

## **COLLATERALS IN ACUTE ISCHEMIC STROKE: AN IMPORTANT DETERMINANT FOR GOOD PROGNOSIS**

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The severity of ischemia at onset of symptoms is the most important determinant of irreversible injury in acute stroke. Irrespective of etiology or the mechanism of ischemia, collateral flow, i.e. perfusion via alternative indirect pathways, may offset potential injury to the brain. Digital subtraction angiography (DSA) has been used to identify collateral vessels in patients with acute stroke but because of its invasive nature it has not gained widespread popularity. Newer imaging techniques, especially multimodal cranial CT scans, can assist with identification of pial collaterals. There is emerging evidence that this information may be very helpful in determining the long term prognosis in acute stroke. Additionally, recent evidence suggests that patients with good collaterals respond better to reperfusion therapy and may have lower risk of hemorrhagic complications from such treatments.

Modern neuroimaging techniques, particularly multimodal CT and MRI, including noninvasive angiography and perfusion imaging allows for identification of cerebral injury in the early hours following arterial occlusion. Detailed imaging studies have shown that progression to complete infarction, especially following occlusion of the middle cerebral artery (MCA), is highly variable between patients. In some cases, infarction is complete in less than an hour, while other patients may show evidence of viable tissue for days, if not indefinitely. In patients where the tissue survives for a prolonged period of time despite proximal arterial occlusion, the retrograde filling of the pial arteries (a surrogate marker for leptomeningeal collateral vessels), is often evident on imaging and may play an important protective role

Enhancement of blood flow through collateral vessels may be therapeutically useful in the treatment of acute stroke. The concept of cerebral blood flow augmentation by volume expansion and induced hypertension has been tested in a number of small trials dating to the 1970s. More recently, newer methods of CBF augmentation in acute ischemic stroke have been evaluated

I will summarize the anatomy and physiology of the collateral circulation and its potential as a therapeutic target in ischemic stroke. The focus will be on the importance of emerging CT and MRI technologies that can help identify very early during an ischemic stroke whether collateral blood vessels are evident on imaging and to present evidence that good collateral circulation can prevent or delay permanent neural damage. I will also review how the presence of collateral blood vessels help improve outcome with thrombolysis in acute stroke. Finally I will present the current literature on therapies that have been used to enhance collaterals in patients with an acute ischemic stroke. A summary of some such modalities is described below.

### **1. Sphenopalatine ganglion stimulation**

Stimulation of the sphenopalatine ganglion (SPG) activates the parasympathetic innervation to the intracranial blood vessels, resulting in vasodilation and increased ipsilateral hemispheric blood flow. The SPG is accessible from the oral cavity and is amenable to electrical stimulation. Experiments in animal focal ischemia models of have shown that SPG stimulation results in an increase in blood flow and a reduction in infarct volume. Treatment effects have been demonstrated using functional behavioral tests, MRI measures of infarct volume and histological studies

The feasibility and utility of SPG stimulation in ischemic stroke patients is currently being investigated. An open-label pilot study indicated that the treatment appears to be well tolerated in acute stroke patients. A multicenter randomized controlled trial of sham versus actual SPG stimulation is about to begin.

### **2. Partial Aortic Occlusion**

Augmentation of blood flow to the brain through restriction of abdominal aortic blood flow was initially tested in animal models of focal ischemia in the late 1980s. Temporary occlusion of the abdominal aorta in a rodent embolic stroke model has also been shown to result in reduced infarct volume when used alone and in combination with rt-PA. The microvasculature was also evaluated in the experiments with double staining techniques showing a significant reduction in perfusion deficits in the treated group.

A catheter capable of restricting the aortic lumen by as much as 80% at two levels (supra- and infra-renal) has been developed for use in acute stroke patients. The device has been shown to be safe in patients treated up to 24 hours after symptom onset. PA. The NeuroFlo catheter has also been tested in patients initially treated with intravenous tPA, and it does not appear to be associated with an increased risk of hemorrhagic transformation. A randomized controlled trial, 'Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial,' (SENTIS trial), of 515 patients enrolled within 14 hours of symptom onset did not demonstrate a clinical benefit over standard medical therapy. There was, however, better outcome in patients treated early with moderate deficits at onset as measured on the NIHSS and in patients over the age of 70 years. This study was likely under powered to demonstrate clinical benefits, which can be expected to be limited in unselected patients treated relatively long after symptom onset. It remains possible that this treatment is effective in patients with persisting penumbral tissue prior to treatment onset. It is apparent that future trials of interventional therapies will benefit from more careful patient selection prior to enrolment.

### **3. External compression devices**

Animal experiments in monkeys and dogs have shown CBF can be increased using intra-aortic counter pulsation/military anti-shock trousers (MAST pants). Blood flow can also be diverted from the capacitance vessels in the lower extremities with external compression. Although this less invasive intervention may theoretically increase CBF, this has never been demonstrated.

'Antigravity suits' and external counter pulsation have been assessed in a small number of acute and subacute stroke patients. These relatively simple interventions appear to be safe, but there are currently no data to support use outside of clinical trial settings..

### **Conclusions:**

In acute stroke, the severity of ischemia determines how fast the brain tissue would suffer irreversible damage. Pial collaterals, if well developed, may allow for prolonged tissue survival in the event of a proximal occlusion of a large intracranial blood vessel. Imaging collateral flow is challenging, but multimodal CT and MRI techniques (perfusion combined with vessel imaging) appear to be the most promising methods of routine assessment and quantifying of this important phenomenon. Recent research has shown that the presence of good collaterals allows for better outcome with intravenous and intra-arterial reperfusion therapy. It has yet to be determined if techniques aimed at improving/maintaining collateral flow are clinically useful. However, this is an area of active research.

### **Reference:**

*Shuaib, Butcher K, Askar M, Saqqur M, Liebeskind D: Collateral blood vessels in acute stroke: potential therapeutic target. Lancet Neurol 2011; 10: 909-921.*