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Vascular Neural Network: the Importance of Vein Drainage in Stroke

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Abstract

This perspective commentary summarized the stroke pathophysiology evolution, especially the focus in the past on neuroprotection and neurovascular protection and highlighted the newer term for stroke pathophysiology: vascular neural network. Emphasize is on the role of venules and veins after an acute stroke and as potential treatment targets. Vein drainage may contribute to the acute phase of brain edema and the outcomes of stroke patients.

Keywords

stroke; apoplex; vein drainage; vascular neural network

Stroke Pathophysiology Evolution

Overview

The initial pathophysiology of Stroke, known previously as cerebral apoplexy, was suggested as stagnation of “vital spirits” or “animal spirit” (blood or blood components) in the brain that resulted in body dysfunctions (Pound et al., 1997, Caplan 2004). This concept continued to evolve up into the late 1800s, when Rudolf Virchow redefined the pathophysiology of apoplexy as primarily a vascular disorder attributed to mechanical blood clots interrupting the blood flow to the brain (Schiller, 1970, Demarin et al., 2011). In 1928, apoplexy was subcategorized based upon the cause of blood vessel dysfunction, either ischemic or hemorrhagic. Smoking, hypertension, gender differences, and those factors directly influencing blood vessels were known as ‘risk factors’ and correction of vascular pathology such as carotid endarterectomy was used for stroke prevention in the 1950s led by the efforts of Dr. Michael DeBakey (Caplan 2004). It was also during the 1950s that scientific advancements in imaging allowed for improved observations in vascular and neuronal changes during stroke. These modalities included tomographic brain imaging, ultrasound imaging, computerized cranial tomography, MRI, PET, and fMRI (Caplan 2004). These modalities allowed for therapeutic and preventative strategies to come about,

targeting specific blood factors which Galen and Wepfer first thought were “vital or animal spirits”. These modalities included antiplatelet therapy by aspirin in the 1970s, anticoagulation therapy by warfarin in the 1990s and finally, thrombolytic tPA therapy in 2000 (Pound et al., 1997, Caplan 2004, Paciaroni & Bogousslavsky, 2009, Nilsen, 2010).

Stroke Pathophysiology in Chinese Medicine

In traditional Chinese medicine, stroke pathophysiology and treatment strategies target both arterial perfusion and venous drainage or “Huo-Xue-Hua-Yu”. “Huo-Xue” means improved perfusion of arterial blood while and “Hua-Yu” indicates improved venous drainage. The idea of stroke appeared in the Chinese literature about 300BC as “Cu-Zhong”, similar times that Hippocrates coined apoplexy, and both apoplexy and “Cu-Zhong” covered other disorders besides stroke (Schiller, 1970, Pound et al., 1997). A more narrowed definition on “Cu-Zhong” which is similar to stroke in today’s meaning, was documented 1700 years ago by Hong Ge, a chemist/physician from the Jin dynasty, in a handbook-like publication for addressing medical emergencies (Leak et al., 2014). Similar to blood “vital spirit or animal spirit” coined by Galen and Wepfer for apoplexy pathophysiology, the pathophysiology of apoplexy in ancient China was considered a “wind-spirit (not necessarily meant wind at today’s meaning)” in the brain or cerebral blood circulation. It is interesting to note that even though both concepts were a few years apart and separated by the vast lands of middle Asia, both Greek/European and Chinese physicians believed that apoplexy was caused by a fast acting supernatural force. The Greek word for stroke meaning struck down with violence in a lightning speed (Pound et al., 1997), or “Cu-Zhong” in Chinese in which “Cu” means fast occurring and “Zhong” means hit by outside forces.

Neuroprotection Era

From the 1950s to 2000, stroke therapy seemed to emphasize both the early Greek concept of “vital spirits” in the blood (blood factors) and later, the concept of blood vessel wall changes (vascular risk factors). It was not until the development of the scientific research industry that allowed detailed studies of brain tissues possible at both systemic and cellular levels, especially with identification of ion channels, and calcium channel blockers (Caplan 2004, Lapchak, 2013). These advances led to stroke clinical management and the experimental studies of stroke pathophysiology at the molecular level – all culminating into a new term coined neuroprotection (Simon et al., 1984, Pound et al., 1997, Caplan 2004).

Neurovascular Unit Era

Large clinical trials on neuroprotection soon followed but quickly failed because of the difficulty with protecting neurons despite ongoing vascular occlusion (Lo et al., 2004, Ayer et al., 2012). This unexpected failure at the clinical level gave rise to two notable events - one was the use of tPA to re-canalize the vessel and two, was the conceptual change from neuroprotection into neurovascular protection after the early 2000s (Lo et al., 2004, Iadecola et al., 2004, Del Zoppo et al., 2007). The neurovascular unit is somehow mixed in with the concept of blood-brain barrier and eventually was named by some researchers as neurovascular unit: blood-brain barrier. This concept emphasizes the significance of capillaries and their interactions with neurons, astrocytes, and pericytes. A neurovascular unit takes the definition of stroke a step further than simply neuroprotection which focuses

more on neuronal cells. However, a neurovascular unit does not emphasize an understanding of upstream arteries/arterioles and especially veins/venules where smooth muscle cells, pericytes, and vascular endothelial cells play vital roles in the control of vascular tone, influence of downstream capillaries, and clearance of venous blood. A new concept was beginning to take shape regarding stroke pathophysiology – the notion that the vascular neural network may in fact be at the center stage of the entire pathology (Zhang et al., 2012).

Vascular Neural Network: Arterial and Venous Flow in Harmony

The vascular neural network is a concept that partially spawned from traditional Chinese medicine and pathophysiological understanding of stroke treatment strategies that arterial and venous blood flow needs to be in harmony during circulation.

The structures of cerebral arteries and veins are distinctly different (Ushiwata and Ushiki, 1990). In arteries or arterioles, in addition to endothelial and adventitial cells, there are multiple layers of smooth muscle cells. All of these cell types generate and release various growth factors, signaling factors, and neurotransmitters that influence arterial tone and autoregulatory functions of cerebral arteries (Zhang et al., 2012). During cerebral ischemia secondarily to a blood clot (thrombus or an embolus), even though hypothetically the upstream artery from the blood clot may detect changes in heart rate and blood pressure to keep the contractile smooth muscle phenotype (for a certain time), downstream artery from the blood clot will definitely not and that may lead to a fast change of smooth muscle phenotype to secretory or a synthetic subtype. These phenotype changes will affect muscle contractility and eventually autoregulatory function of the cerebral arteries (Zhang et al., 2012). When the blood clot is being removed either by a retriever or chemically by tPA, “normal” blood flow will resume and due to the lack of autoregulation of arterial smooth muscle, more blood may enter the arterial system and into the brain parenchyma resulting in reperfusion injury (Zhang et al., 2012). In this case, reduced blood pressure is needed clinically to prevent potential reperfusion injury when an occluded artery is reopened. Other measures presumably such as the use of agents that may prevent or correct smooth muscle phenotype back to contractility, or a balloon that will mechanically narrow the reopened artery and decrease blood flow, may be considered for future development.

In contrast, small veins or venules do not have smooth muscle cells but instead a network of stellates or glia around venous walls. Moreover, veins or at least venules do not contract and the venous valves that prevent back flow of venous blood were not described in cerebral veins (Ushiwata and Ushiki, 1990). In extreme pathophysiological conditions such as in traumatic brain injury, intracerebral or subarachnoid hemorrhages, and in cerebral ischemic patients that have diabetes or hyperglycemia, severe brain edema increases intracranial pressure to levels that may compress or even collapse the thin walls of the venules and capillaries (Østergaard et al., 2013). Oxidative stress and inflammation during these brain attack events may damage not only arterial but also venous and capillary endothelial cells and cause blood clot formation in the venous system (Sehba et al., 2005, Larsen et al., 2010, Schwarzmaier et al., 2010). In these situations, when the blood clot in artery is removed and the arterial system reopened, due to the loss of smooth muscle phenotype and autoregulation (Zhang et al., 2012), more blood enters the brain and puts pressure on the venous system.

While venules or even veins are compressed and pressured by elevated intracranial pressure and brain tissue edema (Østergaard et al., 2013), a reduction of venous flow is unmatched with an increased arterial flow, catastrophic events such as capillary occlusion, collapse, or hemorrhage may follow. An interesting observation indicated that early malignant brain edema development after massive ischemic stroke was associated with poor venous flow (Yu et al., 2009). Tissue edema and elevation of intracranial pressure may selectively affect the venous system but not the arterial system because of the multiple layers of smooth muscle cells in the artery/arterioles that provide thickness (Lassen, 1974, Ushiwata and Ushiki, 1990, Zhang et al., 2012). In this regard, we want to keep in mind that arterial/arterioles and venous/venules are exposed to the same types of stimulations and damages including thrombi/emboli, neutrophils and oxygen species, hemorrhage, endothelial edema and injury, as well as vasospasm or compression, and thrombosis rate is much higher in venules than in arterioles (Sehba et al., 2005, Larsen et al., 2010, Schwarzmaier et al., 2010, Østergaard et al., 2013). Indeed, deep cerebral vein vasospasm/compression was reported in a rabbit model of subarachnoid hemorrhage. Under this situation, the authors presumed that arterial dilatation to treat vasospasm may aggravate brain edema and poor outcomes because of the poor venous drainage (Dai et al., 2012, Zhang et al., 2012b). These experimental observations are consistent with an early clinical report that studied blood flow velocities in deep cerebral basal veins after SAH. Interestingly, when flow velocity in the basal vein was significantly elevated above normal values in the following day, patients were found without neurological deficit; while when flow velocities in the basal vein were significantly below normal in the following day, patients were found to have permanent deficit (Mursch et al., 2001).

In normal cerebral circulation, cerebral autoregulation prevents and protects the brain from over-flow induced injury. When blood flow increases, cerebral arteries contract to prevent excessive blood flow into the brain parenchyma and when blood flow decreases, cerebral arteries dilate to allow more blood into the brain, keeping the total blood flow to the brain constant (Lassen, 1974). This same principle may apply to the relationship between arterial and venous flows, and that blood entering the brain from the arterial system is matched with the amount of blood exiting the brain via the venous system. In this relationship, it seems reasonable to predict from abovementioned studies that veins seem to play a more vital role than arteries in the maintenance of brain blood flow physiology and brain function (Mursch et al., 2001, Yu et al., 2009, Dai et al., 2012, Zhang et al., 2012b). To speculate, an acute reduction of arterial flow at 20% may cause a mild and almost harmless episode of cerebral ischemia, but if arterial flow remains but 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.

Vein Drainage, a Target for Future Studies

Stroke pathophysiology is not only related to neuronal tissues such as neurons, astrocytes, and glia cells, but also a vascular neural network composed of upstream small arteries, arterioles, capillaries and downstream venules and small veins (Zhang et al., 2012). In this

regard, the strategy for stroke management may be a vascular neural network protection which goes beyond neuroprotection and neurovascular protection.

Taken together, the vascular neural network represents stroke pathophysiology and places an emphasis on the role of not only arteries/arterioles but also veins and venules in the acute stroke process (Mursch et al., 2001, Yu et al., 2009, Dai et al., 2012, Zhang et al., 2012b, Shih et al., 2013). The potential roles of veins and especially venules during an acute arterial stroke, both ischemic and hemorrhagic, require further investigation. It needs to be emphasized that veins and venule may play a role in the acute arterial stroke, because of compression of venules by brain edema after cerebral ischemia (Yu et al., 2009, Østergaard et al., 2013) or vasospasm of deep cerebral veins after subarachnoid hemorrhage (Dai et al., 2012). Chronic venous thrombosis or venous stroke (Lauw et al., 2013) as well as acute occlusion of vein or venule (Shih et al., 2013) to induce infarction have been studied for many years and they are not the subject of this article. The potential roles of veins and venules in acute arterial stroke require experimental tests and should be studied under rigorous guidelines for translational studies that encompass proper blinding, randomization, power analysis, and accurate statistical analysis (Lapchak et al., 2013, Tajiri et al., 2013, Wang et al., 2013, Bahjat 2013), and ideally human vein tissues should be evaluated (Antonic et al., 2012). Animal models to observe venule and vein compression after acute arterial stroke are needed, taking age and gender into consideration, and mechanisms established (Herson et al., 2013). Neural imaging technologies to study vein and ideally venule volume and blood flow after an arterial stroke are needed. Currently, imaging technologies detected large vein hemodynamic changes in animals (Kim et al., 2013) and in patients (Pomschar et al., 2013). Other chemical or molecular diagnostic markers specifically for vein and venule dysfunction need to be developed. When there are clinical cases that could not be explained by arterial mechanisms, dysfunction of veins and venules may be considered and their dysfunction may lead to brain hemorrhage, edema and swelling and could be a catastrophic process to patients with acute ischemic stroke. In this regard, clinical observations and carefully designed studies are needed and may be initially modeled as SAHIT investigators (Macdonald et al., 2013). Even though multiple ongoing clinical trials for venous thrombosis are recruiting patients, there is one trial that is dedicated to hemorrhagic stroke patients with potential venous thromboembolism or deep venous thrombosis (PREvention of VENous Thromboembolism In Hemorrhagic Stroke Patients (PREVENTIHS) clinicaltrials.gov/venous+thrombosis&rank=11).

Redefining stroke pathophysiology as a vascular neural network is a step forward from the past classifications schemes including the initial thoughts by Wepfer as a “vital spirit”, inflammation causing brain softening by Rokitsansky, arterial injuries by Virchow (Schiller, 1970), calcium overload neuronal disorders, and at the capillary level with multiple neuronal cells as neurovascular unit (Zhang et al., 2012). Vascular neural network links the functions of both the arterial and venous systems, provides new direction for research, and promotes further studies of stroke pathophysiology as future therapeutic targets.

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