Venous System in Acute Brain Injury: Mechanisms of Pathophysiological Change and Function

Sheng Chen^{#a}, Yujie Chen^{#b}, Liang Xu^a, Nathanael Matei^c, Jiping Tang^c, Hua Feng^b, and JohnH Zhang^{c,*}

^aDepartment of Neurosurgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

^bDepartment of Neurosurgery, Southwest Hospital, Third Military Medical University, Chongqing, China

^cDepartment of Physiology and Pharmacology, Loma Linda University, Loma Linda, California, USA

[#] These authors contributed equally to this work.

Abstract

Cerebral vascular injury is a major component of acute brain injury. Currently, neuroprotective strategies primarily focus on the recanalization of cerebral arteries and capillaries, and the protection of insulted neurons. Hitherto, the role of vein drainage in the pathophysiology of acute brain injury has been overlooked, due to an under appreciation of the magnitude of the impact of veins in circulation. In this review, we summarize the changes in the vein morphology and functions that are known, or likely to occur related to acute brain injury, and aim to advance the therapeutic management of acute brain injury by shifting the focus from reperfusion to another term: recirculation. Recent progress in the neurobiological understanding of the vascular neural network has demonstrated that cerebral venous systems are able to respond to acute brain injury by regulating the blood flow disharmony following brain edema, blood brain barrier disruption, ischemia, and hemorrhage. With the evidence presented in this review, future clinical management of acutely brain injured patients will expand to include the recirculation concept, establishing a harmony between arterial and venous systems, in addition to the established recanalization and reperfusion strategies.

Keywords

Acute brain injury; Vein; Pathophysiology; Vascular neural network

---

*Corresponding author at: Department of Physiology and Pharmacology, Loma Linda University, 11041 Campus Street, Risley Hall, Room 219, Loma Linda, California, 92354, USA. Fax: +1 909-558-0119 johnzhang3910@yahoo.com. .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest None.

Case Report

A 44 year-old man was transferred to the department of Neurosurgery, Zhejiang University Second Affiliated Hospital from a local hospital. He had been in a car accident about one month ago prior to his referral. The accident triggered the onset of chronic moderate headaches. His Glasgow Coma Scale was 15 at admission. Initially, computerized tomography (CT) scan did not reveal any abnormality in his brain (Figure 1 A and B). The value of his D-Dimer, prothrombin time, and activated partial thromboplastin time were 3100 μ g/L FEU $\uparrow$, 12s and 30.5s, respectively. One week later, after conservative treatment with mannitol and an antifibrinolytic agent, his headache resolved, and he was discharged. Two weeks later, he was readmitted with more severe headaches, limb twitching, staring gaze, trismus and foaming of the mouth. His Glasgow Coma Scale was 11 this time. Emergency CT scan showed that multiple fresh small hematomas had developed in the left parietal lobe surrounded by severe brain edema (Figure 1 C and D), which was different from the primary hematoma. No aneurysm or arteriovenous malformation were detected by computerized tomography angiography (CTA) (Figure 1 E and F), but magnetic resonance venography (MRV) indicated thrombosis in superior sagittal sinus, right sigmoid sinus, and right transverse sinus (Figure 1 G and H). The values of his D-Dimer, prothrombin time, and activated partial thromboplastin times were respectively 5590 μ g/L FEU $\uparrow$, 13.5s and 26.7s, indicating that he suffered from hypercoagulability. Subsequently, he left the hospital with paralysis of both right limbs.

This case raises important questions: Why did the patient re-bleed in a non-traumatized area long after the incident? Can acute brain injury impair the cerebral venous system? How do venous system lesions exacerbate acute brain injury? This case highlights the fact that acute brain injury may lead to pathologic changes in cerebral venous system, which demonstrates the value of including vein evaluation in the diagnostic workup of central nervous system disorders and the importance of identifying possible causes that could be reversed with appropriate treatment.

Introduction

Neuroprotective strategies that target attenuation of dysfunction and insult on neuronal cells but do not address vascular injury, fail to exhibit greater beneficial effects on acute central nervous system injuries, including stroke, traumatic brain injury and spinal cord injury (Seifert and Pennypacker, 2014; Silva et al., 2014; Xiong et al., 2014). Cerebral vascular injury, is a major component of acute brain injury. Ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury all result in either immediate or later reduction in cerebral blood flow (Ohkuma et al., 2000; Schwarzmaier et al., 2010). Therefore, the discovery of the “neurovascular unit” advocates that more attention should be given to the role of vascular cells in pathological processes of acute brain injury (Lo and Rosenberg, 2009; Tso and Macdonald, 2014). The neurovascular unit is comprised of endothelial vascular cells, pericytes, vascular smooth muscle cells, glial cells (e.g. astrocytes, microglia and oligodendroglia), and neurons. However, the neurovascular unit focuses on the significance of capillaries and the cells directly attached around capillaries, but does not contain the upstream arteries/arterioles and downstream veins/

venules. Arteries and veins play vital roles in the control of vascular tone, blood supply, and have influence on downstream capillaries, and blood drainage. Therefore, we recently proposed a new concept of a vascular neural network, which is a more comprehensive pathophysiological model of acute brain injury than the neurovascular unit, comprising all of the cells and structures that are required to maintain cerebral blood flow under physiological and pathological conditions (Zhang et al., 2012). To some extent, the vascular neural network is a concept that partially spawned from Chinese medicine “Huo-Xue-Hua-Yu”, which suggested a treatment strategy to maintain arterial and venous blood flow harmony during circulation for acute central nervous system disorders (Leak et al., 2014; Li et al., 2014). In clinical management, the role of vein drainage in the pathophysiology of acute brain injury is often overlooked due to the dearth of information about the impact of veins in circulation and incomplete characterization of them.

In this review, we summarize the changes in the vein morphology and function that are known, or likely to occur related to acute brain injury, and aim to move forward from the goal of reperfusion to a therapeutic strategy incorporating vasculature homeostasis in acute brain injury.

General Anatomy and Physiology of the Cerebral Venous System

The brain receives up to 20% of cardiac output. The entire normal cerebral circulation contains large arteries, arterioles, capillaries, and downstream venules, and veins. The vascular circulation is divided in two categories: extraparenchymal and intraparenchymal cerebral blood vessels. Extraparenchymal vessels include the main feeding arteries, pial blood vessels, and penetrating blood vessels. The penetrating arteries enter the brain parenchyma surrounding by the Virchow Robin space, which filled with cerebrospinal fluid, and their tone is controlled by perivascular nerves (Hamel, 2006). The main feeding arteries subdivide into progressively smaller intraparenchymal branches, in order to transport oxygen and other nutrients to neuronal cells via concentration gradient diffusion. Intraparenchymal blood vessels begin where the Virchow Robin space disappears. Arteriole tone is under the influence of astrocytes, neurons, and perivascular nerves, which have trophic roles in the smooth muscle layer (Badaut and Bix, 2014). Blood flow exchanges oxygen and nutrients in capillaries, with wastes from the brain parenchymal into the venous system. The whole cerebral venous system is surrounded by adrenergic nerve fibers (Edvinsson et al., 1983). Post-capillary venules are covered with pericytes (Allt and Lawrenson, 2001) and surrounded by stellate periendothelial cells, which forms a basket-like network around the vessel wall (Ushiwata and Ushiki, 1990).

The venous compartment contains about 70%~80% of the circulatory volume inside the inflexible cranial cavity. The cerebral venous system can be divided into superficial and deep venous systems. The superficial vein system drains cortical surfaces of both cerebral hemispheres. Superficial veins drain mainly into four groups, according to their territory: superior sagittal sinus, sphenoparietal sinus and cavernous sinus, inferior sagittal sinus and Galen vein along with tributaries of the sinuses (Oka et al., 1985). The deep system comprises deep cortical draining veins, the lateral sinus, straight sinus and sigmoid sinus, which are concerned with the drainage of the central structures of the hemispheres, basal

ganglia, corpus callosum, pineal region limbic system and thalamus. Both two systems afflux into the internal jugular veins (Kilic and Akakin, 2008).

The cerebral venous system contains important structural differences from the cerebral artery system. First, small veins and venules do not have encompassing smooth muscle cells (Takahashi et al., 1994). Thus, they cannot contract as strongly as arteries. The venule is a crucial contributor to cerebrovascular resistance, but its role in regulation of flow is minimal under physiologic conditions (Kulik et al., 2008). In normal conditions, only mild diameter changes occur in cerebral veins according to intracranial pressure (ICP) (Tso and Macdonald, 2013). However, in pathological conditions, the veins may be easily compressed and even flattened by high ICP. Increases in central venous pressure or intracranial venous pressure can lead to an increase in the hydrostatic pressure of upstream cerebral veins and reduce the blood outflow. Secondly, compared with arteries, cerebral veins have thin walls and possess no valves to prevent the back flow of venous blood (Kilic and Akakin, 2008). Because both higher blood pressure and more rapid blood flow occur in arteries than in veins, the risk of thrombosis is much higher in veins.

The change of cerebral venous system after acute brain injury

Under normal conditions, cerebral autoregulation prevents the brain from either hypoperfusion- or hyperperfusion-induced injury. When blood flow increases, cerebral arteries contract to reduce excessive blood flow into the brain parenchyma. On the contrary, when blood flow decreases, cerebral arteries dilate to allow more blood into the brain, keeping the total blood flow constant throughout the brain. This principle governs the relationship between arterial and venous flows; the amount of blood entering the brain from the arterial system should match the blood exiting the brain via the venous system. Acute injuries to the brain affect all these vascular components and interrupt the harmony of cerebral circulation.

Previously, neurogenic influence of the arteries has received intense attention in acute brain injury. For example, fluctuations of arterial blood pressure induced a response in intracranial pressure (Czosnyka, 2000). Taking subarachnoid hemorrhage for example, neurosurgical opinion is that arterial vasospasm is the most targetable pathophysiology that can potentially attenuate mortality and morbidity after subarachnoid hemorrhage (SAH) (Chen et al., 2014a). However, Tureyen et al. demonstrated that an acute mild to moderate narrowing in large arteries may cause a mild and almost harmless episode of ischemia (Tureyen et al., 2005). On the other hand, the response of cerebral veins has not been addressed, and as research shifts its focus, the venous system, rather than the arterial system, may be the most productive target for pharmaceutical intervention in acute injury.

Pathogenesis of cerebral venous system abnormality after acute brain injury

Venous drainage abnormalities might be attributed to several interwoven factors after brain injury (Figure 2). First, after brain injury, severe brain edema increases ICP to levels that may compress or even collapse the thin walls of the venules and capillaries (Ostergaard et

al., 2013). External compression on veins is induced by edema, swollen astrocyte endfeet (Garcia et al., 1994), and adherent leukocytes (Belayev et al., 2002; Ritter et al., 2000). Additionally, the venous system is more susceptible than the arterial system to tissue edema and elevation of ICP, due to the absence of layers of smooth muscle cells. The outflow obstruction contributes to intracranial segment narrowing and proximal vascular dilation, subsequently leading to intracranial venous congestion. This venous congestion is more severe in patients with high ICP than in patients with normal ICP (Si et al., 2008).

Secondly, active vein constriction is mostly due to pericyte contraction (Dalkara and Arsava, 2012; Yemisci et al., 2009). Deep cerebral vein vasospasm/compression was reported in a rabbit model of SAH (Dai et al., 2012; Li et al., 2014; Zhang. et al., 2012). In global cerebral ischemia model, reperfusion yielded a smaller increase of the venular diameters (Abels et al., 2000) and, adversely, phenotypic transformation in smooth muscle cells of veins-- as well as arteries-- may lead to the difficulty in reversing the caliber, or even densities, of vessels after SAH and traumatic brain injury (Badaut and Bix, 2014; Shimamura and Ohkuma, 2014). This may further aggravate the autoregulation of cerebral circulation.

Vessel lumina contain erythrocytes, leukocytes, platelet aggregation and fibrin-platelet deposits which cause the stenosis of venous lumen (Choudhri et al., 1998; Liu et al., 2002). Leukocyte adhesion to venular walls was observed in the rat model of bilateral common carotid artery occlusion (Lapi et al., 2011). In controlled cortical impact (6 m/sec, 0.5 mm), intermittent rolling of leukocytes on endothelium was found both in arterioles and venules, while leukocyte-platelet aggregates were only observed in post-capillary venules (Schwarzmaier et al., 2010). Similarly, in the blood-injected SAH model, leukocyte-platelet aggregates were observed in the cerebral venules at 2 hours following SAH (Ishikawa et al., 2009). Microthrombi occluded up to 70% of all investigated venules and 33% of arterioles after traumatic brain injury in mice (Schwarzmaier et al., 2010). Microthrombi were present at 30 minutes, peaking at between 60 and 90 minutes after injury, and, as time passed, the microthrombi grew to completely occlude venules. At the time of acute brain injury, two major mechanistic pathways have been examined (Zhou et al., 2014), oxidative stress and inflammation, which may have induced the damage to venous endothelial cells and triggered clot formation in the cerebral venous system (Li et al., 2014). Morphological and pathophysiologic changes of venous system occur after the onset of acute brain injury, which suggests that the venous system may contribute to the secondary brain injury in those diseases.

Vein-mediated pathophysiology after acute brain injury

The harmony between the arterial blood inflow and venous output is crucial for brain homeostasis. However, brain ischemic events, brain infarct, and venous hemorrhage occur approximately in 10% to 75% of patients with cerebral venous hypertension, all of which are endpoints of elevated cerebral venous pressure (Otsuka et al., 2000; Saha et al., 2012), and cause detrimental effects on the homeostatic environment. The importance of venous pathogenesis in the pathophysiology of acute brain injury has been underestimated. This can be observed when cerebral venous fluctuations cause venous congestion, cerebral edema, increased ICP, infarction and hemorrhage after acute brain injury (Stam, 2005) (Figure 3).

Brain edema and ICP elevation

The adult brain is surrounded by the inflexible cranial bones and, if arterial flow remains constant, but venous flow decreases acutely, blood will then accumulate in the capillary system to induce brain swelling. Indeed venous outflow deficiency may aggravate early brain edema after massive cerebral infarction (Yu et al., 2009). An increase in ICP will cause vein hyperaemia (Nakase et al., 1996), flow decrease, and capillary hemorrhage.

Venous drainage abnormalities contribute to the development of cerebral edema in certain central nervous system disorders, such as arteriovenous malformation, idiopathic intracranial hypertension and cerebral venous sinus stenosis (Chen et al., 2014b; Horev et al., 2013; Kim et al., 2009), and the compressed venules, veins contribute to the reduction of venous outflow in acute brain injury (Ostergaard et al., 2013). Congenital venous obstruction may resist cerebrospinal fluid absorption, which has been implicated in idiopathic intracranial hypertension (Alperin et al., 2005; Owler et al., 2005), and elevated cerebral venous pressure increases fluid leakage into the perivascular space, resulting in parenchymal edema and brain edema. A high ICP pig model has been established by inserting a balloon catheter into the superior vena cava, which would maintain an ICP of greater than 20mmHg. In this model, the lower limit of cerebrovascular autoregulation is increased, suggesting a pathologic process that obstructs the cephalic venous outflow and elevates ICP to cause impairment of cerebrovascular autoregulation (Nusbaum et al., 2014).

These experimental observations are consistent with published clinical reports. In small case series, Yu et al. found that ipsilateral cranial venous drainage abnormalities due to hypoplasia, or occlusion, play a role in the development of brain edema after arterial ischemic stroke (Yu et al., 2009). However, this study was very small, including only fourteen patients, and may have suffered from selection bias. Another study showed that after SAH, when flow velocity in the basal vein is significantly elevated above normal values in the following day, patients are found without neurological deficit; while when flow velocities in the basal vein are significantly below normal in the following day, patients are found to have permanent deficit (Mursch et al., 2001). Thus, this study of sixty-six SAH patients demonstrates that patients who have a higher mean flow velocity in the basal vein are associated with better outcomes (Mursch et al., 2001). In addition, endovascular stent placement has become a promising treatment for the patients with idiopathic intracranial hypertension due to venous sinus stenosis (Donnet et al., 2008), indicating that the attenuation of intracranial venous outlet obstruction may be a therapeutic strategy for intracranial hypertension after acute brain injury.

Blood brain barrier disruption

The venous component of blood brain barrier (BBB) appears to be the most frequent site of breakdown in a diverse set of conditions (Muller, 2003). Venules and veins are the primary site of disruption of the BBB during superior venae cavae occlusion, acute hypertension, and hyperosmolar solutions (Mayhan and Heistad, 1985, 1986). Therefore, Mayhan and Heistad have postulated that the disruption of the BBB may be closely related to increases in venular pressure rather than increases in arteriolar pressure (Mayhan and Heistad, 1986). Their study demonstrated that disruption of the BBB is associated with an increase in pial venular

pressure and diameter (Mayhan and Heistad, 1986). Therefore, increases in venous pressure can produce significant BBB disruption, putting this pathology on the level of influence of arterial and arteriolar pressure, despite their directionally opposite dynamics. An increase in the jugular vein pressure decreased venous outflow from brain circulation is correlated with plasma biomarkers of BBB disruption, including S100 β protein, and matrix metalloproteinase-9 (Usman and Wasay, 2006). Based on the evidence, it can be asserted that the decrease in venous outflow may play a key role in raised BBB permeability after acute brain injury.

Besides pressure, endothelium dysfunction has been reported to contribute to BBB disruption after acute brain injury. When brain edema occurs, there is an increase in intracranial pressure that induces the secretion of cytokines and chemokines, by dying neurons and glia cells, maybe an initial factor of endothelium attack (Ishikawa et al., 2004a; Ishikawa et al., 2004b), and a cause of following intrinsic harmful mechanisms of inflammation and death cascades (An et al., 2014). Mayhan et al. reported the role of adhesion of leukocytes to cerebral venular endothelium contributed to the disruption of the BBB, measured by FITC-dextran-10K (Mayhan, 2000), and eventually led to secondary insults (Uhl et al., 2000).

Ischemia and hemorrhage

As discussed above, the imbalance between arterial inflow and venous outflow could be the underlying reason for cerebral circulation dysfunction. Current literature reports that immediate reductions in cerebral blood flow are not restricted to the location of the impact after traumatic brain injury, but can affect the whole brain. Microthrombosis and occluded cerebral venules, within the first 2 hours after traumatic brain injury, following decreased cerebral blood flow in arterioles in the traumatic penumbra, are responsible for the second brain insult after traumatic brain injury (Schwarzmaier et al., 2010). Another study indicates that changes in cerebral blood flow correlate better with the mean flow velocity in the basal vein than with arterial flow velocities (Mursch et al., 2001). Besides the thrombophilia after stroke, other brain disorders has been reported to have a strong association with cerebral venous thrombosis (Lauw et al., 2013). Therefore, the venous system is an important contributor for ischemic event after acute brain injury.

On the other hand, once the reduction of venous flow is unmatched with an increased arterial flow, venous congestion may occur and catastrophic events, such as capillary occlusion, collapse, or hemorrhage follows (Ostergaard et al., 2013). Venous hypertension may lead to bleeding into the subarachnoid space or brain parenchyma due to rupture of fragile, thin-walled cortical veins (Pradhan et al., 2007). Moreover, the sinus thrombosis, due to thrombophilia in some patients, may produce dilatation of the cortical veins, which may rupture and bleed into the subarachnoid space and produce subsequent SAH (Cheng et al., 2014; de Bruijn et al., 2000; Etminan et al., 2014). However, the precise mechanism of vein-induced hemorrhage remains unknown.

Implications for treatment and prospective

As interest in cerebral venous drainage evolve, we should have a better understanding of the role of venous circulation in the pathophysiology of acute brain injury and may be able to develop pharmacological treatment interventions to meet clinical needs.

The recent clinical reports support the concept that an increased blood supply is directly proportional to a better outcome in patients with acute brain injury. After cerebral ischemia, when the blood clot in an artery is removed and the arterial system reopens during reperfusion, blood enters the brain and puts pressure on the venous system. Due to smooth muscle phenotype transformation and loss of autoregulation after acute brain injury, more blood than normal may be pumped into the brain (Edvinsson et al., 2014). Over the past three decades, elevation of blood pressure and administration of large volumes of intravenous fluids ("triple-H therapy": hypertension, hypervolemia, and hemodilution) has become the principle method for treating delayed ischemic neurological deficits from vasospasm after SAH, which aims to increase cerebral perfusion and blood in SAH patients. In traumatic brain injury patients, rehydration therapy is also a treatment option. However, if venous drainage is blocked, then a bigger flush will cause overflow, higher ICP, more edema or even hemorrhage, and worsen patient outcomes. We, therefore, suggest that increased arterial reperfusion by angioplasty, infusion treatment, 3H therapy, and nimodipine for anti-vasospasm, may be helpful only when venous drainage is normal. Based on the new paradigm of vascular neural network, future managements of stroke patients should be conducted under a recirculation concept, with a goal of restoring a harmony of arterial and venous system dynamics, not simply emphasizing recanalization or reperfusion or anti-vasospasm.

Imaging examination should cover both arterial and venous aspects, such as DSA/DSV, CTA/CTV, MRI/MRV, even though the direct measurement of cerebral venous pressure is not currently feasible. The jugular vein bulb is the main venous pathway from the brain and the measurement of the pressure in the jugular vein bulb may provide information about cerebral venous pressure.

Needless to say, the predictions and hypotheses presented in this review must be tested in experimental and clinical settings. The morphological change of vein and signaling pathway after acute brain injury should be studied systematically to elucidate how and when these events occur in animal models and patients. More research is needed to define the influence of upstream smooth muscle cells, arterial endothelial cells, and perivascular nerves on downstream vein. The interactions between cell types in the vascular neural network during early and late stages of brain insult should be further explored.

Conclusion

In conclusion, the complex pathophysiology of acute brain injury has raised several questions, which we have attempted to address from the perspective of changes in the cerebral venous system. We hypothesized that veins play an equal, or perhaps even more important role than arteries in the maintenance of cerebral blood flow physiology and brain

physiological function. If this hypothesis is correct, clinical management of acute brain injury will need to evolve and, given the foundational development of venial dynamics, novel pharmacological developments may be made to correct imbalances in this complex arterial and venous system to reduce mortality and morbidity.

Acknowledgement

This work was supported by the National Institutes of Health grants NS081740 and NS084921 to John H. Zhang, and the National Basic Research Program of China (973 Program) 2014CB541600 and National Natural Science Foundation of China grant 81220108009 to Hua Feng.

References

- Abels C, Rohrich F, Corvin S, Meyermann R, Baethmann A, Schurer L. Leukocyte-endothelium-interaction in pial vessels following global, cerebral ischaemia. *Acta Neurochir (Wien)*. 2000; 142:333–339. [PubMed: 10819265]
- Allt G, Lawrenson JG. Pericytes: cell biology and pathology. *Cells, tissues, organs*. 2001; 169:1–11. [PubMed: 11340256]
- Alperin N, Lee SH, Mazda M, Hushek SG, Roitberg B, Goddwin J, Lichtor T. Evidence for the importance of extracranial venous flow in patients with idiopathic intracranial hypertension (IIH). *Acta Neurochir Suppl*. 2005; 95:129–132. [PubMed: 16463836]
- An C, Shi Y, Li P, Hu X, Gan Y, Stetler RA, Leak RK, Gao Y, Sun BL, Zheng P, Chen J. Molecular dialogs between the ischemic brain and the peripheral immune system: dualistic roles in injury and repair. *Prog Neurobiol*. 2014; 115:6–24. [PubMed: 24374228]
- Badaut J, Bix GJ. Vascular neural network phenotypic transformation after traumatic injury: potential role in long-term sequelae. *Transl Stroke Res*. 2014; 5:394–406. [PubMed: 24323723]
- Belayev L, Pinard E, Nallet H, Seylaz J, Liu Y, Riyamongkol P, Zhao W, Busto R, Ginsberg MD. Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. *Stroke*. 2002; 33:1077–1084. [PubMed: 11935064]
- Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, Zhang J, Tang J, Zhang JH. Controversies and evolving new mechanisms in subarachnoid hemorrhage. *Prog Neurobiol*. 2014a; 115:64–91. [PubMed: 24076160]
- Chen W, Choi EJ, McDougall CM, Su H. Brain arteriovenous malformation modeling, pathogenesis, and novel therapeutic targets. *Transl Stroke Res*. 2014b; 5:316–329. [PubMed: 24723256]
- Cheng Y, Xi G, Jin H, Keep RF, Feng J, Hua Y. Thrombin-induced cerebral hemorrhage: role of protease-activated receptor-1. *Transl Stroke Res*. 2014; 5:472–475. [PubMed: 24323711]
- Choudhri TF, Hoh BL, Zerwes HG, Prestigiacomo CJ, Kim SC, Connolly ES Jr. Kottirsch G, Pinsky DJ. Reduced microvascular thrombosis and improved outcome in acute murine stroke by inhibiting GP IIb/IIIa receptor-mediated platelet aggregation. *J Clin Invest*. 1998; 102:1301–1310. [PubMed: 9769322]
- Czosnyka M. Association between arterial and intracranial pressures. *Br J Neurosurg*. 2000; 14:127–128. [PubMed: 10889884]
- Dai Z, Deng X, Zhang Z, Zhu Y, Zhang Y, Li D, Luo X, Mo Z, Han H. MRI study of deep cerebral veins after subarachnoid hemorrhage in rabbits. *Chinese Journal of Clinical Anatomy*. 2012; 30:176–180.
- Dalkara T, Arsava EM. Can restoring incomplete microcirculatory reperfusion improve stroke outcome after thrombolysis? *J Cereb Blood Flow Metab*. 2012; 32:2091–2099. [PubMed: 23047270]
- de Bruijn SF, Budde M, Teunisse S, de Haan RJ, Stam J. Long-term outcome of cognition and functional health after cerebral venous sinus thrombosis. *Neurology*. 2000; 54:1687–1689. [PubMed: 10762517]

- Donnet A, Metellus P, Levrier O, Mekkaoui C, Fuentes S, Dufour H, Conrath J, Grisoli F. Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients. *Neurology*. 2008; 70:641–647. [PubMed: 18285539]
- Edvinsson L, Hogestatt ED, Uddman R, Auer LM. Cerebral veins: fluorescence histochemistry, electron microscopy, and in vitro reactivity. *J Cereb Blood Flow Metab*. 1983; 3:226–230. [PubMed: 6841470]
- Edvinsson L, Larsen SS, Maddahi A, Nielsen J. Plasticity of cerebrovascular smooth muscle cells after subarachnoid hemorrhage. *Transl Stroke Res*. 2014; 5:365–376. [PubMed: 24449486]
- Etmninan N, Buchholz BA, Dreier R, Bruckner P, Torner JC, Steiger HJ, Hanggi D, Macdonald RL. Cerebral aneurysms: formation, progression, and developmental chronology. *Transl Stroke Res*. 2014; 5:167–173. [PubMed: 24323717]
- Garcia JH, Liu KF, Yoshida Y, Chen S, Lian J. Brain microvessels: factors altering their patency after the occlusion of a middle cerebral artery (Wistar rat). *Am J Pathol*. 1994; 145:728–740. [PubMed: 8080052]
- Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *Journal of applied physiology*. 2006; 100:1059–1064. [PubMed: 16467392]
- Horev A, Hallevy H, Plakht Y, Shorer Z, Wirguin I, Shelef I. Changes in cerebral venous sinuses diameter after lumbar puncture in idiopathic intracranial hypertension: a prospective MRI study. *J Neuroimaging*. 2013; 23:375–378. [PubMed: 22913783]
- Ishikawa M, Cooper D, Arumugam TV, Zhang JH, Nanda A, Granger DN. Platelet-leukocyte-endothelial cell interactions after middle cerebral artery occlusion and reperfusion. *J Cereb Blood Flow Metab*. 2004a; 24:907–915. [PubMed: 15362721]
- Ishikawa M, Kusaka G, Yamaguchi N, Sekizuka E, Nakadate H, Minamitani H, Shinoda S, Watanabe E. Platelet and leukocyte adhesion in the microvasculature at the cerebral surface immediately after subarachnoid hemorrhage. *Neurosurgery*. 2009; 64:546–553. discussion 553-544. [PubMed: 19240618]
- Ishikawa M, Zhang JH, Nanda A, Granger DN. Inflammatory responses to ischemia and reperfusion in the cerebral microcirculation. *Front Biosci*. 2004b; 9:1339–1347. [PubMed: 14977549]
- Kilic T, Akakin A. Anatomy of cerebral veins and sinuses. *Frontiers of neurology and neuroscience*. 2008; 23:4–15. [PubMed: 18004050]
- Kim BS, Sarma D, Lee SK, terBrugge KG. Brain edema associated with unruptured brain arteriovenous malformations. *Neuroradiology*. 2009; 51:327–335. [PubMed: 19219601]
- Kulik T, Kusano Y, Aronhime S, Sandler AL, Winn HR. Regulation of cerebral vasculature in normal and ischemic brain. *Neuropharmacology*. 2008; 55:281–288. [PubMed: 18541276]
- Lapi D, Vagnani S, Cardaci E, Paterni M, Colantuoni A. Rat pial microvascular responses to melatonin during bilateral common carotid artery occlusion and reperfusion. *J Pineal Res*. 2011; 51:136–144. [PubMed: 21470301]
- Lauw MN, Barco S, Coutinho JM, Middeldorp S. Cerebral venous thrombosis and thrombophilia: a systematic review and meta-analysis. *Semin Thromb Hemost*. 2013; 39:913–927. [PubMed: 24129682]
- Leak RK, Zheng P, Ji X, Zhang JH, Chen J. From apoplexy to stroke: historical perspectives and new research frontiers. *Prog Neurobiol*. 2014; 115:1–5. [PubMed: 24373958]
- Li Q, Khatibi N, Zhang JH. Vascular neural network: the importance of vein drainage in stroke. *Transl Stroke Res*. 2014; 5:163–166. [PubMed: 24563018]
- Liu S, Connor J, Peterson S, Shuttleworth CW, Liu KJ. Direct visualization of trapped erythrocytes in rat brain after focal ischemia and reperfusion. *J Cereb Blood Flow Metab*. 2002; 22:1222–1230. [PubMed: 12368661]
- Lo EH, Rosenberg GA. The neurovascular unit in health and disease: introduction. *Stroke*. 2009; 40:S2–3. [PubMed: 19064779]
- Mayhan WG. Leukocyte adherence contributes to disruption of the blood-brain barrier during activation of mast cells. *Brain Res*. 2000; 869:112–120. [PubMed: 10865065]
- Mayhan WG, Heistad DD. Permeability of blood-brain barrier to various sized molecules. *Am J Physiol*. 1985; 248:H712–718. [PubMed: 2581459]

- Mayhan WG, Heistad DD. Role of veins and cerebral venous pressure in disruption of the blood-brain barrier. *Circ Res.* 1986; 59:216–220. [PubMed: 3742745]
- Muller WA. Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. *Trends in immunology.* 2003; 24:327–334. [PubMed: 12810109]
- Mursch K, Wachter A, Radke K, Buhre W, Al-Sufi S, Munzel U, Behnke-Mursch J, Kolenda H. Blood flow velocities in the basal vein after subarachnoid haemorrhage. A prospective study using transcranial duplex sonography. *Acta Neurochir (Wien).* 2001; 143:793–799. discussion 799-800. [PubMed: 11678400]
- Nakase H, Heimann A, Kempfski O. Local cerebral blood flow in a rat cortical vein occlusion model. *J Cereb Blood Flow Metab.* 1996; 16:720–728. [PubMed: 8964813]
- Nusbaum D, Clark J, Brady K, Kibler K, Sutton J, Easley RB. Alteration in the lower limit of autoregulation with elevations in cephalic venous pressure. *Neurol Res.* 2014; 36:1063–1071. [PubMed: 24892946]
- Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke.* 2000; 31:1621–1627. [PubMed: 10884463]
- Oka K, Rhoton AL Jr. Barry M, Rodriguez R. Microsurgical anatomy of the superficial veins of the cerebrum. *Neurosurgery.* 1985; 17:711–748. [PubMed: 4069326]
- Ostergaard L, Aamand R, Karabegovic S, Tietze A, Blicher JU, Mikkelsen IK, Iversen NK, Secher N, Engedal TS, Anzabi M, Jimenez EG, Cai C, Koch KU, Naess-Schmidt ET, Obel A, Juul N, Rasmussen M, Sorensen JC. The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* 2013; 33:1825–1837. [PubMed: 24064495]
- Otsuka H, Nakase H, Nagata K, Ueda K, Kempfski O, Sakaki T. Effect of age on cerebral venous circulation disturbances in the rat. *J Neurosurg.* 2000; 93:298–304. [PubMed: 10930017]
- Owler BK, Parker G, Halmagyi GM, Johnston IH, Besser M, Pickard JD, Higgins JN. Cranial venous outflow obstruction and pseudotumor Cerebri syndrome. Advances and technical standards in neurosurgery. 2005; 30:107–174. [PubMed: 16350454]
- Pradhan S, Yadav R, Diwakar H, Phadke RV. Subarachnoid hemorrhage following chronic dural venous sinus thrombosis. *Angiology.* 2007; 58:498–501. [PubMed: 17875965]
- Ritter LS, Orozco JA, Coull BM, McDonagh PF, Rosenblum WI. Leukocyte accumulation and hemodynamic changes in the cerebral microcirculation during early reperfusion after stroke. *Stroke.* 2000; 31:1153–1161. [PubMed: 10797180]
- Saha MK, Hamieh T, Larkin B, McMillan W. Cerebral hemorrhage due to internal jugular vein stenosis in a hemodialysis patient. *Clin Exp Nephrol.* 2012; 16:345–349. [PubMed: 22038186]
- Schwarzmaier SM, Kim SW, Trabold R, Plesnila N. Temporal profile of thrombogenesis in the cerebral microcirculation after traumatic brain injury in mice. *J Neurotrauma.* 2010; 27:121–130. [PubMed: 19803784]
- Seifert HA, Pennypacker KR. Molecular and cellular immune responses to ischemic brain injury. *Transl Stroke Res.* 2014; 5:543–553. [PubMed: 24895236]
- Shimamura N, Ohkuma H. Phenotypic transformation of smooth muscle in vasospasm after aneurysmal subarachnoid hemorrhage. *Transl Stroke Res.* 2014; 5:357–364. [PubMed: 24323729]
- Si Z, Luan L, Kong D, Zhao G, Wang H, Zhang K, Yu T, Pang Q. MRI-based investigation on outflow segment of cerebral venous system under increased ICP condition. *Eur J Med Res.* 2008; 13:121–126. [PubMed: 18499557]
- Silva NA, Sousa N, Reis RL, Salgado AJ. From basics to clinical: a comprehensive review on spinal cord injury. *Prog Neurobiol.* 2014; 114:25–57. [PubMed: 24269804]
- Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med.* 2005; 352:1791–1798. [PubMed: 15858188]
- Takahashi A, Ushiki T, Abe K, Houkin K, Abe H. Cytoarchitecture of periendothelial cells in human cerebral venous vessels as compared with the scalp vein. A scanning electron microscopic study. *Archives of histology and cytology.* 1994; 57:331–339. [PubMed: 7880587]
- Tso MK, Macdonald RL. Acute microvascular changes after subarachnoid hemorrhage and transient global cerebral ischemia. *Stroke research and treatment.* 2013; 2013:425281. [PubMed: 23589781]

- Tso MK, Macdonald RL. Subarachnoid hemorrhage: a review of experimental studies on the microcirculation and the neurovascular unit. *Transl Stroke Res*. 2014; 5:174–189. [PubMed: 24510780]
- Tureyen K, Vemuganti R, Sailor KA, Dempsey RJ. Ideal suture diameter is critical for consistent middle cerebral artery occlusion in mice. *Neurosurgery*. 2005; 56:196–200. discussion 196-200. [PubMed: 15799811]
- Uhl E, Beck J, Stummer W, Lehmberg J, Baethmann A. Leukocyte-endothelium interactions in pial venules during the early and late reperfusion period after global cerebral ischemia in gerbils. *J Cereb Blood Flow Metab*. 2000; 20:979–987. [PubMed: 10894181]
- Ushiwata I, Ushiki T. Cytoarchitecture of the smooth muscles and pericytes of rat cerebral blood vessels. A scanning electron microscopic study. *J Neurosurg*. 1990; 73:82–90. [PubMed: 2161912]
- Usman U, Wasay M. Mechanism of neuronal injury in cerebral venous thrombosis. *J Pak Med Assoc*. 2006; 56:509–512. [PubMed: 17183978]
- Xiong XY, Wang J, Qian ZM, Yang QW. Iron and intracerebral hemorrhage: from mechanism to translation. *Transl Stroke Res*. 2014; 5:429–441. [PubMed: 24362931]
- Yemisci M, Gursay-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009; 15:1031–1037. [PubMed: 19718040]
- Yu W, Rives J, Welch B, White J, Stehel E, Samson D. Hypoplasia or occlusion of the ipsilateral cranial venous drainage is associated with early fatal edema of middle cerebral artery infarction. *Stroke*. 2009; 40:3736–3739. [PubMed: 19762692]
- Zhang JH, Badaut J, Tang J, Obenaus A, Hartman R, Pearce WJ. The vascular neural network--a new paradigm in stroke pathophysiology. *Nat Rev Neurol*. 2012; 8:711–716. [PubMed: 23070610]
- Zhang Z, Deng X, Dai Z, Chen B, Gao B, Xia C, Chen D, Han H. MRI image of the internal cerebral vein and basilar artery of rabbit following subarachnoid hemorrhage. *Chin J Anat*. 2012; 35:137–140.
- Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. *Prog Neurobiol*. 2014; 115:25–44. [PubMed: 24291544]

Figure 1.

Examination images of the patients.

A and B: Computerized tomography scan did not reveal any abnormality in the brain at his first administration. C and D: Computerized tomography scan revealed multiple hematomas with edema in the left cerebral at his second administration. E and F: Computerized tomography angiography did not reveal aneurysms and vascular malformation. G and H: Magnetic resonance venography indicated thrombosis in superior sagittal sinus and right transverse sinus.

Figure 2.

Pathogenesis of cerebral venous system abnormality after acute brain injury. Venous drainage abnormalities might be attributed to several interwoven factors after brain injury, including elevated ICP due to brain edema, active constriction caused by pericyte contraction and phenotypic transformation in smooth muscle cells, and leukocyte-platelet aggregate with microthrombosis.

ICP: intracranial pressure.

Figure 3.

Vein-mediated pathophysiology after acute brain injury. The changes of cerebral venous may lead to venous congestion, BBB disruption, microthrombosis, infarction and hemorrhage, which subsequently cause ICP increase and brain edema.

TBI: traumatic brain injury; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage; ICP: intracranial pressure; BBB: Blood Brain Barrier.