. Acta Neurochir Suppl 2011; 110:233-38.
77.Marsden PA, Heng HH, Scherer SW, et al. Structure and chromosomal localization of the human constitutive endothelial nitric oxide synthase gene. J Biol Chem 1993; 268:17478-88.
78.Nakayama M, Yasue H, Yoshimura M, et al. T-786-->C mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene is associated with coronary spasm. Circulation 1999; 99:2864-70.
79.Starke RM, Kim GH, Komotar RJ, et al. Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab 2008; 28: 1204-11.
80.Hingorani AD, Liang CF, Fatibene J, et al. A common variant of the endothelial nitric oxide synthase (Glu298-->Asp) is a major risk factor for coronary artery disease in the UK. Circulation 1999; 100: 1515-20.
81.Kotani K, Shimomura T, Murakami F, et al. Allele frequency of human endothelial nitric oxide synthase gene polymorphism in abdominal aortic aneurysm. Intern Med 2000; 39: 537-39.
82.McGill JR, Yang F, Baldwin WD, et al. Localization of the haptoglobin alpha and beta genes (HPA and HPB) to human chromosome 16q22 by in situ hybridization. Cytogenet Cell Genet 1984; 38:155-57.
83.Levy AP, Hochberg I, Jablonski K, et al. Strong Heart Study: Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: The Strong Heart Study. J Am Coll Cardiol 2002; 40:1984-90.
84.Borsody M, Burke A, Coplin W, et al. Haptoglobin and the development of cerebral artery vasospasm after subarachnoid hemorrhage. Neurology 2006; 66: 634-40.
85.Chartier-Harlin MC, Parfitt M, Legrain S, et al. Apolipoprotein E, epsilon 4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the

19q13.2 chromosomal region. Hum Mol Genet 1994; 3:569-74.
86.Lanterna LA, Rigoldi M, Tredici G, et al. APOE influences vasospasm and cognition of noncomatose patients with subarachnoid hemorrhage. Neurology 2005; 64:1238-44.
87.Rueffert H, Gumplinger A, Renner C, et al. Search for genetic variants in the ryanodine receptor 1 gene in patients with symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2011; 15:410-15.