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# Understanding and Augmenting Collateral Blood Flow During Ischemic Stroke

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## 1. Introduction

Stroke refers to brain damage and dysfunction that occurs due to the obstruction of blood flow to brain tissue. Stroke is one of the leading causes of death and disability worldwide, accounting for 10% of all deaths (Grysiewicz et al., 2008; Donnan et al., 2008). Risk of stroke is affected by a number of modifiable and non-modifiable risk factors. Age is the primary non-modifiable risk factor, while modifiable risk factors include chronic hypertension, diabetes, smoking, cholesterol and lack of exercise (Simons et al., 1998; Knuiman & Vu, 1996; Iso et al., 1989; Wadley et al., 2007).

Ischemic stroke, the rapid development of a neurological deficit due to the disruption of blood supply to a specific region of the brain, is the most common cause of stroke. Usually caused by the blockage of an artery or vein by an embolus or blood clot, an ischemic stroke is a major cerebrovascular trauma with a mortality rate of 25% after one month (Donnan et al., 2008; Hossmann, 2006). Ischemic strokes are differentiated from transient ischemic attacks by neurological symptoms lasting for more than 24 hours (Albers et al., 2002). Death and extent of disability due to ischemic stroke is largely defined by location of the occlusion and corresponding size and location of the infarct.

Brain injury following ischemic stroke results from an “ischemic cascade” of pathological events triggered by reduced blood flow. Disturbed ion homeostasis, excitotoxicity, elevation of intracellular calcium concentrations, peri-infarct depolarisations, free radical generation, lipid peroxidation and protein synthesis dysfunction are all triggered by reduced blood flow and contribute to necrotic and apoptotic processes in ischemic tissue and expansion of the infarct (Dirnagl et al., 1999 and Hossmann et al., 2006). Notably, necrotic cell death tends to be fast and irreversible in the core or infarct of the stroke area, where blood flow falls below ~20% of baseline perfusion and results in energy failure in resident neurons (Hossman, 2006). However, in “penumbral” regions surrounding the core, partial blood flow is maintained and tissue is considered functionally silent but structurally intact. Importantly, damage in the penumbra is reversible, though this reversibility is time-limited (Hakim, 1987). Because pathophysiology in the penumbra evolves over hours and days after ischemic onset, it is believed that early treatments that restore blood flow or reduce brain damage can reduce damage and improve outcome (Green, 2008). Although hundreds to thousands of prospective treatments to salvage ischemic tissue or halt the pathological ischemic cascade have been identified, few have successfully been translated to clinical practice (Ginsberg, 2008; Wahlgren & Ahmed, 2005). In fact, only thrombolytic drugs have thus far produced significant positive

results for stroke patients in clinical trials. Of the thrombolytic drugs, intravenous recombinant tissue plasminogen activator (rtPA) has proved effective in reducing mortality and disability associated with ischemic stroke (Wardlaw et al., 2000). When it is administered in selected patients with acute ischemic stroke within 4.5 h of symptom onset, rtPA is highly effective in reducing death and disability (Buchan & Kennedy, 2007; Toni et al., 2005 and Lansberg et al., 2009; Clark et al., 1999). Clinically, relatively few patients are treated with rtPA, primarily because the therapeutic window is prohibitively short compared to the usual delays in stroke recognition and patient transport, triaging and neuroimaging (Kwan et al., 2004). Moreover, 40% of patients with early treatment and indications of salvageable tissue still do not respond to rtPA (Kaur et al., 2004). For middle cerebral artery occlusion (MCAo) – the most common cause of focal ischemic stroke – rtPA treatment restores blood flow in only 25–30% of patients (Kaur et al., 2004).

## **2. Collateral blood flow and collateral therapeutics**

With a paucity of effective treatments for acute stroke, new approaches to neuroprotection or reperfusion are needed. One strategy currently under investigation to improve post-stroke outcome is to increase blood supply to ischemic tissue via intracerebral collateral circulation. The collateral circulatory system is defined as the vascular network through which blood flow can be partially maintained after the primary vascular routes are blocked (Liebeskind, 2003). “Collateral therapeutics” attempt to harness these endogenous vascular redundancies to improve blood flow to at-risk tissue.

Cerebral collaterals can be classified as venous, primary or secondary. The venous collateral circulation is highly variable, and augments drainage of cerebral blood flow during primary venous occlusion (Liebeskind, 2003). Primary collaterals refer to short arterial segments in the Circle of Willis, while the secondary collaterals refer to the ophthalmic and leptomeningeal collaterals (Liebeskind, 2003). The Circle of Willis is a circular vascular structure situated on the base of the brain that creates redundancy in cerebral blood flow between the internal carotid arteries and vertebrobasilar system (Hendrikse et al., 2005). In the case of occlusion or stenosis in these feeding arteries, blood can flow through the Circle of Willis and maintain blood flow in regions downstream of the narrowing or occlusion (Cieśliski et al., 1997). Similarly, collateral flow through the ophthalmic artery can partially restore blood flow to the distal carotid in the case of severe internal carotid artery occlusion or stenosis (Henderson et al., 2000; Reynolds et al., 2002). Leptomeningeal collaterals (or pial collaterals) are anastomatic connections between distal branches of the cerebral arteries found along the surface of the brain that permit blood flow from the territory of an unobstructed artery into the territory of an occluded artery (Liebeskind, 2005).

In this chapter, we will review methods for imaging cerebral blood flow relevant to investigations of stroke collaterals and illustrate the important link between stroke outcome and collateral circulation. Our review will focus primarily on the leptomeningeal collaterals and will incorporate both clinical and pre-clinical studies exploring the relevance of collateral blood flow for stroke prognosis and the potential benefits of collateral therapeutics.

## **3. Imaging collateral blood flow in clinical and pre-clinical settings**

In this section, we will briefly outline some of the methods used to image blood flow in the clinical and pre-clinical setting. To image collateral vessels, single vessel resolution is

required. While no ideal strategy to image collateral blood flow has been identified, a number of techniques have been employed in the clinic and in animal research to image cerebral collateral circulation and begin to define the anatomy, physiology, and significance of collateral circulation in stroke. Collateral circulation is an important predictor of infarct size (Angermaier et al., 2011; Bang et al., 2008 and Zhang et al., 2010), and accurate imaging approaches are essential to optimize its predictive value and to properly evaluate the benefits and mechanisms of collateral therapeutics.

### **3.1 Collateral blood flow imaging in humans**

A number of direct and indirect methods can be used to image cerebral blood flow in the clinical setting. Indirect measurements of cerebral blood flow during stroke allow inferences about collateral perfusion of ischemic tissue. Techniques such as magnetic resonance (MR) perfusion imaging, computed tomography (CT) perfusion, xenon-enhanced CT, single-photon emission CT, and positron-enhanced tomography can be used to measure cerebral blood flow and assess the collateral status (Liebeskind, 2003). However, the utility of these methods is somewhat limited since only indirect information about collaterals blood flow is attained (Liebeskind, 2003). Single vessel resolution permits a more direct assessment of collateral blood flow in stroke patients. Direct visualization of collateral vessels can be obtained using cerebral digital angiography, CT angiography, MR angiography, and transcranial Doppler sonography (TCD) (Liebeskind, 2003). Below we will briefly discuss these direct imaging techniques for collateral blood flow during stroke.

#### **3.1.1 Cerebral angiography**

Cerebral digital angiography involves injection of a contrast dye (typically via the femoral artery) during X-ray imaging. A series of radiographs are collected as the contrast agent spreads through the cerebral vasculature, yielding high-resolution images of cerebral blood flow. Digital subtraction angiography improves resolution of vasculature in bony structures such as the cranium by subtracting a “mask” image acquired without contrast.

Conventional angiography is the “gold standard” for observing cerebral blood vessels and angiography during stroke has confirmed the importance of collateral blood flow in determining tissue fate (Bang et al., 2008). However, the various methods used to quantify cerebral collaterals have not been well validated. Moreover, conventional angiography involves radiation exposure and is relatively invasive with a risk of complications including embolism, dissection, hematoma, allergic reaction to contrast dye, and nephropathy (Barlinn & Alexandrov, 2011; Hankey et al., 1990). Such complications are more common in older patients with atherosclerosis, a particularly relevant contraindication in the stroke population where both age and high cholesterol represent significant risk factors (Barlinn & Alexandrov, 2011, Simons et al., 1998; Knuiman & Vu, 1996; Iso et al., 1989).

#### **3.1.2 Magnetic resonance angiography**

Magnetic resonance angiography (MRA) uses MR imaging approaches to map blood vessels in the brain (Hartung et al., 2011). While there are several MRA variants, time-of-flight (TOF) MRA and contrast-enhanced (CE) MRA are most frequently used to image cerebral blood flow in patients with cerebrovascular disease (Barlinn & Alexandrov, 2011). Both techniques allow either 2-dimensional (2D) or 3-dimensional (3D) volume acquisition and are capable of detecting aneurysms, occlusions or stenosis in cerebral vasculature, with the

major differences being the requirement for a bolus injection of a contrast medium (gadolinium) for CE-MRA. Additionally, TOF-MRA permits higher-resolution images while CE-MRA allows faster collection over a larger anatomical volume, and reduced artefacts due to blood flow and vascular pulsation (Barlinn & Alexandrov, 2011; Hartung et al., 2011). Notably, MRA does not use ionization radiation, does not require an invasive catheter, and the “low-dose” contrast agent used with CE-MRA is considered less toxic than contrast media associated with conventional angiography. In fact, MRA techniques are considered the most powerful non-invasive methods to examine collateral circulation and hemodynamically relevant anatomical variations in Circle of Willis (Fürst et al., 1993). Still, MRA is not without limitations. Gadolinium based contrast agents have generally excellent safety profiles, but recent reports suggest a link to nephrogenic systemic fibrosis in patients with impaired kidney function (Weinreb & Abu-Alfa, 2009). Moreover, some stroke patients cannot tolerate or cooperate with the requirements for MRA, leading to movement artefacts, and MR cannot be used in patients with pacemakers or other magnetic appliances (Barlinn & Alexandrov, 2011).

### **3.1.3 Computed tomography angiography**

Because it is widely available and well-tolerated by most stroke patients (Barlinn & Alexandrov, 2011), computed tomography angiography (CTA) is the most commonly used tool for diagnostic vascular imaging in the clinical stroke setting (Schellinger, 2005). A single bolus of iodine injected intravenously permits fast acquisition of high-resolution, thin slice CT images of cerebral vasculature. With proper post-acquisition processing, CTA images are comparable to DSA and allow 3D resolution of brain vasculature. With respect to stroke, CTA is very effective in detecting proximal arterial occlusions, allowing for differentiation between complete and near-occlusions, and stenoses, and provides information to predict functional outcome and response to thrombolysis. While CTA results in fewer motion artefacts than MRA, it requires radiation exposure and the toxicity and dose-size of the iodine used as a contrast agent is greater than that of the gadolinium. Moreover, risk of radio-contrast nephropathy after CTA is a serious concern, particularly in patients with kidney disease or diabetes (Barlinn & Alexandrov, 2011). Such concerns are particularly important with multiple examinations that lead to larger cumulative doses of radiation and iodine.

### **3.1.4 Transcranial Doppler sonography**

Transcranial Doppler ultrasonography (TCD) can be used to measure the velocity of blood flow and waveforms in intracranial blood vessels through spectral Doppler sampling over particular cerebral blood vessels. TCD is relatively quick, non-invasive and inexpensive method to measure blood flow in the brain that offers information complementary to MRA and CTA. By analysing frequency shifts caused by the velocity of moving particles in the cerebral blood vessels, TCD provides real-time information on cerebral blood flow and hemodynamics and can be used to monitor blood flow without exposing patients to repeated doses of radiation or contrast agents. TCD is limited in that it does not allow for 2D or 3D reconstruction of vascular networks in the brain, and is highly dependent on the experience and aptitude of the sonographer (Barlinn & Alexandrov, 2011). While it is primarily used in human patients, a recent study using TCD in a rat model of middle cerebral artery occlusion identified a redistribution of blood flow after stroke (Li et al., 2010).

### 3.2 Imaging collateral blood flow in laboratory animals

Due to the heterogeneity of the clinical population and differences in delay from onset, the availability of diagnostic imaging, and the varying treatment options in human stroke patients, interpretation of data on collateral blood flow from clinical imaging can be difficult. Recent advances in blood flow imaging in animal models of stroke provide new opportunities to study the dynamics, persistence, and importance of collateral blood flow and the mechanisms and efficacy of collateral therapeutics in pre-clinical studies. Below we will discuss two methods for imaging single-vessel blood flow in animal models of stroke: laser speckle contrast imaging and two-photon laser scanning microscopy.

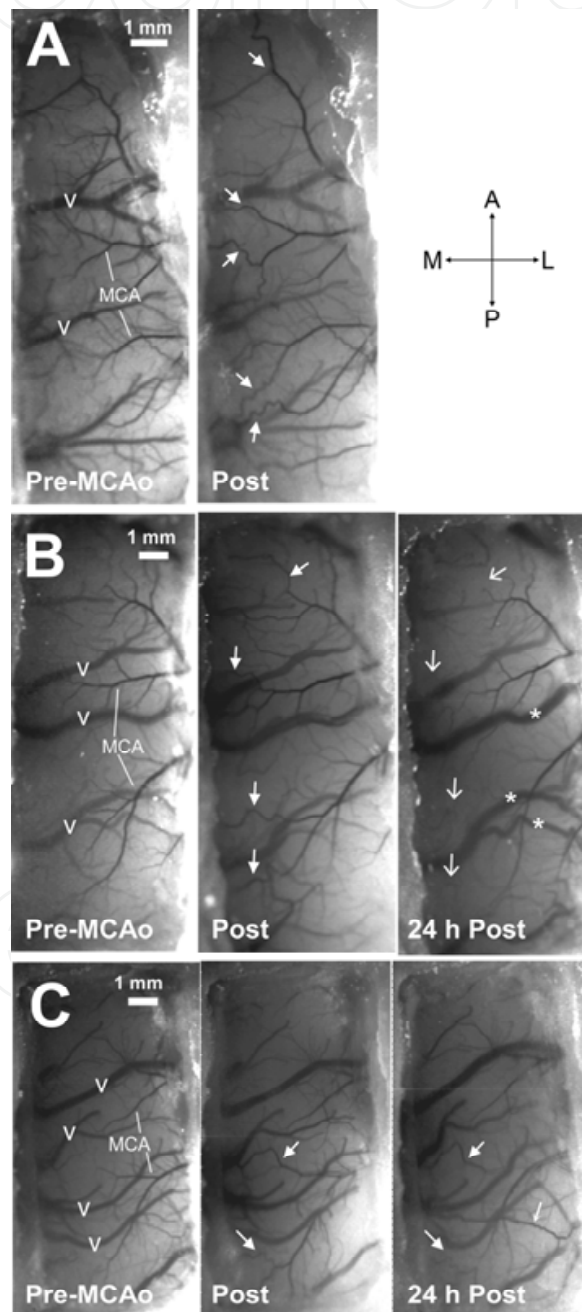


Fig. 1. LSCI of dynamic leptomeningeal collaterals during acute stroke. A, LSCI image showing blood flow in the surface veins (V) and branches of the middle cerebral artery

(MCA) over the hindlimb and forelimb sensorimotor cortex. Note the blood flow through anastomatic connections between the distal segments of the ACA and MCA immediately after MCAo (arrows). B, Left and middle panels show blood flow prior to and immediately after MCAo mapped with LSCI, while the right panel shows blood flow 24 hours after stroke. Spontaneous reperfusion occurred between imaging sessions and blood flow through anastomatic connections ceased by 24 h (large arrows). Darker veins indicative of increased venous blood flow from the territory of the MCA were observed after reperfusion (asterisks). C, Left, middle and right panels show LSCI blood flow maps before, after, and 24 hours after MCAo. Arrows indicate new patterns of collateral flow through anastomatic connections between the ACA and MCA that were apparent soon after MCAo and persisted at 24 h after onset. The small arrow identifies an anastomose with blood flow 24 h after MCAo that was not apparent immediately after onset. A, anterior; P, posterior; M, medial; L, lateral. Figure from Armitage et al., 2010 (used with permission).

### 3.2.1 Laser speckle contrast imaging (LSCI)

LSCI is a technique that allows high spatial and temporal resolution during full-field imaging of changes in blood flow on the surface of the brain. Requiring only inexpensive instrumentation and simple analysis, LSCI provides resolution to individual blood vessels and is extremely effective in mapping changes in collateral blood flow during stroke (Armitage et al., 2010). LSCI maps of blood flow are based on blurring of the characteristic laser speckle pattern produced by illumination of the brain surface (or skull) with coherent laser light. Importantly, the speckle pattern is dynamic and blurred by moving particles (such as blood cells) on or below the illuminated surface. By analyzing fluctuations in the speckle pattern in a particular image, speckle contrast values that provide a measure of relative changes in blood flow can be calculated. The speckle contrast factor ( $K$ ) is a measure of the local spatial contrast of the laser speckle pattern and is defined as the ratio of the standard deviation to the mean intensity ( $K = \sigma/I$ ) in a small region of the speckle image (typically  $5 \times 5$  or  $7 \times 7$  pixels). Speckle contrast and motion of the scattering particles are inversely related.  $K$  values ranges from 0 to 1, with values near 1 suggesting no blood flow in that vessel and values closer to zero reflect greater blood flow. By plotting  $K$  values, LSCI allows for maps of blood flow and can reveal changes in the pattern of blood flow after focal ischemia, including enhanced collateral perfusion or spontaneous reperfusion. LSCI has been used in animal models after middle cerebral artery occlusion (MCAo) to measure cerebral blood flow changes after stroke (Figure 1, Armitage et al., 2010; Dunn et al., 2001; Shin et al., 2008; Strong et al., 2008).

While LSCI permits sensitive mapping of blood flow in surface vessels, the exact quantitative relationship between speckle contrast and blood flow velocity remains undefined (Duncan & Kirkpatrick, 2008). LSCI is susceptible to experimental artifacts that can vary between animals and imaging sessions (Parthasarathy et al., 2008; Ayata et al., 2004) and is best restricted to describing relative changes in the pattern of blood flow rather than quantifying blood flow velocity (Parthasarathy et al., 2008; Ayata et al., 2004).

### 3.2.2 Two photon laser scanning microscopy (TPLSM)

TPLSM permits visualization of fluorescent molecules up to 1 mm below the surface in opaque tissues such as brain. During single photon fluorescence microscopy, short excitation wavelengths prevent deep penetration into tissues and increase light

scattering and phototoxicity (Helmchen & Denk, 2005; Svoboda & Yasuda, 2006 and Mulligan & MacVicar, 2007). Because it uses “pulse lasers” that facilitate multiphoton excitation of fluorophores, TPLSM allows the use of longer excitation wavelengths. In addition to improving penetration into the tissue, these wavelengths have lower phototoxicity. Moreover, multiphoton excitation will only occur in the focal volume of the objective, meaning that all fluorescence collected arises from fluorophores in the focal plane, allowing for optical sectioning and 3D reconstructions of fluorophore distribution. TPLSM has previously been used to demonstrate that stroke induces a rapid loss of this dendritic microstructure in individual neurons (Zhang et al., 2005; Zhang & Murphy, 2007). Importantly, synapses can be restored even after delayed reperfusion (Li & Murphy, 2008) and long-term recovery is associated with enhanced synaptogenesis beside the stroke core (Brown & Murphy, 2008; Brown et al., 2007; Brown et al., 2009), suggesting that methods to facilitate synapse preservation during acute stroke or spine formation during recovery may be of functional benefit. In vivo calcium imaging using TPLSM also demonstrated functional rewiring of sensorimotor neurons as new regions of the cortex adopt the function of tissue lost to stroke (Winship & Murphy, 2008; Winship & Murphy, 2009).

TPLSM has been important in defining the rules governing cerebral blood flow (Zhang & Murphy 2007; Shih et al., 2009; Takano et al., 2006; Nishimura et al., 2010; Mulligan & MacVicar, 2004). Cortical microcirculation can be precisely measured in vivo during TPLSM after blood plasma is labelled with a fluorescent-conjugated dextran (Figure 2). This technique permits resolution of blood flow in veins and arteries on the brain surface as well as arterioles and capillaries in the microvascular bed below the surface of the cortex. Moreover, it allows for precise quantification of the direction and speed of motion of blood cells in these vessels, something that is not possible with LSCI. After stroke, TPLSM can identify vessels at the capillary level that were not previously carrying blood (Schaffer et al., 2006 and Shih et al., 2009). Red blood cell velocity can then be precisely measured in individual arterioles, veins, and capillaries in the penumbral cortex and three-dimensional reconstructions of the microvascular architecture and diameter of these vessels can be created.

#### **4. Collaterals and ischemia**

As noted previously, the collateral circulation is divided into three distinct pathways. Primary collateral circulation is particularly important after occlusion or stenosis of the brain's major feeding arteries, the ICAs and the vertebrobasilar system. In patients with severe stenosis of the ICA, collateral flow through anterior and posterior communicating arteries and retrograde filling through the ophthalmic artery correlate with patient survival rate. Moreover, collateral flow is correlated with a lower risk of hemispheric stroke and transient ischemic attack (Henderson et al., 2000). After severe stenosis of the ICA, enhanced collateral flow through anterior Circle of Willis is observed and the diameter of the communicating arteries is increased (Hartkamp, 1999). Similarly, patients with bilateral ICA occlusion exhibit significant collateral flow through the posterior Circle of Willis and increased posterior communicating artery diameters (Hartkamp, 1999). In fact, in patients with ICA occlusion, blood flow in the territory of the MCA ipsilateral to the occluded ICA is derived primarily from the vertebrobasilar arteries while ACA flow is mainly supplied by the contralateral ICA (Van Laar et al., 2007).



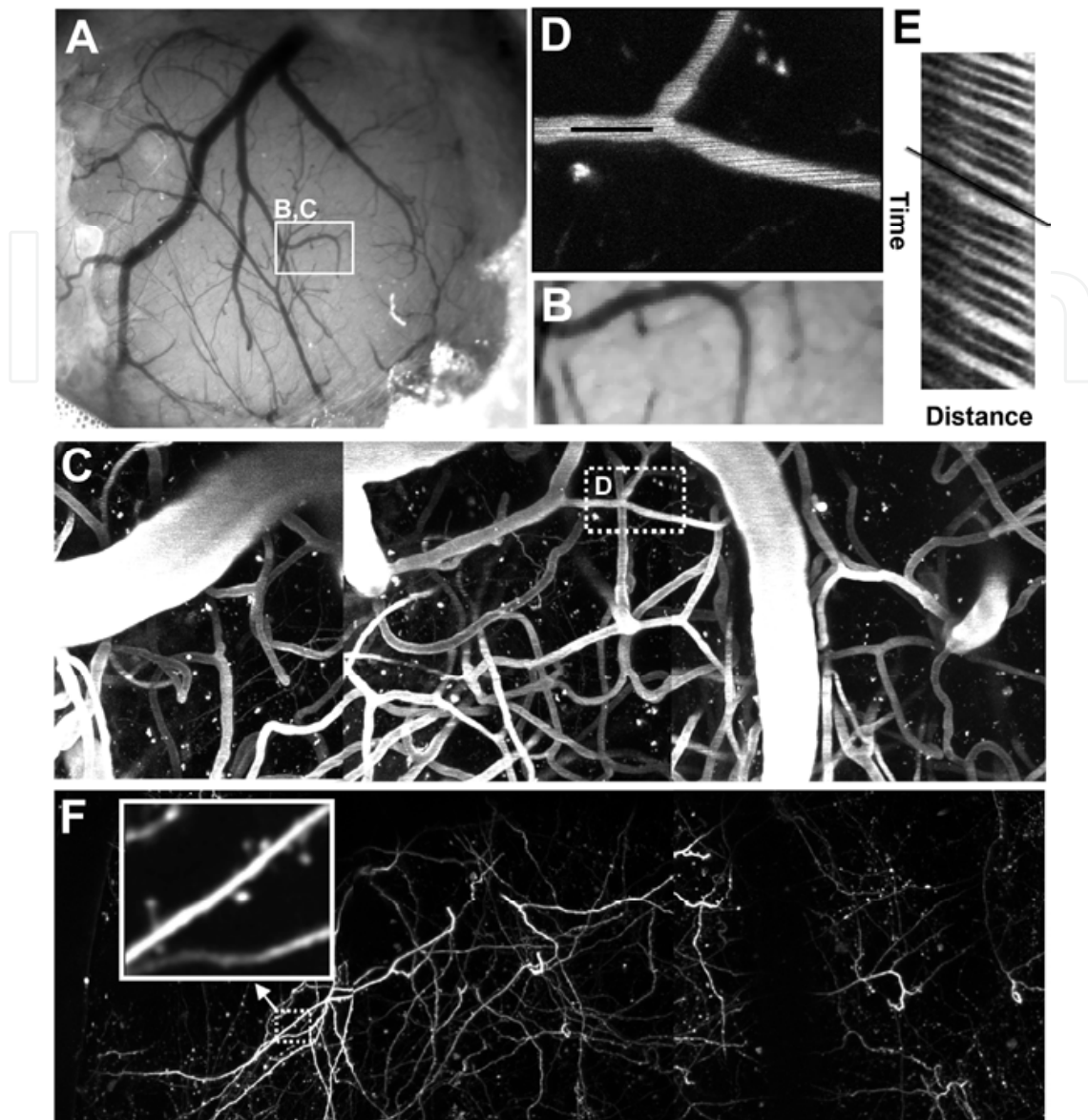


Fig. 2. Quantitative measurement of cerebral blood flow and vascular anatomy. A, B Photomicrographs of the surface of the mouse sensorimotor cortex. C, TPLSM of vasculature loaded with rhodamine dextran, showing surface arterioles and microvascular bed below the cortical surface. D, E, Quantitative measurement of blood cell velocity using line scans was made in the region denoted by the line in D. Resulting line scans are compiled in E, and by calculating the slope (time/ distance), a quantitative measure of blood flow velocity can be calculated. Using two channel imaging in mice expressing green fluorescent protein in subset of neurons, neuronal microstructure can be imaged simultaneously with cerebral blood flow (F). Images complements of Dr. Craig E. Brown, University of Victoria.

#### 4.1 Leptomeningeal collateral vasculature

First described by Heubner in 1874, a leptomeningeal artery is described as a pial artery that connects two major cerebral arteries supplying distinct areas of the cerebral cortex (Heubner 1874; Brozici et al., 2003). Similar to the primary collateral vascular system, it is thought that augmentation of the leptomeningeal collateral vascular system, by flow diversion from the

primary circulation, could lead to increased cerebral blood flow and decreased infarct volume after a focal ischemic stroke.

During middle cerebral artery occlusion (MCAo), high-velocity blood flow in the anterior cerebral artery (ACA) or posterior cerebral artery (PCA) are indicative of flow diversion. In turn, increased blood flow in the ACA and PCA is a potential source of blood flow to leptomeningeal arteries and may improve perfusion in ischemic tissue downstream of the MCAo. Kim et al (2009) used transcranial doppler ultrasonography, in combination with angiography, to measure flow diversion and collateral flow in 51 patients suffering from middle cerebral artery stenosis. Dividing the patients into three groups based on severity of stenosis, they found that patients with less severe stenosis had lower amounts of leptomeningeal collateral circulation, while more severe stenosis correlated with increased leptomeningeal blood flow. These results correlated with flow diversion in the ACA and PCA that was identified in 47% of individuals and increased with the severity of stenosis.

A recent mathematical model of post-stroke blood flow suggests that the leptomeningeal collateral vascular system can maintain approximately 15% of the normal cerebral blood flow during MCAo (Ursino & Gianessi, 2010). Although blood flow at 15% of normal is well below the limit to preserve cellular function, this same study suggests that over time, collaterals may be able to increase their luminal diameter by 50%, thereby preserving normal cellular function until full blood flow can be restored (Ursino & Gianessi, 2010).

#### **4.2 Clinical importance of leptomeningeal collaterals**

While CT, positron emission tomography, MR perfusion and TCD have all been used to assess leptomeningeal collateral blood flow in a variety of different disorders, the most effective single method to visualize leptomeningeal collateral blood flow in humans remains through angiographic assessment (Mori et al., 2009; Derdeyn et al., 1999; Thurley et al., 2009; Wu et al., 2008). However, a combination of multiple imaging modalities is ideal to gain a greater understanding of blood flow in the ischemic cortex (Bang et al., 2008; Wu et al., 2008; Kim et al., 2009). By combining these imaging approaches, leptomeningeal collaterals have been linked to positive outcome after stroke including decreased infarct volumes and decreased National Institute of Health Stroke Scale (NIHSS) scores (Christaforidis et al., 2005; Miteff et al., 2009; Lima et al., 2010).

While leptomeningeal collaterals are seen as a positive indicator of post stroke outcome, it is interesting to note that the presence of leptomeningeal collaterals in humans can indicate cerebrovascular impairment, the presence of vascular occlusive diseases, and are predictive of stroke in certain individuals. For example, Moyamoya disease is a chronic cerebrovascular disorder caused by progressive stenosis or occlusion of the internal carotid artery, leading to headaches, transient ischemic attacks and stroke (Robertson et al., 1997). Due to the long-term occlusive nature of this disease, leptomeningeal arteries become highly developed and have been shown to be a positive indicator of severity of ischemic symptoms (Mori et al., 2009), and are associated with engorged pial networks and slow blood flow (Chung & Park, 2009).

Yamauchi et al (2004) investigated the link between the patterns of collateral circulation and the types of infarcts. This study investigated 42 patients with symptomatic ICA occlusion using four-vessel angiography to assess Willissonian, ophthalmic, and leptomeningeal collaterals and MR imaging to measure infarct type and location. The study showed that the oxygen extraction fraction (a measure of the relative concentration of oxyhemoglobin and

deoxyhemoglobin that can be an indicator of a chronic ischemic condition) was significantly higher in patients with well developed ophthalmic or leptomeningeal collaterals and associated with the presence of striaocapsular infarcts, indicating that those with leptomeningeal and ophthalmic collaterals were suffering from chronic cerebrovascular impairment.

Although the presence of leptomeningeal collaterals are a positive indicator for future stroke risk, they are also associated with positive outcomes after stroke. For instance, in a retrospective angiographic study on collateral blood flow and clinical outcome after thromboembolic stroke, Christoforidis et al (2005), found that infarct volume and modified Rankin scale scores at discharge were significantly lower for patients with better angiographically-assessed leptomeningeal collateral scores. This same study also found that, NIHSS score was significantly higher for patients with lower collateral scores. Similarly, Bang et al (2008) used MRI diffusion and perfusion in combination with angiographic assessment to measure collaterals in patients receiving recanalization therapy for acute cerebral ischemia. While this study found that diffusion-perfusion mismatch (a measure of penumbral or salvageable brain tissue) did not correlate with either good or poor collaterals, it showed that patients with good collaterals had larger areas with only mild hypoperfusion and infarct growth within the penumbra was smaller in these patients. Moreover, the study showed that patients with good pre-treatment collaterals more frequently had good recanalization and less infarct growth. Later studies confirmed that recanalization rate is heavily influenced by the collateral grade in patients undergoing endovascular revascularization therapy (Bang et al., 2011).

Another study using angiographic assessment of collateral status in acute ischemic stroke demonstrated that major reperfusion was associated with good collateral status, and that good collateral status was significantly associated with reduced infarct expansion and more favorable outcomes (Miteff et al., 2009). Similar findings were also reported in a prospective cohort study by Lima et al (2010), which investigated patterns of leptomeningeal collateral blood flow by CTA and evaluated patient outcome after stroke. Lima et al. (2010) studied 196 patients and found that a favourable pattern of leptomeningeal collaterals, along with younger age, lower baseline NIHSS, absence of diabetes and administration of rtPA, predicted improved outcomes 6 months after stroke. Additionally, Christoforidis et al (2009) demonstrated that good collateral blood flow is linked to lower rates of hemorrhagic transformation. Of 104 patients who underwent intra-arterial thrombolysis, 25% of patients with poor leptomeningeal collaterals suffered significant hemorrhage, while only 2.78% of those with good collaterals suffered significant hemorrhage. Interestingly, this study also found that low platelet counts were predictive of significant hemorrhage, indicating that the administration of platelets after intra-arterial therapy may be beneficial.

One explanation for improved patient outcome with increased leptomeningeal collateral circulation in stroke patients is due to the potential facilitation of recanalization and reperfusion. Currently, thrombolysis with rtPA is the most effective therapy for acute ischemic stroke. However, rtPA is ineffective in many patients who receive treatment within its short therapeutic window, particularly in the case of MCAo (Kaur et al., 2004). Part of this low success rate can be attributed to futile recanalization, defined as the lack of clinical benefit due to endovascular treatment of acute ischemic stroke even when recanalization is successful. Futile recanalization may be due to re-occlusion of the artery after initial thrombolysis or due to leptomeningeal collaterals that are insufficient to sustain tissue viability until recanalization occurs (Hussein et al., 2010; Liebeskind et al., 2008).

Good collateral status may also augment the effectiveness of neuroprotective drug therapies by providing increased routes for pharmacological agents such as rtPA to reach the ischemic penumbra and aid in recanalization.

#### **4.3 Animal models and leptomeningeal collaterals**

Clinical evidence strongly suggests that increased leptomeningeal collateral blood flow is a positive indicator for post stroke outcome. Moreover, it is thought that augmenting collateral blood flow via the leptomeningeal arteries by pharmacological or mechanical means may maintain blood supply in the ischemic penumbra and reduce cell death in this at-risk tissue. However, much about the dynamics of collateral blood flow during ischemic stroke remains unknown. As noted, clinical studies are limited by the access to imaging modalities and heterogeneity in treatment options and patient demographics. Animal models offer greater experimental control and facilitate an understanding of collateral vascular dynamics.

When assessing collateral dynamics and therapeutics in animal models, it is important to consider strain differences in the number of collaterals before stroke. While animal studies have shown that collateral growth is enhanced in the weeks after stroke, and highly developed collateral blood flow prior to stroke is associated with decreased infarct size, estimation of the leptomeningeal collateral network size, a number that varies from birth, is difficult (Wei et al., 2001; Lin et al., 2002; Chalothorn et al., 2007; Zhang et al., 2010). In fact, Zhang et al (2010) investigated 16 different mouse strains to determine numbers of native collaterals. This study found statistically significant variation in collateral length, numbers of penetrating arterioles and infarct volume after middle cerebral artery occlusion. As expected, infarct volume correlated inversely with collateral number, diameter and number of penetrating arterioles (Zhang et al., 2010). As in human patients, the number and quality of collateral connections can vary greatly between individuals or animal strains, and is a predictor of stroke outcome. However, by examining collateral dynamics and the mechanisms and efficacy of collateral therapeutics in animal models with different collateral networks, inferences into the importance of leptomeningeal collateral blood flow after stroke can be made regardless of collateral density.

Early studies in animal models focused on the regulation of leptomeningeal collateral blood flow. These studies showed that the pyriform branch of the MCA has collateral communication with the ACA, and that the parietal and temporal branches collateralize with the posterior cerebral artery after MCAo in Sprague-Dawley (SD) rats (Menzies et al., 1993). After a MCAo or common carotid artery occlusion, leptomeningeal arterial blood pressure correlates with blood flow in ischemic areas and these arteries can further dilate to increase blood flow to the brain after stroke (Shima et al., 1983; Morita et al., 1997). Using laser doppler flowmetry in SD rats, Morita et al (1997) showed that pial arteries took ~12 s to become maximally dilated and around 131 seconds to become stable after common carotid artery occlusion. Although this rapid response is promising, it has been suggested that leptomeningeal collateral blood flow does not provide enough blood flow to maintain normal blood flow over a long time period (Derdeyn et al., 1998).

In a recent study, LSCI was used to assess the dynamics and persistence of leptomeningeal collateral blood flow to ischemic territories over the 24 hours following thromboembolic MCAo in SD rats (Armitage et al., 2010). As shown in Figure 1, maps of blood flow revealed several (~ 3 - 6) anastomatic connections between the ACA and MCA that developed soon after vessel occlusion. Notably, these anastomoses were both persistent and dynamic: Blood flow through approximately 75% of these anastomoses persisted for at least 24 hours. The

anastomoses were dynamic during the imaging period: Blood flow through these collateral connections ceased after spontaneous reperfusion and, in some animals, collateral connections that were not apparent immediately after stroke were visible 24 hours post-stroke. Importantly, in this study LSCI confirmed the persistence of blood flow through ACA-MCA anastomoses up to 24 hours after MCAo. However, more quantitative methods (such as TPLSM) will be necessary to better address the persistence of leptomeningeal collateral blood flow velocity as it relates to tissue viability.

Changes in collateral flow in the first hours after stroke, including measures below the cortical surface, have been quantified using TPLSM. Importantly, TPLSM has confirmed flow reversal in distal sections of the MCA downstream from anastomoses with the ACA in a mouse model of transient MCAo (Murphy & Li, 2008). Overall, red blood cell velocity in arterioles downstream MCAo are reduced to 30% of baseline, and lumen diameters in small (< 23  $\mu\text{m}$  diameter) surface arterioles and penetrating arterioles increased by approximately 20% (Shih et al., 2009) during acute ischemia. Importantly, this vasodilation persisted over 90 minutes of MCAo. Schaffer et al (2006) quantified blood flow reversals downstream of the occlusion and showed that approximately half of the arterioles downstream of the MCAo showed flow reversal, as would result from retrograde flow from the ACA into the territory of the MCA, within the two hours after occlusion. More recent studies suggest that these flow reversals are restricted to surface arterioles and do not persist to penetrating arterioles (Shih et al., 2009). Targeted occlusions of penetrating arterioles in the cortex have demonstrated that compensation is somewhat limited in penetrating vessels, as occlusion-induced dilations were restricted to vessels downstream of the occlusion and that neighbouring penetrating arterioles do not dilate to enhance collateral compensation (Nishimura et al., 2010).

In addition to acute changes in collateral circulation, changes in leptomeningeal collaterals are observed after long-term recovery from MCAo. Coyle & Heistad (1987) demonstrated that normotensive Wistar Kyoto rats exhibited extreme collateralization (~27 anastomoses between the ACA and MCA) and little infarct one month after chronic MCAo. In fact, collateral vessels supplying blood to the MCA territory were able to restore blood flow to near baseline levels in the territory of the MCA one month after stroke. Contrasting this, stroke prone hypertensive rats (derived from a WKY background) exhibited the same number of anastomoses one month after stroke, but these connections were significantly narrower than WKY rats and hypertensive rats had significant infarction due to MCAo.

## **5. Augmenting collateral blood flow during stroke**

Animal models and clinical data have clearly demonstrated the importance of collateral circulation during acute ischemic stroke in determining stroke prognosis and response to recanalization therapy. Based on these subsidiary vascular networks, it has also been suggested that enhancing collateral blood flow may reduce ischemia without targeting the clot. While therapies to enhance collateral flow such as adjusting head position, intravenous fluid support, and pressure augmentation have been suggested as neuroprotective strategies, collateral therapeutics remain a relatively unexploited neuroprotective strategy (Liebeskind 2003, 2005). In this section, we will explore different means of collateral blood flow augmentation and their efficacy in the treatment of acute ischemic stroke.

### **5.1 Angiogenesis and collaterals**

A number of studies have highlighted the importance of angiogenesis in the development of collateral channels throughout the vascular system and their role in ischemia. Angiogenesis

is mediated by a number of angiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), granulocyte colony stimulating factor (G-CSF) and angiopoietin (among others) and can be induced by circulating inflammatory cells during atherosclerosis (accounting for the increased collateral vasculature seen with chronic cerebrovascular insufficiencies) (Schirmer et al., 2009; Deb, 2010). After portal vein ligation, VEGF expression and collateral angiogenesis is upregulated, and inhibition of VEGF receptor-2 via a monoclonal antibody (DC101) or autophosphorylation (by SU5416) can decrease portal-systemic collateral density by up to 68% or 52%, respectively (Frenandez et al., 2004). In fact, VEGF expression appears to be critical for the formation of the collateral vasculature in many models of ischemia. In a mouse model of altered lipid metabolism, ApoE<sup>-/-</sup> deficient mice have reduced expression of VEGF and decreased hind limb vascular collateral development (Couffinhal et al., 1999). Strain differences in the expression of the *vegfa* gene account for a 54% difference in collateral remodelling after hind limb ischemia between BALB/C and C57BL/6 mice, as well as reduced collateral density in the intestine and cerebral cortex of BALB/C mice when compared to C57BL/6 mice. The influence of VEGF-A on collateral density has been directly related to models of cerebral ischemia, where it has been shown that transgenic mice that express low levels of VEGF form fewer leptomeningeal collaterals during the perinatal period and have increased infarct volume after MCAo when compared to mice expressing high levels of VEGF (Clayton et al., 2008). Hepatocyte growth factor (HGF) is another angiogenic growth factor which promotes the growth of endothelial cells. HGF has been shown to efficiently increase the number of collateral vessels and improved the blood flow after hindlimb ischemia in rabbits (Pyun et al., 2010).

Perhaps the most promising data relating angiogenic compounds to improved stroke outcome relates to G-CSF and granulocyte monocyte colony stimulating factor (GM-CSF). GM-CSF stimulates angiogenesis by releasing growth factors from mobilised monocytes and macrophages. The importance of G-CSF and GM-CSF was first reported in heart and cerebral artery disease and they were more recently shown effective for treating cerebral ischemia (Buschmann et al., 2003). In fact, a number of groups have identified a neuroprotective role for G-CSF and GM-CSF administered before or after ischemia in rodent models (Todo et al., 2008; Nakagawa et al., 2006; Schäbitz et al., 2008), likely in part due to its upregulation of the formation of collateral vascular channels. Prophylactic injection of GM-CSF in rats for 6 weeks prior to bilateral common carotid artery occlusion has been shown to attenuate functional impairment of cerebrovascular reserve capacity and increase leptomeningeal collateral density (Schneider et al., 2007). A recent study demonstrated that five days of daily GM-CSF or G-CSF administered to C57/BL6 mice after unilateral occlusion of the common carotid artery also promoted leptomeningeal collateral growth and decreased infarct volume (Sugiyama et al., 2011). A subset of these animals received MCAo seven days after common carotid occlusion. Of this subset, animals that were treated with G-CSF or GM-CSF had smaller infarcts and greater cerebral perfusion than untreated animals. Although promising, the feasibility of GM-CSF injection has yet to be tested in humans.

## 5.2 Vasodilation and collateral flow

For the most part, attempts to improve cerebral blood flow during stroke using vasodilatory compounds have not been neuroprotective. This may be because ischemic vasculature is already fully dilated during stroke, and therefore only non-ischemic vasculature dilates, resulting in vascular stealing that is deleterious to ischemic tissue (Bremer et al., 1980 and

Kuwabara et al., 1995). Bath application of N-Methyl-D-aspartate (NMDA) has been shown to enhance blood flow to collateral dependent tissue in a canine model of MCAo independent of neuronal nitric oxide production (Robertson & Loftus 1998). As such, collateral vessels appear to be under additional vasodilatory influences that are yet to be determined. Defining these mechanisms may aid the development of therapies directed at augmenting flow through collateral vessels to reduce infarct size.

### **5.3 Augmenting cerebral blood flow by inducing mild hypertension**

Perhaps the most obvious way to increase collateral blood flow is by inducing systemic hypertension through pharmacological agents or volume expansion. As cerebral autoregulation is impaired during stroke, changes in mean arterial blood pressure have a linear effect of cerebral blood flow. Similarly, decreasing the blood pressure in ischemic patients during acute stroke can exacerbate neurological deficits (Oliveira-Filho et al., 2003; Ahmed et al., 2000; Vlcek et al., 2003). Therefore, it is thought that by artificially inducing hypertension, global cerebral blood flow can be increased, enhancing flow through leptomeningeal collaterals and thereby preserving blood supply to the ischemic penumbra and protecting neuronal function therein (Wityk, 2007; Bogoslovsky et al., 2006). A neuroprotective role for mild induced hypertension has been confirmed in animal models. Shin et al (2008) used intravenous phenylephrine to increase blood pressure after MCAo. The mild hypertension induced by phenylephrine increased blood pressure and cerebral blood flow when injected either 10 or 60 minutes after occlusion (Shin et al., 2008). Treated rats displayed decreased infarct volume after stroke, and the authors hypothesized that this was due to increased perfusion of ischemic territories via leptomeningeal anastomoses between the posterior cerebral artery, ACA, and MCA (Shin et al., 2008). Similarly, hypertensive treatment with phenylephrine that increased blood pressure by 65mm Hg reduced infarct volume by 97% in rabbits after one hour of MCAo and 45% in rabbits subjected to two hours of MCAo (Smrcka et al., 1998). Increasing blood pressure through angiotensin was also demonstrated to increase the mean arterial pressure by 40-60% and reduce infarct volume after transient MCAo in rats (Chileuitt et al., 1996). While mild induced hypertension may be neuroprotective, it is important to note that chronic hypertension worsens stroke outcome (Aslanyan et al., 2003; Geeganage et al., 2011; Toyoda et al., 2009), possibly due to inhibition of collateral blood flow. In spontaneously hypertensive rats, compensatory growth of leptomeningeal collaterals in response to chronic cerebral hypoperfusion is impaired relative to normotensive rats, though this compensatory growth is restored by anti-hypertensive therapies (Omura-Matsuoka et al., 2011).

Clinically, blood pressure is often elevated during MCAo and clinical trials have not demonstrated unequivocal beneficial results in neurological outcome after stroke (Liebeskind, 2003). Moreover, the risks of elevated blood pressure in stroke patients are not well defined, and hypertensive treatments may increase the risk of intracerebral hemorrhage, reflex bradycardia and possibly even ischemic bowel disease (Wityk, 2007).

Still, preliminary data suggest some benefit. An increase in mean arterial pressure of at least 10mm Hg (induced by norephenephrine administration) improved perfusion pressure in patients with MCAo with only a small increase in intracranial pressure (Schwarz et al., 2002). Additionally, several preliminary studies have suggested that inducing mild hypertension may have functional benefits as measured by NIHSS scores and volume of hypoperfused tissue (Hillis et al., 2003; Rordorf et al., 2001). Induced hypertension may be particularly useful for patients ineligible for thrombolysis. In these patients, mild

hypertension induced via pheynylephrine increased mean arterial pressure by 20% resulted in a three point reduction on the NIHSS scale and moderate functional improvement on follow up measured using the Rankin scale (Bogoslovsky et al., 2006).

#### **5.4 Augmenting cerebral blood flow using partial aortic occlusion**

Another approach to facilitating reperfusion of ischemic territories is to increase global cerebral blood flow via temporary partial occlusion of the descending aorta. Using a catheter and balloon introduced via the femoral artery and inflated to occlude 70% of the suprarenal descending aorta, it is hoped that global cerebral perfusion and perfusion of ischemic territories by collateral pathways can be enhanced. Partial aortic occlusion has previously been shown to improve cerebral perfusion and neurological deficits in symptomatic vasospasm after subarachnoid hemorrhage (Lylyk et al., 2005), but its efficacy in ischemic stroke is unproven. Because many focal strokes are resistant to rtPA—particularly MCAo—pilot studies are ongoing to assess the safety and efficacy of aortic occlusion treatment in animal models and stroke patients (Noor et al., 2009 and Shuaib et al., 2011). In a non-ischemic porcine model, it was shown that partial occlusion of descending suprarenal aorta increased cerebral blood flow by 35-52% and that global cerebral perfusion remained elevated for 90 min after deflation (Hammer et al., 2009). Exciting preclinical data in a rat model of thromboembolic stroke supported a neuroprotective role for partial aortic occlusion, and demonstrated that aortic occlusion significantly reduces infarct volume at 24 hours post-occlusion without increasing the risk of hemorrhagic transformation. Notably, treatment in combination with rtPA further reduced the infarct volume (Noor et al., 2009), suggesting a synergistic relationship between aortic occlusion and thrombolysis.

Recently, the safety and efficacy of partial aortic occlusion was tested in patients up to 14 hours after ischemic onset in the Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke (SENTIS) trial (Shuaib et al., 2011). Importantly, the treatment appeared safe with no significant increase in adverse events as compared to standard stroke treatments. While overall efficacy was unclear, preliminary results suggest that aortic occlusion was effective in patients treated within 5 hours of onset, older than 70 years of age, and with moderate stroke severity. Moreover, partial aortic occlusion as an adjunct to thrombolysis appears safe, suggesting that studies of combination therapy are warranted (Emery et al., 2011).

#### **5.5 Augmenting cerebral blood flow with sphenopalatine and cervical spinal stimulation**

While partial aortic occlusion attempts to improve cerebral blood flow and reperfusion of ischemic territories by physically diverting blood from the periphery, other approaches attempt to manipulate the neurovascular interface to improve cerebral blood flow during stroke. One approach involves selective electrical stimulation of the parasympathetic nerves in the sphenopalatine ganglion. These fibres provide parasympathetic innervation of the anterior cerebral circulation, and a number of studies in animal models suggest that sphenopalatine stimulation elicits significant increases in cerebral blood flow (Ayajiki et al., 2005; Suzuki et al., 1990; Yarnitsky et al., 2005). Recently, MR imaging and behavioural assessment was used to assess tissue characteristics and stroke recovery in MCAo rats after sphenopalatine ganglion stimulation treatment that began 18 hours after ischemic onset (Bar-Shir et al., 2010). Notably, n-acetyl-aspartate (NAA) levels (a marker of neuronal density and viability) were significantly greater in treated rats, and measures of neurological impairment at 8 and 28 days after stroke suggested a benefit of sphenopalatine ganglion



stimulation. Conversely, cutting the nerves emanating from the sphenopalatine ganglion increases infarct volume after MCAo (Diansan et al., 2010). Based on preliminary data, the safety of sphenopalatine ganglion stimulation is currently being evaluated in human stroke patients (Khurana et al., 2009).

Spinal cord stimulation has been found effective in treating a number of disorders related to low cerebral blood flow (Robaina & Clavo, 2007). While it has not yet been tested in stroke patients, spinal cord stimulation in non-stroke patients significantly enhances blood flow in the common carotid and MCA (Robaina & Clavo, 2007). In rats, electrical stimulation of the cervical spinal cord increases cerebral blood flow (measured via laser Doppler flowmetry) by over 50% in control rats (Sagher et al., 2003). When initiated 20 minutes after MCAo, cervical spinal stimulation also improved blood flow in ischemic territories by over 30% (~64% reduction in blood flow prior to stimulation and ~30% below baseline after stimulation) and profoundly reduced infarct volume measured six hours after ischemic onset (Sagher et al., 2003). Similarly, cervical spinal stimulation in cats significantly reduced infarct size 24 hours after stroke and mortality due to MCAo (Matsui & Hosobuchi, 1989). Based on these preliminary data, further studies in animal models and human patients are warranted.

### **5.6 Augmenting cerebral blood flow using head positioning**

Cerebral blood flow to the brain can be augmented by supine positioning of head that results in increased arterial flow due to gravity. Importantly, this treatment can be applied as soon as an ischemic stroke patient is diagnosed. When head position is reduced from 30° to 0° elevation during the first 24 hours after ischemic onset, the mean flow velocity of MCA (measured using Transcranial Doppler) is increased by 20%, resulting in functional improvement in 15% of patients (NIHSS) (Wojner-Alexander, 2005). Conversely, a decrease in cerebral blood flow was observed by increasing the head position from 0° to 30° or 45° (Schwarz et al., 2002; Moraine et al., 2000), with cerebral blood flow determined according to the arteriovenous pressure gradient (Moraine et al., 2000). Applying a supine head positioning procedure may increase the intracranial pressure of some patients, and is therefore advisable when a higher perfusion rate is required even at the risk of increased intracranial pressure (Schwarz et al., 2002). More research is required, however, since it is not clear to what extent head position augments collateral blood flow, nor is it known how delay and duration of head positioning influence outcome.

## **6. Summary**

Collateral circulation refers to subsidiary vascular networks in the brain whose pathophysiological recruitment can partially maintain blood flow when primary vascular routes are blocked. With respect to MCAo, clinical imaging suggests that blood flow through the leptomeningeal collaterals, anastomoses connecting the distal segments of the MCA to distal branches of the ACA, can partially restore blood flow to ischemic territories. Based on these subsidiary vascular networks, it has been suggested that enhancing collateral blood flow may reduce ischemia without targeting the clot. While therapies to enhance collateral flow remain relatively unexploited neuroprotective strategies, promising data from animal models and clinical evaluation suggest that collateral therapeutics offer a legitimate alternative and/or adjuvant to thrombolytic therapies. By furthering our understanding of the dynamics, persistence, and regulation of collateral blood flow and expanding on studies evaluating the mechanisms and efficacy of collateral therapeutics, improved strategies for stroke care can be developed.

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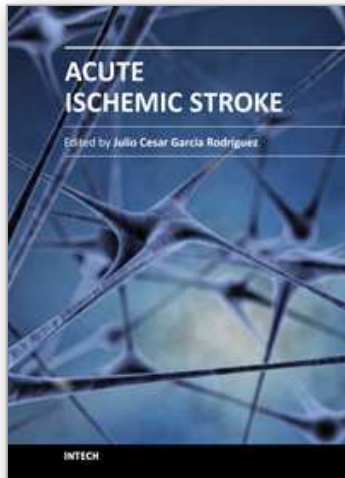
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Despite significant technological advances in recent years, their impact on our overall health and social, well-being is not always clear to see. Perhaps, one of the best examples of this can be highlighted by the fact that mortality rates as a result of cerebrovascular diseases have hardly changed, if at all. This places cerebrovascular diseases as one of the most prominent causes of both disability and death. In Cuba, for instance, a total of 22,000 cases of cerebrovascular diseases are reported each year in a country where life expectancy should increase to 80 years in the near future. In such a situation, to have a book that includes in a clear and summarized way, a group of topics directly related to the preclinical investigations advances and the therapeutic procedures for the cerebrovascular disease in its acute phase constitutes a useful tool for the wide range of the contributors to this affection's problems solution. In this group is included students, professors, researchers, and health policy makers whose work represents one of the greatest social and human impact challenges of the XXI century basic and clinical neurosciences.

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