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Cerebral Venous System in Acute and Chronic Brain Injuries

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Chapter 1
Neurovascular Network as Future Therapeutic Targets

Yujie Chen, Yang Zhang, Zhenni Guo, Ling Liu, Feng Gao, Yanfeng Lv, Meng Zhang, Xiaochuan Sun, Andre Obenaus, Yi Yang, Jiping Tang, Hua Feng, and John H. Zhang

Abstract In recent years, endovascular treatment, including pharmaceutical drugs and intervention therapy, has become one of the most effective strategies for stroke patients. However, neurobiological and neurovascular functions, before, during and after endovascular therapy, have not been fully addressed and remain to be clarified. It is extremely important for basic neurovascular scientists and clinicians to understand the neurobiological and neurovascular fundamentals of neuroimaging mismatches and the infarct size of stroke patients, hyperperfusion or hypoperfusion after thrombolysis or thrombolectomy, and brain swelling and hemorrhage after successful thrombolectomy. These clinical mismatches and complexities after endovascular therapy are related to active tissue connections in the neurovascular

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network and the function of neurobiological and neurovascular components after stroke. This comprehensive review summarizes the fundamental neurobiology and neurovascular function in endovascular therapy for stroke patients, using both basic science research and clinical studies, with a focus on cerebral hemodynamics, cell energy metabolism, and neurovascular injuries such as brain swelling, hemorrhage or over-reperfusion. A major emphasis is the potential role of cerebral collateral circulation and venous circulation during and after endovascular therapy. It is clear that the cerebral hemodynamic balance, venous function, and autoregulation are all involved in endovascular therapy.

Keywords Neurovascular network · Cerebral veins · Stroke

Abbreviations

CBF	Cerebral blood flow
CBF	Cerebral blood flow
CFI	Collateral flow index
CO_2	Carbon dioxide
CPP	Cerebral perfusion pressure
CT	Computed tomography
CTA	computed tomography angiography
CTP	Computed tomography perfusion
CTV	Computed tomography venography

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DSA	Digital subtraction angiography
DVP	Draining vein pressure
DWI	Diffusion weighted imaging
ECD	Echo color Doppler
EG	Emptying gradient
ET	Emptying time
FG	Filling gradient
FLAIR	Fluid-attenuated inversion recovery
fMUS	Functional micro-ultrasound
FT	Filling time
GOS	Glasgow outcome scale
HBinF	Head inflow
HBoutF	Head outflow
MCAO	Middle cerebral artery occlusion
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NIHSS	National Institutes of Health Stroke Scale
NO	Nitric oxide
OPS	Orthogonal polarized spectral
PDGF	Platelet-derived growth factor
PDGF-BB	Platelet-derived growth factor-BB
PPARγ	Peroxisome proliferator-activated receptor-gamma
rCBF	Relative cerebral blood flow
rCBV	Relative cerebral blood volume
ROS	Reactive oxygen species
rtPA	Recombinant tissue plasminogen activator
RV	Residual volume
SPECT	Single photon emission computed tomography
SSS	Superior sagittal sinus
SWI	Susceptibility weighted imaging
VEGF	Vascular endothelial growth factor
VV	Venous volume

1 Introduction

Despite decades of efforts in basic and clinical research worldwide, stroke remains an intractable disease associated with high morbidity and mortality. Since 1847, R. Virchow's observation that venous thrombi often migrate to the lungs and other organs, which were subsequently named "embolism" and "thrombosis", the origins of ischemia, has altered our understanding of stroke [1, 2]. Since then, neurologists started to emphasize the vascular cause of ischemic stroke and prevention in the 1950s, which was followed by the introduction of endovascular therapies in the

1980s and recombinant tissue plasminogen activator (rtPA) in the 1990s [3, 4]. These strategies tended to retard ischemia progression and to re-establish vascular reperfusion. To date, these strategies remain at the frontline of early treatment after stroke [5], partially due to failures related to clinical translational studies of neuroprotective drugs based on the concept of neuroprotection to reduce infarction since 1980s [6].

Upon entering the twenty-first century, the concept of the neurovascular unit presented by Lo del Zoppo and Iadecola et al., gained attention for the discovery of novel strategies for stroke patients [7–9]. In this unit, neurologists attempted to emphasize and protect connections among vulnerable neurons, simultaneously supporting astrocytes and endothelial cells, not only to reduce infarction but also to regenerate and reorganize the ischemic brain tissues after stroke [10, 11]. Thus, the blood brain barrier, as the classical and most typical structure in the neurovascular unit, has become the hot topic for stroke research [12]. However, additional cellular populations and other structures are also present in the central nervous system, such as microglia, pericytes and venules, among others, all of which influence the outcomes of stroke patients [13–15]. Hence, the vascular neural network might provide an advanced comprehension of the neurobiology of stroke, shedding new light on the neurovascular network, reperfusion control and vein drainage during endovascular therapies for stroke patients [16–18] (Fig. 1.1).

Fig. 1.1 History of stroke pathophysiology

As we have introduced, endovascular treatment, including pharmaceutical drugs and intervention therapy, has become one of the most effective strategies for stroke patients since the late twentieth century [19]. However, the neurobiological and neurovascular functions before, during and after endovascular therapy have not been fully addressed and remain to be clarified, which might unveil important pathophysiologies related to clinical mismatches and complexities after endovascular therapy related to active tissue connections in the neurovascular network and the functions of neurobiological and neurovascular components after stroke. Therefore, in the present review, we will summarize the fundamental neurobiology and neurovascular function in endovascular therapy for stroke patients, using both basic science research and clinical studies focusing on cerebral hemodynamics, cell energy metabolism, and neurovascular injuries such as brain swelling, hemorrhage or over-reperfusion. A major emphasis of this review is the potential role of cerebral collateral circulation and venous circulation during and after endovascular therapy.

2 The Mismatch Between Preclinical Models and Clinical Types

Stroke can be divided into two main types: ischemic stroke due to lack of blood flow and hemorrhagic stroke due to bleeding, with a subtype of subarachnoid hemorrhage by aneurysm rupture. Despite preventive strategies, current therapies include intravenous thrombolysis and thrombectomy for ischemic stroke, emergent surgery for hemorrhagic stroke, followed by monitoring and various neuroprotective treatments for better outcomes [20–24]. Nevertheless, these strategies could alleviate stroke patients at a certain level, but they supply unexpected and new problems for the neurologist, such as cerebral hemodynamics, cell energy metabolism, as well as neurovascular injuries such as brain swelling, hemorrhage transformation or over-reperfusion.

Rethinking the critical reasons for these unsatisfactory outcomes and unexpected problems in current therapies for stroke patients, we may want to know whether previous research aims addressed the correct target and whether our research methods were appropriate. Like all disappointing experiments, the first and foremost response is to go back to the basics, especially our preclinical models and to understand the pathophysiology after stroke.

In recent years, the most popular stroke model is middle cerebral artery occlusion (MCAO) in rodents, which is induced by nylon suture insertion into the unilateral middle cerebral artery for 2 h, followed by suture withdrawal and recanalization. Typically, this model causes a massive ischemic lesion in the rodent brain, similarly to stroke patients at a certain level. Whether 2 h' ischemia/reperfusion really matches the clinical situation, or 1 h or 4 h or long of ischemia/reperfusion would be optimal remains unknown. It is known that short-time ischemia might have a neuroprotective effect and be considered an ischemic precondition, and long-term

ischemia might cause a large parenchymal lesion and hemorrhagic transformation. Nevertheless, various types exist in the clinical setting, from transient ischemic attack to longer term endovascular recanalization with over-perfusion, brain swelling, hemorrhagic transformation, or non-perfusion.

2.1 Recanalization Leads to a Small Infarction

As suggested by the guidelines, if thrombolectomy is performed and the clot is removed within 6 h after stroke onset, no infarction or a small infarction will be detected in patients. However, after 2 h of MCAO, the large infarction observed in rats does not match the clinical situation. For example (Fig. 1.2), a 70-year-old female ischemic stroke patient was admitted 3 h after losing consciousness. Immediate computed tomography angiography (CTA) indicated that her left internal carotid was occluded. Interventional surgery was performed, and the clot was removed within the first hour after emergency administration. She then recovered consciousness and muscle strength of the right limb back to level III. Head CT reexamination only showed a small infarction in the left hemisphere. In comparison to the infarction at 2 h in the MCAO rodent model, the ischemic lesion in this patient was much smaller. This is the first type of mismatch between the preclinical model and the clinical type. Sometimes researchers have considered this phenomenon as a species difference, but the precise difference is unknown.

2.2 Unsuccessful Recanalization Leads to a Small Infarction

However, a failed thrombolectomy or unsuccessful clot removal within 6 h after stroke must also be addressed. Another 61-year-old male patient (Fig. 1.3) with a history of smoking suffered from left limb paralysis and alalia for 5 h. Physical examination indicated dysarthria, left facial paralysis, left arm muscle strength level zero, left leg muscle strength level I, and National Institutes of Health Stroke Scale (NIHSS) of 15 points. During surgery, digital subtraction angiography (DSA) indicated stenosis in the proximal middle cerebral artery with thrombosis at the distal end of this vessel. After thrombolectomy and balloon dilatation, DSA showed successful recanalization. However, 5 min later, the artery occluded again. Clearly, this patient experienced middle cerebral artery occlusion for a long time, greatly exceeding the suggested recanalization time window. However, surprisingly, physical examination at 24 h after surgery indicated clear consciousness, mild dysarthria, left arm muscle strength level IV, left leg muscle strength level V, and NIHSS of 3 points. More importantly, the head computed tomography (CT) examination did not reveal a large infarction. This phenomenon represents another type of mismatch between the preclinical model and the clinical situation because unsuccessful

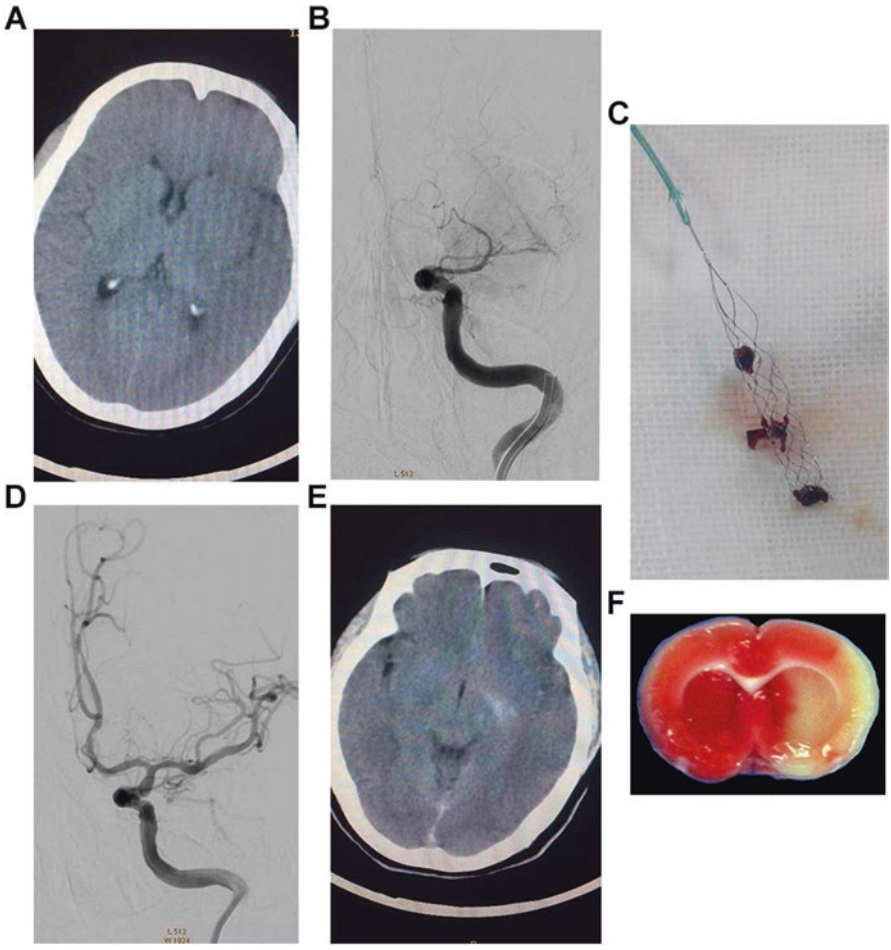

Fig. 1.2 Case I: recanalization leads to small infarction. A female ischemic stroke patient, 70-year-old, was admitted at 3 h after conscious lost (**a**). Immediate digital subtraction angiography (DSA) indicated her left internal carotid occluded (**b**). Interventional surgery was performed and the clot was removed within the first hour after administration in emergency (**c**, **d**). After then, she recovered consciousness and the muscle strength of right limb backed to level III. Head computed tomography (CT) reexamination only showed small infraction in left hemisphere (**e**). Comparing to the infarction in 2 h' middle cerebral artery occlusion (MCAO) rodent model (**f**), the ischemic lesion of this patient is much smaller

thrombolectomy/clot removal induced much smaller infarction than 2 h in the MCAO rodent model. Furthermore, previous studies have indicated that the post-stroke ischemic lesion in rodents automatically vanished after several months, even in the absence of treatment. Whether this phenomenon can be classified as a species difference or something else remains to be determined.

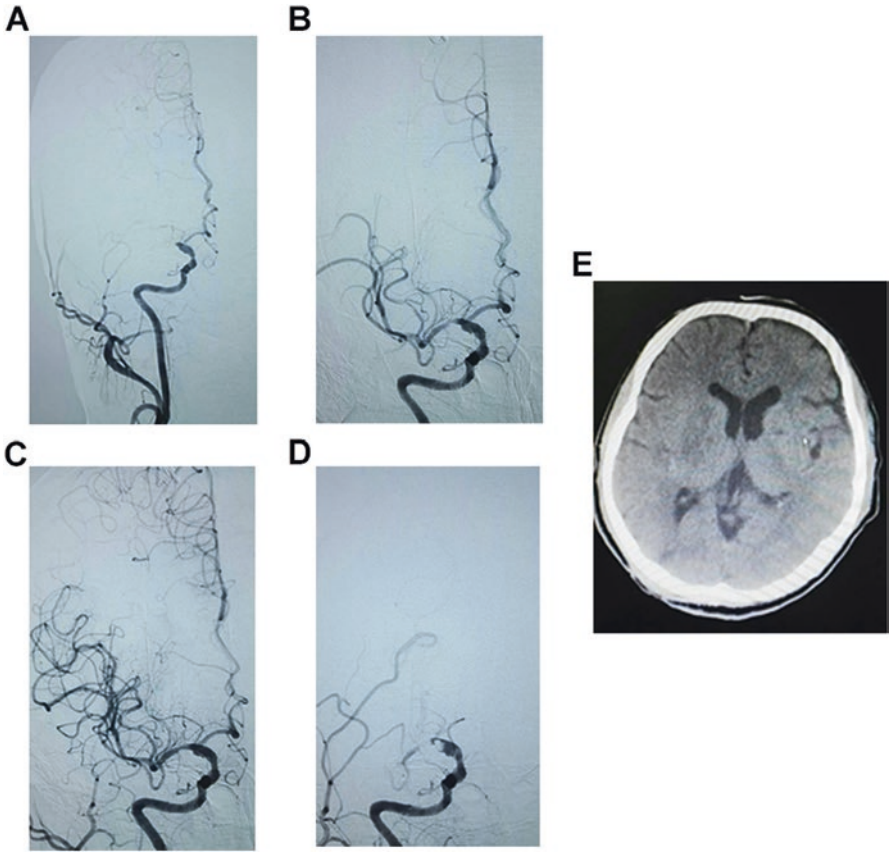

Fig. 1.3 Case II: unsuccessful recanalization leads to small infarction. Male patient, 61-year-old with smoke history, suffered with left lime paralysis and alalia for 5 h. Physical examination indicated dysarthria, left facial paralysis, left arm muscle strength level zero, left leg muscle strength level I, and the National Institutes of Health Stroke Scale (NIHSS) is 15 point. During surgery, the digital subtraction angiography (DSA) indicated the stenosis in the proximal of middle cerebral artery with thrombosis in the far-end of this vessel (**a**, **b**). After thrombolectomy and balloon dilatation, DSA showed successful recanalization (**c**). But 5 min later, the artery occluded again (**d**). Clearly, this is a patient with middle cerebral artery occlusion for a long time, way beyond the suggested recanalization time window. But, surprisingly, physical examination at 24 h after surgery indicated clear consciousness, mild dysarthria, left arm muscle strength level IV, left leg muscle strength level V, with 3 point on NIHSS. More importantly, the head computed tomography (CT) examination did not show large infarction exist (**e**)

2.3 Recanalization Leads to Bleeding, Edema, and Massive Infarction

Despite these two cases with surprisingly good outcomes, the following case may attract a large amount of attention in our clinical practice. A 71-year-old male patient (Fig. 1.4) suffered from right limb weakness and speech difficulty for 7 h.

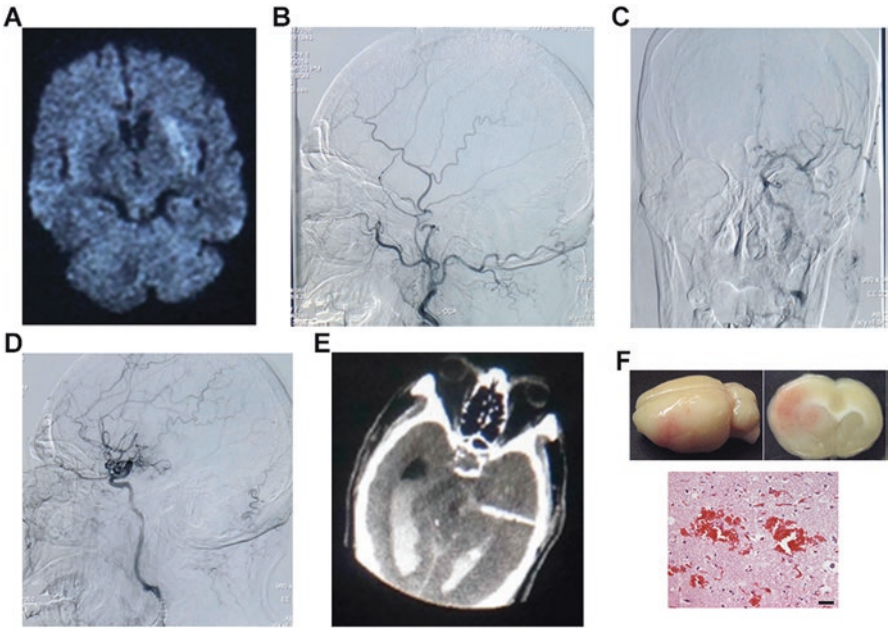

Fig. 1.4 Case III: recanalization leads to bleeding, edema, massive infarction. Male patient, 71-year-old, suffered with right limb weakness and speaking difficulty for 7 h. Emergency computed tomography (CT) showed no infarction at 4 h after stroke onset, and urikanase 60 k unit was administrated intravenously. After admission, magnetic resonance imaging (MRI) indicated left internal carotid artery occlusion and left basal ganglia infarction (**a**). digital subtraction angiography (DSA) was performed and urikanase 30,000 unit was intraarterial injected for thrombolysis (**b**, **c**). The left internal carotid artery recanalized (**d**), but unfortunately, left basal ganglia bleed at 2 h after urikanase administration (**e**), and this patient died at 23 h after stroke onset. Meanwhile, the 2 h' middle cerebral artery occlusion (MCAO) model failed to produce those pathologies, some rodent model even followed with hemorrhagic transformation (**f**)

Emergency CT revealed no infarction at 4 h after stroke onset, and a 60-k unit of urikanase was administered intravenously. After admission, magnetic resonance imaging (MRI) indicated left internal carotid artery occlusion and left basal ganglia infarction. DSA was performed, and 30,000 units of urikanase was injected intra-arterially for thrombolysis. The left internal carotid artery was recanalized, but unfortunately the left basal ganglia bled at 2 h after urikanase administration, and the patient died at 23 h after stroke onset. Such a case may occur infrequently in the clinic, but the reason for the occurrence of thrombolectomy or thrombolysis following over perfusion, brain edema, hemorrhage or sometimes massive infarction remains to be elucidated [25]. The 2-h MCAO model failed to produce those pathologies, and some rodent models even showed hemorrhagic transformation. As proposed in our previous reviews and other studies, blood brain barrier disruption and vasogenic edema may be the underlying cause of these events. However, the effects of blood brain barrier disruption and vasogenic edema in this situation remain to be described.

2.4 Vein Compression Involved in Reperfusion Injury

We usually focus on the arteries during the treatment of a stroke patient. However, the following case indicates that changes occur in the cerebral venous system. An 80-year-old male patient (Fig. 1.5) suffered with aphasia and right limb paralysis for 3 h when he was transferred to the emergency room. The NIHSS was evaluated as 22 points, and rtPA was administered for 30 min without change. The head CT perfusion (CTP) indicated a cerebral blood volume lower than normal in the left temporal lobe. CTA revealed left internal carotid artery occlusion, blood supply compensation by the anterior communicating artery, and occlusion of the left middle cerebral artery. The neurologist made great efforts in the operating room, and the occluded arteries finally recanalized at 10 h after stroke onset. Unfortunately, massive middle cerebral artery infarction occurred after recanalization. Magnetic resonance angiography (MRA) at 16 h after surgery indicated much more abundant vascular imaging of the left middle cerebral artery than the right side, while the magnetic resonance susceptibility weighted imaging (SWI) indicated that ipsilateral venous imaging was much weaker than the right side. The massive brain swelling suggested that this patient needed decompression, but his family gave up. This patient underwent a successful recanalization surgery but had a bad outcome. Why the ipsilateral venous system collapsed after recanalization remains unknown. A reasonable assumption is that the patient had venous infarction and subsequent hemorrhagic transformation.

2.5 Infarction Is Reversible Even After Days

Traditional understanding treats stroke as a catastrophe due to unsatisfactory outcomes of patients irrespective of treatment. However, a few fortunate patients, like this 76-year-old female patient (Fig. 1.6) with a middle cerebral artery occlusion, had a head CT showing no infarction on the first day. Thrombolectomy surgery was successfully performed and clots retrieved, but the patient remained in a coma. On day 7, head CT reexamination revealed a large low density, but this patient

Fig. 1.5 (continued) changed. The head CT perfusion (CTP) indicated cerebral blood volume lower than normal at the left temporal lobe (**a**). Computed tomography angiography (CTA) showed the left internal carotid artery occlusion, blood supply was compensated with anterior communicating artery, and the left middle cerebral artery also occluded (**b**). Neurologist made great efforts in operation room, and the occluded arteries finally recanalized at 10 h after stroke onset (**c**). But unfortunately, the massive middle cerebral artery infarction occurred after recanalization (**d**). Magnetic resonance angiography (MRA) at 16 h after surgery indicated vascular imaging of left middle cerebral artery was much abundant than right side (**e**), while the magnetic resonance susceptibility weighted imaging (SWI) indicated the venous imaging of ipsilateral was much weaker than right side (**f**). The massive brain swelling suggested this patient needed decompression, but his family gave up

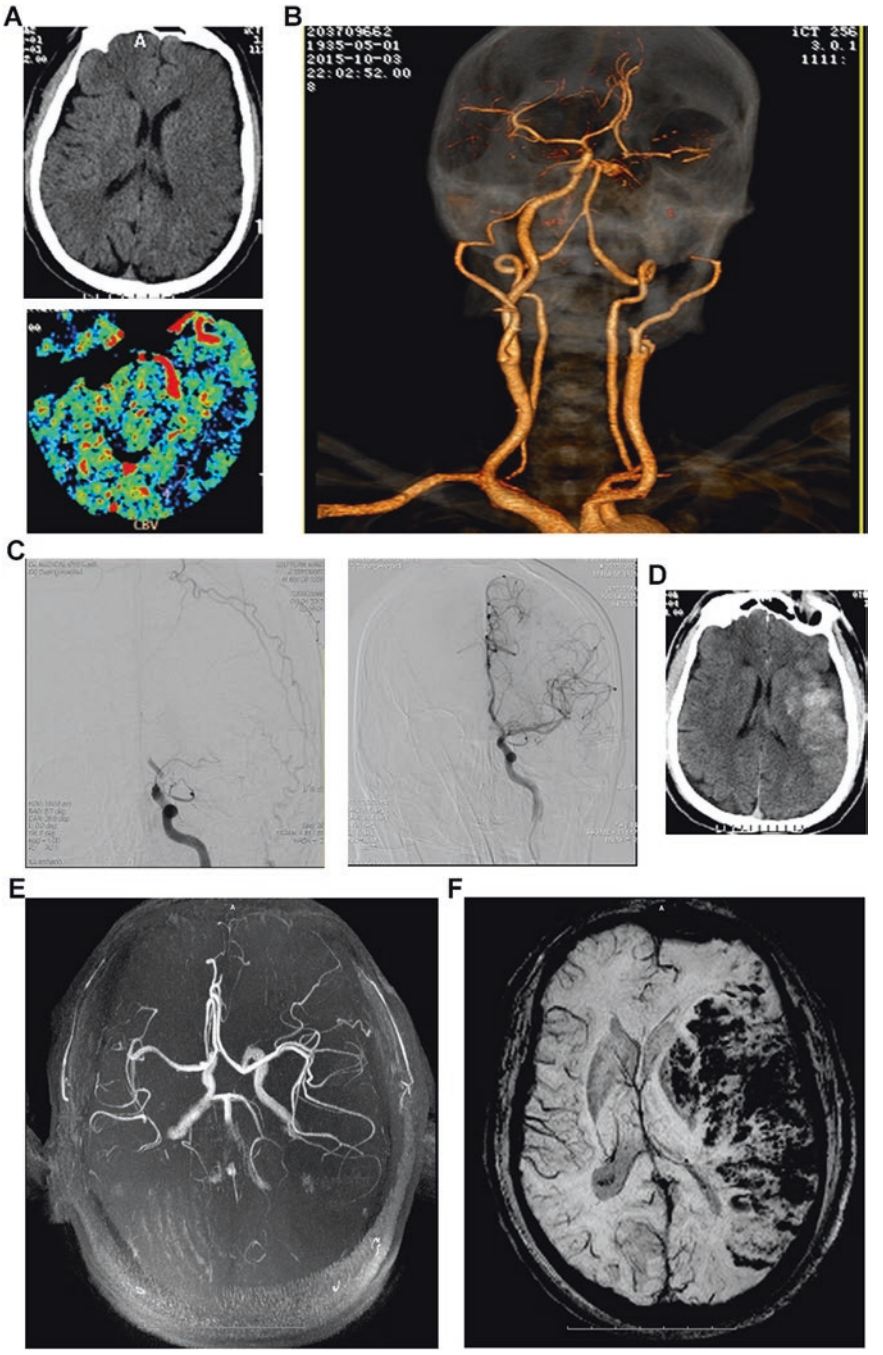

Fig. 1.5 Case IV: veins compression involved in reperfusion injury. Male patient, 80-year-old, suffered with aphasia and right limb paralysis for 3 h when he was transferred to emergency room. The NIHSS was evaluated at the level of 22 point, and rtPA was given for 30 min, but nothing

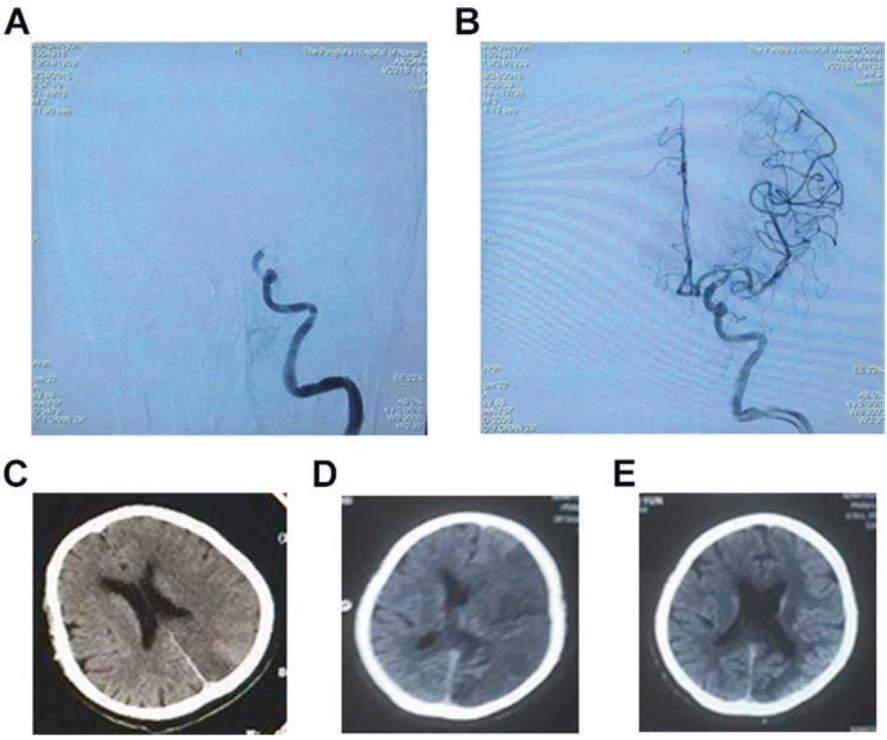

Fig. 1.6 Case V: infarction is reversible even after days. Female middle cerebral artery occlusion patient, 76-year-old, head computed tomography (CT) showed no infarction at the first day (**a**, **c**). Then thrombolectomy surgery was successfully performed and clots were retrieved (**b**, **c**), but the patient was still in coma. On day 7, head CT reexamination showed large low density existed (**d**), but this patient recover consciousness at day 12, then CT on day 14 showed the infraction area significantly reduced (**e**) and the patient awaked with aphasia

recovered consciousness on day 12. The CT on day 14 showed a significantly reduced infarction area, and the patient woke with aphasia. This may be similar to the long-term outcomes observed in rodents, but the brain tissues were clearly damaged during the first few hours after stroke onset. Thus, we must determine how to repeat this favorable outcome.

3 Establishment of New Stroke Pathophysiology to Address Clinical Issues

Based on the above cases in clinical practice, we might wonder why these preclinical models did not match and mimic the actual clinical manifestations. Perhaps other pathophysiologies were missed.

3.1 Emphasis on Recirculation: Both Arterial and Venous Blood Flow

Since the seventeen century, stroke, known previously as cerebral apoplexy, was identified as a major cerebral vascular disorder by Johann Jacob Wepfer [26]. Subsequently in the late eighteen century, Rudolf Virchow defined the pathophysiology of apoplexy as mechanical blood clots that interrupt the blood flow to the brain [27]. Stroke therapy then passed through the time of blood factors and vascular risk factors, entering the time of neuroprotection [26, 28]. However, large clinical trials investigating neuroprotection soon followed but quickly failed due to the difficulty protecting neurons despite ongoing vascular occlusion [6]. This unexpected failure at the clinical level gave rise to two notable events—the use of tPA to recanalize the vessel, and the conceptual change from neuroprotection to neurovascular protection after the early twenty-first century [17, 18, 29–31]. A neurovascular unit takes our understanding of stroke a step further than simply neuroprotection, which focuses more on neuronal cells but is a step short of upstream arteries/arterioles and especially veins/venules, in which smooth muscle cells, pericytes, and vascular endothelial cells play much more important roles in the control of vascular tone, influence capillaries, and in particular clear the venous blood. Thus, a new concept is beginning to take shape regarding stroke pathophysiology—the notion that the vascular neural network may in fact be at the center stage of the entire pathology [17, 18].

Basic Rules for Recirculation (Fig. 1.7)

One of the key issues related to the vascular neural network is that arterial and venous blood flow must be in harmony during circulation. During normal cerebral circulation, cerebral autoregulation prevents and protects the brain from over-flow-induced injury. When the blood flow increases, cerebral arteries contract to prevent excessive blood flow into the brain parenchyma, and when blood flow decreases, cerebral arteries dilate to allow more blood into the brain, maintaining constant total blood flow to the brain [32]. This same principle may apply to the relationship between arterial and venous flows, and the blood entering the brain from the arterial system is matched with the amount of blood exiting the brain via the venous system. In this relationship, veins seem to play a more vital role than arteries in the maintenance of brain blood flow physiology and brain function. Decreases in venous flow and greater venous pressure exceeding the cerebrospinal fluid pressure cause venous dilation and leakage of venules and capillaries, which enhances cerebrospinal fluid pressure, reduces arterial flow and produces a vicious cycle. Reduced arterial flow will form another vicious cycle that the body responds to by increasing blood pressure and dilating arteries, increasing the brain volume and the intracerebral pressure. These two vicious cycles are the basic principles of Starling Resistor Theory, which emphasizes that venous pressure is the key for the cerebral blood supply [33].

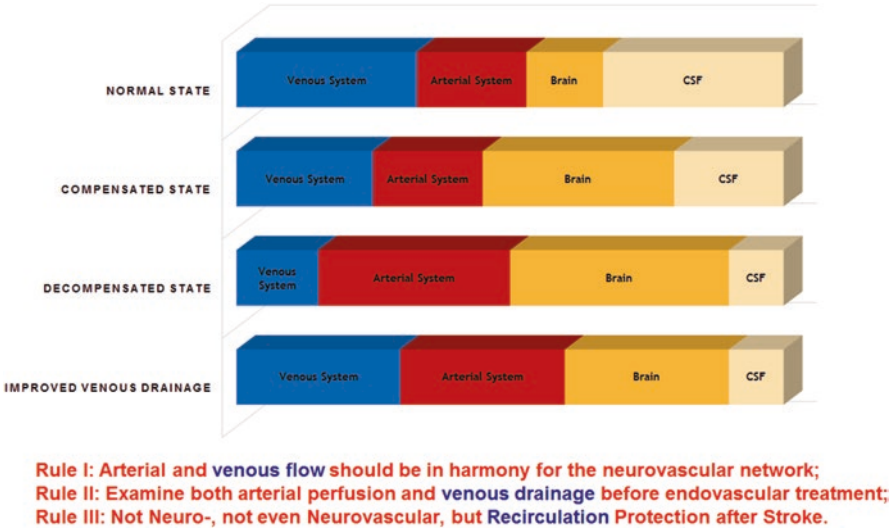

Fig. 1.7 Diagrams for the rules of recirculation. The first and foremost rule is arterial and venous blood flow needs to be in harmony during circulation. In normal state and compensated state, cerebral autoregulation prevents and protects the brain from over-flow induced injury. However, in decompensated state, the venous flow decreased and venous pressure is larger than cerebrospinal fluid pressure, causing venous dilation and leakage of venules and capillaries which enhances cerebrospinal fluid pressure, reduces arterial flow and produces a vicious cycle. Reduced arterial flow will form another vicious cycle, that body responds by increase blood pressure and dilation of arteries, increases brain volume, and increases intracerebral pressure. That is why we should examine both arterial perfusion and venous drainage before endovascular treatment. If we improved the venous drainage at this critical moment, the arterial and venous flow may restore to hemostasis and recirculation, and the patients could be really protected after stroke

An acute reduction of cerebral ischemia, but if the arterial flow remains but venous flow decreases acutely by 20%, blood will subsequently accumulate in the capillary system and lead to brain swelling [34] and an increase in intracranial pressure that causes hyperemia [35, 36], a flow decrease to no-flow [36, 37], and even capillary hemorrhage [35].

Anatomy of the Cerebral Venous System

The cerebral venous system contains sinuses, veins and venules of the brain and can be divided into the superficial venous system and the deep venous system. The superficial system comprises sagittal sinuses and cortical veins, which drain the superficial surfaces of both cerebral hemispheres. They are interlinked with anastomotic veins of Trolard and Labbé. Thus, the superolateral surface of the hemisphere drains into the superior sagittal sinus, while the posteroinferior aspect drains into the transverse sinus. The deep system consists of the lateral sinus, straight sinus and sigmoid sinus, along with the draining deeper cortical veins. The entire deep venous

system is drained by internal cerebral and basal veins, which join to form the great vein of Galen that drains into the straight sinus. Both of these systems mostly drain into internal jugular veins [38–40]. Moreover, the venous valves that prevent the backflow of venous blood have not been described for cerebral veins [39]. Thus, increases in central venous pressure or intracranial venous pressure could easily retroinfluence the hydrostatic pressure of upstream veins and venules and the blood outflow. For example, the enormous pressures generated by power athletes during weightlifting leads to elevations in intracerebral pressure which obstruct venous outflow leading to conjunctival hemorrhage and elevations in intra-ocular pressure [41].

The entire cerebral venous system is surrounded by adrenergic nerve fibers [42]. However, in contrast to arteries, venules and most cerebral veins do not have smooth muscle cells. Instead, postcapillary venules are covered with pericytes [43], while collecting venules contain stellate periendothelial cells that form a basket-like network around the vessel wall. As the size of the venous vessels increases, even in superficial cerebral veins, no smooth muscle cells are recognizable [44]. Thus, small veins or at least venules cannot contract strongly like arteries, but only mildly change the diameter of the vessels due to pressure changes related to this physiological condition [45] (Table 1.1). Although large capacitance veins are covered with smooth muscle cells, their diameter still mainly depends on the venous pressure because only a few vasoactive agents have the ability to contract them (Table 1.1). Under pathological conditions, the contraction might be attributed to three interwoven factors after brain injury. (1) External compression by edema due to blood brain barrier disruption, swollen astrocyte endfeet [77, 78] and adherent leukocytes

Table 1.1 Possible agents implicated in the contraction of pericytes and smooth muscle cells in the cerebral venous system

	Contraction		Dilation
Pericyte	ROS [46]	Angiotensin II [47–50]	NO [51, 46]
	K+ [52]	VEGF (initial phase) [53] VEGF (initial phase) [53]	VEGF (follow-up phase) [53] VEGF (follow-up phase) [53]
	Ca^{2+} [52]	Lipopolysaccharide [54]	Adenosine [55]
	RhoA [56]	Bradykinin [55]	CO_2 [57, 58]
	Acetylcholine [59, 60]	Serotonin [61, 55]	Isoproterenol [61]
	Noradrenaline [59]	IL-2 [62]	
	Lactate [63]	Endothelin 1 [64, 65]	
	Glucose [66, 67] (loss of contractibility)	Histamine [68, 50]	
Smooth muscle cell	Endothelin-1 [69] (less potent [70]) (less potent [70])		NO [71] (but lack of NO synthase NO [71] (but lack of NO synthase [72])
	Noradrenaline [73]		Histamine [74] (in dog, not human [75])
	Neuropeptide Y (less potent) [76] *Neuropeptide Y* (less potent) [76]		

surrounded by other cellular aggregates consisting of fibrin and platelets [79–83]. (2) Active constriction mostly due to pericyte contraction [46, 84] (Table 1.1). (3) Vessel lumina filled with entrapped and aggregated erythrocytes, leukocytes, and fibrin-platelet deposits [78, 80, 81, 85–88].

Venous Flow During Ischemic Stroke

In ischemic stroke patients, blood flow instantly reduces because different kinds of clots block artery lead to brain parenchyma infraction. In the central core regions of the insult, there is almost total cerebral blood flow (CBF) arrest. This area evolves rapidly toward death within minutes. Surrounding this core, CBF levels may fall below functional thresholds yet transiently lie above the threshold of cell death—this zone has been called the penumbra [89]. Unfortunately, edema usually appears in penumbra [90], which leads to increased intracranial pressure. In patients with ischemic stroke, blood flow is instantly reduced because different types of clots blocking the artery lead to infarction of the brain parenchyma. In the central core regions of the insult, there is almost total cerebral blood flow (CBF) arrest. This area evolves rapidly toward death within minutes. Surrounding this core, CBF levels may fall below functional thresholds yet transiently lie above the threshold of cell death; this zone has been called the penumbra [89]. Unfortunately, edema usually appears in penumbra [90], leading to increased intracranial pressure [91], secreted cytokines and chemokines by dying neurons, glia cells [92]. This could cause endothelium dysfunction of cerebral venous system and the secretion of cytokines and chemokines by dying neurons and glial cells [92]. This process could cause endothelial dysfunction of the cerebral venous system [92, 93], which is the initial factor in secondary inflammation and death cascades. Blood brain barrier disruption then causes more damage and forms a vicious cycle [91, 94].

However, injury to the cerebral tissue and veins are usually accomplished with platelet aggregation [93] and thrombosis [95, 96]. A thrombus in the cerebral sinus can cause an increase in intracranial pressure [97], while in cerebral veins, it could lead to venous infarction and brain swelling [98]; even a solitary microthrombus in a venule could lead to infarction followed by cognitive deficits [99]. Furthermore, the reduced venous outflow due to the thrombus and increased intracranial pressure may jeopardize the cerebral perfusion pressure regardless of artery recanalization [34, 84]. This may be one of the key factors underlying the ‘no-flow’ phenomenon [37, 100, 101] in patients with ischemic stroke.

Venous Flow During Intracranial Hemorrhage

Intracranial hemorrhage is the second most common cause of stroke, initiating with brain parenchyma bleeding and hematoma growth, despite direct incentives [102]. Because intracerebral hemorrhage has been considered an arterial hemorrhagic brain injury, little attention has been focused on the role of cerebral veins or venules

in its pathophysiology [102, 103]. However, during the acute phase of intracerebral hemorrhage, a rapid increase in intracranial pressure due to hematoma formation could cause autoregulation failure and reduced cerebral perfusion pressure [104]. Consequently, the guidelines suggest controlled blood pressure lowering treatment rather than aggressive blood pressure lowering, to maintain the cerebral blood flow [105]. Moreover, recent studies have described new ischemic lesions coexisting with acute intracerebral hemorrhage [106–110], suggesting the possible involvement of small vessel pathogenesis [106, 107].

The main secondary brain injury after intracerebral hemorrhage is thought to be three intertwined degenerative cascades adjacent to the hematoma [111], including inflammation [112], red cell lysis and iron deposition [102, 113], and thrombin production [102, 113]. Moreover, in addition to the ischemic lesions near the hematoma, some remote ischemic lesions have also been found [104]. Similar to the ischemic brain injury reviewed above, all of these pathophysiological factors could directly and indirectly cause cerebral venule endothelial dysfunction, microthrombus formation and eventual out-flow reduction. Combined with other pathophysiological mechanisms, such as oxidative stress and apoptosis, among others, these factors could also lead to blood brain barrier disruption, brain edema, and hydrocephalus, further increasing the intracranial pressure and initiating a vicious cycle [111]. However, most intracranial hemorrhages occur in hypertensive patients, the hypertensive vasculopathy, and arteries/arterioles and veins/venules can cause a 'stroke-prone state' to lower the threshold threshold [104] and out-flow dysfunction [114].

Venous Flow During Subarachnoid Hemorrhage

Subarachnoid hemorrhage is a special subtype of intracranial hemorrhage, caused by bleeding into the subarachnoid hemorrhage. For a long time, cerebral vasospasm has been considered the classic cause of delayed neurological deterioration after aneurysmal subarachnoid hemorrhage, leading to cerebral ischemia and infarction and thus to a poor outcome and occasionally death [115, 116]. However, recent clinical trials have demonstrated marked prevention of vasospasm with the endothelin receptor antagonist Clazosentan, yet the patient outcome did not improve [117, 118]. These disappointing results reminded researchers to refocus their strategy during early brain injury [119–121], but this concept is limited to neurons and overlooks the functions of other cell types. Fortunately, recent evolving concepts, such as the neurovascular unit [122], vascular neural network [17, 18] and vasculo-neuronal-glial triad model [123], have noted the contributions of cerebral microcirculation. However, they all maintain cerebral veins and venules at a distance.

Rethinking the failed Clazosentan clinical trials, there may be a missing factor compared with arteries such as endothelin, which has less potent constrictor abilities in cerebral veins [70], which means [70]. Thus, the powerful endothelin receptor antagonist Clazosentan may not alleviate the 'vasospasm' in the cerebral venous system after subarachnoid hemorrhage. Moreover, Clazosentan did not prevent the

formation of microthrombi [124]. Recent studies have also demonstrated vasospasm in deep cerebral veins after subarachnoid hemorrhage [125], with a significant decrease in diameter at 1 day and a peak at 5–7 days after subarachnoid hemorrhage [17, 18]. Whether the diameter of cerebral venules decreases after subarachnoid hemorrhage remains controversial [126–129]. In addition, subarachnoid hemorrhage elicited time- and size-dependent increases in rolling and adherent platelets and leukocytes in cerebral venules [130], leading to microthrombi and microvascular stasis [126, 131]. Similarly to other brain injuries, subarachnoid hemorrhage can also cause brain edema [123, 132, 133] and hydrocephalus [134, 135] followed by cerebral hypoperfusion [136], as reviewed above.

Cerebral venous thrombosis [137–140] or stenosis [141] is also an uncommon etiology of subarachnoid hemorrhage, most of which are perimesencephalic subarachnoid hemorrhage [142–144]. Potential causes may be an elevated intracranial venous pressure or mechanical swelling of the intracranial venous system, leading to variant cerebral venous drainage [145–149], arteriovenous malformation [150], and eventually vein or venule breakdown [136, 139, 151]. In these patients, increased intracranial pressure forced blood into the subarachnoid space and along the optic nerve sheath into the pre-retinal space, or decrease in venous return to the cavernous sinus or obstruct the retinochoroidal anastomoses and central retinal vein, culminating in venous stasis and hemorrhage, then exhibit Terson Syndrome at eyes [152–155].

Venous Flow During Traumatic Brain Injury

Traumatic brain injury is defined as impact, penetration or rapid movement of the brain within the skull that results in an altered mental state [156]. It comprises two injuries: primary and secondary injuries [157–160]. The primary injury occurs simultaneously with the impact that caused the injury, which explains why this injury is not amenable to acute intervention. This stage of cerebral injury is characterized by direct tissue damage and impaired regulation of the CBF and metabolism. Previous studies have shown that cortical CBF significantly decreases after the preliminary stroke [161–163]. During this phase, when CBF does not meet the cerebral metabolic needs of the tissue, this uncoupling can initiate interwoven pathophysiological responses leading to delayed, non-mechanical impairment of neuronal structure and function.

Early after head trauma, the blood brain barrier breaks down due to direct and indirect causes, resulting in a biphasic response [164]. There is a rapid endothelial disruption and swelling of perivascular astrocytes near the sites of the traumatic core, possibly correlated with transient disruption of the blood-brain barrier leading to cerebral edema [164, 165] followed by morphological changes in the endothelium of all vessels that are most marked in arterioles and venules [164], especially venules leading to macroscopic secondary petechial hemorrhage [166, 167]. However, the early breakdown of the blood brain barrier is not correlated with leukocyte adhesion [168]. Similarly to other brain injuries, edema can also lead to a

vicious cycle of brain edema between increased cerebral venous pressure and increased ICP [91]. Additionally, endocrine dysfunction may also aggravate this cycle by altering the variant cytokines associated with the hemodynamic changes [169–171].

Another major secondary insult after traumatic brain injury is the microthrombus, which forms in arterioles and venules of all sizes [172]. A recent study demonstrated that microthrombi occluded up to 70% of venules and 33% of arterioles, suggesting that the immediate post-traumatic decrease in cerebral blood flow is not caused by arteriolar vasoconstriction but by platelet activation and the subsequent formation of thrombi in the cerebral microcirculation [173]. This phenomenon may be a consequence of the observation of leukocyte-platelet aggression only in cerebral venules [173].

Recirculation as an Emerging Understanding of Stroke and Other Acute Brain Injuries

Taken together, we believe that the cerebral venous system plays an important role in the pathophysiology of brain injury. In extreme pathophysiological conditions such as traumatic brain injury, neurodegenerative diseases, intracerebral or subarachnoid hemorrhages, and cerebral ischemic patients with diabetes or hypertension, different types of direct or indirect injuries could cause cerebral venous endothelial dysfunction and then trigger a series of interwoven secondary pathways such as thrombosis, blood brain barrier disruption, and inflammation, among others. Together with acute cerebral vascular autoregulation failure after brain injury, these pathophysiological changes eventually lead to recirculation characterized by postcapillary venule, vein and sinus stenosis or vasoconstriction, increased cerebral venous pressure, cerebral venous reflux or steal. Recirculation ultimately reduces the cerebral blood flow, further activating the detrimental pathophysiological mechanisms and then enhancing the brain injury.

Based on the close relationship between the cerebral venous system and brain injury, we propose cerebral recirculation as a new concept that is one step closer to the original concept of the vascular neural network based on an emerging understanding of the important roles of the cerebral venous system in the pathophysiology of brain injury. The physical components of recirculation also include post-capillary venules, small veins, sinuses and large extracranial drainage veins. The recirculation, therefore, expands the concept of the vascular neural network and other pathophysiology theories to focus on the potentially important functional roles of the cerebral venous system during initial brain injury, evolution and outcome.

In our opinion, the concept of recirculation improves upon the vascular neural network model of brain injury pathophysiology because most brain injury events affect and are affected by the cerebral venous system that is not included in the vascular neural network, excluding postcapillary venules and small veins. As a consequence of cerebral blood flow autoregulation, slightly reduced damage in the cerebral venous system does not immediately cause clinically evident brain injury,