Vascular Neural Network in Subarachnoid Hemorrhage

John H. Zhang

Received: 12 June 2014 / Accepted: 19 June 2014 / Published online: 3 July 2014
© Springer Science+Business Media New York 2014

Keywords Vascular neural network · Stroke · SAH · Venule · Vein

Since Hippocrates coined word “apoplexy” at about 2,400 years ago, the pathophysiology of apoplexy or stroke evolved over years and changed with the development of new technologies. Apoplexy was initially believed to be resulted from stagnation of “vital spirit” or “animal spirit” in the blood in cerebral circulation [1]. In the late 1800s, Rudolf Virchow redefined the pathophysiology of apoplexy as vascular origin, a phenomenon observed from limb gangrenous patients [2]. At around 1980s, calcium channel studies and role of calcium overload in neuronal death were established as new components of the pathophysiology for stroke and neuroprotection strategies were used for stroke treatment [3]. Multiple clinical trials based upon neuronal death pathophysiology followed and failed, and in around early 2000s, a new term was coined as neurovascular unit to represent the pathophysiology of stroke and neurovascular protection strategy was introduced [4, 5]. Neurovascular unit emphasizes the significance of capillaries and those immediately around capillaries such as neurons, astrocytes, and pericytes.

A normal cerebral circulation is maintained by upstream arteries, arterioles, capillaries, and downstream venules and veins, and arterial blood in flow and venous output need to be in harmony. A stroke event interrupts this circulating, and all of

these vascular components are affected and may contribute to poststroke reperfusion and repair. A new concept of the pathophysiology of stroke was introduced that a vascular neural network links both upstream arteries and arterioles but also downstream venules and veins [6]. The concept of vascular neural network is a step advanced from the neurovascular unit and emphasizes all components of cerebral circulation, not only arterial perfusion or reperfusion but also venous outflow in the outcome of stroke patients. Taking the pathophysiology of subarachnoid hemorrhage as an example, large artery vasospasm has been in focus of research in the past 50 years; however, patients’ outcome failed to be improved even after angiographic vasospasm was prevented. The failure of clinical trials promoted new studies on early brain injury and spreading cortical depression in the last 10 years [7]. Therefore, this perspective commentary article tries to explore new pathophysiologies of subarachnoid hemorrhage (SAH) under the umbrella of the vascular neural network. Early brain injury and spreading cortical depression have been reviewed extensively in the past and will not be discussed in this article.

Large Artery Moderate Vasospasm

By the end of 2013, a Pubmed search with keywords “vasospasm and cerebral” showed more than 9,000 articles, in which about 6,000 publications related with vasospasm after subarachnoid hemorrhage, almost one publication every 3 days over the last 50 years. The accepted concept from 1970s to 2000s was that no pharmacological agent can prevent or reverse large arterial vasospasm; therefore, large arterial vasospasm is the single most important treatable cause of death and disability after SAH [9, 10, 8]. However, this concept could not be reproduced in animal models of vasospasm. Vasospasm could be induced by blood injection in monkeys, canines, rabbits, and rodents, but none of those animals suffered focal infarction or had focal neurological

J. H. Zhang (✉)
Department of Neurosurgery, Loma Linda University School of
Medicine, Loma Linda, CA 92350, USA
e-mail: johnzhang3910@yahoo.com

J. H. Zhang
Department of Anesthesiology, Loma Linda University Medical
Center, Loma Linda, CA 92350, USA

J. H. Zhang
Department of Physiology, Loma Linda University School of
Medicine, Loma Linda, CA 92350, USA

deficits after vasospasm. A question needs to be addressed is how much vasospasm or an acute reduction of proximal artery diameter is needed to produce a focal infarct in animal models [11]? An interesting paper from Dempsey laboratory actually accidentally addressed this issue [12]. In an attempt to find the ideal suture diameter for middle cerebral artery occlusion in mice, sutures with tips of 110 to 180 μm were tested for Evan's blue leakage, CBF reduction, and cerebral infarction. While at 170 and 180 μm , middle cerebral artery was completely occluded, and at 110, 120, and 130 μm , sutures failed to occlude artery completely to produce infarction [12]. If one can presume from this study that the middle artery diameter is maximum at 170 μm in mice, 130/170 equals almost to 77 % reduction of the lumen. By this calculation, acute occlusion of middle cerebral artery by 77 % did not lead to infarction in mice [12]. To translate this calculation into vasospasm assessment, moderate vasospasm is a reduction of 34–66 % and severe vasospasm, 67–100 % in arterial diameter after SAH [13]. This means that an acute proximal moderate vasospasm alone (and may be half of the severe vasospasm) will not be able to cause focal infarction or delayed ischemic neurological deficits (DIND). Distal and diffused CBF reduction which is related to small arteries or arterioles may be more important than angiographic vasospasm in large arteries. If this calculation is correct, regional CBF monitoring may provide more meaningful information regarding patients' outcome than the gold standard angiogram [11].

Overall, in large artery, acute, focal, and proximal vasospasm may not be truly "harmful" unless the lumen reduction is more than 77 % [11]. However, large artery vasospasm is often combined with other pathologies in small arteries, capillaries, venules, and veins, and pathologies in those downstream vessels may contribute to the reduction of CBF. This phenomenon may explain the mismatch rate between angiographic (70 %) and clinical vasospasm (30 %) [13]. This may also explain that clazosentan prevented delayed vasospasm but failed to improve SAH patients' outcomes [14]. If distal and peripheral small artery or arterioles are involved in the reduction of CBF, a question needs to be addressed is do they have a role in the delayed brain injury after SAH?

Small Artery Vasospasm or Dilatation

Herz et al. firstly demonstrated that micropuncture caused pial artery contraction, and most small arteries and arterioles were constricted after topical application of blood [15]. The contractile effect may be caused by factors in the blood because diluted serum induced contraction of intraparenchymal microarteries in hippocampus slides which was abolished by heparin [16]. While direct blood contact caused microartery contraction in vitro, small artery or arteriole vasospasm was not observed in a rabbit model of vasospasm [17]. It was not

until 1997 that Ohkuma et al. demonstrated prolonged contraction of arterioles in a dog model of vasospasm, using a cast method for semi-quantification [18]. This observation was supported by a following study demonstrated vasospasm in surface penetrating arteries [19], but this observation was not confirmed in intraparenchymal penetrating arteries in the similar dog model [20]. Small artery vasospasm seemed age related that mild vasospasm in smaller arteries was observed in aged but not in young rabbits [21]. In a recent study, severe vasospasm was reported in microarteries while moderate vasospasm was observed in middle cerebral artery in a mouse model of vasospasm [22]. In an open cranial surgery for SAH, about half of the patients were found to have microvessel vasospasm and some in pear-string-like contractions [23].

An important issue for arteries after injury or hemorrhagic stroke is the switch of smooth muscle phenotypes, typically from contractile changed to secretory/synthetic type and functionally from contraction to repair and migration. Smooth muscle phenotype changes may not markedly affect the size or function of the large arteries [24], but due to the limited two or three layers of smooth muscle cells in smaller arteries or even a single layer of smooth muscle in arterioles, smooth muscle phenotype changes may influence vascular tone and function of small arteries. After phenotype changes, small arteries may be dilated or contracted (spastic), with potential formation of thrombosis and tissue proliferation. These possibilities were discussed in situations like SAH [25] and in blast injury during war [26]. Even though vasospasm was discussed as the major possibility after smooth muscle phenotype changes following SAH and blast injury, interestingly, the intraparenchymal arterioles were actually dilated after SAH in a dog model of vasospasm [20]. A similar tendency of larger diameters of arterioles was noticed in SAH patients during open cranial surgery when compared to patients without rupture of an aneurysm (not compared and unlikely statistically different) [23]. Consistently, arteriole diameter increased about 30 % in a mouse model of traumatic brain injury [27]. Except arteriole dilation, thrombosis formation and microartery vasospasm occurred simultaneously in a model of SAH in mice [28]. Even though multiple factors are involved in the dilation or spasm of arterioles after SAH and traumatic brain injury, a possible involvement of smooth muscle phenotypes needs to be ruled out.

Several studies showed vasospasm in large arteries but not in all penetrating arteries or arterioles in the same model, indicating that small artery or arteriole responds differently than large arteries, some small arteries even dilated after SAH. Technically, vasospasm in small arteries and especially in arterioles may be more harmful than in large arteries because the smaller artery and arterioles do not have collateral circulation reserves and the narrowing of arterioles may affect regional CBF. The weaknesses of most abovementioned studies are the lack of quantification and in some studies

vasospastic arteries or arterioles may be subjectively selected to be discussed. Apparently, smooth muscle phenotype changes need to be studied especially in animal models that produce early brain injury which contributes to mortality and delayed neurological functional deficits ([29]. Overall, morphological and functional deficits of small arteries and arterioles may affect capillaries flow and lead to ischemia and infarction.

Capillary Occlusion and Compression

Capillaries do not have smooth muscle cells but some pericytes are sporadically distributed, and pericytes regulate the diameter and blood flow of the capillaries [30]. Pericytes produce pear-string-type of contractions which have been noticed in Alzheimer's disease, cerebra ischemia, and diabetic retinopathy [30]. Capillary density reduction was firstly reported after topical blood application in vivo [15]. Capillary network was almost completely obliterated in 3 h after SAH in a dog model ([31] indicating a global effect of SAH. In cats, continued plasma dropping over brain surface for 30 min produced marked contraction of precapillaries and capillaries which could not be compensated by raising blood pressure [32]. A potential relationship between brain edema and the capillary density was proposed that edema may compress capillaries to decrease capillary density after SAH in rabbits ([33]. Similar capillary density reduction was observed in a dog model of vasospasm [18]. A clinical observation in SAH patients showed a pear-string-type contraction of arteriolar precapillary [34]. Capillary density reduction was observed in SAH patients and open cranial surgery reduced intracranial pressure and improved capillary density [23]. Interestingly, similar to the controversial observation of diameters of arteries and arterioles after SAH, capillary density was reported increased, actually doubled at 48 h after SAH in a rat model [35].

In general, capillary density reduction may be caused by smooth muscle (precapillary) or pericyte contraction or by compression of brain edema or elevation of intracranial pressure [36]. Pericyte contraction narrows capillary lumen and blocks blood flow. In addition, vasospasm in upstream smaller arteries and arterioles and downstream venules spasm or compression may contribute to the reduction of capillary blood flow and the density of the capillaries. Compensative capillary regeneration may occur due to cerebral ischemia after SAH.

Venule Vasospasm, Compression, and Thrombus Formation

One of the key issues of the vascular neural network is that arterial and venous blood flows need to be in harmony during circulation, and blood entering the brain from the arterial

system is matched with the amount of blood exiting the brain via the venous system. While most published schematic presentations of the pathophysiology of stroke show only arterial system, capillaries, and neuronal cells, venules and veins are omitted from the picture and their functions in acute stroke including SAH under discussed (Fig. 1). After a stroke such as SAH, both arterioles and venules are exposed to many detrimental factors including oxidative stress and inflammatory cytokines, microthrombi/emboli, and suffer similar luminal cellular injury, microhemorrhage, and either vasospasm in arterioles or compression in venules. In addition, small veins or venules do not have smooth muscle cells but instead a network of stellates or glia around venous walls as well as pericytes. The wall of venules is thin with only a layer of endothelial cells and adventitial. Moreover, small veins or at least venules do not contract and the venous valves that prevent back flow of venous blood are not described in cerebral veins [37]. After SAH, elevation of intracranial pressure and brain edema may compress or even collapse the thin walls of the venules. If venous circulation is slowed, oxidative stress and inflammation may damage more easily venous endothelial cells and cause blood clot formation in the venous system than in the arterial system. Therefore, in SAH, arterial perfusion and venous drainage are equally important and both should be protected.

An example of elevation of intracranial pressure that obstructed venous flow was demonstrated in weightlifting athletes that conjunctival hemorrhage and elevations in intraocular pressure were observed [38]. In an in vivo study in rats, hemolysate produced an acute reduction of diameters of pial venules and decreased pial venule blood flow velocity [39], even though similar phenomenon was not observed in intraparenchymal venules in a dog model of vasospasm [20]. In contrast, the venule diameter seemed increased after SAH when compared with non-aneurysm rupture patients (not compared and unlikely statistically different) [23]. Open cranial surgery reduced intracranial pressure and improved venule blood flow, indicating venule compression occurred in SAH patients [23]. These clinical observations indicated that venule may be compensatively dilated either due to venule compression that slowed blood flow or because of large vein flow reduced after SAH in patients. Reducing intracranial pressure by open cranial surgery improved venule flow and may eventually reduce the diameter of the venules. As mentioned above that due to the slow of venous flow, the venules are prone to form thrombus and in a mouse model of TBI, 70 % venules vs. 33 % arterioles have microthrombi [27]. Venule compression or vasospasm by pericyte contraction may contribute to CBF reduction since a single venule occlusion caused a microinfarction in a rat model of cerebral ischemia [40].

Overall, venules have pericytes, and in theory, pericytes can produce contraction. Topical blood application caused

Fig. 1 Aneurysm rupture will affect artery, arterioles, capillary, venule and veins

reduction of venule diameter and blood flow within minutes in a rat model of SAH [39]. This acute effect of blood on the venules however was not observed in intraparenchymal venules in a dog model of vasospasm at several days after SAH, may be due to limited direct blood contact in intraparenchymal venules [20]. In SAH patients, the actual diameters of venules were dilated while venule flow reduced, and the latter was improved by the open cranial surgery which reduced intracranial pressure [23]. This observation indicated that venule compression occurred after SAH, and a compensatory increase of venule diameter may occur since blood flow reduced, and it is presumed that with the improvement of venule flow after surgery, the diameter of the venule may drop back to normal range. Therefore, a potential acute venule compression after SAH needs to be studied or ruled out. Elevation of intracranial pressure, brain edema, pericyte contraction, and thrombus as well as vein blood flow stagnation may all contribute to venule blood flow reduction and brain ischemia.

Large Vein Vasospasm

After SAH, veins may play a vital role even more than arteries in the maintenance of cerebral blood flow and brain function. For example, an acute reduction of arterial flow at 20 % may cause a mild and almost harmless episode of cerebral ischemia, but if arterial flow remains and venous flow decreases acutely by 20 %, blood will then be accumulated in the

capillary system leading to brain swelling and an increase in intracranial pressure causing capillary swelling, flow decrease to no-flow, and even capillary hemorrhage. In a study of malignant brain edema and venous drainage, it seemed only the patients with hypoplasia or occlusion of the ipsilateral cranial venous drainage developed early fatal edema after large middle cerebral artery infarction [41]. The authors suggested a vital role of cranial venous outflow abnormalities in the development of brain edema after arterial ischemic stroke.

So far, deep vein vasospasm after SAH has rarely been studied. An early study used blood flow velocities in deep cerebral basal veins to predict delayed ischemic neurological deficit after SAH. In patients without neurological deficit, flow velocity in the basal vein was significantly elevated above normal values in the following day. In patients with permanent deficit, flow velocities in the basal vein were significantly below normal in the following day [42]. The authors stated that changes in CBF correlated better with flow velocity in the basal vein than with arterial flow velocities. In a study published recently, Dai et al. [43] using MRI demonstrated vasospasm in internal cerebral vein and basal vein of 30 % reduction of lumen on day 5 after SAH in rabbits. In a further study from the same group, a side-by-side comparison between the basilar artery and internal cerebral vein were made [44]. The peak arterial vasospasm of about 30 % was observed on days 3–5, but the peak venous spasm of more than 40 % reduction of the lumen was on days 5–7, indicating low blood flow in internal cerebral vein may due to vasospasm rather than to decreased arterial blood flow. Therefore, after

SAH, deep vein vasospasm or compression by intracranial pressure occurs and that may lead to venule flow reduction, capillary density loss, and cerebral ischemia. The authors predicted that in the presence of vein vasospasm, if vasodilatation was used to treat arterial vasospasm, poor outcomes may be expected due to poor venous flow [43, 6]. Those studies suggested that before anti-arterial vasospasm treatment especially the triple H therapy, venous flow needs to be examined and good venous flow guaranteed; otherwise, enhanced arterial flow may actually worsen patient outcome. Except vein vasospasm, hypercoagulable state and microvessel platelet aggregation were reported after experimental SAH [45, 46]. Consistently anti-thrombi therapy by intravenous heparin markedly improved outcome of SAH patients [47].

Taking together, deep veins have smooth muscle cells but lack of contractile receptors and only mild contraction may be produced. Thrombus and compression in veins may contribute to the size changes beside smooth muscle contraction. Vein smooth muscle vasospasm needs to be studied. Vein flow stagnation will cause slowed venule blood flow and blood accumulation in the capillaries and result in brain venous infarct. For SAH, venous drainage may be one of the major determinant factors in brain edema and poor outcomes.

Finally, arterial and venous flows need to be in harmony; both arterial perfusion and venous drainage need to be protected for patients after SAH. For the above discussed four vascular neural network components, deep veins, venules, capillaries, and arterioles, because of limited or no collateral circulation reserves, dysfunction of these factors contributes to the reduction of CBF and brain infarction after SAH. On the contrary, large artery vasospasm alone at moderate level may not cause brain ischemia or poor outcomes. In the future studies, the potential roles of arterioles should be studied with an open mind. Because of autoregulation (if it is still intact after SAH), arterioles may be dilated when upstream arteries are in spasm, especially those inside the parenchymal that are not in direct contact with blood clots. Capillaries do not usually have vasospasm, and the capillary density decreased after SAH may be caused by elevation of ICP and brain edema; therefore, treatment strategies for SAH may go beyond vasospasm prevention and reduction but emphasizes on reduction of ICP and brain edema to improve cerebral perfusion. Potential roles of venules and veins after SAH were largely ignored in the past, and in theory, without a good venous outflow reperfusion is not possible and may be dangerous and should be emphasized. To do all of those studies listed above, new animal models of SAH and new technologies are needed to study changes of arterioles, capillaries, venules, and veins. Further studies of SAH early and delayed brain injury as well as vasospasm in animal models should follow STAIR criteria [48, 49], and more clinical studies of venous spasm should be conducted following translational

research guidelines [51–54, 50]. In animal models, female and aged animals need to be considered to match clinical aspects [55, 56].

Conflict of Interest None.

References

1. Pound P, Bury M, Ebrahim S. From apoplexy to stroke. *Age Ageing*. 1997;26:331–7.
2. Schiller F. Concepts of stroke before and after Virchow. *Med Hist*. 1970;14:115–31.
3. Caplan L. Cerebrovascular disease: historical background, with an eye to the future. *Cleveland Clinic Journal of Medicine* 71 (supplement 1): S22-S24, 2004
4. Lo EH, Broderick JP, Moskowitz MA. tPA and proteolysis in the neurovascular unit. *Stroke*. 2004;35(2):354–6.
5. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci*. 2004;5(5):347–60.
6. Zhang J, Badaut J, Tang J, Obenaus A, Hartman R, Pearce W. The vascular neural network. A Paradigm in Stroke Pathophysiology *Nature Review Neurology*. 2012;8:711–6.
7. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. *Neurol Res*. 2009;31:151–8.
8. Mayberg MR. Cerebral vasospasm. *Neurosurg Clin N Am*. 1998;9(3):615–27.
9. Wilkins RH. Cerebral vasospasm. *Crit Rev Neurobiol*. 1990;6(1):51–77.
10. Weir B, MacDonald L. Cerebral vasospasm. *Clin Neurosurg*. 1993;40:40–55.
11. Hou J, Zhang JH. Does prevention of vasospasm in subarachnoid hemorrhage improve clinical outcome? *No Stroke*. 2013;44(6 Suppl 1):S34–6.
12. Türeyn K, Vemuganti R, Sailor KA, Dempsey RJ. Ideal suture diameter is critical for consistent middle cerebral artery occlusion in mice. *Neurosurgery*. 2005;56(1 Suppl):196–200.
13. Vergouwen MD, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke*. 2011;42(4):924–9.
14. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011;10(7):618–25.
15. Herz DA, Baez S, Shulman K. Pial microcirculation in subarachnoid hemorrhage. *Stroke*. 1975 Jul-Aug;6(4):417–24
16. Cach R, Smock T, Popejoy S. Blood-borne factors regulating microvascular constriction in the rat hippocampal slice. *Brain Res*. 1987;414(1):1–7.
17. Nihei H, Kassell NF, Dougherty DA, Sasaki T. Does vasospasm occur in small pial arteries and arterioles of rabbits? *Stroke*. 1991;22(11):1419–25.
18. Ohkuma H, Itoh K, Shibata S, Suzuki S. Morphological changes of intraparenchymal arterioles after experimental subarachnoid hemorrhage in dogs. *Neurosurgery*. 1997;41(1):230–5.
19. Zubkov AY, Tibbs RE, Aoki K, Zhang JH. Morphological changes of cerebral penetrating arteries in a canine double hemorrhage model. *Surg Neurol*. 2000;54(3):212–9. discussion 219–20.
20. Perkins E, Kimura H, Parent AD, Zhang JH. Evaluation of the microvasculature and cerebral ischemia after experimental subarachnoid hemorrhage in dogs. *J Neurosurg*. 2002;97(4):896–904.

21. Nakajima M, Date I, Takahashi K, Ninomiya Y, Asari S, Ohmoto T. Effects of aging on cerebral vasospasm after subarachnoid hemorrhage in rabbits. *Stroke*. 2001;32(3):620–8.
22. Sabri M, Ai J, Lakovic K, D'abbonanza J, Ildigwe D, Macdonald RL. Mechanisms of microthrombi formation after experimental subarachnoid hemorrhage. *Neuroscience*. 2012;224:26–37.
23. Uhl E, Lehmberg J, Steiger HJ, Messmer K. Intraoperative detection of early microvasospasm in patients with subarachnoid hemorrhage by using orthogonal polarization spectral imaging. *Neurosurgery*. 2003;52(6):1307–15.
24. Yamaguchi-Okada M, Nishizawa S, Koide M, Nonaka Y. Biomechanical and phenotypic changes in the vasospastic canine basilar artery after subarachnoid hemorrhage. *J Appl Physiol* (1985). 2005 Nov;99 (5):2045–52.
25. Norihito Shimamura, Hiroki Ohkuma (2014) Phenotypic transformation of smooth muscle in vasospasm after aneurysmal subarachnoid hemorrhage. *Transl Stroke Res*
26. Eric S. Hald, Patrick W. Alford (2014) Smooth muscle phenotype switching in blast traumatic brain injury-induced cerebral vasospasm. *Transl Stroke Res*
27. Schwarzman 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(1):121–30. doi:10.1089/neu.2009.1114.
28. Friedrich B, Müller F, Feiler S, Schöller K, Plesnila N. Experimental subarachnoid hemorrhage causes early and long-lasting microarterial constriction and microthrombosis: an in-vivo microscopy study. *J Cereb Blood Flow Metab*. 2012;32(3):447–55.
29. Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, Zhang J, Tang J, Zhang JH (2013 Sep 25) Controversies and evolving new mechanisms in subarachnoid hemorrhage. *Prog Neurobiol*
30. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. *Nat Neurosci*. 2011;14(11):1398–405.
31. Asano T, Sano K. Pathogenetic role of no-reflow phenomenon in experimental subarachnoid hemorrhage in dogs. *J Neurosurg*. 1977;46(4):454–66.
32. Wiernsperger N, Schulz U, Gyax P. Physiological and morphometric analysis of the microcirculation of the cerebral cortex under acute vasospasm. *Stroke*. 1981 Sep-Oct;12 (5):624–7.
33. Johshita H, Kassell NF, Sasaki T, Ogawa H. Impaired capillary perfusion and brain edema following experimental subarachnoid hemorrhage: a morphometric study. *J Neurosurg*. 1990;73(3):410–7.
34. Pennings FA, Bouma GJ, Ince C. Direct observation of the human cerebral microcirculation during aneurysm surgery reveals increased arteriolar contractility. *Stroke*. 2004 Jun;35 (6):1284–8. Epub 2004 Apr 15
35. Joško J. Cerebral angiogenesis and expression of VEGF after subarachnoid hemorrhage (SAH) in rats. *Brain Res*. 2003;981(1–2):58–69.
36. Østergaard L, Aamand R, Karabegovic S, Tietze A, Blicher JU, Mikkelsen IK, et al. The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2013;33(12):1825–37.
37. 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(1):82–90.
38. Dickerman RD, Smith GH, Langham-Roof L, McConathy WJ, East JW, Smith AB. Intra-ocular pressure changes during maximal isometric contraction: does this reflect intra-cranial pressure or retinal venous pressure? *Neurol Res*. 1999;21(3):243–6.
39. Sun BL, Zheng CB, Yang MF, Yuan H, Zhang SM, Wang LX. Dynamic alterations of cerebral pial microcirculation during experimental subarachnoid hemorrhage. *Cell Mol Neurobiol*. 2009;29(2): 235–41.
40. Shih AY, Blinder P, Tsai PS, Friedman B, Stanley G, Lyden PD, et al. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci*. 2013;16(1):55–63.
41. 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 (12):3736–9.
42. Mursch K, Wachter A, Radke K, Buhre W, Al-Sufi S, Munzel U, et al. Blood flow velocities in the basal vein after subarachnoid haemorrhage. A prospective study using transcranial duplex sonography. *Acta Neurochir (Wien)*. 2001;143(8):793–9.
43. Dai Z, Deng X, Zhang Z, Zhu Y, Zhang Y, Li D, et al. MRI study of deep cerebral veins after subarachnoid hemorrhage in rabbits. *Chinese Journal of Clinical Anatomy*. 2012;30(2):176–80.
44. Zhang Z, Deng X, Dai Z, Chen B, Gao B, Xia C, et al. MRI image of the internal cerebral vein and basilar artery of rabbit following subarachnoid hemorrhage. *Chinese Journal of Anatomy*. 2012;35: 137–41.
45. Sehba FA, Mostafa G, Friedrich Jr V, Bederson JB. Acute microvascular platelet aggregation after subarachnoid hemorrhage. *J Neurosurg*. 2005;102(6):1094–100.
46. Larsen CC, Hansen-Schwartz J, Nielsen JD, Astrup J. Blood coagulation and fibrinolysis after experimental subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2010;152(9):1577–81.
47. Simard JM, Aldrich EF, Schreibman D, James RF, Polifka A, Beaty N. Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment. *J Neurosurg*. 2013;119(6):1611–9.
48. Wang MXG, Keep RF. Should the STAIR criteria be modified for preconditioning studies? *Transl Stroke Res*. 2013;4:3–14.
49. Bahjat FR, Gesuete R, Stenzel-Poore MP. Steps to translate preconditioning from basic research to the clinic. *Transl Stroke Res*. 2013;4: 89–103.
50. Macdonald RL, Jaja B, Cusimano MD, Etminan N, Hanggi D, Hasan D, et al. SAHIT investigators—on the outcome of some subarachnoid hemorrhage clinical trials. *Transl Stroke Research*. 2013;4:286–96.
51. Antonic A, Sena ES, Donnan GA, Howells DW. Human in vitro models of ischaemic stroke: a test bed for translation. *Transl Stroke Res*. 2012;3:306–9.
52. Ayer A, Hwang BY, Appelboom G, Connolly Jr ES. Clinical trials for neuroprotective therapies in intracerebral hemorrhage: a new roadmap from bench to bedside. *Transl Stroke Res*. 2012;3:409–17.
53. Lapchak PA. Fast neuroprotection (fast-NPRX) for acute ischemic stroke victims: the time for treatment is now. *Transl Stroke Res*. 2013;4:704–9.
54. Lapchak PA, Zhang JH, Noble-Haesslein LJ. RIGOR guidelines: escalating STAIR and STEPS for effective translational research. *Transl Stroke Res*. 2013;4:279–85.
55. Tajiri N, Dailey T, Metcalf C, Mosley YI, Lau T, Staples M, et al. In vivo animal stroke models. *Transl Stroke Research*. 2013;4:308–21.
56. Herson PS, Palmateer J, Hum PD. Biological sex and mechanisms of ischemic brain injury. *Transl Stroke Res*. 2013;4:413–9.