Published in final edited form as:

Prog Neurobiol. 2018 ; 163-164: 172–193. doi:10.1016/j.pneurobio.2017.11.001.

Cerebral venous collaterals: A new fort for fighting ischemic stroke?

Lu-sha Tong^{a,e}, Zhen-ni Guo^{b,e}, Yi-bo Ou^{c,e}, Yan-nan Yu^a, Xiao-cheng Zhang^a, Jiping Tang^d, John H. Zhang^{e,*}, and Min Lou^{a,**}

^aDepartment of Neurology, The 2nd Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China

^bDepartment of Neurology, The First Affiliated Hospital of Jilin University, Changchun, China

^cDepartment of Neurosurgery, Tong-ji Hospital, Wuhan, China

^dDepartment of Anesthesiology, Loma Linda University, School of Medicine, CA, USA

^eDepartments of Physiology, Loma Linda University, School of Medicine, CA, USA

Abstract

Stroke therapy has entered a new era highlighted by the use of endovascular therapy in addition to intravenous thrombolysis. However, the efficacy of current therapeutic regimens might be reduced by their associated adverse events. For example, over-reperfusion and futile recanalization may lead to large infarct, brain swelling, hemorrhagic complication and neurological deterioration. The traditional pathophysiological understanding on ischemic stroke can hardly address these occurrences. Accumulating evidence suggests that a functional cerebral venous drainage, the major blood reservoir and drainage system in brain, may be as critical as arterial infusion for stroke evolution and clinical sequelae. Further exploration of the multi-faceted function of cerebral venous system may add new implications for stroke outcome prediction and future therapeutic decision-making. In this review, we emphasize the anatomical and functional characteristics of the cerebral venous system and illustrate its necessity in facilitating the arterial infusion and maintaining the cerebral perfusion in the pathological stroke content. We then summarize the recent critical clinical studies that underscore the associations between cerebral venous collateral and outcome of ischemic stroke with advanced imaging techniques. A novel three-level venous system classification is proposed to demonstrate the distinct characteristics of venous collaterals in the setting of ischemic stroke. Finally, we discuss the current directions for assessment of cerebral venous collaterals and provide future challenges and opportunities for therapeutic strategies in the light of these new concepts.

*Corresponding author at: Department of Anesthesiology, Loma Linda University, 11041 Campus St, Risley Hall, Loma Linda, CA 92354, USA., johnzhang3910@yahoo.com (J.H. Zhang). **Corresponding author at: Department of Neurology, The 2nd Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, 310009, China, lm99@zju.edu.cn (M. Lou).

Conflicts of interest
None.

Keywords

Cerebral venous system; Cerebral venous collaterals; Endovascular therapy; Ischemic stroke

1. Introduction

Since t-PA was first introduced decades ago, (Zivin et al., 1985), limited groundbreaking news about treating ischemic stroke had emerged in spite of numerous basic and clinical studies, until 2015. In patients with large artery occlusion, the superiority of endovascular therapy over intravenous t-PA alone has been revealed recently by five randomized clinical trials (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial (MR CLEAN)(Berkhemer et al., 2015), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial (ESCAPE)(Goyal et al., 2015), Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial (SWIFT PRIME) (Saver et al., 2015), Extending the Time for Thrombolysis in Emergency Deficits Intra-Arterial trial (EXTEND-IA) (Campbell et al., 2015b), Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to an Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom onset (REVASCAT) (Jovin et al., 2015)). It has been reported that, compared with intravenous t-PA alone, the absolute benefit of endovascular therapy, with regard to the returning to functional independence, can reach 13.5 to 31 percent (Furlan, 2015). Undoubtedly, ischemic stroke therapy has entered a new era highlighted by the application of endovascular therapy (Lapchak and Zhang, 2016; Linfante and Cipolla, 2016).

It is noteworthy that, in most of these trials, arterial collateral had been considered as a critical predictor of outcome or determinant criteria for therapeutic selection (Boltze and Ayata, 2016; Campbell et al., 2015b; Henninger and Fisher, 2016; Liebeskind, 2014). It was even suggested that the success of recanalization is largely determined by the selection of the patients with good collateral flow (Campbell et al., 2015a; Pennypacker et al., 2017). However, there is also evidence denying that arterial collaterals serve as an outcome predictor after recanalization. In clinical practice, it is not unusual to see a large ischemic zone despite good arterial collaterals (Campbell et al., 2013). Moreover, long-existed enigmas such as non-reflow phenomenon, luxury perfusion and futile recanalization, are now calling for even more attention, since they may lead to progressive infarction, brain swelling or hemorrhagic complication (Campbell et al., 2013; Cho et al., 2015; Henninger and Fisher, 2016). A key possibility is that not only the arterial side but both arterial and venous collaterals, are involved in the outcome in a dynamic and panoramic way, therefore, evaluation of the venous side of collateral circulation is now extremely urgent.

There are several fundamental questions to be answered: Are there other confounding factors besides arterial collaterals that affect the recanalization outcome? Is the cerebral venous system involved in reperfusion injury? Do cerebral venous collaterals exist and how are cerebral venous collaterals defined? We are not denying the importance of arterial perfusion and collateral, but want to call for a broadened vascular perspective that

incorporates the cerebral venous system, in order to overcome persistent barriers to improved post ischemic stroke outcomes.

2. Anatomy of the cerebral venous system

For over a century, the cerebral venous contribution to the brain diseases were far less concerned than arterial structures. It is from late 19th century to latter part of 20th century, adequate venous schematic description of cerebral venous anatomy has been provided. In this section, we described the traditional classification and microstructure of the cerebral venous system, mainly based on anatomic findings.

2.1. The traditional classification of the cerebral venous system

It was not until the late 19th century that literatures started to describe about the cranial and vertebral venous anatomy (Andeweg, 1996; Cruveilhier, 1837; Henle, 1868). Traditionally, the cerebral venous outflow had been assumed to include two different groups: the superficial group (Fig. 1) and the deep group (Fig. 2), based mainly on embryological findings (Andeweg, 1999; Schaller, 2004).

2.1.1. The superficial veins—The superficial veins, located on cortical surface, mainly drain blood from the cortical and subcortical areas into four groups of major veins or bridging veins: (1) superior sagittal group that drains into the superior sagittal sinus; (2) sphenoidal group that courses to the sphenoparietal sinus and cavernous sinus; (3) falcine group that collects venous blood to the vein of Galen, inferior sagittal sinus and straight sinus; (4) tentorial group that comprises of the tributaries of the sinuses around the tentorium cerebelli, the transverse sinuses, and the superior petrosal sinuses (Fig. 1) (Kilic and Akakin, 2008; Rhoton, 2002).

The superior sagittal group mainly includes the cortical veins, collecting blood from the superior part of the frontal, parietal and occipital lobes, as well as the rostral part of frontal lobe (Andeweg, 1996, 1999; Kilic and Akakin, 2008; Rhoton, 2002; Schaller, 2004). These cortical veins are usually small and attached on the surface of the cortex, and may empty into the bridging veins in the subdural space or pass directly into the superior sagittal sinus (Andeweg, 1996, 1999; Kilic and Akakin, 2008; Rhoton, 2002; Schaller, 2004). The sphenoidal group is usually composed of the terminal tributaries of the superficial Sylvian vein and drains part of the frontal, parietal and temporal lobes adjoining the sylvian fissure (Andeweg, 1996, 1999; Kilic and Akakin, 2008; Rhoton, 2002; Schaller, 2004). This group forms anastomosis with the midline bridging veins on one side and with juxta-basal temporal veins on the other side (Schaller, 2004). The tentorial group includes the vein of Labbe, and is responsible for draining the lateral and basal surface of the temporal lobe, as well as the basal face of the occipital lobe. The falcine group wraps around the corpus callosum, upper brainstem and the cortical area around the limbic lobe. The major veins contained in this group drain into the internal cerebral veins, basal veins, the vein of Galen and their tributaries (Kilic and Akakin, 2008; Rhoton, 2002).

Briefly, veins of the lateral hemispheric convexities mostly drain along three major routes: (1) superior sagittal sinus (most Trolard); (2) sphenoparietal sinus or directly to the

cavernous sinus (mainly through Sylvian vein); (3) the transverse sinus (with the prominent branch named Labbe). Each of these routes is determinant and irreplaceable, while communications among them make the distribution of venous blood varied individually and remained to be explored.

2.1.2. The deep venous system—The deep venous system consists of channels surrounding the third and lateral ventricular walls or the basal cisterns and consists of the subependymal veins, internal cerebral veins, basal veins, the vein of Galen and their tributaries (Fig. 2). Some researchers grouped these veins as (1) ventricular group which is responsible for draining the walls of the ventricles, and (2) cisternal group composed of the veins draining basal cisterns (Kilic and Akakin, 2008; Rhoton, 2002). Other researchers have been inclined to view the medullary veins as critical components in deep venous system (Schaller, 2004).

The ventricular veins distribute at basal ganglia, internal capsule, thalamus, septum pellucidum, fornix, and deep white matter (Andeweg, 1996, 1999; Kilic and Akakin, 2008; Rhoton, 2002; Schaller, 2004). Generally, they are responsible for draining the frontal horn and the body of the lateral ventricle emptying into internal cerebral vein, which also receives tributaries from the thalamus and the third ventricle. Additionally, they drain the temporal horn and the atrium of lateral ventricle and then course into basal vein.

The cisternal group drains areas in the frontal part of the third ventricle, the chiasmatic, interpeduncular, crural, ambient and quadrigeminal cisterns. The main members in this group are the basal vein and the vein of Galen (Andeweg, 1996, 1999; Kilic and Akakin, 2008; Rhoton, 2002; Schaller, 2004). The basal vein plays a critical role in the deep venous system. The deep middle cerebral vein, insular veins, peduncular veins are major tributaries draining into the basal vein, with the anterior communicating vein joining bilateral anterior cerebral veins (Schaller, 2004).

The other participator the medullary veins, or so-called intracerebral veins can be divided into superficial medullary veins and deep medullary veins. It is supposed that they drain from cortex to the depth of 1–2 cm of white matter or from the 2 cm under the cortex to the subependymal veins, respectively (Andeweg, 1999; Schmidek et al., 1985).

2.1.3. The veins draining the posterior fossa—Venous drainage in posterior fossa exists through (1) galenic group including precentral, superior vermian and anterior, posterior mesencephalic veins, (2) petrosal group mainly drains into superior petrosal sinus, and (3) tentorial group represented by inferior vermian vein (Kilic and Akakin, 2008).

2.2. The microstructure of the cerebral venous system

Within grey matter, capillaries drain into venules less than 20 μm diameter. These venules converge at almost the right angles, and join larger venules (Schmidek et al., 1985). As the caliber increases, the venules lead toward the cortical surface intersecting at right angles, with the intracortical veins (Andeweg, 1996; Bar, 1980). These intracortical veins often extend the full depth (about 3 mm) of the cortex, and may connect with the intracerebral medullary veins (Schaller, 2004). The principal intracortical veins are usually surrounded by

several intracortical arterioles, connecting with each other by forming pial vascular-anastomosis on the convexity in a two-dimensional pattern spaced about 300–500 μm apart (Schaller, 2004). In some studies, although not settled, the arteriovenule anastomosis were also involved in this pial vascular network (Bar, 1980).

Unlike arterioles having three layers (endothelium, media and adventitia), the wall of venules is only composed of an endothelial cell layer, covered loosely by pericytes in the outer surface facing parenchymal or the Virchow-Robin Space (Schmidek et al., 1985; Ushiwata and Ushiki, 1990). According to the different calibers, the venules can be classified into postcapillary venules (8–30 μm), collecting venules (30–50 μm), and muscular venules (50–100 μm) which, though, have smooth muscle fibers scarcely (Schmidek et al., 1985; Ushiwata and Ushiki, 1990). Smooth muscle cells are rarely reported to be seen in human cortical or meningeal veins with the diameter less than 200 μm (Schmidek et al., 1985). Perivascular collagen bundles and so-called “stellate cells” (indicating pericytes having long process interwoven with adjacent cells and forming basket-like appearance surrounding veins) are probably responsible to support and maintain the venous luminal rigidity (Attwell et al., 2016; Schmidek et al., 1985; Ushiwata and Ushiki, 1990). Decades ago, using scanning electron microscopy, Ushiwata et al. found that “stellate cells” formed a dense network to provide veins with great volume capacitance (Ushiwata and Ushiki, 1990). This may be partly explained by the founding by Edvinsson et al., that an abundant network of sympathetic adrenergic nerve fibers interwoven with these “stellate cells” (Edvinsson et al., 1983).

3. The regulatory mechanisms of the cerebral venous system

Different from the cerebral arterial system, the venous system in brain regulates the outflow of blood in several different ways, mainly including passive regulatory model under increased parenchymal cerebral pressure; sympathetic nerve control due to the abundant sympathetic nerve fibers distribution in veins; and the Windkessel effect, meaning the transmission of pulse oscillation from the arterial side. In these ways, venous system plays important role in maintaining homeostasis of cerebral perfusion, constant intracranial pressure in physiological and pathological settings.

3.1. The Starling resistor model—the passive regulatory mechanism

The Starling resistor model was first proposed by Starling et al. in an isolated heart model (Knowlton and Starling, 1912). Later, scientists found that the Starling resistor model also shed light on the modulatory mechanism of severe brain injury (Gustafsson and Rossitti, 1995; Lofgren, 1973; Luce et al., 1982). Ordinarily, the intracranial pressure is dependent on arterial blood pressure, which is quantitatively dependent on the coordinated action of cerebrovascular resistance, i.e. arteriolar and venous resistance (Gustafsson and Rossitti, 1995). Since the arteriolar resistance normally adapts rapidly by vasoconstriction or vasodilation to different perfusion pressures, the venous resistance remains stable in normal situations (Gustafsson and Rossitti, 1995; Kilic and Akakin, 2008). However, when the autoregulatory response of the arteriolar network is abolished, through reaching the maximum vasodilation or vasoconstriction, this arteriolar resistance becomes constant and

the resistance of subarachnoid veins changes significantly (Gustafsson and Rossitti, 1995; Hallenbeck and Bradley, 1977). This is illustrated as a collapsible tube with pressure at the inflow end (P_i), pressure at outflow end (P_o), and pressure surrounding the tube (P_e). When $P_i > P_e > P_o$, the tube is constricted at the outflow end, and the driving pressure perfusing the tube amounts to $P_i - P_e$ (Luce et al., 1982; Permutt and Riley, 1963).

This “Starling resistor model” also characterized the situation when intracerebral pressure is elevated, that the blood flow perfusion in capillaries varied from usual. There the driving force is generated by the difference between arteriolar inflow and the transmural pressure close to the venous outlet, rather than the gap between arteriolar and venous pressure (Hallenbeck and Bradley, 1977; Permutt and Riley, 1963). Based on the lack of smooth muscle cells in veins, this model indicates that the veins would be compressed when transmural pressure exceeds venous pressure, regardless of the inflow pressure. This theory is supported by evidence that the pressure within the large cortical veins rises progressively with increasing intracranial pressure in a linear fashion, since the extraluminal pressure deforms the veins and raises the venous resistance (Johnston and Rowan, 1974). Some compressible intradural proportion of venous structure exists, some are termed “lacunae” connecting meningeal veins with dural sinuses and some are “bridging veins” emptying cortical veins into dural sinuses (Rhoton, 2002; Yada et al., 1973; Yamashima and Friede, 1984). In fact, these bridging veins are not only formed on the lateral, but also on the medial or inferior area of the brain surface. In these areas, the cortical veins are terminated by the existing subarachnoid space and crossing the subdural space where they transmit to the bridging veins and finally empty into the dural sinuses (Rhoton, 2002). Full of cerebral spinal fluid (CSF) in these subdural spaces, where the elevated intracranial pressure is transmitted by the fluid directly and the bridging veins and lacunae are thus easily affected. Since the dural sinuses are surrounded by bony structures, the pressure in the dural sinus largely remains in a constant range. In contrast, the venous pressure changes in the subdural spaces due to the compressible nature of bridging veins and lacunae. Therefore, the venous pressure decreases sharply in the bridging veins and lacunae before entering dural sinuses. This phenomenon is called “venous waterfall” (Gustafsson and Rossitti, 1995; Magder, 1990; Permutt and Riley, 1963). In global intracranial hypertension, since the bridging vein or the lacunae was compressed before entering superior venous sinus, engorgement of the upstream—cortical veins were observed (Luce et al., 1982; Rossitti, 2013; Yada et al., 1973). On magnetic resonance venography (MRV) and digital subtraction angiography (DSA), it can be demonstrated as the “outflow segment cuff” under elevated intracranial pressure, which showed significant constriction of the bridging veins that connect with the superior sagittal sinus (Chen et al., 2012; Si et al., 2008).

3.2. The sympathetic nerve control—the active regulation

The venous wall is wrapped with rich plexuses of sympathetic nerve fibers. The debate about venous contraction occurring under regular sympathetic control, is ongoing (Chen et al., 2015; Kulik et al., 2008). However, under pathological situations, for example in the circumstance of hypercapnia and acute hypertension, the significant contribution of sympathetic control of venous side has already been supported by series of experiments. (Edvinsson et al., 1983; Mayhan et al., 1987). Moreover, the highly interwoven pericytes

surrounding venules were also reported constrict strongly under stimulation (Edvinsson et al., 1983; Ushiwata and Ushiki, 1990). It is assumed in venous autoregulation, that the sympathetic control may be especially critical rather than other traditional factors, and these other factors include cerebral metabolism, endothelium function and myogenic response, which are important in arterial regulations (Auer et al., 1981; Schmidek et al., 1985). Least evidence has been found supporting the influence of the myogenic response due to the lack of smooth muscle cells in veins. To differentiate between passive collapse and the constrictive response activated by sympathetic stimulation, Schmidek et al. designed an experiment showing a more rapid response in venules and veins consistent with arterial constriction by sympathetic stimulation, which can be abolished by blocking α -receptors (Schmidek et al., 1985).

In pial veins with small caliber (approximately 50 μ m) coursed in the adventitia and parallel with the vessel lumen with occasional branching. In contrast, in larger pial veins (with caliber of approximately 200 μ m), nerve fibers containing putative neurotransmitters, with noradrenaline as the most abundant, formed fine networks in the vessel wall (Edvinsson et al., 1982). Around the cerebri magna vein, even a dense plexus of fine varicose nerve fibers has been observed, which indicating that the nerve fiber distribution mainly dependent on the venous caliber (Edvinsson et al., 1983). Noteworthy, also only large veins with caliber beyond 200 μ m may sometimes present regular smooth muscle cells, and the pericyte may form long and interlaced process outside the vessel wall (Edvinsson et al., 1983; Ushiwata and Ushiki, 1990). In this context, it is not surprising the cervical sympathetic stimulation results in 15% constrictions of pial veins, which provides further evidence of the possible importance of noradrenergic nerve fibres in modifying cerebral venous capacitance (Auer and Johansson, 1981).

With the 70–80% of total cerebral blood volume capacity in the venous system, sympathetic nerve stimulation squeezes the veins to discharge considerable blood flow out, contributing to the rapid cerebral blood volume decrease. And this response can be reversed by sympathetic thrombectomy (Auer and Johansson, 1981; Edvinsson et al., 1983). Under the situation of acute hypertension, which is characterized by abrupt elevation of arterial blood pressure, the venous sympathetic activation slows down the blood outflow into the venous side and thus prevent the sudden impact to the venous vessel wall, and attenuated the disruption of venule side of blood-brain barrier (BBB) (Mayhan et al., 1987). This venous constriction was abolished by sympathectomy procedure, and proved that protection under elevated blood pressure was largely due to the sympathetic control of the venules rather than elastic arteriolar resistance (Mayhan et al., 1987). The regulation of the cerebral venous system by sympathetic nerve control may play a role in attenuating intracranial pressure, cerebral edema and hemorrhagic transformation.

3.3. The windkessel effect – the communication of arteries, veins and CSF regulation

In terms of arterial “Windkessel effect”, the venous system along with CSF provides a cushion effect. That is, the pulses from the heart produce oscillating blood flows in elastic arteries and decay in the venous system (Min et al., 2011). By the “Windkessel mechanism”, the excess arterial blood stored during diastole and is mainly accommodated in the cerebral

capillary bed, thus the rate of venous blood-flow leaving the cranium decreases (Ambarki et al., 2007). This implies that during this period, the volume of venous blood in the cranium probably keeps steadily increasing, whereas more is ejected out of cranium during systole (Ambarki et al., 2007; Beggs, 2013). Discharge of cerebral blood from subdural bridging veins and lacunae is in fact the rate-limiting step, which forms the “venous waterfall” and control the rate of pushing blood into the dural sinuses and then jugular veins (Beggs, 2013). This step is also greatly affected by the CSF pressure in the subdural space. During a cardiac cycle, the rate of the arterial outflow and venous inflow changes due to the pulse, and so is the CSF volume in the cranium. When a deficiency occurs in CSF absorption following venous hypertension, venous pulsation greatly increases and generates backward propagation towards the capillaries and even arteries. This leads to impaired compliance of vessels and even of the brain tissue, which may further develop arteriosclerosis (Bateman, 2007; Bateman et al., 2008; Beggs, 2013).

3.4. The homeostasis between arterial and venous regulation in physiology and pathophysiology settings

The abovementioned studies have emphasized the importance of venous drainage and modulatory mechanisms for maintaining cerebral perfusion. Other studies, in the settings of venous obstruction, reflects the cerebral perfusion deficiency when the venous drainage was impaired (Inao et al., 1997). In one study, blood flow velocity in the superior sagittal sinus was found to reflect cerebral blood flow (CBF) in both normal volunteer and neurosurgical patients (Inao et al., 1997). Moreover, the occlusion of the superior sagittal sinus posterior to the Rolandic vein after 24 h was shown associated with a significant rCBF reduction in the related vascular territory (Schaller et al., 2003). As the novel concept of the “vascular neural network” introduced by Zhang et al., homeostasis in the brain is maintained by the comprehensive components, of both arteries and veins, and the adjacent components such as glial cells and autonomic nerves. Their coherent functional response in physiological and pathophysiological conditions determines the regular work of brain (Zhang et al., 2012). The following evidence may help to illustrate the homeostasis between the arterial and venous vasculatures.

3.4.1. The micro-vascular unit composing arterioles and venules—In microcirculation, the hexagonal unit in the cortex was discovered long before (Andeweg, 1996; Bar, 1980). This so-called vascular unit, which encompasses a perpendicular central vein (intracortical vein) with surrounding companion arterioles, was first discovered by an anatomic study (Bar, 1980). However, it is not until recently that the homeostatic module between the arterioles and venules in the cortex was demonstrated by novel imaging techniques (Aksenov et al., 2015; Dai et al., 2016; Guibert et al., 2012; Harel et al., 2010). Based on high-resolution 3D functional MRI with exogenous contrast agent monocrystalline iron oxide (MION), a fundamental energetic and blood perfusion unit was perfectly observed, that centered on the principle perpendicular vein and surrounded by a set of arteries in the opposite direction (Bolan et al., 2006; Guibert et al., 2012; Harel et al., 2010). In physiological setting, rather than distributed evenly, 80% of blood in one arteriole was drained by two nearby venules, implicating a one-to-two arterial-venous coupling in the cortex (Guibert et al., 2010). In this unit, the arteriolar and venular territories shared

couplings over a long-distance in the cortical area and formed convergence into larger vessels (Guibert et al., 2012). This collaboration between the cortical arteriole and venule is mainly determined by their distribution in space and followed the principle of proximity (Guibert et al., 2012).

3.4.2. The homeostasis maintained by structural potential—The abundant collateral systems, containing arteriole and venule anastomosis sustains the regional perfusion by several means (Guibert et al., 2012; Hoffmann et al., 2016). Firstly, blood flow reversion was most commonly observed for compensation (Schaffer et al., 2006). A sufficient collateral perfusion requires subsidiary routes of both arterial and venous vasculature for redistributing blood flow (Faber et al., 2016). The coupling of arterioles and venules obeys the ratio of 1:2. The abundance of arteriolar collateral gradually increases from surface to deep cortex, so do the venules (Guibert et al., 2012). This suggests that, the deeper a vascular segment is situated, the larger the number of feeding arteries and venules as well as the overall compensatory potential (Avirame et al., 2015; Guibert et al., 2012). When an ischemic event occurred, 50% blood flow of one occluded arteriole would be compensated by neighboring arterioles and every principle venule was able to collect from 14 arterioles on average (Guibert et al., 2012). In this situation, the rule of priority in draining the closest arteriole is modified. Given the extensive anastomotic network at the cortex surface between arterioles, venules and arterio-venule, the compensatory arterioles and venules can reach a range far beyond the nearest collaterals (Feuerstein et al., 2016; Guibert et al., 2010, 2012). According to these findings, intracortical perfusion is emphasized by the settled functional unit in normal conditions and a great potential for collateral supply beyond nearby units during the ischemic ictus.

3.4.3. The homeostasis of intracranial perfusion pressure maintained by passive venous regulation—Aside from the change of venous routes in microcirculation, venules and small veins also function actively and passively by controlling lumen size as a supplementary modulator for regional blood flow in hypo- or over-perfusion settings (Budohoski et al., 2013; Mayhan and Heistad, 1986). In the study designed by Bragin et al., when intracranial hypertension of rat was induced and cerebral perfusion pressure (CPP) decreased, a transition from capillary to microvascular shunt (MVS) flow was observed. Additionally, aggravated tissue hypoxia and impairment of BBB ensued and led to cerebral edema (Bragin et al., 2013). It is understood that with high intracranial pressure (ICP), the venous system outflow in the subdural space is modulated similar as the Starling resistor model. In this setting, the high cranial pressure compressed the bridging veins and lacunae before entering dural sinuses and thus decreased venous outflow (Murtha et al., 2015). Although this may help to keep the cortical veins open, prevent abrupt pressure gap between arterial and venous side and therefore maintain the cerebral perfusion, and reduce the disruption of BBB, it may also bring about the risk of increased intracranial hypertension exacerbated by blood retention.

3.4.4. The homeostasis of blood flow redistribution maintained by active venous regulation—Another determinant mechanism involved in arterial and venous homeostasis is neural control (Kuffler and Potter, 1964; Kulik et al., 2008). Growing

evidence increasingly supports that astrocytes play multiple roles in regulating cerebral functions, not only by providing structural support and regulating transmitters, but also modulating the vascular resistance and the blood flow (Attwell et al., 2010; Jeanneret and Yepes, 2016; Koh and Park, 2017; Takano et al., 2006). Moreover, the sympathetic and parasympathetic autonomic fibers are innervated extensively in both arterial and venous vasculatures, regulating the vasoconstriction or vasodilation under varied conditions (Kulik et al., 2008).

It is known that cerebrovascular resistance largely resides in the superficial and penetrating cortical circulations (Gustafsson and Rossitti, 1995; Heistad et al., 1980), whereas the venous resistance in parenchymal is located mainly in the bilateral centrum semiovale, where the intracerebral veins (medullary veins) traverse (Andeweg, 1996). An “arterial bottleneck” and “venous watershed” was identified between the deep white matter and subcortical white matter (Andeweg, 1999; Xu et al., 2008). This characteristic makes it possible that relative hyperperfusion can be confined in the sub-cortex and cortex. Therefore, the blood flow redistribution cross subcortical and deep white matter requires relative complicated regulations. When blood flow demands in the deep white matter increase, the pial arterioles must dilate first to enhance flow to the deep circulatory area, and activate the anastomosis across the “arterial bottleneck”. Meanwhile, similar response occurs in the venous side that the caliber of medullary veins is enlarged to enhance outflow and to prevent congestion in the deep brain (Andeweg, 1999; Xu et al., 2008). This coordinated response between superficial and deep parenchymal parts of cerebral circulation is pivotal to meet the demands of brain tissue. Autonomic nerve control, metabolic stimulus, and astrocytes signalings are probably involved in these interwoven mechanisms (Zhang et al., 2012).

In fact, the view that veins only passively maintain and drain the arterial inflow is now rather rudimentary. Change of venous pressure also influences the arterial infusion. Nguyen et al. found that, during occlusion of the cortical ascending venule, the regional blood flow decreased, leading to upstream vessel dilation, until the venous anastomosis was established (Nguyen et al., 2011). Wei and his colleagues observed that vasodilation of pial arterioles was the major response to increased venous pressure (Wei and Kontos, 1982). These observations indicate that venous collaterals work together with arterial collaterals to maintain the brain circulation.

Although under normal physiologic conditions, arterial autoregulation is the main mechanism modulating the stability of blood flow (Bragin et al., 2013; Hill et al., 2015; Kontos et al., 1978), veins play a critical role in modifying blood flow during arterial autoregulation failure (Kulik et al., 2008; Mayhan and Heistad, 1986; Mayhan et al., 1987) (Fig. 3).

4. Venous visualization by varied image modalities

Various imaging models are available for evaluating dura venous and cerebral veins. DSA, an invasive imaging method, is the gold standard for the diagnosis of intracranial venous diseases. Currently, various advanced imaging techniques are available, using either non-

enhanced or contrast-enhanced methods (Forster et al., 2016). Here we briefly describe their characteristics and possible applications (Table 1).

4.1. Digital subtracted angiography (DSA)

DSA is a 2-dimensional-signal planar imaging, which is the most traditional and reliable imaging technique for evaluating dura venous sinuses and cerebral veins. DSA is currently well-accepted as the diagnostic standard of intracranial venous disease, because of the widespread availability, excellent spatial resolution, and clinician familiarity. However, it is still an invasive procedure with associated risks, such as artery dissection, microemboli in distal vessels, vasospasm and hematoma at the puncture site. Additionally, the inevitable risk of radiation exposure, allergic and contrast-associated nephrotic injury are major flaws for this method.

4.2. Time-of-Flight magnetic resonance venography (TOF-MRV)

TOF-MRV is a noninvasive and non-contrast angiographic technique, which visualizes hemodynamics through the differences of magnetization between flowing blood and stationary tissue (Huston and Ehman, 1993; Lim and Koktzoglou, 2015; Mandeville et al., 2017). Its exhibited advantage for detecting slow flow, readily demonstrates the dura venous sinuses and large cerebral veins, including superior and inferior sagittal sinus, straight sinus, transverse sinus, sigmoid sinus and the vein of Galen. The TOF-MRV ability to assess deep veins such as intracerebral veins, thalamostriate veins and some cortical veins, is insufficient. Moreover, due to saturation effects, TOF MRV is insensitive to detect in-plane flow. Additionally, tissues with short T1 values like fat, and tissues with abundant methemoglobin, tend to mimic flow signal, resulting in high background noise in TOF-MRV and adversely influencing- the quality of imaging.

4.3. Phase contrast magnetic resonance venography (PC-MRV)

Phase-contrast MR venography uses blood flow velocity-based phase shifts to demonstrate blood flow, by contrasting the flow-encoded data set with flow-compensated reference data set (Huston and Ehman, 1993; Lim and Koktzoglou, 2015). In visualization of intracranial venous structures, PC-MRV is comparable to TOF-MRV techniques. Nonetheless, it more efficiently excludes background noises, and can additionally quantify flow rate as well as the flow direction (Liauw et al., 2000). However, PC-MRV requires a longer acquisition time than TOF-MRV due to the requirement of multiple image sets. Though 2D PC-MRV is commonly used with a short acquisition time, image quality is sacrificed. Due to the visualization limitations of small veins and veins in complex structures, TOF-MRV and PC-MRV are only preliminary methods for screening intracranial disease.

4.4. Susceptibility-Weighted imaging (SWI)

SWI utilizes the magnetic susceptibility artifacts due to local inhomogeneity of the magnetic field (Filippi et al., 2014; McCabe, 2016; Muir and Macrae, 2016; Xing et al., 2017). Signal modification is mainly dependent on the amount and magnetic properties of molecules, and the structures of lesions. Deoxyhemoglobin with unpaired electrons in veins is a paramagnetic substance that generates a local nonuniform magnetic field, resulting in rapid

dephasing of proton spins in SWI sequences (Kudo et al., 2016). Thus, SWI allows clear visualization of cerebral veins, even small veins like medullary veins (Fig. 4). Depending on the blood oxygen level dependence (BOLD) effect, it is feasible to detect changes in venous blood oxygenation based on SWI. SWI has been applied in clinical practice as a venographic MR method for decades, and most recently has been adopted to diagnose venous malformations, occult venous injuries, demyelinated diseases, as well as trauma and tumors (Filippi et al., 2014; Reichenbach and Haacke, 2001).

4.5. Black blood magnetic resonance angiography

This novel technique is based on intentional suppression of signal intensity from flowing blood and simultaneous maximization of signal intensity from stationary tissue (Melhem et al., 1997; Xie et al., 2017). Relative to the surrounding brain tissue normal intracranial vessels in this imaging appear dark. Black blood MRA provides significant advantage over TOF-MRA with regard to in-plane and intra-volume saturation as it does not rely on inflow effect. Vessels of narrow caliber with retrograde or slow flow can still be well visualized on it. Black blood MRA is effective in detecting and even quantifying cerebral venous thrombosis because the thrombus is visible with a hyper-intense signal relative to the intraluminal blood and surrounding brain tissue on black blood MRA. Moreover, the technique is free of risks for allergic reaction and radiation exposure. Recently, it has also been applied to exhibit characteristics of intracranial atherosclerotic plaques (Park and Kim, 2010; Xie et al., 2017).

4.6. Contrast-enhanced 3-dimensional magnetic resonance venography(CE-MRV)

CE-MRV is a non-invasive imaging technique requiring a gadolinium containing contrast agent. The increased signal intensity in CE-MRV is due to the paramagnetic effect of gadolinium through shortening the intravascular T1 relaxation time (Reichenbach et al., 2001). The signal change on CE-MRV is not affected by blood flow velocity. Compared with PC-MRV and TOF-MRV, CE-MRV is superior in visualization of intracranial venous structures. In addition to superior sagittal sinus and sigmoid sinus, venous sinuses including the superior and inferior petrosal sinuses, sphenoid sinus, cavernous sinus, and cortical veins and internal cerebral veins can be clearly seen by CE-MRV (Fig. 5). This technique has high diagnostic value in current venous disease imaging due to the limited radiation exposure.

4.7. Contrast-enhanced 3-dimensional CT venography(CTV)

CTV is another noninvasive cerebrovascular imaging technique which requires iodinated contrast medium (Leonhard and Michalik, 1982). As a “lumenogram” with contrast enhancement of the intravascular space, it is comparable with CE-MRV in visualization of intracranial venous structures (Fig. 6) and provides an alternate technique if there are contraindications to MRV. The time of image acquisition is short and motion-related artifacts are reduced with CTV. Additionally, CTV helps to avoid venous injury during surgery for intracranial neoplasm. However, because of radiation exposure and the possible influence with the fetus thyroid, its application is limited in pregnant women and children (Ibaraki et al., 2015).

4.8. Time-resolved contrast-enhanced 3-dimensional magnetic resonance venography or CT venography

Repeatedly acquired images of contrast agent passing through the veins allows production of a 4D MRA image. It is comparable to CE-MRV in the visualization of the normal structural characteristics of the cerebral venous system (Farb et al., 2009; Petkova et al., 2009). In addition to the information of mono-phasic contrast-enhanced angiography, it provides information on the bolus transit time, thus imitating a classic catheter angiogram. It is especially recommended when the timing of cerebral venous drainage is of interest, such as arteriovenous malformations and dural arterio-venous fistulas. In fact, similar dynamic 4D CT venography can also be re-constructed from CT perfusion (Zhang et al., 2016).

5. The importance of identifying cerebral venous system alterations in different neurological disorders

Veins, are mostly considered as a mere reservoir and drainage system for blood, while its dynamic changes during varied physiological or pathophysiological settings are insufficiently explored. On the other side, increasing puzzling situations are emerging in clinical practice, which are substantially correlated with cerebral venous systems.

5.1. The venous system plays a role in space-occupying lesion-related cerebral edema

For decades, the cerebral venous system seemed to be a minefield for the neurosurgeon. A pile of evidence suggests that some determinant venous occlusion may result in severe symptoms including seizures, hemiplegia, aphasia, coma and even death. Therefore, neurosurgeons have emphasized the importance of preserving venous vasculatures during operation, and special approaches have been invented to avoid venous injury (Sekhar et al., 2002). But with these modifications, fatal edema was still occasionally happen even following a small cortical vein damage (Ferroli et al., 2011). Retrospective studies of patients who underwent extensive brain swelling after meningioma resection, indicated that the clinical deterioration occurred after occlusion of presumably minor venous channels (Asgari et al., 2008). The authors suggested that brain edema may be due to venous infarction or possibly due to increased postoperative tissue permeability. This argument was unconvincing since the drainage territory by those minor veins was not so extensive, and there might be other reasons involved. Higgins et al. also reported a case of a patient who experienced severe bilateral hemispheric brain edema caused by one tentorial medium-sized meningioma, which was finally alleviated with venous sinus stenting (Higgins et al., 2008).

5.2. The venous system contributes to the vascular-related diseases

Sturge-Weber syndrome, a disease manifested with high frequency of seizures and subcortical white matter modifications, was traditionally considered as due to the telangiectasis in skin and brain. However, MRIs on children with Sturge-Weber syndrome showed significant deep vein engorgement and abnormal signal in semi-oval center, as well as perfusion-metabolic mismatch (Alkonyi et al., 2012). Given that regional perfusion-metabolic mismatch was correlated with the corresponding drainage of cortex via the deep venous system, the venous drainage pattern is implicated unfitting with parenchymal

perfusion demands, and thus result in venous congestion and highly irritated cortical neuron (Alkonyi et al., 2012; Bentson et al., 1971). Other neurological disorders, such as migraines, have been reported to be significantly related with venous drainage abnormality through primary or secondary pathways of the upper neck region (Koerte et al., 2011).

5.3. The vein-originated mechanisms involved in various non-vascular neurological disorders

Even neurological disorders that used to be assumed to have nothing to do with the vasculature, including multiple sclerosis and normal pressure hydrocephalus, now have been shown to involve venous hemodynamic mechanisms (Beggs, 2013). Interestingly, special MR sequence revealed that some neurological disorders, such as transient monocular blindness, panic disorder and transient global amnesia were correlated with transverse sinus hypoplasia (Han et al., 2016). Hence, it is now gradually being accepted that venous congestion and insufficiency not only affects the regional blood movement, but also the circulation of CSF, and overall brain metabolism and functional activity (Beard et al., 2015; Muir and Macrae, 2016).

Thanks to the remarkable advancement of imaging techniques and quantitative strategies, including MRV, SWI, black blood MRV, and so on, the delicate structures of cerebral venous system have become visible through non-invasive means (Barhoum et al., 2015; Bednarik et al., 2015; Bergonzi et al., 2015; Mandeville et al., 2017). These advanced techniques have demonstrated that deep medullary veins, cortical superficial veins, and even the venous sinus may play an important role in various neurological disorders (Zhong et al., 2016).

6. The importance of identifying cerebral venous system changes in ischemic stroke

Recently, more and more clinical practices revealed the involvement of cerebral veins in ischemic stroke. In this section, evidence about cerebral medullary veins, cortical veins and venous outflow from cranium is provided. Moreover, possible mechanisms involved are proposed.

6.1. The involvement of cerebral veins in ischemic stroke

It has been established that cerebral veins affect stroke outcomes (Yu and Yuan, 2016). In recent years, accumulating evidence have reinforced the importance of the cerebral venous system in stroke. Rather than a simplistic reservoir containing a large portion of cerebral blood volume (Andeweg, 1999), the venous capacity is indeed not passively dependent on merely blood infusion, or not a rigid outflow channel. As discussed above, veins are indispensable parts of the neurovascular network, fundamental in regulating and responding to cerebrovascular events. The required perfusion will not occur if the venous drainage is severely impaired (Liebeskind and Feldmann, 2016; Zhang et al., 2012).

6.1.1. Involvement of medullary veins—An association between ipsilateral prominence of medullary veins by SWI and poor outcome in ischemic stroke patients after 3 months was suggested (Yu and Yuan, 2016). This prominence of medullary veins usually

related higher proportion of hypoxia hemoglobin in veins and thus may be indicating more extensive and irreversible hypoxia in the affected area, which would later develop into more severe neurologic deficits (Yu and Yuan, 2016). Some may argue that, the contribution of cerebral veins to the outcome of ischemic stroke is merely determined by the arterial inflow. However, the growing body of evidence suggested the stroke outcome may be somewhat independently influenced by venous drainage, apart from the arterial inflow.

6.1.2. Involvement of cortical veins—Cortical veins are now found related with arterial collateral capacity. According to the follow-up imaging by Verma et al., that the extent of prominent cortical veins (PCV) which indicated venous congestion and reduced oxygen saturation, was reversely correlated with leptomeningeal arterial anastomosis. That means, less arterial collateral perfusion would affect the oxygen saturation in ipsilateral cortical veins (Verma et al., 2014). With dynamic CTA (dCTA), the delayed cortical venous filling was found excellently correlated with arterial collateral extent and perfusion rate (Bhaskar et al., 2017). A correlation among mismatch territory, infarct growth and the asymmetric prominent cortical or deep veins on SWI, was additionally proposed (Kao et al., 2012; Mucke et al., 2015).

Based on the combined measurement of extent and velocity of cortical venous filling, van den Wijngaard and his colleagues assessed the cortical venous filling on dCTA in patients suffering acute middle cerebral artery occlusion (MCAO), and found significant predictive value of dichotomized good or poor velocity and filling extent (<50% territory or not) of cortical veins draining into superior sagittal sinus for 3 months' outcome (van den Wijngaard et al., 2016). In this study, patients presenting with poor extent or longer venous filling time than median time, had poor outcomes. It is important to mention that the predictive value of the velocity and extent of cortical veins has superior prognostic value to the extent of arterial occlusion in this study (van den Wijngaard et al., 2016).

Parthasarathy et al. have tried to select some superficial and deep veins from CTA as indicators to predict 90-days outcome, and suggested that the venous drainage may be associated with arterial collateral and infarct volume in stroke patients with proximal arterial occlusion (Parthasarathy et al., 2013). In this study, they established a Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) score, which included the opacification of superficial middle cerebral vein, vein of Trolard, vein of Labbe, and basal vein of Rosenthal to identify the superficial and deep venous drainage status (Parthasarathy et al., 2013). And this score showed additional prognostic value in acute ischemic stroke patients (Parthasarathy et al., 2013). Later, they established a grading scale involving venous drainage and arterial anastomosis and found this scale was superior to those including only arterial collaterals (Parthasarathy et al., 2015). Several additional radiologic studies supported that increased arterial and venous phase information would lead to more accurate collateral evaluations (Beyer et al., 2015a, 2015b). It is therefore assumed that the opacification of venous system provides additional information of both the extent of arterial and venous collaterals and the actual perfusion through the microcirculation, given the unneglectable and coherent role the venous system plays in the ischemic event (Munuera et al., 2017).

Thus, the perfusion changes influenced by venous collaterals may be to some extent, independent of arterial inflow (Abud et al., 2005; Parthasarathy et al., 2013, 2015). Further evidence is gleaned from findings with the angiography-based balloon procedures evaluated for therapeutic occlusion of internal carotid artery for ischemic risk (Abud et al., 2005). If the delay of cortical venous opacification between the ipsilateral and contralateral hemisphere was longer than 4 s, a watershed infarction was still likely to occur, despite synchronous bilateral filling in arterial phase (Abud et al., 2005).

6.1.3. Involvement of venous outflow from the cranium—Besides the deep and cortical veins, other venous structures were referred to as confounding factors for stroke outcome. In a rat model of MCAO, the experimental group with an additional bilateral occlusion of external jugular veins demonstrated significantly larger infarct volumes than the MCAO only group (Yura et al., 1990). Similarly, case series observations of MCAO patients in clinical practice also revealed that hypoplasia or occlusion of the ipsilateral cranial venous drainage turned out to relate to higher risk of early fatal brain edema (Yu et al., 2009).

6.2. Probable mechanisms of venous changes in ischemic stroke-induced hypoperfusion

During ischemic stroke, the changes of venous circulation include: the morphological changes of the venous lumen due to active constriction or passive compression; neovasculature formation; and micro-emboli aggregation to obstruct the venules (Fig. 7).

6.2.1. The venous microemboli and clots during hypoperfusion—It was reported that white cells and platelets tend to accumulate largely in venules rather than in arterioles during ischemic stroke or other brain injuries, where these blood cells concreted together and adhered to the endothelium, forming microemboli (Altura et al., 2002; del Zoppo and Mabuchi, 2003; Jickling et al., 2015; Schwarzmaier et al., 2010). As indicated in a model of experimental rat traumatic brain injury, which was comparable with ischemic stroke, the microemboli were predominantly found in venules within 1 h of injury (Schwarzmaier et al., 2010). By high resolution in vivo imaging measurements, Altura and his colleagues were able to demonstrate increased leukocyte rolling, decreased leukocyte motion and enhanced leukocyte-endothelial wall adhesion (Altura et al., 2002). It has been proposed that, the levels of adherent factors including VCAM-1, ICAM-1 and VE-caderin were increased mainly in post-capillary venules after stroke, together with leukocyte trafficking receptors (Alexander et al., 2013; Altura et al., 2002; Ishikawa et al., 2004). Platelets, in addition, contribute significantly to the formation of microclots, which can be reversed through inhibition of integrin $\alpha\text{IIb}\beta 3$ (Abumiya et al., 2000; Xu et al., 2016; Yao et al., 2017). Fibrin provides frame construction for blood cells to fill in, helps stiff clots to develop, and adhere and deposit in the microvessels (Jeanneret and Yepes, 2016). The time course of this change was illustrated in the setting of acute ischemic stroke in animal studies, where microthrombi in venules were present within 30 min after acute reduction of CBF, (del Zoppo and Mabuchi, 2003; Schaller, 2004). The growth of the venous thrombi coincided with decreases in regional CBF (Wang and Feuerstein, 1995). The obstructed lumen of venules might re-open after arterial reperfusion with venous microemboli being cleared from the microcirculation within 2 h.

6.2.2. Venous stealing involved in ischemic core-penumbra—A “venous stealing” mechanism was proposed to explain the growing core compared with relative benign ischemic penumbra on a lumped-parameter model with two “Starling resistors” (Pranevicius and Pranevicius, 2002). In this model, parenchymal ischemia generated ischemic core and penumbra area shortly after the ischemic ictus. Since the external tissue pressure was higher in the ischemic core due to the cytotoxic and vasogenic edema, the vessel tended to collapse at the site closest to the venous end due to the higher intramural pressure, as “Starling resistor model” suggested. Thus, the penumbra zone kept receiving blood flow diverted from ischemic core until the penumbral venous pressure was increased to equal to the core external tissue pressure (Pranevicius and Pranevicius, 2002).

Additionally, a greater steal from collateral supply was likely to happen when the affected hypoperfusion territory was totally dependent on the collateral blood supply. Under this condition, because of the inherent high resistance of collateral inflow, more severe flow degeneration in the core occurs (Pranevicius et al., 2012). It is therefore explainable that in an experimental global ischemia model, reperfusion was hardly achievable when the intracranial pressure in the whole brain was elevated (Hallenbeck and Bradley, 1977).

6.2.3. The neo-formed venous structure—The collateral recruitment and neocollateral formation are induced after arterial obstruction (Chilian et al., 1990; Faber et al., 2014). Traditionally, the angiogenesis of arteries has drawn most attention, but in fact, the neo-formed collaterals can hardly be capable without the venous side. The recruitment of venous collaterals mainly includes the enlargement and elongation of the pre-existed veins, and the angiogenesis of venules microstructures. The enlargement and elongation of venous vasculature are probably due to the blood flow reversal rather than shear-stress change (Adamson et al., 2013). The shear stress change, however, would result in the arterialization of veins, which is characterized by innervation of peri-luminal smooth muscle cell recruitment (Faber et al., 2014; Schmidek et al., 1985). The neo-formed ring-shaped sinusoid-like venous structure was demonstrated by scanning electron microscopy in a rat model of cerebral cortical ischemia, viewed as venous collateral in microcirculation (Sbarbati et al., 1996). The arteriolar collateral was also observed at both the ventral and dorsal portion of the ischemic lesion in this model (Sbarbati et al., 1996). The smooth muscle can also enter the venous vessel wall which is terminated as arterialization (Faber et al., 2014). All these changes expand the venous drainage territory and strengthen the venous blood brain barrier.

6.3. The possible venous alteration in recanalization-related enigmas

6.3.1. The venous role in non-reflow phenomenon—The “non-reflow” phenomenon, referring to the failure of reperfusion despite successful recanalization, was considered as the main cause of recanalization without reperfusion (Ames et al., 1968; Soares et al., 2010). The cause of this phenomenon remains obscure. The potential reasons include microcirculation deficiency due to endothelial injury, perivascular swollen glial and distal emboli in capillary bed (Chiang et al., 1968; del Zoppo and Mabuchi, 2003).

Evidence suggests that insufficiency of venous drainage might be involved (Gerber et al., 2015). The “non-reflow” phenomenon, characterized by the lack of contrast flow to the

venous side while the arterial opacification is normal after endovascular therapy, (Gerber et al., 2015). As described in the “venous stealing” theory, the venous side of the vessel is likely to collapse due to the higher intramural pressure. In this setting, the more severe the ischemia is, the more serious edema would occur and the less blood flow will pass through the venous end. When the venous pressure in the infarct core is close to zero, the outflow side will be completely compressed and blood flow from collateral or successful recanalization will diverge to the penumbra rather than to the core, thus “no-flow” phenomenon emerges (Pranevicius and Pranevicius, 2002; Pranevicius et al., 2011, 2012).

Microemboli and blood cells also preferred to accumulate in capillary and venules instead of arterioles, adding to the risk of “non-flow” (Chen et al., 2015; Ishikawa et al., 2004; Kalogeris et al., 1999; Ritter et al., 2000). After recanalization, since the white cell and platelet accumulation are more significantly located in venules rather than in the arterioles and capillary, it is less likely for venules to gain sufficient perfusion (Ishikawa et al., 2004). Ritter et al.’s study observed a remarkably reduced shear rate in the venules, exemplifying the difficulty in perfusing the venous side (Ritter et al., 2000). In this context, although the recanalization seems successful and the arterial end can be visualized with contrast medium, the venous occlusion would still prevent blood flow from passing through lead to “non-reflow” (Al-Ali et al., 2015). The density of the occluded capillary bed in penumbra was much higher than that in the ischemic core 2 h following reperfusion in a stroke animal model (Liu et al., 2002). It may be presumed that the “non-flow” problem originates in the capillary bed and venules, while arterial inflow in the penumbra is relatively normal.

Futile recanalization, defined as an unfavorable outcome despite successful recanalization, is usually regarded to be closely associated with the non-reflow phenomenon (Gerber et al., 2015; Hussein et al., 2010). This partially contributes to the proposed “50% barrier”, where no more than 50% of patients would gain extra benefit from endovascular therapy compared with those receiving standard therapy, according to the current data (Al-Ali et al., 2015). Although some risk factors for futile recanalization were identified, such as high baseline NIH Stroke Scale (NIHSS), old age and pre-existing white matter lesions (Hussein et al., 2010), the potential contribution of venous circulation was still poorly investigated.

6.3.2. The contributions of venous early filling to stroke outcome—Another enigma often seen in endovascular therapy is the early filling of some specific veins in the arterial phase of angiography, which may share a similar mechanism with “luxury perfusion”, which means perfusion more than proper and easily lead to hemorrhage (Olsen et al., 1981). Whether the phenomenon of venous early filling indicates poor stroke outcome or hemorrhage remains controversial (Dorn et al., 2012). Its potential pathophysiological process is now considered to include: (1) regional hyperemia, and (2) arterio-venous shunting (Dorn et al., 2012; Marchal et al., 1996; Olsen et al., 1991). Favorable outcomes might occur if venous filling happens in the early phase such as 5–18 h after ischemic stroke (Marchal et al., 1996). In that case, the early filling of veins may indicate sufficient venous collateral around the infarct core (Marchal et al., 1996). If this venous filling showed up later, after approximately 5 days in stroke patients and 2 h in animal ischemic models, poor outcomes were anticipated (Dorn et al., 2012; Ohta et al., 2004). In addition, the early venous filling during endovascular therapy was suggested as a predictive sign for

hemorrhagic complication and indicated unsalvageable ischemic tissue, even with successful recanalization (Dorn et al., 2012; Ohta et al., 2004). A possible explanation was the formation of arterial-venous shunting and resultant insufficient perfusion of the ischemic area (Dorn et al., 2012). The actual perfusion across the capillary bed was decreased due to the relatively low resistance in the arterio-venular shunting, while the high flow passing the shunt easily transpired into hemorrhagic complications, given the thin-wall of the venous side (Ohta et al., 2004; Olsen et al., 1981, 1991).

It is speculated that early-onset “early venous filling” with transient, progressive growth of hyperemia is benign hyper-perfusion, indicating valid collateral compensation. While long-lasting “early venous filling” happened in late-phase of stroke implicates arterial-venous shunting and autoregulation dysfunction, adding to parenchymal hemorrhage risk (Heiss et al., 1997).

6.3.3. The role of veins in hemorrhagic complications related to reperfusion

—Mayhan et al., using fluorescent dextran in a rat model of acute hypertension, illustrated that it was the venule side that tended to suffer hemorrhagic changes due to BBB abruption and increased perfusion (Mayhan et al., 1987). Beyond the range of arterial autoregulation, sympathetic stimulation around venules would provide a protective effect by constriction of pial veins to prevent the abrupt increase in venous pressure (Edvinsson et al., 1983; Fernandez-Klett and Priller, 2015; Mayhan and Heistad, 1986; Mayhan et al., 1987). Adaptation usually plays a role in chronic hyper-perfusion status, and this protective mechanism prevents BBB disruption in the venule side. While in acute phase, this venous autoregulation has the possibility to fail. The abrupt increase of large amount of blood flow rush into the venous system and extensive vasodilatation would then ensue and lead to blood brain-barrier disruption at the most fragile site venules (Budohoski et al., 2013; Mayhan and Heistad, 1986; Mayhan et al., 1987; Shi et al., 2016).

Besides mechanical factors, metabolic factors are also involved. The arterioles are known to dilate up to 5- to 10- fold of original lumen size under hypoperfusion (Kulik et al., 2008). Adenosine released by dying cells and nitric oxide released from the endothelium may further dilate upstream arterioles of the ischemic core, diminish autoregulation and ultimately abolish the contractibility (Ahnstedt et al., 2016; Canavero et al., 2016; Ek et al., 2015; Kulik et al., 2008; Palomares and Cipolla, 2011). When reperfusion happens, capillary and venules suffer a sudden elevation of perfusion pressure leading to regional hyperemia and disturbance of the venous BBB. Noxious hemorrhage transformation probably ensues under these conditions (Linfante and Cipolla, 2016; Mayhan and Heistad, 1986; Mayhan et al., 1987; Shi et al., 2016).

6.3.4. The interwoven white matter changes and cerebral veins—The white matter hypertintensities (WMHs) is branded as “burden of disease” due to the increased risk for functional disability after stroke (Ding et al., 2017; Rost, 2015). Traditionally, hypoperfusion is deemed as a major cause for WMH development, and this hypoperfusion may be due to the arterial microemboli, in this context, the baseline arterial infusion should predict the long-term WMH growth (Bernbaum et al., 2015). However, the baseline parenchymal cerebral blood flow (pCBF) was found not associated with progression of

WMHs in a longitudinal trial, suggesting the development of WMHs could have other cause than impaired arterial infusion (van der Veen et al., 2015). Increased visibility of deep medullary veins was found in WMHs patients, reflecting venous collagenesis and obstruction (Black et al., 2009; Yan et al., 2014). In the elderly, severe WMHs were associated with jugular venous reflux (Chung et al., 2011). Insufficiency of venous outflow might be followed by venous dilation, collapse of interstitial fluid circulation, vasogenic edema and finally loss of white matter integrity (Chung et al., 2011; Yan et al., 2014). A negative correlation between large deep white matter lesions and successful recanalization in endovascular therapy for acute ischemic stroke has also been shown (Tateishi et al., 2015). One may then presume that WMHs contributes to unfavorable collateral decay instead of sustainable collateral supplement and therefore increase the tendency of futile reperfusion (Zhong et al., 2016). Venous insufficiency and WMH do not necessarily coincide, but often interact as both cause and effect.

7. A novel classification for assessing cerebral venous collaterals

Cerebral venous system, given its structural nature, even presents more substantially potency as collaterals than its arterial counterpart. However, it is an unjustified belief that everywhere cerebral veins have sufficient anastomosis. In this section, a three-level classification of venous collateral is proposed to demonstrate distinct roles of venous system in ischemic stroke.

7.1 . Limitations of assessing cerebral arterial collaterals only

7.1.1. The dynamic development of arterial collaterals requires venous facilitation—Collateral circulation is traditionally defined as the alternative network of vasculatures that stabilize cerebral blood flow when principal routs fail (Liebeskind, 2003). Two aspects are crucial for the collateral functions: one is the native collateral tree which forms during embryogenesis, the other is collateral recruitment and remodeling upon ischemic crisis (Faber et al., 2014). The native collateral formations largely relied on genetic background and contribute to the remarkable variation of ischemic injury (Wang et al., 2010; Zhang et al., 2010). Collateral recruitment and remodeling was determined by both the shear-stress-related process and local ischemic environment and was extensively diversified among individuals (Chilian et al., 1990; van Royen et al., 2009). Collateral rarefaction and collateral degeneration are referred to the loss of native collaterals in healthy adults (Menon et al., 2013), and failure of collateral recruitment after arterial obstruction, respectively (Liebeskind, 2012).

Indeed, animal experiments indicated that arterial collaterals may have dynamic changes that they may go through degeneration as well as recruit newly formed collaterals. Legos et al. utilized a permanent MCAO animal model to show core-penumbra mismatch with the time range from 60 min to 150 min and found the peak ratio was achieved at 75 min after operation, indicating a time window exists for collateral recruitment (Legos et al., 2008). It is thus reasonable to infer that a large infarction with good arterial collaterals is probably due to the delayed efficient collateral recruitment or rapid arterial collateral degeneration. In another setting, a large infarct core may already exist before the collateral is capable of fully

responding to the ischemia (Becker, 2016; Cassidy and Cramer, 2017). Dynamic changes in collateral flow rather than a stable collateral state is a determinant for the final infarct injury, since an individual collateral has a largely distinct capacity in the setting of ischemic insult. From this point of view, arterial collateral circulation alone is not a solid marker for treatment decision-making and prediction of patients' outcomes.

7.1.2. The concept of collaterome—Campbell et al. demonstrated that ischemic stroke patients with favorable perfusion-diffusion mismatch on PWI would however end up with development of a large infarct, in the absence of successful recanalization (Campbell et al., 2013). The initial good collaterals after large-artery occlusion would eventually degenerate if reperfusion failed (Campbell et al., 2013). Conversely, Bang et al. and Cho et al. demonstrated large artery occlusion without recanalization could still generate small infarcts and good outcome (Bang et al., 2008; Cho et al., 2015). In the latter reports, good and sustainable collaterals were assumed to help tissue perfusion, while recanalization only had a weak relation to positive outcomes. In fact, the initial evaluation of arterial collateral status could not predict the ultimate outcome of ischemic patients (Beyer et al., 2015a, 2015b; Burrows et al., 2015). This is supported by the widely-used American Society of Interventional and Therapeutic Neuroradiology (ASITN) model or advice for assessing cerebral collaterals, which highlights the importance of the venous phase evaluation. It is thus reasonable to infer that the change of venous flow represents a combined dynamic result of the extent of both initial ischemia and arterial reperfusion.

Venous collaterals should not be torn apart when evaluating cerebral collaterals (Liebeskind, 2012), as Liebeskind et al. have already proposed in the collaterome concept. The collaterome is comprised of all incorporated elements within the neurovascular unit, including neural stimulation and dynamic regulation of arterial, capillary and venous aspects (Liebeskind, 2015; Liebeskind and Feldmann, 2016). A systematic method for venous evaluation is thus required for the dynamic interpretation of the collateral system.

7.2. The features of venous collaterals differ from arterial collaterals

7.2.1. The multiplicity of venous routes—As illustrated above (see Section 2.1), a specific venous structure can be involved in both the superficial and deep venous systems. One vein may receive blood flow from either the superficial or the deep part of the brain. For example, the basal vein of Rosenthal, mainly collects blood flow from deep venous system, including basal and medial parts of the frontal lobe, temporal lobe, basal ganglia and insula, but also drains the falcine group of superficial venous system and occasionally adjoins with the superficial Sylvian vein that drains around the Sylvian fissure (Kilic and Akakin, 2008; Schaller, 2004).

The Sylvian vein is even more multi-faceted. It forms a net-like structure in infants but fuses into one vessel in adult and acts as a transportation hub in hemispheric convexity. It drains into the cavernous sinus sometimes through the sphenoparietal sinus, adjoins with extracranial veins through the pterygoid plexus, connects to the superior sagittal sinus through the Trolard vein, and yet connects to the transverse sinus at the vein of Labbe (Schaller, 2004). Hence, a major venous anastomotic route has already been well portrayed

on the brain surface, consisting of three major cortical veins: the vein of Trolard, Labbe and Sylvian (Fig. 8).

7.2.2. The asymmetry of venous outflow—The major cortical veins of Trolard, Labbe and Sylvian are usually adjoining with each other and often reciprocally constructed: when one is large, the others are relative small. Thus, they are usually asymmetric in the bilateral hemisphere (Schaller, 2004). The bilateral dura sinuses are also asymmetric. The right transverse sinus is usually larger, receiving flow largely from the superior sagittal sinus, whereas the left transverse sinus mainly collects flow from the straight sinus. The right sigmoid sinus and right jugular vein collect blood from the superficial compartment of brain, whereas the left counterparts largely contain blood from the deep parts of the brain (Kilic and Akakin, 2008; Rhoton, 2002).

7.2.3. The different static energy in the venous system—The cerebral venous system, consists of the dura sinuses and veins, is a drainage system with different static energies. That is, the venous pressure in the cortical veins gradually decrease, until facing the “venous waterfall” at the bridging vein or lacunae in the subdural space (Shulman, 1965). There the pressure drops abruptly (usually 50–200 mm H₂O, with a mean value of 161 mm H₂O) when emptied into the superior sagittal sinus (Yada et al., 1973). Only when a venous sinus thrombosis happens, can the superior sagittal sinus pressure exceed the cortical veins, which may generate further rupture of cortical veins.

The arterial system mainly depends on the pumping force of the heart and the elastic nature of the vessels. Whereas the venous system functions more like “rivers” (cortical veins) draining into an “ocean” (dura sinus), the water in the “ocean” cannot be reversed into the “rivers”. As such, the venous blood collected from one hemisphere cannot cross the dura sinus to the contralateral cortical veins. In the angiography, per unilateral internal carotid, the contralateral cortical veins are usually absent despite the superior sagittal sinus opacification. This phenomenon contributes to the static energy gap among the dura sinus and the bilateral cortical veins (Fig. 9).

7.3. The similarities between arterial and venous collateral

7.3.1. The bilateral communication routes—Similar to arterial collaterals, a venous circle simulating Willis circle at the basal of brain exists (Cullen et al., 2005; Schaller, 2004). In the rostral side of this venous circle are anterior cerebral veins connecting to the anterior communicating vein. In the dorsal part, there are the posterior communicating veins. The Rosenthal veins (the basal veins) are paramedian longitudinal vessels (Padget, 1956). Flow in this circle may be bidirectional and may be reversed under pathological conditions (Cullen et al., 2005).

Unlike the Willis circle of the arterial collateral system, the basal venous circle is less known and even usually neglected. A recent study utilizing SWI, revealed that the contralateral prominence of medullary veins instead of ipsilateral ones was an indicator of favorable outcome in subacute stroke patients (Yu and Yuan, 2016). The ipsilateral medullary venous prominence was associated with a remarkable decrease of CBF, while the contralateral medullary venous prominence was associated with an increase of CBF (Yu and Yuan, 2016).

Although more evidence is needed, the venous collaterals including contralateral and ipsilateral hemisphere are recruited to improve ischemic regional perfusion.

Other bilateral venous communication routes include the cavernous sinuses and intercavernous sinus, with the basal plexus sometimes emerging between the bilateral basal veins (Schaller, 2004; Schmidek et al., 1985).

7.3.2. The reversible blood flow in pathological situations—The medullary veins present another noteworthy route for communication between the superficial and deep venous systems. Normally, there is a “venous watershed” located in the margin between superficial and deep white matter, which separate the two parts as one with relative abundant blood flow and the other with relative slow-rate blood flow. And little traverse venous flow presents as well (Schmidek et al., 1985). However, using the injection of a radio-opaque substance, Hassler et al. confirmed the participation of medullary veins, which were assumed to drain mainly from the deep white matter, especially around lateral ventricles, were also able to drain from the cerebral cortex and conversely, the superficial veins as available routes draining from deep white matters and around lateral ventricle (Hassler, 1966). Additionally, Cullen et al. have demonstrated that the blood flow direction in the basal venous circle, may be bidirectional, and can be reversed under pathologic conditions (Cullen et al., 2005). This compensatory ability between left and right, deep and superficial, seems similar as the Willis circle and meningeal anastomosis of arterial collaterals.

Overall, studies about venous collateral function in ischemic stroke are scarce. The classification of superficial and deep cerebral venous system depends on the anatomy of drainage regions across the brain. However, one may be confused, considering the extensive anastomosis and variability in venous courses and drain territories. In addition, this classification provides limited information under the possible regulatory mechanisms of regional perfusion when regional venous function is jeopardized during ischemic stroke. A new classification of the cerebral venous system is needed based on the function of venous flow in the pathological settings.

7.4. The novel classification of cerebral venous collaterals

Herein we proposed a novel classification of cerebral venous collaterals, taking into account the venous regulatory mechanisms involved in ischemic stroke.

7.4.1. The venous collaterals outside the brain—For extracranial veins, the primary venous drainage pattern is through the internal jugular vein, and the secondary venous drainage pattern focuses on the internal vertebral venous plexus, epidural veins and deep cervical veins (Farrar et al., 2015; Pomschar et al., 2013). A reversal to the secondary cervical venous drainage pattern has been identified in patients suffering traumatic brain injury (TBI), multiple sclerosis and white matter diseases (Chung et al., 2011; Pomschar et al., 2013; Sethi et al., 2015). However, few observations have emerged about the cervical venous drainage pattern in stroke patients, and no definite classification for cerebral venous collaterals has been proposed, except that proposed by Qureshi et al. for cerebral sinus thrombosis (Qureshi, 2010). A systematic classification regarding the drainage pattern of cerebral venous collateral circulation in different pathological settings is needed.

7.4.2. The intracranial three-level venous collateral classification—Cerebral arterial collaterals have been previously classified to three classes of collaterals: the primary collateral, the Willis circle responds the most rapidly in the event of a stroke; the secondary collateral, meningeal branches which includes some superficial anastomosis among the distal branches of large arteries, and the extracranial-intracranial collaterals anastomosis; and the thirdly, the neocollaterals in microcirculation (Kaplan, 1961; Liebeskind, 2003). Here, we propose a classification of cerebral venous collaterals that despite the unparallel structure between arterial and venous vasculature in the brain, we also divided the venous collaterals into three classes (Fig. 10).

Firstly, the cerebral venous collaterals communicating the two cerebral hemispheres presents the class I venous collaterals. The basal venous circle, as described above, composed of bilateral basal veins, anterior cerebral veins connected with anterior communicating cerebral veins, peduncle veins and posterior communicating cerebral veins (Cullen et al., 2005). Moreover, the cavernous sinus (including intercavernous sinus) and basilar venous plexus also have the potential to redistribute bilateral venous flow and can be assigned to the class I cerebral venous collaterals. Notably, the midline dura sinuses are not able to communicate bilateral venous flow since bilateral cortical veins draining into the dura sinuses by “venous watershed” and thus are not included in this class of venous collateral.

The class II cerebral venous collaterals are mainly composed of extracranial-intracranial collaterals, collaterals communicating on the convexity of one hemisphere, and deep-superficial collaterals. The extracranial-intracranial collaterals include the ophthalmic veins, occipital veins and facial veins, and some emissary veins which correlate with intracranial venous plexus or sinuses, such as cavernous sinus, pterygoid plexus or superior and inferior petrosal sinuses (Andeweg, 1996, 1999; Liebeskind, 2003; Rhoton, 2002). In addition, other venous collaterals only affecting one hemisphere are also located in the class II cerebral venous collaterals. Including the cortical venous anastomosis communicating with each other or connecting different sinuses in the same hemisphere, such as direct anastomosis between Labbe and Trolard or their connections with the superior sagittal sinus and transverse sinus separately. Venous routes directly or indirectly (such as trans-cerebral veins) communicating deep and superficial venous systems are also sorted to this class.

Whether medullary veins (including superficial medullary veins and deep medullary veins) function as feasible collaterals in connecting those veins draining cortex flow and deep venous system (e.g. thalamostriate vein, choroidal vein and septal vein) remains controversial (Andeweg, 1999; Schaller, 2004). As the “venous watershed” theory suggest that a pressure gap exist between the superficial medullary veins and deep medullary veins (Andeweg, 1999). It has been assumed that the trans-cerebral veins are insufficient drainage routes (Andeweg, 1999), while others have indicated the importance of transcerebral veins in connecting the superficial and deep venous systems (Schaller, 2004).

The class III cerebral venous collaterals are the neovenous vessels and venules. Blood flow reversal and newly formed venous collateral microstructure are known to happen in newly formed venous structures (Adamson et al., 2013; Pranevicius and Pranevicius, 2002; Pranevicius et al., 2011, 2012; Sbarbati et al., 1996). These venous microstructures are

directly adjacent to tissue ischemia during stroke, and certainly influence the stroke pathophysiological and the survival of neuronal cells.

On one hand, during stroke ictus, the regional arterial blood infusion become impaired and regional intracerebral pressure increased, leading to the insufficient flow in the direct downstream veins. As the arterial collateral supplies the complementary infusions to the nearby ischemic core, there must be efficient venous drainage routes that does not easily affected by the tissue edema. On the other hand, in the context of recanalization, the venous collateral probably takes part in “non-reflow phenomenon”, “luxury reperfusion” and “futile recanalization”, and affect the recanalization outcome.

8. Future therapeutic considerations with an eye on the cerebral venous system

In this section, several promising therapeutic consideration have been suggested, which comprised of more aggressive reperfusion strategies, the micro-emboli remover, enhancing recruitment of venous collateral and the veno-active medication.

8.1. Venous refilling with reperfusion therapy

Most recently, in a cohort of 228 acute ischemic stroke patients who received thrombolysis with or without endovascular therapy in our stroke center, we found that the absent filling of ipsilateral superficial middle cerebral vein (SMCV) on 4D CTA was strongly related to severe hypoperfusion, and reperfusion was able to refill the absent SMCV (Zhang et al., 2017). Lack of SMCV filling contributed to poor outcome after thrombolysis, especially when reperfusion was not achieved. The main deleterious effect of poor venous filling appears related to the development of brain edema. Therefore, successful revascularization should still be the primary goal for acute ischemic stroke (AIS) patients. Clinical studies are needed to confirm whether patients with poor venous outflow should undergo more aggressive reperfusion strategies, including thrombectomy.

8.2. Venous refilling with microthrombi-remover

In mice, formation and occlusion of microthrombi in venules was found within 30 min after acute reduction of cerebral blood flow (Altura et al., 2002; Schwarzmaier et al., 2010). Experimental studies in vein occlusion models also demonstrated that the growth of the venous thrombi coincided with a decrease in regional CBF (Nguyen et al., 2011). Therefore, it is reasonable to try the possible means to clear the venous microemboli from the microcirculation and re-open the obstructed lumen of venules. For example, in the transient ischemic model of rats, in vivo surveillance showed that albumin therapy would yield benefits in reversing stagnation, adherence, and thrombosis, within cortical venules during reperfusion (Belayev et al., 2002). In another rat model of ischemic stroke, the selective direct thrombin inhibitor argatroban, was demonstrated to reduce secondary venous microthrombi formation, and improve blood perfusion as well as minimize the ischemic lesions (Berry et al., 2000; Peternel et al., 2005). Treatment of acute paraventricular ischemic stroke within 48 h of onset with argatroban led to increased mean flow velocity in drainage from the basal vein of Rosenthal (BVR) and improved clinical outcomes in 60 patients

(unpublished observations). Currently, anticoagulation is the main therapeutic intervention for reducing secondary clot formation. These observations indicate that anticoagulation may improve outcomes after acute ischemic stroke by increasing venous drainage. In future studies, it may be useful to explore the impact of different clot-removers on venous outflow using advanced venous imaging.

8.3. Recruitment of venous collaterals

The pathophysiologic concept of venous injury in acute ischemic stroke assumes that insufficient venous outflow is associated with poor outcome. Compared with arteries, which are composed of relatively rigid walls, veins with their lack of smooth muscle and relatively thin walls have the potential to collapse at negative transmural pressures. A biophysical analysis of cerebral venous outflow found that the brain may compensate for increased venous resistance, by either elevating the pressure gradient or by reducing the circulatory resistance through recruiting additional drainage pathways, such as venous collaterals. Partial aortic occlusion is a promising method to increase venous pressure and prevent “non-flow phenomenon” (Pranevicius et al., 2011). Numerous theoretical arguments, suggest a probable beneficial effect from improving cerebral collaterals, mainly arterial, in ischemic events, such as elevation of systemic blood pressure, hypervolemic-inotropic support, and hyperventilation. With the development of novel imaging methods, it is possible to improve the sensitivity for delayed contrast arrival in veins. For example, late-filling cortical veins overlooked by conventional CTA could be detected by dynamic CTA. Further understanding of venous collaterals and the possible collateral augmentation approaches may also provide new concerns for specific clinical phenomena, and expand treatment options for acute ischemic stroke.

8.4. Possible application of venoactive medication

As a crucial contributor to cerebrovascular resistance, intracranial veins lack the ability to dilate or constrict significantly during pressure changes or distal extension. Traditionally, venoactive drugs are applied to treat varicose veins in lower extremities. Recent evidence has suggested that most venoactive drugs are capable of increasing the venous tone by a mechanism associated with the noradrenaline pathway (Perrin and Ramelet, 2011). Micronised purified flavonoid fraction (MPFF) is a flavonoid-based venoactive drug that improves venous tone and reduces vein diameter through modulating noradrenergic signaling and prolonging noradrenergic activity (Danielsson et al., 2002). In ischemia-reperfusion animal models, including ischemic/reperfusion model in rat liver, ischaemia-reperfusion in the hamster cheek pouch, MPFF is applied and showed the effect of attenuating ischemia/reperfusion damaging by reducing inflammatory mediators such as oxygen free radicals, prostaglandins and thromboxane (Cyrino et al., 2004; Yildiz et al., 2015). Also, MPFF modulates leukocyte adhesion in small veins and attenuate the endothelial injury (Smith, 2000). Other venoactive drugs such as hydroxyethylrutosides, can strengthen the venous wall by blocking noradrenaline inactivation (Asgeirsson et al., 1994). The study conducted by Asgeirsson et al. reports agonists of the $\alpha 1$ -adrenergic receptors known as ruscus extracts control post-traumatic brain edema from severe head injury (Asgeirsson et al., 1994). Through the combination of precapillary vasoconstriction with venous constriction (dihydroergotamine) and induced hypotension ($\beta 1$ blocker and $\alpha 2$

stimulation), the patients gained normal colloid osmotic pressure but reduced hydrostatic capillary pressure, and the patients achieved a better outcome compared with those in control group (Asgeirsson et al., 1994). Another study revealed that stimulation of sympathetic nerves during acute hypertension increased pial venular pressure and reduced the risk of hemorrhagic complications (Mayhan and Heistad, 1986). Although there are still controversies that those alternative treatments and results from stroke-induced brain ischemia are lacking, it is worthwhile to understand the mechanisms contributing to microcirculation venous homeostasis. This basic understanding will open up future directions for pharmacological venoactive agents in ischemic stroke.

9. Conclusion and perspective

In this review article, we discussed the indivisibility of arterial and venous collaterals in maintaining cerebral perfusion homeostasis, summarized the potential role that venous collaterals play in recanalization, and proposed a novel classification of cerebral venous collaterals developed from stroke pathophysiology.

With the advancement of endovascular therapy and imaging techniques, patients have an improved probability to achieve successful recanalization after an ischemic event (Boltze and Ayata, 2016; Boltze et al., 2016). So far, the newest therapeutic strategies have not crossed the 50% improvement barrier due to the limited understanding of stroke pathophysiology, while the rate of reperfusion injury increases (Ergul et al., 2016). These enigmas are largely related not only to arterial inflow but also venous outflow.

Evidence lends support to the presence of cerebral arterial and venous collateral homeostasis and that a variety of factors influence this collateral equilibrium. While the regulatory mechanisms of the cerebral venous system are strengthened in the settings of physiology and pathophysiology, more information needs to be obtained such as the detailed changes of collateral homeostasis during pre-recanalization and post-recanalization. A novel concept of cerebral arterial and venous collateral homeostasis may open a new understanding of stroke pathophysiology and treatment.

To keep the arterial collateral work sustainable and efficiently, as an additional marker for recanalization decision-making and outcome prediction, the cerebral venous system showed its potential to reinforce the beneficial changes in ischemic stroke. A full evaluation of venous collateral structure and function is required. Further understanding of venous collaterals and the possible therapeutic targets in the cerebral venous system may expand the treatment options, improve prevention of reperfusion injury for acute ischemic stroke and overall post-stroke outcomes. Defining the cerebral venous collaterals is an important step in improving the understanding of cerebral collateral circulation during a stroke event.

Acknowledgments

This work was supported partially by a grant from the National Natural Science Foundation of China (NSFC, 81500991) to L.S.T, a grant from the National Natural Science Foundation of China (NSFC, 81622017) to M. L, a grant from National Natural Science Foundation of China (NSFC, 81501166) to Z.N. G, and a grant from NIHP01NS082184 to JHZ.

Abbreviations

AIS	acute ischemic stroke
ASITN	American Society of Interventional and Therapeutic Neuroradiology
BBB	blood-brain barrier
BOLD	blood oxygen level dependence
BVR	basal vein of Rosenthal
CBF	cerebral blood flow
CE-MRV	Contrast-enhanced 3-Dimensional magnetic resonance venography
CPP	cerebral perfusion pressure
CSF	cerebral spinal fluid
CTV	Contrast-enhanced 3-Dimensional CT venography
dCTA	dynamic CTA
DSA	digital subtraction angiography
ICAM-1	Intercellular adhesion molecule 1
ICP	intracranial pressure
MION	monocrystalline iron oxide
MPFF	Micronised purified flavonoid fraction
MRV	magnetic resonance venography
MVS	microvascular shunt
PC-MRV	Phase Contrast magnetic resonance venography
PCV	prominent cortical veins
SWI	Susceptibility-Weighted Imaging
TOF-MRV	Time-of-Flight magnetic resonance venography
MCAO	middle cerebral artery occlusion
NIHSS	National Institute of Health Stroke Scale
pCBF	parenchymal cerebral blood flow
Pe	pressure surrounding the tube

Pi	pressure at the inflow end
Po	pressure at outflow end
PRECISE	Prognostic Evaluation based on Cortical vein score difference In Stroke
SMCV	superficial middle cerebral vein
t-PA	tissue plasminogen activator
VCAM-1	Vascular cell adhesion protein 1
VE-cadherin	vascular endothelial cadherin
WMHs	white matter hypertintensities

References

- Abud DG, Spelle L, Piotin M, Mounayer C, Vanzin JR, Moret J, 2005 Venous phase timing during balloon test occlusion as a criterion for permanent internal carotid artery sacrifice. *AJNR Am. J. Neuroradiol* 26, 2602–2609. [PubMed: 16286409]
- Abumiya T, Fitridge R, Mazur C, Copeland BR, Koziol JA, Tschopp JF, Pierschbacher MD, del Zoppo GJ, 2000 Integrin alpha(IIb)beta(3) inhibitor preserves microvascular patency in experimental acute focal cerebral ischemia. *Stroke* 31, 1402–1409 (discussion 1409–1410). [PubMed: 10835463]
- Adamson RH, Sarai RK, Altangerel A, Clark JF, Weinbaum S, Curry FE, 2013 Microvascular permeability to water is independent of shear stress: but dependent on flow direction. *Am. J. Physiol. Heart Circ. Physiol* 304, H1077–1084. [PubMed: 23417864]
- Ahnstedt H, Sweet J, Cruden P, Bishop N, Cipolla MJ, 2016 Effects of early post-Ischemic reperfusion and tPA on cerebrovascular function and nitrosative stress in female rats. *Transl. Stroke Res* 7, 228–238. [PubMed: 27125535]
- Aksenov DP, Li L, Miller MJ, Iordanescu G, Wyrwicz AM, 2015 Effects of anesthesia on BOLD signal and neuronal activity in the somatosensory cortex. *J. Cereb. Blood Flow Metab* 35, 1819–1826. [PubMed: 26104288]
- Al-Ali F, Elias JJ, Filipkowski DE, Faber JE, 2015 Acute ischemic stroke treatment, part 1: patient selection the 50% barrier and the capillary index score. *Front. Neurol* 6, 83. [PubMed: 25954243]
- Alexander JS, Prouty L, Tsunoda I, Ganta CV, Minagar A, 2013 Venous endothelial injury in central nervous system diseases. *BMC Med* 11, 219. [PubMed: 24228622]
- Alkonyi B, Miao Y, Wu J, Cai Z, Hu J, Chugani HT, Juhasz C, 2012 A perfusion-metabolic mismatch in Sturge-Weber syndrome: a multimodality imaging study. *Brain Dev* 34, 553–562. [PubMed: 22075184]
- Altura BM, Gebrewold A, Zheng T, Altura BT, 2002 Sphingomyelinase and ceramide analogs induce vasoconstriction and leukocyte-endothelial interactions in cerebral venules in the intact rat brain: insight into mechanisms and possible relation to brain injury and stroke. *Brain Res. Bull* 58, 271–278. [PubMed: 12128152]
- Ambarki K, Baledent O, Kongolo G, Bouzerar R, Fall S, Meyer ME, 2007 A new lumped-parameter model of cerebrospinal hydrodynamics during the cardiac cycle in healthy volunteers. *IEEE Trans. Biomed. Eng* 54, 483–491. [PubMed: 17355060]
- Ames A, 3rd, Wright RL, Kowada M, Thurston JM, Majno G, 1968 Cerebral ischemia. II. The no-reflow phenomenon. *Am. J. Pathol* 52, 437–453. [PubMed: 5635861]
- Andeweg J, 1996 The anatomy of collateral venous flow from the brain and its value in aetiological interpretation of intracranial pathology. *Neuroradiology* 38, 621–628. [PubMed: 8912316]
- Andeweg J, 1999 Consequences of the anatomy of deep venous outflow from the brain. *Neuroradiology* 41, 233–241. [PubMed: 10344506]

- Asgari S, Bassiouni H, Hunold A, Klassen D, Stolke D, Sandalcioğlu IE, 2008 Extensive brain swelling with neurological deterioration after intracranial meningioma surgery venous complication or 'unspecific' increase in tissue permeability. *Zentralbl. Neurochir* 69, 22–29. [PubMed: 18393161]
- Asgeirsson B, Grande PO, Nordstrom CH, 1994 A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. *Intensive Care Med* 20, 260–267. [PubMed: 8046119]
- Attwell D, Buchan AM, Charkpak S, Lauritzen M, Macvicar BA, Newman EA, 2010 Glial and neuronal control of brain blood flow. *Nature* 468, 232–243. [PubMed: 21068832]
- Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T, 2016 What is a pericyte? *J. Cereb. Blood Flow Metab* 36, 451–455. [PubMed: 26661200]
- Auer LM, Johansson BB, 1981 Cervical sympathetic nerve stimulation decreases intracranial pressure in the cat. *Acta Physiol. Scand* 113, 565–566. [PubMed: 7348042]
- Auer LM, Trummer UG, Johansson BB, 1981 Alpha-adrenoreceptor antagonists and pial vessel diameter during hypercapnia and hemorrhagic hypotension in the cat. *Stroke* 12, 847–851. [PubMed: 6117957]
- Avirame K, Lesemann A, List J, Witte AV, Schreiber SJ, Floel A, 2015 Cerebral autoregulation and brain networks in occlusive processes of the internal carotid artery. *J. Cereb. Blood Flow Metab* 35, 240–247. [PubMed: 25388676]
- Bang OY, Saver JL, Buck BH, Alger JR, Starkman S, Ovbiagele B, Kim D, Jahan R, Duckwiler GR, Yoon SR, Vinuela F, Liebeskind DS, 2008 Impact of collateral flow on tissue fate in acute ischaemic stroke. *J. Neurol. Neurosurg. Psychiatry* 79, 625–629. [PubMed: 18077482]
- Bar T, 1980 The vascular system of the cerebral cortex. *Adv. Anat. Embryol. Cell Biol* 59 (I–VI), 1–62.
- Barhoum S, Langham MC, Magland JF, Rodgers ZB, Li C, Rajapakse CS, Wehrli FW, 2015 Method for rapid MRI quantification of global cerebral metabolic rate of oxygen. *J. Cereb. Blood Flow Metab* 35, 1616–1622. [PubMed: 25966941]
- Bateman GA, Levi CR, Schofield P, Wang Y, Lovett EC, 2008 The venous manifestations of pulse wave encephalopathy: windkessel dysfunction in normal aging and senile dementia. *Neuroradiology* 50, 491–497. [PubMed: 18379767]
- Bateman GA, 2007 Magnetic resonance imaging quantification of compliance and collateral flow in late-onset idiopathic aqueductal stenosis: venous pathophysiology revisited. *J. Neurosurg* 107, 951–958. [PubMed: 17977266]
- Beard DJ, McLeod DD, Logan CL, Murtha LA, Imtiaz MS, van Helden DF, Spratt NJ, 2015 Intracranial pressure elevation reduces flow through collateral vessels and the penetrating arterioles they supply. A possible explanation for 'collateral failure' and infarct expansion after ischemic stroke. *J. Cereb. Blood Flow Metab* 35, 861–872. [PubMed: 25669909]
- Becker KJ, 2016 Strain-related differences in the immune response: relevance to human stroke. *Transl. Stroke Res* 7, 303–312. [PubMed: 26860504]
- Bednarik P, Tkac I, Giove F, DiNuzzo M, Deelchand DK, Emir UE, Eberly LE, Mangia S, 2015 Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. *J. Cereb. Blood Flow Metab* 35, 601–610. [PubMed: 25564236]
- Beggs CB, 2013 Venous hemodynamics in neurological disorders: an analytical review with hydrodynamic analysis. *BMC Med* 11, 142. [PubMed: 23724917]
- Belayev L, Pinard E, Nallet H, Seylaz J, Liu Y, Riyamongkol P, Zhao W, Busto R, Ginsberg MD, 2002 Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. *Stroke* 33, 1077–1084. [PubMed: 11935064]
- Bentson JR, Wilson GH, Newton TH, 1971 Cerebral venous drainage pattern of the Sturge-Weber syndrome. *Radiology* 101, 111–118. [PubMed: 5111963]
- Bergonzi KM, Bauer AQ, Wright PW, Culver JP, 2015 Mapping functional connectivity using cerebral blood flow in the mouse brain. *J. Cereb. Blood Flow Metab* 35, 367–370. [PubMed: 25492111]
- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt G.J., Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle

- LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, 2015 A randomized trial of intraarterial treatment for acute ischemic stroke. *N. Engl. J. Med* 372, 11–20. [PubMed: 25517348]
- Bernbaum M, Menon BK, Fick G, Smith EE, Goyal M, Frayne R, Coutts SB, 2015 Reduced blood flow in normal white matter predicts development of leukoaraiosis. *J. Cereb. Blood Flow Metab* 35, 1610–1615. [PubMed: 25966951]
- Berry CN, Visconte C, Lecoffre C, Lochot S, Girard D, 2000 Activity of a sub-cutaneously administered novel mixed micellar formulation of argatroban in rat and rabbit models of venous thrombosis. *Thromb. Haemost* 84, 286–290. [PubMed: 10959702]
- Beyer SE, Thierfelder KM, von Baumgarten L, Rottenkolber M, Meinel FG, Janssen H, Ertl-Wagner B, Reiser MF, Sommer WH, 2015a Strategies of collateral blood flow assessment in ischemic stroke: prediction of the follow-up infarct volume in conventional and dynamic CTA. *AJNR Am. J. Neuroradiol* 36, 488–494. [PubMed: 25523589]
- Beyer SE, von Baumgarten L, Thierfelder KM, Rottenkolber M, Janssen H, Dichgans M, Johnson TR, Straube A, Ertl-Wagner B, Reiser MF, Sommer WH, 2015b Predictive value of the velocity of collateral filling in patients with acute ischemic stroke. *J. Cereb. Blood Flow Metab* 35, 206–212. [PubMed: 25370859]
- Bhaskar S, Bivard A, Parsons M, Nilsson M, Attia JR, Stanwell P, Levi C, 2017 Delay of late-venous phase cortical vein filling in acute ischemic stroke patients: associations with collateral status. *J. Cereb. Blood Flow Metab* 37, 671–682. [PubMed: 26965242]
- Black S, Gao F, Bilbao J, 2009 Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke* 40, S48–52. [PubMed: 19064767]
- Bolan PJ, Yacoub E, Garwood M, Ugurbil K, Harel N, 2006 In vivo micro-MRI of intracortical neurovasculature. *Neuroimage* 32, 62–69. [PubMed: 16675271]
- Boltz J, Ayata C, 2016 Challenges and controversies in translational stroke research an introduction. *Transl. Stroke Res* 7, 355–357. [PubMed: 27581304]
- Boltz J, Wagner DC, Barthel H, Gounis MJ, 2016 Academic-industry collaborations in translational stroke research. *Transl. Stroke Res* 7, 343–353. [PubMed: 27301976]
- Bragin DE, Bush RC, Nemoto EM, 2013 Effect of cerebral perfusion pressure on cerebral cortical microvascular shunting at high intracranial pressure in rats. *Stroke* 44, 177–181. [PubMed: 23204051]
- Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, Pickard JD, 2013 Clinical relevance of cerebral autoregulation following subarachnoid haemorrhage. *Nat. Rev. Neurol* 9, 152–163. [PubMed: 23419369]
- Burrows FE, Bray N, Denes A, Allan SM, Schiessl I, 2015 Delayed reperfusion deficits after experimental stroke account for increased pathophysiology. *J. Cereb. Blood Flow Metab* 35, 277–284. [PubMed: 25407273]
- Campbell BC, Christensen S, Tress BM, Churilov L, Desmond PM, Parsons MW, Barber PA, Levi CR, Bladin C, Donnan GA, Davis SM, 2013 Failure of collateral blood flow is associated with infarct growth in ischemic stroke. *J. Cereb. Blood Flow Metab* 33, 1168–1172. [PubMed: 23652626]
- Campbell BC, Donnan GA, Lees KR, Hacke W, Khatri P, Hill MD, Goyal M, Mitchell PJ, Saver JL, Diener HC, Davis SM, 2015a Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. *Lancet Neurol* 14, 846–854. [PubMed: 26119323]
- Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM, 2015b Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N. Engl. J. Med* 372, 1009–1018. [PubMed: 25671797]

- Canavero I, Sherburne HA, Tremble SM, Clark WM, Cipolla MJ, 2016 Effects of acute stroke serum on non-ischemic cerebral and mesenteric vascular function. *Transl. Stroke Res* 7, 156–165. [PubMed: 26809954]
- Cassidy JM, Cramer SC, 2017 Spontaneous and therapeutic-Induced mechanisms of functional recovery after stroke. *Transl. Stroke Res* 8, 33–46. [PubMed: 27109642]
- Chen J, Wang XM, Luan LM, Chao BT, Pang B, Song H, Pang Q, 2012 Biological characteristics of the cerebral venous system and its hemodynamic response to intracranial hypertension. *Chin. Med. J* 125, 1303–1309. [PubMed: 22613606]
- Chen S, Chen Y, Xu L, Matei N, Tang J, Feng H, Zhang JH, 2015 Venous system in acute brain injury: mechanisms of pathophysiological change and function. *Exp. Neurol* 27, 4–10.
- Chiang J, Kowada M, Ames A, 3rd, Wright RL, Majno G, 1968 Cerebral ischemia. III. Vascular changes. *Am. J. Pathol* 52, 455–476. [PubMed: 5635862]
- Chilian WM, Mass HJ, Williams SE, Layne SM, Smith EE, Scheel KW, 1990 Microvascular occlusions promote coronary collateral growth. *Am. J. Physiol* 258, H1103–1111. [PubMed: 2330998]
- Cho TH, Nighoghossian N, Mikkelsen IK, Derex L, Hermier M, Pedraza S, Fiehler J, Ostergaard L, Berthezene Y, Baron JC, 2015 Reperfusion within 6 hours outperforms recanalization in predicting penumbra salvage lesion growth, final infarct, and clinical outcome. *Stroke* 46, 1582–1589. [PubMed: 25908463]
- Chung CP, Wang PN, Wu YH, Tsao YC, Sheng WY, Lin KN, Lin SJ, Hu HH, 2011 More severe white matter changes in the elderly with jugular venous reflux. *Ann. Neurol* 69, 553–559. [PubMed: 21391231]
- Cruveilhier J, 1837 *Anatomie Descriptive*. Meline, Brussels
- Cullen S, Demengie F, Ozanne A, Alvarez H, Mercier PH, Brassier G, Lasjaunias P, 2005 The anastomotic venous circle of the base of the brain. *Intervent. Neuroradiol* 11, 325–332.
- Cyrino FZ, Bottino DA, Lerond L, Bouskela E, 2004 Micronization enhances the protective effect of purified flavonoid fraction against postischaemic microvascular injury in the hamster cheek pouch. *Clin. Exp. Pharmacol. Physiol* 31, 159–162. [PubMed: 15008958]
- Dai W, Varma G, Scheidegger R, Alsop DC, 2016 Quantifying fluctuations of resting state networks using arterial spin labeling perfusion MRI. *J. Cereb. Blood Flow Metab* 36, 463–473. [PubMed: 26661226]
- Danielsson G, Jungbeck C, Peterson K, Norgren L, 2002 A randomised controlled trial of micronised purified flavonoid fraction vs placebo in patients with chronic venous disease. *Eur. J. Vasc. Endovasc. Surg* 23, 73–76. [PubMed: 11748952]
- del Zoppo GJ, Mabuchi T, 2003 Cerebral microvessel responses to focal ischemia. *J. Cereb. Blood Flow Metab* 23, 879–894. [PubMed: 12902832]
- Ding G, Chen J, Chopp M, Li L, Yan T, Davoodi-Bojd E, Li Q, Davarani SP, Jiang Q, 2017 White matter changes after stroke in type 2 diabetic rats measured by diffusion magnetic resonance imaging. *J. Cereb. Blood Flow Metab* 37, 241–251. [PubMed: 26685128]
- Dorn F, Kuntze-Soderqvist A, Popp S, Lockau H, Haller B, Zimmer C, Andersson T, Liebig T, 2012 Early venous drainage after successful endovascular recanalization in ischemic stroke a predictor for final infarct volume? *Neuroradiology* 54, 745–751. [PubMed: 22015643]
- Edvinsson L, McCulloch J, Uddman R, 1982 Feline cerebral veins and arteries: comparison of autonomic innervation and vasomotor responses. *J. Physiol* 32, 161–173.
- Edvinsson L, Hogestatt ED, Uddman R, Auer LM, 1983 Cerebral veins: fluorescence histochemistry electron microscopy, and in vitro reactivity. *J. Cereb. Blood Flow Metab* 3, 226–230. [PubMed: 6841470]
- Ek CJ, D'Angelo B, Baburamani AA, Lehner C, Leverin AL, Smith PL, Nilsson H, Svedin P, Hagberg H, Mallard C, 2015 Brain barrier properties and cerebral blood flow in neonatal mice exposed to cerebral hypoxia-ischemia. *J. Cereb. Blood Flow Metab* 35, 818–827. [PubMed: 25627141]
- Ergul A, Hafez S, Fouda A, Fagan SC, 2016 Impact of comorbidities on acute injury and recovery in preclinical stroke research: focus on hypertension and diabetes. *Transl. Stroke Res* 7, 248–260. [PubMed: 27026092]

- Faber JE, Chilian WM, Deindl E, van Royen N, Simons M, 2014 A brief etymology of the collateral circulation. *Arterioscler. Thromb. Vasc. Biol* 34, 1854–1859. [PubMed: 25012127]
- Faber JE, Moore SM, Lucitti JL, Aghajanian A, Zhang H, 2016 Sex differences in the cerebral collateral circulation. *Transl. Stroke Res* (Epub ahead of print).
- Farb RI, Agid R, Willinsky RA, Johnstone DM, Terbrugge KG, 2009 Cranial dural arteriovenous fistula: diagnosis and classification with time-resolved MR angiography at 3T. *AJNR A. J. Neuroradiol* 30, 1546–1551.
- Farrar MJ, Rubin JD, Diago DM, Schaffer CB, 2015 Characterization of blood flow in the mouse dorsal spinal venous system before and after dorsal spinal vein occlusion. *J. Cereb. Blood Flow Metab* 35, 667–675. [PubMed: 25564237]
- Fernandez-Klett F, Priller J, 2015 Diverse functions of pericytes in cerebral blood flow regulation and ischemia. *J. Cereb. Blood Flow Metab* 35, 883–887. [PubMed: 25853910]
- Ferropoli P, Nakaji P, Acerbi F, Albanese E, Broggi G, 2011 Indocyanine green (ICG) temporary clipping test to assess collateral circulation before venous sacrifice. *World Neurosurg* 75, 122–125. [PubMed: 21492675]
- Feuerstein D, Backes H, Gramer M, Takagaki M, Gabel P, Kumagai T, Graf R, 2016 Regulation of cerebral metabolism during cortical spreading depression. *J. Cereb. Blood Flow Metab* 36, 1965–1977. [PubMed: 26661217]
- Filippi M, Charil A, Rovaris M, Absinta M, Rocca MA, 2014 Insights from magnetic resonance imaging. *Handb. Clin. Neurol* 122, 115–149. [PubMed: 24507516]
- Forster A, Murle B, Bohme J, Al-Zghloul M, Kerl HU, Wenz H, Groden C, 2016 Perfusion-weighted imaging and dynamic 4D angiograms for the estimation of collateral blood flow in lacunar infarction. *J. Cereb. Blood Flow Metab* 36, 1744–1754. [PubMed: 26661161]
- Furlan AJ, 2015 Endovascular therapy for stroke it's about time. *N. Engl. J. Med* 372, 2347–2349. [PubMed: 25882509]
- Gerber JC, Miaux YJ, von Kummer R, 2015 Scoring flow restoration in cerebral angiograms after endovascular revascularization in acute ischemic stroke patients. *Neuroradiology* 57, 227–240. [PubMed: 25407716]
- Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlathshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, 2015 Randomized assessment of rapid endovascular treatment of ischemic stroke. *N. Engl. J. Med* 372, 1019–1030. [PubMed: 25671798]
- Guibert R, Fonta C, Plouraboue F, 2010 Cerebral blood flow modeling in primate cortex. *J. Cereb. Blood Flow Metab* 30, 1860–1873. [PubMed: 20648040]
- Guibert R, Fonta C, Risser L, Plouraboue F, 2012 Coupling and robustness of intra-cortical vascular territories. *Neuroimage* 62, 408–417. [PubMed: 22548806]
- Gustafsson O, Rossitti S, 1995 Intracranial pressure is a fraction of arterial blood pressure. *Eur. J. Neurol* 2, 31–37. [PubMed: 24283578]
- Hallenbeck JM, Bradley ME, 1977 Experimental model for systematic study of impaired microvascular reperfusion. *Stroke* 8, 238–243. [PubMed: 847789]
- Han K, Chao AC, Chang FC, Hsu HY, Chung CP, Sheng WY, Chan L, Wu J, Hu HH, 2016 Diagnosis of transverse sinus hypoplasia in magnetic resonance venography: new insights based on magnetic resonance imaging in combined dataset of venous outflow impairment case-control studies: post hoc case-control study. *Medicine* 95, e2862. [PubMed: 26962781]
- Harel N, Bolan PJ, Turner R, Ugurbil K, Yacoub E, 2010 Recent advances in high-resolution MR application and its implications for neurovascular coupling research. *Front. Neuroenerg* 2, 130.
- Hassler O, 1966 Deep cerebral venous system in man: a microangiographic study on its areas of drainage and its anastomoses with the superficial cerebral veins. *Neurology* 16, 505–511. [PubMed: 5949064]
- Heiss WD, Graf R, Lottgen J, Ohta K, Fujita T, Wagner R, Grond M, Weinhard K, 1997 Repeat positron emission tomographic studies in transient middle cerebral artery occlusion in cats:

- residual perfusion and efficacy of postischemic reperfusion. *J. Cereb. Blood Flow Metab* 17, 388–400. [PubMed: 9143221]
- Heistad DD, Marcus ML, Said SI, Gross PM, 1980 Effect of acetylcholine and vasoactive intestinal peptide on cerebral blood flow. *Am. J. Physiol* 239, H73–80. [PubMed: 7396021]
- Henle J, 1868 *Handbuch der Gefäßlehre des Menschen*. Vieweg, Braunschweig
- Henninger N, Fisher M, 2016 Extending the time window for endovascular and pharmacological reperfusion. *Transl. Stroke Res* 7, 284–293. [PubMed: 26739964]
- Higgins JN, Burnet NG, Schwindack CF, Waters A, 2008 Severe brain edema caused by a meningioma obstructing cerebral venous outflow and treated with venous sinus stenting. Case report. *J. Neurosurg* 108, 372–376. [PubMed: 18240938]
- Hill RA, Tong L, Yuan P, Murikinati S, Gupta S, Grutzendler J, 2015 Regional blood flow in the normal and ischemic brain is controlled by arteriolar smooth muscle cell contractility and not by capillary pericytes. *Neuron* 87, 95–110. [PubMed: 26119027]
- Hoffmann U, Sheng H, Ayata C, Warner DS, 2016 Anesthesia in experimental stroke research. *Transl. Stroke Res* 7, 358–367. [PubMed: 27534542]
- Hussein HM, Georgiadis AL, Vazquez G, Miley JT, Memon MZ, Mohammad YM, Christoforidis GA, Tariq N, Qureshi AI, 2010 Occurrence and predictors of futile recanalization following endovascular treatment among patients with acute ischemic stroke: a multicenter study. *AJNR Am. J. Neuroradiol* 31, 454–458. [PubMed: 20075087]
- Huston J, 3rd, Ehman RL, 1993 Comparison of time-of-flight and phase-contrast MR neuroangiographic techniques. *Radiographics* 13, 5–19. [PubMed: 8426937]
- Ibaraki M, Ohmura T, Matsubara K, Kinoshita T, 2015 Reliability of CT perfusion-derived CBF in relation to hemodynamic compromise in patients with cerebrovascular steno-occlusive disease: a comparative study with 150 PET. *J. Cereb. Blood Flow Metab* 35, 1280–1288. [PubMed: 25757749]
- Inao S, Kuchiwaki H, Yoshida J, Furuse M, 1997 Magnetic resonance imaging quantitation of superior sagittal sinus flow: correlation to cerebral blood flow measured by xenon-enhanced computed tomography. *Neurol. Res* 19, 35–40. [PubMed: 9090634]
- Ishikawa M, Cooper D, Arumugam TV, Zhang JH, Nanda A, Granger DN, 2004 Platelet-leukocyte-endothelial cell interactions after middle cerebral artery occlusion and reperfusion. *J. Cereb. Blood Flow Metab* 24, 907–915. [PubMed: 15362721]
- Jeanneret V, Yepes M, 2016 The plasminogen activation system promotes dendritic spine recovery and improvement in neurological function after an ischemic stroke. *Transl. Stroke Res* (Epub ahead of print).
- Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR, 2015 Targeting neutrophils in ischemic stroke: translational insights from experimental studies. *J. Cereb. Blood Flow Metab* 35, 888–901. [PubMed: 25806703]
- Johnston IH, Rowan JO, 1974 Raised intracranial pressure and cerebral blood flow. 3. Venous outflow tract pressures and vascular resistances in experimental intracranial hypertension. *J. Neurol. Neurosurg. Psychiatry* 37, 392–402. [PubMed: 4209160]
- Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A, 2015 Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N. Engl. J. Med* 372, 2296–2306. [PubMed: 25882510]
- Kalogeris TJ, Kevil CG, Laroux FS, Coe LL, Phifer TJ, Alexander JS, 1999 Differential monocyte adhesion and adhesion molecule expression in venous and arterial endothelial cells. *Am. J. Physiol* 276, L9–L19. [PubMed: 9887050]
- Kao HW, Tsai FY, Hasso AN, 2012 Predicting stroke evolution: comparison of susceptibility-weighted MR imaging with MR perfusion. *Eur. Radiol* 22, 1397–1403. [PubMed: 22322311]
- Kaplan HA, 1961 Collateral circulation of the brain. *Neurology* 11 (4 Pt 2), 9–15. [PubMed: 13751280]
- Kilic T, Akakin A, 2008 Anatomy of cerebral veins and sinuses. *Front Neurol. Neurosci* 23, 4–15. [PubMed: 18004050]

- Knowlton FP, Starling EH, 1912 The influence of variations in temperature and blood-pressure on the performance of the isolated mammalian heart. *J. Physiol* 44, 206–219. [PubMed: 16993122]
- Koerte IK, Schankin CJ, Immler S, Lee S, Laubender RP, Grosse C, Eftimov L, Milde-Busch A, Reiser M, Straube A, Heinen F, Alperin N, Ertl-Wagner B, 2011 Altered cerebrovenous drainage in patients with migraine as assessed by phase-contrast magnetic resonance imaging. *Invest. Radiol* 46, 434–440. [PubMed: 21317790]
- Koh SH, Park HH, 2017 Neurogenesis in stroke recovery. *Transl. Stroke Res* 8, 3–13. [PubMed: 26987852]
- Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL, Jr., 1978 Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am. J. Physiol* 234, H371–383. [PubMed: 645875]
- Kudo K, Liu T, Murakami T, Goodwin J, Uwano I, Yamashita F, Higuchi S, Wang Y, Ogasawara K, Ogawa A, Sasaki M, 2016 Oxygen extraction fraction measurement using quantitative susceptibility mapping: comparison with positron emission tomography. *J. Cereb. Blood Flow Metab* 36, 1424–1433. [PubMed: 26661168]
- Kuffler SW, Potter DD, 1964 Glia in the leech central nervous system: physiological properties and neuron-glia relationship. *J. Neurophysiol* 27, 290–320. [PubMed: 14129773]
- Kulik T, Kusano Y, Aronhime S, Sandler AL, Winn HR, 2008 Regulation of cerebral vasculature in normal and ischemic brain. *Neuropharmacology* 55, 281–288. [PubMed: 18541276]
- Lapchak PA, Zhang JH, 2016 The high cost of stroke and stroke cytoprotection research. *Transl. Stroke Res* (Epub ahead of print).
- Legos JJ, Lenhard SC, Haimbach RE, Schaeffer TR, Bentley RG, McVey MJ, Chandra S, Irving EA, Andrew AP, Barone FC, 2008 SB 234551 selective ET (A) receptor antagonism: perfusion/diffusion MRI used to define treatable stroke model, time to treatment and mechanism of protection. *Exp. Neurol* 212, 53–62. [PubMed: 18462720]
- Leonhard T, Michalik M, 1982 The significance of computerized tomography for the diagnosis of cerebral venous and sinus thromboses. *Psychiatr. Neurol. Med. Psychol* 34, 161–169.
- Liauw L, van Buchem MA, Spilt A, de Bruine FT, van den Berg R, Hermans J, Wasser MN, 2000 MR angiography of the intracranial venous system. *Radiology* 214, 678–682. [PubMed: 10715029]
- Liebeskind DS, Feldmann E, 2016 Imaging of cerebrovascular disorders: precision medicine and the collaterome. *Ann. N. Y. Acad. Sci* 1366 (1), 40–48. [PubMed: 25922154]
- Liebeskind DS, 2003 Collateral circulation. *Stroke* 34, 2279–2284. [PubMed: 12881609]
- Liebeskind DS, 2012 Collateral perfusion: time for novel paradigms in cerebral ischemia. *Int. J. Stroke* 7, 309–310. [PubMed: 22583523]
- Liebeskind DS, 2014 Collateral lessons from recent acute ischemic stroke trials. *Neurol. Res* 36, 397–402. [PubMed: 24641715]
- Liebeskind DS, 2015 Imaging the collaterome: a stroke renaissance. *Curr. Opin. Neurol* 28, 1–3. [PubMed: 25490198]
- Lim RP, Koktzoglou I, 2015 Noncontrast magnetic resonance angiography: concepts and clinical applications. *Radiol. Clin. North Am* 53, 457–476. [PubMed: 25953284]
- Linfante I, Cipolla MJ, 2016 Improving reperfusion therapies in the era of mechanical thrombectomy. *Transl. Stroke Res* 7, 294–302. [PubMed: 27221511]
- Liu S, Connor J, Peterson S, Shuttleworth CW, Liu KJ, 2002 Direct visualization of trapped erythrocytes in rat brain after focal ischemia and reperfusion. *J. Cereb. Blood Flow Metab* 22, 1222–1230. [PubMed: 12368661]
- Lofgren J, 1973 Effects of variations in arterial pressure and arterial carbon dioxide tension on the cerebrospinal fluid pressure-volume relationships. *Acta Neurol. Scand* 49, 586–598. [PubMed: 4770654]
- Luce JM, Huseby JS, Kirk W, Butler J, 1982 A Starling resistor regulates cerebral venous outflow in dogs. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol* 53, 1496–1503. [PubMed: 6759493]
- Magder S, 1990 Starling resistor versus compliance. Which explains the zero-flow pressure of a dynamic arterial pressure-flow relation? *Circ. Res* 67, 209–220. [PubMed: 2364491]

- Mandeville ET, Ayata C, Zheng Y, Mandeville JB, 2017 Translational MR neuroimaging of stroke and recovery. *Transl. Stroke Res* 8, 22–32. [PubMed: 27578048]
- Marchal G, Furlan M, Beaudouin V, Rioux P, Hauttemment JL, Serrati C, de la Sayette V, Le Doze F, Viader F, Derlon JM, Baron JC, 1996 Early spontaneous hyperperfusion after stroke. A marker of favourable tissue outcome? *Brain* 119 (Pt 2), 409–419. [PubMed: 8800936]
- Mayhan WG, Heistad DD, 1986 Role of veins and cerebral venous pressure in disruption of the blood-brain barrier. *Circ. Res* 59, 216–220. [PubMed: 3742745]
- Mayhan WG, Werber AH, Heistad DD, 1987 Protection of cerebral vessels by sympathetic nerves and vascular hypertrophy. *Circulation* 75, 1107–1112. [PubMed: 3791615]
- McCabe C, 2016 Imaging the ischaemic penumbra with T2* weighted MRI. *J. Cereb. Blood Flow Metab* 36, 281–282. [PubMed: 26661167]
- Melhem ER, Jara H, Yucel EK, 1997 Black blood MR angiography using multislab three-dimensional TI-weighted turbo spin-echo technique: imaging of intracranial circulation. *AJR Am. J. Roentgenol* 169, 1418–1420. [PubMed: 9353471]
- Menon BK, Smith EE, Coutts SB, Welsh DG, Faber JE, Goyal M, Hill MD, Demchuk AM, Damani Z, Cho KH, Chang HW, Hong JH, Sohn SI, 2013 Leptomeningeal collaterals are associated with modifiable metabolic risk factors. *Ann. Neurol* 74, 241–248. [PubMed: 23536377]
- Min KJ, Yoon SH, Kang JK, 2011 New understanding of the role of cerebrospinal fluid: offsetting of arterial and brain pulsation and self-dissipation of cerebrospinal fluid pulsatile flow energy. *Med. Hypotheses* 76, 884–886. [PubMed: 21458167]
- Mucke J, Mohlenbruch M, Kickingereder P, Kieslich PJ, Baumer P, Gumbinger C, Purrucker J, Mundiyanapurath S, Schlemmer HP, Bendszus M, Radbruch A, 2015 Asymmetry of deep medullary veins on susceptibility weighted MRI in patients with acute MCA stroke is associated with poor outcome. *PLoS One* 10, e0120801. [PubMed: 25849958]
- Muir KW, Macrae IM, 2016 Neuroimaging as a selection tool and endpoint in clinical and pre-clinical trials. *Transl. Stroke Res* 7, 368–377. [PubMed: 27543177]
- Munuera J, Blasco G, Hernández-Pérez M, Daunis-I-Estadella P, Dávalos A, Liebeskind DS, Wintermark M, Demchuk A, Menon BK, Thomalla G, Nael K, Pedraza S, Puig J, 2017 Venous imaging-based biomarkers in acute ischaemic stroke. *J. Neurol. Neurosurg. Psychiatry* 88, 62–69. [PubMed: 27807197]
- Murtha LA, McLeod DD, Pepperall D, McCann SK, Beard DJ, Tomkins AJ, Holmes WM, McCabe C, Macrae IM, Spratt NJ, 2015 Intracranial pressure elevation after ischemic stroke in rats: cerebral edema is not the only cause, and short-duration mild hypothermia is a highly effective preventive therapy. *J. Cereb. Blood Flow Metab* 35, 2109. [PubMed: 26621060]
- Nguyen J, Nishimura N, Fetcho RN, Iadecola C, Schaffer CB, 2011 Occlusion of cortical ascending venules causes blood flow decreases, reversals in flow direction, and vessel dilation in upstream capillaries. *J. Cereb. Blood Flow Metab* 31, 2243–2254. [PubMed: 21712834]
- Ohta H, Nakano S, Yokogami K, Iseda T, Yoneyama T, Wakisaka S, 2004 Appearance of early venous filling during intra-arterial reperfusion therapy for acute middle cerebral artery occlusion: a predictive sign for hemorrhagic complications. *Stroke* 35, 893–898. [PubMed: 14976322]
- Olsen TS, Larsen B, Skriver EB, Herning M, Enevoldsen E, Lassen NA, 1981 Focal cerebral hyperemia in acute stroke. Incidence: pathophysiology and clinical significance. *Stroke* 12, 598–607. [PubMed: 6975512]
- Olsen TS, Skriver EB, Herning M, 1991 Radiologic manifestations of focal cerebral hyperemia in acute stroke. *Acta Radiol. (Stockholm, Sweden)* 32, 100–104.
- Padget DH, 1956 The cranial venous system in man in reference to development adult configuration, and relation to the arteries. *Am. J. Anatomy* 98, 307–355.
- Palomares SM, Cipolla MJ, 2011 Vascular protection following cerebral ischemia and reperfusion. *J. Neurol. Neurophysiol* 2011.
- Park J, Kim EY, 2010 Contrast-enhanced three-dimensional, whole-brain, black-blood imaging: application to small brain metastases. *Magn. Reson. Med* 63, 553–561. [PubMed: 20187162]
- Parthasarathy R, Kate M, Rempel JL, Liebeskind DS, Jeerakathil T, Butcher KS, Shuaib A, 2013 Prognostic evaluation based on cortical vein score difference in stroke. *Stroke* 44, 2748–2754. [PubMed: 23887836]

- Parthasarathy R, Sohn SI, Jeerakathil T, Kate MP, Mishra SM, Nambiar VK, Ahmad A, Menon BK, Shuaib A, 2015 A combined arterial and venous grading scale to predict outcome in anterior circulation ischemic stroke. *J. Neuroimaging* 25, 969–977. [PubMed: 26082023]
- Pennypacker KR, Bix G, Fraser JF, 2017 Correcting the trajectory of stroke therapeutic research. *Transl. Stroke Res* 8, 65–66. [PubMed: 28039576]
- Permutt S, Riley RL, 1963 Hemodynamics of collapsible vessels with tone: the vascular waterfall. *J. Appl. Physiol* 18, 924–932. [PubMed: 14063262]
- Perrin M, Ramelet AA, 2011 Pharmacological treatment of primary chronic venous disease: rationale: results and unanswered questions. *Eur. J. Vasc. Endovasc. Surg* 41, 117–125. [PubMed: 21126890]
- Peternel L, Stegnar M, Drevensek G, Budihna MV, Bozic M, Zega A, Stalc A, Cerne M, Urleb U, 2005 Antithrombotic potential of new direct thrombin inhibitors built on the azaphenylalanine scaffold in two rat venous thrombosis models. *Thromb. Haemost* 93, 437–442. [PubMed: 15735792]
- Petkova M, Gauvrit JY, Trystram D, Nataf F, Godon-Hardy S, Munier T, Oppenheim C, Meder JF, 2009 Three-dimensional dynamic time-resolved contrast-enhanced MRA using parallel imaging and a variable rate k-space sampling strategy in intracranial arteriovenous malformations. *J. Magnet. Resonance Imaging: JMRI* 29, 7–12.
- Pomschar A, Koerte I, Lee S, Laubender RP, Straube A, Heinen F, Ertl-Wagner B, Alperin N, 2013 MRI evidence for altered venous drainage and intracranial compliance in mild traumatic brain injury. *PLoS One* 8, e55447. [PubMed: 23405151]
- Pranevicius M, Pranevicius O, 2002 Cerebral venous steal: blood flow diversion with increased tissue pressure. *Neurosurgery* 51, 1267–1273 (discussion 1273–1264). [PubMed: 12383372]
- Pranevicius O, Pranevicius M, Liebeskind DS, 2011 Partial aortic occlusion and cerebral venous steal: venous effects of arterial manipulation in acute stroke. *Stroke* 42, 1478–1481. [PubMed: 21441149]
- Pranevicius O, Pranevicius M, Pranevicius H, Liebeskind DS, 2012 Transition to collateral flow after arterial occlusion predisposes to cerebral venous steal. *Stroke* 43, 575–579. [PubMed: 22246692]
- Qureshi AI, 2010 A classification scheme for assessing recanalization and collateral formation following cerebral venous thrombosis. *Jo. Vasc. Intervent. Neurol* 3, 1–2.
- Reichenbach JR, Haacke EM, 2001 High-resolution BOLD venographic imaging: a window into brain function. *NMR Biomed* 14, 453–467. [PubMed: 11746938]
- Reichenbach JR, Jonetz-Mentzel L, Fitzek C, Haacke EM, Kido DK, Lee BC, Kaiser WA, 2001 High-resolution blood oxygen-level dependent MR venography (HRBV): a new technique. *Neuroradiology* 43, 364–369. [PubMed: 11396739]
- Rhoton AL, Jr., 2002 The cerebral veins. *Neurosurgery* 51, S159–205.
- Ritter LS, Orozco JA, Coull BM, McDonagh PF, Rosenblum WI, 2000 Leukocyte accumulation and hemodynamic changes in the cerebral microcirculation during early reperfusion after stroke. *Stroke* 31, 1153–1161. [PubMed: 10797180]
- Rossitti S, 2013 Pathophysiology of increased cerebrospinal fluid pressure associated to brain arteriovenous malformations: the hydraulic hypothesis. *Surg. Neurol. Int* 4, 42. [PubMed: 23607064]
- Rost NS, 2015 Stroke: more than meets the eye[mdash]big consequences of small strokes. *Nat. Rev. Neurol* 11, 249–250. [PubMed: 25848922]
- Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R, 2015 Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N. Engl. J. Med* 372, 2285–2295. [PubMed: 25882376]
- Sbarbati A, Pietra C, Baldassarri AM, Guerrini U, Ziviani L, Reggiani A, Boicelli A, Osculati F, 1996 The microvascular system in ischemic cortical lesions. *Acta Neuropathol* 92, 56–63. [PubMed: 8811126]
- Schaffer CB, Friedman B, Nishimura N, Schroeder LF, Tsai PS, Ebner FF, Lyden PD, Kleinfeld D, 2006 Two-photon imaging of cortical surface microvessels reveals a robust redistribution in blood flow after vascular occlusion. *PLoS Biol* 4, e22. [PubMed: 16379497]

- Schaller B, Graf R, Sanada Y, Tolnay M, Rosner G, Wienhard K, Heiss WD, 2003 Hemodynamic changes after occlusion of the posterior superior sagittal sinus: an experimental PET study in cats. *AJNR Am. J. Neuroradiol* 24, 1876–1880. [PubMed: 14561619]
- Schaller B, 2004 Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. *Brain Res. Brain Res. Rev* 46, 243–260. [PubMed: 15571768]
- Schmidek HH, Auer LM, Kapp JP, 1985 The cerebral venous system. *Neurosurgery* 17, 663–678. [PubMed: 3903542]
- Schwarzmaier SM, Kim SW, Trabold R, Plesnila N, 2010 Temporal profile of thrombogenesis in the cerebral microcirculation after traumatic brain injury in mice. *J. Neurotrauma* 27, 121–130. [PubMed: 19803784]
- Sekhar LN, Chanda A, Morita A, 2002 The preservation and reconstruction of cerebral veins and sinuses. *J. Clin. Neurosci* 9, 391–399. [PubMed: 12217667]
- Sethi SK, Utriainen DT, Daugherty AM, Feng W, Hewett JJ, Raz N, Haacke EM, 2015 Jugular venous flow abnormalities in multiple sclerosis patients compared to normal controls. *J. Neuroimaging* 25, 600–607. [PubMed: 25316522]
- Shi Y, Leak RK, Keep RF, Chen J, 2016 Translational stroke research on blood-brain barrier damage: challenges perspectives, and goals. *Transl. Stroke Res* 7, 89–92. [PubMed: 26757714]
- Shulman K, 1965 Small artery and vein pressures in the subarachnoid space of the dog. *J. Surg. Res* 5, 56–61. [PubMed: 14258939]
- Si Z, Luan L, Kong D, Zhao G, Wang H, Zhang K, Yu T, Pang Q, 2008 MRI- based investigation on outflow segment of cerebral venous system under increased ICP condition. *Eur. J. Med. Res* 13, 121–126. [PubMed: 18499557]
- Smith PD, 2000 Micronized purified flavonoid fraction and the treatment of chronic venous insufficiency: microcirculatory mechanisms. *Microcirculation (New York, N.Y.: 1994)* 7, S35–S40.
- Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, Smith WS, Wintermark M, 2010 Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. *Stroke* 41, e34–e40. [PubMed: 19910542]
- Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M, 2006 Astrocyte-mediated control of cerebral blood flow. *Nat. Neurosci* 9, 260–267. [PubMed: 16388306]
- Tateishi Y, Wisco D, Aoki J, George P, Katzan I, Toth G, Hui F, Hussain MS, Uchino K, 2015 Large deep white matter lesions may predict futile recanalization in endovascular therapy for acute ischemic stroke. *Intervent. Neurol* 3, 48–55.
- Ushiwata I, Ushiki T, 1990 Cytoarchitecture of the smooth muscles and pericytes of rat cerebral blood vessels: a scanning electron microscopic study. *J. Neurosurg* 73, 82–90. [PubMed: 2161912]
- van Royen N, Piek JJ, Schaper W, Fulton WF, 2009 A critical review of clinical arteriogenesis research. *J. Am. Coll. Cardiol* 55, 17–25. [PubMed: 20117358]
- van den Wijngaard IR, Wermer MJ, Boiten J, Algra A, Holswilder G, Meijer FJ, Dippel DW, Velthuis BK, Majoie CB, van Walderveen MA, 2016 Cortical venous filling on dynamic computed tomographic angiography: a novel predictor of clinical outcome in patients with acute middle cerebral artery stroke. *Stroke* 47, 762–767. [PubMed: 26814234]
- van der Veen PH, Muller M, Vincken KL, Hendrikse J, Mali WP, van der Graaf Y, Geerlings MI, 2015 Longitudinal relationship between cerebral small-vessel disease and cerebral blood flow: the second manifestations of arterial disease-magnetic resonance study. *Stroke* 46, 1233–1238. [PubMed: 25804924]
- Verma RK, Hsieh K, Gratz PP, Schankath AC, Mordasini P, Zubler C, Kellner-Weldon F, Jung S, Schroth G, Gralla J, El-Koussy M, 2014 Leptomeningeal collateralization in acute ischemic stroke: impact on prominent cortical veins in susceptibility-weighted imaging. *Eur. J. Radiol* 83, 1448–1454. [PubMed: 24882785]
- Wang X, Feuerstein GZ, 1995 Induced expression of adhesion molecules following focal brain ischemia. *J. Neurotrauma* 12, 825–832. [PubMed: 8594210]
- Wang S, Zhang H, Dai X, Sealock R, Faber JE, 2010 Genetic architecture underlying variation in extent and remodeling of the collateral circulation. *Circ. Res* 107, 558–568. [PubMed: 20576932]

- Wei EP, Kontos HA, 1982 Responses of cerebral arterioles to increased venous pressure. *Am. J. Physiol* 243, H442–447. [PubMed: 7114275]
- Xie G, Chen H, He X, Liang J, Deng W, He Z, Ye Y, Yang Q, Bi X, Liu X, Li D, Fan Z, 2017 Black-blood thrombus imaging (BTI): a contrast-free cardiovascular magnetic resonance approach for the diagnosis of non-acute deep vein thrombosis. *J. Cardiovasc. Magnet. Resonance* 19, 4.
- Xing C, Hayakawa K, Lo EH, 2017 Mechanisms imaging, and therapy in stroke recovery. *Transl. Stroke Res* 8, 1–2. [PubMed: 27714670]
- Xu HL, Mao L, Ye S, Paisansathan C, Vetri F, Pelligrino DA, 2008 Astrocytes are a key conduit for upstream signaling of vasodilation during cerebral cortical neuronal activation in vivo. *Am. J. Physiol. Heart Circ. Physiol* 294, H622–632. [PubMed: 18055520]
- Xu H, Ping Y, Lin H, He P, Li W, Dai H, 2016 Antiplatelet strategies and outcomes in patients with noncardioembolic ischemic stroke from a real-World study with a five-Year follow-Up. *Transl. Stroke Res*
- Yada K, Nakagawa Y, Tsuru M, 1973 Circulatory disturbance of the venous system during experimental intracranial hypertension. *J. Neurosurg* 39, 723–729. [PubMed: 4759659]
- Yamashima T, Friede RL, 1984 Why do bridging veins rupture into the virtual subdural space? *J. Neurol. Neurosurg. Psychiatry* 47, 121–127. [PubMed: 6707651]
- Yan S, Wan J, Zhang X, Tong L, Zhao S, Sun J, Lin Y, Shen C, Lou M, 2014 Increased visibility of deep medullary veins in leukoaraiosis: a 3-T MRI study. *Front. Aging Neurosci* 6, 144. [PubMed: 25071553]
- Yao Z, Wang L, Wu X, Zhao L, Chi C, Guo L, Tong D, Yang X, Dong Z, Deng R, Novakovic VA, Thatte HS, Bi Y, Tian Y, Shi J, Zhou J, Kou J, Hu S, 2017 Enhanced procoagulant activity on blood cells after acute ischemic stroke. *Transl. Stroke Res* 8, 83–91. [PubMed: 27650774]
- Yildiz F, Coban S, Terzi A, Aksoy N, Bitiren M, 2015 Protective effect of micronized purified flavonoid fraction on ischemia/reperfusion injury of rat liver. *Transplant. Proc* 47, 1507–1510. [PubMed: 26093753]
- Yu X, Yuan L, 2016 Prominence of medullary veins on susceptibility-Weighted images provides prognostic information in patients with subacute stroke. *AJNR Am. J. Neuroradiol* 37, 423–429. [PubMed: 26514606]
- Yu W, Rives J, Welch B, White J, Stehel E, Samson D, 2009 Hypoplasia or occlusion of the ipsilateral cranial venous drainage is associated with early fatal edema of middle cerebral artery infarction. *Stroke* 40, 3736–3739. [PubMed: 19762692]
- Yura S, Sako K, Yonemasu Y, 1990 The effects of disturbance of cerebral venous drainage on focal cerebral blood flow and ischemic cerebral edema. *No to shinkei = Brain Nerve* 42, 269–275. [PubMed: 2369531]
- Zhang H, Prabhakar P, Sealock R, Faber JE, 2010 Wide genetic variation in the native pial collateral circulation is a major determinant of variation in severity of stroke. *J. Cereb. Blood Flow Metab* 30, 923–934. [PubMed: 20125182]
- Zhang JH, Badaut J, Tang J, Obenaus A, Hartman R, Pearce WJ, 2012 The vascular neural network—a new paradigm in stroke pathophysiology. *Nat. Rev. Neurol* 8, 711–716. [PubMed: 23070610]
- Zhang S, Chen W, Tang H, Han Q, Yan S, Zhang X, Chen Q, Parsons M, Wang S, Lou M, 2016 The prognostic value of a four-dimensional CT angiography-based collateral grading scale for reperfusion therapy in acute ischemic stroke patients. *PLoS One* 11, e0160502. [PubMed: 27505435]
- Zhang S, Lai Y, Ding X, Parsons M, Zhang JH, Lou M, 2017 Absent filling of ipsilateral superficial middle cerebral vein is associated with poor outcome after reperfusion therapy. *Stroke* 48, 907–914. [PubMed: 28265013]
- Zhong G, Yan S, Zhang S, Chen Q, Lai Y, Lou M, 2016 Association between leukoaraiosis and poor outcome is not due to reperfusion inefficiency after intravenous thrombolysis. *Transl. Stroke Res* 7, 439–445. [PubMed: 27256491]
- Zivin JA, Fisher M, DeGirolami U, Hemenway CC, Stashak JA, 1985 Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science* 230, 1289–1292. [PubMed: 3934754]

Fig. 1.

The lateral (superior) and sagittal (inferior) view of cerebral superficial veins. The four groups of cerebral superficial veins are indicated in deep blue (the superior sagittal group), deep purple (the sphenoidal group), green (the tentorial group) and light blue (the falcine group), respectively. The veins involved in deep venous systems are indicated with light purple.

Fig. 2. The lateral view of cerebral deep veins.

The main cerebral deep veins are demonstrated as thalamostriate veins, internal cerebral veins, anterior cerebral veins, deep Sylvian veins, the basal veins, and the vein of Galen.

Fig. 3. Mechanisms of the cerebral arterial and venous autoregulation in hypoperfusion. Cerebral arterial and venous systems share traits in autoregulation in hypoperfusion. The mechanisms involve sympathetic control, cerebral metabolism, endothelium function and myogenic response. Compared with the arterial system, the cerebral venous system showed similarities (blue solid line) in sympathetic control and cerebral metabolism. However, data is scarce involving the endothelium function and myogenic response (blue dotted line). CBV: cerebral blood volume; CBF: cerebral blood flow.

Fig. 4.

The ESWAN (enhanced gradient echo T2 star weighted angiography) Imaging of a Patient with Obstruction of MCA: A: the diffusion weighed imaging (DWI) showing a newly-onset infarction in the right middle cerebral artery (MCA) territory; B: the magnetic resonance angiography (MRA) of right ICA occlusion. And the white arrow showed the left anterior cerebral artery (ACA), the wide black arrow pointed to the left middle cerebral artery (MCA), the narrow black arrow indicated the left internal cerebral artery (ICA). All these arteries are not displayed in right side; C and D: the enhanced gradient echo T2 star weighted angiography (ESWAN) showing the engorgement of the medullary veins in the ischemic hemisphere.

Fig. 5. The CE-MRV demonstration for a cranial hypertensive patient with 3D reconstruction. The cerebral venous structures in (A) sagittal, (B) coronal, and (C) axial planes are shown by CE-MRV. (D) and (E) show 3D reconstructed view of cortical veins and dura sinuses, whereas (F) reveals the detailed reconstructed deep veins. CE-MRV, contrast enhanced magnetic resonance venography.

Fig. 6. The cortical veins shown by dCTV.

Using dynamic CT venography (dCTV), the main cortical veins are now assessable. The axial, coronal and sagittal plain are respectively evaluated to ensure the course of veins (Zhang et al., 2017). SMCV, superficial middle cerebral vein (the vein of Sylvian); VOT, vein of Trolard; VOL, vein of Labbé.

Fig. 7. Possible Roles of Venous Collaterals in Stroke and Futile Recanalization.

The possible roles of venous collaterals to maintain sufficient cerebral perfusion and to reduce reperfusion injury are shown in the upper part of the figure. In the settings of futile recanalization, the possible roles that venous collateral involved are depicted when reperfusion happens or not.

Fig. 8. The major anastomosis in the hemispheric convexity. Using dynamic CT venography (dCTV), the major anastomosis in the hemispheric convexity is outlined (Zhang et al., 2017). SMCV, superficial middle cerebral vein (the vein of Sylvian); VOT, vein of Trolard; VOL, vein of Labbé.

Fig. 9.

A Three-dimensional Outline of Cerebral Venous Collateral: Shown are superior sagittal sinus, inferior sagittal sinus, straight sinus, transverse sinus, the vein of Galen, sphenoparietal sinus, superior petrosal sinus, inferior petrosal sinus, cavernous sinus, the vein of Trolard, the vein of Sylvian (the superficial middle cerebral vein), the vein of Labbe, the frontal veins, internal cerebral vein, the vein of Rosenthal (the basal vein), pterygoid plexus, the facial vein, parietal emissary vein, occipital emissary vein. The dura sinuses and some deep sinuses are indicated in grey color, implicating as impossible route for bilateral venous communicating. Traditional deep venous system is indicated in purple color.

Fig. 10.

The Catalogue of Class I and Class II Cerebral Venous Collateral: A: intra-extracranial venous collaterals (Class II venous collaterals); B: the venous circle communicating bilateral venous blood flow (Class I venous collaterals); C: cortical venous anastomoses among dural sinuses and cortical veins (Class II venous collaterals); D: deep and superficial medullary veins (Class II venous collaterals). Shown are (a) superior sagittal sinus; (b) inferior sagittal sinus; (c) straight sinus; (d) transverse sinus; (e) the ophthalmic veins; (f) the occipital sinus; (g) mastoid and condyloid emissary veins; (h) inferior petrosal sinus; (i) cavernous sinus; (j) the vein of Trolard; (k) the vein of Sylvian (the superficial middle cerebral vein); (l) the vein of Labbe; (m) vertebral veins; (n) internal jugular vein; (o) occipital emissary vein; (p) pterygoid plexus; (q) the facial vein; (r) parietal emissary vein; (s) deep medullary vein; (t) anterior cerebral vein; (u) anterior communicating vein; (v) deep middle cerebral vein; (w) the peduncular vein; (x) posterior communicating vein; (y) superficial medullary vein.

Table 1

Imaging models for venous demonstration.

Imaging model	Advantages	Disadvantages
DSA	widespread availability, excellent spatial resolution, and clinician familiarity	invasive procedure; high dose of radiation exposure; contrast-associated allergy and injury
TOF-MRV	non-contrast; non-invasive; good to reveal cortical veins and dura sinuses	insufficient demonstration of deep veins; high background noise; hard to detect in-plane flow
PC-MRV	less background noise than TOF-MRV; quantify flow rate and direction;	Longer acquisition time than TOF-MRV
SWI	clear visualization of even small veins; detect changes in venous blood oxygenation	
Black blood MR angiography	excellent visualization of vessels of narrow caliber with retrograde or slow flow; easy to see venous thrombus	
CE-MRV	superior in visualization of intracranial venous structures comparing with PC-MRV and TOF-MRV	gadolinium contrast related allergy and injury
CTV	comparable with CE-MRV in visualization of venous structures	iodinated contrast medium related allergy and injury; relative high radiation exposure
Time-resolved MRV or CTV	good to show the timing of cerebral venous drainage	longer acquisition time than mono-phase MRV or CTV, higher radiation exposure

DSA: Digital subtracted angiography; TOF-MRV: Time-of-Flight magnetic resonance venography; PC-MRV: Phase Contrast magnetic resonance venography; SWI: Susceptibility-Weighted Imaging; Black blood MR angiography: Black blood magnetic resonance angiography; CE-MRV: Contrast-enhanced 3-Dimensional magnetic resonance venography; CTV: Contrast-enhanced 3-Dimensional CT venography; Time-resolved MRV or CTV: Time-resolved contrast-enhanced 3-dimensional magnetic resonance venography or CT venography.