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Collaterals: implications in cerebral ischemic diseases and therapeutic interventions

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Abstract

Despite the tremendous progress made in the treatment of cerebrovascular occlusive diseases, many patients suffering from ischemic brain injury still experience dismal outcomes. Although rehabilitation contributes to post stroke functional recovery, there is no doubt that interventions that promote the restoration of blood supply are proven to minimize ischemic injury and improve recovery. In response to the acutely decreased blood perfusion during arterial occlusion, arteriogenesis, the compensation of blood flow through the collateral circulation during arterial obstructive diseases can act not only in a timely fashion but also much more efficiently compared to angiogenesis, the sprouting of new capillaries, and a mechanism occurring in a delayed fashion while increases the total resistance of the vascular bed of the affected territory. Interestingly, despite the vast differences between the two vascular remodeling mechanisms, some crucial growth factors and cytokines involved in angiogenesis are also required for arteriogenesis. Understanding the mechanisms underlying vascular remodeling after ischemic brain injury is a critical step towards the development of effective therapies for ischemic stroke. The present article will discuss our current views in vascular remodeling acutely after brain ischemia, namely arteriogenesis, and some relevant clinical therapies available on the horizon in augmenting collateral flow that hold promise in treating ischemic brain injury.

Keywords

arteriogenesis; angiogenesis; stroke; carotid diseases; anastomosis; vascular remodeling

Collateral circulation, the conduit for arteriogenesis, is a specialized vascular network with a distinct phenotype from the regular arteries, veins or capillaries (Faber et al., 2014) and

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plays an important role in the development and outcome of ischemic diseases. Native collaterals are naturally occurring artery-to-artery or arteriole-to-arteriole anastomoses present in healthy tissue, whereas they undergo outward remodeling in order to compensate for reduced blood flow in response to vascular obstructive diseases. However, the development of collaterals over time in the adult CNS can paradoxically be linked to chronic pathophysiology such as hypoperfusion.

1. The role of collateral circulation in the risk and outcome of ischemic stroke

In addition to factors involved in cerebral autoregulation, the extent of cerebral collateralization directly contributes to the cerebrovascular reserve capacity, which in turn, affecting the hemodynamics (Vernieri et al., 2001). For this very reason, cerebral collateral circulation has long been reported to alter the risk of stroke (Norris et al., 1990, Schomer et al., 1994). In patients with symptomatic severe internal carotid artery (ICA) stenosis, the risk at 2 years of stroke or TIA is significantly reduced among those with angiographically defined collaterals compared to those without (Henderson et al., 2000). Ample clinical evidences also suggest that the collateral status is an independent predictor of outcome and response to thrombolytic therapies in patients with ischemic stroke, and a good collateral status can lower the rate of hemorrhagic transformation after thrombolytic and endovascular therapies (Liebeskind, 2003, Shuaib et al., 2011b, Liu et al., 2014).

A number of collateral circuits exist within and between the extracranial and intracranial circulations, making the external carotid artery (ECA) a potential source of collateral flow when the ICA experiences chronic stenosis or occlusion. The intracranial collateral circuits are further divided into primary (i.e., circle of Willis) or secondary (e.g., ophthalmic artery and leptomenigeal vessels) collateral pathways (Liebeskind, 2003, Shuaib et al., 2011b, Liu et al., 2014). Unilateral ICA occlusion often led to enhanced collateral flow through the anterior Circle of Willis as well as an increase in the diameter of the anterior communicating arteries (AComA) (Hartkamp et al., 1999), possibly due to the relatively short distance between the AComA and the Circle of Willis. In contrast, bilateral ICA occlusion led to both increased collateral flow through the posterior circle of Willis and an increase in the diameter of the posterior communicating artery (Hartkamp et al., 1999), likely due to the increased demand for collateral compensation. Furthermore, in patients with ICA occlusion, sometimes vertebrobasilar arteries appeared to be responsible for blood flow in the territory of the MCA ipsilateral to the occluded ICA, whereas the interhemispheric cross flow from the contralateral ICA provided collateral flow to the ACA territory of the ischemic side (van Laar et al., 2007), which could potentially reduce the risk of internal hemodynamic watershed infarction (Hendrikse et al., 2002, Bisschops et al., 2003). In patients with complete occlusion of the intracranial ICA and/or the MCA (M1 or M2 segments), enhancement of leptomeningeal collaterals on CT angiography was correlated with lower post-stroke mortality (Lima et al., 2010). Nonetheless, patients with both MCA occlusion and rapid recruitment of secondary collateral pathways usually fared more favorably in the progression of symptoms post-stroke (Maas et al., 2009). In the patients who received endovascular revascularization therapy, angiographically defined collateral grade

determined the recanalization rate and clinical outcome (Bang et al., 2008, Bang et al., 2011a, Bang et al., 2011b, Liebeskind, 2013).

2. Genetics governing variance in collateral circulation

It has long been recognized that significant variation in infarct volume exist in inbred mouse strains. Using quantitative trait locus (QTL) analysis, a number of loci were mapped from independent laboratories and were found to modulate the stroke severity in mice. Among which, two overlapping loci, namely *Civq1* (cerebral infarct volume QTL1) (Keum and Marchuk, 2009)) and *Canq1* (collateral artery number QTL1) (Zhang et al., 2010, Wang et al., 2012) on mouse chromosome #7, contributes to greater than 50% of the variation in infarct volume among 15–16 inbred strains of mice and 37% of the phenotypic variance in pial collateral number and the extent of collateral remodeling between C57BL/6 and BALB/c respectively. In an elegant follow-up study, among a series of congenic mouse strains in the gene *Dce1*, a refined region of *Candq1*, from C57BL/6 were introgressed into the genome, there was an allele dose-dependent rescue of collateral extent, blood flow and reduction of ischemic severity (Sealock et al., 2014). Although these studies provide indisputable relationship between the extent of native collaterals and ischemic injury, genes modulating infarct volume independently of the extent of collateral circulation have also been identified (Chu et al., 2013), adding to the complexity of biological response to ischemic.

3. Regulation of collateral flow and arteriogenesis

The native collateral system is determined during the embryonic stages and is fully developed by the third week of life in mice (Chalothorn and Faber, 2010). VEGF levels contribute to collateral formation in the embryo, as evidenced by the fewer pial collaterals found in the $VEGF^{lo/+}$ mice compared to wild type or $VEGF^{hi/+}$ mice, or in BALB/c mice compared to C57BL/6 mice (Clayton et al., 2008). A reduction in the number and diameter of collaterals in the adult, also known as collateral rarefaction, occurs with aging (Faber et al., 2011, Hecht et al., 2012), eNOS-dependent endothelial dysfunction (Dai and Faber, 2010) the presence of vascular risk factors (Menon et al., 2013). Similar to humans with metabolic syndrome, type II diabetes mice db/db also exhibit impaired leptomeningeal collateral flow poor outcome after MCA stroke (Akamatsu et al., 2015 In press), coincided with diminished eNOS phosphorylation (Li et al., 2013).

Arteriogenesis is triggered by fluid shear stress (FSS) following a sudden occlusion or a chronically progressing stenosis in the artery, resulting in the activation of endothelium, monocyte invasion and recruitment, activation of additional inflammatory responses, secretion of growth factors and cytokines, followed by matrix digestion and ultimately proliferation of smooth muscle cells involved in the outward remodeling of collateral vessels and the increase of collateral flow (Heil and Schaper, 2004, van Oostrom et al., 2008, Fung and Helisch, 2012, la Sala et al., 2012, Troidl and Schaper, 2012, Liu et al., 2014). The molecular mechanisms involved in this complex process are discussed below.

3.1 Arteriogenesis is triggered by fluid shear stress rather than hypoxia

FSS refers to the tangential component of frictional forces generated at the vessel wall by the flow of a viscous fluid such as blood. Because arterial occlusion lowers the pressure in the distal vasculature, it increases flow through pre-existing collaterals due to the resulting pressure gradient. The initial increase of FSS exerted by the blood on the endothelium as it flows by activates the endothelium and stimulates a cascade of signaling events (Pipp et al., 2004, Schierling et al., 2009a, Schierling et al., 2011), leading to the conductance of the collateral vessels. As the collateral vessels grow in diameter, fluid shear stress falls and collateral flow decreases, providing a self-regulating mechanism. The collateral flow developed proximal to the occlusion does not require the local expression of either vascular endothelial growth factor (VEGF) or hypoxia-inducible factor 1 (HIF1) (Lee et al., 2004), although VEGF is known to play a role in the formation of collateral vessels during development and the continuing remodeling of collateral vessels. It is this mechanosensitive feature of arteriogenesis that prominently differentiates itself from other types of vascular growth such as angiogenesis. By maximizing FSS via an artificial arteriovenous (AV) shunt, collateral artery growth can be induced beyond the physiological extent and can overcome anatomical restrictions (Eitenmuller et al., 2006). FSS can induce arteriogenesis in both peripheral and cerebral circulations. In the latter, Schierling and colleagues created an AV fistula between the distal stump of the ligated carotid artery and the adjacent jugular vein following the ligation of bilateral common carotid arteries. They have observed considerable arteriogenesis and vessel growth in the FSS stimulated arteries in this ligature-shunt model (Schierling et al., 2009a).

3.2 Activation of endothelium and nitric oxide

Endothelial cells lining the blood vessel lumen can directly sense changes in flow shear stress and transmit signals to smooth muscle cells in the media and fibroblast cells in the adventitia that are normally only exposed to transmural interstitial flow. Microarray data identified a potential role for the shear stress sensitive gene *transient receptor potential cation channel subfamily V member 4* (*Trpv4*), a Ca^{2+} channel in endothelial cells, in transducing the stimuli induced by FSS. Pharmacological activation of Trpv4 strongly increased cerebral arteriogenesis and collateral flow (Schierling et al., 2011), while Trpv-channel blocker reduced collateral flow (Troidl et al., 2009a). Complementary to these findings, arteriogenesis was found impaired in mice lacking Trpv4 (Troidl et al., 2009a). Additional evidence suggested that actin-binding Rho activating protein might also be involved in FSS-induced arteriogenesis (Troidl et al., 2009b). Although the precise downstream signaling of Trpv4 has yet to be identified, Ca^{2+}-dependent mechanisms including the activation of endothelial-derived hyperpolarization factor (EDHF), cyclooxygenase, as well as NOS are potential candidates (Troidl et al., 2009a, Schierling et al., 2011). Among these, the most likely molecule transmitting the signal triggered by FSS is NO, which can diffuse through basement membrane that separates the endothelial cells and smooth muscle cells and can also cross talk with prostacyclin (Osanai et al., 2001). Targeted deletion of the eNOS gene led to a loss of vasodilation but not of arteriogenesis, while targeted deletion of iNOS led to partial but not complete impairment of arteriogenesis. Only the deletion of both eNOS and iNOS resulted in a complete loss of collateral vessel

remodeling during arterial occlusion (Troidl et al., 2010). On the other hand, contradictory evidence suggests that eNOS deficiency causes collateral vessel rarefaction and reduced expression of cell cycle genes in the eNOS-KO mice, associated with impaired proliferation of vascular wall cells involved in collateral remodeling (Dai and Faber, 2010). In addition to the key players mentioned above, FSS also upregulates endothelial microRNA-21 which suppresses its target gene phosphatase and tensin homolog (PTEN), contributing to increased eNOS phosphorylation and NO production (Weber et al., 2010).

3.3 Regulation of collateral flow by the immune system

Although the initiation of arteriogenesis does not require the presence of HIFs, hypoxia activates signaling pathways that lead to the production of crucial factors and regulators for collateral growth including VEGF and inflammatory cytokines (Rey and Semenza, 2010, Silvestre et al., 2013). HIF-1 can also induce integrin β2, which in turn induces adhesion and infiltration of leukocytes (Kong et al., 2007) and vascular progenitor cells into the hypoxic sites (Rey et al., 2009). On the other hand, the HIFs themselves are also subjected to regulation, in which the hydroxylation of HIFs for example, by the prolyl hydroxylase domain-containing proteins (PHDs), leads to further degradation of the proteins by proteases (Loinard et al., 2009). Conversely, downregulation of *Phd2* expression in macrophages enhances collateral growth via TIE2-dependent signaling (Takeda et al., 2011, Hamm et al., 2013).

Emerging studies have identified functional roles for various innate and adaptive immune cell subsets as regulators of arteriogenesis, including monocytes/macrophages, T helper 17 (Th17) cells, regulatory T lymphocytes (Tregs), and natural killer (NK) cells (la Sala et al., 2012). Several lines of direct or indirect evidence support the critical role of monocytes and monocyte signaling in arteriogenesis. Pharmacological depletion of monocytes impairs arteriogenesis in rabbit and mouse models of hindlimb ischemia (Heil et al., 2002). Consistent results were also obtained in osteopetrotic mice with natural monocytopenia using a hindlimb ischemia model (Bergmann et al., 2006). In addition, adoptive transfer of wild type bone marrow mononuclear cells enhanced reperfusion following hindlimb ischemia (Capoccia et al., 2008). The improved reperfusion following wild type adoptive transfer was absent in mice defective in MCP-1/CCL2, suggesting that the recruitment of the inflammatory subset of monocytes to sites of ischemia is a critical step in collateral growth (Capoccia et al., 2008). As an indirect evidence for the crucial role of monocytes, mice lacking urokine plasminogen activator (uPA) showed less postischemic collateralization than wild type mice, reflected by an uPA-dependent reduction of leukocyte infiltration (Deindl et al., 2003). In additional to the presence of monocytes, collateral flow is also regulated by the phenotypes of infiltrated monocytes. The M1-type macrophages express iNOS and proinflammatory cytokines such as IL-1 and IL-12, whereas the M2-subset expresses arginase 1, anti-inflammatory cytokine IL-10 and VEGF (Silvestre et al., 2013, Rath et al., 2014). Deletion of one allele of the *phd2* gene not only polarized macrophages toward a M2 phenotype but also promoted arteriogenesis after hindlimb ischemia, which was associated with an increased production of SDF-1 and PDGF-B (Takeda et al., 2011). The *Phd2* gene regression was apparently mediated via Angiopoietin-1 (ANG1)/TIE2 because blockade of ANG1 by a soluble trap prevented the downregulation of *Phd2*

expression in macrophages and their phenotype switch, consequently impeding collateral growth (Hamm et al., 2013). A recent study by Troidl and colleagues determined the temporal and spatial distribution of macrophage subpopulation during arteriogenesis in a rat model of chronic FSS (Troidl et al., 2013). In this model, M2 macrophages appeared early following reperfusion and maintained up to 28 days, concentrated particularly in the region of collateral growth. M1 macrophages were also present, but to a lesser extent. In keeping with data from experimental studies, impaired chemotaxis of monocytes appeared to account for the impaired formation of collaterals in patients with diabetes (Waltenberger et al., 2000, Tchaikovski et al., 2009).

In some ways, arteriogenesis shares similarities with an active inflammatory process. For example, growing collaterals are characterized by the presence of infiltrating monocytes/macrophages in the lumen and in the perivascular space (Arras et al., 1998). However, it is unclear whether a specific type of inflammatory response is needed for arteriogenesis following an ischemic insult, or a usual ischemia-elicited inflammation suffices to induce collateral development if works in concert with sheer stress and gene products of activated endothelium. Gene expression profiling during collateral development in a mouse model of hindlimb ischemia indicated a prominent role for inflammatory response-related genes, including CXCL5, MCP-1, CXCL9, and CXCL10. Furthermore, the nature of a coordinated appearance of proinflammatory genes followed by anti-inflammatory genes suggests that inflammation contributes to the initiation of collateral development (Meisner and Price, 2010). Apart from cells contributing to the innate immunity, reduced infiltrating T lymphocytes were found in apoE−/− mice along with an impaired collateral flow following limb ischemia. In support of the role of T lymphocytes in arteriogenesis, asthymic nude mice had increased macrophage infiltrating the ischemic limb in the absence of T cells and a concurrently decreased VEGF expression and impaired recovery of blood flow following limb ischemia compare to C57 strain with normal T cells (Couffinhal et al., 1999).

Lastly, the infiltrating macrophages that are more commonly associated with inflammatory response also produce a number of angiogenic growth factors including MCP-1, VEGF, FGF, GM-CSF, HGF, TNF-α, TGF-β and PDGF (Schierling et al., 2009b) that are critical for the development and maturation of the collaterals. The infusion of some of the most potent angiogenic factors at high pharmacological doses achieved only a fraction of the maximum conductance obtained by high FSS in a rabbit model of femoral artery occlusion, suggesting that these factors alone cannot fully account for the arteriogenic effects. Nonetheless, the findings implicate potential in using these cytokines or growth factors to promote arteriogenesis.

As a rich source of cytokines and growth factors needed for vessel growth and repair, stem- and progenitor cell-based therapies have gained considerable acceptance in treating ischemic diseases. Endothelial progenitor cells (EPC), derived from either peripheral blood or bone marrow, can respond to shear stress and contribute to collateral formation when transplanted into animals with either limb or cardiac ischemia (Kamihata et al., 2001, Deindl et al., 2006). Other indirect revascularization procedures, such as encephalomyosynangiosis (EMS) followed by implantation of myoblast expressing VEGF164 has also shown to improve functional collateralization in chronic cerebral hypoperfusion (Hecht et al., 2015).

3.4 Collateral vessel remodeling involves the activation of proteases that degrade basement membrane and reorganize the extracellular matrix

Following the infiltration of monocytes and macrophages into the sites of collateral vessel, collateral growth and enlargement requires the proliferation of endothelial and mural cells and remodeling of the extracellular matrix. The orchestrated production of cytokines and growth factors induces the degradation of the extracellular matrix and stimulates the proliferation of endothelial (EC) and smooth muscle cells (SMC) in preparation for the remodeling of extracellular matrix and the expansion of the collateral diameter. However, the mechanisms leading to the production of cytokines and growth factors by monocytes and macrophages at sites of collateral growth are not well understood.

The turnover and remodeling of the extracellular matrix is carried out by the matrix metalloproteinases (MMPs) and their inhibitors, namely tissue inhibitor of metalloproteinases (TIMPs). During arteriogenesis, the external elastic lamina and elastin are broken down by MMPs and plasmin, creating space for the expanding vessel (Fung and Helisch, 2012, la Sala et al., 2012). Earlier studies indicated that MMP-2, MMP-9 and TIMP-1 were up-regulated in the intima during collateral remodeling (Kadoglou et al., 2005), suggesting that it is the balance between MMPs and TIMPs which is critical for the maintenance and remodeling of the vessel wall. Metabolic disorders such as diabetes disrupts this balance during arteriogenesis (Schatteman et al., 2000). For example, Lepr-db/db mutation blunted the ischemia-induced up-regulation of MMP-2, MMP-12 and MMP-16 in the murine hindlimb ischemia model (Schiekofer et al., 2005), contributed to the impaired arteriogenesis. To the contrary, serum level of MMP-9 but not MMP-2 was found to be significantly higher in patients with Moyamoya disease (Fujimura et al., 2009), a chronic cerebrovascular illness that is associated with pathological instability in the vessel wall and abnormal growth of some collaterals.

During the late phase of arteriogenesis, ECs and SMCs proliferate and migrate (Scholz et al., 2000). SMCs account for a large part of the production of new tissue, changing their phenotype from contractile to a synthetic and proliferative phenotype (Schaper, 2009). As the collateral vessels grow in diameter with cell proliferation, FSS falls and collateral flow decreases as a feedback autoregulatory mechanism.

4. Therapies to enhance collateral flow in cerebrovascular diseases

The only approved treatment of acute ischemic stroke at this time is the use of recombinant tissue plasminogen activator (rt-PA) within 3 hours or 4.5 hours in selected patients from the onset (Kwiatkowski et al., 1999, Hacke et al., 2008). However, only a small number of patients with acute ischemic stroke receive rt-PA therapy mainly due to its brief therapeutic time window (Adeoye et al., 2011) and the increased risk of intracranial hemorrhage (Hacke et al., 2008). Therefore, other safer treatments that have longer therapeutic time window are required.

Recently collateral perfusion including pial or leptomeningeal anastomosis is widely recognized as a key element that has significant effects on various aspects of clinical practice or consideration including the time course of ischemic injury, stroke severity and

therapeutic opportunities. Collaterals have also been recognized to influence recanalization, reperfusion, hemorrhagic transformation, and neurological outcomes after stroke (Shuaib et al., 2011b, Liebeskind, 2013). Therefore, it is considered that collaterals are the potential therapeutic targets and many clinical investigations intended to increase collateral perfusion have been attempted and tested.

4.1 Pharmacologic approaches via volume expansion, hemodilution, vasodilation, and induced hypertension

Several studies have investigated the efficacy of volume expanders, hemodilutors and vasodilators, on increasing collateral circulation to improve outcome after stroke (Shuaib et al., 2011b). Previous volume expansion and hemodilution studies with dextran or hydoxyethyl starch have not shown any improvement in outcome or reduction in mortality in acute ischemic stroke (Schneider et al., 1985, Hartmann et al., 1987). Based on these available evidences, the American Heart Association's 2007 guidelines (Adams et al., 2007) conclude that volume expansion or hemodilution is not recommended in patients with acute stroke. However, the use of albumin has provided some early promising results. In addition to its hypervolemic effects, it also has antioxidant, antithrombotic, and anti-inflammatory properties (Prajapati et al., 2011). Base on these findings, high-dose albumin (2 g/kg) treatment was tested in large prospective, double blind, placebo-controlled trials known as ALIAS (albumin in Acute Stroke). Unfortunately, this trial failed to demonstrate an overall clinical benefit among the participants (Ginsberg et al., 2013).

Dilation of cerebral arteries has the potential to increase flow through collaterals. However, some previous small trials with vasodilator have not shown any consistent benefit in neurological outcome (Hsu et al., 1988, Chan and Kay, 1993). In light of these outcomes, it is considered that the possibility of steal phenomenon at ischemic region after using vasodilator could be harmful to ischemic tissue (Kuwabara et al., 1995). Consequently, the American Heart Association's 2007 guidelines also advise against the use of vasodilators in acute ischemic stroke.

A rise in systemic blood pressure could improve blood flow to the brain, possibly through increased collateral flow because cerebrovascular autoregulation is impaired during stroke and changes in mean arterial blood pressure have a linear effect on cerebral blood flow (Wityk, 2007). Some preliminary clinical data suggest that induced mild hypertension may improve NIHSS score with an acceptable degree of safety (Rordorf et al., 2001, Hillis et al., 2003), although there has not been a large, randomized clinical trial of this treatment and many questions still remain unanswered about the safety and potential benefits of pressure therapy (Mistri et al., 2006). The American Heart Association's 2007 guidelines recommend that induced hypertension can be used in "exceptional cases" and that cardiac and neurological status should be closely monitored (Adams et al., 2007).

4.2 Non -Pharmacologic Approaches

4.2.1 External counterpulsation (ECP)—External counterpulsation (ECP) is a noninvasive and well-established treatment for ischemic heart disease with sustained long-term effects (Arora et al., 1999, Michaels et al., 2004). It operates by applying ECG-

triggered diastolic pressure of ~250 mm Hg to the lower extremities by using air-filled cuffs. The diastolic augmentation of the blood flow and the simultaneously decreasing systolic afterload therefore increases blood flow to the heart, brain, and kidneys (Bonetti et al., 2003). Recently ECP has been investigated for ischemic stroke (Han and Wong, 2008), and a recent review suggests that ECP is associated with a remarkable increase in the number of ischemic stroke patients with clinical improvement (Han et al., 2008, Lin et al., 2012). However, at this time, a recent review showed that there are no clear evidence to support ECP therapy from previous RCTs and well-designed and large scale RCTs are needed (Lin et al., 2012).

4.2.2 Partial Aortic Occlusion—Partial occlusion of the abdominal aorta increases the blood volume beyond the occlusion site and augments cerebral blood flow in animal studies (Hammer et al., 2009). Experimental data suggest that the cerebral blood flow increase persists even after the end of the occlusion procedure (Stokland et al., 1980, Saether et al., 1996, Hammer et al., 2009). NeuroFlo device (CoAxia, Maple Grove, MN, USA) was developed with two balloons inflated in the abdominal aorta to occupy 70% of the vessel lumen above and below the renal arteries for 45 min. The Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial is the largest randomized controlled trial of device therapy to date and tested the potential augmentation of collateral perfusion (Shuaib et al., 2011a). A total of 515 acute stroke patients between 0 and 14 hours after symptom onset were randomized to partial aortic occlusion or standard care. Unfortunately the primary efficacy endpoint did not differ between the groups, although safety of this novel treatment was confirmed. However, some findings of subgroup analyses indicate that patients treated in early time-windows (≤6 h) with a moderate stroke severity (NIHSS score of 8–14) might have gained most benefit from aortic occlusion (Shuaib et al., 2013). In addition, in patients older than 70 years, those treated with the NeuroFlo device showed favorable response to this treatment compared with those who were not treated with NeuroFlo (Leker et al., 2012). These findings showed that partial aortic occlusion might still remain a potential tool for treatment of stroke in acute phase at least in selected patients.

4.2.3 Sphenopalatine Ganglion Stimulation—Several animal studies have demonstrated that stimulation of the sphenopalatine ganglion activates the parasympathetic innervation of the intracranial blood vessels and causes vasodilation and increased cerebral blood flow (Seylaz et al., 1988, Suzuki et al., 1990, Toda et al., 2000, Yarnitsky et al., 2005). Based on such findings, a prospective open-label study ‘Implant for Augmentation of CBF trial 1’ (ImpACT-1) is ongoing to investigate the efficacy, safety, and tolerability of the ischemic stroke system in patients with acute ischemic stroke within 24 hours of stroke onset (Khurana et al., 2009). The implantable neural stimulator (1 inch in size) is implanted by using oral procedure with local anesthesia, and the sphenopalatine ganglion will be stimulated for 4 h per day for up to 5 days.

4.2.4 Transcranial Laser Therapy—Transcranial laser therapy (TLT) is a noninvasive technology that uses near-infrared laser energy delivered transcranially to modulate biochemical changes within neural cells. In vivo studies have suggested that infrared laser therapy could be beneficial for the treatment of acute ischemic stroke (Lampl et al., 2007).

The mechanisms of this method are not fully clear, however, it is considered that absorption of infrared laser energy leads to stimulate mitochondrial energy production and increase in ATP production, then suppress apoptosis in ischemic tissue. In addition to the effect of increasing mitochondrial function, in one study using mice, increased CBF was also observed after laser therapy via increasing NO level in the brain (Uozumi et al., 2010).

In prospective, double-blind NeuroThera Effectiveness and Safety Trial 1, 2 (NEST trial 1, 2) (Lampl et al., 2007, Zivin et al., 2009, Stemer et al., 2010, Huisa et al., 2013), the safety and efficacy of TLT were tested. On these studies, patients received transcranial near-infrared wavelength laser treatment within 24 h of symptom onset by using NeuroThera Laser System (Photothera, Carlsbad, California). The NEST-1 trial showed a statistically significant improvement in efficacy with TLT vs. sham in both the 90-day binary NIHSS (success defined as NIHSS 0–1 or decrease of at least nine points vs. baseline) and 90-day binary modified Rankin Scale (mRS) (success defined as mRS 0–2) without any safety concerns (Lampl et al., 2007). In the NEST-2, the primary efficacy endpoint, the mRS score at 90 days dichotomized as 0–2 for success, did not reach statistical significance ($P = 0.09$) (Zivin et al., 2009). However, further analysis showed that by excluding severe stroke subgroup (NIHSS 16–22), the efficacy end point became statistically significant in patients treated with TLT (Zivin et al., 2009). This led to the next step and currently, the NEST-3 clinical trial is ongoing.

4.3 Improving collateral flow in chronic cerebrovascular ischemic diseases

Chronic progressive steno-occlusive changes of extra or intracranial major arteries in the absence of compensatory collateral flow can result in hemodynamic insufficiency and lead to hemodynamic infarction (Vilela and Newell, 2008). Previous studies have shown that elevated oxygen extraction fraction (OEF) and reduced cerebrovascular reactivity (CVR) to acetazolamide may predict the risk of recurrent ischemic stroke in patients with hemodynamic compromise (Grubb et al., 1998, Yamauchi et al., 1999, Kuroda et al., 2001).

Direct bypass surgery is a surgical strategy to enhance the compensation collateral flow and improve the hemodynamic compromise mainly caused by ICA occlusion, MCA occlusion or severe stenosis (Rodriguez-Hernandez et al., 2011). Extracranial-intracranial (EC-IC) bypass with superficial temporal artery to middle cerebral artery cortical branch (STA-MCA) anastomosis is the most common bypass for stroke patients with hemodynamic compromise. However, recent randomized clinical trials showed that clinical indications and efficacy of bypass surgery were controversial. The Japan EC/IC Bypass Trial (JET) study demonstrates in their interim that STA-MCA anastomosis improves the 2-year outcome in patients with reduced CBF and CVR on SPECT (Ogasawara and Ogawa, 2006). However, as a major impediment in validating the benefit of EC/IC bypass in improving hemodynamics, the final results of JET study have yet to be published in a peer review journal. On the other hand, the Carotid Occlusion Surgery Study (COSS) in North America proves no beneficial effects at the 2-year outcome in patients with elevated OEF due to ICA occlusion even though they had achieved excellent bypass graft patency, improved cerebral hemodynamics (Powers et al., 2011, Grubb et al., 2013) and low rate of perioperative ischemic strokes caused by technical problems of bypass surgery (Reynolds et al., 2013). The discrepancies between the

two studies are mainly due to the differences in 30-day postoperative stroke rates (estimated 0% in JET study, 15% in COSS), although the perioperative complication rate in JET remains unknown. These two studies may indicate the benefit of the STA-MCA bypass surgery after perioperative periods (Amin-Hanjani et al., 2012). However, at this point, given the higher stroke rate in perioperative periods in COSS, it is difficult to recommend the bypass surgery for the patients with carotid occlusion.

Moyamoya disease (MMD) is a another chronic cerebrovascular ischemic disease in which progressive bilateral steno-occlusive changes occur at the terminal portion of the internal carotid artery (ICA), leading to an abnormal vascular network at base of the brain (Suzuki and Takaku, 1969). This abnormal vascular network is named as ‘moyamoya’, a Japanese term depicting the hazy appearance of blood vessels on angiograms that bears resemblance to a puff of cigarette smoke. Clinical manifestations include ischemia, hemorrhage, and epilepsy, etc., in which young patients usually present with ischemic symptoms while adult patients with either ischemia or hemorrhage (Kuroda and Houkin, 2008). The abnormal angiogenesis at base of the brain may be specific to MMD because non-MMD patients exhibiting steno-occlusive changes in the intracranial major arteries rarely have collateral vessels similar to moyamoya vessels (Yoshihara et al., 2008, Achrol et al., 2009).

Among the research aimed at understanding the genetics, development and progression of moyamoya disease, investigating mechanisms by which the moyamoya induces pathological changes in vessel wall and aberrant vessel development have become the main focus. As a unique characteristic of MMD, it was noticed that spontaneous leptomeningeal anastomoses developed after placing donor materials supplied by external carotid arteries directly onto the surface of the ischemic brain in both adults and children (Houkin et al., 2000, Isono et al., 2002, Scott et al., 2004). Therefore, various kinds of indirect non-anastomotic bypass procedures have been developed. On the other hand there were few studies showing the efficacy of indirect revascularization to enhance collateral angiogenesis in cases of non-MMD intracranial atherosclerotic arterial stenosis. In addition, previous study showed that indirect bypass surgery did not promote adequate pial collateral artery development in patients with atherosclerotic occlusive cerebrovascular diseases (Komotar et al., 2009).

In indirect revascularization surgery for MMD, angiogenesis is induced in association with wound-healing and the repair process (Nakamura et al., 2009), which is presumably related to the underlying high levels of various pro-angiogenic growth factors such as basic fibroblast growth factor, transforming growth factor beta, platelet-derived growth factor, or hepatocyte growth factor etc. in MMD patients (Weinberg et al., 2011). The efficacy of these treatments is currently assessed by the outcome of perfusion improvement or new vessel formation using perfusion SPECT, cerebral angiography, or MR imaging (Kuroda and Houkin, 2008). The beneficial effects are not immediate because surgical collaterals require 3–4 months to develop (Houkin et al., 2004, Veeravagu et al., 2008). Interestingly, collateral pathways through indirect bypass do not develop in about 40–50% of adult patients, although indirect bypass provides extensive surgical collaterals in almost all pediatric patients (Mizoi et al., 1996). Careful evaluation of new vessel growth after indirect surgery in MMD patient would be insightful in understanding the shared mechanisms between collateral growth and angiogenesis in the ischemic brain.

5. Conclusions

Vascular remodeling of various mechanisms occurs in acute and chronic cerebrovascular occlusive diseases. It is commonly accepted that arteriogenesis, the engagement of collateral flow, is a critical determinant of stroke risk and outcome. On the other hand, angiogenesis, sprouting of new capillaries from postcapillary venules, is active during the chronic process of hypoxia and a driving force for post ischemic neovascularization. Although cell based therapeutic angiogenesis still holds promise for the treatment of ischemic diseases, delivering angiogenic factors in the form of protein or gene therapy has not resulted in clinical benefit (Chu and Wang, 2012, Said et al., 2013). Understanding the mechanisms underlying each remodeling process, regardless whether unique or shared, is the first step towards the development of effective revascularization therapy. In addition, it will also shed light on how vascular risk factors impair vascular homeostasis and remodeling in ischemic diseases.

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- Distinct functional roles of arteriogenesis in the risk and outcome of ischemic diseases are delineated
- Genetics and cellular mechanisms regulating arteriogenesis
- Clinical mplications of arteriogenesis in cerebrovascular diseases
- Potential therapies in promoting collateral flow including those in trials

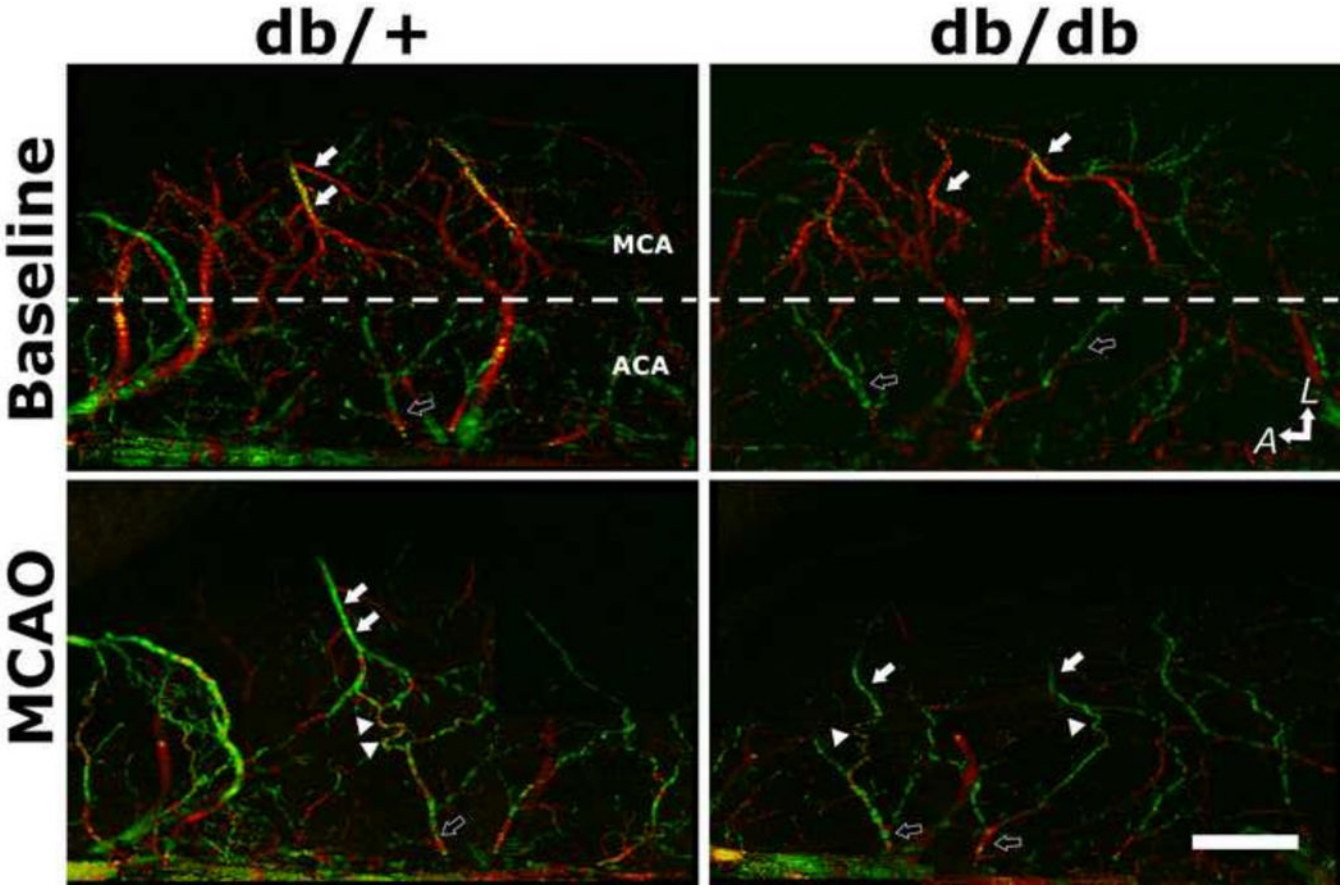

Figure.

Type-II diabetes db/db mice exhibit impaired collateral flow recruitment after experimental stroke compared to their normoglycemic control db/+ mice. Retrograde collateral flow dynamics was assessed by Doppler optical coherent tomography (DOCT), a non-invasive high-resolution three-dimensional optical imaging technique for microangiography. Representative DOCT images of db/+ and db/db mice at baseline and immediately after MCAO were shown. The anatomic orientation is labeled with arrows pointing to the lateral (*L*) and anterior (*A*) directions. Dotted white lines mark the divide between MCA and ACA territory. White- and black-filled arrows indicate MCA and ACA branches, respectively. The direction of blood flow is color-coded, with the blood flowing towards the scanning probe beam or towards ACA territory coded as red, and the retrograde flow towards proximal MCA as green. Arrowheads indicate the tortuous anastomoses between MCA and ACA. Scale bar: 1 mm.